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VASCULAR IMMUNOLOGY: OLD BATTLES – NEW SCARS

100 Natural killer T cells are involved in atherosclerotic plaque instability in apolipoprotein-E knockout mice

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Aims: The infiltration and activation of macrophages as well as lymphocytes within atherosclerotic lesion contribute to the pathogenesis of plaque rupture. We have demonstrated that invariant natural killer T (iNKT) cells, a unique subset of T lymphocytes that recognize glycolipid antigens and secrete a large amount of TH1/TH2 cytokines, play a crucial role in atherogenesis. However, it remains unclear whether iNKT cells are also involved in plaque instability.
Methods and results: Apolipoprotein E (apoE) knockout mice were fed with a standard diet (SD) or a high-fat diet (HFD) from 8 to 16 weeks. The SD- and the HFD-mice were divided into 2 groups according to the intraperitoneal injection of α-galactosylceramide (αGC, 2μg/body, twice a week; SD-αGC, n=7 and HFD-αGC, n=21) that specifically activates iNKT cells or phosphate-buffered saline alone (PBS; SD-PBS, n=6 and HFD-PBS, n=21). ApoE/Jα18 double knockout mice, which lack iNKT cells, were also fed with SD or HFD (SD-KO, n=3 and HFD-KO, n=9). Plaque instability was assessed at the brachiocephalic artery by the histological analysis. In the HFD group, αGC administration significantly enhanced iNKT cell infiltration by 1.9-folds in aortic tissues without affecting plasma lipid levels. Activation of iNKT cells by αGC administration significantly increased the number of buried fibrous caps (0.95±0.18 vs. 0.35±0.11/section, $p<0.05$) and disrupted elastic laminae (0.82±0.16 vs. 0.33±0.07/section, $p<0.05$), and slightly reduced fibrous cap thickness (5.2±0.6 vs. 7.9±0.6μm, p=NS) in HFD-αGC compared to HFD-PBS mice without affecting atherosclerotic lesion area. These increases of buried fibrous caps and disrupted elastic laminae in HFD-αGC group were completely ameliorated in HFD-KO group (0.14±0.14 and 0.18±0.04/section, $p<0.05$). Moreover, fibrous cap thickness was significantly thicker in HFD-KO group than that in HFD-αGC group (11.6±1.7μm, $p<0.01$). Real-time PCR analyses of aortic tissues demonstrated that αGC administration significantly enhanced the gene expression of IFN-γ and MMP-2, while the depletion of iNKT cells attenuated these levels compared to those in PBS-treated mice.
Conclusions: iNKT cells are involved in the enhancement of plaque instability via activating inflammatory cells and up-regulation of MMP-2 in vascular tissues. The regulation of iNKT cells may be a novel preventive strategy for atherosclerotic plaque rupture.

101 Natural killer T cells are involved in aortic valvular calcification in uremic apolipoprotein-E deficient mice

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Objective: The infiltration and activation of macrophages and lymphocytes contribute to the pathogenesis of valvular calcification. We have demonstrated that natural killer T (NKT) cells, a unique subset of T lymphocytes, have a crucial role in atherogenesis. However, it remains unclear whether NKT cells are also involved in the development of valvular calcification.
Methods and results: Female apolipoprotein-E deficient (apoE KO) mice were subtotally nephrectomized and fed with a high-fat diet for 8 weeks, which were divided into 2 groups according to the intraperitoneally injection of α-galactosylceramide (αGC, 0.1 μg/g body weight; n=15), which specifically activates NKT cells, or phosphate-buffered saline (PBS; n=16). As controls, sham-operated mice were served (n=13). αGC administration did not affect plasma urea and lipid levels in uremic apoE KO mice. It significantly enhanced the proportion of calcified area in the aortic valve area by the histological analysis with von Kossa staining (2.5±0.2 vs. 3.5±0.2%, $p<0.05$). It also significantly increased the infiltration of Mac3-positive macrophages in the aortic valve (16.1±2.8 vs. 24.0±2.1%, $p<0.05$). αGC administration significantly enhanced the gene expression of major histocompatibility complex (MHC)-class II (a marker of macrophage activation) and IL-4 (an inhibitory cytokine of osteoclastic differentiation) in the thoracic aorta, whereas it did not affect osteoblastic differentiation genes such as BMP2 and osteopontin. Pathological calcification processes are enhanced by the inhibition of osteoclast-like cell as well as the activation of osteoblast-like cell. To determine whether αGC can directly affect the osteoclastic differentiation in vitro, mouse splenocytes, including mononuclear phagocytes and NKT cells, were cultured with receptor activator of nuclear factor κB ligand (RANKL, 100 ng/ml) and macrophage colony stimulating factor (M-CSF, 100 ng/ml) for 6 days and assessed the differentiation of mononuclear phagocyte into osteoclast with or without αGC (0, 0.1, 1, and 10 ng/mL) by tartrate-resistant acid phosphatase (TRAP) staining. αGC significantly inhibited the osteoclastic differentiation in a dose-dependent manner. It also significantly increased the IL-4 levels in the culture media in a dose-dependent manner.
Conclusions: NKT cells are involved in the enhancement of aortic valvular calcification via the upregulation of IL-4 and the inhibiton of osteoclastic differentiation. The regulation of NKT cells may be a novel therapeutic strategy for aortic valve stenosis.

102 Bone morphogenetic protein 2 is a novel functional regulator of monocyte migration

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Purpose: Monocytes play a crucial role in vascular remodeling and cardiovascular disease. They are recruited to sites of collateral growth where they contribute to arteriogenesis. However, prolonged presence or increased accumulation of monocytes to sites of collateral growth can compromise tissue integrity and lead to atherosclerosis. Bone morphogenetic proteins (BMPs) are multifunctional cytokines, which play important roles in vascular function. Perturbation of BMP signaling leads to cardiovascular diseases including atherosclerosis. BMP-2 was detected in calcified atherosclerotic plaques and it has been implicated as mediator of calcification and inflammation in the vascular wall. It is still unknown whether monocytes play a role in mediating these effects.
Methods: Human monocytes were isolated from peripheral blood through gradient centrifugation and subsequent negative immunological magnet isolation. Monocyte motility was analyzed by the modified Boyden chamber migration assay. Protein phosphorylation was assessed by immunoblotting using phospho-specific antibodies.
Results: Stimulation of monocytes with BMP2 (10-100 ng/ml) induced monocyte migration in a dose dependent manner. Noggin is a natural BMP-2/4/7 antagonist. Addition of noggin (500 ng/ml) hindered monocyte chemotaxis towards BMP2. BMPs signal into the cells by activating both Smad-dependent and Smad-independent signaling pathways. BMP2 stimulation of monocytes resulted in the phosphorylation and activation of the Smad1 pathway as well as the p38 MAPK pathway in primary human monocytes. Noggin inhibited both BMP-induced Smad1 and p38 phosphorylation.
Conclusions: Our results reveal that BMP-2 is a novel positive stimulator of human monocyte function. Our results suggest that BMP-2 may exert its pro-inflammatory effects and pro-calcification function in atherosclerosis by recruitment of monocytes in addition to its direct effects on vascular cells.

103 CD34+CD45- and CD14+VEGFR-2+ cells are mobilised in response to acute myocardial ischaemia

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Background: Acceleration of neovascularisation and the regeneration of necrotic myocardium is a contemporary aspiration for the treatment of myocardial infarction. To realise this, the mechanisms underlying vascular and myocardial cellular repair must be better understood.
Methods: We measured circulating putative progenitor cell populations in 201 patients undergoing coronary angiography for the investigation of stable angina (n=90) or an acute coronary syndrome (ACS) (N=111). Cells expressing CD34, VEGFR-2, CD133 and CD45, or CD14, VEGFR-2 and Tie-2 were determined in whole blood by flow cytometry. Colony forming units (EC-CFU) were quantified by culture of peripheral mononuclear cells.
Results: Patients with ACS were recruited at a median of three days following hospitalization and had a median (inter-quartile range) plasma troponin concentration of 0.42 (0.20-3.3) μg/L. EC-CFU were increased in patients with ACS compared to patients with stable angina [11.5 (3.5-27.0) versus 6.3 (2.5 - 16.5): P=0.005]. CD34+ cells were also increased following acute myocardial ischaemia [3.44 (2.54-4.85) versus 2.84 (2.15-4.18)$\times 10^6$ cells/L; P=0.04], due to an increase in CD34+CD45- cells [1.05 (0.7-1.64) versus 0.9 (0.55-1.30)$\times 10^6$ cells/L; P=0.02]. The concentration of total CD14+ cells were similar in both groups however CD14+VEGFR-2+ and CD14+VEGFR-2+Tie-2+ cells were significantly increased following an ACS [74.81 (47.08-136.9) versus 53.85 (30.58-103.13); P=0.02, and 8.98 (3.89-20.46) vs 4.45 (2.14-8.79)$\times 10^6$ cells/L; P=0.003 respectively]. CD34+CD45- and CD14+VEGFR-2+ populations correlated significantly with the severity and extent of coronary artery disease assessed by the Gensini score (r=0.44; p=0.0001 and r=0.29 respectively, P=0.03).
Conclusions: Putative CD34+CD45- progenitor cells and pro-angiogenic CD14+VEGFR-2+ cells relate to the extent and severity of coronary artery disease and are increased in the peripheral circulation following acute myocardial ischaemia and infarction. Whilst the origins of these populations remain unclear, their concentration in the circulation likely reflects underlying cardiovascular injury.

104 The role of B-lymphocytes in thrombus resolution

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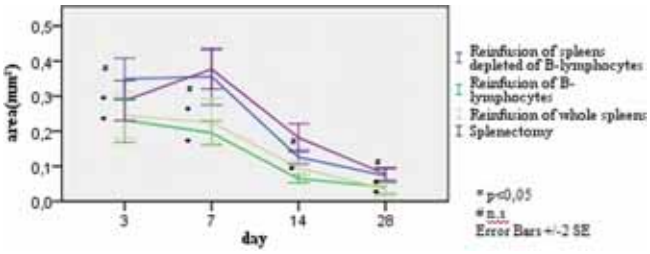
Purpose: Splenectomy is associated with complex venous thromboembolism such as recurrent deep venous thrombosis, portal vein thrombosis, and chronic thromboembolic pulmonary hypertension (CTEPH). The spleen serves not only as a red blood cell filter but also constitutes an immunological organ. The aim of

our study was to decipher the population of spleen cells responsible for misguided thrombus resolution after splenectomy.
Methods: We utilized a mouse model of stagnant flow venous thrombosis to characterize thrombus resolution. Splenectomy was performed one month before vena cava ligation. In defined groups, whole spleens, spleens depleted of B-lymphocytes or B-lymphocytes alone were reinfused intraperitoneally. On days 3,7,14 and 28 after vena cava ligation thrombi were harvested for histology.
Results: Thrombus areas of splenectomized mice were significantly larger than those of controls at all time points (ANOVA, n=8, $p<0.03$). Reinfusion of autologous whole spleen-homogenates reconstituted a normal pattern of thrombus organisation. Reinfusion of spleen tissue depleted of B-lymphocytes could not accelerate thrombus resolution significantly. However, reinfusion of autologous splenic B-lymphocytes in previously splenectomized mice normalized thrombus resolution. (Figure 1)



Conclusion: Reinfusion of spleen cells can restore the normal process of venous thrombus organisation in a mouse model. Our data demonstrate that spleen B-lymphocytes play a role in thrombus resolution.

105 Subcutaneous immunization with hsp65-alum protects apoe-/- mice against atherosclerosis progression independently of CD45RBlow cells and Foxp3+ Treg

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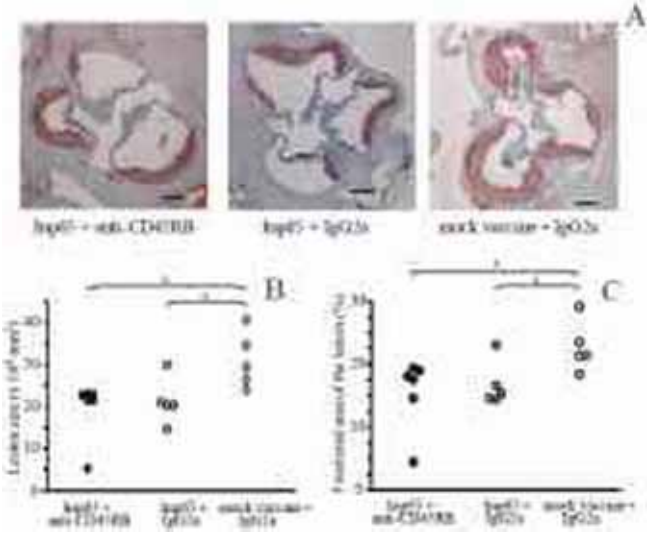
Objective: To modulate atherosclerosis by combining anti-CD45RB monoclonal antibodies (mAb) and subcutaneous immunization with heat shock protein 65 (hsp65) in alum adjuvant.
Methods: 8 week old apoe-/- mice on normal chow were treated for 12 weeks: group A received hsp65-alum immunization combined with anti-CD45RB mAb, group B hsp65-alum immunization combined with isotype control antibody, and group C mock vaccine combined with isotype control antibody.
Results: Unexpectedly, atherosclerotic lesions in the aortic root were significantly reduced in both hsp65-alum immunization groups (A and B) compared with the control group (C). Significantly elevated antibody titers against hsp65 and oxLDL were detected in both groups along with a significant increase in MHC class II expression on B cells. Body weight, total cholesterol and triglyceride levels were not different between groups. Treatment with anti-CD45RB antibody mediated a shift on CD4+ T cells from the CD45RBhigh to CD45RBlow isoform and was associated with a significant increase in CD4+Foxp3+ regulatory T cells Treg). In contrast, anti-CD45RB treatment mediated a transient peripheral leukocyte depletion and increased IFN-gamma and IL-17A plasma levels.



Conclusions: Subcutaneous immunization with hsp65-alum protects apoe-/- mice against progression of atherosclerosis. Our data suggest that hsp65 immunization may lead to B cell cross-presentation of antigens and the generation of a protective humoral response to oxLDL. Administration of anti-CD45RB antibody provided no incremental benefit to the atheroprotective effects of hsp65-alum treatment alone.

HEART FAILURE: PRACTICAL INSIGHTS

114 Short-term prognosis of adaptive servo ventilation therapy in patients with heart failure

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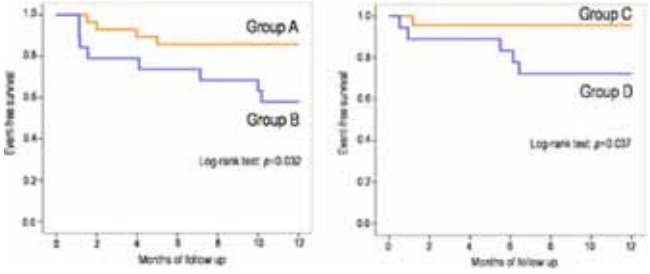
Background: Heart failure (HF) is associated with high mortality. Adaptive-servo-ventilation (ASV; Autset CS®, ResMed, Sydney Australia) is becoming effective therapy in HF patients with sleep-disordered-breathing (SDB). The aim of this study is to clarify whether ASV improves the prognosis of HF patients, regardless of SDB.
Methods: 88 patients diagnosed with HF (left ventricular ejection fraction [LVEF]$<$55%) were divided into four groups based on ASV therapy and SDB severity. Polysonography was done previously, an apnea hypopnea index (AHI)$\geq$20 were defined as moderate-to-severe SDB and an AHI$<$20 as non-to-mild. Patients were divided into four groups; A) moderate-to-severe SDB, ASV-treated; B) moderate-to-severe SDB, non-ASV-treated; C) non-to-mild SDB, ASV-treated; D) non-to-mild SDB, non-ASV-treated. The incidence of HF, brain natriuretic peptide (BNP) levels and LVEF were followed for 12 months.
Results: Kaplan-Meier survival analysis showed that the event-free rate at 12 months was greater than in A and C, when compared to B and D (p=0.032, p=0.037, log-rank test; Figure 1). Regardless of the severity of AHI, the LVEF improved in groups A and C ([group A] 45.5$\pm$7.4 to 50.2$\pm$7.1%, p=0.012, [group C] 43.7$\pm$7.7 to 47.7$\pm$7.6%, p=0.047), but not in groups B and D ([group B] 49.1$\pm$6.4 to 47.6$\pm$7.6%, p=0.463, [group D] 45.6$\pm$10.6 to 42.7$\pm$11.0%, p=0.115). The reduction in BNP was greater in groups A and C ([group A] 202.6$\pm$163.0 to 89.9$\pm$87.1 pg/ml, p=0.005, [group C] 219.8$\pm$154.5 to 150.9$\pm$162.8 pg/ml, p=0.033) than in groups B and D ([group B] 228.4$\pm$220.1 to 239.2$\pm$206.6 pg/ml, p=0.850, [group D] 158.2$\pm$103.7 to 139.1$\pm$114.3 pg/ml, p=0.448).



Figures 1 and 2

Conclusions: This is the first study showing that ASV improves the prognosis of HF regardless of the severity of SDB. ASV could be a new therapuetic option in HF patients.

115 Heart failure management in Octogenarian patients: results of the OCTOCARDIO study

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Purpose: Increase in life expectancy and improvement of cardiac therapies explain the increasing proportion of octogenarians among patients (pts) with heart failure (HF). Underprescription of recommended HF medications has been reported in Europe but factors associated with prescription rates (PR) remain controversial. The aim of this multi-center study was to evaluate the influence of comorbidities on the PR of HF medications recommended by the European Society of Cardiology (ESC) in pts over 80 years of age.
Methods: The OCTOCARDIO study was designed and performed by medical residents and fellows, members of the Group of the Cardiologists in Training of the French Society of Cardiology. The study included all pts$\geq$80 years old under cardiology care in 32 French hospitals on January 27th, 2010. Demographic data, co-morbidities, and medical prescription informations were collected. In this substudy, only pts with a history of HF were included in the analysis. The PR of HF medication at admission were analysed, stratified to the patient's CharIson score (score=0; score=1-2; score=3-4 and score$\geq$5).

Results: 510 pts were included in the OCTOCARDIO study (85±4 years,53% of women). 199 (39%) presented a history of HF and 276 (54%) were hospitalized for HF. HF was associated with atrial fibrillation in 116 pts (23% of the overall population) and with coronary artery diseases in 94 (18%) pts. Preserved left ventricular ejection fraction (LVEF≥45%) was found in 50% of the HF pts. PR of HF medications recommended by the ESC are reported in table. None of the PR was significantly influenced by the Charlson score.

Medications at admission	All patients with history of HF (n=199)	LVEF ≥45% (n=85)	LVEF <45% (n=85)	P
Angiotensin-converting enzyme-inhibitors (ACE-I), n (%)	80 (40%)	32 (38%)	39 (46%)	0.28
Angiotensin receptor blockers (ARB), n (%)	33 (17%)	15 (18%)	14 (16%)	0.84
ACE-I or ARB, n (%)	111 (56%)	45 (23%)	53 (62%)	0.21
Beta-blockers, n (%)	96 (48%)	34 (40%)	50 (59%)	0.01
Spironolactone/eplerenone, n (%)	21 (11%)	6 (7%)	12 (14%)	0.13
Digitalis, n (%)	23 (12%)	12 (14%)	6 (7%)	0.13
Diuretics, n (%)	170 (85%)	71 (84%)	75 (88%)	0.38

Conclusions: PR of the recommended HF medications remain low in octogenarians and are not influenced by co-morbidities in the OCTOCARDIO study population.

116 Impact of diabetes mellitus on chronic life saving therapies in patients hospitalized for acute heart failure: an ALARM-HF survey sub-analysis

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Purpose: Heart failure (HF) and diabetes mellitus (DM) are both common clinical entities that frequently coexist in the same patient population. We sought to investigate the impact of DM on chronic evidence-based medications in patients with acute heart failure (AHF) in ALARM-HF survey.
Methods: The ALARM-HF included a total of 4953 patients hospitalized for AHF in 666 hospitals (cardiology deparments:66%; intensive care units: 33%) in 6 European countries, Mexico and Australia. The prevalence of DM was 45% (n=2229) of the total cohort.
Results: On admission, diabetics received more frequently life-saving medications, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs) and beta-blockers (BBs) (ACEi: 34% vs 29%, p=0.001; ARBs: 30% vs 25%, p<0.001, BBs: 24% vs 22%, p=0.024), as well as nitrates (11% vs 7%, p<0.001), aspirin (38% vs 29%, p<0.001), and clopidogrel (6% vs 4%, p=0.001) in comparison to non-diabetics. This difference was also observed in life-saving medications after hospitalization (ACEi: 65% vs 61%, p=0.022; ARBs: 54% vs 43%, p<0.001; BBs: 50% vs 45%, p<0.01); however, in diabetics and non-diabetics, these agents were administered more frequently compared to admission. Interestingly, diabetics received ACEi, ARBs, BBs, and digitalis in greater extent after hospitalization (65% vs 34%, p<0.001; 54% vs 30%, p<0.01; 50% vs 24% p<0.05; 32% vs 12%, p<0.01, respectively). Nitrates, aspirin, and clopidogrel were also more frequently administered after hospitalization in both subgroups
Conclusion: Oral life-saving medications were more frequently administered in diabetic versus non-diabetic patients with AHF both before and after hospitalization. Hospitalization for AHF results in almost doubling the percentage of discharge treatment, comparing to the treatment at admission. However, prescription of life-saving therapies remains low in both subgroups, a finding suggesting the need for better implementation of HF guidelines.

117 Utility of NT-proB natriuretic peptide combined with other heart failure risk factors in detection of asymptomatic left ventricular dysfunction: main results of the SCREEN-HF study

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Purpose: Increasing concern over rising heart failure prevalence with high mortality and cost are focusing attention on early diagnosis and prevention. We sought to examine the association between HF risk factors, asymptomatic left ventricular (LV) dysfunction and plasma NT-proB natriuretic peptide (NT-proBNP), in a population at high risk for HF.
Method: The SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) population (n=3550), volunteers recruited from health fund members, were at high risk for development of HF (>60years plus >1 HF risk factor), but without a previous diagnosis of HF or left ventricular dysfunction. Past medical history (researcher administered questionnaires), anthropomorphic data and pathology were collected. Following initial screening, 667 participants with NT-proBNP in the highest quintile (>30.0pmol/L) and 51 consecutive participants in the lowest quintile (<5.7pmol/L) had echocardiography to assess systolic dysfunction (defined as Simpson's biplane LVEF<45%) and diastolic dysfunction (defined using comprehensive Doppler echo measures; mitral valve and pulmonary vein inflow and mitral TDI).
Results: Participants in the highest plasma NT-proBNP quintile compared to those in the lowest quintile were older (74.7±6.7 vs. 66.6±5.1years; p<0.001) and more were female (47% vs. 32%; p=<0.001). Coronary artery disease (CAD, 34% vs. 12.6%; p<0.001) and stroke (17% vs. 8%; p<0.001) were more commonly reported in the upper quintile. The number of HF risk factors reported increased ordinally across NT-proBNP quintiles (p<0.001). Systolic dysfunction (6.6%; 95%CI 4-8% vs. 0%) and diastolic dysfunction (at least moderate; 26% vs. 6%; p=0.002) were more frequent in the upper versus lower quintiles. NT-proBNP was independently associated with LV systolic (p=0.001) and diastolic (p=0.01) dysfunction after adjustment for HF risk factors (age, sex, coronary artery disease, diabetes, hypertension and obesity).
Conclusion: A large burden of asymptomatic ventricular dysfunction was observed in elderly subjects with elevated plasma natriuretic peptide levels, independent of conventional risk factors. This suggests that utilising plasma NT-proBNP testing in a population with HF risk factors may help to further stratify those at greatest risk of HF.

118 Wine consumption in chronic heart failure: biohumoral correlates and impact on outcomes

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Purpose: Moderate wine consumption is known to reduce incident ischemic events in the healthy population and in patients with cardiovascular disorders. In chronic HF, moderate alcohol consumption has been reported to reduce mortality, mostly due to fatal MI. It was of interest to assess the effects of wine consumption in a large cohort of patients enrolled to the GISSI-HF trial, and in a subgroup who underwent extensive biohumoral evaluation.
Methods: Data on dietary habits were collected from 6973 patients followed for 3.9 years by a brief questionnaire at randomization. Wine consumption was categorized into 4 groups: never (35.2%), sometimes (19.0%), 1-2 glasses/day (36.9%), ≥ 3glasses/day (8.9%). Cox multivariable analyses were adjusted for known predictors of outcome in HF. In a subgroup of 1233 patients, circulating biomarkers were analyzed by wine intake
Results: Patients never drinking wine were more frequently females, in NYHA class III-IV, diabetics, with history of hypertension. Overall, in fully adjusted models, wine intake did not significantly affect fatal and non fatal outcomes. Increased wine intake was signifcantly associated with lower plasma concentrations of inflammatory markers (pentraxin-3 and osteoprotegerin) and endothelin-1 (C-terminal pro-endothelin 1 or CT-proET-1, Figure 1).

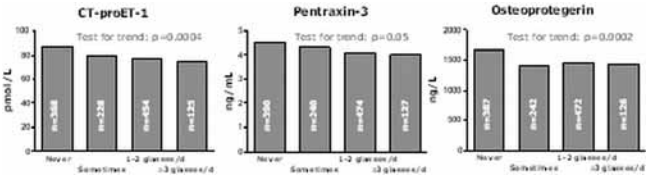

Figure 1. Circulating biomarkers by wine intake.

Conclusions: The lack of effect of wine intake on outcomes may be explained by the relative low frequency of atherothrombotic events in HF, which are expected to be affected by wine. The lower circulating levels of vasoconstrictor and inflammatory markers suggests possible beneficial effects in selected subgroups of patients.

119 Plasma NGAL for the prediction of acute kidney injury in acute heart failure

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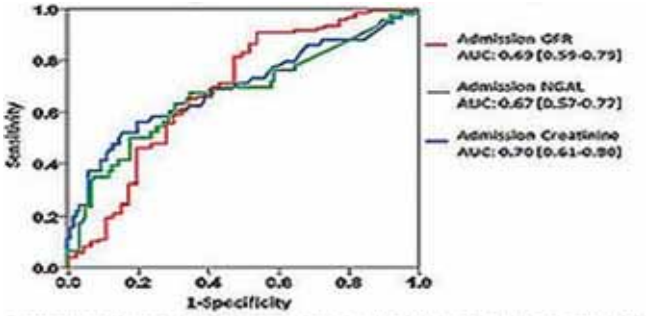
Background: The accurate prediction of acute kidney injury (AKI) in patients with acute heart failure (AHF) is an unmet clinical need. Neutrophil gelatinase-associated lipocalin (NGAL) is a novel sensitive and specific marker of AKI.
Methods: A total of 207 consecutive patients presenting to the emergency department with AHF were enrolled. Plasma NGAL was measured in a blinded fashion at presentation and serially thereafter. The potential of plasma NGAL levels to predict AKI was assessed as the primary, in-hospital worsening renal function (WRF) as the secondary endpoint. We defined AKI according to the AKI Network classification.
Results: Overall 60 patients (29%) experienced AKI. These patients were more

likely to suffer from pre-existing chronic cardiac or kidney disease. At presentation, creatinine (median 140 [IQR, 91-203] umol/l vs. 97 [76-132] umol/l, p<0.01) and NGAL (105 [65–200] ng/ml vs. 74 [60-113] ng/ml, p<0.01) levels were significantly higher, and estimated glomerular filtration rate (eGFR) was significantly lower (37 [24-56] ml/min vs. 54 [36-74] ml/min, p<0.01) in AKI compared to Non-AKI patients. The prognostic accuracy for measurements obtained at presentation, as quantified by the area under the receiver operating characteristic curve was mediocre and comparable for all three markers (creatinine 0.70; 95%CI 0.61-0.80 vs. eGFR 0.69; 95%CI 0.59-0.79 vs. NGAL 0.67; 95%CI 0.57-0.77). Similar results were obtained for in hospital WRF. Serial measurements of NGAL did not further increase the prognostic accuracy for AKI. Creatinine, but not NGAL, remained an independent predictor of AKI (HR 1.15; 95%CI 1.01-1.31; p=0.04) in multivariable regression analysis.



Receiver operating characteristic curves displaying the inability of admission creatinine, estimated glomerular filtration rate and plasma NGAL to predict the occurrence of AKI

Conclusion: Plasma NGAL levels do not adequately predict AKI or WRF in patients with AHF.

NEW CHALLENGES IN ANTI-THROMBOTIC THERAPY IN ATRIAL FIBRILLATION

128 Efficacy and safety of the novel oral factor Xa inhibitor apixaban in atrial fibrillation (AF) patients with chronic kidney disease (CKD): the AVERROES trial

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Background: Apixaban is superior to aspirin for prevention of stroke in AF patients, but is partially renally metabolized, and hence the efficacy and safety in CKD patients need to be separately defined.
Methods: Participants (n=5599) in the AVERROES double-blind randomized trial comparing apixaban 5mg twice daily (2.5mg twice daily in patients with (a) age ≥80 years, (b) body weight ≤60 kg, or (c) serum creatinine ≥1.5 mg/dL or 133μmol/L) with daily aspirin in AF patients unsuitable for warfarin anticoagulation were identified who had stage III CKD (estimated glomerular filtration rate (eGFR) of 30-59ml/min using the CKD-EPI equation). Primary events were all strokes (ischemic and hemorrhagic) and systemic emboli.
Results: Compared to those whose GFR was ≥60ml/min, stage III CKD patients (30% of the cohort) were older (75yrs vs. 68yrs, p<0.001) with more frequent hypertension, diabetes, heart failure, and prior stroke (all p<0.001). The mean CHADS2 scores were 2.4 vs. 1.9 and mean eGFRs were 49ml/min vs. 78ml/min in those with stage III CKD vs. eGFRs >60ml/min, respectively. Stage III CKD patients had higher rates of primary events (5.6%/yr vs. 2.8%/yr, p<0.001), death (7.1%/yr vs. 3.3%/yr, p<0.001) and major hemorrhage (2.2%/yr vs. 0.8%/yr, p=0.03). In multivariate analysis with the CHADS2 score, stage III CKD was an independent predictor of primary events (hazard ratio 1.6, p=0.01) Relative to aspirin, apixaban reduced primary events 68% (5.6%/yr on aspirin vs. 1.8%/yr on apixaban, p<0.001) in stage III CKD patients and 43% (2.8%/yr on aspirin vs. 1.6%/yr on apixaban, p=0.009) in patients with clearance ≥60ml/min (p=0.10 for interaction of treatment with CKD status). There was no significant difference in major hemorrhage (2.2%/yr with aspirin, 2.5%/yr with apixaban) in stage III CKD patients.
Conclusions: Apixaban produces a consistent reduction in stroke and systemic embolism relative to aspirin and no excess of major bleeding in AF patients with stage III CKD compared with those who have clearance ≥60 ml/min. Stage III CKD is an independent predictor of stroke risk in AF patients taking aspirin, and the absolute reduction in primary events (3.8%/yr) by apixaban in these patients is substantial.

129 Concomitant use of P-glycoprotein inhibitors with dabigatran or warfarin in the RE-LY trial

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Purpose: The RE-LY trial (n=18,113 patients) demonstrated that dabigatran etexilate (DE) was non-inferior (110 mg bid) or superior (150 mg bid) to warfarin for the prevention of stroke and systemic embolism (SE) in patients with atrial fibrillation. In vitro studies suggest that the pro-drug dabigatran etexilate, but not dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp). Drugs that inhibit intestinal P-gp may increase the bioavailability of DE. Therefore, we evaluated the impact of co-administration of P-gp inhibitors (mainly amiodarone, verapamil and diltiazem) on the pharmacokinetics of DE and the safety and efficacy of DE and warfarin in RE-LY.
Methods: Cox-proportional hazard models were used to analyze the rates of stroke/SE, major bleeding events (MBE) and intracranial hemorrhage (ICH) and assess interactions with or without concomitant P-gp inhibitors. The plasma concentrations of dabigatran in 9,183 patients were measured by high performance liquid chromatography/tandem mass spectrometry.
Results: Mean dose-normalized dabigatran plasma concentrations at trough and 2 hours post-dose were 15% and 11% higher in patients receiving amiodarone, and 15% and 19% higher with concomitant verapamil than in those without comedication. Diltiazem concentrations increased 5%. The non-inferiority of DE 110 mg bid and the superiority of DE 150 mg bid over warfarin for the prevention of stroke/SE were essentially unchanged: The hazard ratio (HR) for DE 110mg bid with and without (w/wo) comedication was 0.72 (95% Confidence Interval 0.50-1.04) vs. 0.99 (0.78-1.26); for DE 150mg w/wo comedication, HR= 0.58 (0.39-0.85) vs. 0.68 (0.53, 0.89); p-value for interaction (p-int)=0.35. There were no significant treatment interactions by concomitant P-gp inhibitor use on major bleeding events: for DE 110mg bid w/wo comedication, HR=0.95 (0.76-1.20) vs. 0.72 (0.60-0.87); for DE 150mg w/wo comedication HR= 0.99 (0.79-1.24) vs. 0.90 (0.76, 1.07), p-int = 0.17.Rates of ICH were significantly lower for both DE dosages compared with warfarin irrespective of concomitant P-gp inhibitor comedication (p-int = 0.59).
Conclusion: There was a modest increase in dabigatran plasma concentrations with P-gp inhibitor comedication. Combination therapy of P-gp inhibitors with DE did not alter the overall benefits of dabigatran etexilate for stroke prevention, major bleeding events or ICH relative to warfarin in the RE-LY trial. The dosing regimen of dabigatran can be kept unchanged when combined with P-gp-inhibitors (amiodarone, verapamil and diltiazem).

130 LAA closure with the WATCHMAN device in patients with contraindications to Warfarin: preliminary results from the ASA Plavix Registry (ASAP)

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Introduction: The randomized PROTECT AF trial revealed that left atrial appendage (LAA) closure using a filter device (WATCHMAN) was non-inferior to Warfarin for prophylaxis of stroke, systemic embolism and cardiovascular or unexplained death in AF pts with CHADS2 ≥ 1. In PROTECT AF patients were treated with Warfarin post-implant until a TEE (transesophageal echocardiogram) demonstrated LAA closure (≤5mm of peri-device flow) at which point Warfarin was withdrawn and patients continued antiplatelet therapy alone. However, this strategy is not possible in patients with contraindications to Warfarin. Herein, we report the initial results from the ASAP Registry, a multicenter registry of WATCHMAN implantation in patients with contraindications to Warfarin use.
Methods: In AF patients with contraindications to Warfarin, the WATCHMAN LAA closure device was implanted in standard fashion: IV heparinization, transseptal puncture, TEE guidance. Post-implantation, patients were discharged on life-long aspirin and 6 months of clopidigrel. Follow-up TEE was performed at 3 and 12 months to assess for LAA closure and device-associated thrombus.
Results: A total of 113 patients were enrolled at 4 enrolling centers in Europe: age 72.4±7.6 (53 - 93), 37% female, congestive heart failure in 27%, hypertension in 92%, diabetes in 29%, prior stroke or transient ischemic attack (TIA) in 39%, Age ≥ 75 in 42%, CHADS2 score = 2.7±1.2 (1 - 5). Successful implantation was achieved in 105/113 patients (93%). Currently, mean follow-up is 7.9 months with 43 patients followed to one year. Two patients experienced an ischemic stroke although imaging showed no thrombus on the surface of the WATCHMAN or in the left atrium. There were two observations of device-related thrombus; one detected within 45 days of the procedure and one detected on the 3 month TEE. Three device or procedure related safety events occurred; one

pericardial tamponade, one device embolization requiring percutaneous retrieval and one pseudoaneurysm repair. Follow-up is ongoing.
Conclusions: This early experience reveals that WATCHMAN implantation without Warfarin overlap is safely feasible in AF patients with contraindications to oral anticoagulation. LAA closure may prove to be a viable alternative for AF patients with Warfarin contraindications.

131 Comparison of the CHADS2 and CHA2DS2VASc prediction rules for stroke in patients with atrial fibrillation. The Danish diet, cancer and health cohort study

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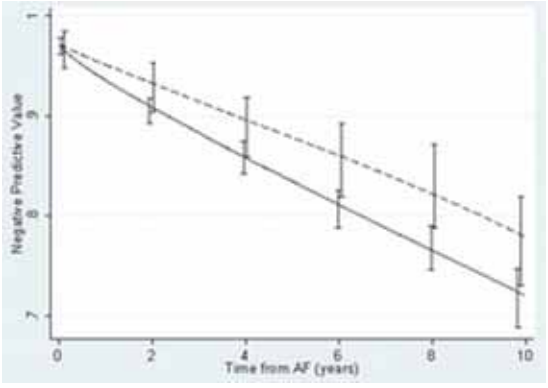
Purpose: We hypothesised that the CHA2DS2VASc score is superior to the CHADS2 score inidentifying a "truly low risk" population with incident AF in accordance to stroke and death.
Methods: Prospective cohort study of 27,178 men and 29,876 women, comparing the CHADS2 and CHA2DS2VASc prediction rules in 3,315 patients with incident AF after a median follow-up of 4.8 years. Crude hazard ratios (HR) were calculated using Cox proportional hazard models. Time dependent ROC curves were used for further comparison of the risk scoring systems. In addition, we calculated the time dependent negative predictive value for both scores usingzero as cut off value.
Results: After one year 4.4% had a stroke, and 8.4% had died. After a mean follow up of 5.5 years (± 3.7 y), 7.8% had a stroke,and 21.4% had died, respectively. Risk estimates for stroke and death in the table. Time dependent area under the ROC curves were similar for the two scoring systems, but the negative predictive value for CHA2DS2VASc, using zero as cut off value, had a tendency to be superior in predicting strokeor death compared to the CHADS2 score (figure).

Risk of stroke or death

Score value	HR (95% CI) One year follow up	for $CHADS_2$ Full follow up	HR (95% CI) One year follow up	for CHA_2DS_2VASc Full follow up
1	1.20 (0.88; 1.64)	1.43 (1.20; 1.70)	1.33 (0.82; 2.16)	1.35 (1.06; 1.73)
2	2.18 (1.55; 3.07)	3.52 (2.93; 4.23)	1.65 (1.03; 2.66)	2.11 (1.66; 2.69)

A score value of zero is used as reference.



Negative predictive value - zero cut of.

Conclusions: The CHA2DS2VASc risk score, using zero as cut off value, had a trend towards superiority compared with the CHADS2, for predicting low risk patients.

132 Prognosis in patients with atrial fibrillation and CHA2DS2VASc score=0 in a real world community based cohort study: the Loire Valley Atrial Fibrillation project

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Based on 2010 ESC guidelines, thromboprophylaxis for patients with atrial fibrillation (AF) without any risk factor (CHA2DS2-VASc score=0) may be aspirin or no antithrombotic therapy, whilst oral anticoagulation is the preferred therapy in all other patients with ≥1 risk factors. The aim of our study was to survey the prevalence of AF patients with a CHA2DS2-VASc score=0 in a "real world" community cohort study, and determine the rate of events during follow up.
Methods: Patients with AF seen between 2000 and 2010 were identified in a database and followed up for mortality, stroke and bleeding events. The CHA2DS2-VASc score was calculated for each patient as initially described, based on 2 points for a history of stroke or TIA, or age ≥75, and 1 point each for age 65-74 years, hypertension, diabetes, recent cardiac failure, vascular disease and female gender.
Results: Among 8962 patients with AF seen between 2000-2010, 692 (7.7%) had a CHA2DS2-VASc score=0. In these patients (age 47±13 years; all men), 502 had paroxysmal AF, 37 had persistent AF, and 153 had permanent AF. An oral anticoagulant therapy (OAC) was prescribed on an individual basis for 208 patients (30%) and an antiplatelet agent or no antithrombotic treatment for 484 (70%). During a follow-up of 839±1103 days, 8 strokes, 8 major bleeding events and 11 deaths were recorded in 23 patients. The adjusted stroke rate was 0.5%/year, rate of major bleeding was 0.5%/year and death rate was 0.7%/year. Prescription of OAC was not associated with a different prognosis in terms of stroke or mortality (relative risk=0.82, 95% CI 0.25-2.70, p=0.75 for the combined risk of death or stroke).
Conclusions: The prevalence of patients with AF and CHA2DS2-VASc score =0 in the real life is higher than that originally previously described (7.7% vs 0.01% in the Euro Heart survey). The annual risk of stroke is "truly low risk"(0.5%/year) and prescription of OAC is not associated with an improved prognosis in these patients. Risk stratification using the CHA2DS2-VASc score may be useful to identify a proportion of patients with AF in whom OAC may not be needed.

133 Left atrial appendage morphology correlates with a reduced risk for stroke in patients with AF

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Introduction: The left atrial appendage (LAA) represents one of the major sources of cardiac thrombus formation responsible for TIA/stroke in patients with atrial fibrillation (AF).
We quantitatively studied various morphologic parameters of the left atrial appendage (LAA) by computed tomography (CT) and by magnetic resonance (MRI) to categorize different LAA morphologies and tried to correlate the morphology with the history of stroke/TIA.
Methods: The study population consisted of 932 patients with drug refractory atrial fibrillation (AF) planning to undergo AF ablation. All patients underwent cardiac CT or MRI and care was taken to obtain LAA frames. All patients were screened for history of TIA/stroke. LAAs were categorized into different morphologies which included Chicken Wing, Windsock, Cauliflower and Cactus.
Results: CT images of 499 patients and MRI images of 433 patients were analyzed (59±10 yrs, 79% male, BMI 27±4, EF 60±7, 14% CHADS2 ≥2). The LAA was categorized into four morphologies: 278 (30%) patients were classified as Cactus, 451 (48%) as Chicken Wing, 179 (19%) as Windsock and 24 (3%) as Cauliflower. Out of the 932 patients, 73 (8%) patients had prior history of ischemic stroke or transient ischemic attack. The prevalence of pre-procedure stroke/TIA in Cactus, Chicken Wing, Windsock, and Cauliflower morphologies were 12%, 4%, 10%, and 18% respectively (p 0.003). After controlling for CHADS2 score, gender, and AF types in a multivariable logistic model, Chicken Wing morphology was found to be more likely to remain stroke-free (odds ratio 19, p=0.043). In separate multivariate model we entered chicken wing as reference group and assessed the likelihood of stroke in other groups in relation to reference. Compared to chicken wing, Cactus had 4.08 times (p=0.046), Windsock- 4.5 times (p=0.038), and Cauliflower 8.0 times (p=0.056) more likely to have an ischemic event.
Conclusion: This study suggests that patients with chicken wing morphology are less likely to have an embolic event even after controlling for comorbidities. If confirmed, these results could have a relevant impact on the anticoagulation management of patients with an intermediate risk for stroke.

ARE THERE GENDER DIFFERENCES IN ARRHYTHMIAS

138 The association between leisure time physical activity and atrial fibrillation in the general population - a longitudinal study

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Purpose: To determine the effect of self-reported physical activity on the risk of AF in subjects without concomitant heart disease in a longitudinal population study.
Methods: Three population-based surveys using standardized methods undertaken during 1974-2003 were merged. The present analysis comprises 428 519 participants, alive and aged 30-81 years by the end of 2003. Having at least one

prescription of flecainide dispensed January 1st 2004 until December 31st 2009, was used as proxy for AF based on the Norwegian Prescription Database, established in 2004. Flecainide is mainly used for prevention of AF recurrence, and structural heart disease is a contra-indication. Subjects with prescription of flecainide or sotalol at survey were excluded from the analyses. Hazard ratios were estimated by Cox' proportional hazards regression with time from January 1st 2004 until first dispensed prescription of flecainid as the time variable.
Results: During the follow-up period, 1183 men and 609 women with prescribed flecainide for the first time constitute the AF cases. The risk of AF increased with increasing level of physical activity in men, whereas no such association was observed among women (Table). The majority of the AF cases were 50-69 years old,non-smokers, and had higher education. Resting heart rate was inversely related to the risk of having AF.The male cases had also lower levels of the major cardiovascular risk factors.

Physical activity and AF hazard ratio

Adjusted for: / Adjusted for:	Walking, etc. for at least 4 hrs/week		Light sports, heavy gardening		Hard exercise several times/week	
	HR	95% CI	HR	95% CI	HR	95% CI
Men (N=204,897)						
Age	1,21	1,03, 1,44	1,47	1,23, 1,76	2,94	2,25, 3,84
Age+height	1,18	1,00, 1,40	1,41	1,18, 1,70	2,84	2,17, 3,71
Age+bmi	1,21	1,02, 1,43	1,46	1,22, 1,76	2,92	2,23, 3,82
Age+education	1,20	1,01, 1,42	1,42	1,18, 1,70	2,75	2,11, 3,60
Age+height+bmi+educ.	1,18	1,00, 1,40	1,39	1,16, 1,67	2,75	2,10, 3,60
Women (N=223,622)						
Age+height+bmi+educ.	1,00	0,82, 1,23	0,78	0,56, 1,08	NA	NA

Reference: sedentary; NA: not applicable.

Conclusion: There was a graded independent increase in the risk of AF with increasing levels of physical activity in this population based study among men with ostensibly no other heart disease.

139 Low bleeding risk of very old atrial fibrillation women on VKA treatment: results from a prospective collaborative study. On behalf of the ad hoc Study Group of FCSA

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Purpose: The increasing number of very old patients with atrial fibrillation (AF) on treatment with vitamin K antagonists (VKAs) requires a better knowledge of the risks associated with this treatment in elderly. We performed a prospective collaborative study among Centres affiliated to FCSA to assess the adverse events of VKAs in AF patients who started treatment after 80 years of age.
Methods: In this study we analyse the difference of clinical event rates (bleeding and stroke) between genders. Quality of anticoagulation and adverse events occurring during follow-up were recorded.
Results: The total number of patients recruited was 3015 patients (males 45%; 7620 patient-years; mean time of follow-up 2.52 years). The total quality of anticoagulation measured as time spent within, above and below the international normalized ratio therapeutic range was 63%, 14% and 23%, respectively (IQR for time in therapeutic range (TTR) 50-75). During follow-up 132 major bleeding events (1.73×100 patient-years) were recorded. Females show a lower bleeding risk than males, even if they are significantly older. We confirmed a trend to a higher risk of stroke in females. No difference in TTR was recorded, however, males spent a longer time above the TR.

Table 1

	Males	Females	RR (95% CI)	p value
Age	82.6 (80–102)	83.1 (80–100)		0.000
Follow-up(years)	3469	4151		
TTR %(IQR)	62 (48–76)	64 (51–75)		0.1
Time above TR % (IQR)	11 (6–19)	11 (5–18)		0.02
Clinical events (rate ×100pt-years)				
Major bleedings	75 (2.2)	57 (1.4)	1.6 (1.1–2.3)	0.001
Stroke/TIA	45 (1.3)	67 (1.6)	1.2 (0.8–1.8)	0.25

Conclusion: In conclusion, very old AF women on VKA treatment carry a low bleeding risk with respect to males, suggesting a more favourable risk/benefit ratio of treatment.

140 Progression of atrial fibrillation in the general population is slower in women: a fundamental finding for a disease management strategy

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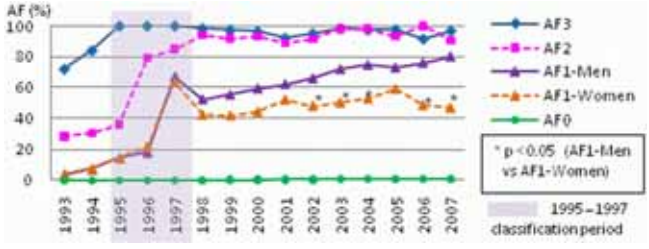
Purpose: For the management of atrial fibrillation (AF), such as rhythm or rate control, precise data of the disease progression in the real world is fundamentally important but lacking. We sought to elucidate the progression of AF.
Methods: We reviewed the annual health examination database of residents in Ibaraki Prefecture, Japan. A total of 112,762 individuals (mean age in 1997, 62.6 years; men, 31%) participated in the examination for at least 3 consecutive years, from 1995 to 1997. Based on the number of AFs identified by 12-lead ECG in the 3-year classification period, individuals were classified into 4 groups, namely, AF3, AF2, AF1, and AF0. They were considered to be probable models of permanent, persistent, paroxysmal AF, and reference, respectively. The occurrence and progression of AF were evaluated using 1,266,694 ECGs recorded for 15 years between 1993-2007.
Results: The groups included 566 individuals in AF3, 159 in AF2, 279 in AF1, and 111,758 in AF0 groups (mean age of groups AF1-AF3, 70.6 years). The mean follow-up period from 1997 was 7.5 years. Prevalence of AF remained more than 89% in the 10-year follow-up among the AF3 and AF2 groups. In the AF1 group, despite prevalence being less than 8% before the classification period, it increased to 48% after 1 year, gradually increasing to 65% in the following 10 years. However, the prevalence and its increase were significantly lower in women ($p<0.05$). AF was found in only 1.1% of the AF0 group after 10 years. AF episodes recorded once in 3 years led to the increasing occurrence of AF, thus reflecting disease progression.



AF (%) before & after the classification.

Conclusion: Our results demonstrated the progression of AF in the general population. They provide fundamental information and may indicate the patients suitable for rhythm control strategy for AF management.

141 Racial differences in atrial fibrillation prevalence

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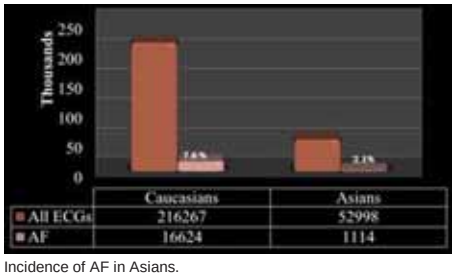
Introduction: Current understanding of the pathophysiology and epidemiology of atrial fibrillation (AF) is based primarily on studies in Caucasians. Surprisingly little is known about racial differences in AF prevalence and whether differences persist after accounting for known risk factors.
We conducted a survey to estimate the prevalence of AF in South Asian adults in Bradford, UK and compared it with prevalence in the local Caucasian population.
Methods: Using the GE muse database system, ECG parameters, demographic data and discharge diagnoses from all the outpatient ECGs done in the cardiology department from 1997-2010 were reviewed.
ECG diagnoses were based on 12 SL system with 98% sensitivity of identifying AF.
All ECGs were divided into AF vs. sinus rhythm. Patient group with diagnosis of AF were further sub-grouped according to race and sex.
Results: Of 269,265 records, 216,267 were Caucasians and 52,998 were Asians. In the Caucasians, 16624 (7.6%) had AF compared to 1114 (2.1%) in the Asians, odds ratio (OR) = 3.8, $p<0.0001$.
Age distribution shows 6368 (38.3%) Caucasians below 50 yrs. vs. 161 (14.4%) in Asians (OR=3.6) and 10256 (63.2%) above 51yrs vs. 953 (85.5%) in Asians (OR=0.76).



Incidence of AF in Asians.

Sex distribution in Caucasians with AF showed 9932 (59.7%) males and 6692 (40.3%) females and in Asians was 576 (51.7%) male and 538 (48.2%) females.
Discussion: This data suggests that prevalence of AF in Asians is lower than in Caucasians.
AF progresses with age but Asians below 50 yrs have very low incidence. Sex distribution pattern is comparative, and AF remains more common in males.
Further research is warranted to establish reasons for racial predisposition to AF in contrasting populations with differences in prevalence possibly explained by protective genetic mechanisms.

142 All-cause mortality in relation to age and gender in patients <86 years with a first time hospitalizaton with atrial fibrillation in Sweden during 15 years, 1995-2009

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Purpose: Atrial fibrillation (AF) is a progressive disease that increases in prevalence, mainly due to better treatment of cardiovascular disease and to demographic changes. An increasing number of patients with AF will continue to impose a considerable burden on the health care system. We aimed to study all-cause mortality in all patients, who were hospitalized with AF in Sweden between 1995 and 2009 as compared to controls from the general population without AF.
Methods: Starting in 1995, all patients with incident AF (main or a secondary diagnosis) in the National Inpatient register, and at least one control free of AF (matched for age, gender and the time of AF of the index patient) in the General Population Register were identified. None of the patients had been hospitalized with AF between 1987 and 1995. Patients and controls were followed from the date of diagnosis to mortality or emigration until the end of 2009 through record linkage of the National Inpatient and Cause of Death registries. Cox regression models were used to estimate age adjusted hazard ratios with 95% confidence intervals (HR, 95% CI).
Results: In total, 287 667 patients (56% men) with a mean age of 72±11 years, 70±12 years in men and 74±9 years in women, were identified with the diagnosis at the time of hospitalization.
The age adjusted HR of all-cause death in AF patients vs. controls was 1.93 (95% CI 1.92-1.95), 1.83 (95% CI 1.81-1.85) in men and 2.07 (95% CI 2.05-2.10) in women. When age at the diagnosis was divided into three age categories: <65 (n=59328 patients), 65-74 (n=78956 patients) and ≥75 (n=149383 patients) years of age, the association was attenuated with increasing age in both sexes; 2.75 (95% CI 2.66-2.85), 2.02 (95% CI 1.98-2.05), 1.69 (95% CI 1.67-1.71) for men, and 3.47 (95% CI 3.26-3.69), 2.57 (95% CI 2.50-2.64), 1.96 (95% CI 1.93-1.98) for women, respectively.
Conclusions: AF was associated with significantly increased all-cause mortality in all age categories in both women and men as compared to controls. AF incidence got higher by increasing of age, with highest mean age in women. AF conferred the highest all-cause mortality risk relative to controls in the lowest age category and especially in women.

143 Gender differences in the QRS duration is related with mortality

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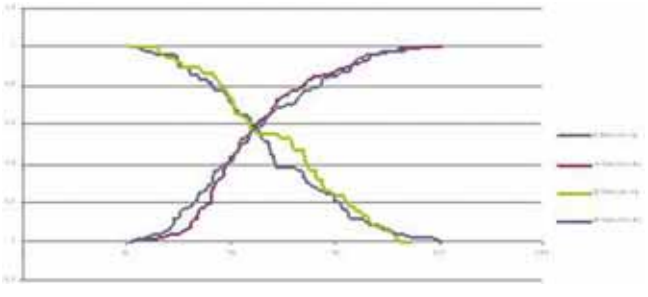
New recommendations advocate the use of cardiac resynchronization therapy (CRT) in patients with heart failure Class II (NYHA) and recent studies showed a better prognosis in women. However, the sex differences in the QRS duration related to the prognosis is not well known. The objective of this study is to evaluate the sex differences in the QRS duration related to the survival rate of patients with heart failure. We evaluated QRS duration of a random sample of 414 patients from a consecutive series of 2234 outpatients with heart failure. The mean age was 57±14 years, 242 (58.5%) men. Statistical analysis was performed with Kaplan Meier method, linear regression model and Cox proportional hazards regression. QRS duration ranged between 52.2 ms and 200.5 ms (mean 113.3; standard deviation 29.7; median 108.9). QRS was >120 ms in 150 (36.2%) patients. QRS duration relative to mortality assessed with a receiver-operator characteristic curve revealed area under the curve 0.604 (standard error 0.037; confidence interval 0.533-0.676; p=0.004). QRS duration between 110.8 ms and 111.8 ms was the tradeoff interval between specificity and sensitivity of QRS duration associated with mortality. Mortality was higher in patients with QRS duration >120 ms (p=0.007). There were differences of 100 ms in the QRS duration of men and women in the mortality curve in the interval of QRS duration between 120-160 ms. In conclusion women had larger QRS duration compared with men in the same level of survival rate.



SEX DIFFERENCES IN HEART FAILURE

144 Gender-related differences in patients hospitalized due to heart failure

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Background: The prevalence of heart failure (HF) among hospitalized patients is steadily growing, affecting males and females alike. However, data is lacking regarding gender-related HF clinical characteristics, echocardiographic parameters and outcomes.
Methods: We identified all HF patients aged 50 or older, who were hospitalized between January 2000 and December 2009 and who had undergone at least one echocardiography study. A comparative analysis of clinical and echocardiographic findings was performed between 5,228 males and 4,107 females, who were followed-up for 2.8±2.6 years.
Results: Female HF patients were older (77.8±10 vs. 74.5±11, p<0.0001), more frequently obese, had higher rates of hypertension and atrial fibrillation and lower rates of ischemic heart disease, COPD and chronic renal failure (Table). Females had mostly HF with preserved LV function (80% vs. 58%, p<0.0001), less regional wall motion abnormalities (29.5% vs. 46.6%, p<0.0001) and more significant valvular abnormalities (36.3% vs. 29.4%, p<0.0001). Admission rates were lower among female patients (2.7±3.7 vs. 2.9±3.4, p=0.002) although hospitalization duration was similar. Females had an increased overall 30-day mortality (27% vs. 24.5%, p=0.006). Several parameters were found as predictors of early mortality in females only, including diabetes (HR 1.77, CI 1.18-2.65, p=0.006), prior CVA (HR 1.76, CI 1.07-2.88, p=0.026) and right ventricle dysfunction (HR 2.88, CI 1.3-6.37, p=0.009), whereas other parameters, such as prior myocardial infarction, chronic renal failure and tricuspid regurgitation proved to be significant in both genders.

Patient co-morbidities

	Males (n=5228)	Females (n=4107)	p
Ischemic heart disease (%)	76	58	<0.0001
Hypertension (%)	48	63	<0.0001
COPD (%)	23	16	<0.0001
Chronic renal failure (%)	42	28	<0.0001
Atrial fibrillation (%)	39	44	<0.0001
Obesity (%)	9	14	<0.0001

Conclusions: Females hospitalized due to HF tend to have higher early mortality. Predictors of mortality vary by gender and identification of gender-specific features may be used for a tailored therapeutic approach.

145 Sex differences in the expression of antifibrotic microRNA-29b in the mouse heart under pressure overload

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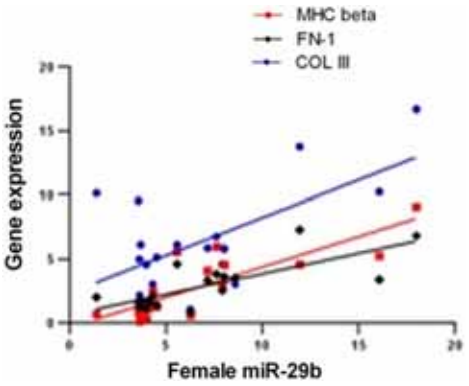
Background: MicroRNAs (miRNA) are small RNA molecules that play an important role in post-transcriptional regulation of gene expression. Mir-29b has been described as negative regulator of fibrotic processes. It was previously reported that males and females display different profiles of miRNAs expression in skeletal muscle. We show here for the first time sex-related differences in left ventricle expression of miR-29b in mice subjected to aortic constriction.
Methods and results: Male and female mice were subjected to transverse aortic arch constriction (TAC) or sham surgery. TAC mice developed similar degree of fibrosis, regardless of sex. Myocardial miR-29b was extracted with NucleoSpin and qPCR expression values were normalized to U6 snRNA. As expected in a fibrotic process, myocardial expression of miR-29b was downregulated after TAC, but only in males (Sham: 45.5±11.6; 1 week TAC: 11.9±5.1**; 4 week TAC: 24.0±7.2*). On the other hand, in females miR-29b was upregulated after TAC (Sham: 4.7±2.4; 1 week TAC: 26.5±16.3*; 4 week TAC: 16.7±5.9**). Moreover,

the expression of miR-29b in females (figure 1) correlated significantly and directly with remodelling related genes (collagen III, R=0.65**; fibronectin, R=0.76***; and myosin heavy chain-beta R=0.80***; linear regression).



Correlations of myocardial miR-29b.

Conclusion: We identified sex-related differences in left ventricle expression of miR-29b which could suggest specific regulatory functions of miR-29b in cardiac remodelling depending on the sex.

146 CA 125 as a novel clinical surrogate for heart failure with preserved ejection fraction and an independent predictor for heart failure hospitalization in women

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Purpose: Carbohydrate antigen 125 (CA 125), a tumor marker for ovarian cancer, has recently been reported to be correlated with the severity of systolic heart failure. However, the relation between such marker and the presence of heart failure with preserved ejection fraction (HFpEF) remains elusive.
Materials and methods: We studied totally 158 women who participated in health evaluation between March to June, 2006 and were divided into three groups: those with known heart failure according to Framingham's criteria (HFpEF group, n=35, mean age: 57), those with at least one heart failure risk factors (Intermediate group, n=78, mean age: 52), and another 45 subjects without any systemic disease or risk factors for heart failure (Normal group, mean age: 47). All subjects were confirmed to have a normal LV systolic function by echocardiography with additional evaluation for 2-dimensional echo-derived ventricular mass, volume, left atrium diameter and mid-wall fractional shortening. Multivariate analysis was performed to depict the independent association between serum markers and the presence of heart failure. Hospitalization for heart failure during 4 years of follow-up was also analyzed.
Results: Our data demonstrated that HFpEF group had significantly higher levels of CA 125, which perfectly paralleled the levels of N-terminal, pro-B type natriuretic peptide (NT-proBNP), a sensitive biomarker for the presence of heart failure. The other tumor markers did not show any significant association. Furthermore, worsened ventricular mid-wall function and enlarged left atrial (LA) chamber size were also observed in the HFpEF group when compared to the Normal group ($p<0.05$). After adjustment for clinical variables, this independent association between CA 125 levels and HFpEF still remained strongly significant ($p<0.0001$). Totally 18 subjects developed worsened heart failure requiring hospitalization during follow-up period. CA 125 levels remained an independent predictor for heart failure hospitalization (OR: 1.08, 95% CI: 1.02-1.15, p=0.012), after the adjustment for NT-proBNP, LV mass, age, body mass index, hypertension, and coronary artery disease.
Conclusion: Serum CA 125 may serve as a novel biomarker for detecting the presence of HFpEF and an independent predictor for the subsequent heart failure hospitalization. This data implies that HFpEF patients with higher levels of CA 125 may need more intensive treatments to prevent future heart failure events.

147 Myocardial deformation at rest and stress and relationship with aortic stiffness are gender-specific: a dobutamine-stress magnetic resonance imaging study

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Background: Women have increased aortic stiffness and reduced exercise tolerance with normal systolic function. We investigated gender differences of myocardial deformation at rest and maximal dobutamine stress and their relations with pulse wave velocity (PWV).

Methods and results: 76 subjects who underwent dobutamine-stress MR without inducible ischaemia (men=42, mean age 63.2±8.9) were included. Myocardial deformation (= total peak systolic strains) was quantified using feature-tracking. At baseline, both genders displayed similar longitudinal deformation (men vs. women, (mean±SD): 0.28±0.07 vs. 0.27±0.08, p=0.3), whereas women showed a greater radial component (0.22±0.06 vs. 0.27±0.07, p=0.01). Resting PWV correlated inversely with longitudinal deformation in men (r= -0.47, $p<0.01$) but not women (r=0.21, NS), and showed a positive correlation with radial deformation in women (r=0.48, p=0.01) but not men (r=0.27, NS). At maximal stress (=85% predicted maximal HR), women showed an increase of their radial strain (mean differences±SD, men:-0.02±0.06 women:-0.05±0.08, p=0.007), with a decrease of longitudinal deformation (-0.05±0.06 vs. 0.02±0.09, p=0.02). PWV at peak stress correlated positively with longitudinal deformation in men (r=0.74, $p<0.01$), and negatively in women (r= -0.78, $p<0.01$) (Figure) even when accounting for changes in stroke volume and LV wall stress.

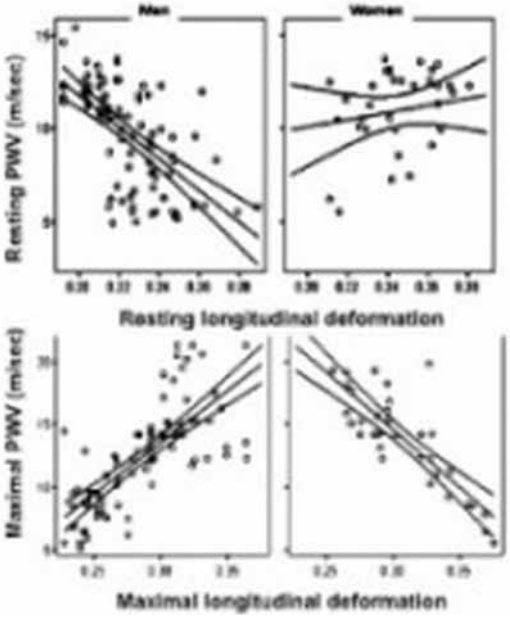

Figure 1

Conclusions: We demonstrate significant gender differences in deformation at rest and maximum dobutamine stress and their relationship with PWV. In men resting longitudinal function and aortic stiffness are interdependent, whereas at stress PWV is determined by longitudinal deformation. On the contrary in women, there is no such relationship at rest, whereas longitudinal function becomes interdependent with aortic stiffness at stress.

148 Altered arterial haemodynamics during exercise in elderly female hypertensives with poor stroke volume reserve

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Purpose: Elderly female hypertensive (EFH) patients are at risk of Heart Failure with Preserved Ejection Fraction (HFpEF), a condition where stroke volume (SV) does not increase with exercise. While poor vascular-ventricular interaction (VVI) may contribute to HFpEF, mechanisms during exercise are unknown.
Methods: EFH patients (n=21, age 67±9 ys; 162±20 mmHg) were studied at rest and during supine bicycle exercise (57±20 W) by echocardiography and using radial arterial tonometry for analysis of aortic blood pressure (BP) waveforms (SphygmoCor, AtCor Medical). Patients were dichotomised into Res (SV reserve present; n=11; range +15 to +100%) or NoRes (no SV reserve; n=10; range +14 to -9%). We analysed end-systolic LV elastance ("contractility"; Ees;

Table 1. Data at rest and during light exercise

Variable	Res	NoRes	Exerc	Res	Inter
cSBP, mmHg	143±12 to 156±10	156±27 to 176±23	0.01	0.05	NS
EDV, mL	91±26 to 106±26	100±22 to 101±29	0.01	NS	0.02
ESV, mL	28±16 to 21±11	46±15 to 46±14	NS	0.01	0.01
Ees, mmHg/mL	3.4 (2.5-4.0) to 4.2 (3.9-4.3)	3.3 (3.0-4.2) to 5.2 (4.8-6.0)	0.01	NS	NS
Ea, mmHg/mL	2.3±0.5 to 2.1±0.5	2.5±0.8 to 3.0±0.8	NS	0.09	0.01
Zc, mmHg·s/mL	0.06±0.02 to 0.08±0.03	0.10±0.03 to 0.12±0.06	0.03	0.02	NS
SVR, mmHg·s/mL	1.36±0.18 to 0.56±0.14	1.72±0.63 to 0.97±0.18	0.01	0.01	0.01
C, mL/mmHg	0.6 (0.5-0.8) to 0.7 (0.6-1.0)	0.7 (0.4-0.8) to 0.4 (0.3-0.5)	NS	0.06	0.03

cSBP = Central systolic BP; Exerc = Exercise; Res = Reserve present; Inter = Exercise × Reserve interaction; p shown on right.

Chen JACC 2001), effective arterial elastance ("lumped afterload"; Ea = stroke volume (SV)/end-diastolic volume (EDV)) and the key components of Ea: aortic characteristic impedance (Zc = pressure-to-flow ratio in early systole; derived aortic pressure waveform vs. digitised flow from pulsed LVOT Doppler), systemic vascular resistance (SVR = mean BP/cardiac output – Zc) and total arterial compliance (C; analysed at end-systole as a function of pressure).
Results: Subgroups had similar changes in Ees but differential changes in LV volumes, Ea and C (Table 1).
Conclusion: In EFH with intact SV reserve (Res), diastolic EDV reserve is matched against arterial vasodilatory reserve. Failure of both produces a high-pressure, high-impedance, low-flow circulatory state (NoRes) which may manifest as HFpEF.

149 Gender differences in the prevalence of asymptomatic left ventricular dysfunction and heart failure in the elderly: a population-based study in central Italy

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Purpose: In Italy Heart failure (HF) accounts for about 200.000 acute hospitalizations every year (88% among people aged 75+ years). We analysed data from a large population-based cross-sectional study to assess the prevalence of both preclinical and clinical HF in the elderly.
Methods: We used a regional population registry to identify a random sample of 65-84 year old residents in the Lazio Region who live near eight Community Hospitals. From June 2007 to January 2010, 40% of invited subjects agreed to participate and 2001 entered the study. All subjects underwent a physical examination by a cardiologist, biochemistry/NT-proBNP assessment, 12 lead-EKG, and Doppler echocardiography. Clinical diagnosis of HF was made according to the European Society of Cardiology criteria. Systolic left ventricular dysfunction (LVD) was defined as LV ejection fraction (EF)< 50%. Doppler-derived indexes of transmitral flow, pulmonary veins flow and Tissue Doppler Imaging of the lateral mitral annulus were used to define diastolic LVD.
Results: Mean age of participants was 72.9 years, 51.7% were men. EKG LV hypertrophy (Perugia criteria) was lower in men (5.6%) than in women (8.8%, p=0.007). The overall prevalence of HF was 6.7% (95%CI=5.6-7.9) with no difference between men (7.4%; 95%CI=5.8-9.1) and women (6.0%; 95%CI=4.5-7.5). Similarly, the prevalence of HF with preserved LVEF did not differ between men (4.7%; 95%CI=3.4-6.1) and women (5.1%; 95%CI=3.7-6.6) (p=0.689). A systolic asymptomatic LVD was detected more frequently in men (2.0%; 95%IC=1.1-2.9) than in women (0.5%; 95%IC=0.1-1.0; p=0.005) whereas the prevalences of either diastolic LVD (men: 46.6%; 95%CI=43.4-49.8; women: 45.5%; 95% CI=42.2-48.8) or diastolic asymptomatic LVD (men: 36.1%; 95%CI=33.0-39.2; women: 35.3%; 95% CI=32.2-38.5) were comparable between genders.
As expected NT-proBNP levels were lower in men (median value =80 pg/mL; interquartile range=41-182 pg/mL) than in women (median value=103 pg/mL; interquartile range =55-188 pg/mL, p<0.001) and were associated with increasing severity of either systolic or diastolic LVD.
Conclusions: This population-based study provides novel information on the epidemiology of HF and asymptomatic LVD in the elderly that could be helpful to re-assess the needs, the feasibility and the cost-effectiveness of HF screening in the elderly in Italy.

HOW TECHNOLOGY CAN IMPROVE DIAGNOSIS OF ARRHYTHMIAS

154 Duration of atrial fibrillation is the most influential component left atrial tissue remodeling in atrial fibrillation patients

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Background: Atrial fibrillation (AF) results in left atrial (LA) tissue remodeling including increased fibrotic deposition and LA dilatation. However, the mechanism of what contributes most to this remodeling process is not well understood. We evaluated the factors most influential in LA remodeling using delayed-enhancement MRI (DE-MRI).
Methods: 487 patients underwent a DE-MRI scan. LA fibrosis was calculated using an algorithm based on LA wall pixel intensity distribution. We then compared the degree of LA enhancement with different clinical characteristics, demographics, structural parameters and other co-morbidities. AF burden was calculated as months since initial AF diagnosis. Patients were categorized based on the percentage of pre-existing LA enhancement seen on DE-MRI into one of four categories: Utah Class I (0-5% LA enhancement), Utah II (5-20%), Utah III (20-35%), and Utah IV (>35%).
Results: There were significant differences between Utah Class for age (p=0.009), female gender (p<0.001) and persistent AF (p<0.001). There was no significant different between number of risk factors and/or any other clinical risk factors across the different class. AF burden (months) was significant across the Utah Classes (p<0.005): Utah I 29.9±46.8; Utah II 60.6±87.7; Utah III 94.5±9.8; Utah IV 129.9±118.7. There were also significant differences between Utah Class and LA volume (cm^3), (p<0.005): Utah I 97.9±34.2; Utah II 98.0±39.7; Utah III 107.9±42.3; Utah IV 130.6±49.3. Multivariate analysis demonstrated age, female gender and AF duration to being significant predictors of fibrosis. AF duration was shown to be the most important predictor for fibrosis (p<0.005).
Conclusion: Duration of time since AF diagnosis was the most powerful predictor of LA fibrosis as assessed with DE-MRI. Age and female gender were also associated with higher levels of LA fibrosis.

155 Visualization of intra-QRS fragmented activation in patients with hypertrophic cardiomyopathy and life-threatening ventricular arrhythmia using magnetocardiography

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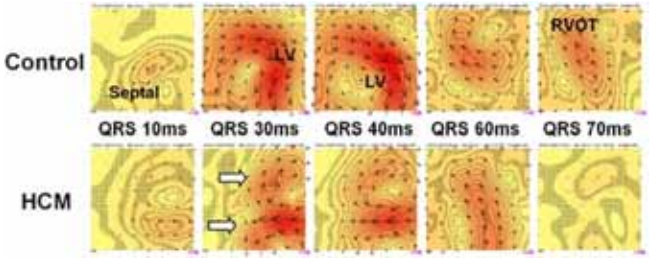
Backgrounds: Several studies indicated that intra-QRS fragmentation (QRSf) on ECG is a possible marker of lethal ventricular arrhythmias in ischemic and other heart diseases, the origin, however, remains unclarified. We hypothesized that patients with hypertrophic cardiomyopathy (HCM) who experienced ventricular tachycardia (VT) or fibrillation (Vf) exhibit similar abnormalities, which can be visualized by high-resolution multi-channel (64-Ch) magnetocardiography (MCG).
Methods: In 11 HCM patients with narrow QRS (<120ms) and a history of VT (n=6) and Vf (n=5), necessitating implantable cardioverter defibrillator (ICD) subsequently, we examined the presence of QRSf on standard 12-lead ECG (500Hz) and analyzed QRS current arrow mapping by using a 64-Ch MCG system (Hitachi). We measured left ventricular (LV) conduction time defined as an interval from QRS onset to LV End, the instant when the visualized LV leftward current disappears. Healthy volunteers (n=40) served as Controls.
Results: In 10 of 11 patients, QRSf was found on ECG. MCG analysis revealed that LV conduction time in HCM patients was markedly prolonged compared with Controls (81±16 vs 51±5ms in Controls, p<0.001). During the period corresponding to the appearance of QRSf on ECG, we recognized abnormal, complicated current patterns (mostly, multi-directional currents appearing simultaneously, as shown in Figure) in 8/10.



Representative QRS maps.

Conclusions: Patients with HCM and a history of life-threatening ventricular arrhythmias often showed intra-QRS fragmentation on ECG. This depolarization abnormality can be noninvasively visualized on the 2-D current arrow mapping of MCGs.

156 Risk of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy can be identified by left ventricular global strain

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Purpose: Identification of patients at risk of ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy (iDCM) is demanding. Indications for primary prevention ICD therapy are based on LV ejection fraction (EF) <35%. Myocardial strain by echocardiography can accurately quantify ventricular function. We therefore hypothesized that global strain may be a better marker of ventricular arrhythmias in patients with iDCM.
Methods: In all, 58 consecutive patients with iDCM were prospectively included. QRS duration was recorded from ECG. By speckle tracking echocardiography, global strain was calculated as average peak strain from a 16 LV segments model. LVEF and body surface corrected LV mass were assessed from standard echocardiography.

Results: During 39 (16-63) months of follow up, 9 patients had arrhythmic events defined as sustained VT or cardiac arrest. Global strain was reduced in iDCM patients with arrhythmic events compared to those without (-7.2±5.9% vs. -12.2±5.9%, p=0.02). iDCM patients with arrhythmias had higher LV mass index (191±54 g/m^2 vs. 149±42g/m^2, p=0.01) and prolonged QRS compared to those without arrhythmic events (138±38ms vs. 97±32ms p=0.002). EF was slightly lower in those with arrhythmic events (32±15% vs. 41±15%, p=0.08). By ROC analysis, global strain could better discriminate between those with and without arrhythmic events compared to EF (AUC 0.79 (95%CI 0.63 to 0.95) vs 0.68 (95%CI 0.47 to 0.89) p=0.04) (Figure 1).

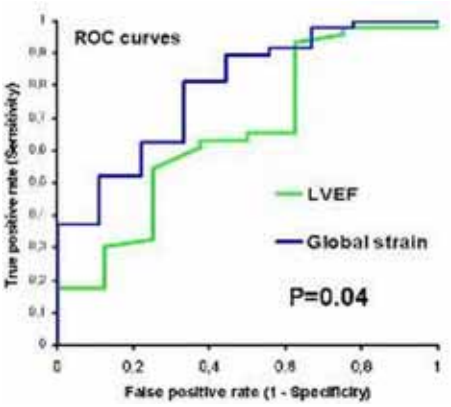

Figure 1. Identifying arrhythmic events in 58 pts.

Conclusions: Global strain, LV mass and QRS duration were markers of arrhythmias in patients with iDCM. Global strain was superior to EF in identifying arrhythmic events. Global strain by echocardiography may provide additional value for risk assessment of ventricular arrhythmias in iDCM patients.

157 Results of MRI for diagnosis of arrhythmogenic right ventricular dysplasia

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Background: ARVDis a genetic cardiomyopathy characterizedclinically by ventricular arrhythmias and progressive right ventricular (RV) dysfunction. The histopathologic hallmark is fibro-fatty replacement of RVmyocardium. New criteria have recently been developed to aid in the diagnosisof ARVD using Cardiac MRI (CMR), however, the yield of these criteria inday-to-day clinical practise has not yet been described.
Methods: All patientswho underwent CMR at ICPS to look for signs of ARVD (tests, n = 306) between November 2009 and September 2010 were identified through the use of the cardiology database. Previously, major and minor abnormalities were identified by the presence of RV dilatation (global or segmental), RV micro-aneurysm, or regional hypokinesis. The revised criteria require the combination of severe regional wall motion abnormalities (akinesis or dyskinesis or dyssynchrony) with global RV dilatation or dysfunction (quantitative assessment). For defining RV dilatation, we used the same cut-off values for original and revised criteria.
Results: 306 patients with a suspicion of ARVD underwent CMR. 15 patients (4.9%) were found to have previously unknown or underappreciated abnormalities (cardiac defect causing right-to-left shunt 7, valvulopathy causing right ventricular (RV) dilation 5, right ventricularinfarct 1, pulmonary embolus 1, 1 accessory papillary muscle in the RV). 1 exam was of unsatisfactory quality. There were no adverse events, and all patients scheduled for examination completed the study. Using the old criteria, 20 (6.5%) patients had major MRI criteria and 27 (8.8%) other patients had abnormalities fitting the minor criteria.Using the new criteria, 17 Patients (5.5%) had major MRI criteria and 13 (4.3%) other patients had abnormalities fitting the minor revised criteria.
Conclusion: In a population of patients suspected of having ARVD, MRI abnormalities fitting major and minor criteria are infrequent. The number of abnormalities has decreased using the revised criteria, this reduction is primarily driven by the reduced number of minor abnormalities. The vast majority of patients will have normal test results (85.3%). New and previously underappreciated cardiac defects are not uncommon.

158 CE-CMR assessment of infarct tissue characteristics in ICD recipients for primary versus secondary prevention following myocardial infarction

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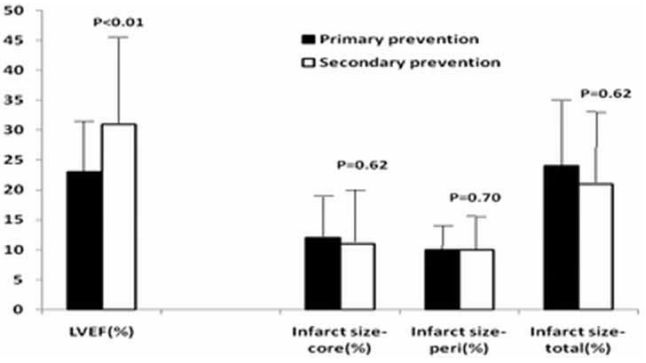
Purpose: Potential differences in infarct tissue characteristics between patients with prior life-threatening ventricular arrhythmia vs. patients receiving prophylactic implantabale cardioverter-defibrillator (ICD), may improve current risk stratification in myocardial infarction (MI) patients, considered for ICD implantation.
Methods: We used contrast-enhanced (CE) cardiovascular magnetic resonance (CMR) to assess potential differences in infarct tissue characteristics between ICD recipients for primary and secondary prevention following MI. A total of 95 ICD recipients were included in this prospective study. Cine-CMR measurements included left ventricular (LV) end-diastolic and end-systolic volumes (EDV, ESV), ejection fraction (LVEF), wall motion score index (WMSI), and mass. CE images were analyzed for core, peri, and total infarct size, infarct localization (according to coronary artery territory), and transmural extent.
Results: In the primary prevention group (n=66), LVEF was lower (23±9 vs. 31±14%; P<0.01), ESV and WMSI were higher (223±75 vs. 184±97ml, P=0.04, and 1.89±0.52 vs. 1.47±0.68; P<0.01), and anterior infarction was more frequent (P=0.02) than in the secondary prevention group (n=29). There were no differences in infarct tissue characteristics between patients treated for primary vs. secondary prevention (p>0.6 for all). During 21±9 months of follow-up, 3 (5%) patients in the primary prevention group and 9 (31%) in the secondary prevention group experienced appropriate ICD therapy for treatment of ventricular arrhythmia (P<0.01).



LVEF and infarcted tissue in both groups.

Conclusion: No difference was found in infarct tissue characteristics between recipients of ICD for primary vs. secondary prevention, while secondary prevention patients showed a higher frequency of applied ICD therapy for ventricular arrhythmia.

159 New real-time loop recorder for diagnosis of symptomatic arrhythmia via telemedicine

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Purpose: One disadvantage of current loop recorders is the long interval between recording an electrocardiogram (ECG), establishing a diagnosis, and taking appropriate medical measures. The "Cardio R" transmits cardiac recordings by cellular communication at the push of a button. Users can concomitantly relay symptoms, thereby providing a symptom/cardio-rhythm correlation. We hypothesized that the "Cardio R" is capable of early detection of cardio-electrical events that could account for patients' symptoms.
Methods: This observational study was designed to evaluate patients who were referred from community physicians/cardiologists for evaluation of various cardiac symptoms that were not observed by regular office ECGs or traditional 24-hour Holter cardiac monitoring. Transmitted recordings were instantly displayed on a monitor for immediate diagnosis by the on-duty medical team at "SHL"-Telemedicine's call center. Abnormal tracings, especially when accompanied by symptoms selected from the prepared list, enabled the staff to instruct the subscriber, notify their physician, and/or dispatch a mobile intensive care unit to the scene.
Results: Between January 2009–December 2010, 18,456 ECG transmissions were received from 743 patients (mean±SD age 57±19, years, range 10-95; 61% females) who completed a 1-month trial with the "Cardio R" device. There was a mean of 36±25 transmissions/patient. Palpitations (n=505 patients), pre-syncope (n=209 patients) and chest pain (n=29 patients) were the leading complaints. A

total of 8,552 (46%) transmissions were made by patients who were in the midst of experiencing the same cardiac complaint(s) for which they were referred: the "Cardio R" device displayed a confirmatory disturbance in rhythm in 93% of these cases. A mean period of 9 minutes (range 6-20) elapsed from transmission until the recorded rhythm was interpreted. The interval between the time the "Cardio R" became available for the patient's use and the establishment of his/her diagnosis was no longer than 2 days.
Conclusions: The "Cardio R" device enables prompt ECG confirmation/exclusion of a probable arrhythmic cause of symptoms, enabling rapid intervention for cardiac-relevant complaints.

HOW CAN THE MANAGEMENT OF SUBPOPULATIONS BE IMPROVED?

160 Current practice in diagnosis and treatment of iron deficiency and anaemia in chronic heart failure: a European study

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Purpose: Iron deficiency (ID) and anaemia are frequent complications in patients with chronic heart failure (CHF) and associated with heart transplantation and death. Prevalence of both ID and anaemia increases with advanced NYHA class. A recent study (FAIR-HF) showed that intravenous (i.v.) iron can significantly improve NYHA class, physical performance and quality of life in iron deficient CHF patients with or without anaemia. This study aimed to evaluate current trends in the diagnosis and treatment of anaemia and ID in patients with CHF.
Methods: From Jun-Sep 2009, cardiologists in 5 countries (France, Germany, Spain, Switzerland, UK) completed records on their last five CHF patients treated for anaemia within six months prior to the survey. Eligible cardiologists that were recruited at random across the country had to spend >50% of working time on patient-care and manage >10 CHF patients per month personally (at least 3 of them for anaemia). Results are presented as median between and [range] across countries.
Results: 1155 cases were recorded by 232 physicians (133 hospital- and 99 office-based). 59% [51-64%] of patients were male and 54% [37-57%] were >70 years old. Blood tests at diagnosis of anaemia and ID included haemoglobin (Hb, 84% [71-86%]), ferritin (51% [35-68%]) and transferrin saturation (TSAT, 9% [7-10%]). Median Hb was comparable between countries (10.0 g/dL [9.2-10.3 g/dL]), but ferritin (50 μg/L [18-62 μg/L]) and TSAT (28% [15-33%]) varied more. 43% [39-65%] had an Hb <10 g/dL at diagnosis and 9% [6-11%] an Hb <8 g/dL; 71% [58-89%] had ferritin <100 μg/L (absolute ID) and 33% [18-59%] a TSAT <20% (functional ID).
Most patients received iron treatment 60% [38-79%]; however, apart from Switzerland (26%), only a very small proportion of patients received intravenous (i.v.) iron (3% [2-6%]). Erythropoeisis-stimulating agents were given in 20% [6-28%] of cases and 23% [13-26%] of patients received blood at some stage in their treatment. The main reason for choosing i.v. iron was its "quick onset of action" (43%). Oral iron was considered as 'well established product' (47%) which is "easy and convenient to use" (47%).
Conclusions: Management of ID and anaemia in CHF patients varies considerably among European countries. Despite the role of chronic inflammation in CHF patients and in iron homeostasis, assessment of iron status is mainly based on the acute phase protein ferritin instead of TSAT. Furthermore, only a minority of anaemic CHF patients receives i.v. iron. Thus, the growing evidence on the possible clinical benefit of i.v. iron in CHF patients needs to be broadened.

161 Diagnostic accuracy of amino terminal segment of B-type natriuretic peptide (NT-proBNP) compared with the electrocardiogram in detecting left ventricular hypertrophy of hypertensive origin

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Purpose: The presence of left ventricular hypertrophy (LVH) in hypertensive patients increases the cardiovascular risk. Despite its low sensitivity, the electrocardiogram (ECG) is the most used method for diagnosis of LVH due to low accessibility of the echocardiography. The aim of our study is to analyze the capability of amino terminal segment of B-type natriuretic peptide (NT-proBNP) for the screening of LVH in patients with hypertension and to compare with the EKG.
Methods: We studied 336 consecutive hypertensive outpatients with 12-lead ECG, echocardiography to calculate left ventricular mass (LVM) and laboratory studies including determination of NT-proBNP. LVH by ECG was defined according to Cornell and/or Sokolow-Lyon criteria. Patients with atrial fibrillation, left ventricular systolic dysfunction (eyection fraction <50%) or significant valve diseases were excluded.
Results: A total of 94 patients had LVH by echocardiography (28%). We found a significant correlation between levels of NT-proBNP and LVM adjusted for body surface area (r=0.41, p<0.001). The area under the ROC curve of NT-proBNP for the diagnosis of LVH was 0.75 (confidence interval [CI] 95%: 0.70 to 0.80). A cutoff point of 74.2 pg/ml had a sensitivity higher than the ECG (76.6% vs. 25.5%, p<0.001) and higher negative predictive value (87.8% vs. 76.6%; p<0.001) in the identification of LVH.

Comparison of NT-proBNP and ECG

	Electrocardiogram		NT-proBNP (>74.2pg/dl)		p*
	%	95% CI	%	95% CI	
Sensitivity	25.5	17.1–35.6	76.6	66.7–84.7	<0.001
Specificity	94.2	90.5–96.8	65.7	59.4–71.1	<0.001
Positive predictive value	63.2	46–78.2	46.5	38.4–54.6	<0.001
Negative predictive value	76.5	71.3–81.2	87.8	82.2–92.2	<0.001

*p value of comparative study using Mc Nemar test for paired data.

Conclusions: Plasmatic levels of NT-proBNP can be useful in screening of LVH in hypertensive patients, improving significantly the capability of ECG and selecting a group of patients who would not need the performance of imaging studies.

162 Impact of ace inhibitors and angiotensin II receptor blockers on all-cause mortality in hypertension trials

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Objective: Despite a well established efficacy ofangiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) to reduce a cardiovascular morbidity, their impact on all-causemortality in hypertensive patients is uncertain.
Design and method: A pooled analysis of morbidity-mortality trials with a renin-angiotensin-aldosterone system inhibitor in which at least two thirds ofpatients had hypertension.
Results: 19 trials in 165 971 patients, of whom 92% were hypertensive, met the inclusion criteria. The pooled results of 7 ACE inhibitor trials in 88 860 patients demonstrated a significant reduction in all-cause death of 6% (HR, 0.94 (0.90-0.98), P=0.007; Figure). No significant reduction in all-causemortality could be demonstrated with ARBs in 12 trials featuring 77 111patients (HR, 0.99 (0.95-1.04), P=0.75; Figure). No heterogeneity was found in treatment effect between ACE inhibitors and ARBs (P for interaction 0.11).Interestingly, significant heterogeneity was found with respect to mortality reduction with different ACE inhibitors (P for heterogeneity <0.001,I^2 99%). Perindopril-based regimens were associated with a statistically significant reduction in all-cause mortality (HR, 0.87; 95% CI, 0.81 to 0.94, P<0.0001),whereas the remaining ACE inhibitors were not. No heterogeneity was observed with respect to the effects of the different ARBs.

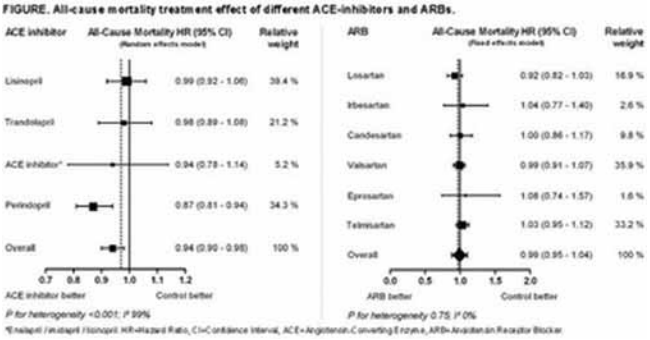

FIGURE. All-cause mortality treatment effect of different ACE-inhibitors and ARBs.

Conclusion: ACE inhibition leads to a robust reduction in mortality in hypertensive patients. Because of the high prevalence of hypertension this treatment may result in a considerable number of lives saved.

163 Effect of enoximone on kidney function after cardiac surgery: a propensity-matched analysis of 2425 patients

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Purpose: To evaluate the impact of a phosphodiesterase inhibitor such as enoximone on renal reperfusion injury after on-pump cardiac surgery.
Methods: A population of 2425 patients that underwent major cardiac surgery at one Institution between May 2004 and November 2010 were reviewed. A Propen-

sity score was built with 32 preoperative and operative characteristics and a 1:1 matching was performed to perform fair comparison of patients receiving or not enoximone in the postoperative period. Renal function was evaluated by highest Creatinine Clearance (CrCL) value reached and the Modification of Diet in Renal Disease (MDRD) Study equation was calculated. Renal failure (RF) was defined as CrCL<60ml/min.
Results: Propensity score-matching provided two cohorts of 712 patients each, receiving or not enoximone infusion after surgery. Overall incidence of postoperative RF was 157/1424 (11%), of which 99/1424 (7%) needed haemodialysis treatment. Overall mortality rate was 1.8%(62/1424). The impact of postoperative RF on mortality was statistically significant: 39/157 (24.8%) versus 23/1267 (1.8%); p<0.0001. Overall CrCL was 59.7ml/min (95%CI:57.6 to 91.8ml/min). Highest postoperative CrCL in patients who received or not enoximone was 63±30.1 and 53.5±26.1ml/min (p<0.0001), respectively. This founding was still confirmed when MDRD Study equation was applied (58±25.7 and 49.2±21.6ml/min/1.73m^2 for patients who received or not enoximone, respectively; p<0.0001).
Conclusions: Patients receiving postoperative infusion of enoximone showed a statistically significant better renal function after cardiac surgery. Further studies are needed to confirm our finding.

164 Microalbuminuria is the most integrated sign of subclinical organ damage in uncomplicated hypertensive patients

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Objective: Microalbuminuria (MAU) and glomerular filtration rate (GFR) are the signs of subclinical kidney damage and independent predictors of cardiovascular morbidity and mortality. ESH-ESC guidelines (2007) list MAU as obligatory assessment in hypertensive patients independently of diabetes mellitus presence. The aim of the study was to investigate the relative role of MAU, cardiac and vascular ultrasonography and carotid-femoral pulse wave velocity (PWV) for the detection of hypertensive target organ damage and risk stratification.
Methods: In 576 non-diabetic hypertensive pts without established cardiovascular or renal disease (291 male, 53.0±10.1 years (M±SD), BMI 29.4±4.4 kg/m^2, 38% smokers, BP 156±13/99±8 mmHg, serum creatinine 94.3±17.4 μmol/l) MAU by albumin/creatinine urine ratio, GFR by MDRD formula, left ventricular mass index (LVMI), carotid intima-media thickness (CIMT), carotid-femoral PWV were assessed. Spearman and multiple regression analysis were performed. P<0.05 was considered statistically significant.
Results: Prevalence of subclinical kidney damage, Echo left ventricular hypertrophy (LVH), CIMT >0.9 mm and/or plaque, carotid-femoral PVW >12 m/s was 37.5%, 46.3%, 23.6% and 25.7%, respectively. There was negative correlation between GFR and LVMI (r= -0.28, p<0.001), end-diastolic relative wall thickness (RWT) (r= -0.22, p=0.02), CIMT (r= -0.19, p=0.04) and PWV (r= -0.07, p>0.05). There was positive correlation between albumin/creatinine urine ratio and LVMI (r=0.46, p<0.001), RWT (r=0.31, p=0.01), CIMT (r=0.38, p<0.001), PWV (r=0.34, p<0.001). Different signs of subclinical organ damage only partly cluster in the same group of patients. The odds ratio (OR) of a microalbuminuric patient having LVH and/or vascular damage is 19.5 (95% CI 5-82); the OR of a patient with LVH having MAU and/or vascular damage is 7.25 (95% CI 3-16); the OR of a patient with PVW >12 m/s having MAU and/or LVH and/or carotid thickening or plaque is 3 (95% CI 1-4); the OR of a patient with CIMT >0.9 mm and/or plaque having MAU and/or LVH and/or PVW >12 m/s is 2 (95% CI 1-4).
Conclusions: Microalbuminuria was the most integrated sign of subclinical organ damage in uncomplicated hypertensive patients. Due availability, low cost and high predictive value combined assessment of GFR by MDRD formula and MAU should be the first step in detection of subclinical organ damage for cardiovascular risk assessment. Cardiac and vascular ultrasonography for assessment of LVMI and CIMT should be performed in patients without signs of subclinical kidney damage.

SPECT – BEYOND DIAGNOSIS OF CORONARY ARTERY DISEASE

194 Stress-induced diastolic dysfunction on myocardial perfusion imaging is useful for detecting significant myocardial ischemia in patients with 3-vessel coronary artery disease

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Background: Gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging is well established to detect coronary artery disease (CAD). Recently, prolonged diastolic dysfunction following stress-induced ischemia on Gated SPECT imaging has been reported. However, it is difficult to find ischemia in the case of multivessel disease. Here we examined the efficacy of stress-induced diastolic dysfunction on myocardial perfusion imaging for detecting myocardial ischemia in cases with 3-vessel CAD.
Method: 34 patients with suspected CAD underwent post-stress and resting gated SPECT. Myocardial perfusion was assessed with a 20-segment model, and the changes in LV systolic and diastolic function were analyzed. The parameters of myocardial perfusion (summed difference score (SDS)), ejection fraction (EF), and diastolic function (one-third of early diastolic mean filling rate (1/3 MFR) were calculated. The change rates of 1/3MFR and EF by stress were defined as △1/3 MFR and △EF, respectively. All the patients underwent coronary angiography, who were divided in significant CAD group (s-CAD), that was defined as possession of >75% narrowing lesion angiographically, and not significant CAD group (ns-CAD).
Result: In the all 34 patients, 3-vessel CAD was found in 18 patients. For all patients, SDS was significantly higher in s-CAD group (3.0±2.2) than in ns-CAD group (1.5±1.6) (p=0.04). △1/3MFR in s-CAD group (-0.13±0.19) were tend to be less than in ns-CAD group (-0.02±0.23) (p=0.16), and so were △EF (s-CAD:-0.10±0.12 vs. ns-CAD:-0.04±0.09; p=0.11). Interestingly, in patients with 3-vessel disease, △1/3MFR was significantly lower in s-CAD group (-0.13±0.19) than in ns-CAD group (0.26±0.01) (p=0.01). On the other hand, there was no difference in SDS and △EF between these two groups (s-CAD: 3.3±2.4 vs. ns-CAD: 2.0±0.0, p=0.48) (s-CAD: -0.13±0.14 vs. ns-CAD: -0.13±0.04, p=0.99) (respectively). An △1/3MFR of <-0.10 was the best predictive cut off value, identifying the patients with significant myocardial ischemia with sensitivities of 68% and specificity of 67% (area under the curve[AUC] was 0.64). These results indicate that the prolonged diastolic dysfunction after stress may be a more sensitive marker than perfusion imaging or the change of ejection fraction in patients with 3-vessel disease, although further investigation should be required.
Conclusions: Stress-induced diastolic dysfunction on gated SPECT imaging may be a novel marker for detecting significant myocardial ischemia in patients with 3-vessel disease.

195 Feasibility of myocardial perfusion imaging with radiation dose reduction by half

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Purpose: The accepted myocardial perfusion imaging (MPI) stress rest study with technetium 99m agents is limited by high radiation dose 10-25 mSv. Recently, several iterative reconstruction software was applied as part of image processing in order to reduce acquisition time. The aim of this study is to assess the feasibility of reducing technetium dose instead of reducing acquisition time with "evolution for cardiac" software.
Methods: The study was done randomly, by one of 2 protocols. Protocol one was the "accepted protocol" stress rest or rest stress study by accepted dose injections of Tc sestamibi (low dose 8-12 mCi, high dose 24 -36 mCi) with time acquisition and image processing performed as accepted. Protocol 2was the "half dose protocol" that is performed with injection of half doses of Tc sestamibi and processed by "revolution for cardiac" software. The radiation doses of technetium 99m were adjusted for each patient weight, and recorded by mCi, Becquerel's units and effective dose equivalent by milisieverts (mSv). The study was approved by local Helsinki committee, each patient signed on inform consent.
Results: In the half dose protocol, 64 patients compared to 27 patients in the accepted protocol. The mean age, weight, BMI, and percentage of men and women were similar in both groups. The mean radiation doses in patients with half dose protocol were 5.75±0.99 mCi and 17.34±1.20 mCi compared to 12.68±5.76 and 32.52±3.02 the accepted radiation dose (p<0.001). Total effective dose for stress rest study was 7.19±0.21 mSv in half dose protocol compared to 14.40±0.61 in accepted dose protocol (p<0.001). All patients except one showed good image quality. Third of the patients with half dose protocol, underwent stress only study and were exposed to 1.9±0.19 mSv only.
Conclusions: MPI with radiation dose reduction by half is feasible with preserved image quality. Further experience is needed in order to tailor dose radiation reduction per patient and assess its diagnostic accuracy.

196 Analysis of left ventricle dyssynchrony by phase analysis of myocardial perfusion imaging GSPECT: one year registry and short term follow-up

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Purpose: Recently, phase analysis software has been developed to assess mechanical left ventricular (LV) dyssynchrony from gated SPECT (GSPECT) myocardial perfusion imaging (MPI) using the Emory Cardiac Toolbox. Phase parameters reported to correlate with wide QRS and low EF. Our aim is to examine the relation of LV dyssynchrony with cardiac events [heart failure (HF) hospitalization and cardiac mortality] in a short follow-up.
Methods: During 2010, in 420 consecutive patients who referred to Tc sestamibi GSPECT MPI, phase analysis software was applied. In the phase analysis, LV dyssynchrony was measured by phase standard deviation (SD) and histogram bandwidth (BW).Patients characteristics, risk factors of CAD and MPI and phase analysis results, EF and functional class were analyzed. The patients were followed-up for HF hospitalizations and cardiac mortality (147±85 days).
Results: See table for univariate analysis.
In a stepwise multivariate regression analysis, NYHA class (OR 3.57, CI 95%

1.16-10.98) and SD of Phase analysis (OR 1.04, CI 95% 1.008-1.075) were the independent predictors for cardiac events.

Table 1

	Events (N=14)	Control (N=406)	p value
Age (years)	71.2±12	65.8±11	0.09
MPI Scar	13 (93%)	168 (41%)	<0.01
Infarct Size (1–5)	3.9±1.7	1±1.5	<0.01
EF	28.9±10	52.9±14	<0.01
NYHA Class	2.7±0.8	1.53±0.7	<0.01
QRS width	129±42	93±25	0.01
SD	60.2±23	26.5±18	<0.01
BW	174.8±81	72.8±57	<0.01

MPI = myocardial perfusion imaging, EF = ejection fraction, SD = standard deviation of phase analysis, BW = bandwidth of phase analysis.

Conclusions: In this registry, patients who referred to GSPECT with Phase analysis, the independent factors to predict events were NYHA class and SD of phase analysis. Prolonged follow up and more cardiac events are needed to enforce these results

197 Reduced myocardial iodine-123-metaiodobenzylguanidine uptake: a strong prognostic marker in familial amyloidotic polyneuropathy

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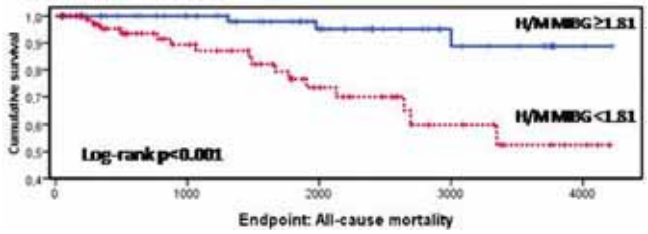
Familial amyloidotic polyneuropathy (FAP) is an inherit form of amyloidosis characterized by peripheral and autonomic neuropathy. Myocardial sympathetic denervation assessed by I-123-metaiodobenzylguanidine (MIBG) imaging often precedes the neurological involvement. Liver transplantation is the only treatment that halts the disease progression. We aimed to evaluate the prognostic accuracy of MIBG imaging in predicting all-cause death in FAP patients (pts).
Methods: 143 pts with TTRVal30Met mutation (46±16yrs; 55% females), referred for cardiac evaluation after FAP diagnose, underwent ambulatory blood pressure (BP) and Holter monitoring, echocardiography and MIBG imaging. Survival was determined by Kaplan-Meier curves and the prognostic accuracy of significant variables in predicting all-cause mortality was assessed by Cox multivariate regression.
Results: 94 pts had neurological involvement (electromyographic score: 27±26 and clinical score: 22±20). The heart-to-mediastinum (H/M) MIBG uptake ratio was 1.8±0.4. Cardiac involvement was present in 69%: 45% had abnormal circadian BP pattern, 32% had conduction disturbances or arrhythmias and 42% had increased septal thickness or diastolic dysfunction. During follow-up (57±40 months), 19 pts died (13%) and 43 (30%) were submitted to liver transplant. Pts who died were older (53±17 vs. 45±15yrs, p=0.024) and had lower H/M MIBG uptake (1.5±0.5 vs. 1.9±0.4, p<0.001). The independent predictors of the primary endpoint were H/M MIBG uptake lower than 1.81 [hazard ratio (HR): 4.82; 95%CI 1.36-17.2; p=0.015] and age (HR: 1.04; 95%CI 1.009-1.08; p=0.012). Survival was seven times lower in pts with reduced H/M MIBG uptake (Figure).



Conclusion: MIBG imaging is a powerful predictor of mortality in FAP pts and should be used for guiding therapeutic decisions.

198 Diagnostic value of phase and left ventricular volumetric analyses in the detection of multi-vessel coronary artery disease as assessed by gated single-photon emission computed tomography

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Background: Although stress-induced LV wall motion abnormality is a well-known marker for extensive CAD, no study was performed to evaluate whether the changes of post-exercise LV volumetric and phase analyses as assessed by gated SPECT may have incremental diagnostic value over conventional perfusion analysis to detect multi-vessel CAD.
Methods: 278 patients with suspected or known CAD underwent gated SPECT after exercise and at rest. All of the patients underwent coronary angiography within 3-months of gated SPECT. Myocardial perfusion was assessed with a 20-segment model, and the changes in LV volume with exercise stress were analyzed. LV mechanical dyssynchrony was evaluated using the SyncTool, and phase SD and histogram bandwidth were derived.
Results: In 128 patients with multi-vessel CAD, summed stress score (19.0±11.3 vs 11.0±9.1; p<0.0001), summed difference score (10.4±7.1 vs 4.8±5.3; p<0.0001), post- exercise increase in end-diastolic volume (EDV) (3.5±8.7ml vs -1.9±8.0ml; p<0.0001), increase in end-systolic volume (ESV) (7.1±8.5ml vs -0.3±4.7ml; p<0.0001), decrease in ejection fraction (EF) (4.5±5.2% vs 0.5±4.3%; p<0.0001), increase in phase SD (8.6±7.6°vs 0.6±6.6°; p<0.0001) and increase in histogram bandwidth (27.7±29.7°vs 3.3±13.2°; p<0.0001) were greater than in 150 patients with insignificant or single-vessel CAD. To detect multi-vessel CAD, summed stress score of ≥14 and summed difference score of ≥9 showed sensitivity of 63%, 52% and specificity of 70%, 81%, while increase in EDV ≥5ml, increase in ESV ≥5ml and decrease in EF ≥5%, increase in phase SD ≥4.4° and increase in bandwidth ≥14° after exercise had sensitivities of 58%, 65%, 52%, 74%, 68% and specificities of 71%, 89%, 84%, 84%, 91%, respectively. The multivariate analysis revealed that the combination of post-stress increase in ESV (OR=8.9 [95%CI:3.3-24.1]), increase in phase SD (OR=7.1 [95%CI:3.0-16.8]), increase in histogram bandwidth (OR=4.7 [95%CI:1.9-11.7]) and a summed difference score (OR=2.6 [95%CI:1.1-6.2]) best identified multi-vessel CAD, with sensitivity of 81% and specificity of 90% (chi-square=212.7), compared with summed difference score only (sensitivity 52%, specificity 81%, chi-square=35.1).
Conclusions: The addition of changes of post-exercise LV volumetric and phase analyses, which evaluate exercise-induced LV dilation and dyssynchrony, on conventional perfusion analysis, helps better identify patients with multi-vessel CAD.

199 Activated platelets in carotid artery thrombosis in mice can be selectively targeted in vivo with SPECT-CT using a radiolabeled single chain antibody

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Introduction: Activated platelets are key players in atherosclerosis and atherothrombosis. They can befound on the surface of inflamed, rupture-prone and ruptured plaques as well as in intravascular thrombosis. Targeting their glycoprotein IIb/IIIa (gp IIb/IIIa) receptor with molecular imaging allows for specific detection of platelet activation. However, the challenge of targeting functional epitopes on vessel walls is the small quantity of contrast agent delivered to areas of interests under arterial shear stress conditions. Therefore, by applying highly sensitive SPECT-CT imaging we here evaluated non-invasive in vivo imaging of activated platelets in carotid artery thrombosis. Using 111Indium-labelled single-chain antibodies we hereby selectively targeted ligand-induced binding sites (LIBS) on the activated gp IIb/IIIa-receptor.
Methods and results: LIBS- or control-antibody were conjugated to DTPA and labelled with 111Indium (111In-LIBS/ 111In-Control). After induction of a wall adherent non-occlusive thrombosis of the right carotid artery in mice using ferric chloride, 111In-LIBS (n=4) or 111In-control (n=4) were injected intravenously. First, detailed anatomical information of the neck region including the exact location of the carotid arteries was received through a CT angiogram of the neck region using iodinated intravascular contrast. Afterwards, SPECT analysis of the same area was conducted and images were reconstructed and fused with CT data according to an externally placed three dimensional fiducial marker. Presence of a relevant but non-occlusive thrombosis was proven by histology of the carotid artery sections. Comparing the target-to-background ratio of the injured carotid artery in the presence of a relevant thrombosis showed a significant increase after application of 111In-LIBS (mean ratio 1.99±0.36) opposed to 111In-control (mean ratio 1.1±0.24); p<0.01.
Conclusions: After having previously depicted activated platelets radiographically by targeting its activated gp IIb/IIIa receptor in vitro and ex vivo we were now able to show the potential of nuclear imaging approaches to detect wall-adherent arterial thrombosis with high sensitivity in vivo. These results encourage further studies to elucidate the role of activated platelets in plaque pathology and atherosclerosis, and might be of interest for further developments towards clinical application.

MODERATED POSTERS
SUDDEN CARDIAC DEATH. PREVENTION AND THERAPEUTIC OUTCOMES

P238 Fish oil for the secondary prevention of cardiovascular events: a meta-analysis

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Coronary Heart Disease iscurrently the leading cause of morbidity and mortality worldwide. Two meta-analyses have already supported the effective-

ness of fish oil on dyslipidemia and in reducing cardiovascular outcomes. This meta-analysis aims to determine the efficacy of fish oil in reducing cardiovascular events, specifically sudden cardiac death, fatal and non-fatalmyocardial infarction, unstable angina pectoris, need for revascularization, restenosis rate after percutaneous transluminal coronary angiography (PTCA), combined major coronary events, and all-cause mortality.
All randomized, controlled trials assessing the effects of fish oil as secondary prevention of cardiovascular events among adults are included in this study. There is no racial or gender preference. Studies on primary prevention and diet-based strategies were excluded. The outcomes of the included studies are cardiovascular deaths, fatal or non fatal myocardial infarction, unstable angina, need for revascularization and restenosis. A thorough search of available online databases was done using the search terms fish oil [MeSH] and myocardial ischemia [MeSH]. The search was limited to all RCTs among adults done from 1990 to present. Three authors reviewed and critically appraised each article to assess for possible inclusion in this review. Agreement of 2 out of 3 authors qualifies a study to be included. Two major outcomes and 6 sub-outcomes were assessed. Mantel-Haenzel statistical analysis of fixed effects to compute the risk ratio using the program Review Manager 5 was used to compute for the risk ratios and to generate the forest plots. 95 abstracts were screened,eventually excluding 88 articles. The remaining 7 articles were critically appraised and were included in this meta-analysis.
The risk of major coronary events is lower with the use of fish oil (RR 0.83 CI: 0.75,0.91), however, the studies included for this outcome were significantly heterogenous (I2=79%, P=0.0001). Thus subgroup analyses were done for several sub-outcomes. Fish oil was found to be significant in reducing sudden cardiac deaths (RR 0.62, CI: 0.47, 0.83, I2=36%) and fatal MI (RR 0.70, CI: 0.56, 0.87, I2= 0%). Fish oil was however found to be non-significant in preventing non-fatal MI, revascularization and restenosis. Prevention of all cause mortality was also significant in the fish oil group (RR 0.79, CI: 0.69, 0.92, I2= 0%).
In conclusion, fish oil supplementation is found to have significant benefit in the secondary prevention of sudden cardiac death, fatal MI and all-cause mortality.

P239 Beneficial effects of therapeutic hypothermia after cardiac arrest: beyond the “Hawthorne effect”

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Purpose: Therapeutic hypothermia (TH) has been widely implemented in survivors remaining comatose after out of hospital cardiac arrest (OHCA) as recommended by the International Liaison Committee on Resuscitation. Implementation of early goal directed protocols for post-resuscitative care with TH and revascularization has improved the outcome after OHCA compared to historic controls. The enthusiasm of implementing new treatment strategies can itself affect outcome, known as the "Hawthorne effect". This study evaluates the outcome of TH in two time periods after implementation of TH at a tertiary heart centre to access whether the effect of TH was sustained over time or was possible an effect of a "Hawthorne effect".
Methods: We prospectively studied and compared comatose survivors (n=185) of OHCA with Return of Spontaneous Circulation (ROSC) consecutively admitted to the ICU in two 2-year periods after implementation of TH; hypothermia period 1 (HT1), (n=94) and hypothermia period 2 (HT2) (n=91). Cerebral Performance Category (CPC) at hospital discharge was evaluated with Chi-square test and Cochran-Armitage test for trend. Long-term survival (180 days) was assessed using proportional hazard analysis.
Results: There was no difference in age (63±14 vs. 61±13, NS), but bystander CPR (74% vs. 42%, $p<0.0001$) was performed more frequently in the HT2 compared to HT1. The cause of cardiac arrest was more frequently acute myocardial infarction (63% vs. 37% $p<0.0006$), with a subsequent more frequent use of acute (<24 h after OHCA) coronary angiography (52% vs. 36% p=0.03). Mean time to ROSC was significantly longer in the HT2 compared to HT1 (21 min vs. 14 min, $p<0.0004$). Good cerebral outcome at hospital discharge was found in 59% and 58% in the HT2 and HT1 (NS). Adjusted proportional hazard analysis found that long-term survival was not statistical different in period HT2 compared to HT1 (1.2, CI 0.7-2.0, p=0.52).
Conclusions: The improved cerebral outcome was maintained in the two periods after implementation of TH, despite prolonged time to recovery of circulation in the most recent period. This suggests a sustained effect of therapeutic hypothermia on cerebral outcome beyond the "Hawthorne effect".

P240 Electrophysiologic effects of therapeutic hypothermia, low risk of proarrhythmia

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Introduction: Induced mild therapeutic hypothermia (MTH) has been shown to be an effective means for improving neurologic outcome after out-of-hospital resuscitation and has therefore been implemented in international guidelines. Adverse events are rare, but arrhythmias and bleeding complications have been reported. We performed an observational study investigating the physiological and pathological reactions as well as electrophysiological changes occurring during therapeutic hypothermia.
Methods and patients: A total of 105 consecutive comatose survivors of out-of-hospital cardiac arrest admitted to our institution between June 2005 and January 2011 underwent therapeutic hypothermia after exclusion of contraindications. We analyzed the preclinical course as well as changes in ECG and occurring arrhythmias as well as heart rate, blood pressure, body temperature and laboratory parameters before, during and after therapeutic hypothermia.
Results: The study included 105 consecutive patients. We found a significant decrease of heart rate (85/min ± 23.4 at admission; 59.5/min ±20.7 during hypothermia, $p<0.01$) as well as significant prolongation of PQ (0.17 sec ± 0.038 before → 0.182 sec ± 0.05 during, $p<0.05$; 0.182 sec ± 0.05 during → 0.169 sec ±0.04 after hypothermia, $p<0.01$) and QTc (0.472 sec ±0.047 before → 0.488 sec ±0.051during, $p<0.05$; 0.488 sec ±0.051 during →0.462 sec ±0.053 after hypothermia, $p<0.01$). Only one patient developed ventricular fibrillation during hypothermia. We could not detect hypothermia induced significant changes in electrolytes (sodium, potassium) nor pathologic alterations of coagulation parameters. Bleeding complications such as pulmonary bleeding, bleeding from puncture lesions or bleeding with need for blood transfusion occurred only in three cases (2.9%).
Discussion: Although therapeutic hypothermia led to significant prolongation of PQ- and QTc intervals, the reduced repolarisation reserve was not found to cause relevant proarrhythmia. Thus, from an electrophysiologic standpoint therapeutic hypothermia requires careful monitoring but carries a low risk of life-threatening arrhythmias.

P241 Biochemical markers of collagen I/III synthesis and collagen formation/degradation: their relation to life-threatening ventricular arrhythmias in ICD recipients with heart failure

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Purpose: Pathological collagen remodeling and fibrosis have been involved in the pathogenesis of sudden cardiac death. Purpose of this study was to investigate, in clinically stable patients with heart failure and an ICD, the relationship between life-threatening ventricular arrhythmias and biochemical cardiac collagen turnover indexes expressing as closely as possible the derangement in collagen physiology, which is observed in heart failure.
Methods: Seventy-four patients were included, all with an ICD and clinically stable heart failure due to coronary artery disease (n=42) or dilated cardiomyopathy (n=32), mean aged 56±5 years, NYHA class I-II, LVEF 33±3%. All had an implanted ICD for secondary (n=46) or primary prevention of sudden death. They were under optimized therapy for heart failure. Patients with ventricular arrhythmias related to unstable coronary artery disease or heart failure deterioration were excluded. We assessed: i) markers of collagen type I and III synthesis and their ratio: procollagen type I carboxyterminal peptide (PICP), procollagen type III aminoterminal peptide (PIIINP), and PICP/PIIINP, ii) markers of collagen degradation, degradation inhibition and their ratio: matrix metalloproteinase-9 (MMP-9), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), and MMP/TIMP, respectively. We also estimated left ventricular ejection fraction (LVEF). Following blood drawing for the assessment of biochemical markers (by ELISA), they were prospectively followed-up for one year. At the end of this period, the number of clinical episodes necessitating appropriate therapeutic interventions for ventricular tachyarrhythmias faster than 170 bpm was related to the assessed parameters. Multiple stepwise regression was used for analysis.
Results: A significant relation was observed between the number of episodes necessitating therapy and i) the ratio between markers of collagen type I and III synthesis PICP/PIINP ($p<0.01$), ii) the ratio between markers of myocardial collagen deposition and degradation MMP/TIMP ($p<0.05$). No significant relation was observed between arrhythmic burden and LVEF, PICP, PIIINP, MMP-9, or TIMP-1.
Conclusions: In patients with heart failure due to ischaemic or dilated cardiomyopathy, biochemical markers indicative of an increased collagen I/III synthesis as well as deranged equilibrium in myocardial collagen deposition/degradation are related to life-threatening ventricular tachyarrhythmias. Further studies are needed to investigate their predictive ability – possibly in association with other noninvasive tests.

P242 Predictors of atrio-ventricular conduction disease, long term outcomes and a strategy to prevent sudden cardiac death in patients with myotonic dystrophy types 1 and 2

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Purpose: Cardiac conduction disease is common in patients with myotonic

dystrophy (DM). Patients with DM have an annual mortality of approximately 3.5%, one-third of which is sudden. Strategies to reduce sudden death are needed.
Methods: A retrospective cohort study was performed of 211 patients with DM type 1 (DM1) and 25 DM type 2 (DM2) followed at a single tertiary centre. Clinical and electrocardiographic (ECG) characteristics were collected along with nucleotide repeat length to determine their relationship to conduction disease. A severe ECG abnormality was defined according to established criteria, as a PR interval of $\geq$ 240 msec or QRS duration of $\geq$ 120 msec.
Results: A severe ECG abnormality was found in 24% of DM1 patients and 17% of DM2 patients. Among DM1 patients, those with a severe ECG abnormality were older and more likely to have cardiovascular disorders, a higher number of nucleotide repeats, and a family history of sudden cardiac death or pacemaker implantation (Table 1). DM2 patients with a severe ECG abnormality were older and more likely to have cardiovascular diseases. Pacemakers or defibrillators were implanted in 32 patients (14%); prophylactically in 87%. During the mean follow-up of 51±44 months, 11 patients died (1.1% per year). Sudden cardiac death occurred in only 2 patients, both of whom had severe ECG abnormality.

Table 1. Characteristics of DM1 patients

Characteristics	Patients with a Severe ECG Abnormality (n=45)	Patients without a Severe ECG Abnormality (n=144)	p-value
Age	41.6±14.6	35.4±12.6	0.006
Hypertension	13.3%	4.2%	0.028
Coronary Artery Disease	6.7%	1.4%	0.05
Atrial Tachycardia or Atrial Fibrillation	6.6%	0.7%	<0.001
Family History of Pacemaker	20.0%	0.7%	<0.0001
Family History of Sudden Cardiac Death	26.7%	5.6%	<0.0001
PR interval (msec)	219±64	174±23	<0.0001
QRS width (msec)	127±26	96±10	<0.0001
CTG Repeat Length	689±451	474±322	0.01

Conclusions: In DM1, atrio-ventricular conduction disease is associated with increasing age, concomitant cardiovascular disease, nucleotide repeat length and family history. The use of prophylactic pacemakers may help minimize the risk of sudden cardiac death.

P243 Lay responders triples survival from out of hospital cardiac arrest in the Italian early defibrillation project Progetto Vita

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This is a prospective observational study on out-of-hospital sudden cardiac arrest therapy organized in the italian city of Piacenza, where a two tiered system of early defibrillation called "Progetto Vita" (PV) was organized within a traditional Emergency Medical System (ACLS-ambulance) and ambulance of volunteers (BLS-ambulance). Lay volunteers were trained to use only the automated external defibrillator (AED) (PV-AED) without performing Cardio-Pulmonary Resuscitation (BLS).
Objective: To evaluate survival rate from out-of-hospital cardiac arrest in this particular setting of early defibrillation program after a decade from the project onset.
Methods: Data were collected with the use of a database according to the Ulstein-style for all cases of out of hospital cardiac arrest from June 1999 to June 2010. Data collection include the cardiac electrical registration recorded by the paddle electrodes of AED positioned in a type lead II, the vocal record of rescuers voices support and the time of all the intervention.
Results: Among 2434 dispatched sudden cardiac arrest, ventricular fibrillation (VF) was recorded as primary rhythm in 323/2434 pts (13,3%) with a total survival rate from VF of 74/323 (22,9%). In the city (1 AED/1272 inhabitants) where Progetto Vita system is mostly operative, survival rate was higher for VF pts treated by PV-AED compared to pts treated by ACLS-ambulance alone (63,3% vs 16,4%; $p<0.05$) or BLS-ambulance (63,3% vs 21,1%; $p<0.05$). In the county (1 AED/2733 inhab.) where the system did operate mostly through BLS-ambulances and ACLS-ambulance the survival rate from VF was similar in pts treated by BLS-ambulance and ACLS-ambulance (21,1% vs 16,4%; p= ns). Time from call to first shock was shorter (5,5 + 3,8 min) in PV-AED compared to BLS-ambulance group (6,8 + 3,8 min) or to ACLS-ambulance (7,0 + 3,7 min) with therefore a confirmed significant relationship between survival rate and time to shock.
Conclusions: PV-AED only trained to defibrillate saved more pts in VF cardiac arrest than ACLS ambulance because of a mean of 2 minutes earlier arrival. The extensive use of AED by lay volunteers saved up to 63,3% of VF cases that was almost three-fold compared to ACLS-ambulance or BLS-ambulance alone. BLS training does not influence survival when AED is applied early after collapse.

P244 The importance of expert cardiac pathology for the investigation of sudden cardiac death; results from a fast track cardiac pathology service in the UK

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Purpose: To report the results of an innovative fast track cardiac pathology service for victims of sudden cardiac death (SCD) in the UK.
Methods: A prospective non-case control observational study of sudden cardiac death (SCD). Detailed histopathological examination of cardiac tissue of victims of SCD referred by coroners and pathologists throughout the UK was performed and pathological data were recorded.
Results: The majority of cases were young males (66%, 2:1), median age 31 years. Most deaths took place at home (57%) and mainly during sleep. The main cardiac pathological diagnoses were normal heart (n=320) (indicating possible channelopathy), cardiomyopathy (n=205) and coronary artery pathology (n=71) (27% of which was non-atherosclerotic). The most common cardiomyopathies were: idiopathic LVH (n=54), HCM (n=42), ARVC (n=29) and obesity related cardiomyopathy (n=29). In a sample of 200 consecutive cases of SCD, a cardiac histopathological diagnosis was provided by referring pathologists in 158 cases, but in 40% (κ=0.49) this differed from the final diagnosis by MNS. Referring pathologists were more inclined to diagnose pathology rather than designate the heart as normal, attributing isolated fatty infiltration of the right ventricle to ARVC and left ventricular hypertrophy in the absence of myocyte disarray to HCM.
Conclusion: This large prospective study highlights the importance of inherited cardiac disease as indicated by at least 75% of our referrals of SCD. It also highlights disparity in diagnoses between pathologists which is of major importance in screening families. We are able to provide a prompt service nationwide helping families come to terms with a traumatic event and facilitating the referral and evaluation of 1st degree relatives to specialist inherited cardiac diseases clinics, in an attempt to prevent further tragedies.

P245 The Japanese registry of CPR for in-hospital cardiac arrest (J-RCPR)

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Background: In-hospital cardiopulmonary arrest (CPA) is an important matter. However, limited data are available in-hospital CPA in Japan.
Methods: Data was collected in 6 major categories of variables: facility data, patient demographic data, pre-event data, event data, outcome data, and quality improvement data in the J-RCPR. The patients with in-hospital CPA were registered prospectively from 12 hospitals, during January 2008 to December 2009 in Japan. All patients, hospital visitors, who experience a cardiopulmonary resuscitation event defined as either a pulselessness or a pulse with inadequate perfusion requiring chest compressions and/or defibrillation of ventricular fibrillation or pulseless ventricular tachycardia were registered with J-RCPR.
Results: 491 adults (71.0yo, M/F 310/180) enrolled. The prevalence of VF/VT as first documented rhythm was 28.3%, asystole was 30.0% and PEA was 41.7%. ROSC (return of spontaneous contraction) was 64.7%, rates of survival on 24 hr after CPA was 50.2%, and rates of good neurological out come at 30 days after CPA was 21.4%. The rate of ROSC, the proportion of 30-day survival, and the proportion of favorable 30-day neurological outcome with a CPC score of 1 or 2 were 79.3%, 46.0% and 40.1%, respectively, in patients with pulseless VT/VF; 65.5%, 23.7%, and 17.3%, respectively, in patients with pulseless electrical activity; and 49.7%, 17.2%, and 9.0%, respectively, in patients with asystole. Immediate cause(s) of event were arrhythmia 31.0%, hypotension 15.9%, and acute respiratory insufficiency 26.3%. 67.1% of the patients were confirmed alive within 10 min before CPA.

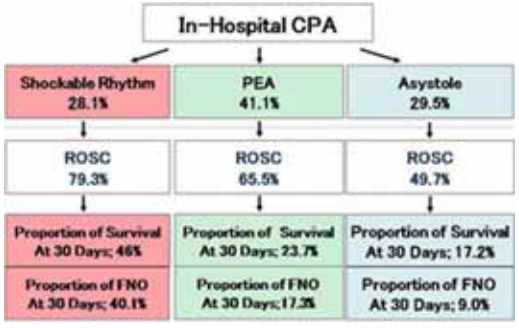

Figure 1

Conclusion: This study reported of in-hospital CPA in Japan. These results were similar as the results reported from NRCPR in the United States.

MODERATED POSTERS
HEART FAILURE PROGNOSIS: FROM BASIC MECHANISMS TO COMORBIDITIES

P246 Albuminuria predicts the mortality in heart failure patients with preserved ejection fraction independent of glomerular filtration rate - an interim analysis of the CHART-2 study

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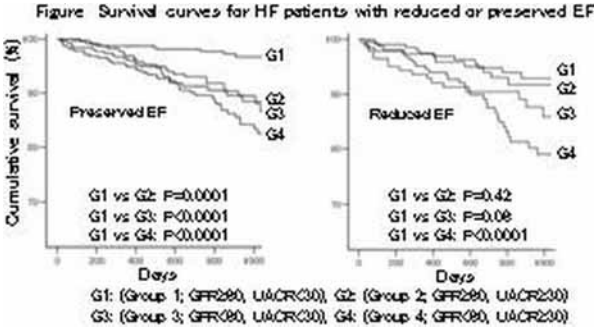
Purpose: The severity of chronic kidney disease (CKD) is usually defined by decreased estimated glomerular filtration rate (GFR). However, the prognostic impact of albuminuria in heart failure (HF) patients is not fully evaluated.
Methods: The Chronic Heart Failure Analysis and Registry in Tohoku District 2 Study (N=10,219) is a multicenter prospective cohort study enrolling Stage-B/C/D patients consecutively. The present study subjects were 1,978 HF patients in this cohort. We divided those into 4 groups based on GFR (ml/min/1.73 m^2) and urinary albumin-to-creatinine ratio (UACR, mg/g) as the followings; Group 1 (GFR≥60, UACR<30, N=719), Group 2 (GFR≥60, UACR≥30, N=372), Group 3 (GFR<60, UACR<30, N=438), and Group 4 (GFR<60, UACR≥30, N=449).
Results: The mean age was 67±12 [SD] years and male accounted for 69%. Totally, 42% of the patients had albuminuria defined as UACR≥30. Patients with albuminuria were characterized by higher BNP level, frequent diuretics use, and frequent histories of hypertension or diabetes. During a mean follow-up of 784 days, patients with albuminuria showed higher mortality independent of GFR levels. Comparing with Group 1, multivariable Cox model including GFR, showed that the hazard ratio of albuminuria for all-cause death was 2.19 (95% CI 1.23-3.90; P<0.01), 1.88 (0.97-3.67, P=0.06), and 2.30 (1.19-4.45; P=0.01) for Group 2, 3 and 4, respectively. Furthermore, prognostic impact of albuminuria in subjects with GFR≥60 was more prominent in HF patients with preserved ejection fraction (pEF, ≥50%) than those with reduced EF (Figure).



Survival curves for HF patients.

Conclusions: Even in HF patients with GFR≥60, albuminuria predicts poorer prognosis. Albuminuria should be evaluated in all HF patients to perform appropriate risk stratification especially in HFpEF.

P247 Prediction of mortality in systolic heart failure: development of an echocardiographic risk-stratification index

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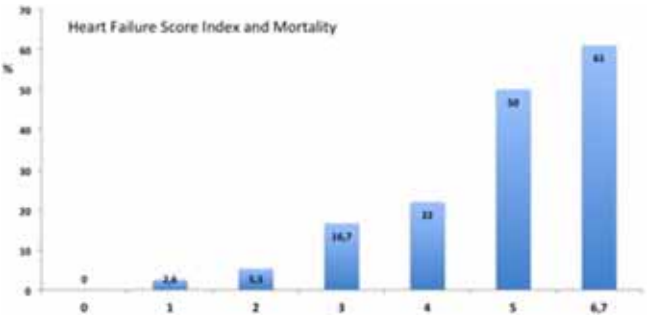
Objectives: Many transthoracic echocardiographic (TTE) measurements have been shown to predict outcome in heart failure (HF). However, it would be interesting to aggregate these variables into a risk-prediction index. The aim of this study was to develop an echocardiographic score index for risk stratification in HF patients (HFESI), by assessing which TTE measurements most strongly predict mortality.
Methods: We performed TTE in 275 outpatients with stable systolic HF and followed them for 30±17 months. Cox proportional hazard model was used to evaluate the association of 15 TTE measurements with death. Measurements that independently predicted mortality were combined into an index. ROC analysis was used to define cut-off values. At each abnormal variable, were assigned points on the basis of strength of association with mortality.
Results: Of the 15 variables, 5 were independent predictors of mortality in multivariate analysis: left atrial volume index (LAVI>40 mL/m^2; HR: 1.6; 95% CI: 0.9-2.7, p=0.05), tricuspid annular peak systolic excursion (TAPSE<16 mm; HR: 2.4; 95%CI: 1.4–4.1, p=0.002), ejection fraction (EF<30%;HR: 3.5; 95%CI: 1.4–8.3, p=0.004), pseudonormal/restrictive filling pattern (PN-RF; HR: 2.16; 95%CI: 1.01-4.6, p=0.046) and mass-to-volume ratio (M/V<1.3;HR: 2.0; 95% CI: 1.2-3.6, p=0.011). Combining these measurements, the HFESI ranged from 0 to 7, representing risk as follows: 2 points for TAPSE and EF, 1 points for PN-RF, M/V, and LAVI. Overall mortality increased as HFESI increased (Fig; p<0.0001). The addition of HFESI to a model containing significant clinical predictors of death, showed incremental predictive power (p<0.001).



Conclusions: The HFESI is able to independently predict mortality in stable patients with systolic HF and might be useful for risk stratification.

P248 The obesity paradox in heart failure with reduced or preserved ejection fraction: insights from the MAGGIC Collaborative group

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Purpose: Obesity is a well known risk factor for the development of heart failure (HF). However, some studies suggest that obese HF patients may have a better prognosis than normal-weight patients, giving rise to the so-called obesity paradox. The objective of this analysis was to assess the relationship between body mass index (BMI) and mortality in patients with HF and reduced ejection fraction (HF-REF) or preserved ejection fraction (HF-PEF).
Methods: This analysis incorporates patient-level data from 14 HF studies and subsequent all-cause mortality. Patients were divided according to their BMI into 5 groups: BMI < 22.5, 22.5-24.9, 25-29.9, 30-34.9, and ≥35 kg/m^2. Cox proportional hazards survival analysis was undertaken for BMI group, adjusted for age, gender, aetiology, hypertension, and diabetes for the overall group and stratified within HF-REF and HF-PEF groups. The primary outcome for this meta-analysis was 3-year all-cause mortality.
Results: BMI data were available for 23967 patients (mean age, 66.8 years; 32% women), most patients were in NYHA class II (46%) or III (50%) and 5609 (23%) patients died. Cox proportional hazards model of death (adjusted for age and gender, stratified by study) modelled within the HF-REF and HF-PEF is shown in Figure. Compared with patients with BMI between 22.5-24.9, patients in higher BMI categories had lower risk of death for both HF-REF and HF-PEF (with the lowest risk in the range 30 to 34.9). Lower BMI was associated with a higher risk of all-cause death. In a fully adjusted model a similar pattern of hazard ratios across BMI strata was seen for both all-cause mortality.

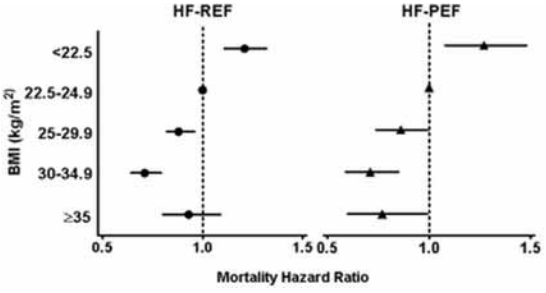

Figure 1

Conclusions: In patients with chronic heart failure the obesity paradox is present among those with reduced as well as preserved left ventricular systolic function.

P249 Renal failure predicts poor long-term survival in patients with heart failure regardless of ejection fraction: a MAGGIC sub-analysis

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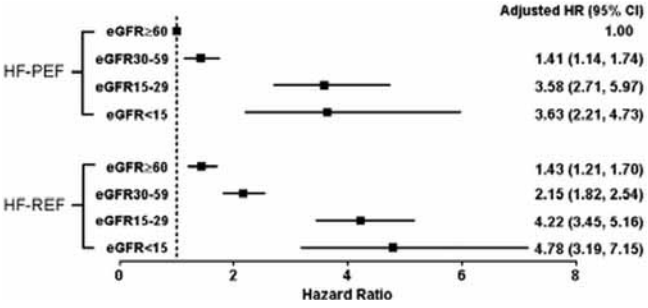
Introduction: Impaired renal function has been linked to poorer outcomes in patients with heart failure (HF) with a reduced ejection fraction (REF) and in a major clinical trial of patients with a preserved ejection fraction (PEF). However, it is uncertain if renal function has a similar impact on long-term mortality in a broad, multi-national cohort of patients with HF-PEF.
Methods: The MAGGIC renal substudy incorporates patient-level data from 20 studies (n=13152 patients), including over 20 baseline variables, with long-term mortality data. Estimated glomerular filtration rate (eGFR) was calculated using MDRD, and patients were divided into REF or PEF by an EF of 50%. Cox proportional hazards models were used for multivariable modeling.
Results: The mean age of the cohort was 66 years of age (standard deviation 12); 31% were female and the median ejection fraction was 43% (IQR 24, 46). During a median follow-up of 2.1 years, 18% (n=453) of PEF and 23% (n=2384) of REF patients died. After adjustment for key baseline variables and compared to an eGFR of >60 mls/min, reduced eGFR was associated with a worse outcome regardless of EF: adjusted hazard ratio for mortality was 1.49 (95%CI 1.36, 1.62) for an eGFR 30-59 mls/min, adjHR 3.00 (2.59, 3.41) for an eGFR 15-29 mls/min and adjHR 3.29 (2.41, 4.50) with eGFR <15 mls/min. The association remained consistent when patients with PEF were modeled separately (see Figure).



Conclusions: Impaired renal function is a powerful negative prognostic marker in patients with heart failure, including those with PEF.

P250 Liver injury in acute heart failure. Evidence for a cardiohepatic syndrome?

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Aim: The aims of this study were to assess i) the prevalence and the clinical profile of patients admitted for ADHF and abnormal liver function tests, namely alanine aminotransferase (ALT), aspartate aminotranferase (AST) and alkaline phosphatase (AP) and ii) the impact of abnormal liver function tests on short and long term outcome.
Patients and methods: Acutely Decompensated Heart Failure (ADHF) patients enrolled in the SURVIVE study (n= 1327) with liver function tests (LFTs) available included in this study. LFTs, namely transaminases (ALT, AST) and alkaline phosphatase (AP) were measured baseline, day 1, day 3, day 5 and day 31 from inotrope infusion.
Results: Abnormal LFTs were seen in 46% of our ADHF patients. Abnormal ALT and/or AST at baseline were associated with various signs of systemic and peripheral hypoperfusion: lower systolic blood pressure (p=0.012), higher heart rate (<0.001), higher prevalence of cold extremities (p=0.022), lower left ventricular ejection fraction (p=0.048) and higher BNP levels (p<0.001), while abnormal AP was associated with signs of systemic congestion [greater incidence of peripheral edema (p<0.001), ascites (p<0.001), tricuspid regurgitation (p=0.04) and higher BNP (p<0.001)].
Patients with at least one of the 2 transaminases abnormal at baseline have almost 2-fold greater 31-day mortality compared to patients with normal transaminases (17.6% vs 8.4%; p<0.001) and a greater 180-day mortality (31.6% vs 22.4%, p<0.001). Abnormal AP at baseline had no effect on 31-day mortality but a marked effect on 180-day mortality compared to patients with normal AP (23.5 vs 34.9%, p=0.001). After adjustment for all parameters derived from the multivariate analysis, the best baseline cut-off values were 55 IU/L for ALT (AUC 0.747), 66 IU/L for AST (AUC 0.747) and 149 IU/L for AP (AUC 0.739) for 180-day mortality.
Conclusion: Measurement of LFTs is very useful to indicate the mechanism of acute heart failure - "backward" when elevated AP and "forward" when elevated transaminase – and help physician to administer the appropriate management in the early phase of ADHF. When elevated, LFTs also indicate negative long term outcome and the need of long term saving therapy for HF.

P251 Soluble gp130 predicts outcome in chronic heart failure: analysis from the controlled rosuvastatin multinational trial in heart failure (CORONA)

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Purpose: Circulating levels of interleukin-6 family cytokines, including soluble glycoprotein 130 (gp130), their common signal-transducing receptor subunit, are elevated in patients with chronic heart failure (HF), with increasing levels according to disease severity. We investigated whether gp130 provided independent prognostic information in patients with chronic HF and examined possible interactions with statin therapy.
Methods: Gp130 as a risk factor for the primary endpoint (cardiovascular[CV] death, nonfatal myocardial infarction, nonfatal stroke; n=408), all-cause mortality (n=422), CV mortality (n=344), death from HF (n=102) or sudden death (n=194), total- (n=804) or HF hospitalizations (n=327) was investigated in 1447 patients (≥ 60 years, New York Heart Association [NYHA] class II-IV, ischemic systolic HF, optimal pharmacological therapy) in the CORONA population, randomly assigned to 10 mg rosuvastatin or placebo.
Results: In multi-variable analyses, adjusting for left ventricular ejection fraction, NYHA class, age, body mass index, diabetes, sex, intermittent claudication, heart rate, estimated glomerular filtration rate, and ApoB/ApoA-1-ratio, gp130 (continuous variable, adjusted by the standard deviation of gp130) was significantly associated with all end-points (HR from 1.10 to 1.39 for the different end points), except the primary endpoint. When NT-proBNP was added to the model, gp130 still provided independent predictive information for all-cause mortality [HR 1.19 (1.06-1.33), p=0.004], CV mortality [HR 1.15 (1.01-1.31), p=0.034] and death from HF [HR 1.50 (1.20-1.86), p<0.0001], but not for hospitalizations. We observed no interactions between gp130 levels and effect of rosuvastatin treatment on outcomes.
Conclusions: Soluble gp130 independently predicts mortality, and especially death due to worsening HF, in older patients with advanced chronic systolic HF of ischemic etiology.

P252 Prognostic additive value of high sensitivity soluble ST2 in ambulatory heart failure patients

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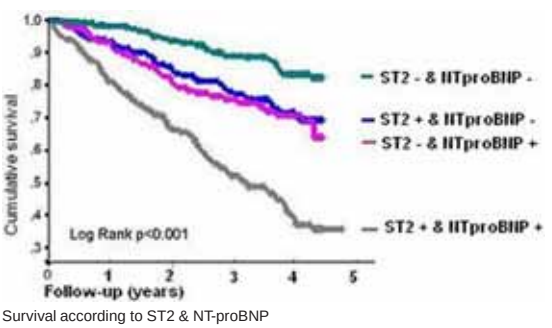
Background: Despite recent therapeutic advances, heart failure (HF) still has a poor prognosis and new tools to identify high-risk patients are needed. ST2 is a novel biomarker that provides prognostic information in several clinical settings.
Aim: To examine whether soluble ST2 levels improve risk stratification in a non-selected outpatient population with HF, and to test if the combination of ST2 + NT-proBNP is actually better than either separately.
Patients and methods: 891 patients (71.6% men, median age 70.2 years [IQR 60.5-77.2]) were studied. Median LVEF was 34% [IQR 26-43%]. Most patients were in NYHA class II (65.5%) or III (26.1%). Median follow-up was 33.4 months [IQR 15.8-50.2]. ST2 was measured from -80°C stored plasma samples via a



Survival according to ST2 & NT-proBNP

highly sensitive sandwich monoclonal immunoassay. NT-proBNP was also measured via a highly sensitive sandwich monoclonal immunoassay, processed by an automatic analyser.
Results: 244 patients died during follow-up. Both ST2 (HR 1.009 [1.007-1.011], $p<0.001$) and NT-proBNP (HR 1.00004 [1.00003-1.00005], $p<0.001$) were good prognostic biomarkers. After adjustment for other significant clinical and therapeutic variables, both remained as independent prognostic factors. When patients were grouped according to NT-proBNP and ST2 median values, the combination of the two biomarkers increased significantly their prognostic discriminator capacity, as shown in Kaplan-Meier survival curves (figure). Taking as reference both values below the median, the HR for patients with both NT-proBNP and ST2 $\geq$ the median was 5.463 [3.777-7.902], $p<0.001$.
Conclusions: ST2 was a marker of risk in this unselected ambulatory HF cohort, and in combination with NT-proBNP improved the long-term prognostic accuracy.

P253 Low desmin expression in cardiomyocytes: a sinister sign in patients with idiopathic dilated cardiomyopathy

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Background: Desmin (DES) plays an essential role in maintaining cell cytoarchitecture and structural integrity, positioning and function of organelles and intercellular signalization. Therefore, it is suggested that remodeling of DES cytoskeleton may contribute to the progression of IDC and patients late outcome.
Aim: To determine the effect of DES expression on survival.
Methods: Diagnostic endomyocardial biopsy (DMB) was performed in 200 patients with idiopathic dilated cardiomyopathy (IDCM) [age: 48.7±13.5 (mean ± standard deviation) years, males: 85%, left ventricular ejection fraction (LVEF): 30±10%, New York Association (NYHA) class (I/II/III/IV): 53/82/55/10]. In each case 5-6 specimens were taken from left ventricle. DES was detected with immunohistochemical staining of cardiomyocytes and western blotting. Study population was divided into four groups: I group – 54 patients with normal expression and distribution (positive reaction in Z lines, intercalated discs), IIA group – 42 patients with regular and increased expression of desmin (strong positive reaction in Z lines, intercalated discs) without formation of aggregates, IIB group – 58 patients with irregular and increased accumulation with formation of aggregates additionally around cardiomyocyte nuclei and III group – 46 patients with weak and abnormal distribution and lack in Z lines or lack expression in cardiomyocytes.
Results: In type III DES expression was observed the highest NYHA class and NT-pro-BNP level, the biggest diameter of LVEDD and the lowest LVEF. The differences was statistically significant ($p<0.001$) between type I and III in all above analysed parameters. At the and of follow-up (mean duration: 50±43 months, there were 43 (21.5%) deaths and 6 (3%) heart transplantation. Type III DES expression was related to an increased risk of death or HTX in univariate Cox proportional hazard regression models (adjusted hazard ratio (HR) 7.18, 95%CI 2.96-17.40, $p<0.001$) and also in multivariable models (NYHA, LVEDD, LVEF, NT-pro-BNP, gender, age) (HR 5.24, 95%CI 1.58-17.38, p=0.007).
Conclusions: In patients with IDCM, low or lack desmin expression is a strong independent predictor of unfavourable outcome. Bedside risk stratification for adverse future cardiovascular events, the outcome of the present study support the relevance of exploring desmin as potential target to treat heart failure disease progression.

NEW INSIGHTS ON BIOLOGICAL EFFECTS OF LIPIDS AND LIPOPROTEINS

257 Vasoprotective effects of high density lipoprotein (HDL) are abolishes in patients with chronic kidney disease (CKD)

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Background: Patients with chronic kidney disease (CKD) exhibit a high mortality, mainly due to an enhanced rate of cardiovascular events. In contrast to patients without CKD, patients with CKD develop a Uremic Dyslipidemia, characterized by low levels of total cholesterol, low density lipoprotein and HDL and elevated levels of triglycerides. In addition to its role in reverse cholesterol transport, healthy HDL exerts several vasoprotective effects. Thus, we compared endothelial effects of HDL isolated from patients CKD and healthy subjects.
Methods: HDL was isolated from patients with End Stage Renal Disease (ESRD) and healthy subjects (n=15 per group) by sequential ultracentrifugation. The effect of HDL on endothelial nitric oxide production (NO) was assessed by electron spin resonance (ESR) spectroscopy. Phosphorylation of the endothelial NO synthase (eNOS) was determined by western blot analysis. To examine the anti-inflammatory capacity of HDL, the expression of VCAM-1 on endothelial cells was assessed. The effect of HDL on endothelial apoptosis was determined by measuring Annexin V+/PI– cells by flow cytometry. Moreover, to assess the endothelial repair capacity after HDL treatment in vitro and vivo gap closure assay and carotid injury model in nude mice were performed.
Results: HDL from healthy subjects stimulated endothelial NO production; this effect was completely abolished in ESRD patients and the NO production was strongly inhibited (-80% by HDL of these patients). Accordingly, phosphorylation of the stimulatory eNOS site S1177 was reduced and phosporylation of the inhibitory site T495 was significantly higher in cells treated with HDL from patients with ESRD compared to healthy subjects. HDL from healthy subjects attenuated the TNFα induced VCAM-1 expression on endothelial cells. This effect was abolished with HDL from ESRD patients. Notably, HDL from patients with ESRD induced basal endothelial VCAM-1 expression, whereas HDL from healthy subjects did not, suggesting a change to a proinflammatory particle. Furthermore, HDL from healthy subjects, but not from patients with ESRD could significantly reduce the number of Annexin V+/PI– cells after treatment with TNFα, indicating a loss of HDL's antiapoptotic capacity in CKD. In vitro gap closure and in vivo reendothelialization after carotid injury were suppressed by HDL of ESRD patients.
Conclusion: Our data demonstrate for the first time that endothelial protective effects of HDL are considerably impaired in patients with ESRD, revealing a new important pathomechanism of cardiovascular diseases in patients with CKD.

258 Overexpression of ABCG1 attenuates arteriosclerosis and endothelial dysfunction in atherosclerotic rabbits

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Background: ABCG1 is a protein which is centrally involved in reverse cholesterol transport from the vessel wall. Investigation of the effects of ABCG1 overexpression or knockdown in vivo has resulted in controversial findings, and strongly depended on the gene intervention model in which it was studied.
Methods: Therefore, we investigated the effect of local overexpression of human ABCG1 in a novel model of vessel wall-directed adenoviral gene transfer in atherosclerotic rabbits. We conducted local, vascular-specific gene transfer by adenoviral delivery of human ABCG1 (Ad-ABCG1-GFP) in cholesterol-fed atherosclerotic rabbits in vivo.
Results: Endothelial overexpression of ABCG1 markedly reduced atheroprogression (plaque size) and almost blunted vascular inflammation, as shown by markedly reduced macrophage and smooth muscle cell invasion into the vascular wall. Also endothelial function, as determined by vascular ultrasound in vivo, was improved in rabbits after gene transfer with Ad-ABCG1-GFP. Therefore, both earlier and later stages of atherosclerosis were improved in this model of somatic gene transfer into the vessel wall.
Conclusion: In contrast to results in transgenic mice, overexpression of ABCG1 by somatic gene transfer to the atherosclerotic vessel wall results in a significant improvement of plaque morphology and composition, and of vascular function in vivo.

259 Microarray analysis of human umbilical vein endothelial cells treated with the omega-3 fatty acid docosahexaenoic acid (DHA) highlights new anti-atherosclerotic and anti-angiogenic properties for fish

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High intakes of omega-3 fatty acids have been associated with systemic anti-inflammatory effects and cardiovascular protection, but the molecular basis for these effects remains incompletely defined. Using a DNA microarray technology we investigated the early gene expression profile of human vascular endothelial cells conditioned by DHA under proinflammatory conditions.
Methods: Human umbilical vein endothelial cells (HUVEC) were treated with 50 μmol/L DHA for 48 hours and then stimulated with 5 ng/mL IL-1beta for 3 hours. Total RNA was extracted, and qualitatively and quantitatively analyzed with a NanoDrop Spectrophotometer and an Agilent Bioanalyzer before RNA labeling and purification. Gene expression profiling was performed with an Agilent Whole Human Genome Oligo Microarray covering 41 000 unique genes and transcripts. Slides were scanned with the Agilent's scanner and images processed using Agilent Feature Extraction software. The raw data were further processed with the GeneSpring® 10 software and differentially expressed RNA identified using Benjamini and Hochberg False Discovery Rate with a p-value <0.05. Functional and network analyses were identified by the Ingenuity Pathways version 8.0 Analysis.
Results: IL-1 stimulation significantly changed the expression of 1474 genes: 815 had decreased, while 659 had increased. Out of the 659 IL-1-upregulated genes, DHA significantly attenuated the expression of 88 genes. The Ingenuity pathway analysis software indicated immunological-, inflammatory- and atherogenic pathways as the most affected. In particular, we identified new target

molecules involved in atherosclerosis, including tubulin beta polypeptide[TUBB]2 A and phosphodiesterase[PDE]5A; and in angiogenesis, including transforming growth factor[TGF]-beta 2 and chemokine (C-X-C motif) ligand 10.
Conclusions: DHA widely affects endothelial gene expression; the identification of novel genes susceptible to regulation by DHA will certainly improve our understanding of mechanisms by which omega-3 fatty acids may prevent or attenuate human chronic diseases including atherosclerosis.

260 Impact of short term or long term reduction of PCSK9 on the metabolism of the mouse

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Purpose: PCSK9 is a modulator of cholesterol synthesis and clearance. Here we study the impact of the short or long term absence of PCSK9 on other aspects of metabolic regulation of the mouse.
Methods: In mice lacking PCSK9 (Pcsk9-/-) body composition measured by NMR before and after a 16 week high fat high carbohydrate (HFHC) diet, long term body weight responses, basal lipids and hormones and acute responses to insulin, oral glucose tolerance and lipid loads were studied. To compare the effects of long term (genetic PCSK9 knockout) versus acute administration of a monoclonal antibody to PCSK9, 1B20, glucose tolerance tests and oral lipid loads were administered to C57Bl/6 mice.
Results: Females Pcsk9-/- mice did not exhibit a body weight or composition phenotype except a 17% decrease of free body fluid on both chow or after HFHC diet. Male Pcsk9-/- mice were lighter on a chow diet than their wildtype counterparts (WT) (WT: 22.2±0.3 g vs Pcsk9-/-: 20.9±0.5 g, $p<0.05$), with both less lean mass and less adipose mass. After 16 weeks of HFHC diet, their weight gain was slightly and significantly greater than that of the wildtype mice (WT: 48.1±0.3 g vs Pcsk9-/-: 49.1±0.3 g, $p<0.05$), resulting in a significantly greater fat mass (WT: 19.1±0.1 g vs Pcsk9-/-: 21.0±0.1 g, $p<0.05$). Plasma total cholesterol and LDL were lower in the Pcsk9-/- mice of both genders on chow or after HFHC diet, although the absolute difference was lessened after the animals were on the HFHC carbohydrate diet. Plasma triglyceride was lower in the female mice on chow, but was not different in the other groups. Neither insulin nor leptin were different between wildtype and Pcsk9-/- mice of either gender. When tested with an ip insulin sensitivity test or oral glucose tolerance test, no differences were seen in the AUC of glucose in either paradigm. C57Bl/6 administered a PCSK9 mAb, 1B20, did not exhibit alteration in oral glucose tolerance or in circulating triglycerides after a lipid challenge despite a 50% lowering of plasma LDL ($p<0.05$).
Conclusions: Taken together, our data indicate that, in the mouse, endogenous PCSK9 modulates cholesterol levels without a significant impact on lipid absorption and synthesis, glucose or insulin sensitivity despite a potential for modest increase in adiposity after long term increased energy intake.

261 Deficiency of progranulin (PGRN) alters lipid metabolism including HDL functions

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Progranulin (PGRN) has a wide variety of functions, including tumorigenesis, development, wound healing, inflammation and also pathophysiology of dementia. Although the association of PGRN with atherosclerosis and lipid metabolism remains to be elucidated, we have recently reported PGRN is expressed in and secreted from human monocyte-derived macrophages, and is bound to apolipoprotein (apo) A-I. Here, we investigated the association of PGRN with lipid metabolism using PGRN-knockout (KO) mice. HPLC analyses showed that plasma triglyceride (TG) levels, especially in the VLDL fraction, of PGRN-KO mice were significantly higher than those of wild-type (WT) mice. Although plasma lipoprotein lipase (LPL) activities were similar between the two groups, the mRNA expressions of genes related to the synthesis of TG, such as SREBP1c and FAS, were significantly increased in the liver of PGRN-KO mice compared with those of WT mice, suggesting that increased plasma TG levels of PGRN-KO mice might be due to the enhanced production of TG in the liver. While plasma HDL-cholesterol levels were not significantly different between the two groups, HDL as well as apo A-I from plasma of PGRN-KO mice took significantly less cholesterol from peritoneal macrophages, indicating that PGRN might affect HDL function. HDL derived from KO mice suppressed the secretion of adiponectin (APN) from 3T3L1 cells compared with HDL of WT mice, possibly due to the decrease of its anti-inflammatory property. Taken together, deletion of PGRN alters lipid metabolism, including HDL function.

262 Reconstituted HDL cholesterol inhibits inflammation-induced endothelial-cell angiogenic processes in vitro

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Purpose: Neovascularisation of atherosclerotic plaque is triggered by inflammation and leads to plaque growth and instability. HDL cholesterol is atheroprotective; which, in part, may be mediated by its anti-inflammatory properties. We examined the effects of recombinant HDL (rHDL or apolipoprotein A-I) on the Endothelial Cell (EC) specific angiogenic response to inflammation, in vitro.
Methods: Human Umbilical Vein ECs (HUVECs) were pre-incubated for 48 hours with rHDL (0-600 μg/ml). EC-specific angiogenic processes were tested: 1) In an EC/fibroblast co-culture tubulogenesis assay; 2) For their ability to migrate in a Boyden chamber. TNF-a (0-0.5 ng/ml) was used to induce inflammatory conditions in the tubulogenesis assay. Human Monocyte Derived Macrophages (HMDMs) stimulated with IFN-g (10ng/ml for 24hours) were used to mimic the inflammation-induced pro-angiogenic conditions in atherosclerotic plaques and EC migration towards the HMDMs was assessed in the wells of Boyden chambers.
Results: Preincubation of HUVECs with rHDL significantly reduced tubule formation (43.5% reduction compared to control, $p<0.001$). This effect was entirely EC-specific as rHDL was removed from the ECs before addition to the fibroblast co-culture. TNF-a significantly increased tubule formation in a dose dependent fashion (Maximum 60% increase at 0.5 ng/ml versus control, p=0.01). However, HUVECs initially pre-incubated with rHDL showed reduced inflammation-induced tubulogenesis (44.9% reduction, $p=<0.001$). EC migration towards IFN-g-stimulated HMDM media was 55.2% greater than towards unstimulated media. Pre-incubation of ECs with rHDL was able to significantly attenuate this increase (77.8% reduction, p=0.019).
Conclusions: rHDL inhibits inflammation-induced angiogenic processes in vitro. These experiments provide evidence that rHDL may be beneficial in abrogating angiogenesis in inflammatory conditions such as atheromatous plaque.

EMERGING RISK FACTORS IN HEART FAILURE

271 Nicotinic receptor N alpha 7 and proinflammatory cytokines in peripheral blood mononuclear cells and parasympathetic drive in patients with systolic heart failure

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Background: Autonomic imbalance (including depleted parasympathetic drive) constitutes a fundamental pathophysiological feature of heart failure (HF). There is evidence suggesting links between depleted cholinergic signalling and augmented inflammatory innate response. The up-regulated expression of nicotinic cholinergic receptors (e.g. Nα7) may reflect the compensatory reaction due to depleted cholinergic stimulation of target cells. We investigated derangements within autonomic nervous system along with the mRNA expression of Nα7 proinflammatory cytokines in peripheral blood mononuclear cells (PBMCs) from patients with and without HF.
Methods: We examined 28 patients with systolic stable HF (age: 61±13 years, LVEF: 33±13%, NYHA class I/II/III: 11%/60%,29% (3/16/8), ischemic etiology: 70%) and 12 healthy controls (age: 59±11 years, LVEF: 66±6%). Spectral analysis of heart rate variability (HRV) and systolic blood pressure variability (BPV) were performed in very low (VLF), low (LF) and high-frequency (HF) bands. Relative transcript levels of Nα7 and proinflammatory cytokines (IL-1, TNF-α) were analyzed using Real-time PCR in PBMCs.
Results: Patients with HF had higher Nα7expression in PBMC as compared to healthy peers (1.51±1.77 vs 0.68±0.35 arbitrary units [AU], p=0.03) which was accompanied by an increased expression of proinflammatory cytokines in PBMC (IL-1 – 39.26±77.17 vs 4.84±6.03 AU, p=0.009; TNF-α – 20.62±64.86 vs 1.74±0.79 AU, p=0.0008). The Nα7 expression in PMBCs correlated inversely with HRV-HF (r= -0.4 p=0.08) and BPV-HF (r= -0.44, p=0.05). The Nα7 expression in PMBCs was also related to LVEF (r= -0.30, p=0.07) and plasma NT-proBNP (r=0.41, p=0.02), and the expression of IL-1 and TNF-α in PBMCs (r=0.45, p=0.004; r=0.53, p=0.0005, respectively).
Conclusions: Depleted parasympathetic drive demonstrated in patients with HF based on physiological tests is related to reduced cholinergic signaling seen within circulating immune cells which results in an augmented production of proinflammatory mediators.

272 Comparative study of short-term exposure to ultrafine particles in patients hospitalized for heart failure and acute coronary syndrome

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Purpose: The relevance of ultrafine particles (UFPs, particles <0.1 μm diameter), the smallest fraction of ambient particulate matter, on heart failure morbidity has not been documented. We studied concentrations of UFPs and analyze its relationship with cardiovascular risk factors on hospital admissions for heart failure and acute coronary syndrome (ACS).
Methods: We used a time-stratified case-crossover design to study the association between short-term exposure to particulate matter <10 μm (PM10), 2.5 to 10 μm (PM2.5-10), <2.5 μm (PM2.5) diameter and UFPs (measured at single background station) and hospital admissions for heart failure and ACS. We considered pollution concentrations on the previous day (lag 1), and up to 7 days (lag 7) before heart failure and ACS admissions and calculated the accumulated exposure over 7 days (mean of lag 1-lag 7).
Results: We analyzed a total of 3229 consecutive patients admitted with the diagnosis of heart failure (n=1090) and ACS (n=2139). There were no statistically significant differences in mean concentrations of particulate matter <10 μm, 2.5 to 10 μm and <2.5 μm. However, concentrations of UFPs were significantly higher in patients with heart failure compared to ACS (19845.35±8806.49 cm-3 vs 16854.97±8005.54 cm-3, $p<0.001$). After controlling for other cardiovascular risk factors (see Table), multiple regression analysis showed that UFPs concentrations were an independent predictor for admission in patients with heart failure.

Multivariate analysis

	OR (95% CI)	p-value
UFPs (×10000)	1.40 (1.15–1.66)	0.02
Age	1.02 (1.00–1.04)	0.05
Sex	1.00 (0.62–1.61)	0.99
Hypercholesterolemia	1.33 (1.21–1.51)	<0.001
Current smoker	2.70 (1.55–4.83)	<0.001
Arterial hypertension	1.63 (1.40–1.99)	0.04
Diabetes mellitus	2.40 (1.52–3.81)	<0.001

UFPs: ultrafine particles.

Conclusions: In our study population and compared to patients with ACS, exposure to UFPs is a novel risk factor for admission for heart failure.

273 CRP on admission of acute heart failure: an independent prognostic value

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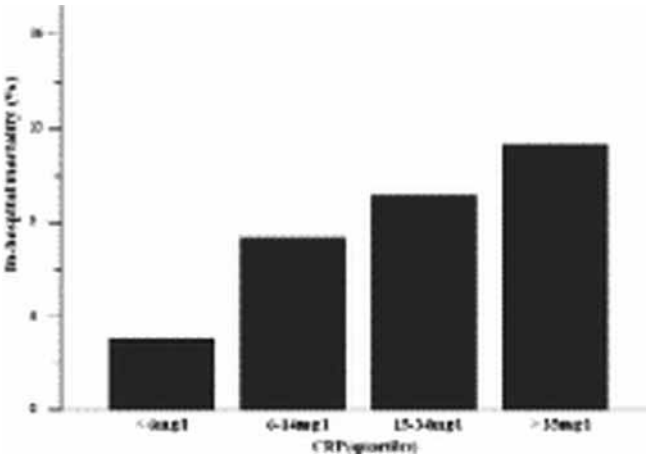
Aims: To analyze the prognostic value of CRP levels on admission from a nationwide, observational study of acute heart failure (AHF).
Methods: A single-day snapshot was performed on 2009 in 170 French hospitals. Investigators were encouraged to include all hospitalized patients with a diagnosis of AHF. Relevant data was recorded including different biological parameters. Outcome was assessed during hospitalization as well as during 12 months after discharge.
Results: The survey included 1658 patients with confirmed diagnosis of AHF (76±13y, 45% females, 30% preserved EF). CRP levels were reported in 1369 patients on admission. Associated infection was diagnosed in 449 patients (27%); mean level of CRP was 49 and median was 65mg/l in these patients. In remaining 960 patients without reported infection (and no antibiotics during hospitalization), mean level was 31±46mg/l, median was 15mg/l and CRP levels was poorly associated with others clinical/biological parameters. In this group without infection, the rate of in-hospital mortality was 7.6%; CRP levels were 47±68 mg/l in deaths as compared to 29±43mg/l in survivors ($p<0.005$) and using stepwise logistic regression analysis, CRP levels (per 10mg/l) predicted deaths (OR 1.15, 95%CI 1.02-1.29), independently of others predictors -age, previous AHF, blood pressure, natriuretic peptides levels and LVEF. The figure shows in-hospital mortality according to CRP quartiles. In the whole population, infection was not associated with mortality. After discharge, CRP levels remain significantly associated with one-year mortality: HR 1.35 (95%CI 1.04-1.73, p 0.02) for CRP above median.
Conclusion: CRP level is an independent predictor of outcome, irrespective of the presence of associated infection. Role of inflammation in AHF deserves further studies.



Mortality according to CRP quartiles.

274 Non-viral gene therapy JVS-100 provides functional benefit to patients with ischemic heart failure

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Background: Stromal cell-derived factor-1 (SDF-1) has been shown to promote tissue repair following injury in multiple organ systems by preventing apoptosis and promoting stem cell recruitment and vasculogenesis. JVS-100 is a non-viral DNA plasmid encoding human SDF-1. We have demonstrated pre-clinical safety and efficacy of JVS-100's delivery via the BioCardia Helical Infusion Catheter (HIC) in a porcine model of ischemic cardiomyopathy. We have completed a Phase 1 open-label dose-escalation study testing the safety and efficacy of JVS-100 in patients (pts) with ischemic cardiomyopathy and NYHA class III heart failure (HF). Here, we report interim safety and efficacy results.
Methods and results: 17 pts with a mean time from MI of 7.5 years and ejection fraction ≤40% were enrolled to receive JVS-100: 5 mg (n=4 pts), 15 mg (n=6 pts) and 30 mg (n=7 pts) delivered to the peri-MI region via 15 endomyocardial injections with the HIC. Pts are being followed at 1, 4, and 12 months after injection. The primary safety endpoint is the number of major adverse cardiac events (MACE) at 30 days. Efficacy is assessed as changes from baseline in: echocardiographic parameters, cardiac perfusion via SPECT and clinical parameters including NYHA class, 6 minute walk distance (6MWd) and quality of life score (QOL). Follow-up has been completed through 4 months in the 5 and 15 mg cohorts and 1 month in the 30 mg cohort. No adverse events have been deemed likely related to the drug to date. The primary safety endpoint has been met, with only 2 MACEs within 30 days of injection, both due to underlying disease. At 4 months post-injection, the 5 mg dose group demonstrated clinically relevant improvements in QOL (Median -12 points; Range -13 to 13) and trends toward improvement in 6MWd (Median 24 m; Range -22 to 127), and overall functional response score, calculated by combining clinically significant changes in NYHA class, 6MWd and QOL. In the 15 mg group at 4 months, clinically relevant improvements from baseline occurred in 6MWd (Median 41 m; Range 3 to 61 m) and QOL (Median -16 points; Range +1 to -32), with a statistically significant ($p<0.05$) improvement in the overall functional response score.
Conclusions: This clinical data suggests delivery of a SDF-1 plasmid, JVS-100, to patients with ischemic heart failure is safe and exhibits dose-dependent improvements in 6MWd, QOL and NYHA class at 4 months. Efficacy data from the 30 mg group and imaging data from cohorts 2 and 3, all available in April 2011, will provide further insight into the effects of JVS-100 on ventricular remodeling and clinical response.

276 Accelerated suicidal erythrocytes death in heart failure

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Purpose: Eryptosis is suicidal death of erythrocytes and observed in various anemic diseases like sepsis and malaria. Eryptosis may be evoked by

several stressors, including oxidative stress, hyperosmotic shock and energy depletion. A high percentage of patients with heart failure (HF) are anemic, and anemia in HF bears an adverse prognosis. To explore the potential role of eryptosis in HF-associated anemia and its mechanisms and regulation, the rate of eryptosis was analyzed in Ren2 rats (with HF and mild anemia) and in human HF patients.
Methods: We measured eryptosis in transgenic Ren2 rats, a model of excessive tissue RAS activity, which leads to hypertension and HF. Furthermore, we studied eryptosis in erythrocytes from patients admitted with acute HF. Blood parameters were analyzed with a hematology analyzer. Eryptosis is characterized by cell shrinkage, cell membrane blebbing and phosphatidylserine (PS) exposure at the erythrocytes surface. Using a fluorescence activated cell sorter (FACS), cell volume (forward scatter), PS exposure (via annexin V binding), and intracellular Ca^{2+} (Fluo3 fluorescence) were determined.
Results: Analysis of peripheral blood revealed a mild microcytic anemia in Ren2 rats as evident from significantly decreased hemoglobin concentrations, hematocrit values, mean corpuscular volumes and mean corpuscular hemoglobin. In addition, upon oxidative stress (30 mins, 0.1mM tert-butylhydroperoxide) and hyperosmotic shock (+550mM sucrose), PS-exposure at the erythrocyte surface, influx of cytosolic calcium and cell shrinkage were significantly increased in blood of Ren2 rats, compared to control (Sprague Dawley, SD) rats (all comparisons: $P<0.05$ Ren2 vs SD). To corroborate our findings, we measured the rate of eryptosis in HF patients, and observed a significant increase. Specifically, erythrocytes from HF patients were more susceptible to oxidative stress and the percentage of PS-exposure at the erythrocytes surface, was significantly higher compared to healthy controls ($P<0.05$). Cytosolic Ca^{2+} influx upon oxidative stress also significantly increased in HF patients ($P<0.05$).
Conclusions: Our data show for the first time that increased eryptosis is present in HF, as observed in both rat and human HF. These observations suggest a contributory role of eryptosis in anemia associated with HF. Eryptosis may present a novel target for therapy in HF-associated anemia.

PREGNANCY IN ADULT CONGENITAL HEART DISEASE

297 Pregnancy in women with congenital cardiac disease

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Background: Pregnancy in women with congenital cardiac disease (CCD) become more frequently due to the progress in the field of diagnostic techniques and surgical interventions. Data regarding the pregnancy complications and neonatal outcome are limited.
Methods and results: 267 pregnant women with partly complex CCD were analysed in one of the largest single centre cohorts in Germany. The median age was 27 years. The frequency of maternal and neonatal outcome and complications were monitored.
The main cardiac complications were arrhythmias (12%) and heart failure (10%). 29% of these symptomatic arrhythmias were treated. 44% of the patients with complex heart diseases, but also 23% with simple lesions lost at least one functional class. 2% had thromboembolic events. Two mothers died within one year after delivery.
The most prevalent neonatal complications were premature birth (12%) and small for gestational age (8%). According to the Federal statistical office of Germany the rate of prematurity was twice as high as in the normal population. 24% of the premature babies were seen in the patients with complex cardiac diseases. Congenital cardiac defects in the neonates were seen in 5% of all pregnancies.
Additionally most women were contacted by mail and asked to fill in the health situation and medical care in/after pregnancy for a long term follow-up. 62% of the women answered the questionnaire. Fortunately most late survivors were active and had a good quality of life. With regard to the functional class of Perloff 58% of the patients considered themselves as healthy and 30% had a reduced functional class after pregnancy. 87% were satisfied with the medical surveillance.
Conclusion: Successful pregnancy can be achieved in most women even with congenital cardiac disease. The rate of cardiovascular morbidity and premature delivery is increased especially in patients with complex heart diseases but also in patients with simple lesions. As a result patients should be monitored closely by a multidisciplinary health care team that includes obstetricians, cardiologists, pediatric cardiologists and obstetric anaesthesiologists.

298 Pregnancy outcome in women with Turners Syndrome

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Introduction: Turners Syndrome (TS) is due to complete or partial loss of the X Chromosome with or without mosacism. Women with TS have short stature and are pre-disposed to malformations of cardiovascular system including coarctation of the aorta (CoA), bicuspid aortic valve (BAV) and aortopathy. Increasingly, there are reports of pregnancies in TS patients, via spontaneous (mosaic TS) or assisted conception with oocyte donation, but recent studies have reported a high risk of aortic dissection (AD) in pregnancy in TS of around 2%. Both Hypertension (HT) and Congenital heart disease are risk factors (RF) for dissection. We therefore reviewed pregnancy outcome for TS patients in our institution, noting in particular any prior cardiovascular pathology and cardiovascular complications.
Methods & results: Of 120 patients followed up by the specialist TS clinic at UCH, 12 were identified as having a pregnancy. All had short stature with mean BSA 1.55 (range1.37-1.76). There 12 pregnancies, with 1 natural conception and 11 by oocyte donation and 10 live births. All patients had prior TTE with CVS diagnoses as follows; BAV (2), and HT (1). The aortic measurements pre-pregnancy were; Aortic root mean 2.72 cm (range $\pm$0.32), indexed to BSA mean 1.76cm (range $\pm$0.19); Asc Ao mean 2.63cm ($\pm$0.43), BSI 1.61cm $\pm$0.27. There were no adverse maternal cardiac adverse events during pregnancy. At post-partum follow-up (mean 4 years range 2-7 years) mean aortic root dimensions were 2.74cm ($\pm$0.27) p=0.74, BSI 1.74$\pm$0.19 and Ascending aorta 2.6 cm ($\pm$0.44cm, p=0.48) BSI 1.66$\pm$0.22. In 1 patient aortic root diameter pre-pregnancy was 2.1cm/m^2 and it is unchanged at 26 months post-partum.
Conclusions: Of 12 women with TS who conceived there were 10 successful pregnancies with no maternal cardiovascular complications. Only 3 of our patients however had Risk Factors for Aortic Dissection. Aortic root and ascending aorta dimensions remained stable post-partum. With prior CVS assessment to exclude CVS pathology, TS patients can have a successful pregnancy.

299 Outcomes of pregnancy in women with Ebstein's anomaly

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Pregnancy in women with congenital heart disease is a challenge for cardiologists and obstetricians, facing the risk of serious events. In women with Ebstein's anomaly, pregnancy may induce arrhythmias or increase cyanosis and dyspnea, and has long been therefore contraindicated
Aim: To assess the tolerance and mother and offspring outcomes in pregnant women with Ebstein's anomaly, in an attempt to define some factors of risk.
Material and methods: Clinical status and outcomes of pregnancy (mother and offspring) in women with Ebstein's anomaly were analyzed. The presence of a Wolf-Parkinson-White syndrome and/or cyanosis was recorded.
Results: 22 women had 47 pregnancies (1 to 6 pregnancies; 2.13 pregnancies/woman): 4 were cyanotic and had 6 pregnancies (1.5/w) with 5 livebirthsand 1 therapeutic abortion. Premature birth occurred in 3 of the 5 livebirths (60%). The 18 non cyanotic women had 41 pregnancies (2.3/w) with 3miscarriages, 1 abortion and 37 live births (90%). Prematurity occurred in 7/37 live births (19%) Mean birthweight was respectively 2.130 and 2.660 kg for the newborns from cyanotic and noncyanotic mothers. All pregnancies were well tolerated, no maternal death occurred. Nine out of 18 noncyanotic women (vs 1 among 4 cyanotic) had no cardiac symptom during pregnancy. Dyspnea increased in 3 of 18 vs 3 of 4, asthenia in 3 of 18 vs 3 of 4. Seven women had a Wolf-Parkinson-White syndrome (32%): of them 4 (57%) had no arrhythmia, 2 experienced palpitations and 1 had a well tolerated supra-ventricular tachycardia (SVT). Among the 15 women without WPW syndrome, 10 (67%) had no arrhythmia, 3 had palpitations and 2 SVT. Neither life-threatening nor severe arrhythmia occurred.
Conclusion: Pregnancy in women with Ebstein's anomaly is well tolerated, especially in non cyanotic mothers (less arrhythmias,less prematurity, greater birth weight). Therefore, Ebstein should not be a contra-indication for pregnancy, even in cyanotic women. However, to insure optimal tolerance, preventive closure of the inter-atrial shunt might be proposed prior to pregancy.

300 The pregnancy in women after transcatheter closure of atrial septal defects

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Purpose: Percutaneous closure of ASD is increasingly performed during the last decade. Many women undergoing this procedure are in childbearing age but the information on the outcome of pregnancy in women with ASD after transcatheter closure is limited. Our aim was to investigate the magnitude and determinants of cardiac and obstetric complications during pregnancy in women with ASD after transcatheter closure.
Methods: Consecutive 52 women with a mean age of 26.2$\pm$16.1 (20-44) with ASD after transcatheter closure with the Amplatz Septal Occluder, were analyzed. A total of 52 women gave birth to 50 full-term healthy babies. In total there were 52 pregnancies, including 2 miscarriages (3.8%).
Detailed recordings of each completed pregnancy (n=50, 28.2$\pm$14.1 (11-359) months after transcatheter closure) were obtained. Cardiac events were defined as heart failure, stroke, TIA, arrhythmias, endocarditis; obstetric events as PIH, preeclampsia, eclampsia, HELLP syndrome, premature labor, postpartum hemorrhage; neonatal events as premature delivery, small-for-gestational age, fetal mortality, neonatal mortality.
Results: Cardiac events were observed during 10% (n=5) of the completed pregnancies and included: supraventricular arrhythmias (n=4, 8%) and right heart failure - shin oedema (n=1, 2%). None of these complications required hospitalization.

Severe obstetric complications during completed pregnancies were not observed except minor ones: moderate hypertension (n=4, 8%), prolonged bleeding (n=3, 6%), premature rupture of membranes (n=2, 4%). Women >30 years appear to be at greater risk for both cardiac and obstetric complications (Table 1).

Table 1

	Cardiac events (n=5, 10%)	Obstetric events (n=9, 18%)
Presence of Pulmonary hypertension	1.73 (0.37–3.11)	1.23 (0.73–2.41)
History of arrhythmia	2.61 (0.40–5.03)	1.33 (0.47–3.11)
Maternal age >30 years	5.69 (1.54–25.3)*	3.22 (1.1–3.1)*
Presence of RV dilatation	1.51 (0.76–2.28)	0.70 (0.36–4.21)

Data are presented as odds ratios (95% CI). *P<0.05. Data are presented as odds ratios (95% CI). *P<0.0.

Conclusions: Most ASD women tolerate pregnancy well after transcatheter closure with the Amplatz Septal Occluder with the risk of complications comparable to that in general population of healthy women. Maternal complications were seen more often in women >30 years.

301 Long term outcome of pregnancy in women with a systemic right ventricle - is the deterioration due to pregnancy or a consequence of time?

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Introduction: The right ventricle (RV) supports the systemic circulation in patients who have had intra-atrial repair of transposition of the great arteries (TGA) or have congenitally corrected TGA (cTGA). There is concern about the ability of a systemic RV to support additional volume load of pregnancy. Previous studies have reported deterioration in RV function following pregnancy in intra-atrially repaired TGA and cTGA. However, both of these conditions are also associated with progressive RV dysfunction over time. To date no study has examined if the deterioration seen with pregnancy is due to the pregnancy or part of the known deterioration that occurs with time.
Methods: We retrospectively identified all women under the care of the ACHD Unit at the Hospital who had undergone pregnancy from 2002-2010. Each woman was matched for age, RV function at baseline and diagnosis (TGA vs cTGA) with a separate male and female control. Seperate controls were used for subsequent pregnancies. NYHA and RV function were recorded for each group at baseline, post pregnancy (or at 1 year for control groups) and at latest follow up.
Results: 18 women had 31 pregnancies (1-4) with 32 live births. At baseline there was no significant difference between groups for age, RV function or NYHA. There were similar follow up periods for each group (pregnant group 51 months, male controls 41 months, female controls 52months, p=0.37). Post pregnancy there was a significant deterioration in the pregnant group for NYHA class (p=0.004) and RV function (p=0.02). No change was seen in either control group. At latest follow up there was significant deterioration in RV function in all 3 groups. There was a maintained reduction from baseline in NYHA of women who had undergone pregnancy (p=0.014) but again this was not seen in the control groups. Within the pregnant group there were no maternal deaths. One lady was hospitalised for atrial flutter. 11 deliveries were preterm, all due to obstetric reasons.
Conclusion: Women with systemic RVs who have a pregnancy can have deterioration in RV function and this occurs earlier than in controls. However, with longer term follow up, the study group and control groups showed similar degree of deterioration in RV function, probably reflecting the natural history of a systemic RV. Women who undertake pregnancy are more symptomatic with a reduction in NYHA class. This may be due to an inability of women with young children to be able to adapt their life to a worsening cardiac status whilst coping with increasing demands of motherhood.

302 Maternal and fetal complications of anticoagulant therapy in cardiac pregnant ladies with prosthetic valves

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Background: In pregnant ladies with a prosthetic cardiac valve, anticoagulation is essential for patient 's life. This carries a considerable risk for both the patient and her baby. The optimal regimen of anticoagulant therapy during pregnancy is still controversial.
Objective: To study the outcome of pregnancy in pregnant ladies with prosthetic valves on anticoagulant regimen adopted at our institute as regard maternal and fetal complications and to study the effect of position of the valve, warfarin dose and mode of delivery on the outcome of pregnancy.
Methods: 66 pregnant women with prosthetic valves were managed according to a certain protocol of anticoagulant therapy throughout pregnancy and the outcome of pregnancy was studied and compared with 132 normal pregnant ladies as a control group. The study was carried out in the high risk obstetric unit at our institute (a tertiary referral center).
Results: 9% of our cases had hemorrhagic complications, 6% had thromboembolic complications. Both of these figures were significantly higher than the control group. Fetal losses were 15% (9% abortion, 3% intrauterine fetal death and 3% neonatal deaths). The position of the valve had no impact on the outcome of pregnancy. Cesarean section was found to be safer than vaginal delivery as it is a scheduled procedure.
Conclusion: Anticoagulant treatment during pregnancy is attended with a considerable possibility of maternal and fetal complications.

UNDERSTANDING MICRODOMAIN SIGNALLING IN CARDIAC ARRHYTHMIAS AND GROWTH

307 Angiotensin II enhances late INa via activation of Ca/Calmodulin Kinase II independent from NADPH oxidase 2

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Angiotensin II (ANG II) signaling has been implicated in the development of heart failure (HF) but the signaling mechanisms involved are poorly understood. We have shown previously that CaMKII-dependent Na channel gating (INa) is involved in the arrhythmogenesis in HF. To test, if ANG II regulates cardiac INa via activation of CaMKII, INa and action potentials (AP) were measured via whole-cell patch clamp in isolated mouse myocytes. In wildtype (WT) myocytes, ANG II (1 μmol/L) significantly increased both peak INa and late INa (ANOVA, Fig. 1A-C, *P<0.05 vs. WT). Interestingly, the increase in late INa was completely abolished in myocytes lacking CaMKIIδ (CaMKIIδ-/-), while peak INa was still enhanced (Fig. 1A-C, †P<0.05 vs. CaMKIIδ-/-). In accordance, ANG II significantly increased the incidence of early and delayed afterdepolarisations (EAD+DAD) in WT but not in CaMKIIδ-/- myocytes (ANOVA, Fig. 1D). ANG II is known to generate ROS via NADPH oxidase 2 (Nox2). To test, whether ANG II activates CaMKII via Nox2-generated ROS thereby regulating Na channel gating, INa was measured in myocytes lacking the gp91phox subunit of Nox2 (gp91phox-/-). Surprisingly, ANG II still enhanced late INa in gp91phox-/- myocytes (Fig. 1B, ‡P<0.05 vs. gp91phox-/-) but the CaMKIIδ-independent increase in peak INa was abolished (Fig. 1C). In conclusion, ANG II regulates peak INa vs. late INa via two different pathways. The former involves Nox2-dependent ROS production and the latter depends on CaMKIIδ.

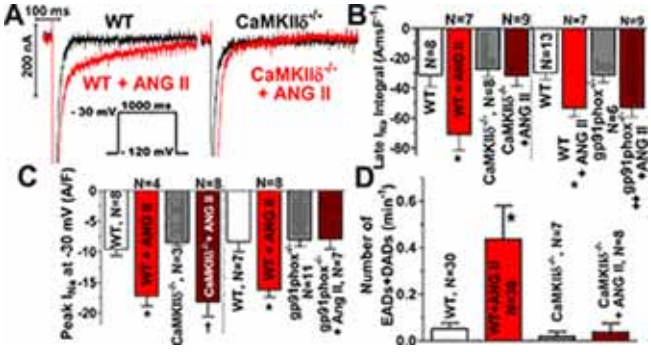

Figure 1

Further experiments are needed to isolate the consequences of the two different pathways but since enhanced CaMKII-dependent late INa has been implicated in arrhythmias, the latter pathway may be involved in the arrhythmogenesis in HF.

308 PKA- and CaMKII-dependent effects on calcium handling proteins in human cardiac hypertrophy and heart failure

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There is controversial discussion about the role of PKA (protein kinase A) and CaMKII (Ca/calmodulin kinase II) regarding the ryanodine receptor (RyR2)-dependent SR Ca-leak in cardiac pathologies e.g. cardiac hypertrophy and heart failure (HF). It was recently shown that inhibition of CaMKII significantly decreases diastolic SR Ca-leak and thereby improves contractility in isolated human failing myocardium via reduced phosphorylation of the cardiac RyR (Sossalla S, Circ Res, 2010). Several animal models, however, suggest that the PKA plays a predominant role in this context. Convincing data from human tissue are still lacking. Performing western blot experiments from samples of hypertrophied human hearts (n=6) with aortic valve stenosis (increased afterload) and preserved ejection fraction (E≥50%) we found an increase in RyR2 expression by 122±33%

($p<0.05$) and slightly increased RyR2 phosphorylation at the CaMKIIδ-specific site Ser2815 by 58±19% (p=0.09) compared to healthy human hearts (n=5). In contrast, there was a tendency towards diminished RyR phosphorylation at the PKA-dependent site Ser2809 (by 25±4%, p=0.20). Further PKA targets, i.e. phosphorylation of phospholamban (PLB) at Ser16 and troponin I (TnI) phosphorylated at Ser23/24 were even significantly decreased in cardiac hypertrophy by 79±6% (PLB-Ser16/PLB, $p<0.005$) and 69±8% (TnI-Ser23/24, $p<0.01$), respectively.
Similar observations were made in end-stage human HF (n=8). The hyperphosphorylation of RyR2 at Ser2815 was even more pronounced (increase by 311±72%, $p<0.05$), which conforms to the fact of elevated CaMKII activity in HF. However, again no significant alteration of RyR2 phosphorylation at Ser2809 could be detected. Furthermore, the amount of phosphorylated TnI (Ser23/24) was also decreased in HF compared to healthy myocardium by 49±9% ($p<0.05$).
Preliminary functional data from trans-aortic constriction induced failing cardiomyocytes of mice did not show any obvious effects of PKA-inhibition on Ca-handling parameters and are currently being validated for human cells.
These findings shed new light on the role of PKA for the regulation of excitation-contraction coupling in human cardiac hypertrophy and HF. So far, RyR-Ser2815 seems to be the dominant phosphorylation site, relevant for functional alterations of RyR2 in this context. Unless PKA contributes to Ser2815 phosphorylation or other not identified RyR phosphorylation sites, an immoderate increase in CaMKII- rather than in PKA-activity seems to be crucial for the phosphorylation changes of key Ca-handling proteins in the transition to human cardiac hypertrophy and HF.

309 Cardiac FKBP12.6 overexpression protects against catecholamine-promoted ventricular tachycardia and transiently blunts maladaptive LV remodeling in mice with TAC-induced LVH

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Aims: Alterations in RyR2 function have been proposed as a major pathophysiological mechanism of heart failure (HF). Cardiac FKBP12.6 overexpression protects against myocardial infarction-induced HF and catecholamine-promoted ventricular arrhythmias. We tested the hypothesis that FKBP12.6 overexpression protects against triggered ventricular arrhythmias and maladaptive left ventricular hypertrophy following transverse aorta constriction (TAC) in the mouse.
Methods and results: One and 2 months after TAC, male transgenic (DT) mice and their littermate controls (Ctr) underwent echocardiography, heart catheterization, ECG telemetry or cardiac pacing with adrenergic challenges. Ventricular expression of the hypertrophic gene program and Ca^{2+} handling proteins were assessed by real-time PCR and Western blot, respectively. One month post-TAC, DT mice showed a less pronounced increase in BNP mRNA and decrease in SERCA2a protein expression, and an unchanged SERCA2a/PLB ratio whereas this ratio was decreased in Ctr mice. These changes were blunted at 2 months. Expression and function of the Na^{+}-Ca^{2+} exchanger were decreased in DT compared with Ctr mice. The increase in myocyte shortening observed in Ctr mice in response to 50 nM isoproterenol was reduced in DT mice, as was the increase in LV contractility observed in response to 3-30ng/g/min dobutamine perfusion in sham-DT and in the 2 TAC mouse groups. Following isoproterenol injection (0.2 mg/kg ip), premature stimuli aimed at identifying reentrant arrhythmias, induced ventricular tachycardia (VT) in 80% and 86% of TAC-Ctr and TAC-DT mice, respectively. Incontrast, trains of 30 stimuli (burst pacing) aimed at identifying triggered arrhythmias, induced VT in 50% of the TAC-Ctrand in none of the TAC-DT mice (P=0.022).
Conclusion: Cardiac FKBP12.6 overexpression in the mouse protects against catecholamine-promoted burst pacing-induced ventricular tachycardia and transiently blunts pressure overload-induced maladaptive LV remodelling.

310 Perinuclear Ca stores and nucleoplasmic [Ca] transients after pressure overload-induced hypertrophy in adult cardiac myocytes

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Purpose: Nucleoplasmic calcium concentration ([Ca]) in cardiac myocytes (CMs) regulates transcription and is involved in remodelling processes. Perinuclear Ca stores contribute to the regulation of nucleoplasmic [Ca] transients (CaTs). How nucleoplasmic [Ca] is changed during the development and progression of hypertrophy remains unknown. We thus characterized alterations in perinuclear Ca stores and nucleoplasmic CaTs after pressure overload-induced hypertrophy in adult CMs.
Methods: Pressure overload was induced by minimally invasive transverse aortic constriction (TAC) in adult wild-type mice. Sham-operated mice served as controls. Ventricular CMs were isolated 1 and 7 weeks after TAC/Sham. Perinuclear Ca stores were visualized using confocal imaging and staining with the low affinity Ca indicator Mag-Fluo-4/AM (10μM, 90-120min). Nucleoplasmic and cytoplasmic CaTs were recorded simultaneously in electrically-stimulated CMs loaded with Fluo-4/AM (8μM, 40min).
Results: In CMs from Sham animals, staining of perinuclear Ca stores revealed a nuclear envelope and tubular structures transversing the nucleus. A significant increase in number of tubules per nucleus was observed during physiological growth (1week: 4.2±0.2 (n=91); 7weeks: 4.7±0.2 (n=88)). Nuclear dimensions as well as cyto- and nucleoplasmic CaTs remained unaltered. Following TAC, mice developed progressive hypertrophy as evidenced by echocardiography and gravimetry. In TAC CMs, the number of tubules per nucleus progressively decreased (1week; 4.3±0.2 (n=87); 7weeks: 3.4±0.2 (n=87)), whereas length and width of nuclei increased (1week: 13.3±0.3 and 4.9±0.2μm; 7weeks: 17.8±0.7 and 5.5±0.2μm). One week after TAC changes in the kinetics and amplitude of CaTs were found in the nucleus (time to peak: 127±2 vs 194±5ms; RT50: 360±7 vs 380±5ms; amplitude: 491±19 vs 376±28nM; Sham (n=15) vs TAC (n=15); all $P<0.05$). Seven weeks after TAC similar changes of CaTs also occurred in the cytoplasm.
Conclusions: Perinuclear Ca stores and nucleoplasmic CaTs undergo significant changes during pressure overload-induced hypertrophy, which appear to precede changes in cytoplasmic Ca regulation. These results raise the possibility that altered nucleoplasmic [Ca] may contribute to the development and/or progression of hypertrophy.

311 Super-resolution microscopy reveals secondary cardiac RyR cluster morphology

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In cardiacmyocytes, Ca^{2+} release from the cell's Ca^{2+} store isregulated by clusters of ryanodine receptors (RyR). Changes in the size ororganisation of these proteins is predicted to alter the behaviour of calciumrelease. However, conventional methods used to examine antibody labelled proteins are impeded by theresolution limit of >200nm of a conventional light microscopy. We report new measurements of ryanodinereceptor (RyR) clusters using the superior spatial resolution of stimulatedemission depletion (STED). Fixed cardiac myocytes from sheep atrial cells wereRyR antibody labelled and then fluorescent tagged with Atto 647N. STED imageswere acquired and subsequently deconvolved. Deconvolution allowed furtherimprovements in both signal-to-noise ratio and resolution. Fitting of thesmallest detectable clusters showed a ∼4x improvement in resolution andallowing a lateral resolution of ∼45 nm.
Using the protein size predicted from ultrastructure and asdocumented in rat ventricular myocytes, calculations of cluster size werepossible, yielding a mean cluster size of 21 RyRs, with a standard deviation of33. Half of the clusters measured had 6 or less RyRs, but many small clusterswere grouped in a secondary level of organisation, resembling that typicallyobserved with conventional microscopy methods.
Doublets ofRyR clusters were observed on the outer membrane of the atrial cells inagreement with previous reports, but a more complex primary structure was shownto underlie these.
In conclusion, these nanoscale measurements of the size andshape of these clusters will inform future studies allowing a more completepicture of the morphological changes which take place subsequent topathological remodelling.

312 Intracellular variability in the kinetics of Ca removal from the cytosol in ventricular cardiac myocytes

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In cardiomyocytes, cytosolic Ca removal is mediated by the sarcoplasmic reticulum Ca ATPase (SERCA) and sarcolemmal Na/Ca exchanger (NCX), with contribution from plasmalemmal Ca ATPase and mitochondria. We quantify for the first time spatiotemporal inhomogeneities in cytosolic Ca removal in ventricular cardiomyocytes.
Cardiomyocytes were isolated from the left ventricle of mice and pigs and electrically stimulated (1 Hz). Cytosolic Ca transients at steady state were measured confocally (Fluo-4 AM, 1.5 ms/scan line). Forskolin (Forsk, 10 μM) was used to stimulate, cyclopiazonic acid (CPA, 1 μM) to inhibit SERCA, SEA0400 (0.3 μM) to inhibit NCX. Contraction was attenuated by blebbistatin (10 μM) or 2,3-butanedione monoxime (10 mM). Time of half-maximal Ca release (TF50), amplitude (Fpeak, F/F0) and time constant of Ca decay (tau) were quantified for local transients (1 μm intervals along the scan line), and for the whole cell transient (global). The coefficient of variation of local tau (st.dev. of local tau/mean tau) was a measure of spatial inhomogeneity of Ca removal. Regions were classified as fast (fastCaR, local tau < global tau) or slow (slowCaR, local tau > global tau) Ca removal at baseline (BSL).
In mouse cardiomyocytes, Ca reuptake was not homogeneous, with amaximal intracellular difference in local tau of 237±29 ms (mean±S.E.M., n=10cells) and a CVtau of 14±7%. Widths of regions were 4.6±0.5 μm (fastCaR) and5.1±1.4 μm (slowCaR). In pigs, inhomogeneities in Ca reuptake were morepronounced

(CVtau=25±5%; P<0.01 vs. mice;n=10/species). Spatial variation inCa reuptake was largely not explained by local Fpeak (inverse correl. R^2=0.15).There was no relationship between TF50 and local tau. In mice, Forsk significantlydecreased global tau (85±8 vs. 116±22 ms at BSL). Forsk decreased local tau morein slowCaR (to 72±4% of BSL vs. 78±5% of BSL in fastCaR; p<0.05, n=7). CPAincreased global TAU from 211±68 to 274±94ms (p<0.01), and increased localtau more in slowCaR than in fastCaR (to 164±5% of BSL vs. 134±6% of BSL, resp.; p<0.05, n=7), resulting in increased inhomogeneity ofCa reuptake with CPA (CVtau 19±5% vs. 15±7% at BSL; P<0.001). SEA0400increased global TAU from 268±61 to 295±67 ms (p<0.001), with no differencebetween fastCaR and slowCaR (108±1% vs. 112±1% of BSL).
In summary, cytosolic Ca removal is not homogenous in cardiomyocytes, and more inhomogeneous in pigs than in mice. Regions of slow cytosolic Ca removal are more responsive to modulation of SERCA activity, suggesting regional differences in the subcellular mechanisms involved in cytosolic Ca removal.

ADVANCES IN GENETICS OF CARDIOMYOPATHIES

361 Genetic basis of left ventricular noncompaction

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Left ventricular noncompaction (LVNC) is a recently defined cardiomyopathy characterized by a pattern of prominent trabecular meshwork. Although LVNC has been classified as a primary cardiomyopathy of genetic origin,the genetic basis of disease in a large proportion of patients with LVNC is still unresolved. The purpose of this study was to investigate patients with LVNC for possible disease causing mutations. We investigated 124 Japanese LVNC patients, including 50 familial cases and 74 sporadic cases, for mutations by polymerase chain reaction and direct DNA sequencing. Three of these genes encoded proteins previously associated with LVNC including LIM domain binding protein 3 (ZASP), α-dystrobrevin (DTNA), tafazzin (TAZ/G4.5), while the remainder encoded sarcomeric proteins including myosin binding protein 3 (MYBPC3), cardiac troponin T (TNNT2), α-myosin heavy chain (MYH7),α-tropomyosin (TPM1), α-cardiac actin (ACTC), and sodium channel α subunit gene (SCN5A) associated with other inherited forms of cardiomyopathy. Of these 107 were isolated cases and 17 were non-isolated cases. We characterized the likely mode of inheritance in the 50 familial cases: autosomal dominant inheritance was the most common while X-linked inheritance was apparent in only 5 families. DNA variants were identified in 27 patients including 21 cases from 9 families and 6 sporadic cases. We identified TAZ mutations in two familial cases and one sporadic case, an DTNA variant in one family, five variants in LDB3, and sarcomeric gene mutations in 3 familial cases and 3 sporadic cases. The prevalence of the mutations in LDB3, TAZ, DTNA or sarcomere gene is only 12%. The sarcomeric gene mutations including MYH7, TPM1, and TNNT2 are most frequently found in our series. In addition, the prevalence of SCN5A variants is significantly higher in LVNC patients with arrhythmias and/or heart failure than those without. The relatively small contribution of known mutations to the disease, compared to higher proportion of familial cases suggests that other elusive genes remain to be identified. Higher incidence of variants in sarcomeric protein-encoding genes supports the concept that LVNC is part of a diverse spectrum of cardiac morphologies triggered by sarcomere protein gene defects and that there is a shared molecular etiology of different cardiomyopathic phenotypes. In addition, higher incidensen of SCN5A variants in LVNC patients with arrhythmias and/or heart failure support the hypothesis that genes encoding ion channels are implicated in the pathophysiology of LVNC modifing the severity of disease.

362 A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy

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Aims: Dilated Cardiomyopathy (DCM) is a major cause of heart failure with a high familial recurrence risk. So far the genetics of DCM remains largely unresolved. We conducted the first Genome Wide Association Study (GWAS) to identify loci contributing to sporadic DCM.
Methods and results: 1179 DCM patients and 1108 controls contributed to the discovery phase. Pools of DNA stratified on disease status, population, age and gender were constituted and used for testing association of DCM with 517,382 SNPs. Three DCM-associated SNPs were confirmed by individual genotyping ($P<5.0\times10^{-7}$), and two of them, rs10927875 and rs2234962, were replicated in independent samples (1165 DCM patients and 1302 controls), with P-values of 0.002 and 0.009 respectively. rs10927875 maps to a region on chromosome 1p36.13 which encompasses several genes among which HSPB7 has been formerly suggested to be implicated in DCM. The second identified locus involves rs2234962, a non-synonymous SNP (c.T757C, p. C151R) located within the sequence of BAG3 on chromosome 10q26. To assess whether coding mutations of BAG3 might cause monogenic forms of the disease we sequenced BAG3 exons in 168 independent index cases diagnosed with familial DCM and identified 4 truncating and 2 missense mutations. Each mutation was heterozygous, present in all genotyped relatives affected by the disease and absent in a control group of 347 healthy individuals, strongly suggesting that these mutations are causing the disease.
Conclusion: This GWAS identified 2 loci involved in sporadic DCM, one of them implicates BAG3. Our results show that rare mutations in BAG3 contribute to monogenic forms of the disease while common variant(s) in the same gene are implicated in sporadic DCM.

363 Clinical profile and genotype-phenotype assessment of arrhythmogenic right ventricular cardiomyopathy/dysplasia due to desmosomal mutations

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Purpose: To evaluate the clinical profile and the genotype-phenotype relation with respect to electrocardiographic abnormalities, functional/structural alterations on two-dimensional echocardiography, and initial symptomatic presentation in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) due to desmosomal protein mutations.
Methods: Seventy-seven consecutive ARVC/D patients (56% male) aged 41±18 years (range: 12-77), carriers of pathogenic desmosome mutations were evaluated. Twenty-nine carried mutations in plakophilin-2 (PKP2), 12 in desmocollin-2 (DSC2), 8 in desmoplakin (DSP) and 28 were homozygotes of a recessive plakoglobin (JUP) mutation. All patients fulfilled the revised Task Force Criteria (TFC) for diagnosis of ARVC/D. Serial cardiac assessment with annual 12-lead ECG and two-dimensional echocardiography was performed during a prospective follow-up of 8±7 years (range: 1-24). The initial clinical event was assessed by age. Detailed historical data were available from medical records. For the comparison of proportions Chi Square and Fisher's Exact tests were used. Mann-Whitney test was used for the comparison of quantitative variables between groups.
Results: Ninety-six percent of patients had 12-lead ECG abnormalities (75% repolarization abnormalities, 66% depolarization abnormalities) and 75% had right ventricular functional/structural alterations according to revised TFC. Left ventricular functional/structural alterations were detected in 39%. Fifty patients (65%) presented clinical events, the first occurring at age 34±18 years (range: 12-72). Repolarization abnormalities were less common among DSC2 and DSP carriers as compared to PKP2 carriers (p=0.034 and p=0.027 respectively). In JUP homozygotes, depolarization abnormalities and right ventricular alterations were more common as compared to PKP2 carriers (p=0.001 and p=0.033 respectively). Left ventricular alterations were more common in DSC2 and DSP carriers as compared to PKP2 carriers (p=0.020 and p=0.019 respectively). Symptomatic disease presentation seemed to be delayed in carriers of DSC2 mutations particularly as compared with PKP2 carriers (p=0.065).
Conclusions: Electrocardiographic abnormalities predominate in ARVC/D due to desmosomal mutations. Repolarization abnormalities, with the best reported reproducibility, predominate in PKP2 whereas they are under-expressed in DSC2 and DSP mutations. Thus, DSC2 and DSP carriers risk escaping of diagnosis on ECG screening, although they present more frequently left ventricular involvement.

364 Clinical and functional consequences associated to a PKP2 founder mutation in north-west Spain

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Purpose: Mutations in Plakophilin-2 (PKP2) gene are the most frequent cause of arrhythmogenic right ventricular cardiomyopathy (ARVC). We found an identical PKP2 frameshift mutation in 7 out of 20 unrelated index cases with ARVC from a small region in north-west Spain. Our objectives were to describe the phenotype associated with this mutation and to study the cellular and molecular alterations of this mutation in cardiomyocyte cell lines.
Methods: Clinical and genetic evaluations were performed in 15 subjects from 7 unrelated families with the same PKP2 mutation (S329RfsX351). To study the cellular and molecular mechanisms implicated in the pathogenesis of PKP2 (S329RfsX351) we have generated two versions of lentivirus to express PKP2 (S329RfsX351); a fusion with monomeric red fluorescent protein mRuby and V5

tagged to distinguish mutated isoform vs. endogenous full length protein. We have used these lentivirus to establish HL1 and H9C9 cardiomyocite cell lines for in-vitro studies.
Results: PKP2 (S329RfsX351) was found in nearly 30% of ARVC index cases from our cohort. This mutation showed high penetrance since 9 of 10 mutation carriers (8 men) were clinically affected. Mean age at diagnosis was 40 years. All affected carriers had patent right ventricular abnormalities and 3 presented mild left ventricular systolic dysfunction (2 of them suffered an ischemic stroke). One carrier suffered an aborted cardiac arrest (aged 41 yo) and a patient with ICD implanted as primary prevention suffered an appropriate shock at age 51. The five relatives without the mutation were unaffected. Cellular analysis of cells expressing PKP2 (S329RfsX351) have shown that truncated PKP2 is not localized in desmosomal complexes, in contrast it appears in nuclei concentrated in heterochromatin complexes where gene transcription happens.
Conclusions: PKP2 (S329RfsX351) is a clearly pathogenic mutation and could represent a common founder effect in north-west Spain. Functional studies in PKP2 (S329RfsX351) suggest that this protein has potentially more functions than structural desmosoma assembly and its nuclear localization in heterochromatin complexes could be at least in part responsible of anomalous cardiomyocyte gene expression. Ongoing studies will try to understand the implication of nuclear PKP2 (S329RfsX351) in ARVC pathogenesis.

365 Twelve year follow-up of clinical screening and predictive genetic testing for hypertrophic cardiomyopathy in children and adolescents

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Background: Screening of children for inherited cardiovascular diseases is associated with medical, psychological, legal and ethical dilemmas. We studied the short- and long-term outcome of clinical screening and predictive genetic testing of child relatives included in family screening for hypertrophic cardiomyopathy (HCM).
Methods and results: Ninety probands and 361 relatives were included in family screening for HCM from 1994-2001. Ten sarcomere genes, CRYAB and Titin were screened. Sixty-six relatives and 4 probands were $<$ 18 years of age at the time of screening. No child relatives were diagnosed with HCM at the time of inclusion. Twelve child relatives were carriers (age 12$\pm$5 years), and 26 relatives "at risk" were from families without identified mutations (n=21) or not tested (n=5) (age 11$\pm$5 years). Twenty-eight non-carriers (age 10$\pm$4 years) served as controls. At follow-up (12$\pm$1 years) 17% of carriers were diagnosed with HCM. Another 50% of carriers had hypertrophy that did not reach the criteria for HCM. Six percent of relatives "at risk" had HCM at follow-up. There were no cardiac events among child relatives during follow-up. We found no differences in prevalence of anxiety, depression, type D personality and current distress in relation to the family screening between carriers and controls. The relatives "at risk", but not carriers, reported increased avoidance behavior in relation to the family screening program.
Conclusion: The majority of children carrying sarcomere gene mutations developed hypertrophy or HCM during puberty and early adulthood. Predictive genetic testing performed in the "best interest" of children seemed to have had no negative long-term psychological impact.

366 A novel type of hypertrophic cardiomyopathy in patients with C-terminal mutations in the four-and-a-half LIM-domain 1 gene: clinical presentation and prognostic implications

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Background: X-linked myopathy with postural muscle atrophy (XMPMA), a novel X-linked myopathy due to mutations in the Four-and-a-Half LIM Domain 1 gene (FHL1), is clinically associated with partial atrophy and generalized hypertrophy of skeletal muscle. The leading cause of death is respiratory and cardiac failure. Due to the X-linked mode of inheritance males mutation carriers (MMC) are more severely affected and frequently develop hypertrophic cardiomyopathy and cardiac arrhythmias. We examined the correlation of FHL1 genotype with cardiac phenotype to establish clinical and prognostic implications.
Methods and results: One large multigenerational Austrian and seven German families included 17 male XMPMA patients, hemizygous for FHL1 mutations, and 23 XMPMA-negative female first-degree relatives, heterozygous for FHL1 mutations. For comparison, 22 healthy age-matched male family members were included. Detailed examinations included electrocardiography, echocardiography, strain rate imaging for regional myocardial function, and MRI for possible myocardial hypertrophy and replacement fibrosis. ECG abnormalities occurred frequently in MMC (71% T-wave inversion in anterior leads, and in 53% Q-wave pathologies), and were less frequent in heterozygous females mutation carriers (FMC) (44% and 17% T-and Q-wave abnormalities, respectively). Left ventricular morphology showed that both MMC and FMC had increased myocardial mass (MMC=115.1$\pm$25.3 g/m^2; FMC=95.1$\pm$19.6 g/m^2; controls=89.0$\pm$15.6 g/m^2) and increased wall thickness, especially in the apical segments. Sixteen out of 17 MMC underwent cardiac MRI; 9 of those 16 had at least one late enhancement positive segment in MRI, indicating replacement fibrosis. As to myocardial function, MMC in particular presented with diastolic dysfunction, and longitudinal systolic function was reduced in both (radial systolic strain: MMC=24.6$\pm$11.8%; FMC=35.9$\pm$12.3%; controls=43.2$\pm$14.8%). All affected males had reduced exercise capacity on spiroergometry (VO2 max: 22.17$\pm$8.04 ml/(min*kg) vs. 27.28$\pm$5.77 ml/(min*kg) in controls, $p<0.05$).
Conclusions: XMPMA patients consistently showed electrical, functional and morphological cardiac abnormalities that translate into reduced exercise capacity. We demonstrate that the reduced systolic and diastolic function is related to left ventricular hypertrophy and myocardial fibrosis. An unexpected finding was, that some cardiac abnormalities were also present in FMC. This suggests that inheritance of XMPMA is not as previously reported X-linked recessive, but rather X-linked dominant with reduced penetrance and variable expressivity in females.

THROMBOSIS AND INFLAMMATION – GENETIC CONTROL MECHANISMS

417 MicroRNA profiling identifies miR-146a and miR-29a and their target genes CD40L and LPL in the regulation of oxLDL-treated dendritic cell maturation, inflammatory response and lipid uptake

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Aims: Increasing evidence shows that microRNAs (miRNAs) play important roles in cardiovascular research. However, whether miRNAs are associated with the immuno-inflammatory responses of atherosclerosis is yet unknown. Our study aimed to explore the linkage of miRNA with lipid overload and the immuno-inflammatory mechanism of atherosclerosis.
Methods and results: Microarrays were used to analyze the expression of miRNAs in oxLDL-stimulated dendritic cells (DCs), several miRNAs (microRNA-146a, microRNA-146b-5p, microRNA-155 and microRNA-29a, microRNA-1974) were aberrantly expressed after oxLDL treatment of human primary monocytes-derived DCs, those dysregulated miRNAs were also found to be upregulated in ApoE knockdown mice with atherosclerotic lesions compared with normol C57BL/6 mice using TaqMan real-time PCR. Moreover, we showed that miR-146a and miR-29a played an important functional role in lipid uptake, pro-inflammatory cytokine secretion and DC maturation process in oxLDL-treated DCs. Bioinformatics analysis suggested that miR-146a and miR-29a are related to CD40L and LPL, this was confirmed by a luciferase reporter assay. Significantly, we suggested an additional explanation for the mechanism of miR-146a and miR-29a regulation of their functional target: the down-regulation of CD40L and LPL by either miR-146a and miR-29a overexpression or inhibition of CD40L and LPL activity by siRNA had similar effects. Furthermore, the anti-miR-146a/29a-mediated functional effect on oxLDL-stimulated DCs was attenuated via the inhibition of CD40L and LPL by siLPL (Table 1).
Conclusions: Our novel approach identified and validated some miRNA protein networks involved in phenotypic and functional role of DC in atherosclerosis.

Abstract 413 – Table 1. Concentration of inflammatory cytokines secreted in 24h culture supernatants by stimulated human primary dendritic cells from pre-miR, anti-miR, pre-neg, anti-neg and sineg, siLPL, siCD40L

	pre-neg	pre-miR -29a	pre-miR -46a	anti-neg	anti-miR -29a	anti-miR -46a	anti-miR -29a+siLPL	anti-miR -46a+siCD40L	sineg	siCD40L	siLPL
IL-6 (ng/ml)	0.67$\pm$0.21	0.15$\pm$0.01*	0.35$\pm$0.02*	0.66$\pm$0.07	1.28$\pm$0.15$^{\#}$	1.32$\pm$0.16$^{\#}$	0.81$\pm$0.1$^{\#\#}$	0.9$\pm$0.12**	0.93$\pm$0.08	0.59$\pm$0.07$^{\&}$	0.51$\pm$0.06$^{\&}$
TNF-α (ng/L)	64$\pm$4.36	39.8$\pm$3.62*	35.6$\pm$2.98*	64.06$\pm$7.88	130.51$\pm$13.6$^{\#}$	108$\pm$12$^{\#}$	90.51$\pm$9.6$^{\#\#}$	60.1$\pm$9.6**	60.42$\pm$7.12	38.1$\pm$6.2$^{\&}$	35.52$\pm$4.8$^{\&}$

*$p<0.05$ compared to pre-neg group. $^{\#}p<0.05$ compared to anti-neg group, $^{\#\#}p<0.05$ compared to anti-miR-29a group, **$p<0.05$ compared to anti-miR-146a group, $^{\&}p<0.05$ compared to sineg group.

418 CXCR7 is expressed on the surface of platelets and mediates their adhesion on vascular wall after ischemia/reperfusion injury in vivo

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Introduction: Platelets play a pivotal role in both thrombosis and inflammation, and stromalcell-derived factor-1 (SDF-1) released at sites of inflammation inducesplatelet activation, aggregation, adhesion and migration. For many years, itwas believed, that CXCR4 was the only receptor for SDF-1. Recently, SDF-1 wasreported to also be a ligand of the novel chemokine receptor CXCR7.
Objectives: To evaluate the expression of CXCR7 in human platelets and toinvestigate the differential role of CXCR7 and CXCR4 on the adhesionof platelets on vascular wall after vascular injury.
Methods and results: Using confocalmicroscopy, flow cytometry and western blot analysis we could determine for thefirst time that CXCR7 is also expressed on the surface of human platelets,being significantly increased after ADP-induced platelet activation (resting plateletsvs. ADP-activated platelets: mean fluorescence intensity ± SD: 13.1±3.6 vs. 26.9±9.1, $P<0.05$).We further investigated the differential role of CXCR7 and CXCR4 onplatelet adhesion inareas of vascular injury with the help of intravital fluorescence microscopyin vivo. The common carotid arteryof C57BL/6J mice was injured by ligation and stained platelets were injectedintravenously. Preincubation of platelets with a blocking mAb toCXCR7, but not control IgG1 or anti-CXCR4, resulted in a decreased adhesion ofplatelets to the injured vessel wall ($P<0.05$). The differential role ofCXCR7 in the platelet-endothelium interaction was investigated in themicrocirculation of the small intestine of mice after ischemia/reperfusioninjury. The preincubation of platelets with a neutralizing anti-CXCR7, but notof control-IgG1 or anti-CXCR4, resulted in decreased adhesion of platelets inthe microvasculature ($P<0.05$).
Conclusions: CXCR7 isexpressed on human platelets and in contrast to CXCR4 regulates SDF-1mediated platelet adhesion in areas of vascular injury in vivo, a mechanism involved in vascularinflammation.

419 Influence of factor XIII v34l genotype on thromboelastographic parameters and permeability in whole blood clot

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Earlier investigations employing a flow measurement with plasma clots have showed interesting contributions of the FXIII V34L polymorphism to the fibrin polymerization. Little information is available concerning kinetic and characteristic features of whole blood clots depending on this genotype. We aim to assess the phenotype-genotype relation, kinetics, stability and permeability features of fibrin in whole blood clots.
Methods: Whole blood was drawn from 66 healthy volunteers, aged 33.0±8.1, in citrated tubes. Kinetic and stability characterization was assessed using a modified thormboeleastography (TEG) analysis (Rotem® delta, Pentapharm GmbH). TEG analysis (Extem, Intem and Fibtem) were performed for one hour within the following two hours of extraction. Results for clotting formation time (CFT) and maximum clot firmness (MCF) were recorded. Permeability was assessed in vitro whole blood clots (20mM CaCl2 and 0.12U thrombin, 120 min in a wet chamber) connected to a sealed container with buffer (0.05M Tris-HCl, 0.15M NaCl, pH7.5). Elution volume flowing through the clot for one hour was recovered. All the measurements were performed in duplicates (variation coefficient <10%). Genotypes were determined by PCR and restriction analysis. Platelet count and fibrinogen levels were also analyzed according to standard methods.
Results: 39 individuals were V/V, 24 V/L and 3 L/L genotypes, without significant deviation from the Hardy-Weinberg equilibrium. Significant differences were observed among FXIII genotypes in CFT-Intem and MCF-Intem (p=0.011 and p=0.029, respectively). Permeability negatively correlated with MCF-Intem (r= -0.48), as well as MCF-extem (r= -0.51), MCF-Fibtem (r= -0.67) (all $p<0.001$), and fibrinogen levels (r= -0.33, p=0.021), although we were not able to find permeability differences between genotype groups. We found no differences in fibrinogen and platelets count between genotypes. MCF-Extem and MCF-Fibtem were also positively correlated with fibrinogen levels (r=0.31 p=0.024, and r=0.41 p=0.002, respectively).
Conclusions: Homozygotes for 34L allele produce stable whole blood clots slower than 34V allele carriers as show CFT results. Clot firmness was also lower when the stable clot is formed. Such results are in concordance with previous results showing differences in fibrin polymerization related to underlying FXIII genotype. TEG is a reproducible method for evaluation of phenotype-FXIII genotype relationship on whole blood samples. No previous studies on whole blood have assessed the FXIII genotype influence on the TEG parameters despite further physiological features than plasma clots.

420 Recurrent arterial thrombotic events are associated with prothrombin gene G20210A variant

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Background: Factor V Leiden (FVL) and prothrombin G20210A mutation (PT G20210A) are the two most common genetic polymorphisms known to predispose an increased risk of recurrent venous thromboembolism (VTE) after a first event. Whether individuals with this genetic background have an increased risk of recurrent arterial thrombosis is uncertain.
Aim: To define the recurrence rates of arterial thrombotic events in patients with FVL and prothrombin PT G20210A.
Methods: The study population included 225 consecutive patients (51.3±11.9 years; 117 male) who were referred to our Unit for genetic testing after an acute episode of arterial thrombosis. For each patient, we retrospectively analyzed clinical history of previous episodes of arterial and venous thrombosis. Genotyping analysis was performed by using a multiplex allele-specific polymerase chain reaction assay (Nuclear Laser Medicine).
Results: In our population, we detected 62 (27.5%) and 10 (4.4%) patients who suffered from recurrent arterial thrombotic events and VTE, respectively. Patients with recurrent events had significantly higher age than patients with a first episode ($p<0.0001$). The frequency of patients carrying FVL (6.9% vs. 5.2%) and PT G20210A (12.5% vs. 3.9%) variants were higher in patients with recurrent events than in patients without recurrence. Specifically, heterozygosity for the prothrombin G20210A variant had a 4-fold increased risk (95% confidence interval, 1.2 to 14.6) of recurrent arterial events compared with noncarriers after adjustments for age, gender, and other vascular risk factors.
Conclusion: Our data demonstrates that prothrombin G20210A heterozygosity is associated with an increased risk for recurrent arterial thrombosis. Testing for prothrombotic mutations may provide critical information for optimal management of patients in the clinical setting.

421 Interleukin 10 1082 G>A polymorphism as a risk factor for coronary artery disease

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Background: Atherosclerosis is believed to be a chronic inflammatory process characterized by lipid accumulation in the arterial wall. Pro-inflammatory cytokines TNF-alpha and IL-6 have been localized in atherosclerotic plaques, and seem to play a role in the development of atherosclerosis. On the other hand, interleukin-10 (IL-10) suppresses immune and inflammatory responses, predominantly by influencing macrophage function, e.g. by inhibiting cytokine synthesis. In experimental models in mice a direct influence of IL-10 on atherosclerotic plaques was demonstrated by inhibiting chronic inflammatory events in lesions and preventing thrombotic complications. It has recently been shown that intranasal administration of an ApoB-fusion protein led to a 35% reduction in aortic lesion size in ApoE(-/-) mice, and was accompanied by the induction of regulatory T cells that markedly suppressed effector T cells rechallenged with apoB-100 and increased numbers of IL-10+ CD4+ T cells. Moreover, in IL-10 knock-out mice, absence of IL-10 leads to an increase in susceptibility to atherosclerosis. Transgenic mice overexpressing IL-10 had significantly less atherosclerotic lesions as compared to wild type mice. It is therefore possible that a promoter polymorphism known to lead to a decreased expression of IL-10 plays a role in the pathogenesis of atherosclerosis which we have addressed in the study reported here.
Methods: 164 patients with coronary three vessel disease (coronary artery disease - CAD - group) were compared to 243 healthy controls examining the distribution of genotype frequencies of a gene polymorphism in the promoter region of IL-10 (IL-10 1082).
Results: IL-10 1082 genotypes carrying the G allele appeared with higher frequency in the CAD-group as compared to controls. This finding is in contrast to those reported by others in 2001, but confirms findings reported in 2005 where a similar association between a matched control group comprising patients with severe CAD preparing for bypass surgery and a population control group were found. In the former study patients were included with angiographically proven CAD of at least one coronary artery. Although not stated in detail, severity of CAD was probably less pronounced in that study as compared to the present study.
Conclusion: The study raises the possibility of a correlation between the IL-10-1082_G allele and the presence of severe coronary artery disease in a German population. The functional IL-10-1082 polymorphism correlates with altered IL-10 levels and might influence susceptibility to atherosclerosis by altered inflammatory responses.

422 Effect of PON1 and CYP2C19 genetic variants on clinical outcomes in young patients treated with clopidogrel after myocardial infarction

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Background: Reduced concentrations of clopidogrel active drug metabolite have

been associated with diminished platelet inhibition and higher rates of adverse cardiovascular events. Paraoxonase-1 (PON1) has recently been proposed as a key enzyme for clopidogrel metabolic activation. We evaluated the effect of PON1 genetic variants on the occurrence of cardiovascular outcomes in clopidogrel-treated coronary patients.
Methods: We performed PON1 (Q192R and L55M)and CYP2C19 (*2 to *6) genotyping in 375 young post-MI patients (aged <45years at the time of MI) enrolled in the AFIJI cohort. The primary endpoint was a composite of death, myocardial infarction and urgent coronary revascularization occurring during clopidogrel exposure. Pharmacodynamic response to clopidogrel 75mg/d maintenance dose was assessed using VerifyNowP2Y12 assay in a subset of patients.
Results: The rate of the primary endpoint was similar in PON1 QQ192 homozygous patients, QR192 heterozygous or RR192 homozygous. The number of events according to genotype was QQ192: 14/169; QR192 14/151 and RR192: 8/55 (HR for R192 allele carriers versus non-carriers: 1.21 95%CI[0.60-2.44], p=0.59). Similarly, there was no significant influence of the PON1 L55M variant (HR for L55 allele carriers versus non-carriers: 0.60 95%CI[0.30-1.18], p=0.13). In contrast, the primary endpoint occurred more frequently in carriers of CYP2C19 loss-of-function alleles (HR for CYP2C19 loss-of-function allele carriers versus non-carriers: 3.10 95%CI [1.52-6.30], p=0.001). In regression analyses, the presence of CYP2C19 loss-of-function alleles was the only significant predictor of pharmacodynamic response to clopidogrel.
Conclusions: In contrast to CYP2C19 loss-of-function genetic variants, PON1 genetic variants do not appear to influence clinical outcome nor clopidogrel antiplatelet response in young post-MI patients.

POSTER SESSION 1

ANGIOGENESIS, ARTERIOGENESIS AND VASCULAR REMODELING

P431 Enhanced endothelial differentiation of endothelial progenitor cells with cilostazol and effect of combined cell therapy with cilostazol in murine hindlimb ischemia

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Purpose: Cilostazol is an antiplatelet agent with vasodilating effect. We and others have reported that it could promote angiogenesis. In this study, we investigated the effects of cilostazol on endothelial progenitor cells (EPCs) and hybrid therapy in murine hindlimb ischemia.
Methods: Various concentrations of cilostazol were added 3 days after isolation and culture of human early EPCs. Colony-forming units were counted 7 days later. Total ribonucleic acid was extracted from EPCs treated without or with cilostazol and subjected to reverse transcription-polymerase chain reaction analysis of endothelial NO synthase (eNOS), vascular endothelial growth factor-receptor 2 (VEGF-R2), and CD31. Eight-week-old male severe combined immunodeficiency mice were divided into 4 groups (vehicle, EPCs only, cilostazol only, and EPCs plus cilostazol, respectively). One million of culture-expanded EPCs were transplanted by multiple intramuscular injections one day after hindlimb ischemia. Single doses of cilostazol (10 mg/kg) were injected intraperitoneally before hindlimb ischemia and everyday for 7 days. Flow recovery in ischemic limbs was measured and capillary density was counted. Phosphorylation of eNOS and Akt in ischemic muscle was performed by immunoblotting. Immunofluorescence staining of ischemic muscle was scanned for incorporation of transplanted cells into circulating vessels.
Results: Cilostazol (30 μM) treatment significantly increased the number of colony-forming units of EPCs by 2.5 folds (25.2±0.9 vs 10.8±0.5 cells/well, $p<0.05$) and expression of eNOS, VEGF-R2, and CD31 as compared to negative control. Blood flow recovery ratio (ipsilateral/contralateral) and capillary density after 14 days in the ischemic hindlimb were highest in EPCs plus cilostazol-treated mice (0.68±0.09; 3588±78 particles/mm^2) than cilostazol only (0.48±0.01; 2991±49 particles/mm^2), EPCs only (0.35±0.03; 2788±49 particles/mm^2), and vehicle (0.21±0.02; 2010±11 particles/mm^2, all $p<0.05$ vs vehicle, respectively), which were attenuated by an eNOS inhibitor injection. Hybrid therapy had the upmost effect on phosphorylation of eNOS and Akt in ischemic muscle. Human CD31+ cells were mostly located around but far from host capillaries in EPCs only; however, they formed more capillaries with host endothelial cells in hybrid therapy.
Conclusions: Cilostazol has significantly beneficial effect on endothelial differentiation in EPCs. It promotes vasculogensis of transplanted human EPCs in murine hindlimb ischemia partly mediated by activating Akt/eNOS signaling pathway and enhancing incorporation of EPCs into neovascularization site.

P432 MicroRNA-100 regulates neovascularization by suppression of mammalian target of rapamycin in endothelial and vascular smooth muscle cells

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Background: The adaptive growth of blood vessels is an important protective mechanism in cardiovascular disease. However, the underlying regulatory mechanisms of this process are only partly understood. Recently, small endogenous RNAs (microRNAs) were found to play an important role in embryonic and postnatal vascular development. Here, we used microRNA-transcriptome analysis following induction of hindlimb ischemia in mice to screen for microRNAs involved in adaptive blood vessel growth following arterial occlusion.
Methods and results: Using microRNA-arrays, we explored the microRNA-expression profile during adaptive neovascularization. We describe specific changes in microRNA-expression patterns and show that the microRNA-100 is significantly downregulated after induction of hindlimb ischemia in mice. Our data demonstrate that miR-100 modulates proliferation, tube formation and sprouting activity of endothelial cells and migration of vascular smooth muscle cells and functions as an endogenous repressor of the serine/threonine protein kinase mTOR. Whereas miR-100 inhibition increased mTOR-levels in endothelial cells, overexpression of miR-100 reduced mTOR-expression and consequently attenuated cellular proliferation. Supporting this notion, overexpression of an mTOR-construct lacking the miRNA-binding site rescued the inhibitory effect of miR-100 on cell proliferation. Accordingly, miR-100 inhibition by specific antagomirs in vivo stimulated angiogenesis and resulted in functional improvement of perfusion after femoral artery occlusion in mice. In contrast, treatment with the mTOR-inhibitor rapamycin had the opposite effect.
Conclusion: Our data demonstrates that miR-100 has an anti-angiogenic function and represses mTOR-signalling in endothelial and vascular smooth muscle cells. Inhibition of miR-100 could be a novel approach for the modulation of blood vessel growth and other mTOR-dependent processes.

P433 Impact of the NAMPT-SIRT1 axis for myocardial regeneration

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Introduction: The nicotinamide adenine dinucleotide (NAD)-dependent classIII histone and protein deacetylase Sirt1, functions in a wide array ofcellular processes, including protection from oxidative stress and apoptosis. Furthermore-SIRT1 seems to be critical for angiogenic activity in endothelial cells (EC). However,the endogenous expression and activity of Sirt1 as well as the regulating-mechanisms in the ischemic heart remain elusive.
Methods & results: Toinvestigate the mechanisms which regulate Sirt1 expression and activity in theischemic heart in vivo we inducedmyocardial infarction by ligating the left coronary artery (LAD) of C57/Bl6 mice. After 24,48h and 72h mice were euthanized and ischemic myocardium was identified byretrograde injection of evans blue dye and dissected for further evaluation. Atall timepoints Sirt1 enzymatic activity decreased in a time-dependent manner. Inparallel, NAD(+)-levels in the ischemic myocardium were significantly decreased. The cellular NAD+ synthesisis regulated by both the de novo and the salvage pathways. Since only thesalvage pathway regulates NAD-levels under ischemic conditions, we focused onthe molecules of this pathway to elucidate the mechanisms which regulatecellular NAD content under ischemic conditions. Real-timePCR analysis revealed a downregulation of the rate-limiting enzyme in thesalvage pathway of NAD synthesis, Nicotinamide phosphoribosyltransferase (Nampt) at 24, 48 and 72h after induction of myocardial infarction as aprobable cause for the reduced NAD-levels invivo. Moreover, miR-374 was identified to regulate Nampt on apost-transcriptional level: miR-374 was significantly upregulated aftermyocardial infarction. A knockdown of miR-374 by a specific o-methylatedmiRNA-inhibitor in vitro resulted inan upregulation of Nampt levels in human coronary artery endothelial cells. Moreover,sprout formation was significantly increased following miR-374 knockdown.
Conclusions: In summary, we identified miR-374 as a keyregulator of NAMPT and thus SIRT1-activity which regulates angiogenesis andmyocardial regeneration following MI.

P434 Improved limb perfusion and neovasculogenesis mediated by intramuscular infusion of erythropoietin is mediated by local expression of angiogenic factors

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Purpose: Angiopoietin (Ang) -1 and -2, their receptor Tie-2,and vascular endothelial growth factor (VEGF) regulate angiogenesisand may be important in myocardial collateral development. In this study weinvestigated whether direct intramuscular infusion of erythropoietin (EPO), alteredthe local balance of the an-

giopoietins and VEGF and improved limbperfusion in a murine model of hind limb ischemia.
Methods: Wild type C57BL/6 male mice underwent unilateral hind-limb ischemia, were divided in two groups (n=14/group)and received either EPO or normal saline intramuscularly (im). Each group mice underwent Laser Doppler perfusion Imagingon days 1, 7 and 28 after surgery for the estimation of the bilateral hind-limb perfusion. At day 28 they weresacrificed and quantitativereal time RT-PCR was performed to the muscle tissues from both limbs to analyzethe differential gene expression of vascular endothelial growth factor (VEGF),Tie-2, Ang-1 and Ang-2. Muscle tissue sections were stained with rat anti-CD31antibody. Capillariesand arterioles in the ischemic areas were counted with confocal microscopy atday 28.
Results: Ischemic/non-ischemic ratio was significantlyincreased in ischemic limbs of EPO-treated mice versus control miceat 7 days ($p<0.01$ vs control for EPO), which was maintained at 28 days ($p<0.02$ vs control). Capillary density was increased in the EPO-treatedgroup compared to control (2,01±0.65 vs 0.69±0.49 cap/cm^2 $p<0.05$). Comparedto the control group, in the ischemic limbs of the Epo-treated group there wasa significant elevation in the expression of VEGF (9.1±0.4 vs 13.2±0.7 RLU, p=0.01), Ang-2 (10.3±0.9 vs 14.7±0.3 RLU, p=0.04) and sTie-2 (11.2±0.4 vs 15.6±0.8, p=0.03) respectively. Incontrast, the Ang-1 expression didn't significantly differ between the twogroups (10.2±0.8 for the Epo-treated group vs 9.7±0.6 for the control group).
Conclusions: Erythropoietin treatment improvesperfusion in ischemic limbs, promotes vasculogenesis and increasesneoangiogenesis by upregulation of the Ang-2/Tie-2 pathway. These findingssuggest that erythropoietin exerts beneficial effects on muscle neoangiogenesisand perfusion after limb ischemia by interfering with the local expression ofangiogenic factors.

P435 Connexin 43 acts as a counter regulatory molecule of caveolin-1 via activation of MEK/ERK pathway

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Background: Apart from an important component of the gap junction, connexin 43 (Cx43) has been known to regulate other cellular functions like cell proliferation. This regulatory role of Cx43 could be of much importance in therapeutic angiogenesis. On the other hand, recently it has been shown that caveolin-1 (Cav-1) acts as a negative regulator of angiogenesis. The aim of the present study was whether Cx43 acts as a counter regulator of Cav-1 in the control of endothelial cell proliferation and migration.
Methods: Study was performed on cultured human umbilical vein endothelial cells (HUVEC). Niflumic acid, flufenamic acid and 18-α-glycyrrhetinic acid were used as Cx43 inhibitors. PD98059 was used as a MEK1/2 inhibitor. Downregulation of caveolin-1 was carried out by siRNA transfection. Proliferation, migration and sprouting of endothelial cells were quantified by crystal violet staining, migration assay, and spheroid sprouting assay, respectively.
Results: Inhibition of Cx43 with niflumic acid, flufenamic acid and 18-α-glycyrrhetinic acid (50 μM for 48 hrs) in HUVEC resulted in a decreased phosphorylation of p42/44 MAPK and increased expression of Cav-1. Furthermore, inhibition of Cx43 resulted in 50±7% decrease (n=5; $p<0.05$ for all further parameters) in cell proliferation, 48±5% decrease in migration, and 49±6% decrease in endothelial cell sprouting compared to control. Similar results were obtained with specific inhibition of Cx43 by mimetic peptides (Gap26 and Gap27; 0.25 μg/ml). Accordingly, inhibition of MEK/ERK pathway with PD98059 (10 μM, 48 hrs) resulted in an increased expression of Cav-1, a reduction in Cx43 expression and impaired cell proliferation, migration and sprouting of endothelial cells. Contrariwise, down-regulation of Cav-1 by small interference RNA resulted in an increased expression of Cx43 and increased phosphorylation of p42/44 MAPK. Accordingly, the cell number increased by 35±5% compared to controls.
Conclusion: The data of the present study show that cav-1 suppresses the cell proliferation via suppression of Cx43 activity upstream to p42/44 MAPK. Knockdown of Cav-1 results in loss of this suppressive activity of Cav-1 and cells undergo cell cycle progression. This counter regulatory role of Cx43 can be of importance in therapeutic angiogenesis.

P436 Androgens stimulate endothelial progenitor cell-mediated angiogenesis and are associated with increased human coronary collateralization

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Purpose: The role of androgens in cardiovascular diseases remains controversial. Recent studies have described an inverse relationship between androgen levels and cardiovascular mortality in men. Endothelial progenitor cells (EPCs) are important for angiogenesis, and it has been linked to cardiovascular outcomes. We hypothesize that androgen plays a role in enhancing human male angiogenesis through EPC.
Methods: EPCs were isolated from healthy young male donors (n=12), and treated with dihydrotestosterone (DHT, 4-400nM),±androgen receptor (AR) antagonist, hydroxyflutamide, ±oestrogen receptor antagonist, ICI182780, and their functions were assessed. To assess angiogenesis in vivo, DHT-treated Early- and Late-EPCs were xenotransplanted into BalbC nu/nu male mice following hindlimb ischemia. Male patients (n=15) having elective percutaneous coronary intervention were recruited to assess coronary collateralization, including collateral flow index (CFI).
Results: DHT induced a dose-dependent increase in ulex-lectin+/AcLDL cells ($P<0.05$), in Early-EPC migration ($P<0.05$) and tubulogenesis ($P<0.001$). Hydroxyflutamide completely abolished DHT-mediated effects on Early-EPC number and migration; ICI182780 had no effect. Similar findings were also observed for Late-EPCs (all $P<0.05$). Mice xenotransplanted with Early-EPCs treated with 400nM DHT showed better recovery using Doppler imaging at Day14 ($P<0.05$) and Day21 ($P<0.05$) post-surgery than control mice, and mice xenotransplanted with DHT treated Late-EPC showed even more robust response ($P<0.02$ at Day 14 and 21). In the human coronary collateral study, free testosterone levels correlated significantly with CFI (r=0.786, P=0.021). No relationship was established between oestradiol and CFI. Free testosterone levels correlated negatively with Early-EPC (r= -0.78, P=0.036), but positively with Late-EPC (r=0.9, P=0.037) number.
Conclusions: This study provides in vitro, in vivo, and clinical evidence of proangiogenic effects of androgen. These effects are likely to be mediated through AR on Late-EPCs. This study highlights the potential benefit of androgen replacement for men's cardiovascular health.

P437 Smooth muscle cell specific deletion of HIF-1alpha results in an unstable plaque phenotype after vascular injury in apoE deficient mice

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Purpose: Hypoxia inducible factor (HIF)-1alpha is a transcription factor which is upregulated following vascular injury and plays an essential role in neointima formation probably through the recruitment of smooth muscle progenitor cells (SPCs). The role of cell-type-specific HIF-1alpha activation, however, is unknown. We studied the function of smooth muscle cell (SMC) specific HIF-1alpha in neointima formation.
Methods: Smooth muscle myosin heavy chain (SMMHC)-CreT+/HIF-1alpha flox/flox/ApoE-/- (SMC-HIF KO) mice and SMMHC-CreT+/HIF-1alpha WT/WT/ApoE-/- (SMC-HIF WT) mice were treated with tamoxifen (IP, 1mg/20g/day for 6days) to induce SMC specific HIF-1alpha deletion. Wire induced injury of the carotid artery was performed in SMC-HIF KO and SMC-HIF WT mice fed a western type diet (8-9 week old males, N=8-9 each group). To verify the knock down of HIF-1alpha, qRT-PCR was performed in carotid artery samples which were harvested 6 hrs following injury. The peripheral Sca1+/Lin- SPC population was quantified before and 1 day after injury in the circulation by flow cytometry. The neointimal area was analyzed after 28 days in Elastic Van Gieson stained sections by morphometry. Furthermore, immunostaining for Mac-2 and smooth muscle actin (SMA) was performed to study the cellular plaque composition.
Results: Tamoxifen treatment reduced the HIF-1alpha mRNA expression after carotid injury by 76% in the SMC-HIF KO mice as compared to control. Double immunostaining for HIF-1alpha and SMA revealed that the knock down was SMC-specific. The injury-induced mobilization of SPCs at one day is not affected by the SMC specific HIF-1alpha knock down. In SMC-HIF KO mice, the neointimal area was not significantly different from SMC-HIF WT mice (0.033±0.002 versus 0.033±0.004 mm^2, N=8-9 each group, P=0.98). The loss of SMC specific HIF-1alpha increased the neointimal Mac-2-immunopositive area by 45% (19.0±3.4 versus 34.4±7.1%, N=5-8 each group, $P<0.05$) without altering the number of Mac-2+ cells (25.1±3.2 versus 25.7±4.6%, N=4-6 each group, P=0.92). In addition, HIF-1alpha deletion reduced the neointimal SMC content by 27% (19.1±1.6 versus 13.9±0.9%, N=5-7 each group, $P<0.01$).
Conclusions: SMC-specific HIF-1alpha deletion produces an unstable plaque phenotype following vascular injury due to a reduced accumulation of SMCs and an increased macrophage cell size, probably through enhanced lipid accumulation. Thus, HIF-1alpha activation in SMCs might play a protective role in plaque formation partly through anti-atherogenic effects on macrophages.

P438 MiR-126 deficiency augments neointima formation following arterial injury in ApoE-/- mice

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Purpose: We aimed to study the role of miR-126 in neointima formation and vascular repair after endothelial denudation.
Methods: Wire-induced carotid injury was performed in miR-126-/-/ApoE-/- (miR-126-/-) and miR-126+/+/ApoE-/- (miR-126+/+) mice fed a western-type diet. MiR-

126-3p and miR-126-5p expression after vascular injury was studied by quantitative RT-PCR. Carotid arteries were harvested following in-situ perfusion with paraformaldehyde at 7, 14, and 28 days after vascular injury. In addition, miR-126+/+ and miR-126-/- mice after reciprocal bone marrow (BM) transplantation were studied after wire injury. MiR-126+/+ mice transplanted with miR-126+/+ BM cells were used as controls. The neointimal area was determined by morphometry in carotid sections stained with Movat's pentachrome. Quantitative immunostainings were performed for cell-specific markers, such as SM22 (smooth muscle cells, SMCs), macrophages (Mac-2), and endothelial cells (von Willebrand factor, CD31).
Results: The expression of miR-126-3p, miR-126-5p, and premiR-126 was reduced at day 1 and again up-regulated from day 7 on. Whereas the neointimal area was not different between miR-126-/- and miR-126+/+ mice at 7 days after vascular injury, a 2-fold increase of the neointima was detectable in the absence of miR-126 after 14 and 28 days (N=5-7; $P<0.05$). The neointimal macrophage content was 2.2-fold higher and the endothelial coverage reduced by 31% in miR-126-/- mice after 28 days ($P<0.05$), whereas the SMC accumulation was not affected. The neointimal area in miR-126-/- recipients with miR-126+/+ BM was increased 2-fold, whereas in mice with miR-126-/- BM the neointimal size was not different from miR-126+/+ mice with miR-126+/+ BM. The medial area, however, was increased in mice with miR-126-/- BM due to increased macrophage accumulation. Furthermore, the re-endothelialization was significantly reduced only in miR-126-/- recipient mice ($P<0.05$).
Conclusions: The absence of miR-126 critically impairs endothelial recovery after arterial injury which results in accelerated neointima formation and increased neointimal macrophage accumulation. Thus, miR-126 plays a protective role in vascular repair and might provide a promising therapeutic tool to limit restenosis.

P439 Effect of small hairpin RNA molecules targeting endothelin-converting-enzyme-1 in monocrotaline-induced pulmonary hypertensive rats

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Purpose: Pulmonary hypertension is characterised by elevations in pulmonary artery pressure and pulmonary vascular resistance. The two pathological features that are common are abnormal pulmonary vasoconstriction and pulmonary vascular remodelling. The purpose of the present study was to investigate the therapeutic effects of an small hairpin RNA (shRNA) molecules targeting endothelin converting enzyme-1 (ECE-1) in monocrotaline (MCT)-induced pulmonary hypertension in rats.
Methods: Sprague-Dawley rats were treated with a subcutaneous normal saline (control group), with a subcutaneous MCT (60mg/kg, MCT group), and with MCT + recombinant lentiviral vectors carrying shRNA targeting ECE-1 (shRNA group). Mean right ventricular pressure (RVP) was estimated. Histologic, immunohistochemial, western blot and RT-PCT analyses were performed in the lung tissues. To assess the effects of shRNA targeting ECE-1 on the time course, hearts and lungs were dissected after 4, 7, 14, or 28 days.
Results: The mean body weights of the MCT- and shRNA-treated rats were significantly lower than that of the control group on days 4, 7 and 28. Compared to control group, MCT group showed a marked increase in mean RVP on days 4, 7, 14 and 28. These group also showed increase in right ventricle/(interventricular septum+left ventricle [RV/(IVS+LV)] ratio on days 7, 14 and 28, indicating marked RV hypertrophy. The shRNA group showed a significant improvement in mean RVP days on 4, 7, 14 and 28, but no differences were observed in RV/(IVS+LV) ratio, lung weight, and mean arterial pressure. The serum concentration of ET-1 was significantly lower in shRNA group. The expression of ECE-1, ET (endothelin)-1 and ETA receptor of the lung were significantly increased in MCT group on days 14 and 28. The expression of ETA receptor was significantly decreased in shRNA group on day 14, but other gene expressions did not changed in shRNA group. Quantitative analysis of peripheral pulmonary arteries revealed that medial wall thickness was significantly increased after MCT injection, and significantly decreased in shRNA group on days 14 and 28. The number of intra-acinar muscular arteries after MCT injection was significantly decreased in shRNA group on day 14.
Conclusions: Recombinant lentiviral vectors carrying shRNA targeting ECE-1 prevented RVP and RV hypertrophy, exerted an anti-proliferative effect on pulmonary artery smooth muscle cells. Our results indicate that this treatment modality is a promising that could protect against hemodynamic and histopathological changes in pulmonary hypertension.

P440 Physical exercise prior to femoral artery ligation stimulates collateral artery growth in an nitric oxide-dependent manner

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Background: Physical exercise is an important cornerstone in cardiovascular prevention and therapy. Following arterial occlusion, exercise increases collateral flow by enhancing fluid shear stress. The effects of physical exercise prior to arterial occlusion on collateral artery growth are currently unknown.
Methods and results: Mice were subjected to four weeks voluntary treadmill running before unilateral femoral artery ligation (FAL). Animals ran 4.0±0.4 km/day until FAL and 0.5±0.2 km/day thereafter. Hindlimb perfusion was assessed using pressure controlled infusion of fluorescent microspheres into the abdominal aorta under conditions of adenosine-induced maximal vasodilation, and expressed as percentages ligated/unligated hindlimb. Directly after FAL, perfusion fell to 3.5±0.7% in sedentary wildtype (C57/Bl6) mice. Exercise prior to FAL did not change perfusion acutely after ligation (4.0±0.8%), indicating that exercise did not lead to growth of pre-existing collateral anastomoses in their functional resting state. One week after FAL, perfusion was restored to 37.4±2.7% in the sedentary ("S") group. Exercise until the final experiment ("run", "R") augmented perfusion restoration to 52.8±4.1% ($p<0.005$ compared to sedentary). When exercise was stopped at the time of FAL ("run and rest", "RR"), perfusion recovery after one week was 50.3±4.7% ($p<0.001$ compared to S, p=ns compared to R). In collateral-containing hindlimbs, inflammatory cytokine mRNA expression was reduced (TNFalpha to 54±8% in R and to 39±7% in RR compared to S; MCP1 to 26±5% in R and to 20±6% in RR compared to S. mRNA-expression of inducible NO-synthase (iNOS) was increased to 179±40% ($p<0.05$) in R and to 172±34% ($p<0.05$) in RR mice. Endothelial NO-synthase activity (phospho-eNOS/total eNOS protein) was increased to 211±46 ($p<0.05$) in R and to 211±35% ($p<0.05$) in RR animals. We thus investigated the effects of physical exercise in eNOS-/- and iNOS-/- mice. eNOS-/- sedentary mice showed a strongly impaired perfusion restoration to 4.3±1.0% one week after FAL, which was stimulated by prior exercise (RR) to 8.2±0.8% ($p<0.01$ compared to S). iNOS-/- mice, while showing near to normal perfusion restoration at sedentary conditions (30.5±3.2%), failed to increase perfusion restoration by exercise.
Conclusion: Physical exercise before femoral artery occlusion reduces inflammatory cytokine expression and stimulates collateral artery growth in an NO-dependent manner. These data underline the vascular risk profile associated with a sedentary lifestyle and identify exercise as a prophylactic means to enhance vascular growth.

P441 A hyaluronidase inhibitor attenuates the development of experimental abdominal aortic aneurysm by modulating the interaction between hyaluronic acid and CD44

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Background: Abdominal aortic aneurysm (AAA) is a common disease characterized by mobilization of inflammatory cells into vessel walls, leading to degradation of extracellular matrix (ECM). Hyaluronic acid (HA) is one of major ECM components in vessel wall. Recently, small fragmented HA by degradation has been shown to play an important role in inflammation through CD44, a principal receptor of hyaluronic acid. We investigated whether HA fragmentation contribute to the pathogenesis of the development of AAA in mice.
Methods: For induction of AAA, we applied 0.5 M CaCl2 to the infrarenal aortae of mice. Aortic diameters and aortic tissues were assessed after six weeks in CD44-deficient mice, wild-type (WT) mice, and WT mice treated with a hyaluronidase inhibitor, L-ascorbic acid 6-hexadecanoate (Vcpal).
Results: We first assessed HA metabolism in AAA lesion. In WT mice, six weeks after application of CaCl2, the increased expression of hyaluronidase 2 and hyaluronidase 3, and hyaluronan synthase 2 were observed. Electrophoresis also showed the increased in smaller size HA in AAA. For evaluating the role of HA degradation, Vcpal was given to the AAA model. The enlargement of aortic diameter in Vcpal-treated WT mice (n=8) was found to be significantly less than that in non-treated WT mice (n=10) (15%±24% vs. 53%±12%, $p<0.01$). In vitro experiment showed that Vcpal inhibited the HA fragmentation by hyaluronidase dose-dependently. Next, we evaluated the interaction between HA fragmentation and CD44 in AAA model. Six week after application of CaCl2, CD44-/- mice (n=8) showed less aortic dilatation than that in WT mice (n=10) (12%±13% vs. 53%±12%, $p<0.01$). The elevated aortic expression of matrix metalloproteinase (MMP)-2, -9, and monocyte chemotactic protein-1 in WT mice were significantly reduced in CD44-/- mice. The recruitment of macrophages to AAA lesion in WT mice was found to be significantly greater than that in CD44-/- mice. Finally we found that low-molecular-weight (fragmented) HA, but not high-molecular-weight (non-fragmented) HA stimulated MMP-9 production in peritoneal macrophages, considerably more than those from CD44-/-mice.
Conclusion: HA fragmentation contributes to the pathogenesis of the development of AAA in mice through CD44. The Vcpal, a hyaluronidase inhibitor, may be one of regulators that maintain HA homeostasis, and thus the inhibition of HA fragmentation may have therapeutic potentials.

P442 Relationship between epicardial adipose tissue and coronary arterial remodeling as assessed by intravascular ultrasound in patients with coronary artery disease

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Background: Recently, the interest in epicardial adipose tissue (EAT) is rapidly

growing. Several study suggest that EAT induces inflammation of the artery wall by secretion of pro-inflammatory proteins and plays a role in the pathogenesis of coronary artery disease. However, there is no information regarding the impact of EAT on coronary arterial remodeling and plaque vulnerability.
Objectives: The aim of this study was to evaluate the relationship between EAT and intravascular ultrasound (IVUS) findings, mainly remodeling, in patients with coronary artery disease.
Methods: One hundred and eight consecutive patients with de novo lesions located in native coronary artery were studied. The EAT thickness on the right ventricle was measured using transthoracic echocardiography, and arterial remodeling of culprit lesion was assessed by preinterventional IVUS. The remodeling index (RI) was calculated as lesion divided by the reference external elastic membrane cross-sectional area, Positive remodeling (PR) was defined as RI$>$1.05, intermediate remodeling (IR) as between 0.95 and 1.05, and negative remodeling (NR) as $<$0.95. IVUS findings included plaque characteristics-lipid rich, mixed and calcified plaque and plaque eccentricity.
Results: There was significant relationship between EAT thickness and RI (r= 0.36, p=0.0001). Higher EAT thickness ($\geq$10mm, n=55) were associated with higher BMI (25.2$\pm$3.6kg/m^2 vs. 23.9$\pm$2.8 kg/m^2, p=0.04), plasma triglyceride level (189.1$\pm$103.8mg/dl vs. 146.1$\pm$80.9 mg/dl, p=0.02), and plasma urinary acid level (6.8$\pm$1.5mg/dl vs. 5.9$\pm$1.5 mg/dl, p=0.02). PR and more lipid rich and mixed plaque were observed in patients with higher EAT thickness than lower EAT thickness (PR; 43.6% vs. 18.9%, p=0.02. lipid rich and mixed plaque; 89% vs. 66%, p=0.004). Multiple analysis showed high EAT thickness was independent factors affecting coronary positive remodeling (OR3.05, p=0.02).There was no significant association EAT thickness and plaque eccentricity.
Conclusion: High EAT thickness was significantly correlated with the coronary positive remodeling and non calcified plaque characteristics.

P443 GLP-1 receptor agonist attenuates vascular remodeling after endovascular injury

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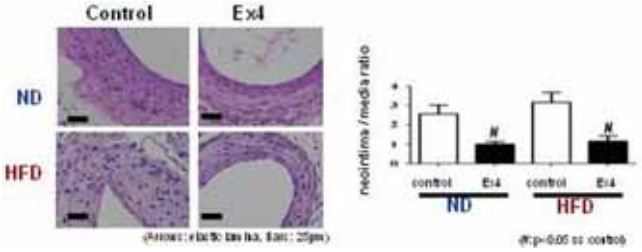
Purpose: It has been reported that exogenous administration of glucagon-like peptide-1 (GLP-1) or GLP-1 receptor agonists such as exendin-4 has direct beneficial effects on the cardiovascular system. However, the mechanism of their effect on vascular remodeling has not been elucidated. The aim of this study is to investigate the effects of GLP-1 on neointimal hyperplasia after the endovascular injury.
Methods: We performed wire-mediated endovascular injury of femoral arteries in C57BL/6 mice. We administrated exendin-4 (24nml/kg/day: Exendin group, n=10) or PBS (PBS group, n=10) with osmotic pump for 4 weeks after the injury. Mice received normal diet (360kcal/100g, 13% lipid) or high fat diet (506kcal/100g, 62% lipid) for 4 weeks.
Results: Exendin-4 treatment did not affect the body weight change, the serum lipid profile, and results of glucose tolerance test. Neointimal hyperplasia was significantly attenuated in Exendin group compared to PBS group (neointima/media ratio, 1.1$\pm$0.4 vs 2.9$\pm$1.4, p$<$0.05 in normal diet, 0.6$\pm$0.3 vs 3.2$\pm$1.4, p$<$0.05 in high fat diet). In vitro treatment of rat smooth muscle cells with exendin-4 suppressed PDGF-BB-induced cell proliferation, and this effect was reversed by either MDL-12330A, a cAMP inhibitor or PKI14-22, a protein kinase A-specific inhibitor.



Exendin-4 attenuated neointimal hyperpla.

Conclusions: Our data suggests that GLP-1 receptor agonists reduced neointimal hyperplasia after vascular injury by inhibiting the proliferation of smooth muscle cells, and that this effect may contribute to the attenuation of atherosclerotic lesion by Exendin-4.

P444 IGFBP-7 contributes to micro-vascular remodeling during hypertension development in spontaneously hypertensive rats

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Purposes: The aim of this study was to elucidate the potential new targets for vascular remodeling with hypertension and explore the role of Insulin-like growth factor-binding protein 7 (IGFBP-7) in micro-vascular remodeling in SHR.
Methods and results: In this study, we used the spontaneously hypertensive rats (SHR) as our animal model, the blood pressure were observed during the process, the micro vessel hypertrophy were detected, and the level of ET-1, NO were tested and the expression of VEGF, TGF-β1, PCNA, PKC, NOS in vessel tissue were observed during the development of remolding. Furthermore, we observed that the micro-vascular remolding occurred prior to major-vascular remolding. We analyzed the protein expression profiles of micro vessels in SHR of various degrees during the development of vascular remolding in hypertension, as well as in matched no treated SD rats, using a proteomic analysis of relative and absolute quantification (iTRAQ). The expressions of 33 proteins were altered 1.5-folds in SHR compared with no-treated rats. Of these proteins, Non-muscle caldesmon (CDM), Citrate synthase, Alpha-S1-casein, Alpha-S1-casein, Destrin (Actin-depolymerising factor) (ADF) and Insulin-like growth factor-binding protein 7 (IGFBP-7) were upregulated in SHR compared with contrast rats. The results from a PCR analysis revealed that the expression of the above protein meet the results respectively. The level of IGFBP-7 was more in remolding micro vessels from SHR than from rats without remolding. There are linkage between the expression of IGFBP-7 and vascular function and hypertrophy. Moreover, silence the expression IGFBP-7 treatment with siRNA technology inhibited vascular remolding in SHR, while over-expression of IGFBP-7 promote the vascular hypertrophy. Interesting, the expression of IGFBP-7 lead to the change of level of ET-1, NO, and the change of VEGF, TGF-β1 in vessel hypertrophy, so as to support the opinion of the role of IGFBP-7 in miro-vascular remodeling in SHR.
Conclusion: These results suggest that the IGFBP-7 is involved in vascular remolding in SHR and it may be the key target protein of vascular remolding during hypertension.

P445 Reduced wire-injury induced stenosis in the femoral artery of aging thromboxane receptor knockout mice

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Objective: Platelet activation, inflammation, vascular smooth muscle cell migration/proliferation and extracellular matrix remodelling are the most important events that lead to luminal stenosis following endovascular interventions. Neointimal hyperplasia has been described to be enhanced during aging, which may be in correlation with higher expression of thromboxane synthase and vasoconstrictor prostaglandins. Our aim was to evaluate the role of thromboxane receptor in the development of injury-induced arterial stenosis in young as well as in aging mice.
Methods: An angiography guide-wire (0.015 inch in diameter) was introduced into the predilated (1% lidocaine) muscular branch of the left femoral artery of male mice, pushed forward 8 mm and left in place for 2 minutes to dilate the artery. Four groups of animals have been studied: young wild type (C57Bl6, n=6, age: 113$\pm$21 days), aging C57Bl6 (n=8, age: 447$\pm$21 days), young thromboxane receptor knockout (TPKO, n=8, age: 110$\pm$26 days) and aging TPKO mice (n=8, age: 497$\pm$2 days). Animals were perfusion-fixed with 4% formaldehyde 14 days after the intervention, femoral arteries were embedded in paraffin and serial sections were made across the entire artery (every 0.5 mm). Sections were immunohistochemically stained for CD45 leukocyte marker, Ly-6G neutrophil marker, and alpha smooth muscle actin, and they were stained with haematoxylin-eosin to evaluate arterial stenosis.
Results: Two weeks after wire-injury, the average luminal stenosis did not differ significantly between young wild type (31.5% $\pm$ 10.2%) and young TPKO mice (34.9% $\pm$ 10.1%). In both cases, stenosis consisted mainly of neointimal cells and less inflammatory cells. The aging wild type mice developed a significantly greater stenosis compared to that of young wild type mice (53.0% $\pm$ 14.3% vs. 31.5% $\pm$ 10.2%, p$<$0.05), which consisted of more inflammatory cells and less neointimal cells. In aging TPKO mice, luminal stenosis was significantly reduced as compared to the aging wild type mice (30.3% $\pm$ 12.5% vs. 53.0% $\pm$ 14.3%, p$<$0.05) with similar proportion of inflammatory and neointimal cells. We did not notice significant difference in the occurrence of occlusive thrombosis between any types of mice studied.
Conclusion: According to our results, thromboxane receptor plays a more important role in the pathologic response to arterial injury in aging animals. This association may help to explain the different extent of injury-induced vascular stenosis in elderly compared with younger patients.

P446 CXCR4 antagonism is equally effective as sirolimus in reducing neointima formation after arterial injury without impairing re-endothelialization

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Background: The chemokine receptor CXCR4 (CXC motif receptor 4) is crucial in neointima formation, which is an issue in restenosis after stent implantation. Drug-eluting stents (e.g., coated with sirolimus) have reduced the restenosis risk, but delayed re-endothelialization promotes late stent thrombosis. We compared CXCR4 antagonism with sirolimus treatment in preventing neointima formation after arterial injury in mice.
Methods: Apolipoprotein E-/- mice after carotid wire injury were treated with a CXCR4 antagonist (POL5551 (P), a Protein Epitope Mimetic (PEM)) or sirolimus (n=6-8 per group). The drugs were administered either continuously (P: 2 and 20 mg/kg/d; sirolimus: 1.25 mg/kg/d) or intermittently (P: 20 mg/kg; IP, once daily) for 28 days. The neointimal area, smooth muscle cell (SMC) content, macrophage content, and endothelial coverage were quantified by planimetry of histological sections from injured arteries stained with Elastica van Giesson, or after immunostaining for α-smooth muscle actin, Mac-2, and von Willebrand Factor, respectively. Peripheral Sca-1+/Lin- smooth muscle progenitor cells (SPCs) were measured by flow cytometry.
Results: Sirolimus treatment for 28 days reduced the neointimal area greatly compared to vehicle (69%). Similarly, continuous (C) and intermittent (I) treatment with a high (H) or low (L) dose (D) of POL5551 (P) for 28 days reduced the neointimal area compared to corresponding vehicle (CHD-P: 70%, CLD-P: 63%, I-P: 53%). Treatment with I-P for just 3 days did not affect the neointimal area.
The neointimal macrophage content markedly increased by sirolimus application (70%). In contrast, the macrophage content decreased by CHD-P and I-P application (57% and 37%, respectively). However, CLD-P application did not alter the macrophage accumulation.
Sirolimus, CHD-P, and I-P highly diminished the neointimal SMC content (78%, 85%, and 67%, respectively), while CLD-P treatment did not. SPC increase in the circulation 1 day after injury was prevented in mice given sirolimus, CHD-P, and I-P, but not in mice given CLD-P.
The endothelial coverage was significantly reduced by 14% in sirolimus-treated mice, whereas no POL5551 treatment impaired the re-endothelialization.
Conclusions: CXCR4 antagonism by POL5551 is equally effective as sirolimus in reducing neointima formation after arterial injury in mice. POL5551 might be more beneficial than sirolimus because it leads to a more stable lesional phenotype and, of note, does not impair re-endothelialization. These results indicate that POL5551 might be a promising alternative to sirolimus for restenosis prevention after stent implantation.

P447 Inhibition of miR-92a accelerates reendothelialization and prevents neointima formation following vascular injury

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Background: MicroRNAs (miR) are small noncoding RNAs that regulate gene expression by binding to thecellular transcript leading to translational repression or degradation of the target mRNA. So far, the impact of specific microRNAs on atherosclerosisand restensosis following vascular injury is widely unknown.
Methods/results: Using microarray based expression analysis we screened for regulated miRNAs duringthe development of atherosclerosis and restenosis. For this, aortic arches ofApoE/LDLr-/- mice were isolated and differential expression of miRNAs wasassessed by microarrays analysis after 2 weeks (control), 6 and 12 months.Neointima formation was induced in C57BL6/N by dilation of the femoral arteryand miRNA was isolated at 10 and 21 days after injury. Here as well as duringatherosclerosis development, the majority of all known miRNAs was aberrantlyregulated. Noticeably, miR-92a was significantly upregulated during thedevelopment of atherosclerosis (12 months) as well as restenosis (10 and 21d),which was confirmed by subsequent qPCR analysis. Further expression analysis inisolated human primary vascular cells revealed that miR-92a, one of the moststrongly regulated miRNAs, is highly expressed in human coronary artery endothelialcells (ECs) but to a much lower extent in human coronary artery vascular smoothmuscle cells (SMCs). To further assess the functional role of miR-92a in vivo, C57/Bl6 mice were systemically treatedwith novel, highly effective, specific antisense molecules (LNAs) followingwire-induced injury of the femoral artery. Inhibition of mir-92a expression in vivo resulted in a significantacceleration of reendothelialization of the denuded vessel area at 10 daysfollowing injury (69$\pm$7 vs. 42$\pm$9%; n=6; $p<0.001$).In ongoing experiments, we are evaluating whether the acceleratedreendothelialization, induced by mir-92a inhibition, will also affect neointimaformation.
Conclusion: Thesedata provide evidence, that the expression of micro RNAs is strongly regulatedduring the development of atherosclerosis and restenosis. Specifically, miR-92ais upregulated in dysfunctional and regenerating endothelial cells and it'sinhibition increases the healing- and reendothelialization capacity of EC atvascular lesion sites, thus representing a putative novel target to enhance thefunctional recovery following acute or chronic vascular injury.

P448 Nitorosonifedipine is a new class drug to improves angiotensin II-induced vascular remodeling

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Background: Nifedipine is extremely sensitive to light and can be converted to its nitroso analog, nitrosonifedipine (NO-NIF). The ability of NO-NIF to block calcium channels is quite weak compared with that of nifedipine. Recently, we have demonstrated that NO-NIF changed to NO-NIF radical when it interacted with unsaturated fatty acids, a major component of lipid bilayer, and the NO-NIF radicals are responsible for the prevention of lipid peroxidation. In addition, we have reported that NO-NIF showed protective effects against TNF-α-induced cytotoxicity in cultured human glomerular endothelial cells. In this study, we investigated the effects of NO-NIF on angiotensin II (Ang II)-induced vascular remodeling.
Methods: Cell migration and proliferation were evaluated by MTT and boyden camber assay. Phosphorylation of each kinase was detected by western blotting. Reactive oxygen species (ROS) was measured by dihydroethidium staining and lucigenin chemiluminescence assay. Intracellular Ca^{2+} concentration was measured by Fluo-4 AM staining. Vascular remodeling was estimated by Hematoxylin-Eosin staining. Blood pressure was measured by tail cuff methods. Urinary 8-OHdG was detected by ELISA. Each mRNA expression was measured by real-time PCR.
Results: NO-NIF (10 μM) significantly inhibited Ang II (100nM)-induced cell migration and proliferation of cultured rat aortic smooth muscle cells (RASMCs). NO-NIF significantly reduced ROS as well as apocynin, a NADPH oxidase inhibitor, in RASMCs. NO-NIF significantly suppressed phosphorylations of Akt and EGF receptor induced by Ang II in RASMCs. On the other hand, NO-NIF had no effects on intracellular Ca^{2+} increase and PKCδ phosphorylation induced by Ang II in RASMCs. Moreover, we performed the effects of NO-NIF on vascular remodeling using Ang II-infused mice (1.44 mg/kg/day). Ang II-induced thickening of aorta was suppressed by NO-NIF administration (30 mg/kg/day, i.p.) (-41%, $p<0.01$). NO-NIF suppressed Ang II-induced hypertension (systolic blood pressure; Ang II vs Ang II+NO-NIF; 128.5$\pm$4.2 mmHg vs 115.5$\pm$3.0 mmHg, $p<0.05$). NO-NIF significantly decreased urinary 8-OHdG (-68%, $p<0.01$) and mRNA expression in aorta, such as p22phox, CD68, MCP-1, and collagen 1, induced by Ang II.
Conclusions: These findings suggest that NO-NIF protects Ang II-induced vascular remodeling via the attenuation of oxidative stress.

P449 Smooth muscle cell growth inhibition by alpha v beta3 integrin modulating peptide coated stent system

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Background: The processes that control vascular healing following percutaneous coronary intervention (PCI) are poorly understood but seem to involve a complex interaction of arterial remodelling, vascular smooth muscle cell proliferation and reendothelialization. The purpose of the present work was to develop a novel stent platform that selectively interferes with key processes relevant to neointimal growth without impeding vascular healing.
Methods: A bare metal stent (BMS) backbone was coated with alpha.v beta.3-integrin selective peptides with an arginine-glycine-aspartate (RGD) sequence. Surface treatment was performed without the use of a polymer by using the ISAR stent coating system. Dosage adjustment was evaluated by in-vitro-tests validating the efficacy of smooth muscle cell growth inhibition. Integrity of the inhibited smooth muscle cells was demonstrated by LDH cytotoxicity assay. Preclinical efficacy and safety of the RGD-peptide-coated stent (n=6) was investigated in a rabbit iliac stent implantation model compared to stenting with BMS (n=4) and

Figure 1. Neointima formation after stenting.

sirolimus eluting Cypher stent (n=2). Analysis was performed by means of histomorphometry, immunohistochemistry and High Pressure Liquid Chromatography (HPLC).
Results: Neointimal hyperplasia measured by histomorphometry following RGD-peptide coated stent implantation was reduced compared to the use of a BMS and comparable to the use of a Cypher stent in a rabbit iliac stent implantation model. Reendothelialization was enhanced in the RGD-peptide coated stent group compared to stenting with BMS or Cypher stent after 28 days.
Conclusion: Integrin modulating RGD-peptide coated stents may selectively reduce smooth muscle cell growth and enhance vascular healing after PCI without the use of a polymer.

P450 The role of Akt and mitogen-activated protein kinase systems in the vasoprotection elicited by PARP inhibition in hypertensive rats

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Purpose: Hypertension can induce cell death (apoptosis) and fibrotic remodeling in the arterial wall via oxidative stress and consequent poly(ADP-ribose)polymerase enzyme (PARP) activation. Previously we have shown that PARP inhibition decreases vascular remodeling elicited by sustained high blood pressure. Thus in the present study we hypothesized that in spontaneously hypertensive rats (SHR) the PARP inhibitor (L-2286), via modulation of Akt and MAPKs signaling pathways reduces oxidative stress, apoptosis and improves vasomotor function.
Methods: Male 10-weeks-old SHRs received 5 mg/kg/day L-2286 orally for 32 weeks (SHR-L). As positive control placebo-treated SHRs were used (SHR-C). Male Wistar rats belonged to the negative control group. At the end of the experimental period to detect the oxidative damage 3-nitrotyrosine formation was measured in histological samples from carotid arteries and aortas. PARP activation was determined by immunohistochemistry. The activation state of vascular signal transduction proteins (Akt-1 and MAP-kinases) were monitored by Western blotting. Furthermore, caspase-independent cell death provoking apoptosis inducing factor (AIF) translocation was also studied. Vasomotor answers of carotid arteries were registered with wire myograph.
Results: In vascular tissues L-2286 treatment decreased significantly ($p<0.05$) the expression of nitrotyrosine and PARP activation in SHR-L. In addition PARP inhibition enhanced the phosphorylation of the pro-survival factor Akt-1 ($p<0.05$) while phosphorylation of ERK, JNK and p-38 MAPK were significantly ($p<0.05$) decreased in SHR-L group. In SHR-C group upregulated translocation of AIF was demonstrated which was decreased in SHR-L animals due to L-2286 treatment. Relaxation of carotid arteries to ACh was significantly increased in SHR-L group compared to SHR-C (22.3±8% vs. 41±5%, $p<0.05$), but responses to SNP did not differ.
Discussion: These data suggest that in SHR PARP inhibition decreases oxidative stress and apoptosis via modulation of Akt and MAPKs signaling pathways resulting in significant vasoprotection.
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P451 PI3Kalpha deficiency critically reduces proliferation of smooth muscle cells in vitro and in vivo during neointima formation following balloon injury

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Proliferation of vascular smooth muscle cells (SMCs) is a hallmark of neointima formation following balloon angioplasty. Proliferation of SMCs is induced by peptide growth factors which activate receptor tyrosine kinases. Previously, we were able to demonstrate that inhibition of the catalytic PI 3-Kinase isoform p110alpha (PI3Kalpha) completely abrogated growth factor mediated proliferation of SMCs. Here, we assessed the hypothesis that gene deletion of PI3Kalpha in mice significantly reduces proliferation of SMCs and thus diminishes neointima formation following balloon angioplasty in vivo. We isolated aortic smooth muscle cells from SMC specific PI3Kalpha knock out mice and investigated by means of a BrdU incorporation assay growth factor induced proliferation of PI3Kalpha deficient cells compared to SMCs from wild type littermate control mice. Additionally, we analysed cellular proliferation in neointimal SMCs three weeks following balloon injury in carotid arteries via immunohistochemical staining of proliferating cell nuclear antigen (PCNA). Finally, we assessed the extent of neointima formation in balloon injured carotid arteries in SMC specific PI3Kalpha knockout mice versus wild type littermate control animals.
Platelet-derived growth factor BB (PDGF, 30 ng/ml), or fetal calf serum (FCS, 10%) caused an 2.8±0.8 fold and a 4.3±1.2 fold increase in the proliferation of wild type cells, respectively. In contrast, PDGF or FCS induced proliferation were completely abrogated in SMCs from PI3Kalpha knock out animals. Consequently, SMC specific gene deletion of PI3Kalpha significantly reduced the percentage of PCNA stained proliferating SMCs in the carotid arteries following balloon injury (12.8±3.1% in wild type vs 3.3±0.9% in PI3Kalpha knock out). Consistently, the neointimal area was significantly reduced in SMC specific PI3K knock out animals ($7997±2921\mu m^2$) compared to wild type mice ($37420±7284\mu m^2$).
In conclusion, our results indicate that in vitro and in neointimal hyperplasia, PI3Kalpha is crucial for growth factor induced proliferation of SMCs. Therefore, PI3Kalpha represents a promising therapeutic target for the treatment of restenosis.

P452 Toll-like receptor signal adaptor protein MyD88 regulates NAD(P)H oxidase-generated oxidative stress and vascular remodeling in angiotensin II-induced hypertension

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Purpose: Toll-like receptor 4 (TLR4) and angiotensin II (AngII) have been shown to play a critical role in vascular remodeling through the production of reactive oxygen species (ROS). Furthermore, AngII generates ROS by the activation of NAD(P)H oxidase through AngII type 1 (AT1) receptors. It is also reported that TLR signal adaptor protein MyD88 is involved in the activation of NAD(P)H oxidase. However, the relationship between TLR4 and MyD88 in regulating oxidative stress and vascular remodeling remains unknown. We investigated the effects of MyD88 and TLR4 on oxidative stress and vascular remodeling in AngII-induced hypertension.
Methods: TLR4-dificient (TLR4lps-d) and wild-type (WT) mice were randomly subjected to pressure overload by AngII or norepinephrine (NE). We also examined the effects of AT1 receptor antagonist irbesartan (IRB) in AngII-induced hypertension. Systolic blood pressure (SBP) was obtained by tail-cuff plethysmography. Wall-to-lumen (W/L) ratio and perivascular fibrosis (PVF) of the aorta was measured. Superoxide ($^{\bullet}O2^-$) content was assessed with fluorescent DHE staining by a laser scanning confocal microscope. The expression of TLR4 receptor, MyD88 and interleukin-1 receptor associated kinase 4 (IRAK4), downstream of MyD88, in the vascular wall was evaluated with immunoblots. The activity of NAD(P)H oxidase was assessed by a luminoassay.
Results: The untreated control WT and TLR4lps-d mice showed similar levels of SBP, $^{\bullet}O2^-$ content, W/L ratio, PVF and total cell number. However, MyD88 expression of the control TLR4lps-d mice was lower by half than that of the control WT mice ($P<0.05$). In both WT and TLR4lps-d mice, AngII and NE equally increased SBP compared with the untreated control mice ($P<0.05$), whereas the expression of TLR4 receptor and IRAK4 remained unchanged. In WT mice, AngII induced a 10-fold increase in $^{\bullet}O2^-$ content and a 3-fold increase in NAD(P)H oxidase activity and a 1.3-fold increase in MyD88 expression ($P<0.05$), and also increased W/L ratio and PVF, but not total cell number, in the vascular wall compared with the untreated control WT mice ($P<0.05$). IRB treatment completely abolished these effects of AngII. In contrast, TLR4lps-d mice showed little effects of AngII on NAD(P)H oxidase activity, $^{\bullet}O2^-$ content, and vascular morphology as well as MyD88 expression in the vascular wall. In both WT and TLR4lps-d mice, NE showed little effects on these indices in the vasculature.
Conclusions: MyD88 may play a critical role in regulating NAD(P)H oxidase-generated ROS levels in the vascular wall and vascular remodeling in AngII-induced hypertension.

MEDIATORS OF INFLAMMATION: KEEP THE FIRE BURNING

P453 Activation of endothelial Toll-like receptor 3 impairs endothelial function

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Rationale: Endothelial dysfunction and atherosclerosis are chronic inflammatory diseases characterized by activation of the innate and acquired immune system. Specialized protein receptors of the innate immune system recognize products of microorganisms and endogenous ligands such as nucleic acids. Toll like receptor 3 (TLR3) for example detects long double-stranded RNA and is abundantly expressed in endothelial cells. Whether innate immunity contributes to atherogenic mechanisms in endothelial cells is poorly understood.
Objective: We sought to determine the effects of TLR3 activation in endothelial cells.
Methods and results: We first investigated if stimulation of TLR3 influences

endothelial biology in mice. Intravenous injection of polyIC, a synthetic dsRNA-analogon and TLR3 ligand, impaired endothelium-dependent vasodilation, increased vascular production of reactive oxygen species (ROS) and reduced re-endothelialisation after carotid artery injury in wild-type mice compared to controls, but had no effect in TLR3-/- animals. TLR3 stimulation not only induced endothelial dysfunction but also enhanced the formation of atherosclerotic plaques in ApoE-/- mice. In vitro incubation of endothelial cells with polyIC induced the production of the proinflammatory cytokines IL-8 and IP-10, increased ROS formation, diminished proliferation and elevated apoptosis, suggesting that endothelial cells are able to directly detect and respond to TLR3 ligands. Neutralizing the produced cytokines antagonizes the observed effects. We found elevated levels of circulating EPC in polyIC treated mice although they displayed increased endothelial dysfunction. Stimulation of TLR3 in cultured EPC however, led to raised ROS formation, increased apoptosis and reduced migration. Injection of EPC that had been incubated with polyIC ex vivo hindered the re-endothelialisation after carotid artery injury. Therefore, also EPC function is affected by TLR3 stimulation.

Conclusion: Immunorecognition of long double-stranded RNA by endothelial cells may be an important mechanism involved in endothelial cell activation and development of endothelial dysfunction.

P454 Antagonising CCR2 leads to altered distribution of the different activation types of macrophages and favorable tissue remodelling after myocardial infarction in mice

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Background: An important pathomechanism after myocardial infarction is a strong inflammatory response. Aim of the present study was to investigate whether modulation of the activation dynamics (classical and alternative) using a CCR2-antagonist leads to a favourable scar tissue formation and improves cardiac function in mice.

Methods: Mice (C57bl6) (n= 100) were subjected to occlusion of the left anterior descending artery and randomized in the following groups: (a) coronary artery occlusion (MI) and (b) coronary artery occlusion combined with administration of 8 mg/kg BW Propagermanium (PPG, a CCR2-antagonist) daily until the end of the experiment (MI +PPG). Sham operated mice served as control (sham). Mice were euthanized 2, 5 and 10 days after myocardial infarction for isolation of total RNA, total protein and immunohistochemistry. Flow cytometry was used to investigate peripheral blood leucocytes. Infarct size and functional parameters were determined by trichrome staining (after 21d) and MRI-investigations (at baseline and after 10d).

Results: PPG treatment lead to decreased mortality (MI +PPG: 20.0±7.4 vs. MI: 33±10.5, n=30, $p<0.05$) and improved ejection fraction (MI +PPG: 38±3.4% vs. MI: 23.8±3.0, n=20, $p<0.05$) after myocardial infarction. MRI analysis revealed decreased wall motion abnormalities, which were confirmed by trichrome staining demonstrating a lower number of transmural infarcts after PPG-treatment. Flow cytometry confirmed decreased numbers of peripheral blood monocytes in MI +PPG compared to MI 2d after treatment (7.3±3.3% vs 13±0.6% of total leucocytes, n=5, $p<0.05$). Immunostaining and qRT-PCR using activation type specific markers (Mrc1, Arg1 and CCR2) demonstrated that the proportion of alternatively activated macrophages within the infarct zone increased, whereas the over all number of macrophages was reduced after PPG treatment. Western blot analysis and qRT-PCR demonstrated reduced expression of collagens and TGFβ in the infarct border zone. MMP-activity did not change in MI +PPG compared to MI, which was confirmed by zymography.

Conclusion: Classically activated macrophages are stimulators of an innate immune response shortly after myocardial infarction. However, the inflammatory phase is followed by the recruitment of alternatively activated macrophages, which are important mediators for tissue repair and scar formation. Our results demonstrated that altering the activation type and distribution of invading macrophages in favour of alternative activation improves remodelling and cardiac healing.

P455 HMGB1/TLR9 pathway plays a critical role in chronic inflammation and vascular remodeling after endovascular injury

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Purpose: High-mobility group box-1 (HMGB1) is a highly conserved nuclear protein that modulates chromatin structure. Recent reports suggest that HMGB1 acts as an important mediator in inflammatory disorders such as sepsis. In addition, the receptors of HMGB1 signal are reported to be Toll-like receptors (TLRs) or receptor for advanced glycation end-products (RAGE). The aim of this study is to clarify the role of HMGB1 in chronic vascular remodeling after endovascular injury.

Methods and results: We performed wire-mediated endovascular injury of femoral arteries in C57BL/6 mice, and neointimal hyperplasia in injured arteries was examined at 4 weeks after the injury. We delivered neutralizing anti-HMGB1 antibody (2μg/mouse, αHMGB1 group, n=5) or PBS (PBS group, n=5) into perivascular area with gelatin-hydrogel. In PBS group, serum level of HMGB1 was elevated at 4 days after the injury, not 0 or 1 day. Neointimal hyperplasia was significantly attenuated in αHMGB1 group compared to PBS group (neointima/media ratio, 1.3±0.6 vs 4.0±2.1, $p<0.05$).

Next, we performed endovascular injury in TLR-2, 4, 9 KO mice (n=5-7 for each group). Interestingly, neointima formation was attenuated in TLR9-KO mice compared to wild type mice (WT), whereas neointimal hyperplasia was not affected in TLR2- and TLR4-KO mice. Immunohistochemical study revealed that Mac3-positive macrophage infiltration around the injured arteries was significantly decreased in TLR-9 KO mice compared to WT mice.

To evaluate the involvement of bone marrow derived cells to neointima formation, we performed bone marrow transplantation (BMT) between TLR9-KO mice and WT mice (n=7-9 for each group). Neointima formation was attenuated in BMT (KO→WT) mice compared to BMT (WT→WT) mice ($p<0.05$), whereas there was no difference between BMT (WT→KO) mice and BMT (KO→KO)mice. These results suggest that TLR9 in bone marrow derived cells play a critical role in vascular remodeling after vascular injury.

In vitro study, we stimulated rat smooth muscle cells (SMCs), mouse macrophages (RAW 264.7), human endothelial cells (HUVECs) with LPS for 24 hours, and measured the HMGB1 concentration in the conditioned medium. HMGB1 level was elevated in the medium of macrophages in time dependent manner, but was not changed in SMCs and HUVECs. These findings suggest that HMGB1 was not only secreted from necrotic cells, but also secreted from macrophages.

Conclusions: Our findings suggest that HMGB1 acts as chronic inflammatory mediator in vascular remodeling after endovascular injury. HMGB1/TLR9 pathway may play a critical role in the pathogenesis of vascular disease.

P456 MicroRNA-100 modulates endothelial inflammation by suppressing endothelial adhesion molecule expression

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Background: MicroRNAs are small endogenous RNAs that modulate a broad range of biological processes by inhibiting target mRNA expression. We recently identified the microRNA-100 (miR-100) as an important regulator of neovascularization. Since our transcriptome analysis after miR-100 overexpression in endothelial cells also suggested the modulation of several inflammatory signalling pathways, we now aimed to explore the regulation and function of this microRNA in the endothelial inflammatory response.

Methods and results: We screened several pro- and anti-inflammatory cytokines with regards to their effects on miR-100 expression. Treatment of endothelial cells with the pro-inflammatory mediator TNF-alpha resulted in a 50% decrease of miR-100 expression ($p=0.04$). This TNF-alpha mediated regulation of miR-100 was shown to be NFkappaB dependent. To further investigate the function of this microRNA, microarray-based transcriptome analysis was performed 48 h after overexpression of a miR-100 precursor oligonucleotide in endothelial cells. Pathway analysis revealed endothelial adhesion molecules as one of the top regulated biological processes. On individual gene level, miR-100 suppresses the expression of at least three distinct adhesion molecules in endothelial cells. PCR and Western Blot analysis showed a nearly 90% decrease in the upregulation of ICAM-1, VCAM-1 and E-Selectin in response to inflammatory stimuli on mRNA ($p<0.005$) and protein level. Overexpression of miR-100 in endothelial cells inhibits leukocyte rolling and adhesion ($p<0.005$) under physiological flow conditions in a flow chamber apparatus (shear stress: 1 dynes/cm^2), whereas the inhibition of miR-100 has the opposite effect. In addition, we observed that miR-100 levels are rapidly decreased by 40% after blood vessel injury by carotid ligation as a model of inflammatory-driven vascular remodelling ($p<0.05$; n=3).

Conclusion: We show that the microRNA miR-100 is expressed in endothelial cells and blood vessels and is downregulated in response to vascular injury as well as after exposure to pro-inflammatory cytokines. This decrease in miR-100 levels results in an increased expression of at least three adhesion molecules and subsequently in an enhanced leukocyte adhesion to the endothelium. MiR-100 could therefore represent a novel target for the modulation of the endothelial inflammatory response to injury and vascular inflammatory processes such as atherosclerotic disease.

P457 Cleaved high molecular weight kininogen (HKa) prevents neointima formation following vascular injury

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Purpose: The cleavage of high molecular weight kininogen (HK) results in the release of bradykinin and a cleaved form of HK (HKa). We previously could show that HKa and its peptide domain 5 (D5) alone exert anti-adhesive properties during inflammatory cell recruitment via binding to extracellular matrix proteins and integrins, promoting apoptosis in vascular cells. In this study, we investigated the effects of HKa and D5 on the accumulation of circulating cells and the function of resident vascular cells in a mouse model of neointima formation.
Methods: C57BL/6 mice were lethally irradiated and rescued with bone marrow from transgenic mice expressing enhanced green fluorescence protein (EGFP). Wire induced injury of the femoral artery was performed on chimeric mice with local application of HKa, D5, or control to the dilated artery in a thermosensitive pleuronic gel. Vessels were harvested 1 day after injury to document the sustained release of the substances and at 3 weeks after injury for morphometric analysis and immunohistochemistry (n=6).
Results: NI formation was significantly reduced after treatment with HKa and even more prominent after D5 application (HKa: 0.981±0.174; D5: 0.549±0.076 vs. 1.54±0.150; $P<0.05$). The attenuation of the neointimal lesion was accompanied by a reduced accumulation of EGFP+-cells and monocytes/macrophages in the treatment groups. Confocal microscopy revealed that EGFP+-cells did not co-express smooth muscle myosin heavy chain or calponin, indicating that BM-derived cells did not trans-differentiate into bona fide SMC. Importantly, HKa and D5 significantly reduced the number of proliferating resident smooth muscle cells in the vascular wall ($P<0.05$). In contrast, the ratio of apoptotic cells/all neointimal cells was increased in the treatment groups, although the absolute numbers of apoptotic vascular cells as well as re-endothelialization were not different.
Conclusion: These data identify the cleaved form of kininogen (HKa) and especially its peptide domain 5 as an endogenous inhibitor of the inflammatory response following vascular injury due to its anti-adhesive properties, which also reduces proliferation of local vascular cells. Moreover, the application of HKa or D5 may provide a novel therapeutic strategy for the treatment of vascular proliferative diseases.

P458 Glutathione peroxidase-1 deficiency augments proinflammatory cytokine-induced redox signaling through multiple pathways

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Glutathione peroxidase-1 (GPx-1) is a crucial antioxidant enzyme, the deficiency of which causes a proinflammatory phenotype by increased expression of ICAM-1 and VCAM-1 in the presence or absence of TNF-α stimulation in microvascular endothelial cells (HMVEC) and endothelial cells cultured from GPx-1 knockout mice. Adenoviral overexpression of GPx-1, cells from transgenic mice overexpressing GPx-1 and N-acetyl-cysteine attenuated these responses. Suppression of GPx-1 enhanced TNF-α-induced ROS production and prolonged TNF-α-induced IκBα and activation of ERK1/2 and JNK. NFκB or JNK-inhibition attenuated TNF-α induction of ICAM-1 and VCAM-1 expression in GPx-1 deficient and control cells and thus was tested by the pretreatment of pyrrolidinedithiocarbamate (PDTC) (50-200 uM), an NFκB inhibitor, prior to TNF-α exposure or with SP600125, a JNK inhibitor, (10-50 uM). To analyze further signaling pathways involved in GPx-1 mediated protection from TNF-α-induced ROS, microarray analysis of HMVEC treated with TNF-α in the presence and absence of GPx-1 was performed. Among the genes whose expression changed significantly, dual specificity phosphatase 4 (DUSP4), an antagonist of MAPK signaling, was downregulated by GPx-1 suppression. Targeted DUSP4 knockdown enhanced TNF-α-mediated ERK1/2 pathway activation and resulted in increased adhesion molecule expression, implicating a mechanism for modulating ERK1/2-signaling in TNF-α-treated GPx-1 deficient cells. To determine whether DUSP4 overexpression could rescue the increased adhesion molecule expression in GPx-1 deficient cells, we used an adenovirus construct to overexpress DUSP4 in cells transfected with siRNA to knockdown GPx-1 (siGPx-1). DUSP4 overexpression diminished TNF-α-induced VCAM-1 protein expression compared to empty adenovirus but had no effect on ICAM-1 expression. These results are consistent with our findings that UO126, an ERK1/2 inhibitor, blocked TNF-α-induced VCAM-1 expression in the presence or absence of GPx-1, whereas it had little effect on TNF-α-induced ICAM-1 expression in GPx-1 deficient cells. Taken together, these data demonstrate that GPx-1 deficiency promotes a proinflammatory phenotype mediated by NFκB mechanisms in the absence of cytokine stimulation. Furthermore, both NFκB and JNK pathways contribute to increased responses to TNF-α in GPx-1 deficient cells. These data indicate that GPx-1 deficiency augment inflammatory signaling via multiple redox-sensitive pathways to enhance pro-inflammatory responses in endothelial cells.

P459 Exendin-4 inhibits iNOS expression at the protein level but not at the transcriptional levels in LPS-stimulated RAW264.7 macrophage

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Purpose: Macrophages play a key role in the pathogenesis of various diseases including atherosclerosis. Meanwhile, the roles of glucagon-like peptide-1 (GLP-1) and its potent analogs have been widely studied in respect of islet β-cell function and diabetes mellitus. We recently reported that exendin-4 (EX-4), a potent GLP-1 receptor agonist inhibited IL-1β-induced iNOS expression in islet β-cells (J Endocrinol 2009;202:65-75). Furthermore, GLP-1 receptors are present in many extrapancreatic tissues including macrophages, and thus GLP-1 seems to have diverse actions on these tissues and cells. Therefore, we examined the mechanism by EX-4 inhibits lipopolysaccharide (LPS)-induced iNOS expression in Raw264.7 macrophage cells in respect of anti-inflammatory effect of EX-4.
Methods: The expression of iNOS protein, IκBα phosphorylation and nuclear translocation of p65 were detected by Western blot analysis and content of nitrite was measured using Griess reagent. Additionally, iNOS mRNA expression and iNOS promoter activity were observed by Northern blot analysis and luciferase assay, respectively. To observe the stability of iNOS mRNA and protein, actinomycin D chase and cycloheximide chase studies were performed, respectively. Also, the cellular cAMP content was measured using Cyclic AMP Assay kit.
Results: Western blot analysis and nitric oxide assay showed that EX-4 inhibited dose-dependently LPS-induced iNOS protein expression and nitrite production. In contrast, Northern blot and promoter analyses demonstrated that EX-4 did not inhibit LPS-induced iNOS mRNA expression and iNOS promoter activity. Consistent with the result of iNOS promoter activity, LPS-induced IκBα phosphorylation and nuclear translocation of p65 was not affected by EX-4 treatment. Also, actinomycin D chase study showed that EX-4 did not affect iNOS mRNA stability. We further analyzed the mechanism about the EX-4 inhibition of LPS-induced iNOS protein. EX-4 increased cAMP production dose-dependently. Additionally, EX-4 treatment restored the LPS-induced decrease in cAMP level toward normal control level. Cycloheximide chase study demonstrated that both EX-4 and forskolin significantly accelerated iNOS protein degradation, which was reversed by H-89, a PKA inhibitor.
Conclusions: We, therefore, concluded that EX-4 inhibition of IL-1β-induced iNOS protein is mainly dependent on cAMP/PKA system, and this inhibitory effect of EX-4 appears to be regulated at posttranslational level but not at transcriptional mechanism of iNOS gene.

P460 Role of TRAIL (TNF-related apoptosis-inducing ligand) and its decoy receptors in the inflammatory response of acute myocardial infarction

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Introduction: In addition to necrosis, apoptosis, and also the inflammatory response seem to contribute to the total cell loss after acute myocardial infarction (AMI).There is evidence of the key role of neutrophils in the ventricular remodeling through the inflammatory response initiated at the cascade of tumor necrosis factor-alpha (TNF-α) and perpetuated by interleukin-8 (IL-8). Little is known yet about the role of TNF-related apoptosis-inducing ligand (TRAIL) and its decoy receptors TRAIL-R3 and TRAIL-R4 in signaling the neutrophil apoptosis in the context of AMI.
Objectives: To evaluate the time course of soluble TRAIL and its anti-apoptotic receptors R3 and R4 on neutrophils in peripheral blood of patients with AMI and to study their relationship with the inflammatory response.
Methods: Prospective, observational study of 12 patients admitted for ST-segment elevation AMI, without concomitant inflammatory or autoimmune disease and 10 healthy controls. Samples were obtained from peripheral blood before primary angioplasty (T0) and after one month (T1) in patients and in a single moment in the control group. The quantification of soluble TRAIL was performed by ELISA (enzyme-linked immunosorbent assay) and its receptors R3 and R4 by flow cytometry as mean fluorescence intensity (MFI).
Results: The mean age of patients was 53.2±13 years. The maximum c-reactive protein was 4.5±5.3 mg/dl, maximum troponin I 78.6±68.3 ng/ml and left ventricular ejection fraction 49.3±15.8%. The soluble TRAIL was decreased in the population under study in T0 compared to the control group (29.9±15.3 vs 52.2±18.3 pg/ml, $p\leq0.05$), keeping this trend in T1 (36.7±12.5 vs 52.2±18.3, $p\leq0.05$). In both T0 and T1, there was an increase in the percentage of neutrophils expressing TRAIL-R3 (79.4±9.1 vs 69.1±5.8 vs 59.4±6.7% respectively, $p\leq0.05$) and TRAIL-R 4 (80.9±8.6 vs 67.6±6.8 vs 59.9±6.9% respectively, $p\leq0.05$) comparing with the control group.
Conclusion: TRAIL and its decoy receptors seem to play an important role in the inflammatory response of AMI. The increase in expression of anti-apoptotic receptors in blood neutrophils in the context of AMI, coupled with the reduction of soluble TRAIL, may translate neutrophil resistance to apoptosis and potentiation of myocardial lesion. Manipulating these anti-apoptotic mechanisms may be promising as a future therapeutic target.

P461 Impairment of immunoproteasome function results in severe enterovirus myocarditis

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Proteasomes recognize and degrade poly-ubiquitinylated proteins. In infectious disease, cells activated by interferons (IFNs) express three unique catalytic subunits LMP2, MECL-1 and LMP7 forming an alternative proteasome isoform, the immunoproteasome (IP). The in vivo function of IPs in pathogen-induced inflammation is still a matter of controversy. IPs were mainly associated with MHC class I antigen processing. However, recent findings pointed to a more general function of IPs in response to cytokine stress. Here, we report on the role of IPs in acute coxsackievirus B3 (CVB3) myocarditis reflecting one of the most common viral disease entities among young people. Cardiac proteasomes from LMP7-deficient mice show severe impairment of IP formation in CVB3-challenged hearts. Despite the finding of identical viral load in both control and IP-deficient mice, IP-deficiency was associated with severe acute heart muscle injury being reflected in large foci of inflammatory lesions and severe myocardial tissue damage. As suggested by the detection of increased proteotoxic and oxidative stress in cytokine-challenged cardiomyocytes from IP-deficient mice, exacerbation of acute heart muscle injury in this host was attributed to disequilibrium in protein homeostasis in viral heart disease. In fact, IPs protected CVB3-challenged mice from oxidant-protein damage, which was attributed to efficient removal of harmful poly-ubiquitinylated protein aggregates in the injured myocardium by IPs. Together with the fact that NFκB activation was impaired in cardiomyocytes lacking IPs, increased proteotoxic stress resulted in severe apoptotic cell death in CVB3-challenged hearts from IP-deficient mice. In agreement with data pointing towards an effective CD8 T cell immune response as shown here in adoptive T cell transfer studies in IP-deficient mice; this study demonstrates that IP formation primarily protects the target organ of viral infection from excessive inflammatory tissue damage in a virus-induced proinflammatory cytokine milieu. Thus, preservation of protein homeostasis and maintenance of cell viability by cytokine induced IPs represents the key innate function of IPs in viral infection.

P462 Adenosine prevents toll-like receptor 4 activation. Implication for limitation of left ventricular remodelling

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Purpose: Left ventricular remodelling is a main trigger of the development of heart failure following acute myocardial infarction. Toll-like receptor 4 (TLR4) has been described as a mediator of left ventricular remodelling through induction of inflammatory response. Therefore, TLR4 is a potential therapeutic target. In this study, we determined whether adenosine regulates the expression of TLR4.
Methods: Primary macrophages were differentiated from blood monocytes obtained from healthy volunteers and MI patients. Expression of TLR4 was studied by quantitative PCR, immunofluorescence, flow cytometry and immunoblotting. Expression of selected cytokines was assessed by flow cytometry and ELISA.
Results: We observed that TLR4 expression is higher in MI patients than healthy volunteers ($P<0.01$, n=12 in both groups). TLR4 positively correlated with peak troponin T levels ($r^2=0.75$; $P=0.01$) but not with the levels of white blood cells or C-reactive protein. In macrophages obtained from healthy volunteers, adenosine down-regulated TLR4 surface expression and the effect was maximal after 24 hours (-50%, $P<0.05$). In these cells, the production of IL-6, IL-10 and TNF-α induced by LPS was potently inhibited (-75% for TNF-α, $P<0.005$). Similar inhibition of cytokine production was observed when macrophages were stimulated with matrix degradation products hyaluronic acid and heparan sulfate. This inhibition was reproduced by the non-selective adenosine receptors agonist NECA and the A2A-specific agonist CGS21680. The A2a antagonists SCH58261 and ZM241385 reversed the effect. Blockade of TLR4 internalization by dynamin inhibition partially restored the production of cytokines.
Conclusion: In acute MI, activation of TLR4 correlates with circulating markers of myocardial damage and matrix degradation but not with markers of inflammation. Adenosine down-regulates this activation through its A2A receptor. This observation may be important to find new ways of limiting post-MI LV remodelling.

P463 Mediators of thrombotic activation and inflammatory processes in atrial fibrillation as measured by protein and biochip array methods

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Atrial fibrillation (AF) represents a major cardiovascular syndrome affecting nearly 2.5 million Americans per year. Both the inflammatory and thrombotic processes are known to contribute to the pathogenesis of AF. Activation of proteases during these pathogenic processes results in the generation of specific mediators and various protease cleavage products which are usually absent from normal blood. To investigate theses unique biomarkers in the plasma of patients clinically diagnosed new onset AF: untreated (n= 50), multiple profiling methods including Surface Enhanced Laser Desorption Ionization spectroscopy (SELDI, Ciphergn) and a Biochip array system (Randox) were profiled. In addition ELISA methods for C reactive protein (CRP), monocyte chemotactic protein 1 (MCP-1), CD 40 ligand (CD-40L), tumor necrosis factor alpha (TNFa) and micropartiles were also employed. The proteomic profile revealed a unique biomarker peaks at 8.1 and 11.4 kDa which were found in 27/50 (54%) of the AF patients and absent in the normal population. The mean amplitude of these peaks in the AF patients was 30. In the Biochip arrays, Variable increases (30-210%) were noted in the D-dimer, thrombomodulin, tumor necrosis receptor-1, neuron specific enolase and neutrophil gelatinase associated lipocalin gal. The circulating levels of CRP (AF 12.1±2.1 vs. N 2.1±0.5 ug/ml), MCP-1 (AF 256±28.4 vs. N 120±16.3 pg/ml), CD 40 L (AF 245±32.1 vs. N 65±9.8 pg/ml), and TNFa (AF 312.±32.4 vs. N 25±7.5 pg/ml), were all elevated compared to the normal controls. The microparticle levels were also markedly higher in the AF group (AF 21.6+ 4.2 vs 4.2+0.8). These observations suggest that inflammatory and thrombotic processes contribute to the generation of various unique biomarkers in AF. The recognition of unique biomarkers along with the mediator profiling in AF may be helpful in the understanding of the pathogenesis of AF. Moreover, therapeutic approaches for AF may result in a down regulation of these parameters in particular while investigating the newer oral anti Xa and IIa drugs.

P464 Chronic exposure of low concentration of nonylphenol aggravates the deterioration of long-term adenine feeding-induced chronic renal dysfunction: role of rosuvastain therapy

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Purpose: Nonylphenol (NP), an environmental-organic compound, has been demonstrated to enhance reactive-oxygen species (ROS) synthesis. Chronic exposure to low-dose adenine (AD) has been reported to induce chronic kidney disease (CKD). We tested the hypothesized that chronic exposure to NP will aggravate adenine-induced CKD through increasing generations of ROS, apoptosis and fibrosis that could be attenuated by rosuvastatin.
Methods and results: Fifty Wistar rats were equally divided into group 1 (control), group 2 (AD was supplied in fodder at a concentration of 0.25% for 28-weeks), group 3 (NP: 20.0 mg/kg/day), group 4 (combined AD & NP), and group 5 (AD-NP + rosuvastatin). Rosuvastatin (10 mg/kg/day) and NP were given from 17-week after AD-induced CKD. By 28-weeks, serum BUN and creatinine levels were significantly increased in group 3 than in groups 1-2, more remarkably increased in group 4 than in groups 1-3, but significantly reduced in group 5 as compared with group 4 and they did not differ between groups 1 and 2 (all $p<0.05$). Histopathology scoring of renal-parenchymal damage was significantly higher in group 2 than in groups 1 and 3, more markedly higher in group 4 than in groups 1 to 3 that was significantly reversed in group 5 as compared with group 4 (all $p<0.01$). Protein expressions of oxidative stress, caspase-3, Bax, NFκ-B, TGF-β, phosphorylated Smad-3 and JNK, membrane PKC-α and NOX-2 were significantly increased in groups 2 and 3 than in group 1, more notably increased in group 4 as compared with groups 1-3, but they remarkably reduced in group 5 than in group 4 (all $p<0.05$). Conversely, the protein expressions of phosphorylated Smad1/5 and ERK, BMP-II, NQO-1 and Bcl-2 were notably lower in groups 2 and 3 than in group 1, more significantly lower in group 4 than in groups 1 to 3, but they were notably reversed in group 5 as compared with group 4 (all $p<0.05$).
Conclusion: NP worsened AD-induced CKD that could be reversed by rosuvastain.

SIGNALING MOLECULES: MEDIATORS OF VASCULAR DAMAGE AND REPAIR

P465 Obesity is characterized by increases in membrane-type-1 matrix metalloproteinase and its activating convertase furin

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Matrix metalloproteinase (MMP) dependent remodelling of the extracellular matrix (ECM) is a key feature in cardio-metabolic syndrome associated atherosclerosis, hypertension and adipose tissue formation. Among the group of MMPs, membrane-tethered MT-MMPs are unique in that they are expressed as locally active enzymes on the cell surface. Activation of the prototype pro-MT1-MMP depends on intracellular cleavage by furin. This proprotein convertase (PC) is highly expressed in macrophages in human atheromas. The regulation of furin, its natural inhibitor serpin-8, as well as MT1-MMP in mononuclear cells (MNCs), however, is unknown.

Results: Transformation of human monocytes to macrophages was accompanied by increased expression of furin and MT1-MMP mRNA and protein, whereas serpin-8 was downregulated. Subcellular fractionation, immunofluorescence and pharmacological inhibitor studies with the furin-like PC-inhibitor dec-CMK and the trans-Golgi-network (TGN)-inhibitor BFA in macrophages demonstrated that furin and MT1-MMP colocalize in the TGN, were furin activates MT1-MMP. Likewise, overexpression of serpin-8 protein inhibited furin-dependent pro-MT1-MMP, and subsequent MT1-MMP-dependent pro-MMP-2 activation. In accordance, monocyte-chemoattractant protein (MCP)-1 directed macrophage chemotaxis was inhibited by treatment with either dec-CMK, an hydroxamate class MMP-inhibitor (GM6001), the naturally occurring MT1-MMP-inhibitor TIMP-2 or serpin-8. In monocytes isolated from obese hypertensive patients (n=14; BMI 32.7±2.1kg/m^2) significantly higher furin and MT1-MMP mRNA levels were detected compared to overweight hypertensive patients (n=12; BMI 26.6±1.9kg/m^2). The BMI significantly correlated with furin (r=0.426; p=0.03) and furin strongly correlated with MT1-MMP (r=0.855; p<0.01). Furthermore, the adipocytokine resistin was significantly increased in obese patients. In vitro stimulation of macrophages with resistin increased furin and MT1-MMP mRNA and protein levels, whereas MCP-1 had no effect.
Conclusion: Monocyte transformation is characterized by a misbalance of furin and its inhibitor serpin-8. Furin activates MT1-MMP, which facilitates macrophage migration. Increased MT1-MMP and furin levels are found in obese hypertensive patients and correlate with resistin, which induces furin and MT1-MMP expression in vitro. Thus, this enhanced adipocytokine-regulated proteolytic activation cascade potentially contributes to the increase in cardiovascular risk in obese patients.

P466 The stress hormone corticotropin influences cardiac structure and function under basal and stressful conditions

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Purpose: The myocardial response to stressful stimuli is influenced by the hypothalamic-pituitary adrenal axis. We investigated the contribution of the stress hormone corticotropin (CRH) to cardiac function in basal and stressful conditions in Crh-null (Crh-/-) and wild-type (Crh+/+) mice.
Methods: Endotoxemia was induced by LPS administration. Echocardiographic analysis using a high frequency system was performed in adult mice (Crh+/+ n=27, Crh-/- n=12) injected with normal saline or LPS (120μg/ animal). Two-D targeted M-mode imaging was obtained in anesthetized mice. Heart Rate (HR), percentage of LV fractional shortening (FS) and Ejection Fraction (EF) were calculated.
Results: At baseline (BS), cardiac function was compromised in Crh-/- mice compared to Crh+/+ mice, as demonstrated by cardiac hypertrophy, significantly lower FS (20%) values and lower heart rate (16%). TUNEL revealed increased levels of apoptosis (1.3-fold), and H&E and Sirius red stainings showed increased perivascular fibrosis, increased vasculature and hyperplastic intima, as well as increased vascular thickness, only in the Crh-/- mice. They also exhibited greatly reduced Erk1/2 and Akt phosphorylation (75%). LPS administration significantly reduced FS at 6 and 20 hours in Crh+/+ (23% and 25%) and Crh-/- mice (33% and 47%) and EF (10% and 40% in Crh+/+ and Crh-/- respectively). TUNEL assay revealed significantly increased number of apoptotic/necrotic cells in LPS-treated mice (1.2-fold in Crh+/+ and 2.5-fold in Crh-/- mice). After LPS, histological findings in Crh-/- cardiac muscle showed increased levels of infiltration and development of fibers surrounding the hyperplastic vessels and fibrosis-like reactive collagen production. Furthermore, there was 50% reduction in the expression of AMPKα in Crh-/- after LPS and compromised expression of PPARγ; both myocardial protective agents. Crh-/- mice showed elevated levels of mortality (90-100% after 16-28h post-LPS treatment), compared to no mortality observed among Crh+/+. In order to dissect the contribution of glucocorticoid insufficiency in the Crh-/-, corticosterone was replaced for a week prior to LPS treatment. When accompanied with acute dexamethasone injection (50 μg/animal), it ameliorated the effect of LPS in Crh-/- mice, by attenuating FS decrease; whereas histological analysis showed amelioration of the inflammatory indices.
Conclusions: To our knowledge, this is the first indication of endogenous CRH acting directly in cardiac function and development under basal conditions and as a cardioprotective factor in response to systemic inflammatory stress such as endotoxemia.

P467 Calcium-independent phospholipase A2-beta modulates receptor-mediated contraction in human internal mammary arteries

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Background: Animal studies suggest a role for calcium-independent phospholipase A2 (iPLA2β) in G-protein coupled receptor-mediated but not ion channel-induced constriction in cerebral arteries and the abdominal aorta.
Purpose: We assessed whether iPLA2β may be implicated in regulating tone in human vascular conduits, using S-bromoenolactone (S-BEL), a stereo-selective suicide substrate inhibitor of iPLA2β, with its stereo-isomer R-BEL as control.
Methods: We studied isolated internal mammary arteries (IMA: n=14), obtained with written informed consent from patients with ischaemic heart disease undergoing coronary artery bypass grafting [CABG]. The study was approved by the Local Research Ethics Committee. We assessed receptor-mediated constriction to phenylephrine (PE) at 80% of maximal concentration. We used immunohistochemistry (IHC) with anti-human iPLA2β vs. control antibody to assess presence and distribution of iPLA2β in IMA. Results are data±SEM.
Results: IHC revealed iPLA2β staining in endothelium, smooth muscle and adventitia of IMA, adjacent small arteries and veins and capillary endothelium, and in corresponding bowel vessels. Compared to the response to PE alone, there was a significant increase in contraction to PE during incubation of arteries in the presence of S-BEL 25μM [PE alone: 6.9±2.4 mN; PE with S-BEL 12.7±2.5 mN: P=0.028, Wilcoxon]. In contrast, there was a significant time-dependent decrease in contraction to PE during artery incubation with control reagents [methyl acetate [the BEL solvent], Krebs buffer or R-BEL; PE alone: 9.8±2.5mN; PE with control reagents: 7.1±2.0mN: P=0.012, Wilcoxon]. There was no difference in contraction to KCl 60mM after incubation with S-BEL compared with control solutions [methyl acetate, Krebs buffer or R-BEL]. The post-S-BEL washout contractile response to PE was abolished [PE post-S-BEL: -1.2±0.7 mN; P=0.002, Friedman test; P=0.028 vs. pre-S-BEL PE response, Wilcoxon]. Contraction to PE after washout of control solutions was similar to the initial PE response.
Conclusions: Our findings suggest that iPLA2β influences receptor but not ion channel effects on tone in human internal mammary artery, mediating both early relaxant signalling and a longer-term contractile response. These results may provide new insight into mechanisms for ischaemia and are relevant to arteries widely used for CABG surgery. Further work is needed to elucidate the pathophysiological and therapeutic significance of iPLA2β as a signalling target for these biphasic, selective, receptor-mediated effects on artery tone.

P468 Akt inhibitors attenuate telomerase activation by the PPAR-gamma agonist pioglitazone in endothelial cells and endothelial progenitor cells

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Background: PPAR-γ agonists (thiazolidinediones, TZDs) such as pioglitazone are used for the treatment of type II diabetes. In addition to their action as insulin sensitizers, TZDs may mediate glucose-independent vascular effects. Telomerase and telomere-associated proteins regulate cellular regeneration and survival. Senescence of endothelial cells and endothelial progenitor cells (EPC) may be involved in the pathogenesis of vascular disease. Our previous studies demonstrated that pioglitazone activates aortic telomerase and prevents stress-induced endothelial apoptosis in mice in-vivo. The aim of this study was to determine the effect of pioglitazone on Akt and telomerase in cultured endothelial cells.
Methods and results: Bovine aortic endothelial cells (BAEC, passages 3-6) and human EPC (isolated by cultivation of mononuclear cells in selective medium for 4 days) were treated with 10μM/l pioglitazone for 24 hours. Western blots revealed that Akt phosphorylation was increased in both BAEC (178±27% vs. control, p<0.05) and EPC (282±56% vs. control, p<0.01) after pioglitazone treatment. The PPAR-γ agonist induced telomerase activation in BAEC (175±13% vs. vehicle-treated control cells, p<0.001, TRAP assay) and EPC (195±15% vs. control, p<0.01). Furthermore, protein expression of the telomere repeat-binding factor (TRF) 2 increased to 235±41% vs. controls (p<0.01) in BAEC and to 281±41% vs. control in EPC (p<0.01). In EPC, pioglitazone mediated downregulation of the protein expression of senescence marker p16 (23±16% vs. control, p<0.05) and the cell cycle inhibitor p53 (31±16% vs. control, p<0.01). Pinpointing further downstream mechanisms, bcl2/bax ratio was increased in TZD-treated bovine endothelial cells (284±92%, p<0.001), implicating that pioglitazone may inhibit the endothelial mitochondrial death pathway. TZD effects in BAEC and EPC require Akt, because pioglitazone-induced telomerase activation and TRF2 up-regulation were abolished in both cell types by co-incubation with the upstream Akt inhibitor LY294002 (10μM/l) or a direct Akt inhibitor (10μM/l).
Conclusion: Pioglitazone treatment activates telomerase, up-regulates telomere-stabilizing proteins and reduces senescence marker expression in

differentiated endothelial cells and endothelial progenitor cells. The effects depend on protein kinase B/Akt as an upstream regulator and involve down-regulation of the mitochondrial death pathway. These observations suggest that PPAR-γ agonists may improve endothelial stress resistance and susceptibility to senescence stimuli.

P469 Inhibition of monocyte chemotaxis by regulation of RhoA, a novel role for BNP in inflammation and immunity with potential therapeutic benefits for hypertensive heart disease and heart failure

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Purpose: B-type natriuretic peptide (BNP) is a quantitative marker for prognostic and diagnostic assessment of heart failure (HF).
Recent animal model data has ascribed an anti-inflammatory, cardioprotective role for BNP based on experiments with BNP receptor (NPRA) knock-out animals. The animals had enhanced proinflammatory cytokine gene expression and were more likely to develop or exacerbate pressure overload-induced fibrosis and HF.
Pressure overload-induced perivascular inflammation and fibrosis, early hallmarks of hypertensive heart disease (HHD), are thought to be mediated by monocyte chemoattractant protein (MCP)1–driven monocyte activation and migration to cardiac areas of injury. Since BNP has been linked to inflammation our research aimed to investigate the effects of BNP on monocyte function in healthy controls and in patients with HHD and HF.
Methods: THP1 monocytic cells and human primary monocytes (PM) were used. BNP signaling pathway components (NPRA, cGMP, PKG1) were identified in THP1 by Western blotting, ELISA, QPCR. Transwell migration assays with(out) BNP treatment (1uM) were done to assess monocyte chemotaxis to MCP1. MCP1 receptor (CCR2) expression was assessed by flow cytometry. RhoA pull-down assays and intracellular calcium measurements were done to study downstream effects of BNP/NPRA signaling.
Results: Novel expression of NPRA was identified on monocytes. NPRA was proven functional as treatment with BNP increased intracellular cGMP levels (2- to 3-fold). Importantly, BNP was shown to inhibit MCP1-induced THP1 chemotaxis (70%, n=6) and PM chemotaxis (50%, n=4). Migration assays with PM derived from patients with HHD with/without HF (grouped based on plasma BNP levels) also showed an effect of BNP on monocyte chemotaxis.
To identify mechanisms by which BNP inhibits chemotaxis, effects on CCR2 were investigated. BNP didn't interfere with CCR2 regulation. Effects of BNP on RhoA and calcium were also studied. BNP could inhibit RhoA activation in MCP1-stimulated THP1 (40%, n=3). BNP didn't alter intracellular calcium levels in MCP1-stimulated THP1.
Conclusion: Our data provide novel evidence for a direct role of BNP/NPRA pathway in human monocytes. BNP could inhibit monocyte migration to MCP1, which was consistent with the inhibition of RhoA activation by BNP. Thus, the data implicate BNP as an anti-inflammatory agent opposing the recruitment of leukocytes to areas of injury. Although elevated BNP levels confer an adverse prognosis, our research provides further evidence for BNP as a cardio-protective hormone upregulated as part of an adaptive compensatory response to combat excess inflammation.

P470 Autoregulation of human relaxin-2 critically involves relaxin, glucocorticoid receptor and stat5 binding to glucocorticoid response half-sites in the relaxin-2 promoter

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The relaxin (Rlx) peptide family exerts diverse biological effects - from regulating central nervous processes and reproduction to modulating cardiovascular and kidney function as well as connective tissue composition - through different G protein-coupled receptors (RXFP1 through 4). We reported earlier that relaxin-2 acts as compensatory mediator in human congestive heart failure and reported encouraging results in the first clinical pilot trial. Additionally, relaxin interacts with the human glucocorticoid receptor (GR) in an agonistic manner. We have recently shown that a positive self-regulatory loop of human relaxin-2 expression exists which involves GR activation and relaxin/GR binding to half-glucocorticoid response elements (half-GREs) in the relaxin-2 promoter. The following experiments were designed to investigate potential transcriptional co-factors of Rlx/GR, particularly factors of the signal transducer and activator of transcription (Stat) and CCAAT/enhancer-binding protein (c/EBP) families.
Transient transfections of truncated or selectively mutated GR into HT-29 cells, devoid of constitutive GR expression, revealed full dependence of Rlx-GR signaling of an intact GR-Stat5 binding site. Correspondingly, Stat inhibitors were capable of completely inhibiting the Rlx-induced but not the dexamethasone-related response in GRE luciferase reporter assays in HeLa cells. In Stat luciferase reporter assays performed in HeLa, Rlx increased Stat3 activation and DNA binding but inhibited that of Stat5. Rlx enhanced protein expression and promoted phosphorylation of the Stat3, Stat5, and c/EBP transcription factors in HeLa cells. We visualized, by immunofluorescence, nuclear co-localization of relaxin and GR with Stat5 but not with Stat3 or c/EBP in response to relaxin exposure. In contrast, the structurally related peptide insulin did not induce nuclear translocation of Stat5. Gel shift assays indicated binding of relaxin-activated GR together with Stat5 but not with Stat3 or c/EBP to half-GREs located between 160 and 200 bp upstream of transcription start of the Rlx-2 promoter.
These results indicate that Stat5, but not Stat3 or c/EBP, is a pivotal transcriptional co-factor of the Rlx/GR signaling cascade regulating Rlx-2 gene expression. This finding deepens our understanding of the complex relaxin signaling and may also be relevant to the emerging clinical cardio-vascular use of the peptide.

P471 Chronic limb ischemia increases coronary blood flow and improves left ventricular function in the post-ischemic isolated rat heart

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Purpose: The responsible for collateral growth angiogenetic stimuli released during chronic limb ischemia, may also act remotely, at ventricular myocardium. We examined the functional effect of new developed myocardium coronary collaterals on infarct size without reperfusion, on left ventricular function after ischemia/reperfusion, on coronary flow after regional myocardial ischemia.
Methods: In 45 Wistar rats, hind limb ischemia was induced by excision of the left femoral artery, while 45 were sham-operated. Four weeks thereafter, in first series (n=50) myocardial infarction was induced by permanent left coronary artery ligation. Infarct size was measured 24 hours post-ligation. In second series (n=20), indices of left ventricular function were measured in isolated, beating hearts after zero-flow global ischemia (20min), followed by reperfusion (45min). Coronary flow was measured (n=20) under maximum vasodilatation at 5 different perfusion pressures before and after coronary ligation in third series.
Results: Infarct size was smaller ($p<0.001$) after limb ischemia (24.4±8.1%) compared to controls (46.2±9.5%). Indices of left ventricular function at the end of reperfusion (divided by baseline values) were improved after limb ischemia (left ventricular peak systolic pressure: 0.96±0.11 versus 0.83±0.09, p=0.018; developed pressure: 0.68±0.06, versus 0.59±0.05, p=0.008; max+dp/dt: 0.70±0.08 versus 0.59±0.04, p=0.004; max-dp/dt: 0.86±0.14 versus 0.72±0.10, p=0.041, respectively). Ischemic contracture occurred at 11.92±3.85 min and 15.18±1.66 min of ischemia in control and limb ischemia hearts respectively (p=0.045). In contrast to controls (F=5.65, p=0.00182) where a significant decrease was observed, coronary flow post-ligation (F=1.36, p=0.28) remained unchanged after limb ischemia.
Conclusions: Chronic hind limb ischemia decreases infract size and attenuates left ventricular dysfunction by increasing coronary collateral blood flow.

P472 Classical macrophage activation induces an adverse spectrum of matrix metalloproteinases through mitogen activated kinases and NF-kappaB

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Background and purposes: Overproduction of matrix metalloproteinases (MMPs) from foam cell macrophages occurs in atherosclerotic plaques. However, the mechanisms underlying detrimental MMP expression is uncertain.
Methods: We studied expression of a broad range of MMPs in M-CSF differentiated human macrophages using quantitative RT-PCR and western blotting. All experiments were replicated 5-7 times. Macrophages were classically (bacterial lipopolysaccharide and interferon-r) or alternatively activated with interleukin-4 for 18 (mRNA) or 48 (protein) hours. ERK 1/2, c-Jun N-terminal Kinase (JNK) and phosphoinositide-3 kinase (PI3K) were inhibited pharmacologically (PD98059, Sp600225, Ly294002) and NFkB was inhibited by gene transfer of IkBα or dominant negative-IKK2.
Results: Classical activation significantly up-regulated expression of MMPs-1, -10, -12, -14, and 25 by 10, 12, 4, 8, 7-fold and MMP-3 became detectable. TIMP-3 was downregulated 2-fold. Upregulation of MMPs was dependent on active ERK 1/2 (except MMPs-12, -14 and -25), JNK (except MMP-12), PI3K and NFkB. Alternative activation of macrophages increased MMP-12 and TIMP-3 by 5.1 and 2.3-fold, which was reversed by ERK 1/2, JNK and PI3K inhibitors for MMP-12 only. Changes in MMPs-10, -12, -14 and TIMP-3 were confirmed at the protein level. There was no significant activation or inhibition of MMPs-2, -7, -8, -9, -11, -17, -19, -23 and TIMPs-1, -2 expressions. Similar patterns of activation were found in macrophages loaded with ox-LDL.
Conclusions: Classical activation favours MMPs-1, -3, -10, -12, -14 and -25 over TIMPs expression while alternative activation selectively increases MMP-12 and TIMP-3. Differential dependence of MMP induction on signalling kinases underlies these effects and suggests targets for intervention.

P473 An alteration in monocyte subsets despite preserved endothelial function in young survivors of childhood acute lymphoblastic leukemia-marker of future cardiovascular events?

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Purpose: Adult survivors of childhood malignancy are at risk of late cardiovascular (CV) complications. Endothelial dysfunction and subendothelial accumulation of monocytes-derived macrophages precede atherosclerotic plaques. Our aim was to assess the CV risk profile, endothelial function and monocyte heterogeneity in young adult survivors of childhood acute lymphoblastic leukemia (post-ALL).
Methods: Brachial artery flow-mediated dilatation (FMD), classical CV risk factors, high sensitivity CRP, fibrinogen, resistin, plasminogen activator inhibitor type 1 (PAI-1), asymmetric and symmetric dimethylarginine (ADMA, SDMA) were determined in 24 young (age: 21±3 yrs) adult survivors of childhood ALL who completed chemotherapy ≥5 years ago as well as in 15 controls (age:23±3 yrs). Flow cytometry was used to identify monocyte subpopulations (CD14++CD16-, CD14++CD16+ and CD14+CD16++), which were further characterized by their expression of HLA-DR and β2-integrin CD11b/CD18.
Results: FMD did not differ between post-ALL (7.3±8.8%) and controls (6.6±4.6%). The analyzed risk factors were comparable in both groups except for higher level of fibrinogen (3.3±0,6 vs. 2.8±0,7 g/l, p=0.03) and SDMA (0.99±0.34 vs. 0.67±0.18 μmol/l, p=0.006) in post-ALL patients. There were no intergroup differences in total monocyte counts. In post-ALL subjects we observed a higher relative frequency of CD14++CD16+ monocytes (6.7±3.9 vs. 4.3±2.4%, p=0.03), with lower HLA-DR expression (median fluorescence intensity [MFI]: 40182±8780 vs. 50277±16104, p=0.04). The percentage of CD14+CD16++ monocytes was similar (3.5±1.4 vs. 3.8±1.4%), yet this subset exhibited higher expression of CD11b/CD18 integrin in the patients vs. controls (MFI: 940±426 vs. 697±246, p=0.04).
Conclusion: Higher prevalence of CD14++CD16+ monocytes and altered expression of cell surface receptors within both CD16+ monocyte subsets suggest immune dysregulation in young adult survivors of childhood ALL without endothelial dysfunction. As CD16+ monocytes are considered pro-inflammatory, this might be a very early marker of future CV morbidity.

P474 Immediate effects of cardiac resynchronization therapy on N-terminal pro-brain natriuretic peptide and systemic inflammation

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Purpose: We aimed to investigate the immediate effects of cardiac resynchronization therapy (CRT), on the serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), proinflammatory cytokines (IL-1β, IL-8 and TNF-α), matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-2 (TIMP-2) in patients with HF.
Methods: 40 patients (21M, 61±10 years) with HF (baseline NYHA class 3.2±0.6), wide QRS, significant LV dyssynchrony (time difference in peak septal wall to postero-lateral wall strain >130 msec by speckle-tracking radial strain) were investigated before (baseline), immediately and 1 week after CRT. The serum levels of NT-proBNP, IL-1β, IL-8, TNF-α, MMP-2 and TIMP-2 were measured at the same time by ELISA. Cardiac function was assessed echocardiographically.
Results: Immediately after CRT, there was an unexpected mild reduction in serum levels of some biochemical parameters. CRT led to an early decrease in NT-proBNP potentially. Thus, after the initiation of CRT, the serum level of NT-proBNP decreased with 11.07%. Also, immediately after CRT there was a positive correlation between changes in NT-proBNP and IL-1β (r=0.59, p<0.05). One week after CRT, there was a significant clinical improvement in all patients (NYHA class 1.2±0.6 vs. baseline 3.2±0.6), an extensive recovery of LV function (LVEF 29.31%±6.04% vs. baseline 20.83%±5.39%, p<0.05) and a LV reverse remodeling (i.e. LVTDV 213.78±90.22 mL vs. baseline 231.85±79.18 mL, p<0.05; LVTSV 157.15±75.75 mL vs. baseline 182.89±71.22 mL, p<0.05). It was observed a good correlation between changes in LVEF and NT-proBNP (r=0.45, p<0.05). Also, CRT positively influences extracellular matrix remodeling by decreasing serum levels of MMP-2 and increasing TIMP-2. The MMP-2/TIMP-2 ratio had decreased from 6.84 (baseline) to 4.18 at 1 week after CRT.
Conclusions: Our results suggest that CRT could immediately improve the systolic and diastolic synchrony of the LV and ventricular function. After the initiation of CRT, neurohormonal and proinflammatory activity were reduced and the decrease in serum concentration of NT-proBNP, IL-1β and TNF-α predicts a clinical improvement during follow-up. The decrease in NT-proBNP potentially immediately post CRT, seem to be, at least in part, determined by the reduction of the peripheral markers of immune activation in patients responding to CRT. Also, changes in proinflammatory cytokines activity were related to changes in serum MMP-2 and TIMP-2 levels. This suggests, that the decrease in MMP-2/TIMP-2 ratio leads to reverse LV remodeling.

P475 Transcriptional control of intracellular adhesion molecule-1 (ICAM-1) promoter in human endothelial cells by mineralocorticoid receptor activation

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In clinical trials, Mineralocorticoid Receptor (MR) antagonists decrease cardiovascular mortality and ischemia suggesting beneficial role of MR function inhibition.We have shown that human coronary and umbilical endothelial cells (HUVEC) express functional MR. In endothelial cells MR activation by aldosterone promoted transcription of ICAM-1 (1.5 fold). Most importantly cell adhesion assays demonstrated that aldosterone promotes leukocyte adhesion to ECs, an effect that was inhibited by spironolactone and ICAM-1 blocking antibody. Furthermore, MR activation was able to up-regulate VCAM and E-selectin mRNA expression (2 and 3.5 fold respectively), whereas P-selectin was not regulated by MR. In transient transfection experiments performed in HUVEC, we have shown that aldosterone is able to activate (2 fold) a 3 Kb promoter region upstream the transcription start site of human ICAM-1 gene. Co-incubation with spironolactone was able to inhibit the effect of aldosterone, confirming the presence of elements responsive to signaling pathway(s) activated by MR. In order to localize and characterize MR responsive cis-element(s) and the corresponding transcription factor(s) binding to this regulatory region, five 5'-deletion constructs of ICAM-1 promoter were subcloned in a vector upstream of the luciferase gene. Data of transcriptional activity showed the presence of regulatory element(s) required for ICAM-1 expression via MR in the promoter region between nt-872 and -1141. Bioinformatics analysis of this region revealed the presence of four different potentially involved regulatory elements: three SP1 binding sites, one NF-κB binding site, one AP1 binding site and one GRE/MRE. The role of each of these transcription factors in MR-mediated regulation of ICAM-1 expression has been explored, using both dominant negative transcription factors and site specific mutagenesis of the putative binding sites. Specific inhibition of c-jun and NF-κB signaling determined a significant reduction of aldosterone-induced ICAM-1 transcription. These studies explore the molecular mechanism for the pro-inflammatory effects of MR activation in the vasculature that may contribute to the protective effects of MR antagonists in clinical trials.

P476 Induction of heme oxygenase ablates epicardial and perirenal adiposity, and suppress diabetic cardiopathy and nephropathy in insulin-resistant Zucker diabetic fatty rats

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Visceral adiposity has been implicated in the pathophysiology of vital organs including the heart and kidneys. With the escalation of obesity and related cardiometabolic complications, novel therapeutic strategies are needed. We investigated the effects of an upregulated heme oxygenase (HO) system on epicardial and perirenal adiposity in Zucker diabetic fatty (ZDF) rat, an obese model of type-2 diabetes (T2D).
The administration of the HO inducer, heme-arginate to ZDF rats markedly reduced epicardial and perirenal adiposity, and suppressed several pro-inflammatory/oxidative mediators including, nuclear factor-kappaB (NF-kB), c-Jun-N-terminal kinase (JNK), activating-protein (AP-1), endothelin (ET-1), tumour necrosis factor-alpha (TNF-α) interleukin (IL-6), IL-1β, and 8-isoproatane whereas adiponectin, HO-1, HO activity, cGMP and the total anti-oxidant capacity were markedly enhanced. These were accompanied by reduced cardiac fibrosis and hypertrophy as well as reduced albuminuria and proteinuria, but enhanced creatinine clearance, suggesting improved renal function. Furthermore, heme-arginate reduced insulin resistance (HOMA-IR), suppressed protein-tyrosine phosphatase-1B (PTP1B), but increased GLUT4, suggesting improved glucose metabolism. In contrast, the HO-blocker stannous-mesoporphyrin (SnMP) nullified the protective effects of heme-arginate, aggravating glucose metabolism, cardiac fibrosis/hypertrophy and renal function.
Since TNF-α and JNK impair insulin-signaling, and NF-kB activates TNFα, IL6 and IL-1β, the high levels of these proinflammatory cytokines and oxidative transcription factors would create a vicious cycle that together with elevated levels of 8-isoprostane and ET-1 would exacerbate tissue injury and cellular compromise function in obesity. Therefore, the concomitant reduction of epicardial/perirenal adiposity and PTP1B in heme-arginate-treated animals, coupled to increased adiponectin, GLUT4 and creatinine clearance may account for improved glucose metabolism. and renal function. These data suggest that upregulating the HO system may be explored as a novel avenue in the search for remedies against visceral obesity and related complications like diabetic nephropathy and cardiopathy.

P477 The association between arterial stiffness, pulmonary impairment and inflammatory status in sarcoidosis

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Purpose: Sarcoidoisis (Sar) is a multisystemic granulomatous disease characterized by extensive local inflammation and affects multiple organs mainly lungs and lymph nodes. However, the relationship of pulmonary dysfunction with the vascular function remains unknown. In the present study we assessed the hypothesis that pulmonary impairment is associated with arterial stiffness in Sar patients.
Methods: 155 patients with Sar and 130 matched in age and sex healthy subjects (Cl) were included in the study. Sar patients were subdivided in 3 groups according to the pulmonary function test. Group "A was consisted from patients with normal pulmonary function-total lung capacity (TLC) >75% and diffusion lung capacity for carbon monoxide (DLCO) >75%- group "B" from patients with restrictive pulmonary Physiology - TLC >75%, DLCO <75% - and group "C" from patients with pulmonary fibrosis - TLC <75%, DLCO >75%. Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as a measure of arterial wave reflections. Serum levels of soluble intercellular cells adhesion molecule 1 (sICAM-1), tumor necrosis factor alpha (TNF-α) and IL-6 were measured in Sar patients by ELISA.
Results: Compare to Cl, Sar patients had significantly higher values of AIx (17.67±15.54% vs. 22.09±11.11%, p=0.004) and PWV (7.08±1.56 m/sec vs. 7.59±1.69 m/sec, p=0.009). Bivariate correlation showed that AIx in the Sar group was significantly correlated with age (r=0.563, p<0.001), TLC (r= -0.199, p=0.037), DLCO (r= -0.223, p=0.019), and sICAM-1 (r=0.181, p=0.05)). PWV was significantly associated with the age of the patient (r=0.498, p<0.001), TLC (r= -0.249, p=0.009), DLCO (r= -0.209, p=0.029) and sTNFα (p=0.200, r=0.05). Moreover post hoc test revealed that Sar patients with major pulmonary impairment (group "C") compared to those with normal pulmonary function test (group "A") had significantly increase serum levels of sICAM [372 (230, 704) ng/ml vs. 255 (208, 397) ng/ml, p=0.01] and IL-6 [1.26 (0.54, 2,69) pg/ml, 0.65 (0.40, 1,18) pg/ml, p=0.046] and significantly increase PWV (8.53±1.54 m/sec vs. 7.29±1.67 m/sec, p=0.02).
Conclusion: Pulmonary impairment is associated with arterial stiffness and increase inflammatory status in Sarcoidosis patients. These findings indicate that inflammation is probably the common pathogenetic mechanism causing arterial wall impairment and pulmonary dysfunction in this specific population.

P478 S100A12 is a marker of unstable thoracic aneurysms - a review of 50 cases

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The pathomechanisms for thoracic aortic aneurysms (TAA) and -dissection (TAAD) are multifactorial and poorly understood. We have previously shown that C57BL6/J mice that express human S100A12 in smooth muscle develop TAA in vivo. We explored expression of S100A12 in aortic tissue obtained from patients undergoing surgery for TAA/TAAD.
Methods: The pathology tissue bank of the University was searched and 20 cases of elective TAA repair were randomly chosen, along with 30 selected cases of urgent TAAD or stable TAA>6.5cm.
Results: In a series of 20 elective TAA repairs we found S100A12 expression in VSMC in 7 cases that localized to (i) atherosclerotic plaque, (ii) aortitis with necrotizing granulomas, and to the (iii) medial degeneration with chronic dissection. The remaining 13 cases had no histologic evidence of dissection and no S100A12 immunoreactivity. Six of the seven S100A12-positive patients had a complicated postoperative course including prolonged intubation, bleeding, cardiac arrest, and sepsis. In contrast, the 13 cases without S100A12 expression had no complications. The mean length of hospitalization was 24 (5-49)days for S100A12 positive and 8 days (5-13) for S100A12 negative cases (p=0.02).There were no statistically differences in age, gender, white blood cell count, renal function and Euroscore between those two groups. To test the hypothesis that S100A12 may predispose to TAAD, we examined additional 30 cases of either urgent TAAD or elective repair of TAA larger than 6.5 cm to account for severity. In TAAD (n=14) all had S100A12 positive cells within the dissected media; most of these S100A12-positive cells also expressed MPO, a marker for inflammatory cells, and S100A12 positive VSMC nearby the dissection plane. S100A12 was mildly expressed in 4 of 16 cases with severe TAA without clinical evidence of dissection.
Furthermore we found that knockdown of endogenous S100A12 in VSMC cultured from various patients with TAA/TAAD using shRNA attenuated gene and protein expression of critical mediators of apoptosis such as Fas, caspase 3 and DFFA.
Conclusion: S100A12is strongly expressed in inflammatory cells and in VSMC associated with necrotizing aortitis and with atherosclerosis, but not or only minimally in"stable" TAA associated with bicuspid aortic valve and Marfan Syndrome. In TAAD, S100A12 is strongly expressed in inflammatory and VSMC in all cases. Weaker expression was observed in VSMC adjacent to the necrotizing tissue, suggesting that S100A12 may not be only a marker of tissue necrosis, but could mediate VSMC apoptosis or necrosis and predispose to aortic dissection.

CARDIOVASCULAR MAGNETIC RESONANCE – MISCELLANEOUS

P479 Diagnostic performance of comprehensive magnetic resonance imaging for assessment of myocardial inflammation in patients with suspected acute vs. chronic myocarditis

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Objective: We sought to define prospectively the diagnostic performance of MRI for the assessment of myocarditis as compared to endomyocardial biopsy (EMB) in an unselected cohort of consecutive patients with suspected acute and chronic myocarditis.
Methods: 132 consecutive patients with suspected acute or chronic myocarditis were included. Patients had to fulfill indications for CMR imaging in suspected myocarditis according to a published consensus report ("JACC White Paper"). All patients underwent left ventricular EMB, cardiac catheterization for exclusion of coronary artery disease, and MRI on a 1.5 Tesla scanner (Intera, CV, Philips Medical Systems). Imaging protocols included T2-weighted imaging for calculation of the edema ratio (ER), T1-weighted imaging before and after contrast agent administration for calculation of the global relative enhancement (gRE) and assessment of late enhancement (LE) for detection of myocardial damage. Assessment and interpretation of ER, gRE, and LE were performed according to the JACC White myocarditis consensus paper. MRI imaging results were considered to be consistent with the diagnosis of myocarditis if 2 out of 3 (ER, gRE, LE) of the MRI criteria were positive.
The patient cohort was divided into patients with presumed acute myocarditis (symptoms equal to or < 14 days) and those with presumed chronic myocarditis (symptoms >14 days).
Results: In all patients, sensitivity, specificity and accuracy were 76, 54, and 68% respectively. Best diagnostic performance was seen in patients with suspected acute myocarditis (sensitivity 81%, specificity 71% and accuracy 79%). In contrast, diagnostic performance of MRI in patients with suspected chronic myocarditis was found to be in adequate (sensitivity 63%, specificity 40% and accuracy 52%).
Conclusion: The results of our study underline the usefulness of MRI in patients with suspected acute myocarditis. In contrast, with the current criteria, techniques and sequences, the diagnostic performance of MRI in patients with suspected chronic myocardial inflammation/myocarditis might be not sufficient to guide clinical management.

P480 Aortic stiffness estimated by cardiovascular magnetic resonance correlates with clinical events in patients with hypertrophic cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) is an autosomal hereditary disease characterized by inappropriate hypertrophy with loss of diastolic function. Sudden cardiac death can be the most devastating clinical events of HCM.
Noninvasive cardiovascular magnetic resonance (CMR) plays a paramount role in the diagnosis and management of HCM. Scarring, detected on late gadolinium-enhanced (LGE) CMR, has been correlated with wall thickness and ventricular arrhythmias.
Aortic stiffness has been identified as an important predictor of cardiovascular outcome independent of traditional cardiovascular risk factors. The value of Pulse wave velocity (PWV) as a marker of arterial stiffness and a predictor of fatal and nonfatal cardiovascular events over traditional risk factors has been established. Assessment of aortic stiffness with velocity-encoded cardiac magnetic resonance (VENC-CMR) is an attractive and promising strategy as this measurement does not depend on the knowledge of central arterial pressure. Recently, aortic stiffness as indicated by PWV estimated by VENC-CMR is increased in HCM which suggests the vascular involvement as well as myocardium. The aim of this study was to investigate correlation with PWV by VENC-CMR and clinical events in patients with HCM.
Methods: Fifty patients with HCM were studied by CMR. Aortic arch PWV was acquired using the transit time of the flow curves and the distance between the ascending and descending aorta locations of the phase contrast acquisition. Cardiac fibrosis was evaluated according to the presence of LGE on CMR. The extent of LGE was expressed as a percentage of enhanced area in the total myocardium on short axis views. We evaluated the relationship between PWV and LGE, ventricular tachycardia (VT), BNP and maximum LV wall thickness.
Results: Mean age was 69±12 years. The prevalence of LGE was 68%. Patients

with LGE had a significantly higher PWV than patients without LGE (mean±SD 10.6±7.2m/s versus 8.06±4.0m/s, P<0.05). Patients with ventricular tachycardia showed a higher PWV than patients without. The extent of LGE had positive correlation with PWV.
There were no statistically significant correlations between PWV and Left ventricular wall thickness.
Conclusion: In HCM, vascular dysfunction indicated as increase aortic stiffness exists in patients with myocardial damage and ventricular arrhythmias. PWV by VENC-CMR might provide an additional clinical marker for risk stratification of patients with HCM.

P481 Magnetic resonance angiography versus computed tomographic angiography in hemodialysis patients with suspected coronary artery disease

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Background: Although computed tomographic angiography (CTA) for the non-invasive detection of coronary artery disease (CAD) has been established, the presence of severe calcified lesions remains a limitation. The aim of this study was to compare non-contrast magnetic resonance angiography (MRA) with CTA in hemodialysis patients presenting with suspected CAD.
Methods: In hemodialysis patients who had undergone 32-channel 1.5 Tesla free-breathing whole-heart coronary MRA and 256-slice CTA, coronary lesions were assessed using X-ray coronary angiography (CAG) as the reference standard. CAD was defined as the presence of a ≥50% reduction in diameter on CAG. We used an analysis of the receiver-operating characteristic (ROC) curves to assess MRA and CTA. Two independent blinded observers evaluated all MRA and CTA studies for coronary stenosis using curved multi-planar reconstruction image.
Results: Forty-nine patients (age 64.7±11.3 years, 52% male) were evaluated, and 147 coronary vessels were analyzed. CTA was successfully completed in all vessels (Agatston score 535.5±804.3). However, 2 vessels failed to be evaluated on MRA. We identified CAD in 12 vessels of 6 patients. In the vessel-based analysis, the area under the ROC curve for MRA (0.89) was greater than that for CTA (0.81). MRA had similar sensitivity (92% vs. 92%, p=1.00), higher specificity (87% vs. 71%, p=0.035), and higher diagnostic accuracy (87% vs. 74%, p=0.045) for detection of CAD as compared with CTA. Inter-observer agreement for detection of coronary stenosis was 0.74 in MRA and 0.80 in CTA.
Conclusions: Non-contrast MRA clinically offers feasible diagnostic performance in detecting CAD noninvasively in hemodialysis patients with severe calcified coronary lesions. MRA evaluation is a more reliable method to detect CAD as compared with CTA.

P482 Cardiac magnetic resonance evaluation of unexplained cardiac arrest survivors

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Purpose: Cardiac magnetic resonance (CMR) may be useful for the diagnosis of cardiovascular disease associated with unexplained cardiac arrest (UCA). Accordingly, aim of the present study was to assess the prevalence of CMR structural abnormalities in UCA survivors, and to evaluate their relation with follow-up events.
Methods: Consecutive patients with resuscitated cardiac arrest due to documented ventricular tachycardia (VT) or ventricular fibrillation (VF) were enrolled. UCA was defined on the basis of normal ECG after resuscitation, normal coronary arteries on coronary angiography, and preserved LV ejection fraction (≥45%) on echocardiography. Patients fulfilling these criteria underwent comprehensive CMR study, to assess LV and right ventricular function, myocardial fatty infiltration, edema, and necrosis/fibrosis. After CMR, all patients received an implantable cardioverter defibrillator (ICD). Follow-up was performed evaluating the occurrence of cardiac death and appropriate ICD intervention.
Results: Between January 1, 2009 and December 31, 2010, 37 patients were admitted because of resuscitated cardiac arrest; 7 (19%) patients fulfilled the diagnostic criteria for UCA (Table). CMR identified structural abnormalities in 4 (57%) patients (Table). After a median follow-up of 161 days, no patient died, while 2 (29%) patients experienced new major arrhythmias, requiring ICD intervention. In both patients, baseline CMR had shown structural abnormalities.
Conclusions: CMR shows major structural changes in a significant number of UCA survivors. New major arrhythmias occurred in half of the patients with abnormal CMR. Consequently, CMR may be useful to better characterize the pathologic substrate of UCA and to better tailor specific therapy, in order to prevent follow-up events.

N°	Gender/Age	Cardiac Rhythm	Time from UCA to defibrillation (min)	Time from UCA to CMR (days)
1	F/62	VF	13	5
2	M/68	VF	8	9
3	F/48	VF	9	2
4	M/51	VF	6	7
5	M/33	VF	14	9
6	M/40	VF	15	8
7	M/61	VT	7	1

N°	CMR structural abnormalities	Postulated etiology	Length of follow-up (days)	Follow-up events
1	+	Acute MI with spontaneous recanalization	161	-
2	+	Chronic myocarditis	105	1 SVT, several NSVT
3	-	-	97	-
4	-	-	166	-
5	-	-	476	-
6	+	Chronic MI with spontaneous recanalization	638	1 SVT and 1 NSVT
7	+	Arrhythmogenic RV cardiomyopathy	67	-

Characteristics of study population.

P483 Coronary angiography during percutaneous coronary intervention in STEMI: estimation of myocardial area at risk and microvascular obstruction

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Background: Quantification of myocardial area at risk (AAR) and microvascular obstruction (MVO) in acute coronary syndromes has important prognosis implications. BARI and APPROACH scores are angiographic methods widely used to provide a quick estimation of the AAR, but they have not been directly validated. Also Myocardial Blush grade (MBG) is an angiographic method to assess myocardial perfusion after a myocardial infarction, but the correlation with MVO estimated with cardiac magnetic resonance (CMR), the reference technique, has not been tested.
Objectives: To compare the calculated AAR and MVO obtained with CMR and the angiographic methods for the quantification of both parameters in the setting of patients with an AMI: BARI and APPROACH for AAR and MBG for MVO.
Methods: In a prospective study, 70 patients with a first successfully reperfused ST-segment elevation AMI, CMR was performed in the first week after percutaneous coronary intervention. T2-STIR sequences were used to assess AAR and late enhancement sequences to evaluate MVO. Two experienced hemodinamists estimated AAR using both angiographic scores, and MBG for myocardial perfusion. The collateral blood supply was measured using the Rentrop scale.
Results: The mean percentage AAR in T2-STIR was 36,9% (SD: 14,3%). The Rentrop scale was ≤1 in 86% of the patients. BARI and APPROACH showed a strong correlation with T2-STIR to estimate the AAR (r=0,77; p<0,001 and r= 0,8; p<0,001 respectively). Better correlations were observed for anterior AMI rather than other locations (r=0,7 vs r=0,5 respectively for both scores). Moreover, patients with an excellent MBG presented minimal areas of MVO (median values): 2,4 gr, 2,8 gr and 0,7 gr for MBG 1 to 3, respectively (p=0,04).
Conclusions: The BARI and APPROACH angiographic scores constitute excellent methods for the estimation of the AAR in current clinical practice with more accurate results when used in anterior infarctions. Furthermore, the presence of an excellent MBG is a useful indicator of preserved microvascular flow.

P484 Left ventricular volumes, mass and function normalized to the body surface area, age and gender from CMR in a large cohort of well-treated thalassemia major patients without myocardial iron overload

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Purpose: Our aim was to establish the ranges for normal left ventricular (LV) parameters normalized to the influence of body surface area (BSA), age and sex from Cardiovascular Magnetic Resonance (CMR) in a large cohort of TM patients without myocardial iron overload.
Methods: We selected 142 patients with no known cardiac risk factors or disease, normal ECG, no myocardial fibrosis and no myocardial iron (all segments with T2*≥ 20 ms). Moreover, we studied 71 healthy subjects matched for age and sex. LV parameters were evaluated by cine images using MASS® software. End-diastolic, end-systolic and stroke volumes and mass were normalized to BSA (EDVI, ESVI, SVI, massI).
Results: Table 1 (see p. 43) shows the comparison of CMR parameters in TM patients and healthy subjects and the cut-off of normality (mean – 2SD). Significantly higher EDVI and SVI were found only for males <14 and >30 years. Higher LVEF was found for males <14 years. In TM patients all volume indexes were significantly larger in males than in females. In males the ESVI and the EF were significant different among the age groups.
Conclusion: In well-treated TM patients significant differences in LV parameters compared to controls were limited to males <14 years and >30 years. Appropriate "normal" reference ranges normalized to BSA, sex and age should be used to avoid misdiagnosis of cardiomiopathy.

Abstract P480 – Table 1

	< 14		14-20		20-30		30-40		>40	
	TM	H	TM	H	TM	H	TM	H	TM	H
Males	N=7	N=7	N=6	N=6	N=25	N=15	N=23	N=11	N=6	N=5
EDVI (ml/m^2)	94±18 (58)	75±11	96±20 (56)	91±20	103±17 (69)	101±13	92±15 (62)	80±11	94±9 (76)	75±11
ESVI (ml/m^2)	31±6 (19)	24±6	38±8 (22)	35±14	38±8 (22)	39±9	32±6 (20)	29±6	29±6 (17)	28±10
SVI (ml/m^2)	63±14 (35)	51±7	57±12 (33)	56±8	65±10 (45)	62±9	59±10 (39)	51±10	64±8 (48)	47±8
Mass I (g/m^2)	57±7 (43)	68±5	57±13 (31)	71±7	66±12 (42)	77±12	62±12 (38)	66±10	68±16 (36)	74±11
EF (%)	66±4 (58)	54±6	60±2 (56)	66±14	63±3 (57)	62±6	65±3 (59)	65±8	68±6 (56)	62±9
Females	N=2	N=2	N=8	N=6	N=24	N=6	N=33	N=8	N=8	N=5
EDVI (ml/m^2)	63±8 (47)	62±4	81±8 (65)	80±9	83±16 (51)	78±9	77±11 (55)	79±10	82±19 (44)	77±16
ESVI (ml/m^2)	23±1 (21)	22±8	30±6 (18)	31±3	30±8 (14)	30±4	26±6 (14)	29±7	28±8 (12)	28±12
SVI (ml/m^2)	40±7 (26)	41±4	49±3 (43)	49±6	53±9 (35)	48±6	51±6 (39)	50±8	54±11 (32)	49±6
Mass I (g/m^2)	34±3 (28)	59±19	47±8 (31)	56±6	53±9 (35)	54±12	52±9 (34)	55±13	51±12 (27)	56±5
EF (%)	63±3 (57)	46±17	63±4 (55)	62±4	65±5 (55)	62±3	66±5 (56)	63±7	66±4 (58)	63±7

P485 Right ventricular volumes and function normalized to body surface area, age and sex in a large cohort of well-treated thalassemia major without myocardial iron overload

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Purpose: Cardiovascular Magnetic Resonance (CMR) allows to quantify right ventricular (RV) parameters with excellent reproducibility and accuracy. We aimed to establish the ranges for normal RV parameters normalized to the influence of body surface area (BSA), age and sex from CMR in a large cohort of TM patients without myocardial iron overload.
Methods: We selected 142 patients enrolled in the MIOT network with no cardiac risk factors or disease, normal ECG, no myocardial iron overload (all segments with T2*$\geq$20 ms) and no myocardial fibrosis. Moreover, we studied 71 healthy subjects matched for age and sex. RV parameters were quantitatively evaluated in a standard way by cine images using MASS® software. End-diastolic, end-systolic and stroke volumes were normalized by BSA (EDVI, ESVI, SVI).
Results: Table 1 shows the comparison of the CMR parameters in TM patients and healthy subjects and the cut-off of normality. TM males (except age group 14-20 yrs) showed significantly higher ejection fraction (EF). In TM patients all volumes indexes were significantly larger in males than in females while the EF was not different. In both sexes the volumes were no different among the age groups, while in males the EF was significant different.
Conclusion: In a large cohort of well-treated TM patients males showed significantly higher RV EF compared to controls. Appropriate "normal" reference ranges normalized to BSA, sex and age should be used to avoid misdiagnosis of cardiomiopathy in TM patients.

P486 Non-invasive screening of coronary artery disease in a healthy population by using coronary magnetic resonance angiography

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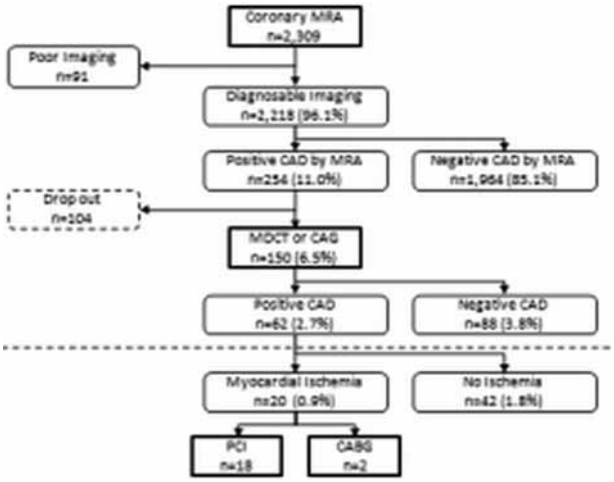
Purpose: Coronary magnetic resonance angiography (MRA) is a non-invasive modality that requires no contrast medium or radiation exposure. It is therefore considered an appropriate diagnostic tool to screen for coronary artery disease (CAD). We examined the performance of MRA in a healthy population.
Methods: A total of 2,309 consecutive healthy subjects who visited our hospital for a medical checkup between August 2004 and May 2010 were examined. MRA was performed using 1.5T-MRI (Intera Achieva, Philips) with a 5ch cardiac coil. Significant stenosis was defined as $\geq$75% diameter, and the cases whom significant stenosis was detected were confirmed by coronary CT or CAG. We also analyzed the accuracy and sensitivity of coronary MRA.
Results: We obtained diagnosable MRA images from 2,218 (96.1%) subjects, and 254 cases (11.0%) with significant stenosis were identified by MRA. Of these, 150 (6.5%) received a coronary CT or CAG, and 62 cases (2.7%) had significant stenosis corresponding to the MRA. The positive predictive value for CAD by MRA was 41.3%. In addition, 20 cases (0.9%) were positive for myocardial ischemia on myocardial perfusion imaging, 18 required PCI, and 2 had CABG.



Flow chart.

Conclusion: The screening value of MRA for detecting significant CAD was relatively high (2.7%) compared to screening methods for other disease. Coronary MRA is therefore a useful method for screening the healthy population for CAD.

P487 Blood oxygen level dependent cardiovascular magnetic resonance (BOLD-CMR) can detect changes in myocardial hemoglobin oxygenation during mild hypo- and hypercapnia in healthy volunteers

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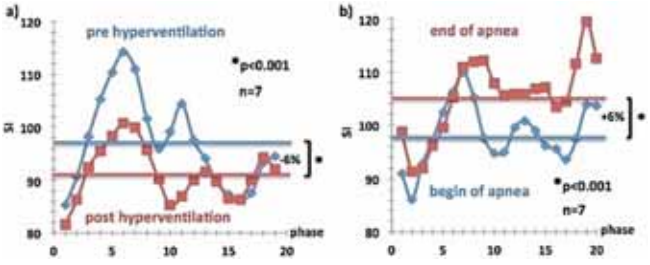
Purpose: BOLD-CMR uses de-oxygenated hemoglobin (Hb) as an endogenous contrast. The signal intensity (SI) depends on Hb-oxygenation, O2-extraction, and blood flow. The aim of this study was to investigate whether BOLD-CMR can detect changes in myocardial oxygenation during mild hypo- and hypercapnia in healthy individuals.
Methods: Fifteen healthy volunteers were scanned with a BOLD sensitive modified SSFP cine sequence on a clinical 1.5T scanner (hypocapnia n=8, hypercapnia n=7). BOLD images were acquired and SI was measured and averaged for the first and last two BOLD cines during 1 min of apnea in the hypercapnic group, whereas images were acquired prior to and post 1 min of hyperventilation in the hypocapnic group. SI were averaged and compared over all cardiac phases. Immediately before and after image acquisition capillary blood gases were measured.

Abstract P481 – Table 1

	<14		14-20		20-30		30-40		>40	
	TM	H	TM	H	TM	H	TM	H	TM	H
Males	N=7	N=7	N=6	N=6	N=25	N=15	N=23	N=11	N=6	N=5
EDVI (ml/m^2)	88±16 (56)	80±12	89±16 (57)	89±17	96±21 (54)	103±17	91±16 (59)	82±13	90±13 (64)	81±9
ESVI (ml/m^2)	26±3 (20)	31±8	36±7 (22)	35±9	34±8 (18)	44±12	33±8 (17)	33±8	28±6 (16)	35±3
SVI (ml/m^2)	61±16 (29)	49±6	53±11 (31)	54±10	61±18 (25)	60±9	58±11 (36)	45±17	62±8 (46)	46±8
EF (%)	68±6 (56)	62±5	59±5 (49)	61±5	64±4 (56)	58±6	64±5 (54)	61±7	69±3 (63)	57±5
Females	N=2	N=2	N=8	N=6	N=24	N=6	N=33	N=8	N=8	N=5
EDVI (ml/m^2)	53±16 (21)	61±1	77±8 (61)	79±9	78±14 (50)	78±12	73±13 (47)	77±9	74±11 52)	70±16
ESVI (ml/m^2)	18±1 (17)	20±4	29±5 (19)	30±5	28±8 (12)	31±9	24±7 (10)	26±6	26±5 (16)	25±12
SVI (ml/m^2)	35±5 (25)	41±3	47±4 (39)	49±7	51±9 (33)	47±7	49±8 (30)	51±10	47±6 (35)	45±5
EF (%)	64±9 (46)	68±6	62±3 (56)	62±6	65±6 (53)	61±7	68±5 (58)	66±8	67±6 (55)	66±8

Results: One subject was excluded in the hypocapnia group due to motion artifacts. The hypocapnia groups showed a mean SI drop of 6% ($p<0.001$, n=7) after 1 min of hyperventilation (fig. 1a) while a mean SI increase of 6% ($p<0.001$, n=7) was observed over 1 min of apnea (fig. 1b). PCO2 dropped significantly from 27.9±4.1 mmHg to 22.0±3.2 mmHg (p=0.02) after hyperventilation. Post breathhold, no significant change in pCO2 was noted. PO2 did not change in either group.



Changes in BOLD-SI

Conclusion: Our data suggest that BOLD-CMR detects changes of myocardial oxygenation related to vasoconstriction/vasodilatation during hypo- and hypercapnia

P488 Blood oxygen level dependent cardiovascular magnetic resonance (BOLD-CMR) for assessment of significant coronary artery stenosis, a comparison with fractional flow reserve (FFR)

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Purpose: Changes in myocardial tissue oxygenation can be detected with blood oxygen level–dependent (BOLD) cardiovascular MRI (CMR) using the magnetic properties of haemoglobin. The objective of this study was to validate whether BOLD-sensitive CMR images can detect an abnormal myocardial tissue response to adenosine infusion in patients with CAD, when compared to fractional flow reserve (FFR).
Methods: Patients undergoing clinically indicated coronary angiography underwent BOLD CMR scans using a clinical 1.5T scanner. Three short axis BOLD cine images were captured during baseline and during adenosine-induced coronary hyperaemia. The mean segmental percent signal intensity (SI) changes were calculated between baseline and hyperaemia in the subendocardial myocardium at basal, mid, and apical regions using the 16-segment model. Segmental ΔSI% in the corresponding coronary territory was defined as ischaemic (using a cut-off of <0.80) or non-ischaemic by FFR.
Results: Twenty-six patients were enrolled in the study (3 were excluded, as they were unable to tolerate CMR) leaving 23 patients (average age 61±9 years) with 262 myocardial segments (baseline and adenosine) subtended by an FFR for analysis. 77 (29%) segments were excluded due to pre-defined criteria for poor image quality, 24 (9%) at baseline and 53 (20%) during adenosine. Sixty-seven paired myocardial segments subtended by a FFR were compared, 38 segments had FFR values <0.80, 29 had FFRs of ≥ 0.80. Mean SI change was significantly less in patients with abnormal FFR values (0.23% ± 9.40%), in comparison to patients with normal FFR values (9.37% ± 10.07%; p=0.0003) when comparing all segments. There was also a significance difference when the average of all segments subtended by a single FFR were compared (0.73% ± 5.34% vs. 10.53% ± 8.25%; p=0.02).
Conclusion: A blunted hyperemic response to adenosine detected with BOLD-sensitive CMR using a 1.5T scanner can identify functionally significant coronary artery stenosis. However, image quality remains a limitation of the approach. Most excluded segments were from early studies, suggesting improved acquisition quality with experience.

P489 Recurrence rate after atrial fibrillation ablation and comparison of different ablation techniques in patients with variant pulmonary vein anatomy detected by cardiac MRI

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Background: Cardiac MRI (cMRI) has become an effective tool to identify the anatomy of the left atrium and the pulmonary veins (PV) prior to pulmonary vein-ablation (PVI) in atrial fibrillation (AF) patients. Anatomical variations of the PVs are achallenge for a successful ablation procedure.
Objective: We sought to evaluate the success of catheter ablation in patients with anatomical variations of the PVs and the influence of different ablation techniques on the ablation success rate.
Methods and results: 254 patients (176male, 62.3±10.5 years) with AF were included into this study. All patients received a cMRI angiography of the PVs prior to PVI. Normal anatomy of the PVs (2 left, 2 right) was found in 178 patients (70.08%), whereas a common trunk/ostium of the left PVs was detected in 72patients (28.35%), with a common trunk of the right PVs was detected in 4 patients (1.57%, Figure 1). 11 patients (15.28%) with a common trunk of theleft PVs underwent Cryo-Ablation, whereas 61 patients (84.72%) received ablation with radiofrequency energy (RF). Mean follow-up time was 136 days. Recurrent AF was detected in 54 patients (30.34%) with normal anatomy, in 32 patients (44.44%) with common trunk of the left PVs (p=0.04, Figure 2) and 3 patients (75%) with common trunkof the right PVs. Percentage of recurrencewas not significant different comparing Cryo- and RF-Ablation (18.18% vs. 49.18%, p=0.097, Figure 3).

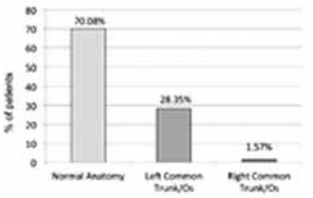

Figure 1: Percentage of patients with normal anatomy, left common trunk/ostium and right common trunk/ostium.

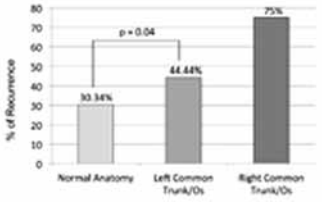

Figure 2: Recurrence rate in patients with normal anatomy, left common trunk/ostium and right common trunk/ostium.

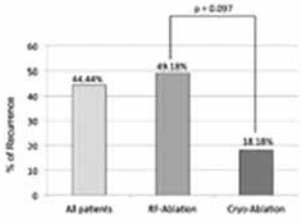

Figure 3: Recurrence rate in patients with variant PV anatomy according to ablation technique.

Conclusion: From our preliminary results, patients with a variable anatomy of the left or right PVsappear to have a higher risk of recurrence after PVI. Cryo- and RF ablation arefeasible techniques in these patients, as both techniques appear to have acomparable ablation success rates. Nevertheless, new ablation strategies shouldbe considered to improve overall outcome in these patients.

P490 The natural time-course of myocardial oedema in the first 3 months post ST-elevation MI in patients treated with primary angioplasty

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Background: Myocardial oedema and salvaged area at risk (ARA) have previously been described as markers of prognosis following myocardial infarction and as surrogate markers for clinical trials. The time-course of myocardial oedema has been described in a canine infarct model but the in-vivo time course following successfully revascularised MI has not been described. CMR is able to characterise oedema in myocardial tissue using T2-weighted sequences. We therefore aimed to determine the time-course of post infarct myocardial oedema using serial CMR imaging.
Methods: 9 patients were recruited following acute ST-elevation MI who underwent primary PCI with stent implantation within 12 hours of symptom onset. Patients underwent CMR scans on days 1, 3, 10, 20 and 90 following their PPCI with a 1.5T Philips Achieva (Philips Medical Systems). Images were obtained as continuous short-axis stacks covering the entire left ventricle with a slice thickness of 8mm and gap of 2mm. Myocardial oedema was assessed at all time points using T2-weighted triple inversion turbo spin echo STIR imaging (TE 80ms, TR 1667ms). Scans performed on days 3 and 90 included assessment of scar after administration of a bolus of Gadodoteric acid (0.15 mmol/kg) using a T1-weighted TFE sequence. Image analysis was performed using dedicated software, CMR42 (Circle CVI, Calgary, Canada). Myocardial scar and oedema volumes were calculated by manually drawing endocardial and epicardial contours followed by semi-automated selection of normal remote myocardium per slice. The scar and oedema were described as >5SD and >2SD in signal intensity from remote normal myocardium respectively. Values are expressed as a percentage of the LV mass (%LVM).
Results: Patient age was 56.6±5.4 years (88% male). Myocardial oedema peaks at day 3 (31.1±4.3%LVM) and is significantly greater than the area of scar (13.7±4.5%LVM) p=<0.0001, with an average salvaged ARA of 17.3±5.7%. There is no difference in myocardial oedema between days 1 and 3 or between days 10 and 20. There was a reduction of 8% in oedema between days 3 and 10 (p=0.0003, 95% CI 2.8 – 13.1). Oedema persists at 90 days and is the same size as the scar (10.6±6% vs. 10±5.1% p=ns).

Conclusions: Myocardial oedema post myocardial infarction peaks at day 3 and persists for 90 days. There is no significant change between days 10-20 which may provide the most appropriate time period to assess myocardial oedema. Myocardial oedema may also persist much longer than previously thought.

P491 Function of remote non-infarcted myocardium after STEMI - analysis with cardiovascular magnetic resonance

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Purpose: To investigate remote myocardial function after ST-elevation myocardial infarction (STEMI) and to study the impact of infarct size (IS) using cardiovascular magnetic resonance (CMR).
Methods: 161 patients and 15 controls underwent CMR at 1st week and 6th month after STEMI. Using the 17-segments model, segments were categorized into infarcted, adjacent and remote myocardium. Relative systolic wall thickening (SWT, %) was assessed using the centerline method. IS (% of left ventricular mass) was determined in late enhancement imaging.
Results: 2816 segments were analyzed (900 infarcted, 966 adjacent, 710 remote and 240 controls). Overall, in remote myocardium, SWT was significantly larger (82%±50) compared to controls (75±50, $p<0.03$) and increased at the 6th month (87±53, $p<0.05$ vs. 1st week). When IS was categorized into tertiles (<11.8%, 11.8-27%, >27%), SWT in the remote area at the 1st week was significantly larger in small infarctions compared to controls (89±50 vs. 75±50, p=0.002) and significantly improved at the 6th month (99±55, p=0.02 vs. 1st week). In medium sized and large infarctions there was no difference in SWT of the remote area compared to controls (78±51 and 75±45, p=ns), but an increase at the 6th month of the SWT in medium sized infarctions resulted in a larger SWT compared to controls (84±53, $p<0.05$).

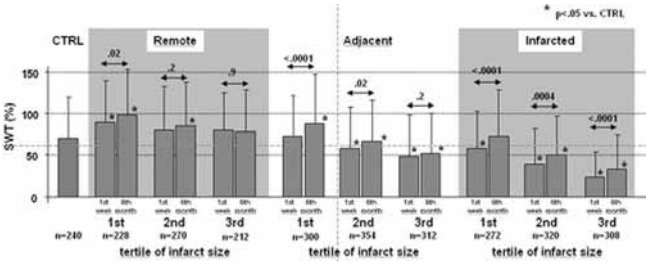

Figure 1

Conclusions: In remote myocardium there was mild compensatory hypercontractility increasing over time after STEMI. This hypercontractility can only be observed in small infarctions. In medium sized infarctions remote myocardium develops a certain hypercontractility at the 6th month while in large infarctions no difference of SWT compared to controls can be observed.

P492 Imaging a large animal model of chronic thrombembolic pulmonary hypertension (CTEPH) by cardiac magnetic resonance (CMR)

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Background: CTEPH developes in about 5% of all cases of acute pulmonary embolism. Pulmonary Thrombendarterectomie (PEA) is a possible cure but not feasible in all patients. An animal model can guide the developement of drugs for medical treatment. CMR is the gold standard to assess remodelling of the right ventricle and pulmonary vasculature. The present study measures changes of right ventricular structure and pulmonary flow characteristics after introduction of a copper based foreign body into the pulmonary artery.
Methods: 10 domestic pigs underwent embolization with a novel copper foreign body and autologous thrombi. Afterwards we continued therapy with 500 mg of tranexamic acid twice daily. CMR was performed at baseline and after 24 weeks. EF, enddiastolic and endsystolic volume (EDV,ESV) of the right ventricle (RV) as well as RV mass were measured on 10 contiguous SSFP Cine short axis slices from base to apex (SLT 8 mm, interslice gap 2 mm, Flip Angle, TR, TE). Pulmonary flow was measured orthogonally about 10 mm above the pulmonary valve on phase contrast turboflash sequences. All measures were normalized for body surface area. Metric measures are given as median and (IQR).
Results: Mean pulmonary pressure and PVR increased to 30 (27.4-33.1) mmHg and 469 (368-546) dyn sec m^2/cm^5 respectively at 24 weeks follow up. Enddiastolic volume and RV Mass increased significantly over time reflecting right ventricular remodelling (EDV 86.9 (72.9-100.9) to 105.7 (75.7-135.9) p=0.043; Mass 30.9 (23.8-38) to 37.1 (27.4-46.8) p=0.04). The ejection fraction did not change significantly (EF 40.6 (28.1-53.1) to 35.2 (22.2-48.2) p=0.34).
All animals developed a dicrotic notch in the flow curve, which was not present at baseline. The maximum velocity in the PA decreased, although not significantly (PA max velocity 95.7 (48.5-135.9) to 84.7 (54.6-110.8) p=0.35).
Conclusion: As demonstrated by CMR in a novel animal model not only hemodynamic changes occur but also remodelling of the right ventricle and pulmonary vasculature that are typically seen in CTEPH. Therefore this model appears qualified to investigate new therapeutic options in CTEPH.

P493 Impact of infarct healing pattern on left ventricular remodelling in patients with acute ST-segment elevation myocardial infarction

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Background: Infarct healing consists in replacement of necrotic tissue with fibrotic scar. In animals this process is highly anisotropic showing different patterns which may influence left ventricular (LV) remodelling. We aim to investigate the influence of infarct healing on post-infarction LV remodeling in patients with acute myocardial infarction (MI).
Methods: Seventy-eight patients with acute ST-segment elevation MI treated by primary PCI were studied by cardiac magnetic resonance within one-week (baseline) and at four-month (follow-up) after MI. Cine CMR was used to assess LV volumes, mass and function. Post-contrast 3-dimensional late gadolinium enhancement (LGE) CMR in short and long-axis orientations was utilized to depict microvascular obstruction (MO) and myocardial necrosis/fibrosis. On post-contrast short-axis images, the following parameters were measured: infarct mass, infarct-wall thickness, infarct-thickness (ie, radial extent of infarction), infarct transmurality and circumferential infarct length (CIL). Longitudinal infarct length (LIL) was derived on long-axis post-contrast images. Infarct-surface was calculated multiplying CIL by slice thickness (ie, 5 mm).
Results: Infarct size was 25±19g (19±12% of LV) at baseline and 13±9g (12±8% of LV) at follow-up ($p<0.001$), yielding an infarct size reduction of 45±17%. Infarct shrinkage was not influenced by the initial MI size and location or the presence of MO. Infarct resorption was more pronounced in the radial (31±15%) than circumferential (10±14%) or longitudinal (10±11%) directions ($p<0.001$). Infarct-surface reduction was 10±16% (range -26% to 53%), and 14 patients increased infarct-surface during follow-up (-12±6%) indicating late infarct expansion. Infarct-wall thinning was positively and strongly related to the infarct-thickness reduction ($r=0.76$, $p<0.001$) but not to overall MI shrinkage or to infarct-surface reduction. At multivariable analysis the magnitude of infarct surface expansion was independently associated with the LV end-diastolic increase during follow-up even after correction for baseline LV ejection-fraction, infarct size, infarct transmurality and MO extent (β-coefficient= -0.340, p=0.010).
Conclusions: Infarct resorption is a highly anisotropic process occurring preferentially along the radial rather than the circumferential or longitudinal directions. The magnitude of infarct radial resorption is the major determinant of infarct-wall thinning whereas the increase of infarct surface during follow-up (ie, late infarct expansion) is an independently associated with adverse LV remodelling.

P494 Total aortic volume measurement as a new, reliable method to determine progressive global aortic dilatation

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Background: The entire aorta can be visualized by three dimensional (3D) imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT). Here we show that these imaging techniques facilitate total aortic volume calculation, which may be useful for surveillance of total aortic dilation rate in patients with connective tissue disease such as Marfan syndrome.
Aim: 1) to assess total aortic volume from a 3D data set of the aorta in Marfan patients 2) to determine intra- and inter-observer variability of aortic volume calculation and 3) to compare aortic volume with aortic diameters.
Methods: Gadolinium enhanced 3D MRI of the aorta, acquired by a standard available MRI sequence (T1 weighed Turbo FLASH spoiled gradient echo) was performed in 60 Marfan patients without previous aortic dissection (mean age 37±13 years, 30 males (50%), 17 (28%) after prophylactic aortic root replacement). Dedicated semi automated 3D segmentation software (3Mensio, Eindhoven, the Netherlands) was used to measure total aortic volume. The volume of the aorta was measured from the aortic valve to the aortic bifurcation. Intra- and inter-observer variability was determined in 10 patients. Aortic diameters of

the 60 patients were measured at five levels (aortic root, ascending and descending thoracic aorta, at the level of the diaphragm and just above the bifurcation). Aortic volume was correlated with mean aortic diameter (sum of the 5 diameters divided by 5). Intra- and inter-observer variability of diameter measurement was determined in15 patients.
Results: Mean aortic volume in 60 Marfan patients was 230 ml (SD=64 ml) (Normalized for BSA: 116 ml/m^2, SD=32). Intra-observer difference was 4.63 ml (ICC= 0.996; SD=4.63). Inter-observer difference was 0.058 ml (ICC=0.979; SD=11.96). Aortic volume showed a high correlation with mean aortic diameter (R=0.8, $p<0.005$). Intra- and inter-observer difference of aortic diameter measurement was comparable to that of aortic volume measurement (ICC=0.971 and 0.974 respectively).
Conclusions: Total aortic volume measurement is a highly reproducible novel method facilitating surveillance of global aortic dilation rate in patients with connective tissue disease.

P495 Quantification of infarct size and mixing of necrotic and viable myocardial tissue with signal intensity-based percent infarct mapping

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Purpose: Currently used threshold techniques for the quantification of myocardial infarct (MI) with late gadolinium enhancement (LGE) CMR assume that the whole myocardial slab that corresponds to the hyperenhanced area is 100% non-viable. This assumption is, however, incorrect. The 3D structure of the infarct could be tortuous, having occasional branches at the border zone. To resolve this conflict, the signal intensity percent infarct mapping (SI-PIM) approach is proposed and validated in this study.
Methods: In swines (n=6) reperfused MI was generated occluding either the LAD or the LCx coronary artery by an angioplasty balloon for 90 min. LGE images were acquired on day 28 after MI, 15 minutes after intravenous injection of 0.2 mmol/kg Gd(DTPA). 2,3,5-triphenyltetrazolium chloride (TTC) staining was used to validate the existence and to determine the accurate size of myocardial infarct. With the SI-PIM approach, a percent-infarct (PI) value was determined in each myocardial voxel, and the amount of infarcted tissue per voxel was then calculated. Total left ventricular (LV) Infarct volume (IV) was determined as the sum of the PI values times the volume of all individual voxels in the entire LV. Percent Infarct values were illustrated on color scale images (SI-PIM images). SI-PIM data were compared with data from LGE images analyzed with the SIremote+2SD thresholding level, and with that of TTC. Tissue samples were taken and stained with H&E and Masson's trichrome for histological assessment of the infarct and the periinfarct zone.
Results: The median IV determined by the TTC, SIremote+2SD, and SI-PIM methods were 3.04 [2.74, 3.45], 13.62 [9.06, 18.45], and 4.27 ml [3.45, 6.33], respectively. The median IV determined by SIremote+2SD significantly differed from IV determined by TTC ($p<0.05$). The Bland-Altman's overall bias was 12.49% of the LV volume. Median IV determined by SI-PIM, however, did not differ significantly (NS) from that obtained by TTC. SI-PIM yielded only a 1.99% Bland-Altman's overall bias of the LV volume. The analysis of correspondence between SI-PIM and histology revealed that SI-PIM was able to visualize the mixing of necrotic and viable tissue.
Conclusions: This in vivo study in the porcine, reperfused myocardial infarct model demonstrates that SI-PIM is a highly accurate method for the determination of the extent of myocardial infarct. SI-PIM can help the cardiologist in the assessment of the often complex structure of the infarct scar by in vivo visualization of infarct inhomogeneity on a color percent scale. SI-PIM is a practical method for clinical implementation.

P496 Increased pulse wave velocity in type 1 diabetic patients is related to early left ventricular diastolic dysfunction

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Purpose: Pulse wave velocity (PWV), a marker of aortic stiffness, can be accurately assessed by velocity-encoded magnetic resonance imaging (MRI). Increased PWV has been shown to confer an augmented risk of cardiovascular disease. Whether an increased PWV translates in early left ventricular (LV) diastolic dysfunction in patients with diabetes mellitus type 1 (DM1) remains unexplored. Therefore, the relationship between PWV and echocardiographic indices of LV diastolic function was evaluated.
Methods: First, normal PWV age-relation was determined in 25 healthy volunteers (age 18-65 years). Accordingly, PWV of the total aorta was obtained by transit-time method, from two through-plane velocity-encoded MRI acquisition on 1.5Tesla scanner. Linear regression describes the normal age-relation: PWV=A$\times$AGE+B (with A$\pm$SE=0.07$\pm$0.01m/s/year and B$\pm$SE=2.32$\pm$0.23m/s, R=0.93). Secondly, 41 DM1 patients (age 50$\pm$9years, 61%male) without history of coronary disease and with normal LV ejection fraction were recruited and aortic PWV was assessed and all measurements were adjusted for age. Subjects were divided into 3 groups: group 1 (normal PWV) had normal PWV values up to 1$\times$SE, group 2 (moderately increased PWV) had values up to 2$\times$SE and group 3 (high PWV) had a PWV$>$2$\times$SE. Echocardiography was performed to assess conventional LV diastolic function indices (isovolumic relaxation time (IVRT), transmitral early (E), and atrial (A) velocities, deceleration time (DT), E/A-ratio). Mitral annulus velocities (E') were acquired by tissue Doppler. Longitudinal speckle tracking strain analysis was performed to derive indices of early LV diastolic function: peak LV strain rate value during isovolumic relaxation period (SRIVR) was recorded and the ratio of E wave velocity to SRIVR velocity (E/SRIVR) was calculated; left atrial (LA) systolic strain value was also measured.
Results: Of the 41 DM1 patients, 19 were in group 1 (PWV 5.72$\pm$0.78m/s), 9 in group 2 (PWV 6.37$\pm$0.58m/s) and 13 in group 3 (PWV 9.87$\pm$2.06m/s). After correction for age, gender and mean arterial pressure, no significant correlation between MRI PWV and conventional indices of LV diastolic function (IVRT, E, A, DT and E') was found (p=0.101, β=0.33 for correlation with IVRT, p=0.275, β= -0.21 with E/A and p=0.379, β= -0.14 with E'). In contrast, MRI PWV was significantly correlated with SRIVR (p=0.000, β= -0.71), E/SRIVR (p=0.002, β=0.61) and LA strain (p=0.014, β= -0.47).
Conclusion: In patients with DM1, aortic PWV is correlated with advanced echocardiographic indices of LV diastolic function. Therefore, increased MRI PWV may translate into early LV diastolic dysfunction.

P497 Pericardial effusion as a predictor of infarct size, transmural infarction and remodelling in acute myocardial infarction

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Background: Moderate to severe pericardial effusion (PE) is related to an increased number of complications in acute myocardial infarction (AMI). However, there is no data about myocardial characteristics of AMI associated with PE assessed by cardiac magnetic resonance imaging (CMR).
Objectives: To evaluate CMR parameters related to the presence of PE in the early course of AMI and at 6 months follow-up.
Methods: 214 patients with a ST-segment elevation AMI were prospectively included. Moderate to severe PE was defined as an echo-free space $>$ or = 10mm in the transthoracic echocardiogram at admission. CMR studies were performed within the first month, and six months later. Cine and late gadolinium enhancement sequences were used to assess left ventricular mass, volumes and infarct size. Transmural necrosis was defined as a necrosis involving $>$50% of myocardial wall.
Results: 27 patients (12.6%) showed moderate to severe PE. These patients showed larger end-diastolic volume (p=0.007), end-systolic volume ($p<0.001$), infarct size ($p<0.001$), greater number of transmural necrotic segments ($p<0.001$) and lower ejection fraction (p=0.034) than those without significant PE. Only patients with at least one transmural necrotic segment presented significant PE. The multivariate logistic regression analysis demonstrated that end-diastolic volume, end-systolic volume, infarct size and ejection fraction were independent predictors of significant PE. These patients also showed greater left ventricular dilatation at 6 months.
Conclusions: Patients with AMI and PE present a consistent association with a transmural necrosis and exhibit a larger infarct size and greater left ventricular remodelling at 6 months than those without PE.

P498 Diagnostic performance of cardiac magnetic resonance parameters in arrythmogenic miocardiopathy causing sudden death

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Recently, the spectrum of arrythmogenic miocardiopathy (AC) has been expanded with newly described biventricular (BVAC) and left-dominant (LDAC) forms. Cardiac magnetic resonance (CMR) with its superb tisular discrimination abilities, and high reproducibility for ventricular volume calculation, offers potentially relevant information for their diagnosis. Objective: To analyze the diagnostic performance of different CMR parameters in the diagnosis of AC.
Methods: Patients included in this study come from a prospective protocol evaluating cases of familiar cardiac sudden death (SD), with a clinical or anatomopathological diagnosis of AC in the index case. All patients underwent the following diagnostic tests: EKG, cicloergometry, Holter study, echocardiography, CMR, and genetic study specific for AC. Diagnosis was based on Task force criteria (TFC) in patients without the mutation, while in carriers, the presence of findings suggestive of AC in at least two diagnostic tests of different categories was considered as diagnostic. The diagnostic value of the following CMR parameters was evaluated: 1- presence of late gadolinium enhancement (LGE) in left ventri-

cle (LV) and right ventricle (RV); 2- LV ejection fraction (LVEF) ≤55% and RV EF ≤45%, and 3- biventricular dilatation (LVEDVi ≥98ml/m^2 and RVEDi ≥100ml/m^2.
Results: The group comprised 59 patients:29 (49%) male. There were 5 probands (3 resuscitated, 2 with cardiogenic syncope and no SD), and 54 first-degree relatives. AC was diagnosed in 10 pts (17%), 6 (60%) with LDAC, 4 (40%) with BVAC. The diagnostic value of LGE was, in the LV (Sensitivity 100%, Specificity 94%), and in the RV (sensitivity 20%, specificity 97%); for LVEF (Sensitivity 60%, specificity100%), for RVEF (sensitivity:30%; specificity:97%), and for RV dilatation (sensitivity:10%, Especificity: 94%). No patient showed LV dilatation.
Conclusion: 1- In this clinical context,with high prevalence of left and biventricular forms of AC, left ventricular delayed gadolinium enhancement is the parameter with the highest diagnostic performance. 2- The other parameters are very specific, though poorly sensitive for diagnosis.

P499 Importance of symptomatic and silent coronary artery disease progression very late after successful coronary stent implantation

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Background: To assess the safety of drug-eluting stents (DES), long-term follow-up studies have been mandated. However, during very late follow-up, ischemic events may be due to coronary disease progression rather than due to late stent-related problems.
Methods: To define the importance of coronary disease progression, all 442 patients of the BASKET trial with successful complete revascularization by stenting documented by lack of events up to 6 months and no ischemic perfusion defects (PD) 6 months after the intervention (rest/stress SPECT study) were followed prospectively and invited to undergo a 2nd SPECT study after 5 years. At baseline, patients were randomized 2:1 to DES or bare-metal stents (BMS). Events and PDs were analyzed for target-vessel (TV) vs remote-vessel origin (remote indicating disease progression) and compared between patients with DES vs BMS.
Results: During follow-up, 97/428 (22,6%) patients had 148 clinical events: 43 (10%) died, 34 (8%) suffered a myocardial infarction and 71 (17%) needed revascularization. Event rates were significantly higher in TV versus remote areas (14.3% vs 9,8%, p=0.019). Remote infarcts or revascularizations were not different between DES and BMS patients (10.6% versus 8.3%; p=0.5) A 2nd SPECT study performed in 206/331 (62%) patients without follow-up events (125 did not consent) showed 48 (23,3%) new PDs, which were asymptomatic in 67% of patients. Remote PDs accounted for 18/48 (37,5%) PDs with similar rates for DES and BMS patients (9.2% vs 7.7%, p=0.8).
Conclusions: In addition to 23% of patients with very late clinical events after successful stenting, another 23% had new PDs, of which a majority were asymptomatic. These findings occurred in remote areas in more than one third of cases, similarly after DES and BMS implantation, indicating relevant symptomatic and silent disease progression. This underscores the importance of 2nd prevention after stenting.

P500 New ischemic index based on combined parameters of coronary angiography and intracoronary pressure measurement predicts the severity of the ischemia on the myocardial perfusion scintigraphy

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Background: According to the current guidelines the indication of percutaneous coronary interventions on coronary lesions with intermediate severity is based on the fractional flow reserve (FFR), independently of the localization of coronary stenosis.
The aim of this study was to search for correlation between the severity of perfusion abnormality detected by scintigraphy and the FFR value as well as the localization of a particular coronary lesion.
Methods: The coronary angiograms of 28 patients (male: 22, female: 6, age 62+7.6) were analyzed by a computer program called Holistic Coronary Care. The software registered 23 epicardial coronary segments using the modified Syntax segmentation system. The supplied left ventricular segments on the standard 17-segment polar map were rendered to each coronary branch by an appropriate algorithm. FFR measurements of 36 vessels (20 LAD, 6 LCx, 10 RCA) were compared with the myocardial perfusion SPECT studies performed before the invasive procedure. The lesions belonged to 6.5+ 2.5 myocardial segments (range: 1-12). We introduced a new ischemic index by combining the FFR with the number of the corresponding myocardial segments (left ventricular ischemic index: LVIi). This index was correlated with the regional myocardial perfusion defects identified on the scintigrams. Perfusion reversibility score of 2 or above was considered as indicative of active ischemia (regional Difference Score: rDSc).
Results: Close linear relationship was found between the LVIi and the rDSc ($P<0.001$) (y=-2.20+3.75x, r=0.88, $p<0.001$). Also a linear relationship (y=17.1-17.9x, r=0.83, $p<0.001$) could describe the connection between the FFR and the rDSc among the cases with lesion-associated myocardial territory of similar extensions (7-8 segments). Analyzing all the FFR values independently of the localization of the lesions, they also correlated significantly with the rDSc, but the relation was less tight (r=0.60). LVIi predicted active ischemia (>2 rDSc) on myocardial scintigraphy with 77.8% sensitivity and 94.4% specificity when the cut off value was set to 0.96. FFR alone predicted the ischemia on the scintigraphy with 72% sensitivity and 94% specificity at the best 0.8 cut off value. The area under the Receiver Operating Characteristic (ROC) curve was significantly higher for LVIi than FFR (0.92 vs. 0.78; p=0.03).
Conclusion: Our results shows that the LVIi >0.96 indicates clinically relevant stenotic lesion. In this concept the FFR value together with the number of corresponding left ventricular segments rather than alone predicts the severity of myocardial ischemia.

P501 Cadmium-zinc-telluride gamma camera allow quarter-dose MPI SPECT

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Objectives: We evaluated a myocardial perfusion imaging (MPI) protocol using improved sensitivity and linear count response of cadmium-zinc-telluride detectors (CZT) to allow low radiopharmaceutical dose.
Methods: Thirty patients (Mean: 64 y) performed a 1-d adenosine/rest SPECT MPI twice with different protocols (A and B). Protocol A used a dose of 99m Tc-tetrofosmin of 320 MBq stress/960 MBq rest and acquisition duration of 5 min stress/rest under a CZT camera (DNM 570c, GE Healthcare). Protocol B was performed with a dose of 160 MBq stress/160 MBq rest and acquisition duration of 15 min stress/rest. Background subtraction was applied on the rest MPI of B using P-mod software. Anonymized data were evaluated separately by two experienced readers blinded to the acquisition protocol for image quality, perfusion findings (normal/abnormal) and the presence and extent of ischemia. The extent of perfusion defect was compared using paired t-test. Pearson's correlation was used to compare ejection fraction (EF), end diastolic and systolic volumes (EDV,ESV) between A and B.
Results: Image quality by A and B were optimal/fair in 28/2 and 29/1 patients for the stress MPI as well as 29/1 and 28/2 patients for the resst MPI, respectively (p= NS). Protocol A revealed normal/abnormal perfusion findings in 13/16 patients in stress MPI (one equivocal) and 18/12 patients in rest MPI. Using A, ischemia was considered for 12/29 patients vs 12/30 patients with B. The clinical agreement between A and B on abnormal finding was perfect for both rest and stress MPI (k=1) and they agreed in the diagnosis of ischemia in 27/29 patients (agreement rate: 93%; k= 0.85). The extent of defect was comparable between A and B for the stress (10% vs 11% respectively, p= NS) and rest studies (5% vs 7% respectively, p= NS). An excellent correlation between A and B was found for EF (r= 0.93), EDV (r= 0.95) and ESV (r= 0.97).
Conclusions: CZT cameras may enable similar MPI results using protocols tailored for a factor 4 decrease in radioactive dose.

P502 Clinical implications of a new high-speed SPECT camera for detecting myocardial ischemia in stable patients

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Purpose: Recently introduced high-speed cardiac SPECT cameras with cadmium-zinc- telluride based (CZT) detectors may reduce scan times and radiation dose when compared to conventional SPECT scanners. We compared the efficiency of a conventional SPECT to a CZT-based SPECT scanner, with regard to the need for additional rest imaging after initial stress testing.
Methods: 456 stable patients without known coronary artery disease (CAD) and low-intermediate pre-test likelihood, underwent non-invasive stress testing with a hybrid SPECT-CT (64-slice) scanner using either conventional SPECT (n=225) or CZT-based SPECT (n=231). An individualized stepwise decision algorithm was applied beginning with low-dose stress SPECT imaging combined with coronary calcium scoring with subsequent further rest imaging when initial stress testing was equivocal or abnormal. Acquisition times for stress and rest imaging were 12 and 15 minutes for conventional SPECT, and 5 and 4 minutes for CZT-based SPECT.
Results: There were no differences between the 2 cohorts in baseline characteristics, mean calcium score or pre-test likelihood of CAD. Patients scanned with CZT-based SPECT required additional rest imaging in 36% compared to 58% scanned with a conventional SPECT ($p<0.001$). Additional coronary CT was less frequently performed in patients scanned with CZT-based SPECT compared to the traditional SPECT (21% vs. 31%, p=0.02). Final diagnosis of a normal scan was significantly higher in patients scanned with the CZT-based SPECT (86% vs. 72%, $p<0.001$). Total administered isotope dose in the CZT-group was reduced compared to the conventional scanner (658±390 MBq vs. 840±421, $p<0.001$).
Conclusions: Implementation of a new high-speed cardiac SPECT camera re-

sulted in a significant decrease in need for subsequent rest imaging. This results in a faster diagnosis, lower effective radiation exposure and enables a more efficient scanner use. Long-term follow-up studies should prove the diagnostic accuracy and safety of the new camera.

P503 Identification of complete non-responders to CRT with phase analysis of gated myocardial perfusion SPECT

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Purpose: Prior studies have demonstrated that the degree of LV dyssynchrony assessed with phase analysis of gated myocardial perfusion SPECT (GMPS) in heart failure patients can be useful in predicting response to cardiac resynchronization therapy (CRT) based change in NYHA class. The aim of this study was to determine if phase analysis of GMPS can identify complete non-responders to CRT, based not only on change in NYHA class but also on change of LVEF.
Methods: Twenty one patients (18 M, 4 F, mean age 67, range 46 -87) with severe heart failure (NYHA class III) underwent CRT. Parameters indicating dyssynchrony on GMPS obtained prior to CRT, including histogram bandwidth and phase standard deviation were calculated. Clinical status, LV volumes, and LVEF were evaluated at baseline and after CRT. Patients without improvement of LVEF of more than 5% and without improvement of NYHA class were classified as complete non-responders.
Results: Complete non-responders (N = 8) demonstrated a shorter histogram bandwidth (124.25± 30.6°) than complete and partial responders (182.2± 60.9°) (p=0.02358). In addition, receiver operating characteristic curve analysis demonstrated that histogram bandwidth (AUC = 0.7801, Standard Error = 0.1035) could better identify complete non-responders to CRT than phase standard deviation (AUC = 0. 0.5662, SE = 0.1362, p=0.0337) and QRS complex width (AUC = 0.5150, SE = 0.1362, p=0.0288). Furthermore, Kaplan Meier analysis showed that complete non-responders demonstrated worse overall survival than complete and partial responders (p=0.0443).

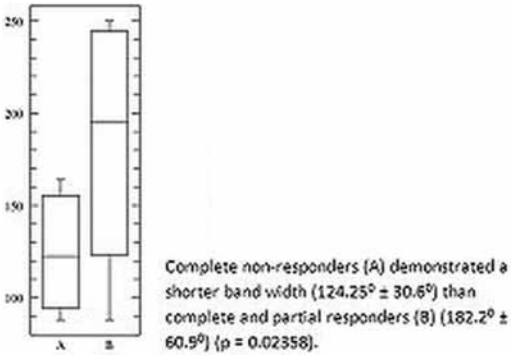

Figure 1

Conclusion: Predicting response to CRT remains challenging. The use of phase analysis of GMPS in heart failure patients may represent a novel method for identifying complete non-responders to CRT.

ECHOCARDIOGRAPHY – MISCELLANEOUS

P504 Correlation between ischemic mitral valve regurgitation and remodeling of the left ventricle evaluated by magnetic resonance imaging

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Purpose: Ischemic mitral regurgitation (IMR) is a frequent complication of dilated cardiomyopathy due to coronary heart disease and is due to the tethering and apical displacement of subvalvular apparatus.
Previous echocardiography studies measured the degree of displacement between papillary muscles at mid ventricular level
Only a few studies to date have used Magnetic Resonance Imaging (MRI) to identify this abnormality. MRI advantages are high resolution, the capacity to identify the insertion of papillary muscle on lateral wall and to identify the scar location after gadolinium (Gd) administration.
The aim of this study was to evaluate the correlation between IMR and remodeling of left ventricle evaluated by MRI.
Methods: A prospective echocardiography study was carried out on 39 patients with severe ischemic dilated cardiomyopathy. All patients underwent (MRI) with contrast agents. We assessed the interpapillary distance at medioventricular level during systolic and diastolic phase. The presence of IMR was evaluated by Echocardiography using a quantitative method (PISA) and classified as 0 degree or absence of IMR, 1st degree or mild IMR (defined as EROA $< 0{,}20 cm^2$) and 2nd degree or significant IMR (defined as EROA $>0{,}20\ cm^2$)
Results: We found that the degree of IMR was correlated with interpapillary distance at medioventricular level during diastolic phase (p=0.0021) and systolic phase (p=0.0007) and also with interpapillary distance at level of insertion of papillary muscles (p=0.0016).
The severity of left ventricle remodeling has a direct impact on mitral valve remodeling: interpapillary distance is correlated with End Diastolic Left Ventricle Volume (EDVol) in diastole ($p<0.001$, r=0.4740) as well as in systole ($p<0.001$, r=0.5266) and interpapillary distance in diastole is correlated with End systolic Left Ventricle Volume (ESvol) ($p<0.001$, 0.4219).
Conclusions: Due to the high spatial correlation the MRI is a good modality to asses the displacement of papillary muscles. Left ventricle severe remodeling has a direct impact on the valve tethering in systole as well as in diastole.

P505 Tissue Doppler and contrast echocardiography: new methods in diagnosing intracardiac structures

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Background: Standard echocardiography is currently used to assess patients (pts) with intracardiac masses, but sametimes gray-scale echo features are not clear. The precise morphologic characteristic of intracardiac structures has important therapeutic implications. The aim of the study was to assess the role of Tissue Doppler (TDI) and Contrast Echocardiography (CE) in detecting intracardiac structures.
Results: Echocardiographic study (TTE, TEE) was performed in 195 pts with: valvular disease (n-60), atrial myxoma (n-23), angiosarcoma (n-6), aneurysm of left ventrucle (n-46) and after septal occluder implantation (n-60). CE (Optison) was used to improve detection of endocardial border and to reduce artifacts. Comparing the motion of intracardiac masses with the surrounding tissue three types of motion were differentiated related to direction, velocity and phase: A-concordant motion with no difference in direction, velocity and phase; B-coherent motion with a phase difference depending on motion of the surrounding tissue but out of phase; C- incoherent motion due to free oscillation. Concordant motion was found in rigidly fixed left ventricular clot and septal occluder (n-95), small left atrial myxoma (n-3) and angiosarcoma (n-6). Coherent motion was present in mural left atrial clot (n-10) and large myxoma (n-20). Incoherent motion was noted in valvular vegetation, mobil myxoma (n-52) and right heart clot (n-9). Out of 195 pts 43 (22,1%) had one or more embolic events. The incidents of embolism were compared with the echocardiographic characteristics (localization, size and mobility) of the vegetations and clots. In 19 pts with dense spontaneous echo contrast and artifacts CE excluded clots.
Conclusions: TDI improves the detection of intracardiac masses and allows correct definition of their morphology and motion. TDI characteristics of vegetations and clots is helpful in predicting embolic events and suggests urgent operation. CE is a useful additional diagnostic tool in evaluating cardiac structures and improves their visualization.

P506 Is left ventricular vortex flow related to the clinical response to cardiac resynchronization therapy? A quantitative vorticity imaging study using contrast echocardiography

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Background: Evaluating and optimizing appropriate response after cardiac resynchronization therapy (CRT) is challenging issue. Currently used criteria for evaluating response were mainly focused on left ventricular (LV) mechanical dyssynchrony, however, there was no study focusing on LV flow pattern. The aim of this study was to assess the usefulness of LV vortex flow analysis for evaluating response to CRT.
Methods: Fifteen patients who received CRT (10 responder group and 5 non-responder group) underwent two-dimensional (2D) transthocacic contrast echocardiography (CE) with intravenous infusion of Definity® (Lantheus Medical Imaging, Inc. North Billerica, MA) and imaged at an mechanical index of 0.4-0.6 in the A4C and APLX views after CRT. Quantitative LV vortex flow parameters including morphology and pulsatility were measured using Omega flow® (Siemens Medical Solutions, Mountain View, CA) and compared between two groups. The dynamic variation of vortex were estimated by means of maximal and minimal vortex flow size (TVS, %) and phasic variation in the vortex flow size (PV-TVS, %).
Results: The morphologic and pulsatility parameters of LV vortex flow did not showed significant difference between two groups. However, PV-TVS was significantly larger in responder group than non-responder group (61.6±14.8 vs 33.7±2.3, $p<0.05$). But there were no significant difference in maximal-TVS (Max-TVS) and minimal-TVS (Min-TVS) between two groups. Figure shows phasic variation of vortex size during cardiac cycle (Lt panel) and parametric rep-

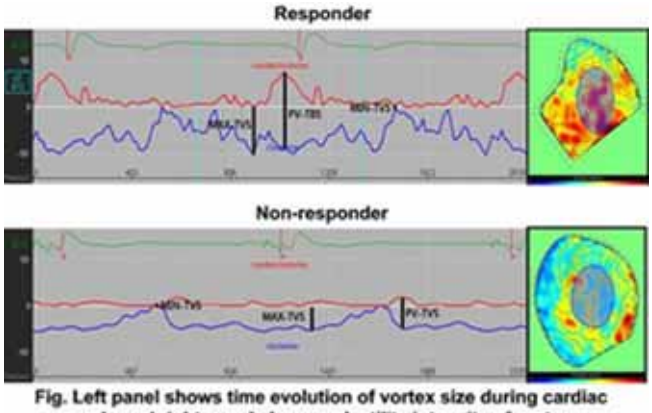

Fig. Left panel shows time evolution of vortex size during cardiac cycle and right panel shows pulsatility intensity of vortex

resentations of the pulsatile strength field (right panel) in responder and non-responder group.
Conclusions: Quantitative LV vortex flow analysis may have potential role for evaluating response after CRT.

P507 Change in blood oxygen level-dependent signal intensity of the left ventricular blood pool reflects arterial hemoglobin saturation

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Purpose: Signal intensity (SI) in blood oxygen level-dependent (BOLD)-sensitive cardiovascular magnetic resonance (CMR) is dependent upon the oxygenation status of hemoglobin (Hb). Therefore, changes in arterial Hb saturation (SaO2) contribute to changes in SI. In this study, we investigated the change in SI within the blood pool of the left ventricle (LV) during a one-minute period of apnea using BOLD-sensitive CMR.
Methods: Arterial blood gas levels of five anaesthetized swine were adjusted to pO2 levels of 100 and 80 mmHg and pCO2 levels of 30, 40 and 50 mmHg through alteration of ventilation parameters. During one minute of apnea, BOLD-sensitive CMR images were acquired using a modified SSFP cine sequence. Immediately prior to and after apnea, arterial blood gases (pCO2, pO2) were measured and used to calculate the expected ΔSaO2 (Severinghaus, 1979). SI of the LV-blood pool was analyzed for the first and last two BOLD cines during apnea and averaged for each phase of the cardiac cycle. The mean SI of all phases was calculated and expressed as %SI change between the beginning and the end of apnea.
Results: Calculated changes in SaO2, observed changes of left ventricular blood-SI and arterial blood gas measurements are shown in Table 1. The change in LV blood pool SI at pO2=80 mmHg and pO2=100 mmHg levels over 1 minute of apnea follow the expected ΔSaO2.

Table 1

Pre pO2 (mmHg)	Post pO2 (mmHg)	Pre pCO2 (mmHg)	Post pCO2 (mmHg)	Expected ΔSaO2	% SI Change
84.2±2.1	53.4±10.3*	28.9±1.4	33.9±3.1*	–9.8	–10.5**
82.0±4.2	56.2±2.2*	39.8±2.2	47.4±4.4*	–10.4	–11.4**
82.4±1.9	56.2±4.4*	49.4±2.8	52.9±2.9*	–11.0	–13.1**
102.6±2.1	69.9±13.8*	28.7±1.9	32.9±0.8*	–3.9	–4.0**
99.9±4.6	66.4±13.6*	40.3±0.9	47.6±2.5*	–7.1	–5.4**
97.9±2.2	68.9±12.5*	51.2±1.8	58.6±4.8*	–7.2	–1.4**

Arterial blood gases (*$p<0.04$), expected ΔSaO2, and % change in SI (**$p\leq0.001$) over 1 minute of apnea, n=5 (mean ± standard deviation).

Conclusion: The findings suggest that changes of signal intensity in the LV blood pool of BOLD-sensitive CMR images reflect the extent of desaturation of arterial blood during one-minute apnea, as expected by the characteristics of the oxygen-binding curve of Hb.

P508 Controversial effects of atrial septal defect closure in adults

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Purpose: The aim of the study was to evaluate the influence of ASD closure in adults on right ventricular (RV) function assessed by conventional and tissue Doppler imaging.
Methods: Thirty consecutive pts with a history of ASD type secundum and 30 healthy subjects were involved in our research (42% male, mean age 36.7±12.4 yrs). 23.3% patients had transcatheter ASD closure. All patients were observed before and a year after closure. Standard echocardiography with pulsed and continuous Doppler examinations, as well as pulsed TDI on lateral segment of tricuspid annulus were performed. The difference between values before and after ASD closure as well as in healthy controls was assessed.
Results: Despite dilatation, RV didn't show significant diastolic dysfunction (Table 1) because of outstanding compliance. There was significant difference of RV isovolumic relaxation time (IVR) in patients with ASD compared to healthy controls (60±13 vs. 39±7 ms, p=0.000). Its shortening after closure was a sign of improved RV diastolic function (60±13 vs. 44±9 ms, p=0.000). In patients with ASD, RV is overloaded according to value of IVC. Closure decreased this value, but there was significant difference comparing to controls (54±8 vs. 49±6, p=0.0130). Tei index as a parameter of global myocardial function was improved after closure (0.53±0.07 before vs. 0.39±0.04 a year after, p=0.000). These values approached to those in healthy controls (0.39±0.04 a year after vs. 0.38±0.04 in healthy controls, p=ns).

Table 1

Parameters	Before closure	12m after closure	Controls	P (before–12m after)	P (before–controls)	P (controls–12m after)
E, cm/s	0.87±0.21	0.60±0.17	0.73±0.11	0.000	0.001	0.001
Em, cm/s	23±5	21±4	24±5	0.029	ns	0.003
E/Em	3.93±0.95	2.95±0.93	3.09±0.62	0.000	0.000	ns
IVR, ms	60±13	44±9	39±7	0.000	0.000	0.015
IVC, ms	66±11	54±8	49±6	0.000	0.000	0.013
Tei	0.53±0.07	0.39±0.04	0.38±0.04	0.000	0.000	ns

Conclusions: Before closure, there is almost normal diastolic, preserved systolic and disturbed systolic-diastolic RV function. Closure of ASD improves global RV function. Maintenance of deviations a year after hangs out significance of earlier ASD closure in reducing future morbidity and mortality.

P509 Pericardial fat but not calcium score correlates with oxidative products in patients with known coronary artery disease

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Purpose: Aortic valve sclerosis (AVS), mitral annulus calcification (MAC), aortic root sclerosis (ARS) and pericardial fat detected by echocardiography have been associated with atherosclerosis. Our aim was to evaluate the relationship between total heart calcification score index (CSI, as the sum of AVS, MAC and ARS) and pericardial fat versus advanced glycation end-products (AGEs), as markers of oxidative stress in patients with coronary artery disease (CAD).
Methods: We enrolled 38 consecutive patients with known or suspected CAD; among them, 16 had a negative test for myocardial ischaemia and 22 had a history of myocardial infarction and/or significant CAD at angiography (age 53±18 years vs 61±14 years), body mass index (BMI, 27.4±3.0 kg/m^2 vs 27.3±4.1 kg/m^2, mean±SD, p=ns). We evaluated, by transthoracic echocardiography, ejection fraction (EF, Simpson's rule), left ventricular mass index (LVMI), CSI (from 0= normal to 10= diffuse calcification of aortic valve, mitral annulus and aortic root) and carotid intima-media thickness (IMT). Moreover, we evaluated presence of ectopic fat by measuring ultrasound epicardial (EPI) and mediastinal (exPERI) thickness, hepatic steatosis, waist circumference and waist/hip (W/H) ratio as indexes of abdominal obesity. All patients underwent AGEs skin accumulation by autofluorescence (AF).
Results: Patients with CAD had significantly lower EF (53±12% vs 61±3% $p<0.05$), increased LVMI (107.5±32.7 g/m^2 vs 68.5±20.9 g/m^2, $p<0.01$), CSI (2.58±2.14 vs 0.93±0.88, $p<0.01$), EPI (0.64±0.26 cm vs 0.37±0.20 cm, $p<0.01$), and W/H (0.99±0.08 vs 0.92±0.08, $p<0.01$), while IMT, mediastinal fat and hepatic steatosis were not different in the two groups. AGEs skin accumulation was also significantly increased in CAD (2.86±0.66 vs 2.01±0.51, $p<0.001$) and correlated with LVMI (r=0.51) and EPI (r=0.47, both $p<0.01$), but not with EF, CSI and BMI.
Conclusions: Echocardiographically assessed CSI, epicardial fat and AGEs are increased in patients with CAD. However, only epicardial fat is correlated to AGEs, as markers of oxidative stress.

P510 Quantitative assessment of perivascular echogenicity of coronary arteries in acute kawasaki disease using native DICOM datasets

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Kawasaki disease, an acute febrile vasculitis syndrome affecting young children, can complicate with serious coronary artery aneurysm. Current guideline specifies coronary perivascular echo brightness as a subjective finding for diagnosis of KD.
Purpose: We attempted to quantify the echo brightness in KD and compare with those in children with innocent murmur and viral febrile illness.
Methods: Complete echocardiographic studies, using Philips iE33 echocardio-

graphic system were performed in all subjects. Native DICOM datasets were exported for analysis with Photoshop CS4 extended for medical professionals. A standard convention assigns the brightest value as 255 and the black value as 0. Measurement of brightness, thickness, and area of perivascular echogenicity of right coronary artery (RCA) and left coronary artery (LCA), left anterior descending (LAD), left circumflex (LCX), lumen of both RCA and LCA, and right ventricular free wall were performed and averaged from 3 repeated measurements for each region.
Results: Forty nine complete KD, 22 incomplete KD, 20 innocent murmur, and 20 viral febrile syndrome patients, ranging in age from 3 months to 7 years, were enrolled in this study during January 2007-September 2010. Both complete and incomplete KD patients demonstrated statistically significant brighter (181±16) and larger area (1.3±0.02 mm^2) of coronary perivascular echogenicity as compared to patients with innocent murmur (132±14 and 0.4±0.03) and viral febrile illness (142±18 and 0.6±0.03) ($p<0.05$). The intraobserver and interobserver reliability were in the range of fair to good (k=0.4-0.8). The brightness and area of echogenicity lessened at 2 and 6 months convalescent follow up. Small to medium coronary aneurysm developed in 5 patients (7%).
Conclusion: Quantitative objective, rather than subjective, DICOM data assessment of coronary artery perivascular echogenicity may assist in identification of patients with acute Kawasaki disease

P511 Usefulness of contrast echocardiography for prediction procedure success of coronary artery chronic total occlusion lesion

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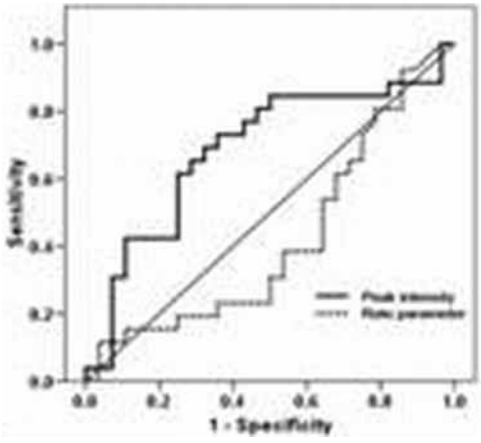
Purpose: To investigate the usefulness of myocardial perfusion image using a contrast echocardiography for prediction procedure success of coronary artery chronic total occlusion (CTO) lesion.
Risk factors for failure include CTO length >15 mm or not measurable, moderate to severe calcification, and lesion duration ≥180 days. Peak intensity (α) and rate parameter (β) with contrast myocardial perfusion and wall motion score segments of patients with CTO lesion before percutaneous coronary intervention (PCI). 90 segments of 25 patients (63.0±14.9 years, 19 males) with CTO lesion were divided into two groups. Successful intervention performed segments (group I: 48 segments) and failed segments (group II: 42 segments). Peak intensity (α) by contrast myocardial perfusion were significantly higher in group I than in group II (5.76±2.74 vs. 3.96±2.47, p=0.015). But, Rate parameter (β) by contrast myocardial perfusion (0.088±1.55 vs. 2.63±10.47, p=0.389) and wall motion score (WMS) (2.04±0.662 vs. 1.68±0.819, p=0.083) were not different. By receiver operation curve analysis, the area under the curve to predict successful intervention for CTO lesion was 0.769 in peak intensity (α). The optimal cutoff value to predict successful intervention for CTO lesion was 3.58 in α of CTO segments (sensitivity: 76.9%, specificity: 57.1%).



The present study suggested that peak intensity measured by myocardial perfusion of contrast echocardiography can predict favorable for intervention CTO lesion.

P512 Apical rotation during exercise echocardiography in patients with and without exercise-induced wall motion abnormalities

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Left ventricular (LV) torsion has been found to be increased after inotropic stimulation and decreased after transmural acute myocardial ischaemia in animals. The main determinant of LV torsion is the counterclockwise rotation of the apex. However apical rotation (AR) has been only sparsely assessed during exercise. In fact the effect of exercise-induced ischaemia on AR has not been well studied. We aimed to assess the effect of ischaemia on AR on patients with known or suspected coronary artery disease referred for treadmill exercise echocardiography (TME).
Methods: AR rotation was assessed at rest, peak, and immediately after exercise (Post) by speckle tracking in 38 consecutive patients. Of them, 17 (45%) had wall motion abnormalities (WMA) that involved the left anterior descending coronary artery (LAD) territory, and 21 (55%) normal TME results. Age, % of males and % of patients with LV hypertrophy were similar between patients with and without WMA (66±13 vs. 58±18 years; 71% vs. 67%; and 53% vs. 67%, respectively).
Results: Feasibility for the assessment of AR was 95% at rest, 89% at peak, and 79% at post-exercise. The wall motion score index increased during TME from 1.2±0.4 to 1.6±0.3 in patients with WMA. Achieved METs were lower in them (7±3 vs. 12±4, p=0.007), although the peak heart rate and peak pressure product were similar between patients with and without WMA at TME (144±28 vs. 157±20 bpm, and 22,603±6,190 vs. 24,412±5,164, respectively). AR was similar at rest in patients with and without WMA (4.7±2.3 vs. 4.1±2.7 degrees) whereas at peak exercise was higher in the former group (8.5±3.5 vs. 5.4±2.7 degrees, p=0.03) and at Post slightly higher (7.2±3.1 vs. 5.4±2.7 degrees, p=0.09). There was a tendency to higher ΔAR from rest to peak exercise in patients with WMA (3.7±2.5 vs. 1.4±4.6, p=0.08), whereas the % of increase in AR from rest to peak exercise and from rest to Post was similar in patients with and without WMA (90±70% vs. 110±230%, and 80±80% vs. 90±120%, respectively). AR values were not different in patients with and without diastolic dysfunction at rest or at exercise as defined by an early LV inflow wave/early mitral annulus wave >1.3, as they were not in patients with or without LV hypertrophy. AR values did not correlate with age or functional capacity.
Conclusion: In conclusion, assessment of AR during TME is feasible. Patients with WMA affecting the LAD territory do not have decreased AR during exercise.

P513 Increased central aortic stiffness and left ventricular hypertrophy in Fabry disease

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Aim of this study aimed todetermine the dilatation of the aortic arch and the aortic stiffness impairmentin patients with Fabry Disease (FD) and its relationships with the leftventricular hypertrophy.
Methods: Forty-six FD patients (30males and 16 womens) matched for age, sex and blood pressure to 46 controlsunderwent a cardiac and thoracic aorta Magnetic Resonance Imaging (MRI)investigation. Both ascending and descending aortic diameters, aortic distensibility and beta-stiffnessindex (BSI) were measured and calculated. Aortic arch Pulse Wave Velocity (PWV) and Left Ventricular (LV) masswere also assessed.
Results: Excepted to thoracicdescending diameter, aortic diameters were significantly higher in FD patientsthan in controls, predominantly at the sinus of Valsalva (37.0±5.2 vs. 31.9±2.9 mm $P<0.0001$). Patients with FD had a markedly decrease in aorticdistensibility (4.0±1.9 vs. 5.0±2.9 $mmHg^{-1}\times10^{-3}$, $P<0.05$) and an increase in BSI (1.7±1.3 vs. 1.2±0.9, $P<0.05$) at ascending aorta.
PWV was no significantly different between controls and patients (5.68±2.94 vs 4.56±1.06 m/s, P=0.26). LV hypertrophy was significantlyassociated with BSI – r2=0.42, P=0.0045) wich persist in multivariateanalysis.
Conclusion: This is the first study determining both aortic stiffnessand distensibility impairments in Fabry disease at thoracic ascending aorta,wich correlates with LV hypertrophy

MULTIMODALITY IMAGING

P514 Vendor-independent echocardiographic quantification of left ventricular circumferential strain: validation with cardiovascular magnetic resonance

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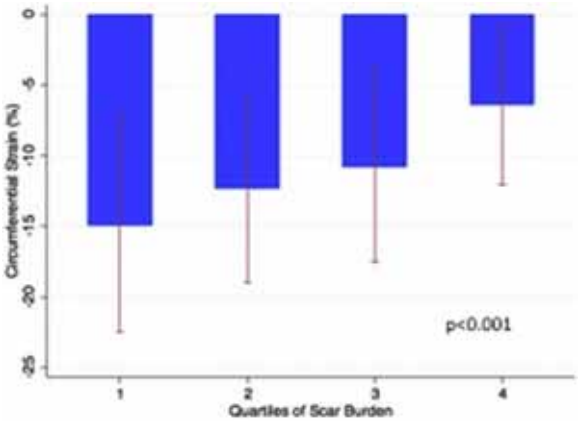
Purpose: Myocardial strain by speckle-tracking echocardiography is able to identify scar from myocardial infarction. The software for strain analysis has to date been vendor specific thus limiting its widespread use. The aim of this study was thus to validate speckle-tracking strain measurement using novel vendor-independent software.
Methods: Forty patients (mean age 59±11 years), who underwent late-gadolinium enhancement cardiac magnetic resonance (LGE-CMR) and echocardiography (TTE) a median of 8 weeks following acute myocardial infarction, were evaluated. Myocardial scar was quantified from LGE-CMR using a 16-

segment model and the full-width at half maximum technique.Transmural scar was defined as ≥50% transmural enhancement on LGE-CMR. TTE was performed on commercially available machines and stored in DICOM format. B-mode echocardiographic images were analysed offline using dedicated software. Segmental circumferential strain was measured in 3 parasternal short-axis views to generate16-segment strain scores.
Results: Of 640 segments, 509 (80%) segments were deemed evaluable for speckle-tracking strain analysis. In segments exhibiting enhancement byLGE-CMR, median myocardial scar burden was 5.4% of wall thickness (interquartile range 0.38-22%). There was a significant relationship between segmental circumferential strain and scar burden quartiles (Figure). The area under the receiver-operating characteristic curve for circumferential strainscore to predict transmural scar was 0.73 (95% CI 0.60-0.85).



Conclusions: This study has shown that segmental circumferential speckle-tracking strain as measured by novel,vendor-independent software is predictive of scar burden following myocardial infarction. This software may permit more widespread quantification of myocardial strain across different vendors.

P516 A comparison between dual axis rotational coronary angiography and conventional coronary angiography

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Purpose: Conventional coronary angiography (CA) remains the gold standard for the investigation of coronary artery disease (CAD). It utilises x-ray radiation and iodine, which are deleterious to health and should be kept to the minimum possible dosages while ensuring diagnostic accuracy. Dual axis rotational angiography (DARA) is an alternative technique wherein the c-arm rotates around the patient in a pre-programmed single acquisition, exposing the entire coronary artery at different angulations. The purpose of the study was to investigate whether DARA differs significantly in radiation, contrast loads, and procedure time, when compared with conventional CA.
Methods: Patients referred for the investigation of CAD, for whatever indication, including acute coronary syndromes, were included in the study. Graft studies, angiography related to valvular heart disease, and emergency primary percutaneous coronary interventions were excluded. 463 consecutive patients were randomly assigned to one of four groups: monoplane CA (MCA), monoplane DARA (MDARA), biplane CA (BCA) and biplane DARA (BDARA).
Results: T-tests comparing MDARA and BDARA with MCA and BCA showed that DARA was significantly superior in almost all values measured ($p<0.01$) (Table 1). Percentage reductions ranged from 12% (contrast used) to 71% (procedure time).
Conclusions: DARA was significantly superior in dose area product (DAP), fluoroscopy time, amount of contrast used, and procedure time in both monoplane and biplane machines. Patients benefit by significantly lower doses of radiation and contrast and shorter procedure time. DARA may prove to be an important milestone in the refinement of coronary angiography.

Table 1. Radiation, contrast and timings

		DAP (mGy cm^2)	Fluoroscopy time (min)	Runs (n)	Extra views (n)	Contrast (ml)	Procedure time (min)
MCA	Mean	32.7	03:01	8.3	0.6	38.1	07:35
	SD	17.8	02:57	1.2	1.1	11.3	04:09
MDARA	Mean	22.0	01:53	3.0	0.9	22.5	05:27
	SD	16.3	01:12	0.2	1.2	9.2	02:20
BCA	Mean	56.7	02:33	9.7	1.2	27.8	06:19
	SD	28.6	02:38	0.7	1.6	10.8	03:35
BDARA	Mean	30.9	01:57	4.0	0.6	24.4	05:21
	SD	18.5	01:28	0.4	1.0	7.7	03:11

P517 Feasible setting of single-beat 3-dimensional echocardiography to assess left ventricular volume measurements: a comparison study with cardiac magnetic resonance imaging

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Background: Recently 3-dimensional echocardiography (3DE) with a single-beat image acquisition (Single-3DE) has been introduced, and may have more clinical application to assess left ventricular (LV) volume and ejection fraction (EF) compared to 3DE with multibeat image acquisition (Multi-3DE). However, the lower spatio-temporal resolution is a limitation; lower scanning volume rate provides more adequate image quality, but may affect the accuracy of LV end-systolic timing, and subsequent volume (LVESV) and LVEF measurements. In contrast, adequate image quality may not be obtained in higher volume rate setting.
Aim: This study was designed to determine the feasible volume rate settings of Single-3DE to measure LV volume and LVEF.
Methods: 3DE examinations with a Vivid E9 system (GE) and cardiac magnetic resonance imaging (cMRI) were performed on the same day in 65 patients. Temporal resolution for LV full-volume data sets obtained by Single-3DE were divided into low (4.0±0.7 volume per second: vps), mid (8.2±1.9vps), and high (16.4±2.8vps), and that of Multi-3DE (4beats acquisition) was 27.5±7.7vps.
Results: Adequate images could be acquired in all patients at the low and mid temporal resolution, and Multi-3DE, which could not be acquired in 8 patients (12%) at the high temporal resolution. As shown in Table, LV end-diastolic volume (LVEDV) at high temporal resolution was smaller than other 3DE settings, and LVESV at low temporal resolution was larger than other 3DE settings. Correlation of LVEF at low temporal resolution with cMRI was the weakest followed by LVEF at high temporal resolution.
Conclusions: Single-beat 3DE with the mid temporal resolution (volume rate around 8 vps) provides feasible image quality to obtain acceptable LV volume and LVEF compared to multi-beat 3DE and cMRI.

P518 A layer specific comparison of speckle-tracking echocardiography and strain-encoded cardiac magnetic resonance imaging (SENC)

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Background: Speckle tracking echocardiography (Echo) as well as strain-encoded cardiac magnetic resonance imaging (SENC) allow quantitative analysis of segmental myocardial function of different myocardial layers. Both methods were evaluated to differentiate segments with different myocardial function.
Methods: In 44 patients (mean age 60.8±12.9 years, 34 male) 2-dimensional speckle tracking echocardiography and SENC using a 1.5-Tesla scanner was performed. Segmental function was defined as normokinetic, hypokinetic or akinetic by visual analysis of magnetic resonance imaging cine sequences. Analysis included 494 segments. Peak systolic circumferential strain was assessed by Echo and SENC to quantify endocardial and epicardial myocardial layer function.
Results: Layer specific deformation analysis by Echo and SENC allowed a differentiation of myocardial segments with different functional states. In normokinetic segments peak systolic circumferential strain in the endocardial layer was more negative by Echo (bias=7.3% CI -10.0 to 24.7%) than by SENC as well as in the epicardial layer (bias=0.2% CI -14.0 to14.4%). In hypokinetic segments strain values were slightly higher by Echo than by SENC in the endocardial layer (bias=-1.3% CI-13.3 to 10.6%) as well as in the epicardial layer (bias=-3.1%; -14 to 7.9%). In akinetic segments circumferential strain by Echo was less negative compared to SENC in the endocardial layer (bias=-1.4% CI -13.7 to 10.9%) as well as in the epicardial layer (bias=5.1% CI -16.8 to 6.6%). Furthermore, endocardial strain by Echo allowed better distinction of hypokinesia or akinesia

Abstract P513 – Table 1. Comparison and relation of measurements

	LVEDV		LVESV		LVEF	
	LVEDV, ml	vs. cMRI	LVESV, ml	vs. cMRI	LVEF, %	vs. cMRI
Single-3DE Low TR	102±35	R^2 = 0.82, y = 1.1x + 20	63±34 †	R^2 = 0.88, y = 1.4x – 6.5	40±15‡	R^2 = 0.25, y = 0.6x + 22
Mid TR	105±37	R^2 = 0.86, y = 1.0x + 20	54±41	R^2 = 0.93, y = 1.1x + 11	53±20	R^2 = 0.79, y = 0.8x + 2.7
High TR	95±32†	R^2 = 0.79, y = 1.2x + 15	51±34	R^2 = 0.89, y = 1.5x + 3.8	50±19	R^2 = 0.60, y = 0.7x + 7.5
Multi-3DE	108±38	R^2 = 0.82, y = 1.0x + 26	55±41	R^2 = 0.91, y = 1.2x + 13	55±20	R^2 = 0.78, y = 0.8x + 2.0
cMRI	125±41*	–	70±45*	–	50±16	–

TR, temporal resolution. *$p<0.01$ vs. 3DE data, †$p<0.05$ vs. other 3DE data, ‡$p<0.01$ vs. other data.

from normokinesia than endocardial strain by SENC (AUC ROC 0.945 vs 0.889, p<0.001). Similarly, epicardial strain by Echo allowed better distinction between normokinesia and impaired segmental myocardial function than by SENC (AUC ROC 0.882 vs 0.796, p<0.001).
Conclusion: Quantitative deformation analysis of an endocardial layer and an epicardial layer by Echo and by SENC allows an accurate differentiation of segments with normal from impaired myocardial function. Strain values for the two imaging modalities are on different levels. Strain by Echo is more negative in myocardial segments with normal function and less negative in myocardial segments with impaired function compared to strain by SENC.

P519 The utility of a novel off-line approach to quantify circumferential strain from routine cardiac magnetic resonance images: comparison with echocardiographic speckle tracking

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Purpose: Circumferential strain by cardiac magnetic resonance (CMR) is a powerful tool to quantify left ventricular (LV) function; however previous strain methods have required sophisticated and time-consuming tagging. Our aim was to assess the utility of a novel simplified CMR method to determine circumferential strain and compare to strain by speckle tracking echo in the same patients.
Methods: We studied 30 subjects (56±14 yrs): 13 with heart failure (HF) and 17 normal controls who had both CMR and echocardiography. Mid-LV short axis CMR images were processed and analyzed from routine DICOM data sets using a novel software program (TomTec, Germany.) and compared with similar short axis echo images for speckle tracking circumferential (CS) strain. Segmental and global CS (GCS%, Fig) were determined for each.
Results: Imaging data were suitable for quantitative analysis in 100% of CMR images and 89% of echo images. Global circumferential strain by the new CMR (off line, untagged) was significantly reduced in HF patients -15.2±8.9% vs. -31.4±6.6% in normal controls (p<0.01). Measures of circumferential strain by CMR correlated favorably with similar echo speckle tracking measures over a wide range of values (-6% to -42%): r = 0.84 (p<0.0001), limits of agreement -0.7±6% by Bland-Altman analysis. Furthermore, circumferential strain by this CMR method was highly reproducible with <5% variability.

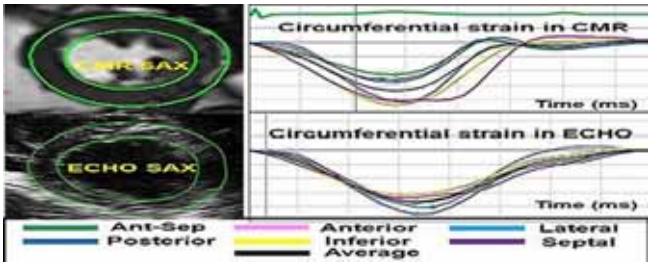

Figure 1. Comparison: GCS%: CMR vs. ECHO

Conclusion: A novel simple software approach can quantify circumferential strain in routine CMR images and compares favorable with similar strain measures by speckle tracking echo. This novel CMR method that is untagged, bedside, and fast has promise for clinical applications.

P520 Assessment of left ventricular 3D speckle tracking echocardiography using vendor dependent and vender independent software with CMR correlation

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Purpose: 3D speckle tracking echocardiography enables assessment of LV function. Vender independent speckle analysis software is now available (TomTec, Germany). We compare 2 commercially available 3D speckle tracking software (Toshiba Medical Systems and TomTec) using cardiac magnetic resonance (CMR) as a reference.
Methods: 14 volunteers had 3D echo on Phillips iE33 and Toshiba 4D Artida systems on the same day. 3D LV apical 4 chamber views were obtained using a frame rate of 13-25 frames/second. The same transducer frequency and similar sector width were used.
All participants had CMR (3 Tesla) in standard short axis and apical views. Systolic strain was measured using semi-automatic quantification.
Two observers analysed all echo data. Agreement between echo speckle tracking software and CMR was determined using Bland-Altman analysis.
Results: Agreement between echo (irrespective of vender software) and CMR were excellent for longitudinal strain (difference 0.99-1.8%), good for circumferential strain (difference 0.05-3.71%) and poor for radial strain (difference 12.81-25.32%).
Similarly interobserver echo variability was excellent for longitudinal strain (difference 0.16 – 1.83%); good for circumferential strain (difference 1.36- 6.2%) and modest for radial strain (difference 7.55-13.5%).
Analysis of Toshiba datasets on Toshiba and TomTec software showed that agreement was excellent for longitudinal strain (difference 1%), good for circumferential strain (difference 5.6%) and poor for radial strain (difference 15.5%).
Conclusions: Vender independent and dependent 3D speckle tracking software show good levels of agreement when compared with CMR for the measurement of longitudinal and circumferential strain. The high variability for radial strain assessment is a concern and further work on speckle tracking algorithms may be needed to identify a cause for this.

P521 Myocardial fibrosis affects left ventricular contractile reserve: noninvasive assessment by cardiac magnetic resonance and stress echo

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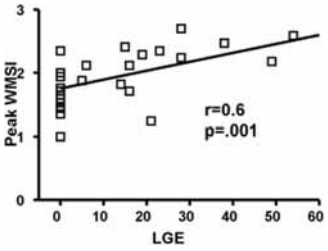
Background: Fibrosis is a common endpoint of many pathological processes affecting the myocardium, influences regional and global left ventricular (LV) function and can be accurately measured with late post-gadolinium myocardial enhancement (LGE) cardiac magnetic resonance. Aim. To assess the value of resting function and contractile reserve evaluated by stress echocardiography in predicting myocardial fibrosis.
Methods: We studied 42 patients (32 men; 63±12 years) with idiopathic (n=21) or ischemic (n=21) dilated cardiomyopathy (EF <40% by selection). They underwent, on separate days and within 1 week, stress echo with exercise (n=13), dobutamine (n=28, up to 40 mcg/kg) or dipyridamole (n=1, up to 0.86 mg/kg). By selection, no patient had inducible ischemia with stress echo. We measured LV ejection fraction (EF, Simpson method) and wall motion score index (WMSI) by 2D-echo at rest and peak stress. LGE was semiauthomatically quantified and expressed as left ventricular mass percentage (LGE%).
Results: Resting Ejection was 29±7%. LGE score was 13.6±18.2 (range 0-60). WMSI was 2.1±0.3 at rest and 1.9±0.4 at peak stress (p<0.0001). LGE was correlated with peak WMSI (r=0.6, p<0.01, see figure) and - more weakly - with resting WMSI (r=0.47, p=0.009), whereas no correlation was detected with resting EF (r=0.2, p=ns) or peak EF (r=0.1, p=ns).



Conclusion: Severity of myocardial fibrosis by LGE correlates with contractile reserve during stress echo in a broad range of myocardial fibrosis in patients with ischemic and non-ischemic dilated cardiomyopathy.

Abstract P516 – Table 1

	Circumferential Strain (%)		Radial Strain (%)		Longitudinal Strain (%)	
	Mean % ± STD	BAA Mean difference % strain / (CI) vs. MRI	Mean % ± STD	BAA Mean difference % strain / (CI)	Mean % ± STD	BAA Mean difference % strain / (CI) vs. MRI
TomTec analysis of Philips data sets	–19.47±3.2	1.16 / (–3.27 to 0.95)	53.39±13.99	25.32 (–32.27 to –18.74)	-15.58±2.29	0.99 / (-2.27 to -0.31)
TomTec analysis of Toshiba data sets	–20.47±5	0.05 / (–3.58 to 3.45)	53.94±10.3	25.07 (–32.32 to –17.82)	–15.2±2.27	1.8 / (–3.47 to –0.13)
Toshiba analysis of Toshiba datasets	–24.05±4.6	3.71 / (0.74 to 6.70)	35.82±11.07	12.81 (–20.88 to –4.74)	–16.12±2.32	1.54 / (–2.69 to –0.37)
CMR	–20.61±2.03		28.39±5.22		–17.09±1.6	

BAA = Bland Altman Analysis; CI = Confidence Interval.

P522 Correlation between myocardial perfusion & contractility by single photon emission computed tomography, magnetic resonance and electromechanical mapping in patients with severe coronary artery disease

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Purpose: Electromechanical mapping (EMM) of the left ventricle is a new technique that provides us with voltage (unipolar and bipolar voltage, UV) and contractility (linear localshortening, LLS) information of the left ventricle (LV). It is a validated method to identify both ischemic and viable myocardium, with diagnostic and therapeutic intentions. The objective of this study was to assess the correlation between EMM parameters and technetium-single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI), in patients with advanced chronic coronary artery disease (CAD).
Methods: Twenty-seven consecutive patients with chronic stable CAD, reversible perfusion defects detectable by SPECT and not amenable for revascularization were included in the study. All of them had been enrolled in the PRECISE clinical trial of freshly isolated adipose-derived stem cells for angiogenesis. Wall motion (WMSI) was assessed with MRI imaging in all patients not bearing an ICD, utilizing a 17-segment polar map of the LV (normal WMSI=1; hypokinetic=2; akinetic=3). Perfusion was studied with SPECT Tc-99m sestamibi (normal = grade 0; most impaired = grade 4) and EMM was performed with the NOGA XP system (BDS, Johnson & Johnson), both using the same 17-segment polar map of the LV as recommended by the ACC/AHA. All studies were performed and analyzed by independent observers blinded to the results of the other techniques.
Results: 62±8 years and 77% male. A total of 865 SPECT and MRI segments were correlated with the corresponding EMM data. Segments with better rest perfusion showed better UV (grade 0: 10.2±5.9mV; grade 1: 10.4±5.3mV; grade 2: 9.4±5.1mV; grade 3: 8.6±4.7mV; grade 4: 6.9±3.4mV; $p<0.0001$) and LLS parameters (grade 0: 9.8±6.9mV; grade 1: 10.7±6.6mV; grade 2: 8.8±6.3mV; grade 3: 7.4±7.6mV; grade 4: 5.8±0.5mV; $p<0.0001$). Similar results were obtained with stress-SPECT. Similarly, segments with better WMSI by MRI showed better UV (grade 1: 10.5±6.1mV; grade 2: 9.2±5.2mV; grade 3: 8.4±4.4mV; $p<0.0001$) and LLS values (grade 1: 10.7±7.7mV; grade 2: 8.5±5.8mV; grade 3: 7.2±6.0mV; $p<0.0001$).
Conclusion: EMM is auseful technique for assessing myocardial health status in terms of perfusion and contractility in chronic CAD patients. Therefore, UV and LLS values can beused for a precise delivery of gene and stem cell therapy.

P523 Relationship between left ventricular myocardial systolic strain derived from three-dimensional speckle tracking and myocardial fibrosis assessed by magnetic resonance in patients with chagasic cardio

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Purpose: Recent studies have demonstrated the association between peak systolic strain by two-dimensional speckle tracking and the degree of fibrosis in myocardial infarction. However, these aspects have not yet been evaluated in chagasic cardiomyopathy (CCM) in which one has either diffuse or focal myocardial fibrosis. We aimed to evaluate the relation between left ventricular peak systolic strain derived from three-dimensional speckle tracking (3DST) and myocardial fibrosis detected by magnetic resonance (MRI) in patients with CCM.
Method: We measured the three orthogonal components (longitudinal, circumferential and radial) of peak systolic strains derived from 3DST with a commercially available equipment in 221 myocardial segments of the left ventricle (LV) of 13 patients with CCM (mean age=55±8 yrs; mean LV ejection fraction=0,46±13). The model of 17 myocardial segments was used. Myocardial fibrosis was characterized by the presence of late contrast enhancement detected by MRI. The 221 myocardial segments were divided in 2 groups according to the absence (GI) or the presence (GII) of fibrosis. A non-parametric test (Mann–Whitney) was used to test differences between the groups, with a significance level of 0.05.
Results: Of 221 segments analyzed, 69 had fibrosis detected by MRI. The remaining 152 segments were found to be free from fibrosis. It was observed differences in the values of peak systolic strain of the GII, which were significantly lower than in the GI, with median values respectively: longitudinal = - 9 vs - 14%; circumferential = - 17 vs - 27% and radial = 10 vs 27% ($p<0.0001$).
Conclusion: Our preliminary data suggest that myocardial fibrosis in patients with CCM is related to significant reduction of longitudinal, circumferential and radial peak systolic strains derived from 3DST. This method can be potentially useful in identifying fibrotic myocardial segments in these patients. Further studies with a larger number of individuals will be necessary to establish the role of this new tool in this clinical scenario.

P524 Patency of the aorto-coronary by-pass anastomoses in patients with previous coronary stenting: a lesson from 64-MDCT coronary imaging

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Background: A substantial proportion of patients with a history of previous percutaneous coronary stents implantation are finally referred to CABG surgery. An impact of stents' presence upon coronary by-passes' patency remains a subject of conflicting data.
Methods: From May 2006 to December 2010 we examined consecutive 445 patients after coronary surgery (CABG) for evaluation of native vessels and coronary anastomoses by means of a 64-multidetector computed tomography (Aquilion,Toshiba). There were 337 patients with CABG alone (CABG) and 108 patients with a previous coronary stenting (CABG+stents). The overall grafts patency rate and its dependence upon previously implanted stents' patency were compared.
Results: In the CABG group, among 937 coronary anastomoses, the patency rate was 80.5% over a period of 39 months (median), while in the CABG+stents group, among 271 grafts, the patency rate was 75.3% over a period 34 months (chi2, p=0.06). In a subgroup of 72 patients of the CABG+stent group who had both interventions on the same coronary artery, the overall patency rate was 72% (133/184), however, if the analysis was restricted to the grafts to the same artery that had been previously stented, the patency rate was found to depend on the anatomical status of the stents alone (table below). In a subgroup of the remaining 36 patients with a previous stent implantation to the vessel(s) other than anastomosed surgically, the patency rate did not differ from that in CABG only group (81.6%, 71 out of 87).

	By-passes			All
	Patent	Stenosed	Occluded	
Stents				
Patent	11	3	20	34
Stenosed	3	1	4	8
Occluded	29	0	5	34
All	43	4	29	76

Conclusions: In patients with a previous stent implantation, the patency of the latter influences the patency of anastomosis to the same artery. The highest patency rate of grafts is associated with an occlusion of previous stents.

P525 Two years experience of the novel mobile telemedicine system in real-time transmission of prehospital 12-lead ECG for cardiac emergency

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Background: AHA/ACC guidelines recommend prehospital 12-lead ECG for patients with acute coronary syndromes (ACS). However, transmission of prehospital 12-lead ECG to emergency department (ED) is still not spread and ECG interpretation on the prehospital and ED is not established. Therefore, we developed and tested the clinical usefulness of the mobile telemedicine system (MTS) to transmit 12-lead ECG and other parameters between moving ambulances and physicians in cardiac emergency.
Methods: We set up the MTS on an ambulance in clinical condition. Real time 12-lead ECG was transmitted together with vital signs and live video during transferring the patient by the ambulance. We assess the efficacy and usefulness of the MTS for the triage on 222 cardiovascular emergency cases in the super-acute phase from June 2008 to August 2010. During the same period, we had 325 ST-segment elevation myocardial infarction (STEMI) cases. 37 of these were used this MTS. Then, we compared various data between MTS (n=37) and non-MTS (n=288) groups with STEMI patients.
Results: We applied the MTS for 222 patients during the transfer to our ED. The mean time of using this MTS was 14±8 minutes. Of these, there were 60 patients (27%) with ACS [including 37 STEMI, 3 Non-STEMI, 19 unstable anginas, and 1 recent MI], 29 patients (13%) with arrhythmia, 6 patients (3%) with acute aortic dissection, 15 patients (7%) with congestive heart failure and 112 patients (50%) with the others. Real-time 12-lead ECGs were checked in clinical condition and all of them were comparable to those original ECGs in the ambulance and were useful for the triage to diagnose all AMI patients before arrival at hospital and for the rapid activation of catheterization laboratory. Door to balloon time (DBT) was shorter in MTS group (median 84 minutes) compared with non-MTS group (median 108 minutes) ($p<0.001$).
Conclusions: This report demonstrate the usefulness of transmitting real-time 12-lead ECG and vital signs using novel MTS for the patients with cardiac emergency. Accurate real-time 12-lead ECG transfer is useful for early diagnosis and the improvement in DBT for STEMI patients.

P526 Home monitoring manpower, sensitivity and positive predictive value of adverse event detection. Preliminary results from the homeguide registry

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Purpose: A standard organizational model for implementing remote monitoring in ordinary follow-up of patients with cardiac implantable electronic devices (CIED) has been established by the Italian Arrhythmology Association (AIAC) Task Force for Telemedicine. The HomeGuide Registry is a survey in sites adopting such model with the aim of estimating manpower and clinical effectiveness of remote monitoring (Biotronik Home Monitoring [HM]) in terms of sensitivity and positive predictive value of adverse event detection during follow-up.
Methods: The organization model is based on defined rules: appointed operators (AO) for ordinary management (expert nurses or technicians), and a responsible physician (RP) for medical decisions. All the patients are being followed up with HM with scheduled in-hospital visits once a year. Each site received a custom software for electronic data capture, including automatic storage of HM session durations and decision processes. Events were defined as any cardiovascular or device-related occurrence affecting patient's general conditions and adjudicated by an independent 5-member board.
Results: One thousand two hundred and fifty consecutive first-implant patients (315 [25%] PM, 603 [48%] single or dual-chamber ICD, 23 [2%] CRT-P, 309 [25%] CRT-D) were enrolled so far from 71 Italian sites. Patient population resembled the expected characteristics of CIED patients. There were 2109 HM sessions in a mean follow-up of 16.1±9.1 months (71% by the AO, 29% by the RP): the median duration was 5.0 min (interquartile range 1.8-10.3) for the AO, 4.8 min (1.8-9.6) for the RP, p=0.02; with a median of 2 (1-5) patients seen per HM session. The total required manpower was 1.3 (0.6-2.5) hours×health-personnel-unit per month every 100 patients of which 45 (0-102) minutes for AOs and 2 (0-39) minutes for RPs ($p<0.10$-6) with a RP/AO manpower ratio of 1:22. Documented events were 1090 (43 deaths, 1 stroke, 2 myocardial infarctions, 71 worsening heart failures, 381 atrial and 180 ventricular arrhythmias, 353 device-related complications, 59 other events) from 438 patients (35%): 878 were detected during HM sessions; 101 during scheduled in-hospital visits; 111 in other circumstances. Thirty seven events were classified as false-positive (32 during HM sessions). The overall sensitivity and positive predictive value estimates of HM were 80% (95% CI, 78%-83%) and 96% (95-97%), respectively.
Conclusions: The HomeGuide organization model for HM required a remarkably low manpower with a low RP/AO ratio, while ensuring a high clinical event detection sensitivity and positive predictive value.

POPULATION AND INDIVIDUAL RISK – STILL MORE TO LEARN

P527 Population characteristics and prognostic factors of patients with a first acute coronary syndrome in France in 2006

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Purpose: Compared to patients with a history of coronary heart disease, those presenting with a first ever episode tend to be younger, with less advanced coronary disease and a lower hospital lethality. However, little is known about factors associated with short-term mortality after a first acute coronary event. We aimed to describe the characteristics and predictors of death at 28 days of incident hospitalised acute coronary syndrome (ACS) patients identified at the population level in 2006.
Methods: The French MONICA registry is a population-based registry from three geographical areas in France: the Urban Community of Lille (North) and the districts of Bas-Rhin (East) and Haute-Garonne (South). The clinical, biological and electrocardiographic characteristics of all patients, aged 35-74 years, hospitalised for a first ACS were recorded. Examination of medical files and death certificates was used to assess 28-day case-fatality. Characteristics and prognostic factors were analysed according to ST-segment elevation (STEMI) or not (NSTEMI) during the episode. Associations were assessed by logistic regression.
Results: 1960 patients were hospitalised with an incident ACS. Due to missing ECGs, analyses concerned 1907 patients among which 76.2% were men (mean age 56.7±10.0 years) and 23.8% were women (61.4±10.2 years). STEMI represented 57.7% and NSTEMI 42.3% of these events. STEMIs were more frequent in the North than in the South (OR 95%CI: 1.3[1.0-1.6]), in younger than in older (2.3[1.6-3.2]; 1.6[1.2-2.0]; 1.1[0.9-1.4] in 35-44y, 45-54y, 55-64y vs. 65-74y, respectively). Major adverse events were more frequent in STEMI than in NSTEMI: resuscitated death (5.4[2.9-10.3]) and cardiogenic shock (3.5[1.8-6.7]), independently of age, gender and centre. CPK and troponin increased more in STEMI than NSTEMI (all $p<0.0001$). 28-day case-fatality occurred in 86 patients and was more frequent in the North (5.4[2.6-11.1]) and the East (3.4[1.6-7.1] than in the South, in older (1.5[0.5-4.0], 1.6[0.6-4.4] and 3.8[1.5-9.9] in 45-54y, 55-64y, 65-74y vs. 35-44y, respectively) than younger subjects. No significant difference was observed between gender (1.5[0.9-2.6] men vs. women). In age, gender and centre adjusted analysis, 28-day case-fatality was more frequent in STEMI than NSTEMI (3.7[2.1-6.4]), in those with resuscitated death (24.0[13.9-41.5]), cardiogenic shock (25.8[14.1-47.2]) and pulmonary oedema (2.3[1.2-4.6]).
Conclusions: In France, geographical factors, age and serious clinical presentation, but not gender, were associated with 28-day case-fatality after a first acute coronary event.

P528 Trends in coronary heart disease morbidity and mortality in France from 2000 to 2007: data from the three French coronary heart disease population-based registries

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Purpose: To assess recent trends in coronary heart disease (CHD) morbidity and mortality from data obtained in the three French population-based registries covering three geographical areas of about one million inhabitants each: the Urban Community of Lille in the North, the districts of Bas-Rhin in the East and of Haute-Garonne in the South.
Methods: All cases of fatal and non-fatal acute myocardial infarction (AMI) as well as coronary death (CD) in inhabitants aged 35-74 years were registered. AMI was assessed from the clinician diagnosis and 28-day case-fatality was assessed. All death certificates in the relevant population were identified and validated, leading to the diagnosis of either fatal AMI, CD, possible CD or no CD. Event rates in the 35-74 year range were age-standardized to the European standard population. They are given per 100,000 population [95% confidence interval] and compared between two 4-year periods (2000-2003 and 2004-2007).
Results: From 2000 to 2007, 25,202 events were registered (55% fatal/non-fatal AMI, 17% CD and 28% possible CD). Overall rates of AMI and CD decreased from 292 [286-299] to 237 [231-242] in men (-19%) and from 69 [66-72] to 56 [53-59] in women (-19%). The decline was present in all areas although less markedly in the North (-14%). Among women it also differed according to age, being found only in the oldest age groups (55-74 years). The same patterns of decline were observed when possible CD were included in the events. Furthermore, mortality rates (fatal MI+CD) decreased from 87 [83-90] to 74 [71-77] in men (-15%) and from 23 [21-25] to 18 [17-20] in women (-22%). The fall in the North was smaller and not significant in both genders. Although still significant, inclusion of possible CD reduced the overall fall to -13% in both genders, with similar patterns of trend according to age and area. Finally, overall incident rates of AMI and CD decreased significantly among men (-16%) and women (-19%), but less markedly in the North (-11%) and, in women, significantly only among the oldest ones. Whether assessed in hospital or in all settings, 28-day case-fatality showed no declining trends between the two periods. In hospital AMI 28-day case-fatality was low (9% in men, 10% in women) whereas 28-day case-fatality for all events in all settings reached 50% in men and 55% in women.
Conclusions: CHD morbidity and mortality decline in France in recent years in both genders and in all areas except mortality in the North. The fall in the incidence explains the major part of this decrease as case-fatality appears to be stable.

P529 Occurrence of acute myocardial infarction doubled in a country still in socio-economic transition

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Purpose: Acute myocardial infarction (AMI) is the leading cause of mortality due to cardiovascular disease (CVD), which in turn remains the major cause of all deaths worldwide and in Albania. This study sought to investigate whether risk factors associated with AMI in two different socio-economic systems: centralized and free market economy, have changed overtime.
Methods: Medical files of 544 patients admitted with AMI to the Department of Cardiology during 2009 were reviewed. Trend in AMI incidence and the prevalence of major risk factors in this group of patients were examined and further compared to those of a similar study conducted on 402 patients admitted with AMI to the same hospital during the 5-year period 1976-1980.
Results: The incidence of AMI increased from 0.27 per 1000 population in 1980

to 0.57 per 1000 population in 2009. In addition, the prevalence of major risk factors during 2009 was found to be higher than during the period 1976-1980, e.g. the high blood pressure (BP) 69.7% vs. 51.9%, dyslipidemia 75.9% vs. 68.1%, obesity almost doubled 20.7% vs. 13.3%, and diabetes tripled 37.8% vs. 13.01%. Strikingly, there was a decline in the prevalence of smoking, from 65.9% during the period 1976-1980 to 45.6% during 2009. The impact of psychosocial factors on incidence of AMI could not be evaluated because of lack of such information in the medical files of both reference and present studies.
Conclusions: The incidence of AMI has conspicuously increased in Tirana during 2009 in comparison with 1980. This can be partly explained by a marked increase in prevalence of major risk factors, including high BP, dyslipidemia, diabetes and obesity, but not smoking, which was paradoxically decreased. An evaluation of the influence of psychosocial factors is necessary and may help to further elucidate such an increase in the incidence of AMI in Albania.

P530 Electrocardiographic abnormalities in a young male southeast Asian population undergoing pre-participation cardiovascular screening: results from the safe study

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Purpose: Although the inclusion of routine electrocardiograms (ECG) in preparticipation cardiovascular screening remains controversial, there is increasing evidence that cardiomyopathies, arrhythmogenic and ion channel disorders have ECG abnormalities as the first manifestation. We aim to determine the prevalence of ECG abnormalities in a young male Southeast Asian population.
Methods: SAFE is an ECG-based preparticipation screening programme modelled after the Italian system. 18,476 young male conscripts [mean age 19.5, Range 16-27] underwent mandatory pre-enlistment screening at a single medical facility from Oct 08 to May 09. Subjects with abnormal ECG findings were classified into 2 groups: Group A had ECG changes that fulfilled a pre-specified checklist were referred for transthoracic echocardiogram (TTE); Group B had other ECG abnormalities (eg Brugada sign, WPW pattern, Long QTc) were referred for secondary screening at a tertiary institution.
Results: ECG abnormalities were noted in 7.0% (n=1285) of the subjects. Of note, 19 (0.10%) had Brugada sign, 25 (0.14%) had WPW pattern, and 30 (0.17%) had prolonged QT interval on ECG. As part of the workup, 94.6%(n=1203) of the subjects underwent TTE, and 7.5%(n=90) of them had abnormal TTE findings. Table 1 illustrates the prevalence of ECG and TTE abnormalities.
Conclusion: The prevalence of ECG abnormalities in a young, South-East Asian male population is 7.0%. The inclusion of universal ECG improves the sensitivity of a cardiovascular screening programme. Knowledge of the prevalence of ECG abnormalities would be pivotal in designing customised screening programmes.

P531 Predictors of early mortality in patients with critical limb ischemia

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Background: It has already been reported that presence of critical limb ischemia (CLI) associated with high mortality and morbidity. However, predictors of early mortality in patients with CLI remain unclear.
Methods: This study was multicenter retrospective observational study of prospective maintained database. From April 2004 to October 2010, total of 744 patients (872 limbs) with CLI who underwent endovascular treatment or bypass surgery were enrolled. Outcome measure was all-cause mortality within a year.
Results: Mean follow-up period was 524±464 days. Sixty-six percent were male, 68% had diabetes, 67% had chronic renal failure (defined as creatinine >2.0 mg/dl), 35% had Cerebro-vascular disease, and 15% were with anemia (defined as hemoglobin < 9.0g/dl). Mean age was 72±10 years. Rutherford class IV was found in 218 limbs, V in 514 limbs and VI in 140 limbs. Mean ankle-brachial index before initial procedure was 0.66±0.31. All-cause death within a year was accounted for 19.8%. Limb salvage rate was 89.6% during the follow-up. Multivariate logistic regression analysis was performed to determine predictors of early mortality. Age, anemia, chronic renal failure, less than 0.5 of ABI before procedure, and Rutherford class were independent predictors of all-cause death.

characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age, years	1.03 (1.01-1.04)	0.003	1.05 (1.02-1.07)	<0.001
Anemia	2.28 (1.49-3.51)	<0.001	2.23 (1.35-3.71)	0.002
CRF	2.26 (1.48-3.45)	<0.001	2.24 (1.35-3.73)	0.002
CVD	1.44 (1.04-1.20)	0.023	1.26 (0.81-1.99)	NS
ABI<0.5	1.56 (1.08-2.34)	0.020	1.98 (1.20-3.25)	0.007
Rutherford class, 4-6	1.97 (1.53-2.54)	<0.001	1.67 (1.18-2.38)	0.004

Predictors of early mortality.

Conclusion: In patients with CLI, Age, anemia, chronic renal failure, less than 0.5 of ABI before procedure, and Rutherford class were the independent predictors of early mortality.

P532 Trends in hospitalization rates due to cardiovascular diseases since 1980: national hellenic data

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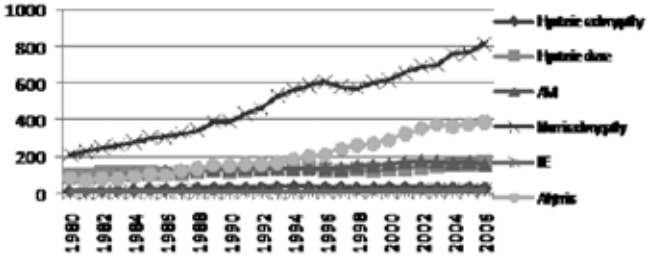
Aim: The aim of this study was to assess the Hellenic hospitalization rates in cardiovascular diseases since 1980.
Materials and methods: Data concerning the cause of hospitalization were retrieved from the National Hellenic Statistical Foundation. Disease coding was based on ICD-9. Diseases of the circulatory system, such as hypertensive cardiomyopathy, other types of hypertensive disease, acute myocardial infarction, ischemic cardiomyopathy, pulmonary embolism and arrhythmias were selected for studying. Absolute number of hospitalizations and days of hospitalization were collected for the period 1980-2006. Hospitalization rates, defined as number of hospitalizations per 100.000 inhabitants, were calculated for male, female and total population.
Results: The trend in hospitalization rates for the cardiac diseases of the total population is shown in figure 1. Hospitalization rates have been increased for all categories. The more dramatic increase though appears to be for arrhythmias (al-



Abstract – Table 1. Prevalence of ECG and TTE abnormalities

ECG abnormalities	No. of subjects, n (%)	TTE findings (n)
Increased R/S wave voltages	782 (4.23%)	Atrial septal aneurysm (4), atrial septal defect (1), Bicuspid aortic valve (6), Mitral valve prolapse (39), Dilated coronary Sinus (1), Dilated left ventricle (1)
T wave inversions	55 (0.30%)	Atrial septal aneurysm (1), Mitral valve prolapse (3)
ST Segment Depression	14 (0.08%)	No Structural Abnormality
AV Conduction Defect: Second Degree Mobitz Type I AV Block, WPW pattern	30 (0.16%)	Mitral valve prolapse (2)
Ventricular Conduction Defect: RBBB, LBBB, LAFB, LPFB	105 (0.57%)	Mitral valve prolapse (5), Atrial septal aneurysm (1),
QRS Axis Deviation	163 (0.88%)	Hypertrophic cardiomyopathy (1), Atrial septal aneurysm (1), Atrial septal defect (1),Mitral valve prolapse (13)
Q wave: ≥0.04 seconds in duration or ≥25%, or QS pattern in two or more leads	20 (0.11%)	No Structural Abnormality
Arrhythmias: Sinus Bradycardia, Sinus Tachycardia, Intermittent SVT, Frequent Atrial/Junctional/Ventricular Ectopics, Atrial Fibrillation	51 (0.28%)	Mitral valve prolapse (1)
Others: R in V1 >0.5mV, R:S >1, P wave abnormalities, Brugada pattern ECG, Prolonged Corrected QT interval (≥440ms in males) ,Epsilon wave	141 (0.75%)	Bicuspid aortic valve (2), Mitral valve prolapse (7)

most by five,) ischemic cardiomyopathy (almost by four) and pulmonary embolism (by four). Acute myocardial infarction and other hypertensive disorders have a minor increase in hospitalization rates.
Conclusion: In Greece the hospitalization rate has been increased in all cardiovascular diseases studied. One of the most striking increases is the one of ischemic cardiomyopathy.

P533 Reduction in global and cardiac mortality as a result of the implementation of a standardized protocol to transfer patients with acute myocardial infarction

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Introduction: A standardized protocol of emergent transfer for primary percutaneous coronary intervention (PPCI) for all patients with ST elevation myocardial infarction (STEMI) has been implemented since June 2009 in our regional health system. The protocol consists of fast diagnosis and subsequent immediate high priority transfer directly to the catheterization lab where the interventional cardiology team is awaiting for the patient.
Objective: To evaluate the impact on in-hospital mortality of the new protocol compared with the previous period when emergent PPCI was not sustained by a highly effective emergent transfer protocol.
Methods: We prospectively enrolled all consecutive patients with STEMI that underwent PPCI in our hospital during a 12 months period (June 2009-may 2010).We analyzed basal characteristics, transfer delays, procedural data and in-hospital evolution and compared them with the previous year (June 2008-may 2009).
Results: An increase in the number of patients treated with PPCI was observed during the study period (514 patients) compared with the previous year (242 patients). Age, sex and cardiovascular risk factor were similar in both groups (median age 61,4 and 61,6 years, female sex 19,8% and 19,2%, diabetes 26,7% and 23,6% respectively). No differences were observed in prevalence of coronary disease, previous revascularization or anterior STEMI. The Door-to-Balloon (DTB) time was clearly lower in the protocol period (median 80 vs 35 minutes, $p<0.001$) and the total ischemia time was slightly but significantly diminished (median 240 to 230 minutes, p=0.043). The Zwolle Score was 3,2 in the protocol group vs 3,6 in the previous group (p=0,07). Succesful PCI rates were similar in both groups. Total in-hospital all cause mortality was reduced from 8,3% to 4,3% (p=0.04) and the cardiovascular cause mortality was reduced from 7,9% to 3,5% (p=0.017). In the logistic regression analysis the in-hospital mortality was significantly related to age, killip class $\geq$ III at presentation, post-PCI TIMI flow $<$ 2 and DTB time.
Conclusion: The introduction in our regional health system of a highly standardized protocol for emergent transfer and PPCI in patients with STEMI clearly demonstrates a significant reduction of in-hospital mortality.

P534 Abdominal aortic aneurysm screening in a selected population of 600 patients referred for transthoracic echocardiography

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Purpose: The utility of screening for abdominal aortic aneurysm (AAA) is controversial in many countries, and so it is in Spain. Our aim was to study the feasibility and clinical utility of AAA screening in a selected population (men over 50 years and women over 60 years) of 600 consecutive patients referred for conventional transthoracic echocardiogram (TTE). We also wanted to know the prevalence of AAA in this population and to identify the characteristics related to an increased risk of having an AAA in these patients.
Methods: Prospectively, an ultrasound examination of the abdominal aorta was performed at the end of regular TTE, in the same probe. AAA was defined as a diameter of 3 cm or more. We included in the study the following clinical conditions and echocardiographic parameters: hypertension, hypercholesterolemia, diabetes, smoking, coronary artery disease, peripheral arterial disease, diameter of the ascending aorta, left ventricle (LV) ejection fraction and diameters, LV mass and LV wall thickness.
Results: Among 600 patients, 556 aortas were properly visualized (92,6%). Although we did not measure the time employed to study the aorta, it could be done easily without a significant prolongation of the time of TTE. The AAA prevalence was 7,01% (9,85% in men and 2,71% in women). Male sex, large diameter of the ascending aorta and smoking were found to be significant risk factors in the univariate and in the multivariate logistic analysis: AUC= 0,73 (C.I. 95% 0,65-0,81).

Table 1

	NO AAA (n=517)	AAA (n=39)	p-value
Age (y)	70.94±9.15	69.64±8.56	0.3112
Male sex (%)	302 (58.4)	33 (84.62)	0.0013
Smoking (%)	50 (9.67)	8 (20.51)	0.0297
Ascending aorta diameter (mm)	35.00±4.72	38.35±5.25	<0.0001

AAA: abdominal aortic aneurysm. The rest of the other clinical conditions and echocardiographic parameters we studied were not found to be significant risk factors for AAA.

Conclusions: AAA is prevalent in patients referred for regular TTE. The study of abdominal aorta as an extension of TTE in this population is feasible with very low extra time consuming and with potential clinical benefit. We therefore recommend it, specially in men over 50 years, in patients with a smoking history or with a dilated ascending aorta.

P535 Implementation of AMI clinical pathway for uncomplicated acute myocardial infarction at a local hospital: three years experience, outcomes and impacts

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Introduction: Development of Acute Myocardial Infarction (AMI) Clinical Pathway was aiming at incorporating evidence-based medicine into clinical practice in the management of uncomplicated AMI patients. The use of Clinical Pathways has increased over the past decade in many developed countries. Less regular adoption of Clinical Pathways is noted in developing countries and in Asia. There is no published data on the implementation and the subsequent impacts of Clinical Pathways in Hong Kong. This study explored the logistics, results and impacts of such development, in a university teaching hospital receiving acute patients in Hong Kong. The parameters focused included the magnitude of improvement in quality care of patients with AMI, the length of hospital stay, the in-patient and 30-day mortality, the door-to-needle time (DNT) in thrombolytic therapy (TT) and door-to-balloon time (DBT) in primary percutaneous coronary intervention (primary PCI) in ST-segment elevation myocardial infarction (STEMI) patients.
Methods and results: AMI Clinical Pathway was implemented in a university teaching hospital since January 2007. A total of 535 AMI patients were recruited and managed according to the pathway protocol. 402 patients had successfully completed the pathway and 72.9% had a diagnosis of STEMI. At the beginning, the average length of hospital stay was 4.0±2.6 days, the in-patient and 30-day mortality were 6.0% and 9.6% respectively, the mean DNT was 105.9±66.4 minutes and the DBT was 161.3±95.6 minutes. In 2009, after 3 years of implementation of the Clinical Pathway, the average length of hospital stay was shortened to 3.9±1.8 days (p=0.627), the in-patient and 30-day mortality improved to 0.9% (p=0.013) and 0.9% (p=0.003) respectively as well, the mean DNT reduced to 39.6±17.3 minutes ($p<0.001$) and the DBT 107.2±24.9 minutes (p=0.018).
Conclusions: AMI clinical pathway helps to streamline and standardize patient care in those with uncomplicated AMI. All clinical outcome parameters, including the DNT, DBT and mortality rate have improved since its implementation in 2007.

P536 Cardiac screening in schoolchildren

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Objectives: Undetected heart disease is the most common cause of sudden death in children. We conducted cardiac screening in schoolchildren to detect the heart diseases.
Methods: Every child entering elementary school was enrolled for cardiac screening. Questionnaire regarding past history of heart disease, family history and cardiac symptoms was used. A 4-lead computerized electrocardiogram (ECG) & phonocardiogram were performed in each child in school. All cardiac suspects (positive questionnaire, ECG or phonocardiogram) were referred for evaluation in a hospital.
Results: During a 10-year period between 1999 & 2008, 806,521 schoolchildren underwent cardiac screening. Congenital heart disease was identified in 3,890 children (4.8 0/00) of whom 262 children had not been diagnosed before. Atrial septal defect was the most common undiagnosed congenital heart disease being found in 137 children (52%). Complete heart block, WPW syndrome & prolongation in QTc ($>$450ms) were found in 14, 678 & 76 children, respectively. Cardiomopathy was diagnosed in 52 children of whom 13 children had not been diagnosed.
Conclusions: Cardiac screening in schoolchildren using questionnaire, ECG & phonocardiography is quite cost effective. Atrial septal defect was the most common previously undiagnosed congenital heart disease. Many life-threatening heart diseases can be diagnosed & treated in time.

P537 Increased rate of total and cardiovascular congenital abnormalities in Brindisi: a legacy of environmental pollution?

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Background: Total and cardiovascular congenital abnormalities are the most prevalent and fatal birth defects worldwide, result from a combination of genetic predisposition and environmental factors. Areas under high environmental pressure can expose offspring to higher risks of abnormalities. Aim-To validate and estimate diagnosed cases of total and cardiovascular congenital abnormalities from

hospital discharge records among newborns and to compare the prevalences observed with those reported by the registries operating in Europe (EUROCAT).
Methods: The diagnoses of the regional hospital claims, coded according to the International Classification of Diseases, 9th Revision, Clinical Modification, have been abstracted for newborns in the period 2001-2008. They have been validated with Intensive Therapy Neonatal Unit (UTIN) data base for the same period through a record linkage. In particular, the validity, sensitivity and specificity of the method were measured by individual-level comparisons with data in the UTIN, gold standard for its accuracy of diagnostic information.
Results: For total and cardiovascular congenital abnormalities we estimated high sensitivity (69% and 80% respectively) and a specificity for both of almost of 100%. We recorded 195 congenital malformations in 6,596 newborns, accounting for a prevalence rate of 295.6/10,000 total births, approximately 1.5 times significantly higher than those reported by the EUROCAT registries. Significant excess were 51.9 and 157.1 for congenital abnormalities and cardiovascular anomalies, respectively.
Conclusions: Our results support the hypothesis for a possible causal role of environmental risk factors present in the risk area on the etiology of malformation, especially for cardiovascular abnormalities. The findings also suggest the possibility to use the regional hospital claims to identify cases of congenital abnormalities and to estimate their occurrence in absence of a register.

P538 Maternal exposure to toxicants and congenital heart disease: the role of GSTM1 and GSTT1 polymorphisms

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Background: There is growing concern about the potential health effects of maternal exposure to various environmental chemicals and the risk of congenital malformations, including congenital heart disease (CHD). Glutathione S-transferases (GST) detoxification enzymes (GSTM1 and GSTT1) are involved in the metabolism of various environmental toxicants and endocrine-disrupting chemicals.
Aim: The purpose of this study was to evaluate the joint effects between environmental maternal exposures and the GSTM1 and GSTT1 polymorphisms.
Methods: In a case-only design, we enrolled 180 CHD patients (104 male, 4.9±5.8 years). A detailed questionnaire was used in order to record demographics and environmental and occupational exposures from mothers with specific questions on potential teratogens/mutagens that have been linked to human reproductive impairment, such as ionizing radiation, solvents, pesticides, asbestos and heavy metals.
Genetic analysis was determined using a co-amplification PCR approach with GSTM4 gene, which is never deleted, as internal control in order to distinguish the GSTM1 and GSTT1 null genotypes.
Results: Maternal exposure to occupational/environmental toxicants was associated with a 3.6 fold increased CHD risk (95% CI=1.1-11.2, p=0.03) among the offspring with both deleted GSTM1 and GSTT1 genes.
Mothers who had exposure to toxicants and carried the GSTM1-null genotype (OR=4.5; 95% CI= 1.6-12.7, p=0.005) and GSTT1-null genotype (OR=3.5; 95% CI= 1.0-13.1, p=0.05) had an increased risk for having a child with CHD compared with the wild type genotype.
The risk was five times greater (OR= 5.6; 95% CI=1.1-29.2; p=0.05) in mothers and infants both having the GSTM1-null genotype compared with both having the wild genotype
Conclusions: Our findings show that maternal exposure to environmental toxicants interacts with GSTM1 and GSTT1 null genotypes to increase the risk of CHD, supporting the evidence for a pivotal role of the environmental risk factors.

PSYCHOLOGICAL, CULTURAL AND ECONOMIC FACTORS IN HEART DISEASE

P539 Depressed patients are less likely to return to work after an acute cardiac event: results of a longitudinal study

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Purpose: Many patients do not return to work (RTW) after an acute cardiac event, particularly older patients and those with poorer health status. However, the role of psychosocial factors such as depression and social support in influencing RTW has not been adequately examined. Our study aimed to investigate rates of RTW and to identify the psychosocial factors associated with non-RTW in cardiac patients.
Method: 210 patients currently in the workforce and consecutively admitted to hospital with acute coronary syndrome (16%) or to undergo coronary artery bypass graft surgery (84%) were interviewed in hospital about their attitudes and intentions regarding RTW. Both qualitative and quantitative data were collected. Depression was assessed using the Hospital Anxiety and Depression Scale (HADS). Patients with HADS-D scores of 8 and above in hospital were classified as "depressed". Patients were re-interviewed by telephone four months after hospital discharge to investigate resumption of work.
Results: Patients ranged in age from 29-73 years (M=51.8). Most (88%) were male. 38 patients (18%) were classified as depressed in hospital and 25 (12%) indicated having no close confidant. By four months post-event, 74% patients had resumed work. Patients who were depressed at the time of their event were less likely to RTW (p=0.032). The rate of RTW for depressed patients was 57% compared with 77% for those not depressed. Non-RTW was also associated with lacking a close confidant (p=0.040). Rates of non-RTW did not vary by demographic factors including age, education level, type of work previously undertaken or the number of hours previously worked, or medical factors such as event type or perceived health status. When the significant variables were entered into a backward stepwise logistic regression, only depression status uniquely predicted non-RTW (Wald=4.44, p=0.035, OR = 2.5). Depressed patients were 2.5 times less likely than non-depressed patients to have resumed work.
Conclusions: Patients who are depressed or, to a lesser extent, lacking a close confidant at the time of a cardiac event are at increased risk of non-RTW following convalescence after an acute cardiac event. These high-risk patients need additional support during convalescence and specific vocational rehabilitation to assist in work resumption.

P540 Association of cardiac factors, anxiety and depression with Health Related Quality of Life in NSTEMI PCI patients

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Purpose: Our study aims to identify to which extent cardiac parameters, anxiety and depression contribute to MacNew HRQoL in NSTEMI PCI patients.
Methods: 1121 NSTEMI PCI patients in Spain and Austria completed the Hospital Anxiety and Depression Scale and the MacNew HRQoL questionnaire before discharge. Hierarchical multiple regressions analysis with MacNew-Global-Score as dependent variable was used to identify factors contributing to MacNew-HRQoL. Age and gender (block 1), cardiac parameters (block 2: hypercholesterolemia, hypertension, diabetes, obesity, history of MI, family history of cardiac disease, multivessel disease) and anxiety and depression (block 3) were included as independent variables.
Results: The multiple regression model (r^2=0.542; p<0,001) identifies 5 individual variables significantly influencing MacNew HRQOL. Age (p<0,001), diabetes (p<0.001) and obesity (p<0,007) have a relatively small negative influence on MacNew HRQoL (standardised beta: -0.09, -0.10, -0,06). Only 6,4% of the variance of MacNew HRQoL is explained by these variables. The explanatory power of the model mainly based on anxiety (p<0,001) and depression (p<0,001) which both have a more pronounced negative impact on MacNew HRQoL (standardised beta: Anxiety -4.76, Depression -2,93). Collinearity testing shows that the model is reliable, although independent variables, especially anxiety and depression, are associated (variance inflation factors all < 2.5, tolerances all >0.4).

Table 1. Multiple hierarchical regression model for MacNew HRQoL

	Cumulative adjusted r^2	Variables included in block*	Unstandardised coefficients (s.e.)	Standardised beta	p
Block 1	0.022	Age (years)	–0.009 (0.002)	–0.088	<0.001
Block 2	0,064	Diabetes	–0.236 (0.049)	–0.101	<0.001
		Obesity	–0.130 (0.049)	–0.055	< 0.007
Block 3	0.542	Anxiety	–0.123 (0.007)	–0.476	<0.001
		Depression	–0.080 (0.008)	–0.293	<0.001

*Non-significant variables have been excluded from the table.

Conclusion: Anxiety and depression are strongly associated with MacNew-HRQoL in Non-STEMI PCI patients. Age, diabetes and obesity have a small impact on MacNew HRQoL, whereas all other tested clinical variables have no impact.

P541 Depression and the progression of carotid intima-media thickness

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Background: Depression are associated with increased cardiovascular disease (CVD) morbidity and mortality; suggesting that depression disorders could accelerate atherosclerosis progression and its clinical complications. We investigated the progression of intima-media thickening (IMT) as an expression of preclinical atherosclerosis and coronary risk factors, and their relationships between autonomic nervous system, endothelial function and inflammation markers, in depressed subjects free from coronary artery disease.

Methods: This study enrolled 389 patients with cardiac risk factors and without evidence of clinical CVD. We evaluated depression using the Beck Depression Inventory. At study entry, traditional risk factors for atherosclerosis were recorded Markers of inflammation (C-reactive protein, CRP; interleukin 6, IL-6) and heart rate variability (time domain) were determined. IMT of the common carotid artery was determined by B-mode ultrasound imaging at baseline and after 5 years of follow-up.
Results: Regression analyses indicated that higher depressive symptoms at baseline were associated with greater 5-year change in carotid IMT ($p < 0.001$), Depression was a significant predictor of progression of carotid IMT (hazard ratio 3.05; IC=1.76-5.31; $p<0.001$). Adjustment for cardiovascular risk factors, heart rate variability and endothelial function did not substantially affect the results. Addition of CRP decreased the estimate for depression by 43%. Both depression and inflammatory biomarkers remained independent predictors of progression of carotid IMT.
Conclusions: Higher levels of depression are associated with greater subclinical atherosclerosis independent of age, CVD risk factors, and therapy. Despite their robust association with depression, inflammatory biomarkers explain only a small portion of the association between depression and IMT progression.

P542 Cardiovascular risk factors and lifestyle profile of persons suffered from depressive symptoms. The results of the national multicentre health survey

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Purpose: There is an evidence of strong and independent relation of psychosocial risk factors to cardiovascular diseases (CVD) risk. Recently there has been observed an increase in prevalence of psychosocial risk factors all over the world and especially in Poland as a country after big socio-economic transformation. Depression can cause the disapproval of life and can reflects the lifestyle. We try to analyze the CVD risk factors profile of persons with depressive symptoms (DS), their lifestyle and health knowledge.
Methods: The data presented are based on a nationwide survey on representative sample of Polish population (13545 persons), aged 20-74, screened in 2003-2005 in the frame of WOBASZ study. Questionnaire, physical examination and laboratory data were collected. DS were recognized if person's score in Beck Depression Inventory was $\geq$ 10pts.
Results: Out of screened persons 24% of men and 34% of women had DS. Persons with DS were older, lower educated, more often had coronary artery disease (CAD) (men: 15,2% vs 4,0%, $p<0.0001$; women: 8,8% vs 3,6%, p=0.0007), arterial hypertension (AH) (men: 49,0% vs 40,0%, p=0.0028; women: 32,9% vs 19,5%, $p<0.0001$), metabolic syndrome (MS) (men: 32,0% vs 24,0%, p=0.0028; women: 45,5% vs 28,4%, $p<0.0001$ and diabetes (men: 14,8% vs 6,1%; women: 11,3% vs 4,0%, $p<0.0001$). Additionally, persons with DS had significantly lower knowledge on prevention methods and about 43% of men and 38% of women with DS knew nothing about prevention compared to 34,0% and 26,0% of persons without DS. Besides both men and women with DS, significantly more often smoked cigarettes, rarely made a regular physical activity, more often drank alcohol more than 3 times a week and more often did not take the prescribed medication.
Conclusions: Persons with depressive symptoms are still growing population all over the world and still growing group among persons seeking for medical assistance and hospitalization. They had much worse CVD risk profile, more unhealthy lifestyle and smaller knowledge on prevention methods than persons without depression. So depression is not only the risk factor, but also a significant limiting factor for prevention.

P543 Psychological distress and its impact on life quality of patients with multiple cardiovascular pathology

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Purpose: Study the prevalence of type D personality and its impact on the life quality of patients after myocardial infarction or stroke.
Materials and methods: 850 patients, treated in the Clinic, were examined. The mean age was 57.7±7.3, females made up 360 (35.5%) and 490 patients were male (64.5%).All the patients were divided into 4 groups according to the history of myocardial infarction (MI) or stroke: group 1 (n=280, 40%) included MI patients, group 2 (n=167, 15%), stroke patients, group 3 (n=149, 11%) enrolled patients with the history of both MI and stroke and group 4 (n=254, 34%) included coronary artery disease patients with no history of MI or stroke. The questionnaire DS-14, comprising NA ("negative affectivity") and SI ("social inhibition") subscales, was used to assess type D personality. The questionnaire SF36, including GH scale – general health, PF – physical function and SF –social function, was used to asses the quality of life.
Results: NA scores were higher in group 1 and 3 (11.9±1.3 vs. 11.4±0.6, respectively), and group 2 and 4 had 8.3±0.4 vs. 9.4±0.5 NA scores, respectively ($p<0,005$). MI patients with multiple cardiovascular pathology had higher SI scores (10.3±1.2 vs. 11.6±0.6, respectively). Type D personality was less often observed in group 2 and group 4 (9.74%, 11.78%) and more often in group 1 and 3 (42.38% vs. 35.1%, respectively) (p=0.0001). GH, PF and SF scores were significantly lower in group 3 patients (35.2±2.2, 41.0±2.5, 41.3±1.6, respectively) compared with the coronary artery disease patients (71.4±1.3, 73.8±1.2, 59.2±1.3, respectively, $p<0.0001$ in all of the cases).
Conclusions: The prevalence of type D personality, which is characterized by the joint tendency towards negative affectivity and the restriction of negative emotions, is higher in patients with multiple cardiovascular pathology. These patients constitute a high-risk group for an adverse course of systemic atherosclerosis and require a closer follow-up including programs of psychological correction.

P544 Perceived control and total and cardiovascular mortality in Eastern Europe: prospective results from the HAPIEE cohort

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Purpose: Perceived control has been found to be associated with socioeconomic disadvantage and numerous health outcomes but results on objective outcomes in cohort studies are sparse. This presentation has two aims: first, to investigate the association of perceived control with total and cardiovascular disease (CVD) mortality in eastern European populations, and second, to examine whether perceived control can help explaining the high mortality in Russia.
Methods: The HAPIEE study examined random urban population samples of men and women aged 45-69 years at baseline (in 2002-05) in Novosibirsk (Russia), Krakow (Poland) and six Czech towns. Participants provided data on a wide range of socioeconomic, psychosocial and behavioural factors. Perceived control was assessed by 10 questions; responses were summed into a score and subjects were divided into quartiles. The cohorts were followed up for mortality using national and local registers until end of 2008; the mean follow up was 5.0 years. A total of 10,237 men and 11,672 women with complete data were included in the analyses.
Results: Among subjects with complete data, the numbers of deaths from all causes, CVD and coronary heart disease (CHD) were 1207, 406 and 239, respectively. The mean control score was lowest in Russia and highest in Poland. As the association between perceived control and mortality was similar in men and women, data from both genders were pooled. In models adjusted for age, sex and country, the hazard ratios for being in the lowest quartile of control, compared with the highest quartile, for total, CVD and CHD mortality were 1.88 (95% CI 1.60-2.22), 2.66 (1.95-3.62) and 2.30 (1.56-3.41), respectively. Further adjustment for socioeconomic factors, CVD risk factors and depressive symptoms reduced these hazard ratios to 1.51 (1.26-1.81) for total mortality, 1.99 (1.43-2.77) for CVD mortality and 1.86 (1.22-2.82) for CHD mortality; the largest contribution to the attenuation was made by socioeconomic factors and depressive symptoms. Perceived control made only a small contribution to explaining differences in mortality between countries. For example, the age-sex adjusted hazard ratio for Russia vs. Czech Republic for CVD mortality of 2.50 (1.94-3.23) was reduced to 2.36 (1.83-3.04) by inclusion of control into the model (reduction by 9%).
Conclusions: Low perceived control was significantly associated with increased total and CVD mortality, although the attenuation of its effect by adjustment raises a possibility of residual confounding. The contribution of low control to the high mortality in Russia was small.

P545 New evidence on the effects of acute exposure to hypobaric hypoxia at high altitude on cognitive functions

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Purpose: Exposure to high altitude (HA) reduces the amount of oxygen available to the central nervous system (CNS) and can lead to a wide range of cognitive impairment. Studies of HA can be considered as an ecological model for analysis of changes in cognitive functions of patients with clinical conditions associated with hypoxemia. Data previously obtained from HIGHCARE project have shown cognitive changes at HA mostly involving frontal efficiency, and have demonstrated a greater sensitivity of computerized assessment with respect to traditional neuropsychological measures in these settings. Aim of the present study was to obtain a deeper insight into the cognitive effects of acute exposure to HA hypobaric hypoxia, by means of computerized measures focused on executive-attentional efficiency.
Methods: 39 healthy subjects (18 females, 21 males, mean age: 37.15±8.87 years; mean education: 18.71±3.68 years) were enrolled and underwent a short neuropsychological assessment at sea level (SL) and during acute exposure to hypobaric hypoxia at 4559 m. Attentional skills and frontal functioning were in-

vestigated with a computerized neuropsychological battery named TEA (Test for the Examination of Attention), focusing on attention and frontal functions. A clinical tool for assessing anxiety was also administered. The data so obtained were correlated with parameters of respiratory and cardiovascular function.
Results: Our data show quantitative differences in cognitive performances between SL and HA, mainly in some attentional and frontal abilities assessed by TEA. In particular, at HA a significant increase in reaction times (in msec) was found in the Alert subcomponent, both without warning (SL 246.71±56.65 vs HA 274.30±56.07; $p<0.0001$) and with warning (SL 254.6±66.70 vs HA 271.59±60.62; $p<0.02$); in Divided Attention subcomponent (Auditory task, SL 520.07±77.77 vs HA 545,87±81.11; $p<0.01$); in Sustained Attention subcomponent, in the 5-10 minutes condition (SL 643.00±128.85; HA 614.86±128.01; $p<0.05$) and in the left Incompatibility subcomponent (SL 490.05±104.98; HA 464.23±89.53; $p<0.05$).
Conclusions: By means of a computerized neuropsychological assessment even small frontal cognitive changes could be outlined in the hypoxic condition at HA. In particular, reaction times, more than error assessment, seem more useful to detect the influence of hypoxia over cognitive performance. These results may have implications also for the cognitive assessment of chronic patients with diseases associated with hypoxemia.

P546 Increased risk of death in single-living men with chronic heart failure

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Purpose: To study the impact of single-living on all-cause mortality in patients with chronic heart failure (HF), and to examine whether this association was modified by gender.
Methods: This historical cohort study included 637 patients identified by the Danish National Registers of Patients. All patients fulfilled the European Society of Cardiology criteria for the diagnosis of HF and were admitted to Herlev University Hospital during the period 1.07.2005 - 30.06.2007. Cox-proportional-hazard analysis was used to compute the hazard ratio (HR) of all-cause mortality controlling for confounding factors. Residual analyses were used to check the assumptions and the overall model fit.
Results: The median age was 74.9 years and the median follow-up time was 2.9 years. After adjustment for a number of potential confounding factors the risk of death among single-living patients was significantly increased (HR 1.53; 95% CI 1.19-1.96). A gender stratified analysis of the living arrangements and all-cause mortality with adjustment for confounding factors showed that the risk of death was greatest in single-living men (Table 1). Other predictors of death were high age, diabetes, left ventricualr ejection fraction, previous stroke and severe functional mitral valve regurgiation.

Table 1

	Hazard Ratio (95% CI)
Male* living with a partner	reference
Female* living with a partner	0.67(0.43–1.05)
Female* living alone	1.15(0.85–1.56)
Male* living alone	1.51(1.12–2.02)

Conclusions: Single-living is an independent risk factor for all-cause mortality in men with chronic heart failure

P547 Living alone is associated with a poorer prognosis of incident acute coronary syndrome

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Purpose: To determine whether living alone vs. living with a spouse is associated with a poorer prognosis in cases of first acute coronary syndrome (ACS).
Methods: The population-based FINAMI Myocardial Infarction register recorded 2,526 cases of incident ACS among men and women aged 35-64 years in Finland in 1993-2002. Record linkage with the files of Statistics Finland provided us with information on sociodemographic characteristics prior to the event. Case fatality (CF) was determined as the proportion of fatal events of all events at different points in time (before hospital, 28 days and one year) after the onset of the event.
Results: CF of men and women living alone was significantly higher at all time points than the CF of men and women living with someone (Table). No differences by sociodemographic characteristics were observed in the proportions of patients reaching the hospital in less than 4 hours after the onset of symptoms. However, 20% (95% CI 16-23) of men living alone received thrombolysis, while the proportion was 31% among men living with one person (95% CI 28-34) or more (95% CI 28-35). No such differences were found among women. The proportions of patients undergoing revascularization during the first 28 days did not differ by sociodemographic characteristics, either.

Table 1. CF (%) of incident ACS among 35-64 year-old men and women according to household size in the FINAMI Register during 1993-2002. The 95% CIs in parenthesis

	Household size	Before hospital	0–27 days	0–365 days
Men	>2 people in household	23 (20, 27)	31 (28, 35)	33 (29, 37)
	2 people in household	23 (20, 26)	31 (28, 34)	34 (31, 37)
	living alone	41 (36, 45)	49 (44, 54)	52 (48, 57)
Women	>2 people in household	10 (5, 16)	21 (14, 28)	24 (16, 32)
	2 people in household	14 (9, 18)	25 (19, 31)	28 (21, 34)
	living alone	32 (24, 39)	43 (35, 51)	45 (37, 53)

Conclusions: Single living is associated with a higher CF of incident ACS. Most of this difference seems to be due to a greater proportion of sudden prehospital coronary deaths among people living alone but the differences remained significant at least until one year after the onset of the event. The differences cannot be fully explained by delays in hospitalization or differences in access to thrombolysis or revascularization.

P548 Socioeconomic gradients in cardiovascular risk factor prevalence and screening, and in knowledge of determinants of cardiovascular disease, in rural India

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Background: There is little information on the socioeconomic patterning of cardiovascular (CV) risk factors in under-resourced rural areas of developing countries. The objective of this analysis was to investigate the socioeconomic patterning of CV risk factors, screening and knowledge of CV risk determinants in a rural Indian population.
Methods: Participants were an age- and sex stratified random sample of 4535 adults from twenty villages in rural Andhra Pradesh. Information on education, CV risk factors, screening and knowledge were obtained from a structured questionnaire and brief physical examination. Information on socioeconomic position (SEP, educational level), was ascertained through questionnaire.
Results: Tobacco use was more common in lower SEP individuals. Diabetes, overweight, physical inactivity, previous vascular disease, family history of vascular disease and hypertension were more common in higher SEP individuals. Lower SEP individuals were less likely to have received blood pressure, diabetes or cholesterol screening and were less knowledgeable of nine CV risk determinants (all $p<0.001$).

Percentage with risk factors/screening

	Educated	No education	Age-adjusted p-value
N	2,385	2,150	–
Age (mean, SD)	48.3(13.5)	50.6 (13.6)	<0.001
Current smoker	22.3	29.0	<0.001
Diabetes	16.9	12.6	<0.001
Hypertension	30.6	29.0	0.001
BMI>25	27.8	16.3	<0.001
Physical inactivity	45.8	38.1	<0.001
Family history of CVD	18.2	10.7	<0.001
Previous vascular disease	8.2	6.1	<0.001
Blood pressure checked	71.8	65.8	<0.001
Blood sugar checked	41.7	35.2	<0.001
Cholesterol checked	8.1	2.5	<0.001

Percentage of those with risk factors, and blood pressure, blood sugar and cholesterol checks, by level of education.

Conclusion: While CV risk factors (except smoking) remain less in lower SEP in rural India, this study indicates that those with lower SEP are poorly equipped to address the rising burden of chronic disease in India.

P549 Low socioeconomic status is a significant predictor of incidental stroke risk in Chinese population from a prospective cohort study in Beijing

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Background and objectives: The association between socioeconomic status (SES) and the risk of stroke is a combined effect of the knowledge and practice of health protection, accessibility to the health care services and early life development on the disease. The inverse associations are usually reported from high-income countries while positive associations are more likely to be observed from low-income countries. We aim to estimate the impact of SES (measured with education level and household income) on the risk of stroke using data from a prospective cohort study in China.
Methods: The cohort incepted in 2004 with 2367 volunteers (50.5% women, mean age 59y) in west suburban of Beijing in 2004 and followed up till the end of

2008. The data were collected with the interviewer- administered questionnaire for the socio-demographic information and medical history. Blood pressure (BP), body height and weight and blood lipids, glucose, creatinine etc were measured at baseline. The incidental event of stroke was recorded during the follow-up. The hazard ratios (HR) of stroke for each SES group compared to the lowest SES group were estimated using the Cox model and controlled for conventional cardiovascular risk factors.
Results: The incidence of stroke in this cohort was 6.1 per 1000 person-year. Compare to the lowest SES group, the HR was 0.35 (0.13-0.91) for the highest SES group, 0.45 (0.18-1.10) for the second SES group and 0.69 (95%CI: 0.36-1.32) for the third SES group, after controlling for age, baseline BP, ever smoking, history of cardiovascular diseases, diabetes or renal disease, and stratified by sex; $p<0.002$ for trend test.
Conclusion: People with less education and lower income are at an increased risk of developing stroke in China. More efforts should be put on the less privileged populations to prevent stroke in economically emerging countries.

P550 British south Asians have nocturnal onset of myocardial infarction compared to morning onset of their white counterparts

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Objectives: The morning peaking of myocardial infarction may not apply to patients of Indian subcontinent origin (Asians). We compared British Asians with their White counterparts in symptom onset times (symptom times) and hospital presentation times (door times) for ST-elevation myocardial infarction (STEMI).
Methods: The symptom times of consecutive patients undergoing primary angioplasties from August 2003 to October 2009 were grouped in six 4-hourly intervals. Likewise was performed on door times. White to Asian ratios were obtained for total sample & for each interval. Odds ratios (OR) were calculated for odds for Whites to Asians in one interval relative to odds for Whites to Asians in the remaining five intervals.
Results: There were 605 Whites and 184 Asians. Of these, 514 (85%) Whites and 159 (86%) Asians (ie White to Asian ratio 3.2) with symptom times and door times were analysed. For any interval, ratio >3.2 suggested higher number of Whites than expected and < 3.2 suggested higher number of Asians than expected.
Whites had the highest ratio 4.8 and OR 1.61 (95% CI 0.97-2.66, p 0.077) in interval 0401-0800 for symptom times. They had the highest ratio 4.2 and OR 1.42 (95% CI 0.94-2.15, p 0.108) in interval 0801-1200 for door times.
Asians had the lowest ratio 1.9 and OR 0.55 (corresponding to highest Asian to White ie reciprocal OR 1.81, 95% CI 1.05-3.11, p 0.043) in interval 2001-2400 for symptom times. They had the lowest ratio 1.7 and OR 0.47 (corresponding to highest Asian to White ie reciprocal OR 2.11, 95% CI 1.23-3.60, p 0.008) in 0001-0400 interval for door times.
Conclusions: British South Asians are more likely to develop and present with STEMI during night time. This is in contrast to their White counterparts whose morning onset is in keeping with literatures. This difference suggests possible benefits of altering the timing of cardiac medications to cover the at-risk period and providing out-of-hours interpreters in Asian languages.

P551 Female gender is only in elderly patients a significant predictor for mortality after coronary stent implantation

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Background/objective: Female gender is discussed to be a major issue of outcome in patients with symptomatic coronary heart disease (CHD). Clinical significance of coronary risk factors was discussed as a potential cause.
Methods: We retrospectively assessed 1,809 consecutive CHD-patients who had undergone PCI in the Department of Medicine III of the University. Kaplan-Meier-analyses with log rank test and Cox regression analyses on predefined models regarding the primary endpoint of all-cause mortality were performed. Univariate analyses investigated the influence of gender on the primary endpoint. Multivariate analyses included the classic risk factors (BMI, smoking, diabetes mellitus, hypertension, dyslipidemia and family history for CHD).
Results: Follow-up data concerning the primary endpoint of death was complete for 1,726 patients (95.6%). Kaplan-Meier analysis including all patients showed a significant increase in the incidence of the primary endpoint in females in comparison to males (25.6% of 526 females died during the mean follow-up of 137 ± 61 weeks in comparison to 20.0% of 1,202 males, p=0.011). However, in multivariate Cox regression model female gender was no longer a predictor for death (p=0.834), whereas age was ($p<0.001$).
For further evaluation, we compared females and males regarding baseline variables and found as a major difference that females were significantly older than males (70.5 ± 10.3 years of age females vs. 64.3 ± 11.2 males).
Thus, we hypothesized that age is a major confounder for the influence of gender on outcome and performed further analyses after stratification by median of age (67.4 years).
Now, in univariate analyses female gender was significantly related to primary endpoint only in patients with an age above the median (p=0.010), this remained stable also in multivariate analyses including classical risk factors (OR 1.347, 95%CI 1.017-1.784, p=0.037). In younger patients gender was not a predictor for outcome (p=0.418).
Conclusion: In our single center study older females with an age above 67 years are at higher risk for dying after coronary stent implantation than men, whereas younger females were not.

P552 Birth prevalence of congenital heart disease; meta-analysis on geographical differences

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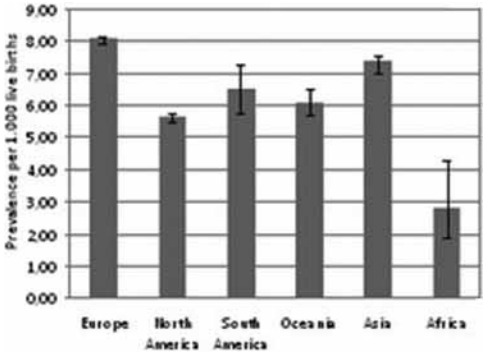
Purpose: With an estimated birth prevalence of 8 per 1000 live births, congenital heart disease (CHD) is the most common form of congenital abnormalities. Variation in the birth prevalence of CHD worldwide has been suggested; however a complete overview is missing.
Methods: On September 23rd 2010 a PubMed literature search was conducted with the search terms: "heart defects, congenital/epidemiology" and "incidence" and "prevalence". Weighted averages of CHD birth prevalence per continent and World Bank income groups were calculated using the generic inverse variance method and compared with a Chi square test.
Results: Including 131 articles, a total population of 25,172,760 live births was studied of which 166,899 were diagnosed with CHD. Significant geographical differences were found (Figure 1). The reported CHD birth prevalence in Europe was significantly higher than in North America (8.0 vs. 5.6/1000 live births; $p<0.001$). Asia reported the second highest CHD birth prevalence (7.3/1000), with relatively more right and less left ventricular obstructive lesions. Worldwide, VSD was the most common CHD type (2.6/1000), followed by ASD, ductus and pulmonary stenosis (resp. 1.6, 0.9 and 0.5/1000). CHD birth prevalence in high income countries was 7.6/1000 live births, significantly higher than upper middle income (7.2/1000; p=0.041), lower middle income (3.3/1000; $p<0.001$) and low income countries (1.3/1000; $p<0.001$).



Birth prevalence of CHD per continent.

Conclusions: Major geographical differences in the reported CHD birth prevalence exist. Data about CHD birth prevalence in Africa and low income countries are scarce and probably less reliable. Observed differences may be of genetic, environmental, socio-economical or ethnic origin, and need further investigation in order to tailor the management of this global health problem.

P553 Does level of education compromise symptom-to-first-medical-contact time amongst STEMI patients?

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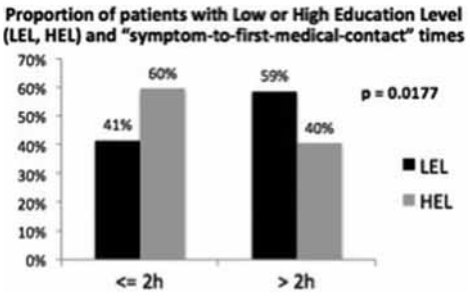
Background: One of the major objectives of the European "Stent For Life" initiative is to ensure equal access to percutaneous coronary intervention (PCI) for all STEMI patients. It is well known that the "symptom-to-first-medical-contact" time strongly affects prognosis. The impact of educational factors on this critical time period is poorly known.
Aim: To evaluate the impact of educational factors on the "symptom-to-first-medical-contact" time in the state of Vaud area (Switzerland) in patients receiving primary PCI for STEMI.
Method: Retrospective observational study of all STEMI patients (n=402) extracted from our primary PCI hospital's database between 01-01-2009 and 06-

31-2010. The main exclusion criteria were a "symptom-to-first-medical-contact" time >12 hours or other diagnosis at angiography. 352 patients were finally included. Times at onset of symptoms and at admission were retrieved from the patients' record files. The Swiss official education's grading system was used to classify patients into 2 educational levels.
Results: A "symptom-to-first-medical-contact" time ≤2 hours had been recorded for a majority of patients with a High Education Level (HEL) but only for a minority of patients with a Low Education Level (LEL) (59.5% vs 41.4% respectively; $p<0.05$). In a sub-group of patients (n = 88), the exact "symptom-to-call" time was available (median = 55 minutes). A "symptom-to-call" time ≤55 minutes had been recorded for a majority of HEL but only for a minority of LEL (57.1% vs 35.9% respectively; $p<0.05$).



Conclusion: In the state of Vaud, a High Education Level is associated with shorter "symptom-to-first-medical-contact" and "symptom-to-call" times. Therefore, health education and prevention should particularly focus on the population with a low level of scholar education.

P554 Differential lipid profiles according to ethnicity in the heart of Soweto study cohort of de novo presentations of heart disease

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Background: Historically low levels of atherosclerotic forms of cardiovascular disease (CVD) have been reported in sub-Saharan Africa. With epidemiological transition, this balance may well change; particularly among urban-dwelling, black Africans consuming more saturated fats and exercising less.
Methods: Hospital services the black African community of 1.1 million people in Soweto, South Africa. A clinical registry captured data from all de novo cases of heart disease presenting to the Cardiology Unit during 2006 - 2008. We examined fasting lipid profiles in 1,798 patients according to their ethnic/cultural background.
Results: The cohort comprised 1798 black Africans (61% female, aged 57±14 years), 138 Caucasians (37% female, aged 58±13 years), 131 Indians (49% female, aged 59±12 years) and 86 of mixed ancestry (41% female, aged 56±12 years). Consistent with different patterns in communicable (e.g. rheumatic heart disease) versus non-communicable (e.g. hypertensive heart disease) forms of heart disease, as shown in Figure 1 there were clear gradients in respect to the distribution (frequency of mean ± sd) of total cholesterol, low-density lipids (LDL) cholesterol and triglycerides, but not high-density lipids (HDL). Adjusting for age and sex, black Africans were significantly less likely to record a total cholesterol of >4.0 mmol/L compared to all other races (OR 0.27, 95% CI 0.17 - 0.40; Africans versus Indians).

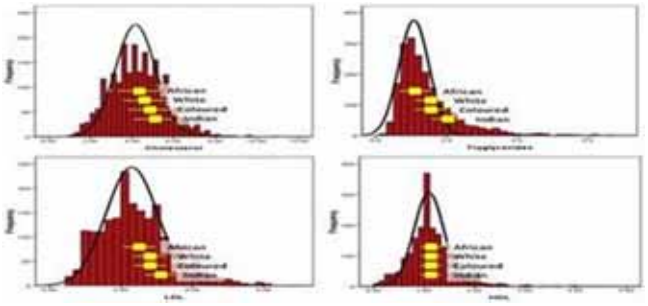

Figure 1

Conclusion: These data confirm ethnic differences in the lipid profiles of de novo heart disease patients in Soweto, South Africa; reflecting differential patterns of disease in the region. Primary and secondary prevention strategies (e.g. the polypill) in the region need to adjust to the ethnic/cultural profile of target individuals and communities.

P555 The role of ethnicity on clinical outcome of women with premature coronary artery disease after percutaneous coronary intervention

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Background and aim: Women account for a significant proportion of all cardiovascular-related deaths in our multi-ethnic society. Previous registry data have suggested that ethnic differences in clinical outcome exist following percutaneous coronary intervention (PCI). It is not known if women from different ethnic backgrounds below the age of 65 years with premature coronary artery disease demonstrate similar differences in clinical outcome. Therefore, we aim to examine the differences in clinical outcome following PCI between women aged below 65 years and those above 65 years of age.
Methods: We prospectively collected data on consecutive patients with CAD who underwent PCI. Baseline clinical characteristics including cardiovascular risk factors of hypertension, hyperlipidemia, diabetes mellitus, smoking and family history of premature coronary artery disease as well as patient follow up data were obtained from medical records or telephone follow-up. Primary outcomes were major adverse cardiovascular events (MACE) of myocardial infarction (MI), repeat revascularization and all-cause death at one month and six months.
Results: Out of 7889 patients, we identified 2137 females with CAD (mean age 65 years, SD 10). There were more ethnic Chinese (68%), compared to Malays (15%), Indians (13%) and other races (4%). 953 (45%) were aged 65 years and below. Compared to women above 65 years old, a family history of premature CAD was associated with premature CAD [OR 3.61 95%CI 2.51-5.18 $p<0.001$ (27% vs. 73%)]. Women below 65 years were more likely to have MI at one month [OR 10.1 95% 1.26-81.1 p=0.013 (89% vs 11%) compared to older women. After adjusting for risk factors, Indian women below 65 years had higher rates of MI and repeat revascularization at one month [OR 26.6 95%CI 6.59-107.6 $p<0.001$ (4% vs 0.2%); OR 3.07 95%CI 1.60-5.88 p=0.02 (8% vs 3%)] as well as six month composite MACE (OR 2.15 95%CI 1.34-3.46 p=0.003) compared to older Indian women.
Conclusion: Women who develop premature coronary artery disease are at risk of early cardiac events after PCI. Amongst the Asian subpopulations, Indian women with premature CAD have the highest risk.

P556 Economic impact of smoking cessation among motivated quitters in Norway

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Background: Tobacco use is the most important health-risk that can be prevented, and an important cause of premature death. More than 10% of all deaths from cardiovascular disease (CVD) are due to smoking. After diagnosed CVD, around 50% of smokers continue to smoke. Smoking cessation (SC) is potentially the most cost-effective life-saving intervention for patients with CVD, and costs of interventions for SC are small in comparison with the long-term benefits both in terms of prevention, mortality, morbidities and treatment costs for smoking-related diseases. The purpose of this study is to explore the economic impact of SC by treating motivated quitters with varenicline (Champix).
Method: An Excel-based model was developed to compute per-member-per-year costs associated with SC among motivated quitters in general population. The model assumes that smokers make only one SC attempt using varenicline. Model inputs on smoking-related costs were 80 billion NOK per year and 2-3 billion NOK reduced costs per year per % reduction in smoking prevalence, both in accordance with cost data from the Norwegian Health Directorate. Inputs included also smoking prevalence, drug costs and the proportion of motivated quitters. Norwegian statistics on smoking prevalence, Medline search for statistics regarding motivated quitters and varenicline effect as shown by the Norwegian Knowledge Center for Health Services (NKCHS). The primary model outcome will be costs of treating with varenicline and costs avoided.
Result: If 50.000 of 900.000 Norwegian daily smokers use varenicline in one SC attempt, 13.000 will remain smoke free after one year. This will reduce the smoking prevalence in Norway by 1.4%. Since reduced costs per year per % reduction in smoking prevalence is 2-3 billion NOK, the cost-effectiveness is substantional as treatment cost for medicines is 115 million NOK. Net gain from SC in motivated quitters amount to 2.8-4.2 billion NOK in year one. Assuming the applied average cost is too high, the model predicts a "first year break even cost" of 8.800 NOK per patient.
Conclusion: Our analysis demonstrates that the alarmingly high smoking-related costs can be influenced by significant cost savings already in year one. Reduced smoking prevalence, also among smokers with CVD, will have substantial short- and long-term cost-effects as both disease progression and smoking related CVD deaths will be influenced, and the CVD related treatment costs will be reduced.

DYSGLYCEMIA; BITTER SWEET

P557 Type-2 diabetes and hypogylcaemia - insights from the 6 months prospective DiaRegis follow-up

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Purpose: To investigate the risk of therapy associated complications such as hypoglycaemia in patients with type-2 diabetes when treatment is intensified.
Methods: Prospective registry of pts with type-2 diabetes insufficiently controlled on oral mono- or dual antiabetic therapy and intensification of therapy at baseline. Comparison of patients with and without hypoglycaemia and 6 months follow-up.
Results: 409 out of 3808 (10.7%) had hypoglycaemia within the last 12 months. Patients with hypoglycaemia had lower blood glucose and frequent co-morbidity (heart failure/depression). They received less metformin and more sulfonylureas (SU). SU was frequently dismissed as a result (44.5 prior vs. 18.6% after therapy change), while SU prescription did not change significantly among pts without hypoglycaemia. Further insulin (26.7 vs. 16.1%; $p<0.0001$) and DPP-4 inhibitors (29.8.vs. 39.9%; $p<0.0001$) were frequently introduced at baseline. After a 6 months follow-up 25% of patients with previous hypoglycaemia had recurrent events (6.5% in pts without prior hypoglycaemia; $p<0.0001$). In patients with hypoglycaemic events during the 6 month follow-up there was a higher use of insulin (45.6 vs. 14.6%; $p<0.0001$). In contrast, the DPP-4-inhibitors use was lower (17.4 vs. 41.1%; $p<0.0001$). Incident unstable angina (1.0 vs. 0.3; $p<0.05$), peripheral neuropathy (8.4 vs. 4.3; $p<0.001$) and non-proliferative retinopathy (2.6 vs. 1.2; $p<0.05$) were more frequent in patients with prior hypoglycaemia.

Patients with or without hypogylcaemia

	With hypoglycaemia	Without	p-value
HbA1c (%)	7.2	7.4	<0.0001
Fasting blood glucose (mg/dl)	133	143	<0.0001
Postprandial blood glucose (mg/dl)	172	186	<0.0001
Heart failure (%)	16.4	9.1	<0.0001
Relevant depression (%)	12.0	4.6	<0.0001
Metformin prior / after enrolment (%)	78.0 / 78.7	84.8 / 85.2	<0.001 / <0.001
Sulfonylureas prior / after enrolment (%)	44.5 / 18.6	26.9 / 27.2	<0.0001 / <0.001
DPP-4 inhibitors prior / after enrolment (%)	3.2 / 29.8	5.1 / 39.9	0.08 / <0.0001

Conclusions: Hypoglycaemia is a frequent complication of antidiabetic therapy, especially in patients receiving sulfonylureas. It is associated with co-morbid heart failure and with incident morbidity during follow-up.

P558 Nearly doubled rate of hypoglycemia in diabetic patients with heart failure in clinical practice: results of DiaRegis

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Background: Patients with type 2 diabetes have an increased risk of heart failure (HF). However data on the co-morbidity burden and in particular the incidence of hypoglycaemia are scarce.
Methods: DiaRegis is a German prospective registry including patients with type-2 diabetes treated with oral mono- or dual anti-diabetic combination therapy in 2009/2010. We examined differences in co-morbidity and the incidence of hypoglycaemia in diabetic outpatients with and without heart failure.
Results: Of 3,746 patients, 9.9% had HF. Median (IQR) age was 66.0 (57.7-72.9) years, 46.8% were female. HF patients were older, had a longer diabetes duration and more co-morbidities. Hypoglycaemia was significantly more frequent in patients with heart failure in the 12 months preceding enrolment, which was most pronounced for those requiring medical assistance and help from 3rd persons. They received less metformin (Met) in monotherapy and more sulfonylureas (SU), both drugs known to interfere with the incidence of heart failure. After enrolment, more patients with HF received insulin treatment. Hypoglycaemic events were 50% more frequent in patients with HF during the 6 months prospective follow-up. Patients with HF more often had vascular adverse events during the 6 months follow-up.

Diabetes and heart failure

	Heart failure (n=370)	No heart failure (n=3376)	p-value
Age (years)	73	65	<0.0001
Diabetes duration (%)	6.2	5.5	<0.05
Hypertension (%)	95.4	83.1	<0.0001
Coronary heart disease (%)	52.9	13.8	<0.0001
Stroke/TIA (%)	9.5	4.1	<0.0001
Periph. arterial disease (%)	15.6	4.9	<0.0001
Auton. neuropathy (%)	7.2	2.9	<0.0001
Met prior enrolment (%)	76.8	85.0	<0.000
SU prior enrolment (%)	32.7	28.3	0.07
DPP4-inh. prior enrolment (%)	7.3	4.7	<0.05
Insulin start at baseline (%)	21.4	16.6	<0.05
Hypoglycaemia last 12 months (%)	17.8	10.0	<0.0001
Requ. 3rd persons help (%)	2.7	0.7	<0.0001
Requ. med. assistance (%)	2.1	0.5	<0.0001
6 months stroke/TIA (%)	1.4	0.3	<0.01
6 months unstable angina (%)	2.3	0.2	<0.0001
6 months PCI (%)	1.1	0.2	<0.01
6 months periph. angioplasty (%)	2.0	0.4	<0.0001
Hypoglycamia 6 month FU (%)	12.1	8.1	<0.05

Conclusions: Patients with type 2 diabetes and heart failure have a substantially increased co-morbidity burden compared to patients without heart failure and report to have experienced nearly twice as much episodes of hypoglycaemia, especially those requiring medical assistance. Particular attention should be given to an appropriate pharmacotherapy.

P559 Validation of type 2 diabetes risk scores in Switzerland (CoLaus study)

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Purpose: Numerous risk scores for Type 2 diabetes have been recently developed, but few have been validated locally. The aim of this study was to validate various Type 2 diabetes risk scores in the Swiss population.
Methods: Prospective study conducted in 3,060 non-diabetic participants (44.6% men, mean age 52.6±10.6), followed for 5 years. The Area under the ROC curve (AROC), sensitivity, specificity, negative and positive predictive values were assessed for seven published risk scores including clinical and biological variables.
Results: 169 patients (5.5%) developed Type 2 diabetes during follow-up. Overall, most risk scores had a high AROC, which ranged between 76.1 and 89.9% (see table). They also presented a high specificity (85.2 to 99.1%) and a high negative predictive value (94.8 to 97.7%). Conversely, their sensitivity was rather low (10.1 to 65.7%), which was also the case for their positive predictive values (17.8 to 35.7%). The highest AROC was found using clinical + biological score from Kahn et al. (89.9%) followed by the clinical FINDRISC score (85.1%), and the online score from the Swiss Diabetes Association (84.7%)
Conclusions: Risk score from Kahn et al. can be used for the best accuracy in prediction of Type 2 Diabetes in Switzerland. However, the clinical FINDRISC score may be more convenient for preventive screening.

P560 Genetic markers do not improve type 2 diabetes prediction in the CoLaus study

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Purpose: To assess the extra clinical value of genetic risk scores in predicting the occurrence of Type 2 Diabetes.
Methods: Prospective study conducted in 2,113 participants (44.7% men, mean age 52.9±10.7) free from diabetes at baseline, followed for 5 years. Different genetic risk scores for diabetes were computed using published data. Their pre-

Abstract P555 – Table 1. Performance of the tested risk scores

Risk Score	AROC (95% CI)	Kappa (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Balkau et al. (C)	76.3 (73.1–79.5)	0.095 (0.038–0.152)	10.1 (6.0–15.6)	97.4 (96.8–98.0)	18.5 (11.1–27.9)	94.9 (94.0–95.6)
Kahn et al. (C)	79.2 (76.0–82.3)	0.209 (0.152–0.266)	32.5 (25.5–40.2)	93.2 (92.2–94.1)	21.8 (16.9–27.4)	95.9 (95.1–96.6)
Griffin et al. (C)	79.9 (76.9–82.9)	0.199 (0.154–0.243)	50.9 (43.1–58.6)	86.3 (85.0–87.5)	17.8 (14.5–21.6)	96.8 (96.0–97.4)
Wilson et al. (CB)	83.0 (79.9–86.1)	0.123 (0.059–0.186)	8.9 (5.1–14.2)	99.1 (98.6–99.4)	35.7 (21.6–52.0)	94.9 (94.1–95.7)
Swiss Diabetes Association (C)	84.7 (82.2–87.2)	0.253 (0.201–0.305)	49.7 (41.9–57.5)	90.0 (88.9–91.1)	22.5 (18.4–27.1)	96.8 (96.1–97.5)
FINDRISC (C)	85.1 (82.7–87.6)	0.251 (0.207–0.294)	65.7 (58.0–72.8)	85.2 (83.8–86.5)	20.6 (17.3–24.3)	97.7 (97.0–98.2)
Kahn et al. (CB)	89.9 (87.9–91.9)	0.339 (0.278–0.399)	49.1 (41.4–56.9)	93.7 (92.8–94.6)	31.4 (25.9–37.4)	96.9 (96.2–97.5)

Abbreviations: C, clinic; CB, clinic + biology. Score references: Balkau et al. Diabetes Care (2008) 31:2056; Kahn et al. Ann Intern Med (2009) 150:741; Griffin et al. Diabetes Metab Res Rev (2000) 16:164; Wilson et al. Arch Intern Med (2007) 167:1068; Swiss Diabetes Association: www.diabetesgesellschaft.ch; Lindström et al. Diabetes Care (2003) 26:725-731.

dicting effect was assessed separately after adjustment for an established risk score including clinical and biological variables.
Results: 112 participants (5.3%) developped type 2 diabetes during follow-up. On bivariate analysis, no differences were found between diabetic and nondiabetic participants for all genetic scores studied. After adjusting for a clinical and biological risk score, no improvements were found regarding the area under the ROC curve (AROC), sensitivity, specificity and predictive values (see table).

Risk Score	Odds ratio (95% CI)	AROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Gain (%)
Kahn et al.	1.10 (1.09-1.11)	89.8	7.1	99.2	33.3	95.0	–
+ Lin et al. (unweighted)	1.07 (0.97-1.17)	89.9	8.9	99.2	38.4	95.1	0.1
+ Lin et al. (weighted)	1.45 (0.66-3.20)	89.9	7.1	99.2	34.7	95.1	0.1
+ Meigs et al.	1.07 (0.98-1.17)	90.1	7.1	99.1	32.1	95.1	0.2
+ Lyssenko et al.	1.01 (0.91-1.12)	89.9	7.1	99.2	33.3	95.1	0.1
+ Shared SNPs by Lin, Meigs, and Lyssenko (9)	1.13 (1.00-1.29)	89.9	8.9	99.3	41.6	95.1	0.1
+ All SNPs used in Lin, Meigs, and Lyssenko (24)	1.03 (0.97-1.10)	90.1	6.2	99.2	30.4	94.9	0.1

PPV, Positive predictive value; NPV, Negative predictive value. Score references: Kahn et al. Ann Intern Med (2009) 150:741; Lin et al, Diabetologia (2009) 52:600; Meigs et al, N Engl J Med (2008) 359:2208; Lyssenko et al, N Engl J Med (2008) 359:2220;.

Conclusions: In this study, adding genetic information to a clinical + biological risk score does not seem to improve prediction of type 2 diabetes. Further studies or follow-up time may be needed to precisely assess the importance of genetic scores in predicting type 2 diabetes risk.

P561 Gap between the recommendations of the European Society of Cardiology and clinical practice for diabetic patients in primary health care

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Purpose: Evaluate the implementation of the recommendations of the European Society of Cardiology (ESC) in patients with diabetes mellitus in the counseling center of the family medicine. department.
Methods: A retrospective study was conducted for diabetic, aged over 18 and taking insulin therapy, that regularly visited the diabetes counseling center in 2009-10. Data on BMI, blood pressure, fasting glucose, HbA1c, smoking status, diabetic foot examination and pharmacologic therapy was analyzed in relation to ESC guidelines for prevention. Lipid status was not included because the data in patient files was incomplete.
Results: 421 diabetic patients (43.9% men, 56.1% women) came for regular follow-ups of HbA1c and counseling. HbA1c levels $\leq$6.5% were achieved in 56 (13.3%) patients, with the mean level of 6.2%. HbA1c levels $>$6.5% were present in 365 (86.7%) patients, with the mean level of 8.6%. Fasting glucose levels $<$ 6 mmol/l were reached in 34 (8.1%) patients, with the mean level of 4.9 mmol/l. Fasting glucose levels $\geq$ 6 mmol/l were found in 387 (91.9%) patients, with the mean level of 9.7 mmol/l. Well-controlled blood pressure levels $<$ 130/80mmHg were present in 173 (41.1%) patients (mean level 122/79), 49 (28.3%) of them taking antihypertensive therapy. 248 (58.9%) patients had blood pressure $\geq$130/80mmHg (mean level 152/91), among them 166 (66.9%) are taking antihypertensive therapy. Out of 215 patients taking antihypertensive therapy 181 (84.2%) are taking ACE inhibitors, 1 (0.5%) angiotensin II receptor blockers, 37 (17.2%) Ca antagonists, 27 (12.6%) beta blockers, 30 (14.0%) diuretics. Aspirin is used by 42 (10.0%) patients and statins by 18 (4.3%). Some of them are taking antiarrhythmic drugs, nitrats and digoxin. 103 (24.5%) patients had normal body mass index (BMI) ranging from 18.5 to 24.9 (mean level 22.8), while 318 (75.5%) patients were overweight with BMI $>$25 (mean level 30.2). There were 201 (47,7%) patients with all elevated parameters (blood pressure $>$130/80mmHg, BMI $\geq$ 25, HbA1c $\geq$6.5% and fasting glucose $>$6). Each of the 421 patients has at least one unregulated parameter. Out of the 421 patients, 46 (10.9%) were smokers, 52 (12,4%) had numbness and 4 (1.0%) amputated foot as the complication of diabetes.
Conclusion: None of the patients has achieved all the target levels recommended in ESC guidelines. It is necessary to educate both doctors and patients about lifestyle, risk factors and therapy in order to minimize cardiovascular risk in diabetic patients.

P562 Prevalence of subjects at high-risk for type 2 diabetes mellitus according to various algorithms in Switzerland (CoLaus study)

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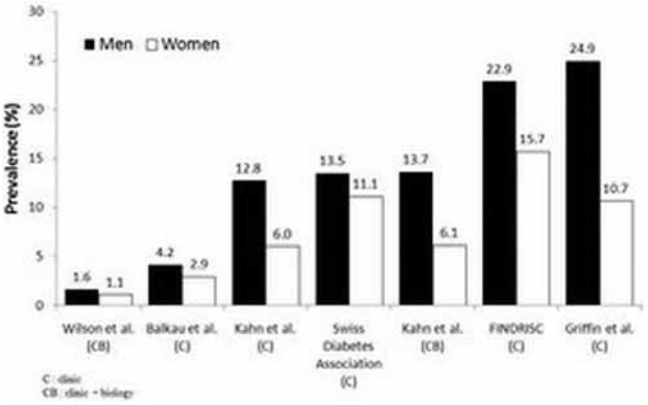
Purpose: To compare the results of several risk scores for developing type 2 diabetes in the Swiss population.
Methods: Single-center, cross-sectional study conducted between 2003 and 2006 in Lausanne, Switzerland. Overall, 3,251 women and 2,937 men aged 35 to 75 years were assessed, of which 5,760 (93%) were free from diabetes and included in the present study. The risk of developing type 2 diabetes was assessed using seven different risk scores including clinical $\pm$ biological data. Participants were considered as eligible for primary prevention according to the thresholds provided for each score. The results were then extrapolated to the Swiss population of the same sex and age.
Results: The risk increased with age in all scores. The prevalence of participants at high risk ranged between 1.6% and 24.9% in men and between 1.1% and 15.7% in women. Extrapolated to the Swiss population of similar age, the overall number of participants at risk, and thus susceptible to intervention, would range between 46,708 and 636,841. Further, scores including the same clinical variables led to significantly different prevalences of participants at risk: 4.2 (95% CI: 3.4-5.0) vs. 12.8 (11.5-14.1)% in men and 2.9 (2.4-3.6) vs. 6.0 (5.2-6.9)% in women.



Prevalences according to each score.

Conclusions: The prevalence of participants at risk of type 2 diabetes varies considerably according to the scoring system used. Further research is needed to assess the validity of these scores before they can be applied in the primary prevention in the Swiss population

P563 Glycaemic control and left ventricular hypertrophy in patients with diabetes mellitus

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Purpose: Type 2 diabetics (T2DM) are particularly susceptible to developing left ventricular hypertrophy (LVH) which carries a poor prognosis. The pathophysiology of LVH in T2DM is likely to be multi-factorial and may be related to insulin resistance and hyperinsulinaemia, formation of advanced glycation end products, increased oxidative stress and associated obesity and hypertension. The importance of glycaemic control in the development of LVH has not been defined. The level of glycosylated haemoglobin (HbA1c) provides a measure of the glycaemic control of patients with T2DM. The aim of this study was to assess the relationship between HBA1c level and LVH.
Methods: The Diabetes Audit and Research in Tayside Scotland (DARTS) database includes prescribing and biochemistry information and all patient healthcare activities of all patients with diabetes within Tayside, Scotland, from 1992 onwards. Using record linkage to the Health Informatics Centre-dispensed prescribing database and to the Tayside echocardiography database (n$>$100,000), T2DM patients with incident LVH from 1998 to 2009 were identified. LVH was defined as an inter-ventricular septal thickness (IVS) $\geq$1.2 cm as per ASE guidelines. The updated mean HbA1c from diagnosis of T2DM until the date of LVH diagnosis was calculated for each patient and the relationship between HbA1c and LVH was assessed.
Results: A total of 5052 T2DM patients had a transthoracic echocardiogram (mean age 72$\pm$12.7 years; 53% male) performed between 1998 and 2009. Of these T2DM patients, 2355 were identified to have LVH. The mean updated HBA1c level was 7.45$\pm$1.33% and mean duration of T2DM was 11.7$\pm$8.8 years. Patients with no LVH (IVS $<$ 1.2), mild LVH (IVS 1.2 – 1.3), moderate LVH (IVS 1.4 - 1.7) and severe LVH (IVS $\geq$ 1.7) had a mean HBA1c of 7.46, 7.42, 7.44 and 7.40 respectively (p=0.451). For the different levels of HBA1c (HBA1c $<$7%, 7 - $<$ 8, 8 - $<$9 and $\geq$9), LVH was identified in 41.5%, 29.26%, 16.53% and 12.71% respectively. There was no association between increasing levels of updated mean HbA1c and the prevalence of LVH (R=- 0.08; p=0.12).
Conclusions: In patients with T2DM, poor glycaemic control, assessed by updated mean HbA1c, was not associated with LVH.

P564 Long-term prediction of all-cause mortality in diabetic autonomic neuropathy: simple function tests or 24-hour heart rate variability (HRV)?

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Purpose: To compare the long term prognostic power of 24-hour HRV with 5 simple function tests in the diabetic population.
Methods: The diabetic part of the municipality of Horsens was delineated by the prescription method and an age and gender stratified sample of 240 diabetic persons were randomly selected. A 24-hour ECG recording (Tracker, Reynolds Medical) and five function tests were conducted: Valsalva ratio, heart rate response to standing up (30:15-ratio), expiration/inspiration ratio (E/I ratio), ortostatic blood pressure (Orto BP) and increase in diastolic blood pressure during sustained handgrip (Handgrip). HRV parameters were obtained in time and frequency domain (Pathfinder 700, RR-Tools Program, Reynolds Medical). After a follow up period of $15\frac{1}{2}$ years vital statistics were obtained from the Danish Civil Registration System. The predictive value of the readings were analysed in Cox proportional hazard analysis correcting for age and gender in all analyses.
Results: 178 pts. participated in the study and 136 pts. with all function tests completed and ECG recordings of acceptable quality were included in analyses (57.9 yrs, 60% male, IDDM 43%).
For HRV parameters in time domain only SDNNindex and triangular index were significant predictors ($p<0.05$) when analysed one by one.
In the frequency domain all parameters were significant predictors when analysed one by one, but in the multivariate analyses including all HRV parameters, in time as well as frequency domain, only the low frequency power (LF) was independently associated with all-cause mortality. All 5 function tests were significant predictors when analysed one by one, but in multivariate analyses only Valsalva ratio, 30:15 ratio and Handgrip were significant.
In the final multivariate analysis including variables with independent predictive powers among both HRV parameters and function tests, LF was found not significant (p=0.44, chi square 0.6) leaving only Valsalva ratio (p=0.002, chi square=9.4), 30:15 ratio (p=0.04, chi square=4.3) and Handgrip (p=0.04, chi square=4.6) in the model.
Conclusion: Simple function tests are more powerful prognostic predictors compared to 24-hour HRV parameters in diabetic autonomic neuropathy.

P565 Positive family history of type 2 diabetes reduces heart rate variability: responses to mental stress test and isometric exercise

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The objective of the present study was to compare the heart rate variability (HRV) at rest and in response to a mental stress test (ST) and to an isometric exercise (IE) between sedentary or physically active offspring of type II diabetic or of normoglicemic parents. Young healthy males subjects were assigned into 4 groups: sedentary (CS, n=12) or physically active (CPA, n=12) offspring of normoglicemic parents and sedentary (ODS, n=12) or physically active (ODPA, n=12) offspring of diabetic parents. The subjects were submitted to a world color stroop test (ST) and to a handgrip exercise session (IE) (3 min/30% maximal voluntary contraction). Hemodynamics and HRV (time and frequency domains, FFT) were evaluated at rest and immediately after the MT and IE. At rest: 1) the physically active groups showed decrease in insulin and increase in HOMA index compared to sedentary groups, despite no differences in blood glucose, systolic (SBP) and diastolic blood pressure (DBP) between studied groups; 2) bradicardia was observed in physically active subjects (CFA:64±3 and ODPA:68±4bpm) as compared to sedentary subjects (CS:71±3 and ODS:75±3bpm); 3) physically active groups presented higher values of R-R variance in relation to sedentary groups; 4) the R-R variance was lower in ODS group when compared to other groups and the sympathetic-vagal balance (LF/HF) was higher in ODS subjects (4±0.78) in relation to CS (1.69±0.14), CPA (1.35±0.10) and ODPA subjects (1.57±0.28). After the ST: 1) the ODS group (83±1mmHg) showed an increase in DBP as compared to the other groups (CS:76±2, CPA:76±2, ODPA:73±2mmHg); 2) the LF/HF were increased in ODS group in relation to CPA and DPA groups, which presented similar responses to ST. Post IE: 1) there was an increase in LF/HF only in CS group, reaching values similar to the observed in ODS group in this condition; 2) similar values of hemodynamics and HRV were obtained between CPA and ODPA groups. In conclusion, sedentary adults with positive family history of type II diabetes that presented normal insulin sensitivity showed reduced HRV and also exacerbated hemodynamic response to sympathetic stimulation tests. Moreover, the results suggest that a physically active life can prevent early dysfunctions that may be associated with increased risk of developing type II diabetes in genetically predisposed populations.
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P566 Is the diastolic dysfunction associated with metabolic syndrome due to subclinical coronary artery disease? A multimodality study

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Purpose: A significant number of patients with obesity and diabetes mellitus have coronary artery disease (CAD), diastolic dysfunction (DD) and also recently found to have increased epicardial fat volume (EFV). However, the contribution of CAD to DD in these patients is unclear.
Methods: All outpatients undergoing cardiac CT with echocardiography within 6 months were eligible. Exclusion criteria were: a) history of CAD (myocardial infarction and/or revascularization), b) moderate (2+) or greater valvular regurgitation or any valvular stenosis and c) systolic dysfunction (LVEF<50%). Subclinical CAD was defined by either total Agatson score ≥400 and/or presence of >mild coronary plaque. Diastolic function was defined as per American Society of Echocardiography guidelines. Epicardial fat volume (EFV) was measured using previously validated CT software by 2 independent cardiologists blinded to the echo data.
Results: Of 93 pts (age 56±12 y, 69% men, body mass index 29±5 kg/m^2, LVEF=58±4%, left atrial volume index=26±9 cm^3/m^2), DD defined by mean e'< 8 cm/s was present in 23%, E/e'>14 in 3% and LAE in 26%. In a univariate analysis, only higher triglyceride levels (153±92 vs 118±61 mg/dL, p=0.05) and EFV (129±55 vs 76±32 cm^3, p<0.0001) were significantly associated with impaired DD. Furthermore, DD was not associated with presence of subclinical CAD, whether patients had higher metabolic risk (BMI ≥ 30 kg/m^2 and diabetes, p=0.6) or not (p=0.7). Multivariate model for predictors of e' in shown in the Table. These findings suggest that changes in myocardial function are not associated by presence of subclinical CAD and visceral adiposity but rather strongly affected by epicardial fat.

Predictors of mean e' velocities

Variables	β	p
BMI ≥30 kg/m^2 and diabetes mellitus	0.32	0.10
CAD	–0.06	0.66
EpiFatVol (cm^3)	–0.77	<0.0001

Conclusions: Presence of significant coronary artery disease is not correlated to impaired diastolic function. Epicardial fat volume appears to be strongly associated with diastolic function.

P567 Left ventricular hypertrophy and glycemic control: a bitter sweet symphony of the heart

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Purpose: Hypertension is associated with increased left ventricular hypertrophy (LVH), which is a predictor of cardiovascular risk. Glycemic control, as assessed by hemoglobin A1c (HbA1c) levels, is an independent predictor of cardiovascular morbidity and mortality in hypertensives. We assessed the hypothesis that LVH is associated with glycemic control in never-treated hypertensives.
Method: We enrolled 1225 consecutive essential hypertensives (mean age 52.9±11.7 years, 728 males, 86 diabetics). HbA1c was measured in venous blood samples. Left ventricular mass index (LVMI) was assessed by echocardiography. M-mode imaging was used for wall-thickness measurements. LVMI was calculated using the Devereux formula. LVH was defined as a LVMI≥125 g/m^2 in men and ≥110 g/m^2 in women. Glomerular filtration rate (GFR) was estimated by the Cockcroft-Gault formula.
Results: In multivariable regression analysis, HbA1c exhibited significant positive association with LVMI, which was independent of age, gender, mean blood pressure, smoking habits, body-mass index, blood glucose, low-density lipoprotein, GFR and C-reactive protein (p=0.007, adjusted R2 of model=0.301). HbA1c levels were significantly higher in patients with LVH compared with patients with normal ventricular mass (5.8 vs. 5.4 mg/dl, respectively, P<0.001). (Figure 1) In

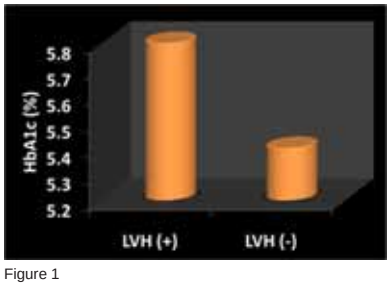

Figure 1

multivariable logistic regression models adjusting for the abovementioned confounders, HbA1c levels were significantly associated with LVH (OR=1.357, 95% CI:1.017-1.812, p=0.038).
Conclusions: Higher HbA1c is an independent predictor of increased LVMI and LVH in essential hypertensives. These findings support the significance of adequate glycemic control in patients with hypertension regardless of the presence of diabetes.

P568 Impact of preoperative glucose levels on perioperative cardiovascular outcomes in patients undergoing intermediate-risk, major noncardiac surgery

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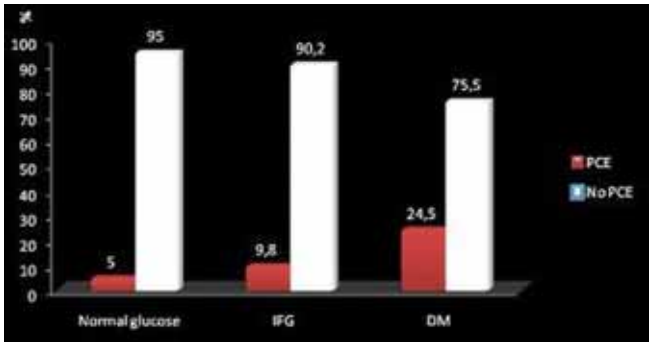
Background: Diabetes mellitus (DM) is a well-established risk factor for perioperative cardiovascular morbidity and mortality in patients undergoing noncardiac surgery. However, the impact of preoperative glucose levels on perioperative cardiovascular outcomes in patients undergoing nonemergent, intermediate-risk major noncardiac surgery (IR-NCS) is unclear.
Methods and results: A total of 680 patients undergoing IR-NCS were prospectively evaluated. Patients older than 18 years who underwent an elective, nonday case, open surgical procedure were enrolled. Electrocardiography and cardiac biomarkers were obtained 1 day before surgery, and on days 1, 3 and 7 after surgery. Preoperative risk factors and laboratory test results were measured and evaluated for their association with the occurrence of in-hospital perioperative cardiovascular events. Impaired fasting glucose (IFG) defined as fasting plasma glucose values of 100 to 125 mg/dl; normal fasting glucose values are below 100 mg/dl, and DM was defined as fasting plasma glucose $\geq$126 mg/dl and/or plasma glucose $\geq$200 mg/dl or the current use of blood glucose–lowering medication. Plasma glucose levels were significantly higher in patients with perioperative cardiovascular events (n=80, 11.8%) in comparison to those without cardiovascular events (131$\pm$42.5 vs 106.5$\pm$37.5, p$<$0.0001). Multivariate analysis revealed that patients with IFG and DM were at 2.1- and 6.4-fold increased risk of perioperative cardiovascular events, respectively. Every 10 mg/dl increase in preoperative plasma glucose levels was related to a 11% increase for adverse perioperative cardiovascular events.



Perioperative cardiovascular events.

Conclusions: Not only DM but also IFG is associated with increased perioperative cardiovascular event rates in patients undergoing IR-NCS

P569 Early adverse effects of abnormal glucose metabolism on albumin excretion in never treated hypertensive patients

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Purpose: Microalbuminuria is an independent predictor of cardiovascular events and mortality in both diabetic and non diabetic patients. Moreover, it is used as a screening tool in the stratification of hypertensive patients. Although diabetes mellitus has been strongly associated with microalbuminuria, the effect of earlier stages of abnormal glucose metabolism on kidney function and albumin excretion in hypertensives, is less clear.
Methods: We studied 1286 consecutive, never treated hypertensive patients (mean age=52 y) who were categorized into 3 groups according to glucose metabolic status: 1. Hypertensives with normal glucose regulation (glucose concentration$<$100 mg/dl, n=822). 2. Hypertensives with impaired fasting glucose (IFG, n=286) and 3. Hypertensives with impaired glucose tolerance (IGT, n=178). Albumin excretion was measured in all patients after 24h urine collection and albumin/creatinin ratio (ACR) was estimated. Kidney function was assessed by estimated glomerular filtration rate (eGFR) using the MDRD formula. High sensitivity CRP (hsCRP) was measured as a marker of inflammation.
Results: Patients with abnormal glucose metabolism (either IFG or IGT) were older, had higher systolic blood pressure (SBP) values and increased levels of hsCRP (p$<$0.001 for all). After adjustment for age, gender, smoking, BMI, SBP and hsCRP, a significant increase in ACR was observed in patients with IFG and IGT compared to euglycemic patients (23.79 vs 26.74 vs 29.70 μg/mg, from group 1 to group 3, p=0.02). After adjustment for the same confounders, eGFR did not differ between the 3 groups (from 82.09 to 80.07 to 79.98 ml/min/1.73m^2, p=NS).
Conclusions: Hypertensives with IFG and IGT have higher albumin excretion compared to those with normal glucose regulation. Given the adverse prognostic effect of microalbuminuria, hypertensives with impaired glucose metabolism may require more careful monitoring and strict control of blood pressure.

P570 Diabetes as coronary artery disease equivalent revisited. Results of the prospective REACH-registry

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Background: Diabetes has been shown to be a major risk factor for the development of atherthrombotc disease. There are conflicting data on the impact of diabetes on the prognosis of patients with and without coronary clinical ouvert coronary artery disease.
Methods: The REACH registry prospectively followed outpatients with known atherthrombotic diseases (coronary artery disease, cerebrovascular disease, peripheral artery disease) or patients without clinically ouvert disease but $>$3 risk factors. For this analysis we divided the patients into 4 groups: patients without diabetes and without history of myocardial infarction, patients with diabetes and without history of MI, patients without diabetes and with history of MI, and patients with diabetes and with history of MI.
Results: A total of 23307 patients were enrolled in Europe and followed over 3 years. The event rate is shown in the table.

	No DM, no MI (n=9363)	DM, no MI (n=5927)	No DM, MI (n=5498)	DM, MI (n=2519)
Death	7,4%	10,6%	8,6%	16,1%
CV Death	4,4%	7,0%	6,0%	11,5%
Non-fatal MI	2,1%	3,0%	4,4%	6,8%
PCI	5,6%	6,2%	10,5%	12,4%
CABG	1,9%	2,3%	4,1%	4,6%
Non-fatal stroke	5,9%	6,4%	4,5%	5,7%

Conclusions: In this large real life registry diabetes at baseline was a predictor of subsequent cardiovascular morbitidy and mortality, equivalent to a history of myocardial infarction. Therefore prevention therapy measures should be as intense as in patients with a history of myocardial infarction.

P571 Effects of pioglitazone versus metformin on endothelial function in patients with type 2 diabetes treated with sulfonylureas

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Purpose: Pioglitazone and metformin are insulin sensitizers used for the treatment of type 2 diabetes mellitus (T2DM), with established value in glycaemic control. Pioglitazone has been associated with improved cardiovascular (CV) prognosis and a beneficial effect on endothelial function in T2DM patients. The effects of metformin on endothelium have been little studied in T2DM patients. The aim of the present study was to compare the effects of pioglitazone and metformin on endothelial function in T2DM patients treated with sulfonylureas.
Methods: Thirty-one T2DM patients treated with sulfonylureas (mean age 63$\pm$9 years, 8$\pm$6 years since diagnosis) were randomly assigned to pioglitazone 30mg od (n=15) or metformin 850mg bid (n=16) for 6 months in order to improve glycaemic control. Insulin resistance was measured by Homeostatic Model Assessment index (HOMA). Endothelial function was assessed using brachial artery flow-mediated dilation (FMD) and hs-CRP was measured as an index of vascular inflammation.
Results: There were no significant differences between groups at baseline. Addition of pioglitazone resulted in a significant decrease in glycated hemoglobin (by 8% compared to baseline, p=0.01), fasting insulin (by 23%, p=0.01), and HOMA index (by 21%, p=0.003), while metformin induced only a significant decrease in glycated hemoglobin (by 9% compared to baseline, p=0.01). Hs-CRP did not change significantly with either treatment. Pioglitazone resulted in an increase in FMD (from 2.18$\pm$1.30% to 3.85$\pm$1.59%, p=0.002) while metformin pro-

duced a non significant improvement of endothelial function (from 2.15±1.06% to 2.87±1.46%, p=0.08). However, repeated measures ANOVA showed that the improvement in FMD was not significantly different with pioglitazone compared to metformin (p=0.11). The improvement in FMD was associated only with a decrease in LDL cholesterol (B -0.027, P=0.03), but not with the improvement in glycaemic control or insulin resistance.
Conclusions: In T2DM patients treated with sulfonylureas, improvement in FMD does not differ greatly when pioglitazone, as compared to metformin, is added to their treatment. Larger studies are needed to investigate whether these two insulin sensitizers may have a differential effect on vascular function and also CV prognosis. Improvement in endothelial function does not seem to depend on improved glycaemic control or insulin resistance, but mainly on lipid control in these T2DM patients.

P572 Rosiglitazone and cardiovascular disease - reassessment of meta-analyses - an uncompelling case of harm

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Objective: 1) To review the published meta-analyses of Rosiglitazone trials designed for glycaemic control regarding cardiovascular risk. 2) To evaluate methods used and explain contradictory findings.
Methods: To review the published meta-analyses on Rosiglitazone using a Medline search and subsequently to evaluate meta-analyses according to Cochrane Collaboration criteria.
Results: The NEJM Nissen meta-analysis assessed 48 Trials meant to be of duration >24 weeks (only 3 trials >52 weeks, none >3 years). The Peto fixed-effects model (less robust when there are major imbalances) was used and showed an apparent increase in AMI rates - OR 1.43 (1.03-1.98) and non-significant increase in CV death - OR 1.64 (0.98-2.74). In contrast, in Diamond's analysis, accounting for fixed and random effects (the Mantel-Haenszel and DerSimonian-Laird Models), there is no increase in AMI rates OR 1.26 (0.93-1.69) nor CV deaths - OR 1.17 (0.77-1.77). Furthermore, if Nissen's criteria for inclusion in meta-analysis were to be followed strictly, 8 trials would need to be excluded from his analysis and a one trial involving heart failure patients included then the total number of AMI events would be identical (n=71) between the Rosiglitazone and Placebo groups.
Conclusions: 1) There is no compelling data that cardiovascular disease increased with Rosiglitazone compared to standard diabetic therapy.
2) Rosiglitazone may cause fluid retention but rarely, if ever, causes heart failure when patients are carefully assessed clinically by cardiologists aided by echocardiography.

CHANGING PRACTICE, CHANGING BEHAVIOUR

P573 Decreasing bedrest following cardiac catherization: implementing an evidence-based protocol

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Purpose: Despite the benefits of reducing the amount of time patients must remain on bed rest, there are no established standards or guidelines for ambulation following cardiac catheterization. A prospective quasi-experimental design (N=595) completed in 2007 demonstrated no significant difference in complication rates between the comparison group who were ambulated 3-4 hours after the procedure and the experimental group who were ambulated at 90 minutes. Based on these findings, a new protocol was implemented. The purpose of this study was to determine the extent to which an evidence-based practice (ambulation 90 minutes post cardiac catheterization) is being implemented and to re-evaluate safety (as measured by incidence of bleeding and hematoma formation) of ambulating patients at 90 minutes post femoral left heart catheterization sheath removal one year following implementation of a new policy.
Methods: All data collected were from the institutions' database. De-identified data from all patients who were eligible for ambulation at 90 minutes were collected. Descriptive stats were used to determine the prevalence of complications and the extent to which eligible patients were ambulated at 90 minutes.
Results: Of the 2676 patients who underwent LHC, 329 patients were eligible to be ambulated at 90 minutes. Of those, 49 patients were actually ambulated at 90 minutes
Conclusions: Despite positive results from the previous study, the new protocol was not well implemented. Only 15% of eligible patients were ambulated at 90 minutes. Incidence of complications was low and minor in nature. The limited uptake could be multifactorial: physician preference for use of vascular closure devices, insufficient in-servicing, insufficient dissemination of previous research findings to physician groups, increased use of closure devices in eligible patients based on workload issues. The findings of this and the previous study conducted at this site, along with existing literature, support the continued use of early ambulation.

P574 Developing a prediction model to identify non-compliance in a nurse-led familial hypercholesterolemia clinic

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Purpose: Familial hypercholesterolemia (FH) is an autosomal dominant disorder, associated with a high risk of premature coronary heart disease (CHD). CHD prevention consists of lifelong statin treatment combined with lifestyle changes. Good adherence to the statins reduces the risk of events substantially. This study was designed to identify predictors of non-compliance. We aimed to develop a prediction model to identify non-compliant FH patients.
Methods: A single centre survey including all consecutive heterozygous FH patients above age 18 years, who were treated by a nurse specialist in the outpatient clinic of a university hospital in the Netherlands between 2008 and 2009. In addition to clinical data, patients completed a questionnaire concerning medication compliance. Patients, who were pregnant or started a statin within the prior 12 months were excluded.
Results: We included 321 patients (169 women, mean age of 46, BMI 26 and secondary CHD prevention in 13%). The mean highest total cholesterol ever was 10±2.3 mmol/l. On average patients were 10 years on statin prescription (range 1-29 yrs). Fifty-four percent of patients reported ever having side effects. Only 19% of all patients achieved an LDL-cholesterol below 2.5 mmol/l.
The majority of patients (n=286,89%) reported that they rarely forget to take their medication (>90% adherence), whereas 11% regularly forgot to take the statin (< 90% adherence). Younger age (OR = 0.13, 95% CI 0.03–0.46), high total cholesterol level during prescription (OR = 1.46, 95% CI 1.17–1.81) and a relatively low untreated cholesterol level (OR= 0.26 95% CI 0.09–0.74) were associated with non compliance. A ROC curve of including these parameters had an AUC of 0.80 (95% CI 0.74 to 0.87).
Conclusion: In our nurse led FH population, we found a high adherence to statins, despite frequent side effects. We developed a prediction model to identify the non compliant FH patients. This information could be used by medical doctors and nurses to emphasize the need for statin treatment to further maximise statin compliance in this extremely high risk group and should be tested prospectively in future research.

P575 What keeps us from sexual counselling of cardiac patients?

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Purpose: Sexual dysfunction is a common problem in cardiac patients. Although healthcare providers acknowledge the importance of this subject, they seldom discuss sexual concerns with their patients. We therefore aimed to study which factors restrain healthcare providers from discussing sexual concerns with patients.
Methods: Data were collected from all cardiac rehabilitation centers (n=127) and heart failure clinics (n=120) in the Netherlands. The "nurses" survey of sexual counselling of MI patients, was used as basis for the questionnaire. Additional questions were added concerning barriers on withholding healthcare providers from sexual counselling. The scores of healthcare providers who report discussing sexual concerns were compared to those who do not.
Results: In total 460 respondents completed the questionnaire (75% female, age 44±9 years), and working as a nurse (45%) or physical therapist (23%).
Most reported reasons for not discussing sexual concerns were: not knowing how to initiate the subject (46%), the patient does not initiate the concerns (43%) and lack of training (42%). Barriers withholding healthcare providers from discussing sexual concerns were: lack of an organizational policy on sexual counselling ($p<0.001$), lack of knowledge ($p<0.001$), not knowing how to initiate the subject ($p<0.001$).
Conclusion: Barriers of healthcare providers in sexual counselling of cardiac patients are related to their (lack of) knowledge and to patient- and organization related factors. To improve patient care, interventions should be focused on improving knowledge of health care providers and on describing the policy in organizations according to sexual counselling.

P576 A retrospective audit of screening practices used to detect abnormal glucose regulation in a cohort of AMI patients admitted to a coronary care unit - an Australian study

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Purpose: Diabetes causes abnormal glucose regulation and chronically elevated

blood glucose levels termed hyperglycaemia. Diabetes is a major risk factor for cardiovascular disease, in particular, coronary heart disease. Compared to those with normal glucose regulation, the incidence of coronary heart disease is two to three times greater among individuals with diabetes. For these reasons screening patients with acute myocardial infarction (AMI), for diabetes, is warranted. Effective screening in the coronary care unit allows for early detection and treatment of diabetes. Early treatment can reduce the risk of developing diabetic microvascular complications, being retinopathy and nephropathy.
Methods: A retrospective clinical audit was carried out to determine the current screening practices utilised in a coronary care unit in a tertiary Melbourne Hospital to detect potential abnormal glucose regulation. Eighty-seven medical records of AMI patients with no history of diabetes admitted over a two month period, were audited. The screening practices were compared against those recommended by the National Health and Medical Research Council and Diabetes Australia for the detection of abnormal glucose regulation.
Results: The number of patients who appropriately received initial screening tests (fasting plasma glucose or random plasma glucose test) and completed repeat screening tests (fasting plasma glucose or oral glucose tolerance test) was 78% (n=68) and 5.4% (n=3), respectively. Eighty-one percent (n=55) of patients who received initial testing had potential abnormal glucose regulation based on an initial fasting or random plasma glucose $\geq$5.5 mmol/L and, of these, only 11% (n=6) had their glucose abnormalities communicated to the general practitioner.
Conclusions: The study findings will be used to inform practice at a local level, and provide future direction for improving the quality of screening practices within the coronary care unit. The results will also be used to formulate clinical practice guidelines, for case detection of abnormal glucose regulation amongst patients with AMI.

P577 Relationship between educational level and self-care behaviour in heart failure patients

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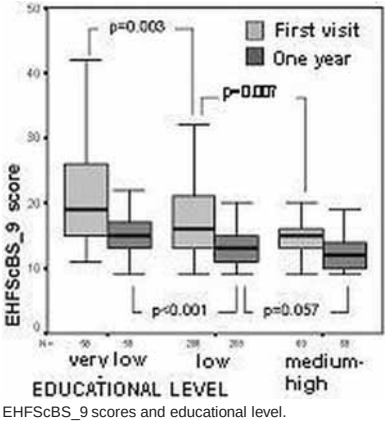
Background: Self-care is important for heart failure (HF) management and might be influenced by patient's educational level.
Aims: To assess the relationship of patients' educational level with their baseline self-care behaviour and its changes after one year of nurse intervention, using the 9-item version of the European Heart Failure Self-care Behaviour Scale (EHFScBS_9), in a cohort of HF outpatients attended in a multidisciplinary HF Unit.
Patients: 335 HF patients were studied (245 men and 90 women). Median age was 69 years [IQR 57-75]. Median duration of HF was 6 months [IQR 1-36]. Aetiology of HF was mainly ischemic heart disease (53.4%). Median LVEF was 30% (IQR 24-37%). Most of patients were in NYHA in class II (66.3%) and III (25.7%). Educational level was: very low 17.3%; low 62.1%; medium or high: 20.6%.
Results: Median scores obtained by our patients differed both in the initial (19 [IQR 15-26] vs 16 [IQR 13-21] vs 15 [IQR 12.5-15.5] and in the one-year evaluation (15 [IQR 13-17] vs 13 [IQR 11-15] vs 12 [IQR 10-14] for educational levels very low, low and medium-high respectively (figure). Differences were highly statistically significant between educational levels (p=0.007 to p<0.001) except between low and medium-high education at one-year (p=0.057). In the one-year evaluation patients showed a significant improvement in self-care behaviour in all three educational groups (p<0.001). The magnitude of improvement was similar in the 3 groups, without statistical significant differences.



EHFScBS_9 scores and educational level.

Conclusions: Self-care behaviour at baseline and after one year of nurse intervention was better in patients with higher educational level. However, the improvement obtained with the nurse intervention was similar irrespective the educational level.

P578 Long-term effects of a tailored education on lifestyle modification among patients with first-time acute coronary syndrome in Korea

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Background: Tailored educational strategies are needed for the first-time patients with acute coronary syndrome (ACS) to enhance their self-efficacy promoting long-term adherence to lifestyle modification.
Objectives: To develop a tailored educational program for ACS patients and their family, and to evaluate its long-term effectiveness on patients' self-efficacy for lifestyle modification and compliance with self-care activity.
Methods: The 1 h-length educational multimedia content was developed including voice-recorded texts, images, sounds, Flash animation, and video. The multimedia comprised of five learning subjects including understanding of coronary artery disease, management of hypertension and diabetes, healthy diet, stress and smoking, and exercise. A quasi-experimental pre- and post-test design was used. A total of 88 hospitalized patients (Exp. 46 and Cont. 42) underwent percutaneous coronary intervention were recruited at a national university hospital, Korea. Data were collected from September 2009 to February 2011. Experimental group participated in risk factor-tailored small group education using the multimedia content and telephone counseling (3 times, 30 min), and risk factor-tailored periodical cellular-phone massages (6 times, every 2 weeks). Control group received usual cares and counseling based on their needs while the survey conducted. The structured questionnaire was used to measure the levels of self-efficacy and self-care activity.
Results: Self-efficacy for lifestyle modification was significantly higher in the experimental group after 1 year compared to the control group (p<0.05). Until 6 months follow-up, there was no significant difference in the level of self-care activity between the two groups. However, the self-care activity in the experimental group was significantly increased and higher than the one of control group, especially in the areas of smoking cessation, exercise, and healthy diet practice (p<0.05).
Conclusions: These findings suggested that risk factor-tailored education and continuous counseling was effective in having a long-term adherence to lifestyle changes through increasing their self-efficacy among first-time ACS patients.

P579 Long term forearm and leg complications after coronary revascularization: superior patient satisfaction with radial artery harvest

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Introduction: The radial artery (RA) has gained increasing popularity as a conduit for coronary surgery due to its promising performance as a graft. Despite this, there is a paucity of data evaluating long term quality of life after its removal. We sought to further characterise this.
Methods: Patients from a radial artery trial completed a validated questionnaire a mean of 9.3 years after primary coronary surgery (range 4-14 years). This included 7 statements concerning hand and forearm function and symptoms and 4 questions regarding scar appearance and discomfort in the arm and leg. Response rate was 83% of 491 patients (n=408) with 231 having received a RA graft (RA group). Responses were graded in order of severity from 0 to 7, with >3 (mild concern) being regarded as clinically significant. Mean responses were compared with pre-operative responses to the same questionnaire and with post operative responses from the non-RA group whose forearm was not operated on (n=177). In patients who had both RA and saphenous vein removal (n=168), we compared the impact of forearm scar on quality of life against that of a leg scar at 3 months post-operatively and after long term follow up.
Results: In the RA group, mean scores were less than 2 (where 2=trivial concerns) for all questions, and 92% to 99% reported no significant symptoms. The most frequent concerns related to pain and numbness (8% each). Compared with the non-RA group, neither average scores nor the prevalence of significant forearm symptoms were different. Symptom severity was significantly lower in 6 out of 7 questions for pre-operative responses, indicating a general deterioration in forearm function over long term follow up irrespective of surgical incisions. In those who sustained both arm and leg scars, concerns for scar discomfort in the arm were significantly less than that of the leg at 3 months after surgery (p<0.001) and in the present questionnaire (p=0.002), indicating greater satisfaction with RA removal which is sustained in the long term. There was equivalent satisfaction with scar appearance at both time points.
Conclusion: Radial artery harvesting is associated with high long term patient satisfaction and less scar discomfort than saphenous vein removal. Overall, functionality declines with time and a small proportion of patients appear to experience residual forearm pain and numbness. This, however, is not different to those without radial artery harvesting and may therefore be unrelated to surgery.

P580 One-year cost-effectiveness of cytochrome p450 2c19 genotype-guided antiplatelet therapy in patients with acute coronary syndromes in France

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Objectives: Cytochrome P450 2C19 (CYP2C19) genotype has been shown to affect cardiovascular (CV) outcomes for clopidogrel but not prasugrel. This study evaluates the cost-effectiveness of CYP2C19-guided vs. routine antiplatelet therapy in ACS patients in France.
Methods: We constructed a literature-based, decision analytic, Markov model to estimate the annual cost-effectiveness of CYP2C19-guided aspirin plus either clopidogrel or prasugrel therapy vs. no genotyping using the French National Health Insurance perspective. Post-initial ACS CV events were based on the TRITON-TIMI 38 study and genetic substudy. Cost data sources were: Technical Agency for Hospitalization Information reference cost for 2008-10 - nonfatal MI and stroke, CV death, intracranial hemorrhage, other life-threatening bleed, and minor bleed; French National Health Insurance - drugs; Biologie Hors Nomenclature - CYP2C19 genotyping; and US-based reference pricing converted to € using appropriate exchange rates - monthly CV disease maintenance cost. Disease-state utilities were obtained from published sources. The model allowed for clopidogrel/prasugrel discontinuation and aspirin monotherapy. Model sensitivity was assessed using 1-way analysis of parameters varied by quartile or at least ±25%.
Results: The base case model demonstrated that CYP2C19 genotype guided antiplatelet therapy yielded lower overall annual cost and greater efficacy vs. no genotyping (Table 1). The model was most sensitive to monthly clopidogrel costs, monthly CV care cost, prasugrel costs, NFMI cost, proportion of patients that are extensive metabolizers, cost of genetic tests, as well as life-threatening bleeding cost.

Table 1. Results

Strategy[1]	Annual Cost	Incremental Cost	QALY	Incremental QALY	Cost/QALY	Incremental Cost Effectiveness (ICER)
CYP2C19 Genotype-Guided	€ 985.0		0.7299		€ 1,349	
No Genotyping	€ 1,007.5	€ 22.5	0.6767	–0.0533	€ 1,489	(Dominated)

QALY: Quality Adjusted Life Year. [1]Base case values: Drug wholesale acquisition cost/day: clopidogrel = € 1.32, prasugrel = € 1.87; Baseline post-ACS utility = 0.83; Monthly cost for post-CV event management = € 265.08; CYP2C19 genotyping = € 64.80; After genotyping: 80% of extensive metabolizers, 20% of intermediate metabolizers and 10% of poor metabolizers on clopidogrel; 80% on clopidogrel without genotyping; Willingness to pay = € 20,000.

Conclusions: CYP2C19 genotype-guided clopidogrel or prasugrel therapy is cost-effective for up to 1 year in ACS patients in France.

P581 Nitinol Flexigrip sternal closure system and chest wound infections: insight from a prospective comparative analysis of complications and costs

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Background: Complications associated with traditional use of parasternal stainless steel wires are reported at an average of 2-6% of cases. We sought to assess the efficiency of 2 different sternal closure techniques in preventing sternal wound infection or instability. A cost analysis has also been taken into consideration.
Materials and methods: Between January 2008 and April 2010, 1644 consecutive cardiac surgery patients operated on were prospectively collected in our database. A total of 1072 patients received a standard parasternal wiring technique (Group A) and 572 patients received a new method of sternal closure based on the use of thermoreactive Nitilium clips (Flexigrip®) (Group B). After sternal closure the technique for wound suturing was the same for both groups. Propensity matching for available patient intrinsic and operative risk factors was ultimately used to investigate whether the use of standard or Flexigrip closure would impact upon sternal wound outcome. Results were analyzed according to the intention to treat principle.
Results: By propensity score analysis 56,4% of the patients (928/1644 pts) were perfectly matched for eleven available risk factors, with an equal distribution of risk covariates. Totally 464 patients for each group were matched. Overall incidence of sternal wound complication was significantly higher in Group A (4.1%) versus Group B (1.7%) ($p<0.032$). Additionally, mechanical sternal instability, either in presence or absence of infection, were significantly higher in Group A (1.9% versus 0.2%) ($p<0.011$). In case of wound infection, the incidence of sternal instability was significantly lower in Group B than in Group A ($p<0.02$). Flexigrip closure technique offered a 25.7% cost savings in comparison with standard steel wiring technique. Overall costs for Group A and B were 318,300.00 € and 236,600.00 €, respectively.
Conclusions: The Flexigrip nitinol clip sternal closure achieved a greater sternal stability, resulting in a lower incidence of sternal dehiscence and related complications. The use of Flexigrip favored a higher sternal stability in case of wound infection, preventing mediastinitis. Additionally, Flexigrip closure costs were lower compared to standard sternal wiring technique, proving to be a cost-effective approach in cardiac surgery.

P582 Cardiac surgery and sternal wound complications: iodine impregnated drape (Ioban® 2) versus standard drape. Insight from a prospective comparative analysis of complications and costs

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Background: Most postoperative wound infections result from the resident skin flora. The prevention of bacterial contamination in the region of coutaneus incision is an important key-point. The use of iodine-impregnated incision drape in addiction to the standard skin antiseptics should minimize the potential migration of bacteria. The aim of the study was to evaluate the role of the Ioban® 2 in reducing the incidence of wound infection and related costs.
Materials and methods: Between January 2008 and April 2010, 1418 consecutive cardiac surgery patients operated on were selected from our prospectively collected database. A total of 1072 patients received a standard steri-drape (Group A) and 346 patients received Ioban® 2 drape (Group B). Propensity matching for available patient intrinsic and operative risk factors was ultimately used to investigate whether standard or iodine steri-drape impact upon sternal wound outcome. Results were analyzed according to the intention to treat principle.
Results: By propensity score analysis 39,2% of the patients (556/1418 pts) were perfectly matched for eleven available risk factors, with an equal distribution of risk covariates. Totally 278 patients for each group were matched. Overall incidence of sternal wound complications was 4.31% (12 pts) in group A versus 2.16% (6 pts) in group B ($p=0.15$). Superficial wound complications occurred similarly in both groups (8 pts Group A vs 6 pts Group B). Deep sternal wound complications resulted higher in Group A (1.8%) in comparison with Group B (0%), although the difference was not significant ($p=0.06$). The need for VAC therapy incidence was 2.52% in Group A compared to an incidence 1.08% in Group B ($p=0.12$). The Ioban® 2 offered a 36.4% cost savings in comparison with standard steri-drape. Overall costs for Group A and B were 224,720.00 € and 142,860.00 €, respectively.
Conclusions: Ioban 2 drape allowed a reduction of overall incidence of sternal wound complications after cardiac surgery. Additionally, being the deep sternal wound complications almost significantly reduced, the use of Ioban 2 provided superior results protecting against life-treathening settings such as mediastinitis. Additionally, Ioban® 2 drape costs were lower compared to standard steri-drape, proving to be a cost-effective approach in cardiac surgery.

P583 Usefulness of urinary biomarker NGAL in the management of postoperative renal replacement therapy (RRT, hemofiltration)

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Background: Acute kidney injury (AKI) potentially requiring initiation of hemofiltration (HF) is seen in approx. 6-10% of patients after cardiac surgery and is associated with high costs, mobidity and mortality. There are currently no guidelines for initial management of HF therapy. Neutrophil Gelatinase Associated Lipocalin (NGAL) is a novel urinary biomarker suggested to be released by renal tubules very early in response to ischemic damage. A new algorithm including NGAL was used to improve management criteria for early HF treatment.
Methods: Urinary NGAL was tested routinely in all consecutive patients undergoing cardiac surgery at our institution in 2010 before and 4, 24 and 48 hours postoperatively. In contrast to previous years, HF therapy was only initiated when NGAL at 4 hours was markedly increased versus baseline and/or urine production decreased within 4 days (<0.5mL/kg/h>4h) independent of plasma creatinine and urea. The number of HF tehrapies (2010) was compared with previous years.
Results: HF therapy in 2006-2009 was initiated at day 3 (mean) after surgery in 7.5% to 9.0% of patients with an average length of therapy of 7.7 days. Using the new algorithm, the number of HF therapies was reduced to 4.9% without morbidity to patients the previously would have been considered for HF. The cumulative Euroscore and patients characteristics were nearly identical for all years. Preliminary data suggests no difference in extrarenal complications and permanent dialysis requirement.
Conclusions: Urinary NGAL can be used safely as an early predictor for HF requirement in patients after cardiac surgery. Inclusion of NGAL can help in RRT management and may substantially reduce costs by decreasing the number of truely required HF treatments, length of therapy and length of stay.

P584 Predictors for adequate knowledge of symptom clusters of heart attack in the general population of Extremadura, Spain

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Purpose: To prevent the consequences in Myocardial Infarction (MI), in order to provide timely and effective treatment the time from onset symptoms to hospital arrival is paramount. Several factors contribute to delay in seeking treatment for MI; however, lack of knowledge of MI symptoms is known to be one of the main reasons of this delay.
Aim: To assess the knowledge of cardiovascular risk factors, warning symptoms of MI and attitude towards them in a representative statewide sample of Extremadura, a region of Spain.
Methods: The study was conducted between June 2009 and October 2009. A representative sample of the region population was selected by double randomization, based on census units and conglomerates. Face-to-face interviews were carried out by previously trained medical students using a structured questionnaire with open and closed questions. Adequate knowledge was defined as: to know what is a MI, to appoint correctly at least one symptom or one risk factor of MI, to mention a risk lifestyle for MI and have a hypothetical ideal attitude to the symptoms. Univariate and multivariate logistic regression analysis was used to identify predictors of adequate knowledge of MI.
Results: 2411 subjects were interviewed during the study period (59.9% women; mean age, 49.0±18,7. Only half of the population (53,8% (95%CI 51,8-55,8)) had adequate knowledge of MI. Ninety-two percent reported at least one warning symptoms of MI, but three only seventeen. The most frequently mentioned warning symptoms were chest pain (1804 (74,8%) answers), arm pain (1244 (51,6%)) and breathing problems (673 (27,9%). Seventy-nine percent named at least one risk factor for MI and 18% reported three. The most frequently mentioned risk factor was hypertension (49.3%). Smoking was the most frequent harmful lifestyle mentioned (63.3%). Age, high educational and economic level, and previous family experience with the disease were independent predictors for adequate knowledge of MI. The respondents with vascular risk factors did not have better knowledge.
Conclusions: The knowledge of MI, symptoms and risk factors is inadequate in a significant proportion of our population, especially those with low socioeconomic level and those with vascular risk factors. These findings have implications for public health initiatives in the management of MI.

P585 Point of care prehospital cardiac markers to indicate the likelihood of ambiguous acute chest pain signaling an ongoing coronary event or the probability of another etiology

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Background and objectives: The presentation of a life-threatening acute coronary syndrome is often not straight-forward. Electrocardiographic (ECG) features can also be equivocal. The objectives of this retrospective study were to assess the impact of cardiac markers (troponin I/CK-MB/myoglobin) measured with a stat kit in the prehospital setting on decisions taken in the management of patients with ambiguous recent-onset chest pain and inconclusive ECGs.
Methods: The analyzed data were retrieved from the database of a telemedical call center ("SHL-Telemedicine"). Those relevant to subscribers who called to complain of ≥6 hours of non-specific chest pain and who had an inconclusive ECG were analyzed. All subjects had been examined in the prehospital setting by a physician of the system who also checked their cardiac markers. A kit result was positive if any of the 3 markers read at the point of care was positive, and those patients were taken immediately to the hospital. Subjects with a negative result were left at home for additional strict telemedical follow-up for up to 72 hours.
Results: A total of 821 subscribers (age range 39-98 years, 57% males) fulfilled entry criteria during the 10-year (1/1/2001-31/12/2010) study period, of whom 180 had a positive result and 176 were immediately transported to hospital (4 refused to be taken to the hospital). Of these, 51% (90/176) were discharged from hospital with the diagnosis of acute myocardial infarction (AMI). Of the remaining 641 patients (those with a negative result), 20% (126/641) were reexamined within the 3-day follow-up because of continuing complaints, and another 15 AMIs were diagnosed. Overall, on the index day the positive and negative predictive values of the markers' results were 54% and 98%, respectively.
Conclusions: This report demonstrates the utility and high negative predictive value of assessing cardiac markers at the point of care for the diagnosis of patients with ambiguous acute chest pain by avoiding unnecessary hospitalizations and decreasing misdiagnosis in these patients.

P586 The HASBLED score predicts bleeding complications during bridging of chronic oral anticoagulation: results from the national multicenter BNK Online bRiDging REgistRy (BORDER)

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Background: Patients who receive long-term oral anticoagulant (OAC) therapy often require interruption of OAC for an elective surgical or an invasive procedure. Current guidelines allow bridging therapy with either unfractionated heparin (UFH) or low molecular weight heparins (LMWH). There is still debate on the optimum perioperative management of such patients in an ambulatory setting. The aims of this prospective, observational, multicenter registry were to identify risk factors predicting adverse events in such patients.
Methods and results: Between the years 2009 to 2011 invasive procedures were performed in 1000 patients with OAC (age, 72.3±9.2 years; 64.8% male). 61 (6.1%) of those patients did not receive bridging therapy during interruption of OAC, 937 (93.7%) patients were treated with LMWHs, 2 patients (0.2%) received UFH. In 22 patients (2.2%) LMWHs were given according to low dose requirements for thrombosis-prophylaxis, 729 patients (72.9%) were treated with halved therapeutic LMWH doses and only 188 (18.8%) received weight adapted therapeutic LMWH doses. 4 thromboembolic complications were observed during 30 days of follow up (2 retinal embolisms, 1 stroke, 1 myocardial infarction; 0.4%). 1 major bleeding (0.1%) and 35 clinical relevant bleedings (3.5%) occurred. Re-hospitalisation after bleedings was mandatory in 24 patients. Bleedings occurred independent of LMWH dosage (3.6%, 4.8%; p=0.4), type of intervention (p=0.9); or single clinical variables. However, patients with a HASBLED score ≥ 3 had significantly more clinical relevant bleedings than those patients with a HASBLED score <3, (1% versus 11%, p<0.0001). After multivariate regression analysis independent predictors for hemorrhagic complications during bridging OAC were an increasing HASBLED score (p=0.002) and a history of bleeding (p=0.04).
Conclusion: Clinical relevant bleedings in patients who undergo bridging for oral anticoagulation is frequent with approximately 4%. A HASBLED score ≥ 3 was highly predictive of bleeding events in this patient cohort.

P587 Unreadability of current informed consent forms in cardiology - and how to improve them

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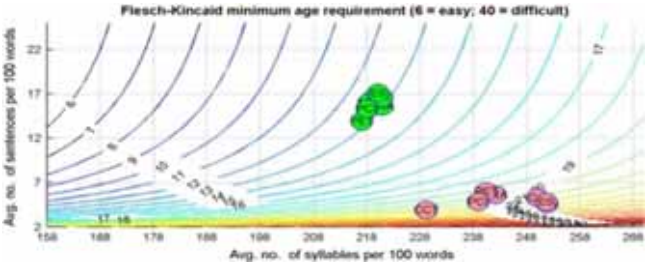
Background: Guidelines on informed consent for clinical practice and research trials recommend the use of standard plain language to enhance patient comprehension and to facilitate shared decision-making. Aim: To assess readability of our current informed consent forms used in cardiology.
Methods: We evaluated the informed consent forms, currently used in an Italian tertiary care and research center and previously set according to the recommendations of scientific societies, of 7 common examinations: coronary angiography (CA), percutaneous coronary intervention (PCI), myocardial perfusion imaging (MPI), cardiac positron emission tomography (PET), cardiac computed tomography (CCT), cardiac radiofrequency ablation (CRA) and stress echocardiography (SE). For each test, we also developed a revised informed consent form written by language experts assisted by cardiology specialists following federal plain language guidelines (Plainlanguage.gov, revised December 2010). We analyzed each text (standard and revised) with Flesch-Kincaid (F-K) grade level (high numbers indicating harder-to-read text) and the Italian language-tailored Gulpease level (from 0, easy, to 100, difficult).
Results: Readability was poor for the standard consent forms (red points in figure) and visibly improved with the revised form (green points) with higher readability evidenced by changes in both F-K grade level (standard: 21±1% vs revised: 12±0.4%, p<0.001) and Gulpease (standard=45±2 vs revised=84±2, p<0.0001).



Conclusion: Current informed consent forms are unreadable for the average patient. Substantially higher readability scores can be achieved with novel forms

which explicitly discuss risks and are prepared following standard recommendations of plain writing.

P588 Out-of-hours computerised activation of primary angioplasties improves door-to-balloon times

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Purpose: A new protocol for out-of-hours (OOH) primary percutaneous coronary interventions (PPCI) was implemented in our institution since mid 2009. Activation of cardiac interventional team by individual telephone calls was changed to computerised simultaneous alert to mobile telephones of the cardiology intervention team. We assessed the impact of this new protocol on door-to-balloon (DTB) times.
Methods: DTB times for consecutive patients receiving PPCI for 6 months (January 2009 to July 2009; group 1; n=124) and subsequent 6 months (July 2009 to January 2010; group 2; n=119) were examined. There were 78 (63%) patients in Group 1 and 87 (73%) patients in Group 2 having PPCI OOH (defined as weekdays 5pm to 9am, weekends and public holidays).
Results: With the new protocol, proportion of OOH PPCI achieving target DTB time $\leq$90 minutes increased from 51% (40/78) in Group 1 to 67% (60/89) in Group 2 (p=0.040). Median DTB time for OOH PPCI decreased from 88 (IQR 63-110) minutes in Group 1 to 71 (IQR 60-111) minutes in Group 2 (p=0.04, Kruskal-Wallis test).
Conclusions: Following computerised activation of PPCI, OOH DTB times are shortened. The improved median DTB time and proportion achieving target DTB time are now similar to those for routine-hours PPCI.

P589 Influence of the time on the prevalence of drug-related resuscitated sudden death during these past 20 years

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Most of sudden cardiac arrests are related to a ventricular fibrillation (VF) and ischemic heart disease. However, some sudden deaths (SD) occur in patients without apparent heart disease (HD) and some of them are drug-related. Many recommendations were published during these last years. The purpose of study was to evaluate the prevalence of drug-related SD's and the possible changes during these past 20 years.
Methods: 236 patients, 179 men, 57 women, aged from 12 to 88 years (mean 60$\pm$15) were consecutively admitted after resuscitation of a sudden cardiac death outside the acute phase of a myocardial infarction; 139 were admitted before 2000 and 97 between 2000 and 2010. Clinical data, treatment, electrolytes, echocardiography, ECG Holter monitoring, exercise testing, signal-averaged ECG, electrophysiological study (EPS) and evaluation of coronary status associated with ergonovine test when coronary arteries were normal, were collected.
Results: The analysis of the causes of resuscitated SD's did not change significantly during these 2 periods of studies. There is a trend for more unexplained SD's occurring in patients without apparent HD (34/97 vs 34/139; p$<$0.087 NS), for less history of ischemic HD (33/97 vs 58/130, p$<$0.2). All other classical substrates favouring SD did not change: idiopathic dilated cardiomyopathy 10/97 (10%) vs 16/139 (11.5%), valvular HD 6/97 6%) vs 17/139 (12%), various HD 2/97 (2%) vs 5/139 3.5%), coronary spasm 4/97 (4%) vs 3/139 (2%), preexcitation syndrome or ion channel disorders 5/97 (5%) vs 7/139 (5%). Drug-related SD's did not change during these periods: 37 patients presented a drug-related VF or asystole. 20 patients (14%) seen before 2000 had a drug-related SD and 17 patients (17.5%) seen since 2000 had drug-related SD. The fatal event was generally caused by hypokaliema or a direct effect on QT interval and was facilitated by the presence of an HD or an abnormal ECG in 19 of them. Digoxin, diuretics, calcium inhibitors, antiarrhythmic drugs were the main drugs implicated in SD's.
Conclusion: Surprisingly, although several recommendations were published, the main causes of resuscitated SD's have not changed during the periods 1990/2000 and 2000/2010. Furthermore, the prevalence of drug-related resuscitated SD's remains unchanged. Drug-related arrhythmias continue to explain or favour at least 15% of SD's.

P590 Linking the cardiologist to the primary care doctor through eConsultation

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Cardiovascular disease (CVD) is a major source of disease burden worldwide and primary care has a crucial role in its prevention and management. By improving the communication between primary care physicians and specialists, an enhancement in patient's quality of care is expected. The Champlain BASE Project: Building Access to Specialists through eConsultation is a web-based service that was developed to allow primary care practitioners to submit a patient specific clinical question to a specialist, such as a cardiologist, by using a standardized electronic form through a secure system in which confidentiality and privacy of patient information is ensured.
When a consultation request is made by one of the participating primary care physicians, it will be assigned to an appropriate specialist (based on availability and specialty) who will have one week to respond. Supplementary patient information such as laboratory results, digital images and health history can also be included to assist the specialist in making an informed recommendation. Based on the received information, the specialist may 1) provide the primary care physician with answers to questions (so that the primary care physician can make further actions without sending the patient for a formal referral to the specialist), 2) ask for additional information before being able to provide his/her recommendations, or 3) recommend a formal referral (if required, additional diagnostic tests can be requested and courses of treatment can be started by the primary care physician before patient's appointment with the specialist).
The pilot phase of the project was launched in January 2010 and currently involves 40 primary care physicians and 28 specialists (3 cardiologists and 1 internist) from across the Champlain region in Ontario, Canada. By February 2011, a total of 68 consultation requests were made and 9 of them were assigned to a cardiologist. Only in 1 out of 9 cases the referral was recommended by the cardiologist and 8 other potential referrals were avoided. The content of the questions ranged from questions about potential diagnosis to possible treatments, concerning high-risk to low-risk patients in different age-groups. Ongoing analysis of pilot phase data will help improve the system and address the issues raised by participants. Hopefully, the implementation of the project can improve access to clinics, reduce the number of visits for patients and waiting times, and lead to individualized specialist advice in the region. Subsequently, the experience can be adapted to be used in other health regions across Canada and internationally.

NON CORONARY CARDIOVASCULAR INTERVENTIONS

P591 Predictors and clinical consequences of acute renal injury following transfemoral and transapical transcatheter aortic valve implantation

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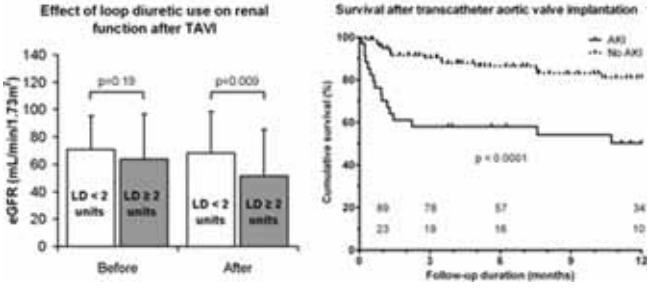
Background: During transcatheter aortic valve implantation (TAVI), periods of hypotension, contrast injection and calcium or plaque embolization may result in acute kidney injury (AKI). In cardiac surgery, AKI is known to be strongly associated with post-operative short- and long-term mortality. Therefore, our purpose was to investigate the incidence, predictors and prognostic importance of AKI in TAVI.
Methods: In a prospective observational single-centre study we included 132 patients (age 80$\pm$8 years, 58 male), who had undergone a TAVI either through transfemoral approach with the Medtronic-CoreValve® bioprosthesis (n=96) or through transapical route with the Edwards SAPIEN bioprosthesis (n=36). Pre- and post-procedural clinical data were collected from the medical history, laboratory analysis and echocardiography. Acute kidney injury was defined as a decrease in estimated glomerular filtration rate (eGFR) of 25% or more within 5 days after the procedure compared with baseline.
Results: Following TAVI the incidence of AKI was 26%. Independent predictive factors for AKI were loop diuretic use $\geq$ 2 units (OR: 8.63; 95% CI: 3.07-24.30), postprocedural aortic regurgitation grade $\geq$ 3 (OR: 9.58; 95% CI: 1.92-47.76) and age (OR: 1.07; 95% CI: 1.00-1.13). In-hospital mortality following TAVI was 14%, which was independently predicted by STS risk score (OR: 1.62; 95% CI: 1.25-2.08) and AKI (OR: 5.22; 95% CI: 1.49-18.28).



Conclusion: The incidence of acute kidney injury following transcatheter aortic valve implantation is 26%. More preprocedural loop diuretic use, a higher post-procedural aortic regurgitation grade and higher age are the main predictors for AKI. Together with STS risk score, acute kidney injury was identified as an independent predictor for in-hospital mortality following TAVI.

P592 Transarterial Medtronic corevalve system implantation for degenerated aortic valve bioprostheses

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Purpose: To assess the early and mid-term results of transcatheter aortic valve implantation (TAVI) using the Medtronic CoreValve System, via the transarterial approach, in high-risk patients with degenerated surgical aortic bioprostheses.
Methods: Of 241 patients who consecutively underwent TAVI in our institution, 10 (4%) had a degenerated surgical bioprosthesis. The decision for favouring TAVI over redo surgery was reached by consensus of a heart team. The approach was percutaneous transfemoral in 9 cases, and surgical transaxillary in 1, with either general anaesthesia or conscious sedation and locoregional anaesthesia. As general principles, procedures were performed without balloon predilatation, with rapid pacing, and aimed at placing the CoreValve as high as possible within the surgical bioprosthesis. Outcomes were assessed using the Valve Academic Research Consortium definitions.
Results: Patients were aged 75±10 years. They all were in New York Heart Association (NYHA) classes III or IV, and at high risk for repeated surgery, with severe extracardiac comorbidities (EuroSCORE, 26±17%). The mean delay between surgery and bioprosthesis failure was 11±4 years (range, 6-20). The bioprostheses were stented in 7 cases, stentless in 2, and there was 1 homograft. The failure mode was a predominant regurgitation (grade 3 or 4) in 7 cases, and stenosis (aortic valve area: 0.7±0.2cm^2, mean gradient: 58±16mmHg) in 3. Based on the echographic measurement of inner prosthesis diameters, 8 patients received a 26mm, and 2 a 29mm diameter CoreValve System. Procedural success rate was 100%. There was 1 in-hospital death, not procedure-related, and 1 stroke with moderate sequellae. Pace-maker implantation was required in 1 case. There was no other adverse event at 30 days. The mean post-implantation transprosthetic gradient was 13±7mmHg, periprosthetic regurgitations were absent or trivial in 9 cases, and grade 2 in 1. After a mean follow-up of 9±7 months, there were neither additional adverse non fatal, nor fatal events. Hospital survivors were all but 1 in NYHA classes I or II.
Conclusion: These results suggest that transarterial Medtronic CoreValve implantation in degenerated aortic bioprostheses is feasible and safe, and leads to early and mid-term haemodynamic and clinical improvement. If favourable long-term outcomes are confirmed by larger series with longer follow-up, this option may be an attractive alternative to redo surgery in high-risk patients.

P593 Early and mid-term outcomes in patients undergoing transcatheter aortic valve implantation after previous coronary artery bypass grafting

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Purpose: To evaluate the impact of previous coronary artery bypass grafting (CABG) on outcomes in patients who undergo transcatheter aortic valve implantation (TAVI).
Methods: Of 201 high-risk patients who underwent TAVI between October 2006 and June 2010, 54 (27%) had a history of CABG. TAVI was performed using either the Edwards SAPIEN or the Medtronic CoreValve prosthesis.
Results: Main baseline characteristics and outcomes of the whole study population are described in the table. Overall, patients with previous CABG were younger, and more frequently male than those with no previous CABG, but they had more frequently cerebrovascular disease and previous myocardial infarction. Echographic characteristics were similar in both groups: Mean gradient: 52±18mmHg, aortic valve area: 0.7±0.2cm^2, left ventricular ejection fraction: 50±15%. The transapical approach was more frequently used in patients with previous CABG than in the others (43%, vs 26%, p=0.007). Implantation success rate was 98% in both groups. No peri procedural myocardial infarction was observed. There were no significant differences in 30-day rates of death, stroke and severe bleeding between both groups. Multivariate analysis identified 3 predictive factors of mid-term mortality: transapical vs transarterial approach, early experience, and absence of previous CABG.

	Overall (n=201)	Previous CABG (n=54)	No previous CABG (n=147)	p
Age	81±8	80±9	82±8	0.02
Female gender	96 (48%)	15 (28%)	81 (55%)	0.0006
EuroSCORE	28±15%	37±18%	24±12%	<0.0001
CharIson index	6±3	7±3	6±2	0.46
Previous myocardial infarction	39 (19%)	18 (33%)	21 (14%)	0.002
Cerebrovascular disease	48 (24%)	24 (44%)	24 (16%)	<0.00003
30-day survival	182 (91%)	51 (94%)	131 (89%)	0.25
2-year survival	70±5%	80±8%	66±6%	0.12

Conclusion: Previous CABG does not adversely affect outcome in patients undergoing TAVI. Those results, put along with the risk of redo surgery, suggest that TAVI could be an attractive treatment of severe aortic stenosis in this high risk patients' subset.

P594 Presence of subannular calcification as a new predictor of significant aortic regurgitation following percutaneous aortic valve implantation

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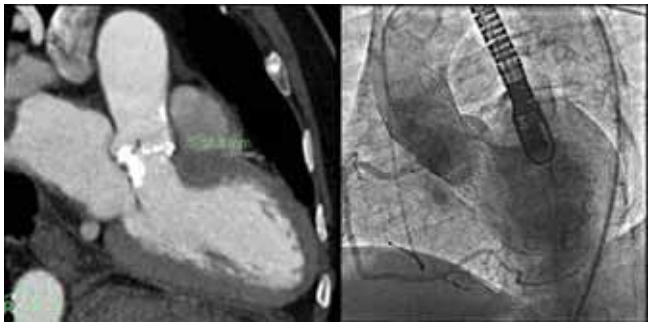
Background: Transcatheter aortic valve implantation (TAVI) has been shown to be effective in patients with severe aortic stenosis. However,significant aortic regurgitation may occur after valve implantation. The aim of this study was to assess the impact of subannular calcium detected by 64-slice computed tomography, on the incidence of significant aortic regurgitation after TAVI
Methods: We analyzed our series of 110 patients, 77±5 years old, with severe aortic stenosis treated with TAVI. Clinical, ecocardiographic, angiographic and CT variables were analized
Results: Implant success was obtained in 109 patients (99%). Valve size was 29 mm in 37 (34%), and 26 mm in 72 (66%). Posdilation was required in 42 patients (38%). After the procedure, significant regurgitation was observed in 22 patients (17 with grade II and 5 with grade III), and mild regurgitation (grade I) in 51 (47%). The remaining 36 (33%) had no regurgitation. In the AngioCT- scan performed before treatment, subannular calcification was detected in 30 patients (27%). This subannular calcification had a thicknes of 4.4±1.9 mm, and a depth of 10 mm±3,9. This feature was the only predictor of significant regurgitation after TAVI. Twelve out of 30 patients (40%), with this sign developed significant regurgitation p<0.05. Indeed, 4 out of 5, patients with aortic regurgitation grade III after valve implantation presented subannular calcium (p<0,01). The incidence of aortic regurgitation after valve implantation was not affected by valve depth in the outflow tract, annular size or valve size.



Conclusios: The presence of subannular aortic calcification detected by the CT scan is a predictor of significant regurgitation after TAVI.

P595 The impact of peripheral arterial disease on outcome after transcatheter aortic valve implantation. Results from the German TAVI registry

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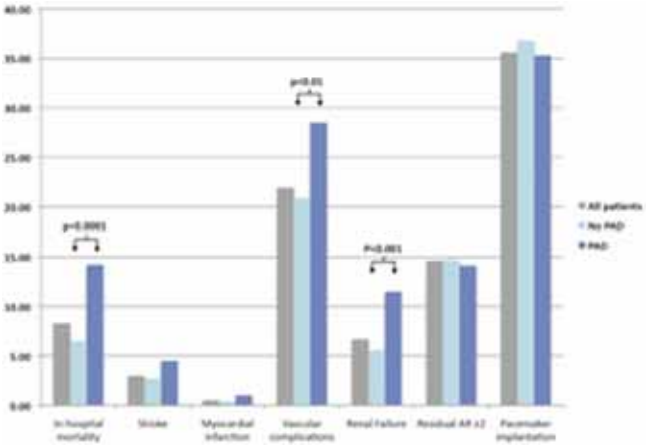
Objective: The aim of this study was to determine the impact of peripheral arterial disease (PAD) on outcome after transcatheter aortic valve implantation (TAVI).
Background: A significant proportion of patients undergoing TAVI has concomitant PAD which plays a crucial role in the selection process and may be associated with worse outcomes.
Methods: In the prospective, multi-center German TAVI registry, TAVI was performed in 1378 patients with a mean age of 81.7±6.2 years (42.1% males, logistic EuroSCORE 20.6±12.9%). TAVI was performed percutaneously in 1282 patients (93.1%).
Results: 296 patients suffered from PAD (21.5%): these patients had significantly smaller diameters (P<0.0001), more stenoses >50% (26.2 vs. 3.2%; P<0.0001) and more kinking (25.4 vs. 10.8%; P<0.0001) of the ilio-femoral system. Furthermore, patients with PAD had a higher logistic EuroSCORE (28.5±16.2 vs. 18.4±12.0%; P<0.0001) and suffered more often from comorbidities: coronary artery disease (82.3 vs. 55.2%, P<0.001), diabetes (42.6 vs. 32.3%; P<0.01), and chronic obstructive pulmonary disease (31.4 vs. 22.6%; P<0.01). After TAVI, the rate of dialysis-dependent renal failure (11.5 vs. 5.6%; P<0.001), vascular complications (28.5 vs. 20.9%; P<0.01), and in-hospital mortality (13.2 vs. 7.0%; P<0.0001) was increased in PAD patients. In multivariate analysis, PAD patients had a 1.5-fold higher risk of short-term mortality [Hazard ratio (HR): 1.5, 95% CI: 1.0-2.1; P=0.03] after TAVI.



Clinical outcomes according to PAD

Conclusions: In this real-world TAVI registry, patients with apparent PAD had a significantly worse outcome compared to patients without PAD. PAD plays a crucial role in the selection process and for access site evaluation and is one of the major predictors of outcome after TAVI.

P596 Causes of early and late death after transcatheter aortic valve implantation: a pooled analysis from 12 studies

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Purpose: Transcatheter aortic valve implantation (TAVI) has become an alternative for patients with severe aortic stenosis unsuitable for surgery. However, experience with TAVI is still short.
Methods: Published studies of TAVI with available data about causes of death were selected. We performed a pooled analysis of causes of death, comparing early (<1 month) and late (≥1 month) mortality.
Results: 12 studies with 1,233 patients were selected, with 249 (20.2%) reported deaths. Mortality during the procedure was 2.4%; and at 1 month was 9.7%, lower than that predicted by the mean EuroScore of the population (>20%). Causes of death after TAVI are shown in Table 1. There were 119 early deaths (47.8%), 30 of which were intra-procedural. Early deaths were more frequently of cardiac origin than late deaths (56.3% vs. 34.3%; p=0.001).

Table 1. Cause of death after TAVI according to early (<1 month) or late (≥1 month) event

Cause of death	Overall (249)	Early (119)	Late (130)
Cardiac	103 (41.4%)	67 (56.3%)	36 (27.7%)
Heart failure	41 (16.5%)	28 (23.5%)	13 (10%)
Sudden death	25 (10%)	20 (16.8%)	5 (3.9%)
Cardiac tamponade	14 (5.6%)	13 (10.9%)	1 (0.8%)
AMI	4 (1.6%)	2 (1.7%)	2 (1.5%)
Prosthetic dysfunction	5 (2%)	5 (4.2%)	0 (0%)
Other	15 (6%)	0 (0%)	15 (11.5%)
Non cardiac	121 (48.6%)	52 (43.7%)	69 (53.1%)
Bleeding/Vascular complication	28 (11.2%)	22 (18.5%)	6 (4.6%)
Stroke	20 (8%)	13 (10.9%)	7 (5.4%)
Sepsis	23 (9.2%)	13 (10.9%	10 (7.7%)
Respiratory failure	23 (9.2%)	4 (3.3%)	19 (14.6%)
Renal failure	10 (4%)	0 (0%)	10 (7.7%)
Other	19 (7.6%)	2 (1.7%)	17 (13.%)
Unknown	25 (10%)	0 (0%)	25 (19.2%)

Conclusions: Intra-procedural mortality of TAVI is low (2.4%). Early mortality is mainly of cardiac origin (56.3%), followed by vascular complications and stroke. Late mortality is still high (11%), and driven mainly by comorbidities and heart failure.

P597 Bioprosthetic aortic valve failure - transfemoral treatment using the Medtronic corevalve revalving system

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Conventional aortic valve replacement for aortic valve stenosis or regurgitation is safe and performed with excellent results. More recently, bioprosthetic valves are used more often since they have a favourable flow profile and do not require oral anticoagulation as compared to mechanical valves. However, a significant number of these valves fail within 15years, at a time when the patient's risk of redo-surgery has increased due to co-morbidities. Transfemoral aortic valve implantation (TAVI) with the Medtronic CoreValve ReValving System (MCV) represents an alternative. Therefore, the aim of the study was to elucidate whether TAVI using the MCV in patients (pts) with a failing aortic valve bioprosthesis is safe, feasible and associated with an improvement in hemodynamics.
Methods: Pts with symptomatic aortic valve disease, aged ≥ 65years with a logistic EuroSCORE ≥ 10% were enrolled. MCV implantation was performed using the retrograde transfemoral approach under local anaesthesia and cautious sedation. At 30days and one year, respectively, clinical events were recorded and a transthoracic echocardiography was performed to evaluate hemodynamics at follow-up.
Results: A total of 25pts (age 76±7years) with a Logistic EuroSCORE of 33±18% were treated so far. The duration between conventional AVR and MCV implantation was 56±44months, the inner diameter of the bioprosthesis was 21.7±2.1mm. Twenty pts received the TAVI for treatment of a stenotic bioprosthetic valve, whereas five were treated because of severe regurgitation. The MCV was successfully implanted without mechanical ventilation and support of a heart-lung machine in all patients (n=25,100%). In those with stenosis, the mean gradient declined from 46±16mmHg before to 12±7mmHg after TAVI ($p<0.05$), in those with AR the level declined by two. These excellent results were persistent throughout one year of follow up. There was no intraprocedural death, but one patient died from a severe stroke and one patient from cardiac failure within 24hours after TAVI. There were no further deaths within the 30day but one during the one-year follow-up period (30day/one year mortality: 8%/12%). Only one patient (4%) required a pacemaker implantation due to AV-Block grade three. Applying the VARC criteria device success was achieved in 21pts (84%). Freedom from death, major stroke, MI, life-threatening bleeding, stage 3 kidney injury or major vascular complication was detected in 18pts (72%).
Conclusion: These results suggest that TAVI using the MCV into a failing aortic bioprosthetic valve is feasible, safe and improves hemodynamics in these high risk patients.

P598 Feasibility and safety of transfemoral transcatheter aortic valve implantation without general anesthesia and transesophageal echocardiography with the Edwards' Sapien and Edwards' Sapien XT prosthesis

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Purpose: We report in this prospective, single-center study the early safety and efficacy of transfemoral aortic valve implantation (TAVI) using the Edwards Sapien (ES) and Sapien XT (SXT) prosthesis, all implanted without general anesthesia (GA) and without on-line transesophageal echocardiography (TEE).
Methods: Between May 06 and Jan 11, 127 consecutive high-risk patients (Log EuroSCORE: 23.8±11.8) had TAVI (ES: n=74, SXT: n=53) under conscious sedation: Midazolam 1-2 mg and Nalbuphine 5 mg. Primary end-point was a combination of all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury (AKI) stage 3, peri-procedural myocardial infarction (MI), major vascular complication, and repeat-procedure for valve-related dysfunction at 30 days.
Results: Transarterial access consisted in surgical cutdown (ES: 100%), or percutaneous approach (SXT: 92.7%) with preclosing, and was well tolerated in all cases. Conversion to GA was required in 3.9% (all ES cases) and related to complication. Vasopressors were used in only 5.5%. Procedural success was 96.9%. The combined-safety end-point was reached in 15.0%, including death (6.3%), major stroke (1.6%), life-threatening bleeding (9.5%), AKI stage 3 (0.8%), peri-procedural MI (1.6%), major vascular complication (7.9%), and repeat-procedure for valve-related dysfunction (1.6%) at 30 days. Permanent pacemaker was required in 4.7%. Comparison between ES and SXT results is shown in table.

Abstract P594 – Table 1. Edwards Sapien vs Sapien XT results

Variables	Conversion to GA	Use of vasopressors	Procedural failure	Combined safety end-point	Death	Major stroke	Life threatening bleeding	AKI stage 3	Peri-procedural MI	Major vascular Major vascular	Repeat procedure for valve-related dysfunction
Edwards Sapien (n=74)	5 (6.8%)	6 (8.1%)	3 (4.1%)	13 (17.6%)	6 (8.1%)	1 (1.4%)	9 (12.2%)	1 (1.4%)	1 (1.4%)	6 (8.1%)	2 (2.7%)
Sapien XT (n=53)	0 (0%)	1 (1.9%)	1 (1.8%)	6 (11.5%)	2 (3.8%)	1 (1.9%)	3 (5.7%)	0 (0%)	1 (1.9%)	4 (7.5%)	0 (0%)
p	0.06	0.13	0.44	0.25	0.27	0.66	0.36	0.49	0.67	0.59	0.26

GA: general anesthesia; AKI: acute kidney injury; MI: myocardial infarction.

Conclusions: This single-center prospective registry demonstrated the feasibility and safety of transfemoral TAVI performed without GA and TEE in high-surgical-risk patients with severe AS. The trend to less complications with the SXT prosthesis would deserve further evaluation on larger series.

P599 Survival and predictive factors of late mortality after percutaneous implantation of the corevalve aortic prosthesis

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Background: Percutaneous treatment of aortic stenosis is now an accepted therapy for patients with symptomatic aortic stenosis and a high surgical risk. We studied the medium-term survival and factors predicting late mortality after percutaneous implantation of a CoreValve aortic valve prosthesis.
Methods and results: From April 2008 to October 2010 we used the CoreValve aortic prosthesis to treat 133 patients with severe symptomatic aortic stenosis and a high surgical risk. Their mean age was 79.5±6.7 years and the logistic EuroSCORE was 21.5±14%. The implantation success rate was 97.7%. In-hospital mortality was 4.5% and the combined endpoint of death, vascular complications, AMI or stroke was 9%. Survival at 12 and 24 months was 84.5% and 79% after a mean follow-up of 11.3±8 months. The NYHA functional class improved from 3.3±0.5 to 1.18±0.4 and remained stable at one year. The quality of life of the patients for activities of daily living assessed with the Barthel test increased from 70.5±22.7 to 90.5±12.7. The Charlson index (HR 1.44; 95% CI, 1.09-1.89; $p<0.01$) and a worse Karnofsky score prior to the procedure (HR 0.95; 95% CI, 0.92-0.99; p=0.021) were predictors of late mortality.
Conclusions: Percutaneous treatment with the CoreValve prosthesis for patients with aortic stenosis and a high surgical risk is a safe, efficient option resulting in a medium-term clinical improvement. Survival during follow-up depends on the associated disorders.

P600 Acute hemodynamic changes after percutaneous mitral valve repair

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Aims: Percutaneous mitral valve repair (MVR) using the Evalve MitraClip device has recently been developed. This method delivers a clip via atrial trans-septal puncture grasping the mitral leaflets and thereby creating a double orifice valve. The aim of the present study was to assess immediate hemodynamic changes after MVR with the MitraClip device using right heart catheterization.
Methods: Patients with moderate to severe (3+) and severe (4+) mitral regurgitation (MR) due to functional (62%), degenerative (26%) or mixed (12%) disease were selected. MitraClip implantation was performed under general anesthesia with fluoroscopy and echocardiographic guidance. Hemodynamic variables were obtained before and after MVR using standard right heart catheterization and oximetry.
Results: A total of 42 consecutive non-surgical patients (age, 72±15 years, EuroSCORE 26±15) underwent percutaneous MVR between May 2009 and September 2010. Mean ejection fraction was 46±18% and 35 (83%) patients were in NYHA functional class III-IV. Acute procedural success (reduction in mitral regurgitation (MR) to grade 2+ or less) was achieved in 38 (90%) patients. Mitral valve clipping reduced mean pulmonary capillary wedge pressure (PCWP) (from 17±7 to 12±4 mmHg), PCWP v-wave (from 24±12 to 16±6 mmHg) and, mean pulmonary artery pressure (PAP) (from 30±12 to 23±5 mmHg), and increased cardiac output (from 5.0±1.8 to 6.9±1.9 L/min) and cardiac index (CI) (from 2.8±1.1 to 3.8±1.2 L/min/m^2) (all $p<0.05$). No changes in mean arterial pressure and left ventricular filling pressures were recorded. Hemodynamic response to MVR was similar in patients with degenerative versus functional MR.
Conclusion: In a heterogenous population with functional and degenerative MR, percutaneous MVR with the Evalve MitraClip system lowers PCWP and PAP by 21% and 20%, respectively, and increases CI by 31%.

P601 Optimal projections for angiographic imaging and percutaneous closure of the left atrial appendage. Lessons learned from the intraprocedural reconstruction of the left atrium and the pulmonary veins

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Purpose: Percutaneous left atrium appendage (LAA) obliteration is a new alternative strategy for prevention of embolic events in patients with atrial fibrillation (AF) and contraindications to anticoagulation. However, selective angiography of the LAA in standard fluoroscopic projections as guidance for device implantation does not always achieve optimal depiction of the individual LAA-ostium anatomy. This study aimed to define the projections that provide the optimal LAA depiction in the majority of the patients.
Methods: The intraprocedural rotational angiography of 100 patients (67 men,age: 60±12 years) with AF and indication for left atrium (LA) ablation was evaluated by two independent physicians in 33 angiographic projections, from right anterior oblique (RAO) 80° to leftanterior oblique (LAO) 80°. The optimal projections of the LAA ostium diameter were arbitrary defined according to the following criteria. Sagittal plane: (i) clear identification of both superior and inferior segments of the LA-LAA junction and (ii) no overlapping between LA and LAA ostium. Frontal plane: (i) clear identification of all four quadrants of the LAA ostium and (ii) visualisation of the maximal horizontal ostial diameter.
Results: The optimal ostial fluoroscopic projection for the LAA ostium in a sagittal plane was RAO 30° in 82 out of 100 patients (82%). Every 5° deviation from RAO 30° led to a 10% reduction of the optimally depicted LAA-ostia. The optimal ostial projection in a frontal plane for the LAA ostium was LAO 40° in 60 out of 100 patients (60%) and every 5° deviation led to a reduction of the optimally depicted LAA-ostia of about 15%, so that the anteroposterior diameter of LAA was not visible in RAO projections.
Conclusion: If selective angiography of the LAA ostium anatomy is performed to facilitate the implantation of an occlusion device, fluoroscopic projections should be carefully selected to avoid suboptimal visualisation. The preselected projections proposed in our study: RAO 30° and LAO 40° result in optimal sagittal and frontal angiographic projections of the LAA ostium respectively in the majority of patients.

P602 Thrombus formation on the new Amplatzer Cardiac Plug for LAA occlusion: a word of caution

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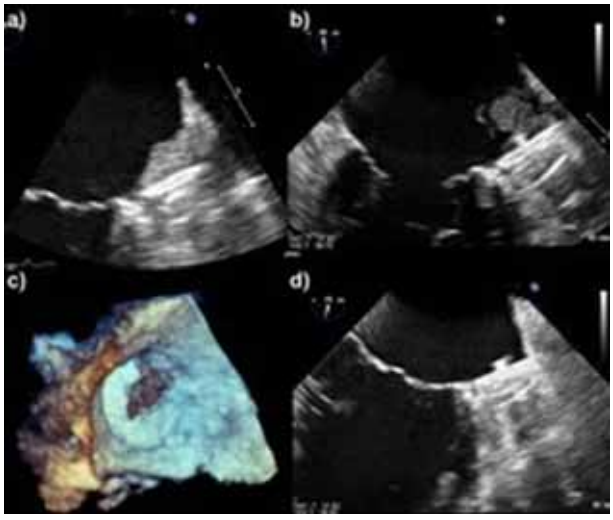
Background: Percutaneous left atrial appendage (LAA) occlusion is a novel approach for stroke propyhaxis in patients with atrial fibrillation (AF) and relative contraindications for oral anticoagulation. The new Amplatzer Cardiac Plug (ACP) device consists of a lobe anchored in the LAA with a connected disk shielding the LAA ostium. Limited experience of possible complications like thrombus formation exists so far. We report results of one of the largest series currently published. As a possible reason for thrombus formation the placement of the ACP disk in relation to the rim of the LAA is discussed.
Methods: LAA occlusion was performed in 31 consecutive AF patients (CHADS2 score ≥2) with the ACP under mild sedation without mechanical ventilation. Post intervention dual antiplatelet therapy was initiated according to company's recommendations. Pre discharge and after 3 and 6 months a transesophageal echo (TEE) was performed.
Results: In 32 procedures 31 ACP were implanted successfully. 1 ACP could not be placed due to an inappropriate anatomy. Mean occluder size was 24.0±3.1 mm. In 3 patients thrombus was detected in the pre discharge TEE, in 3 further patients after 3 months. Thrombi resolved after i. v. heparin administration for one week in 3 patients. In 3 patients oral anticoagulation was reinitiated for 3 more months. No significant difference can be found in the implantion site (placement on the rim in 32% in the non-thrombus vs. 33% in the thrombus group).



Thrombus formation/resolution on the ACP.

Conclusions: Thrombus formation on the new ACP device is a serious complication that should lead to caution. A change of the anticoagulation regime post implation has to be discussed. Our data does not support the thesis of a too deep implantation into the LAA as a risk factor for thrombus formation.

P603 Percutaneous paravalvular mitral leak closure with amplatzer vascular plug III device in presence of metallic aortic prosthesis

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Purpose: Several technical aspects has been described for percutaneous closure of mitral paravalvularleaks (PVL), however, the presence of metallic aortic prosthesis (MAP) is frequently thought to be a relative contraindication to cross the leak by retrograde approach. The purpose of this study is to describe the immediate result of a series of cases using the retrograde approach to close mitral PVLs through MAP using the Amplatzer Vascular Plug III (AVP III) device.
Methods: Prospective, observational study of all consecutive patients (P) with mitral PVL plus MAP treated in our Institution with AVP III device from December 2008 to December 2010. Procedure consisted in obliteration of the mitral PVL by retrograde passing of the leak with the wire, wire snaring and establishment of an arteriovenous loop. Transesophageal echocardiography was performed during the procedures.
Results: A total of 18 P were included. Mean age was 65±11 years and 10 (56%) were female. There were 4 (22%) P with diabetes, 3 (17%) had chronic renal failure, 15 (83%) had pulmonary hypertension and 2 (11%) ischemic heart disease. Indication for PL closure in most of cases (n=13, 72%) was decompensated heart failure plus haemolysis (mean Hb: 9,4 gr/dL ± 1,4; mean LDH: 1696 U/L ± 1133). Most P had moderate to high surgical risk as determined by logistic EuroSCORE (mean=16% ± 11) and 13 (72%) P had 2 or more previous surgical valvular interventions. All prosthesis were metallic. Most of P (11, 61%) were in FC III NYHA. Eight P (44%) had 2 or more PVL. Retrograde approach was performed in 14 P (78%), 1 P presented transient asystole when the catheter was intra-prosthesis, which was solved withdrawing the catheter and leaving the wire intra-prosthesis. In four P anterograde approach was performed because inability to cross the PVL with the delivery system catheter (one case) and 3 P for transient hemodynamic instability. In all these 4 cases an arteriovenous loop was performed through MAP without complications. Three P had mitral and aortic PVL, which were closed simultaneously, with complete success in 2 of them. A total of 22 procedures were performed with a rate success of 82% (18 procedures). Three P required new closure attempt, which was successful in all cases. Only 1 P was unable to implant the device, resulting in a rate success per P of 94% (17 P). No procedure-related deaths were observed.
Conclusions: Percutaneous mitral PVL closure with AVP III device, in presence of MAP, can be performed by retrograde or anterograde approach, establishing an arteriovenous loop through the MAP without major complications.

P604 Transcatheter closure of atrial septal defect with Amplatzer devices in children less than 3 years old

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Introduction: Elective closure of atrial septal defect type II (ASD) is usually delayed until the patients are at least 4 years old. Retrospective analysis of ASD closure in children ≤3 years of age was carried out.
Material and methods: Between 1997-2011 attempts of transcatheter closure of ASD were performed in 929 patients (pts) in our institution. In this group there were 120 children ≤3 years old. Their mean age was 2.1 (0.4-3.0) years and weight 12.5 (3.5-20) kg. In 54 of them (45%) special indication for the closure existed: body weight ≤25 percentile - 40 pts, frequent respiratory infections (7 pts) or coexistant pulmonary valvular stenosis - PVS (7 pts). In all but 2 pts the indication for ASD closure was RA/RV overload and ASD diameter (mm) /weight (kg) ratio (D/W) more than 0.5. Eleven children had body weight ≤10 kg. Single ASD had 85 pts and multiple/double 35. In 2 children with borderline RV hypoplasia a right-left (R-L) shunt with desaturation was present. In all children only Amplatzers (118 ASO and 2 Cribriformis devices) were used – without measurements of stretch diameter in 79/120 (65.8%).
Results: Mean device size was 12 mm, mean D/W 0,98. The procedure was effective in 117/120 children (97.5%) and 786/810 (97.0%) in the rest of pts. In 3 children (2 with body weight ≤10 kg) the device repeatedly straddled the septum and the procedure was abandoned. Embolization occurred in none of the small children and 7/810 in older patients. In small children the mean fluoroscopy time was 4.6 (0.5 - 20) and 4.8 (0-39) min in older pts. All but 2 symptomatic patients profited markedly from the closure. Two children with multiple pediatric problems had no significant increase in body weight after the procedure. In children with PVS undergoing simultaneous pulmonary valvuloplasty the gradient diminished from 60.6 to 19.4 mm Hg. In 2 children with R-L shunt after closure the saturation increased from 79 and 88 to 96 and 97% respectively. In follow-up no complications were observed.
Conclusions: Transcatheter ASD closure is safe and effective in children less than 3 years of age.

P605 Large devices for transcatheter closure of atrial septal defects in adult patients: immediate results and long-term follow-up

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Introduction: Percutaneous closure of atrial septal defects (ASD) has established as first choice treatment in selected patients. Large or complex (multiperforated, rim deficient, septal aneurysm) defects often require very large devices, making deployment more difficult and increasing short and long-term complications. There is little information regarding success rate and follow-up with this kind of devices.
Methods: Patients with an ASD who had undergone percutaneous intervention with devices ranging from 26 to 40 mm were included in this multicenter registry. Clinical, echocardiographic and procedural data were analyzed, as well as clinical follow-up. Data were collected retrospectively.
Results: One hundred and seventy adult patients were included, mean age 47 years (17-78), 59% females, 87% were in sinus rhythm. ASD median size was 24 mm (unstretched), 13% had septal aneurysm, 6% were multiperforated and 32% had at least one deficient rim (19% retroaortic, 5% anterosuperior, 4% inferior, 4% posterior). Imaging during intervention was intracardiac echo in 48%, transesophageal echo (TEE) in 45% and 3D-TEE in 7%. Amplatzer ASD devices were used in all patients, mean size 31±4 mm. Immediate success was achieved in 92% of patients. In 7 patients (4,1%) the device was not released, and 6 patients (3,4%) had embolization in the first 24 hours (2 were retrieved percutaneously and 4 were sent to emergent surgery). One patient (0,6%) suffered a stroke and 4 (2,4%) had atrial fibrillation (AF). No mortality was related to the procedure. Follow-up has been 4,6±2,8 years. New onset AF was diagnosed in 13 patients (7%). Severe late complications were 1,7% (1 embolization, 1 malposition, 1 perforation), all of them required surgery. A defect size larger than 30 mm was the only independent predictor of failure.
Conclusions: Transcatheter closure of complex ASD with large devices (≥26 mm) is feasible and safe, with a low rate of complications. Failure to implant the device and early embolization were the most serious complications. Defects larger than 30 mm were associated with a higher rate of failure.

P606 Recurrence of crytogenic stroke or transient ischemic attacks in patients with patent foramen ovale successfully treated by using percutaneous occluder devices: ten-year follow-up

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Background: Criptogenic stroke remains the final diagosis in 40% of ischemic acute cerebrovascular events.
The percutaneous closure of fpatent foramen ovale (PFO) has been practiced in some centers in cases of cryptogenic embolism, but there is little clinical evidence that this procedure can prevent the recurrence of stroke or Transient Ischemic Attacks (TIA)
Purpose: Evaluate the incidence of recurrence of stroke or TIA in patients with prior cryptogenic thromboembolic events who underwent percutaneous closure of PFO.
Methods and results: A retrospective study of all consecutive patients admitted in our department for percutaneous closure of PFO. We registered demographic, clinical indications, procedural success, complications, peri-procedure, existence of residual shunt at 12 months assessed by transesophageal ecocardiograhy (ETE) and clinical events such recurrent embolic events.
From August 2000 to November 2010, 260 patients were admitted, (140 female (52%), average age 44 years, range 21-74) with a diagnosis of cryptogenic embolism (242 stroke and 18 TIAs) for FOP closure. The existence of atrial septal aneurysm (ASIA) was documented in 45% of patients. Four different occluder devices were used (233 Amplatzer, 21 Premère, 5 Cardia, 1 Biostar).
Successful device deployment was achieved in 99.2% (2 failures). The periprocedural complication rate was 2.3% (1 embolization, 5 pseudoaneurysms - 1 requiring surgery). 0% in-hospital mortality. The follow-up was complete in 90% of the cases (median - 48 months, range: 1-124 months). The ETE evaluation (n = 157) showed 99.6% of the devices good appositioned and there was a residual shunt at 8.3%. The shunt was more common in patients with larger devices (p=0.08) and ASIA association (p=0.1).
Mortality during follow-up was 1.15% (3 patients died: 1 pulmonary embolism, 1 hemorrhagic stroke, 1 suicide). The recurrence of cerebral ischemic events was documented in 3 patients (1 stroke, 2 TIA - one of which in the context of atrial fibrillation) - annual recurrence rate of 0.8%. There were no relationship between embolic events and the existence of ASIA or residual shunt.
Conclusion: Our 10 year experience suggests that percutaneous closure of PFO

is safe and beneficial at the medium and long term follow-up for secundary prevention since the low recurrence of acute cerebrovascular events. The results obtained for residual shunt and the rate of recurrent cardiovascular events documented were similar to previous publicated papers.

P607 Percutaneous treatment of aortic isthmus atresia: use of radiofrequency perforation and covered stents

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Background: Limited data exist concerning the percutaneous treatment of aortic isthmus atresia.
Patients and methods: Four pts had complete aortic isthmus atresia. Median age at procedure was 48 years. All subjects had history of arterial systemic hypertension. All procedures were performed under general anesthesia and orotracheal intubation. Radial and femoral artery access were obtained. Radiofrequency system (Baylis MedComp Inc, Montreal, Canada) consisting in a Nykanen 0.024" RF guidewire and a coaxial microcatheter were used to perforate the atretic segment. Guidewire was snared and an artero-arterial circuit was created. The area was pre-dilated by using coronary angioplasty balloons. A 12 Fr Mullins long sheath was advanced and an E-PTFE covered 8Zig Cheatham-Platinum stent was implanted.
Results: Percutaneous recanalization of the atresia was performed successfully in all subjects. Mean fluoroscopy and procedure times were 30±6 and 90±15 minutes, respectively. After implantation, the gradient decreased significantly (pre stent: mean value 52.25 mm Hg [range 33-70 mm Hg] versus post stent: mean value 3 mm Hg [range 0-10 mm Hg] [$P<0.0001$]). The stents were placed in the correct position in all subjects. No complications occurred. During a mean follow-up of 19 months (2-41 months), the results were stable without complications. All subjects had a perfectly normal arterial systemic pressure. In two out of 4 patient one anti-hypertensive drug was needed. One patient needed further stent dilation because of a conservative approach. Procedure was performed 8 months after the initial stent implantation without problem.

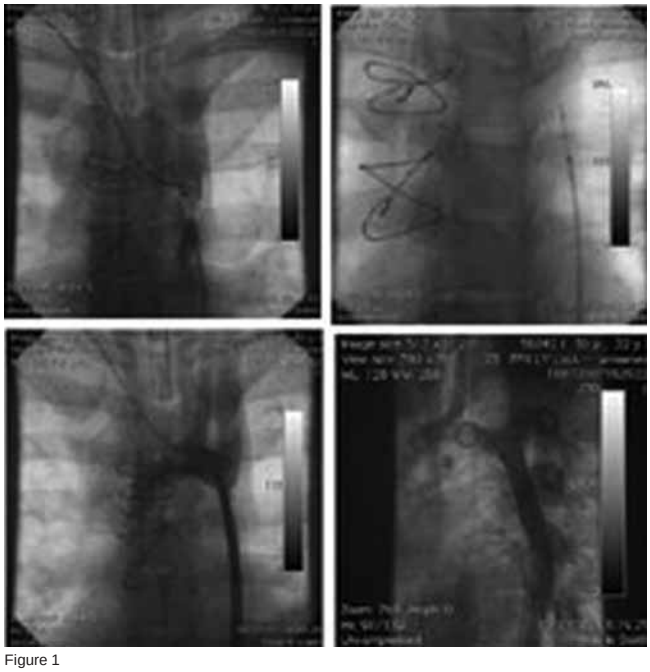

Figure 1

Conclusions: Our data show that use of radiofrequency energy and Covered CP stents is a safe, effective and promising tools for treatment of aortic isthmus atresia.

P608 Safety and efficacy of endovascular therapy with simple homemade carbon dioxide delivery system

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Background: Carbon dioxide (CO2) has been used as an arterial contrast agent for high-risk patients who were allergic to iodinated contrast material and for those with renal insufficiency. To retrospectively evaluate the feasibility, safety, imaging quality and therapeutic role of CO2 digital subtraction angiography (DSA) using a simple homemade delivery system in the endovascular therapy (EVT) for iliofemoral artery disease.
Methods and results: EVT was performed in consecutive 67 patients (97 limbs; mean age, 74 years) who were admitted to College of Medicine Hospital with iliofemoral artery disease from January 2010 to October 2010. Intravascular ultrasound (IVUS)-guided EVT with CO2 was applied for the treatment of 33 patients (49 limbs) with preexisting renal insufficiency (group1). IVUS-guided EVT with iodinated contrast media was applied for the treatment of 34 patients (48 limbs) without preexisting renal insufficiency (group 2). CO2 was injected by hand using a simple homemade delivery system. The overall technical success was 100% between the both groups without major complication. Preprocedure and post-procedure ankle-brachial indices were significantly improved between the both groups (0.60±0.21 to 0.93±0.11, 0.62±0.24 to 0.94±0.13 respectively). Combining the results of two independent observers, we found that 100% of the CO2 arteriogram was of good or acceptable imaging quality.
Conclusion: CO2 using a simple homemade delivery system is a feasible and safe in patients with preexisting renal insufficiency in the evaluation and the EVT for iliofemoral artery disease. Adequate image quality of the iliac and femoral arteries can be obtained with proper injection technique. We suggest that CO2 DSA can be used as the initial contrast agent for the evaluation of iliofemoral artery disease in patients with renal insufficiency and iodine contrast allergy.

P609 Transcatheter closure of ruptured sinus of Valsalva aneurysm with an A4B2 double-disk occluder

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Purpose: Recently transcatheter closure of ruptured SVA has been reported and may be a reliable therapeutic alternative to surgery in selected patients. to evaluate the safety and efficacy of transcatheter closure of ruptured sinus of Valsalva aneurysm using a newly designed double-disk occluder.
Methods: Between September 2005 and December 2010, 6 patients underwent transcatheter closure of a ruptured sinus of Valsalva aneurysm at our institution. A newly designed double-disk occluder was used in all subjects. The median Qp/Qs ratio was 1.7 (range, 1.4 to 2.1). Five patients had ruptured sinus of Valsalva aneurysm from the right coronary sinus to the right ventricle. The non coronary sinus aneurysm ruptured into right ventricle in another patient.
Results: Transcatheter closure with the double-disk occluder was attempted in all 6 patients successfully. One patient underwent combined percutaneous ventricular septal defect closure. The size of the double-disk occluder selected was 4 to 6 mm larger than the narrowest diameter of the opening of aneurysm. Follow-up transthoracic echocardiography showed neither residual shunt nor interference with the adjacent cardiac structures.
Conclusion: The newly designed double-disk occluder described herein is safe and effective in selected patients with ruptured sinus of Valsalva aneurysm. Additional studies with larger cohorts and longer follow-up are needed to evaluate its safety.

P610 Stent implantation in aortic coarctation in adults: ten year experience

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Aim: To report our experience on stent implantation in aortic coarctation (AC) in children.
Methods and patients: Between January 2000 and December 2010, 69 consecutive patients aged >18 years with AC had a percutaneous treatment in our institution (29 females; age 32.5±12.7 years; weight 68±15 kgs). Fifty-five subjects (80%) had a native AC while 14 (20%) had a recurrent AC (10 post-surgery, 2 post balloon angioplasty, 2 post-bare stent implantation). Procedures were performed under general anhestesia. The following stents were used: Palmaz stents, Genesis stents, Cheatham-Platinum, covered Cheatham-Platinum. Bare stents (BS) were used in 34 patients, while covered stents (CS) were used in 35 subjects.
Results: Peak-to-peak gradient reduced significantly from 39±12 mmHg to 6±3 mmHg ($p<0.001$). AC diameter increased significantly from 6±mm to 14±4 mm ($p<0.001$). Fluoroscopy time was a median of 16 minutes (range 7-48 minutes). The median balloon to aortic coarctation ratio was 3 (range 1,5-6). Early complications occurred in 13 subjects (20%): artero-venous femoral fistula (3 pts); stent embolization (2 pts treated with BSs); arrhythmias (2 pts); aortic hematoma (1 pt); TIA (1 pt) brachuial plexus injury (1 pt).
Comparing Bare versus covered stents there were no differences complications, age, gender, native coarctation/recoarctation rate, mean drop of peak systolic gradient, increase of diameter of coarcted segment, mean fluoroscopy and procedure times between BS and CS. Subjects treated with CSs had tighter stenosis (4.8±2 versus 7±3 mm; p=0.001) and needed larger sheath (median 12 versus 11 Fr; p=0.01). The balloon-to-stenosis ratio was larger for covered stents (median 3.3 versus 1.9; p=0.001). Follow-up was a median of 6 years (range 1-10 years).
Redilatation was needed 10 subjects (8 BS and 2 CS). In two subjects treated with BS another stent (CS) was implanted because of restenosis and development of aneurysm of the aortic wall.When needed, both CS and BS were redilated

successfully 1 to 4 years after the initial procedure. Fifteen subjects still need anti-hypertensive drugs at latest follow-up.
Conclusions: Percutaneous treatment by using stents in aortic coarctation is a safe and effective procedure. Introduction of CS allowed the reduction of risks and the treatment of tighter aortic coartcation.

UPDATE IN CARDIOVASCULAR SURGERY

P611 Atorvastatin rapidly reduces myocardial superoxide and peroxynitrite generation in human atherosclerosis, by suppressing NADPH-oxidase activity independently of LDL lowering

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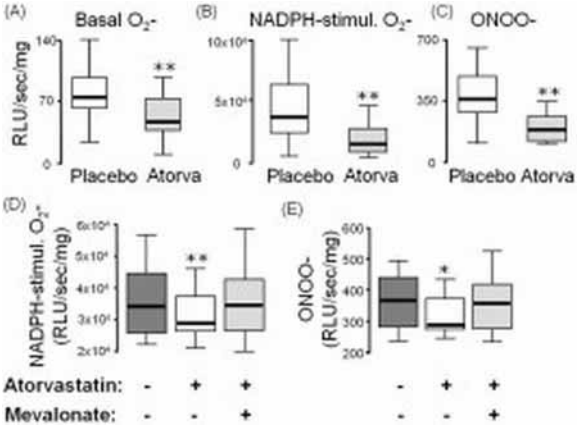
Background: The myocardial redox state is a key determinant of clinical outcome in ischaemic heart disease. We examined the effect of short-term treatment with atorvastatin on the mechanisms regulating myocardial redox state in patients undergoing elective CABG.
Methods: In study 1, 42 statin-naïve patients scheduled for elective CABG were randomized to receive either atorvastatin 40mg/d or placebo (n=21 per group) for 3 days preoperatively. Blood samples were obtained at randomization and on the day of surgery. A sample of the right atrial appendage (RAA) was obtained during CABG. In study 2, RAA from 26 patients in sinus rhythm undergoing CABG were incubated with atorvastatin (20μmol/L) +/- mevalonate 200μmol/L for 1h. Myocardial superoxide (O2-) generation was evaluated by lucigenin-enhanced chemiluminescence, and myocardial peroxynitrite (ONOO-) by the urate-inhibitable luminol chemiluminescence. NADPH oxidase activity was estimated by NADPH-stimulated O2- and the activity of mitochondrial oxidase complex I by using rotenone.
Results: In study 1, 3-day treatment with atorvastatin reduced basal myocardial O2- (A), NADPH-stimulated O2- (B) and ONOO- (C). In study 2, in vitro incubation of RAA with atorvastatin 20μmol/L reduced NADPH-stimulated O2- (D) and ONOO- (E); these effects were reversed by mevalonate. There was no effect of treatment on the rotenone-inhibitable O2- fraction.



*P<0.05; **P<0.01 vs placebo or control.

Conclusions: Short term atorvastatin treatment rapidly reduced myocardial O2- and ONOO- release by inhibiting NADPH-oxidase activity via a direct effect on cardiac HMGCoA reductase; a finding that partly explains the beneficial effect of preoperative statin treatment on post-operative CABG complications.

P613 The development and validation of a model to assess total morbidity burden after cardiac surgery

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Purpose: Low post-operative death rates make mortality an inadequate outcome measure. As post-operative morbidity is more common, its measurement would be more sensitive. The Post-Operative Morbidity Survey (POMS, Bennett-Guererro et al 1999) is the only prospective tool for standardised morbidity measurement in general surgical patients. No such tool exists in cardiac surgery. We sought to develop and validate a tool (C-POMS) for identifying morbidity post cardiac surgery.
Methods: Morbidity was prospectively assessed in 450 cardiac surgery patients on post-operative days 1, 3, 5, 8 and 15 using POMS criteria (presence/absence of infectious, pulmonary, cardiovascular, wound, haematological, pain, renal, gastrointestinal complication) and cardiac-specific variables (from expert panel). Other morbidities were noted as free-text. Items were considered for inclusion into C-POMS if prevalence >5%, missingness <5% and mean severity-importance index score >8 (derived from expert ratings on 5-point Likert scales). Construct validity was assessed by expert panel review, Cronbach's alpha (internal consistency) and linear regression (predictive ability of C-POMS with length of stay (LOS)).
Results: Further to POMS, 175 additional morbidities were identified. Following item-reduction, C-POMS resulted in a 13 domain model: modified POMS categories plus new endocrine, electrolyte, review (clinical review/investigation) and assisted ambulation domains. Internal consistency (>0.7) on D3-D15 permits use of C-POMS as a summative score (0-13) to denote total morbidity burden. A C-POMS summary score was calculated for each participant. ≥1 post-operative morbidity was observed in 92.2%, 85.7%, 95.0% and 100% of patients remaining in hospital on D3, D5, D8 and D15, respectively. Overall, the mean C-POMS scores were 3.4 (D3), 2.6 (D5), 3.4 (D8) and 3.8 (D15). The maximum score of any participant was 11 (D3, D8 and D15). Comparing those with/without C-POMS defined morbidity on D3, D5 and D8 those with had an extra LOS of 4.6 (p=0.012), 5.3 days (p=0.001) and 7.6 days (p=0.135), respectively. There were no patients without C-POMS defined morbidity on D15. For every unit increase in C-POMS summary score there is a 1.7 (D3), 2.2 (D5), 4.5 (D8) and 6.2 (D15) increase in subsequent LOS (all p=0.000).
Conclusions: C-POMS is the first validated tool for identifying total morbidity burden post cardiac surgery. C-POMS identifies considerable morbidity in these patients and may find application in modelling causation, pre-operative risk assessment, and in identifying preventative and therapeutic targets.

P614 The fate of the internal thoracic arteries after served as bypass conduits in dialysis patients

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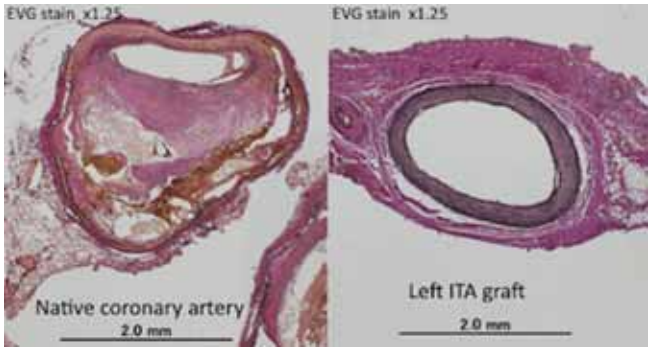
Purpose: Dialysis patients have a high prevalence of coronary artery disease and cardiovascular death because of accelerated atherosclerosis. Meanwhile, follow-up angiographic studies in this population after coronary artery bypass grafting (CABG) have demonstrated excellent patency rate of internal thoracic arteries (ITAs). Although prior histological studies show that ITAs have little atherosclerotic change before serving as bypass grafts, knowledge is limited regarding the histology of ITAs that have been functioning as bypass grafts. We investigated the fate of ITAs from the histological point of view in dialysis patients who have been postulated to be high atherosclerotic burden.
Methods: Five ITAs that had been served as coronary artery bypass grafts were harvested and examined histologically in 4 dialysis patients who died at 28, 57, 96, and 126 months after CABG. Atherosclerosis of these ITAs was analyzed using the subjective evaluation proposed by Kay and colleagues, comprising a scale of 0 (none) to 4 (lumen completely obliterated).
Results: Patency of all the ITA grafts was confirmed. Despite the severe calcification in the native coronary arteries, the mean degree of histology for the ITA was 0.2; the grafts had little atherosclerotic change. A representative case is shown in the image. The patient was a 75-year-old man who was on dialysis for 27 years and died 5 years after CABG.



Native coronary artery and left ITA.

Conclusions: This histologic study corroborates the reported excellent patency rates at long-term follow-up of the ITAs used as coronary artery bypass grafts among dialysis patients. The results of the study support the continued use of ITA grafting in dialysis patients.

P615 Continuous monitoring of risk-adjusted mortality improves outcome of CABG surgery in a medium-sized university centre

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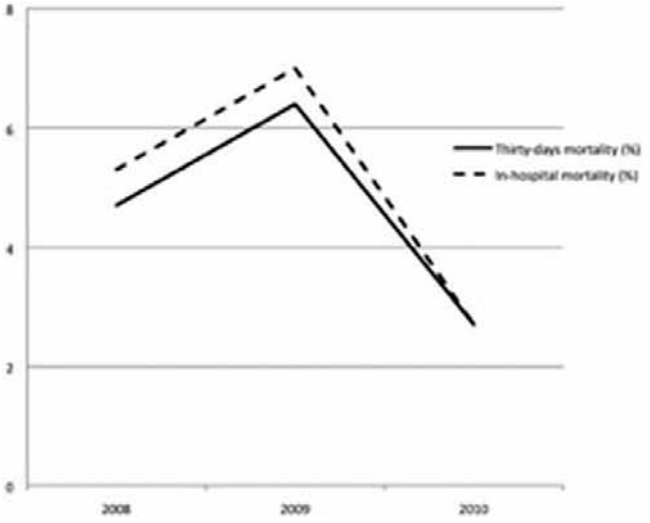
Aim: To report how instituting a continuous monitoring of risk-adjusted mortality improved results of lone coronary surgery.
Methods: Following the general recommendations for cardiac surgery of the national High Authority of Health, we progressively established a continuous monitoring of activity and results in our centre. Operations were categorized as lone CABG, valvular surgery or surgery of the thoracic aorta with or without CABG and other procedures. For each category, a risk-adjusted analysis of mortality was performed annually using the additive EuroScore risk scale. A specific action plan was proposed whenever the observed mortality for one category exceeded the expected mortality or the national average plus one standard deviation.
Results: The EuroScore was calibrated on the 1488 patients included in the risk-adjusted mortality analysis with an area under the ROC curve of 0.75. Considering the lone CABG population, the annual ratio of observed/expected mortality was 1,07 and 1,55 for 2008 and 2009 respectively. Unacceptable tendency toward thirty-days and in-hospital over-mortality was observed in 2009 (Figure 1). Mesenteric infarction was identified as the main cause of over-mortality. This, and the acknowledgment of the national mortality average after lone CABG, made us propose to redefine our practical management of lone CABG patients during and after surgery in order to improve microcirculation. As a result, observed mortality after lone CABG in 2010 dropped to 2,7%, with a significant reduction of mesenteric infarction events (p=0.02).



Evolution of operative mortality (%).

Conclusion: Closely monitoring risk-adjusted mortality and being reactive against identified causes of over-mortality improves results and standard of care of lone CABG surgery even in a medium-sized University centre.

P616 Risk factors and validation of Fowler infection score in a public cardiology teaching hospital in South America

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Purpose: Infection after coronary artery bypass graft surgery (CABG) is infrequent but serious complication. Fowler described an infection risk score to identify patients at elevated risk utilizing the Society of Thoracic Surgeons National Cardiac Database (STS). The aim of this study is to identify risk factors of infection, validate Fowlers infection risk score in public cardiac teaching hospital utilizing an prospective active infection control surveillance and association with the causal pathogen.
Methods: This is a retrospective analysis of a prospective data bank of all CABG performed in a single institution from 2006 to 2008. Chi-square was used for categorical variables and "t" test for quantitative variables. Logistic regression was utilized with infection as the dependent variable. $P<0.05$ was considered significant.
Results: The overall study population consisted in 1975 CABG patients, 143 (7.2%) with sternal wound infections, 38 (1.9%) with superficial, 58 (2.9%) profound and 47 (2.4%) with mediastinitis. Logistic regression analysis identified female sex (Odds 2,01 CI 95% 1,36-2,95; $p<0.001$), Diabetes, (Odds 2.33 CI 95% 1.56-3.49; $p<0.001$), body mass index (BMI) >40 (Odds 6.27 CI 95% 2.53-15.40; $p<0.001$), number of disease coronary arteries (Odds 7.78 IC 95% 1.04-57.79; $p<0.001$)and bilateral use of internal mammary artery (Odds 3.85 CI 95% 2.10-7.07; $p<0.001$) as infection risk factor. The Fowlers median score for the infected patients vs non infected was 9 vs 7 ($p<0.001$). Gram negative pathogens caused 52 (34.2%) of the infections, with a Fowlers median score of 11, compared with a 9 score of the Gram positives (p=0.063). The most common pathogen was Staphylococcus epidermidis 42 (27.6%), Staphylococcus Aureous 33 (21.7%), Klebsiella sp 29 (19.1%), Streptococos coagulase negative 19 (12.5%). Mortality rate was not altered by infection compared with no infection (8.4%vs 6.8%, p=0.309).
Conclusions: Female sex, diabetes, BMI >40, number of arteries involved, and bilateral use of internal mammary artery were associated with elevated risk of infection. The Fowler risk score can be applied in a Brasilian Tertiary Public Hospital in patients submitted to coronary artery bypass surgery. In this population, there was no correlation between risk score and pathogens.

P617 Perioperative dynamics of sP-selectin as marker of endothelial dysfunction and subclinical inflammation following on-pump coronary artery bypass grafting

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Purpose: Evaluate the dynamics of sP – selectin, an endothelial dysfunction marker, in coronary heart disease (CHD) patients undergone on-pump coronary artery bypass grafting (CABG) with respect to the presence of postoperative complications.
Materials and methods: 22 CHD patients, undergone scheduled CABG, were examined, of them 16 were male (72.7%) and 6 female (27.3%). The mean age of all the patients was 57±3.25 years (mean female age 58±1.5 years, mean male age 57±3.5 years). sP-selectin levels were measured by immunoenzymatic assay before the surgery, at day 1 and day 7 after the surgery. Early postoperative complications were observed in 54.5% patients (n=12), among them paroxysmal atrial fibrillation (50%; n=6); increase in serum creatinine levels (25%; n=3); worsening of heart failure symptoms (17%; n=2) and left-sided hydrothorax (8%; n=8). All the complications were resolved by conservative therapy.
Results: Preoperative sP-selectin levels in the whole study population made up 118.80±22.00 ng/ml, at day 1, 156.50±29.00 ng/ml (p=0.03) and at day 7, 146.95±21,03 ng/ml. The group of patients with early postoperative complications demonstrated significantly higher concentrations of sP-selectin 7 days after CABG: 177.90±24.00 vs. 137.20±17.24 ng/ml (p=0.04). Dividing the patients into the group with postoperative paroxysmal atrial fibrillation and the group without any postoperative complications showed the same pattern: more marked increase in sP-selectin levels at day 7 in the paroxysmal atrial fibrillation group compared with the group free of inhospital complications: 177.00±26.09 vs. 137.20±19.56 ng/ml (p=0.04).
Conclusions: The increase in sP-selectin levels is observed after CABG. The increase in this endothelial dysfunction marker at day 1 and day 7 after the surgery is significantly higher in patients who develop postoperative complications, in particular, paroxysmal atrial fibrillation. The given fact supports an important role of inflammation in paroxysmal atrial fibrillation development after CABG.

P618 Curcuminoids prevent myocardial infarction after coronary artery bypass grafting

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Purpose: Myocardial infarction (MI) associated with coronary artery bypass graft surgery (CABG) predicts the poor outcome. Nevertheless, the cardioprotective therapies to limit MI after CABG are lacking. Previous animal study has shown that curcuminoids suppress pro-inflammatory cytokines during cardiopulmonary bypass surgery and decrease cardiomyocytic apoptosis after cardiac ischemia/reperfusion injury. The purpose of the present study was to evaluate whether curcuminoids prevent MI after CABG, compared to placebo.

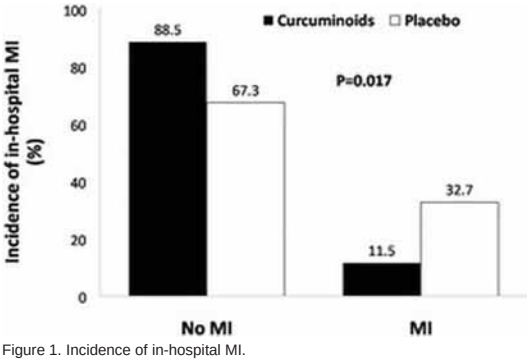

Figure 1. Incidence of in-hospital MI.

Methods: The 104 consecutive patients undergoing CABG were randomly allocated to receive either placebo or curcuminoids 4 grams/day on top of standard therapy, beginning 3 days before the scheduled surgery and were continued until 7 days after surgery or the patients were discharged from the hospital. The primary end point was incidence of in-hospital MI. Secondary end point was composite endpoint of death and non-fatal MI at 30 days after CABG.
Results: Baseline characteristics were comparable between two groups. Mean age was 60±10 years. On-pump CABG procedures were performed on 48.1% of patients. Postoperative CK-MB level was lower in curcuminoids than placebo group (43±18 ng/ml vs. 58±44 ng/ml,P=0.02). Incidence of in-hospital MI was significantly reduced in curcuminoids group, compared to placebo group (P=0.02), as shown in Figure 1. The lower incidence of combined death and non-fatal MI at 30 days was also demonstrated with curcuminoids group (13.5% vs. 34.6%,P=0.02). The drug-related adverse effects were not different between the two groups.
Conclusions: This is the first study assessing the cardioprotective effects of curcuminoids in patients undergoing CABG. We demonstrated that curcuminoids could significantly reduce myocardial infarction associated with CABG.

P619 Safety of coronary artery bypass surgery during therapeutic oral anticoagulation

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Background: Therapeutic (international normalized ratio, INR 2.0-3.5) oral anticoagulation (TOAC) is assumed to increase perioperative bleeding complications and a standard recommendation is to discontinue warfarin before coronary bypass grafting (CABG).
Methods: To assess the safety of TOAC we retrospectively analyzed consecutive patients (n=270) with long-term warfarin therapy referred for CABG in two centers where TOAC strategy is employed. The main in-hospital outcomes of interest were death, stroke, acute myocardial infarction, new onset renal failure, resternotomy, and their composite. In the TOAC group of 103 patients CABG was performed during therapeutic oral anticoagulation and in the control group (81 patients) preoperative INR was lowered to a subtherapeutic (≤1.5) level.
Results: The patients in TOAC group were more often operated on an emergency basis (p=0.02) and their EuroSCORE was higher (p=0.02). There were no significant differences in the major outcome events or their composite (17.5 vs. 11.1%, p=0.30) between the groups. Patients in the TOAC group had more postoperative blood loss (941±615 vs. 754±610 ml, p<0.01) and received more fresh frozen plasma (2.8±3.0 vs. 1.3±2.4 units, p<0.001), but transfused red blood cells (2.1±2.8 vs. 2.1±3.4 units) were comparable in the groups. Preoperative clopidogrel (OR 4.8, 95% CI 1.4-16.2, p=0.01) and enoxaparin therapy (OR 2.6, 95% CI 1.1-6.5, p=0.04) were the only significant independent predictors for any major adverse event.

Table 1. Postoperative outcome in patients with therapeutic (TOAC group) and subtherapeutic (Control group) oral anticoagulation

	TOAC group INR 2.0–3.5 (n=103)	Control group INR ≤1.5 (n=81)	p-value
Mortality	5 (4.9)	2 (2.5)	0.40
Myocardial infarction	2 (1.9)	0 (0)	0.28
Stroke	4 (3.9)	3 (3.7)	0.95
Reoperation	12 (11.7)	5 (6.2)	0.20
Postop. drainage bleeding (ml)	941±615	754±610	p<0.01
Red blood cells units	2.1±2.8	2.1±3.4	0.61
Fresh frozen plasma units	2.8±3.0	1.3±2.4	<0.0001

Conclusions: Our study suggests that CABG is a safe procedure during TOAC with no excess bleeding or major complications, but prospective trials are needed to assess this approach.

P620 Gender differences and early outcome after coronary artery bypass graft surgery

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Purpose: The outcome of female patients after coronary arterybypass graft (CABG) surgery has been reported to be less favourable compared to the outcome of male patients. Especially, the gender-specific in-hospital mortality risk has been reported to be higher in female patients. The most accepted theory for this difference is that women having the operation are higher-risk patients than men. The objective of the present study was to compare women with men with respect to baseline characteristics and short-term outcome in a contemporary cohort of patients that underwent CABG surgery.
Methods: A retrospective single-centre cohort study was conducted in patients (N=2653) that underwent CABG surgery between January 2003 and December 2009. Differences in baseline characteristics were assessed using chi-square analysis or the Fisher exact test for discrete variables, and 2-sample student t-tests for continuous variables. Gender was studied as independent risk factors for short term outcome (<30 days) using binary logistic regression.
Result: During the study period, CABG surgery was undertaken in 2017 (76%) males and 636 (24%) females. Female patients were generally older (mean age, 67 versus 65 years, p<0.001) and presented more often with unstable angina pectoris (13.2% versus 9.9%; p=0.02), diabetes mellitus (28.2% versus 23.7%; p=0.02), and higher EuroScore (mean score, 4.85 vs. 4.11, p<0.001); female patients tended to be less likely to receive arterial grafts (90.0% versus 92.6% in male patients, p=0.09). Female patients presented less often with extracardiac arteriopathy (8.8% versus 12.7%; p=0.01). No differences could be found in the left ventricular function (p=0.29), and the urgent or emergent status (p=0.13). Furthermore, no differences could be found in the rate of postoperative rethoracotomy (due bleeding or tamponade) between female and male patients (5.7% versus 5.8%; adjusted OR 0.99, 95% confidence interval [CI] 0.67-1.47; p=0.96). Women demonstrated equal 30-day mortality (1.6% vs. 2.1%) on both univariate analysis (OR 0.75, 95% CI 0.38 – 1.51; p=0.42) and multivariate analysis (OR 0.48, 95% CI 0.23 – 1.01; p=0.053).
Conclusions: Although female patients undergoing CABG surgery are older and have higher EuroScore, the 30 day mortality is comparable to male patients. Therefore, there seems to be no longer gender differences in short term outcome anymore once patients are in the invasive part of the treatment (cardiac surgery). Nevertheless, there appears to be room for improvement of outcome in female patients by increased utilization of arterial grafts.

P621 Statins and lower mortality following coronary arterial revascularization

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Objective(s): Dyslipidemia is common in patients undergoing coronary artery revascularization and is usually treated with statins. Numerous studies have shown that statins decrease the systemic inflammatory response (SIRS) that follows different surgical procedures. The aim was to evaluate the effect of statin-use on complications and operative mortality after CABG or OPCAB.
Methods: A retrospective study of 720 consecutive patients that underwent CABG (n=513) or OPCAB (n=207) in Iceland from 2002-2006. Patients taking statins preoperatively (n=529) were compared to patients not taking statins (n=154). Using uni- and multivariate analysis, predictors of complications and mortality were evaluated.
Results: Cardiovascular risk factors, type of surgery and operative time were comparable between the groups. However, hypertension was more common in the statin group but EuroSCORE was slightly lower (4.6 vs. 5.6). There were no significant differences in the incidence of major complications (i.e. stroke, mediastinitis and reoperations for bleeding), but trends for lower incidence of acute respiratory distress syndrome (ARDS) and multi organ failure (MOF) were seen in the statin group. Operative mortality was significantly lower in patients taking statins (1.7 vs. 5.8%, p=0.001). Multivariate analysis showed that statin treatment independently predicted lower operative mortality (OR 0.20, 95% CI: 0.05-0.81, p=0.02), even after adjusting for EuroSCORE (OR 1.36, p=0.003) and advanced age (OR 1.13, p=0.02).
Conclusions: Patients taking statins had lower operative mortality compared to controls. The reason for this is not obvious but might be linked to pleiotropic effects of statins, such as anti-inflammatory effects and/or improvement in endothelial function.

P622 Bypass surgery versus percutaneous coronary intervention for the treatment of unprotected left main disease - a meta-analysis of randomised controlled trials

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Purpose: Current guidelines state that percutaneous coronary intervention (PCI) with stents may be considered in patients with unprotected left main stenosis (LM) as an alternative to coronary artery bypass surgery (CABG) in the presence of anatomic conditions that are associated with a low risk of PCI procedural complications and clinical conditions that predict an increased risk of adverse surgical outcomes. However, there is still considerable debate and ongoing controversy concerning the choice of treatment for a given patient. We performed a meta-analysis of randomised, controlled trials comparing CABG and PCI for the treatment of unprotected LM disease.
Methods: The electronic databases MEDLINE, EMBASE and CENTRAL (The Cochrane Controlled Clinical Trials Register) were searched for randomised, controlled trials comparing CABG and PCI for the treatment of unprotected LM disease. Clinical events (death, non-fatal myocardial infarction, stroke and repeat revascularization) occurring during the first year after randomisation were analyzed.
Results: The search strategy identified 3 randomised controlled trials eligible for inclusion enrolling a total of 1011 patients (Buszman 2008; Morice 2010;

Boudriot/Thiele 2011). There was no relevant heterogeneity across trials. No significant differences between the treatment groups could be found for the risk of death (risk ratio [RR] 1.35 [95% CI 0.74 to 2.47], p=0.32) and non-fatal myocardial infarction (RR 1.07 [95% CI 0.58 to 1.98], p=0.83). The risk of stroke was significantly higher with CABG (RR 7.06 [95% CI 1.62 to 30.82], p=0.009) whereas the risk of repeat revascularization was higher with PCI (RR 0.48 [95% CI 0.32 to 0.70], p<0.001).
Conclusion: In this largest series of randomised patients with unprotected LM stenosis to date, the risk of death and myocardial infarction during the first year of follow-up was comparable between CABG and PCI. However, patients undergoing CABG had a higher risk of stroke whereas patients undergoing PCI were at a higher risk for repeat revascularization.

P623 Minimally invasive hybrid myocardial revascularisation. Short and long-term clinical follow-up

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Background: The intentional combination of minimally invasive direct coronary artery bypass grafting (MIDCABG) and percutaneous coronary intervention (PCI), hybrid revascularisation strategy, provides the patients with the advantage of a complete "arterial" revascularisation while avoiding sternotomy and cardiopulmonary bypass. Here we report the short- and long-term results of a minimally invasive hybrid approach in 86 patients.
Methods: Eighty-six patients (66 men and 20 women, aged 63.4±9.3 years) with multivessel coronary artery disease (two-vessel, n=52 and three-vessel, n=34) were referred for hybrid revascularisation combining MIDCAB and fractional flow reserve (FFR)-guided PCI. Surgery consisted of off-pomp beating heart (robotically enhanced) MIDCAB graft of IMA to LAD and/or the first diagonal branch. There were 6 cases (6.9%) of double IMA implantation (right IMA to LAD and left IMA to left circumflex coronary artery). Surgery was performed after successful PCI in 41 cases and prior to PCI in 45 patients. Two patients were converted to open chest surgery. PCI failed in one patient and the lesion was found to be haemodynamically non-significant in 13 patients.
Results: Postoperatively there was one case of re-intervention for bleeding but no significant deterioration of preexistent organ dysfunction was observed. The mean length of in hospital stay was of 8.1±4.4 days (from which in Intensive Care Unit, 1.4±0.9 days). One patient developed transient cerebro-vascular accident post-catheterisation. At 30 days there was no death, no recurrent ischaemia nor need for revascularisation. The mean long-term follow-up was of 50±33.9 months. During this period, 19 patients (22%) had at least one major adverse cardiac event. Eight (9.3%) patients died, three (3.4%) of proven cardiac cause. Four deaths occurred more than 5 years after hybrid revascularisation. There was no documented non-fatal myocardial infarction. Thirteen patients (15.1%) required a repeat PCI, 7 (8.1%) target vessel revascularization, 6 (6.9%) in another vessel, two of these patients requiring also repeat CABG.
Conclusions: Our results indicate that in selected patients with multivessel disease hybrid myocardial revascularization strategy combining FFR-guided PCI and Robotic enhanced MIDCAB is a safe and efficient procedure, providing a functionally complete revascularization with minimal surgical trauma and excellent early and good long-term results.

P624 Clinical outcomes of aortic valve repair in asymptomatic patients with chronic severe aortic valve regurgitation

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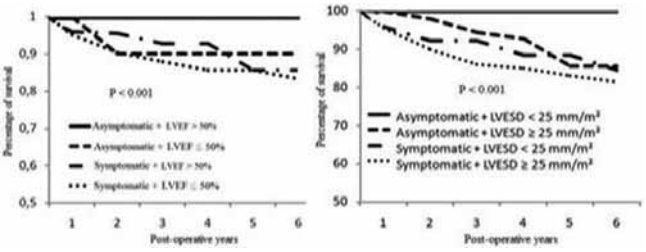
Objective: Surgical management of chronic severe aortic valve insufficiency (AI) in asymptomatic patients with LVEF>50%, LVESD≤55mm and LVEDD≤75mm is still debated and controversial. Although the outcomes of valve replacement have steadily improved, there are several prosthetic valves-related events, especially for younger population. Nowadays, aortic valve repair (AVR) is a useful valid alternative to aortic valve replacement. Aim of our study was to assess the clinical outcomes of AVR in patients with chronic severe AI.
Methods: Since February 2003, 128 patients with chronic severe AI underwent AVR in our institute. There were 62 asymptomatic patients. A perioperative 2D-TTE and 2D-TEE were performed. We assess the impact of AVR on 6-year freedom from cardiac-related deaths and cardiac and valve-related events. We evaluated the late outcomes according to preoperative ejection fraction, symptoms, and LVESD/m^2. Mean follow-up was 36±12 months.
Results: Overall in-hospital death was 1.5%. Survivors were followed prospectively in our out-patient clinic. There were 8 cardiac-related deaths. Actuarial survival rate for asymptomatic vs symptomatic patients were 98.7% vs 86.9%, respectively (p<0.01). Five-years survival rate according with symptoms, LVEF, and LVESD/BSA were illustrated in the figure. Freedom from recurrent aortic valve regurgitation (grade ≥2+) was 96.8%; at follow-up, 7 patients have residual mild AI and 2 patients have moderate AI.



Conclusion: AVR can be performed with low risk and excellent late freedom from valve-related morbidity and mortality. Late survival rate is major in asymptomatic patients and is similar to the one expected for general population matched by sex and age. AVR may be considered for early surgery in asymptomatic patients with normal ejection fraction and LVESD.

P625 The impact of right ventricular function upon 2-year actual cardiac mortality of patients with ischemic mitral regurgitation undergoing mitral valve surgery

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Purpose: The aim of this retrospective study was to evaluate if right ventricular dilatation or dysfunction might affect mid-term actual cardiac mortality of patients with ischemic mitral regurgitation (IMR) undergoing mitral valve surgery (MVS).
Methods: From March 2006 to May 2008, 103 patients with IMR, electively operated on by a single surgeon (AMC), were enrolled in the study. Patients with severe tricuspid regurgitation were excluded from the study due to misleading assessment of tricuspid annular plane systolic excursion (TAPSE); the last item was used to evaluate RV function. Diastolic RV diameter was also evaluated. Follow-up ended at May 2010 and was 100% completed. The primary end-point was 2-year actual cardiac mortality. March 2006 to May 2008, 103 patients with IMR, electively operated on by a single surgeon (AMC), were enrolled in the study. Patients with severe tricuspid regurgitation were excluded from the study due to misleading assessment of tricuspid annular plane systolic excursion (TAPSE); the last item was used to evaluate RV function. Diastolic RV diameter was also evaluated. Follow-up ended at May 2010 and was 100% completed. The primary end-point was 2-year actual cardiac mortality. All the analyses were validated in 1000 bootstrap samples.
All the analyses were validated in 1000 bootstrap samples.
Results: Sixteen patients (15.5%) died by two-year from the operation, 14 due to cardiac cause. Right ventricular diameter (RVD) was inversely correlated to TAPSE (r= -0.349). Thus, logistic regression was performed including either RVD or TAPSE separately. Lower TAPSE (OR=0.71, 95%CL=0.56-0.91) and larger RVD (1.2, 1.1-1.3) were risk factors for increased 2-year actual cardiac mortality regardless of tricuspid surgery. To identify cut-off values of TAPSE and RVD, ROC curve analysis was performed: TAPSE (AUC=0.80) and RVD (AUC=0.83); TAPSE≤15mm (sensitivity=80%, specificity=78.5%, OR=14.5) and RVD≥35mm (sensitivity=80%, specificity=85%, OR=23.5). When both conditions occurred, the risk bristled (OR=47.3).
Conclusions: Right ventricle cannot be still considered "the Cinderella" like cardiac surgery has been done so far, and should be considered in risk stratification. Dilated RV is more often dysfunctioning as well. The presence of both conditions provides the highest risk.

P626 Factors affecting operative indication for moderately dilated ascending aorta in patients with bicuspid aortic valve: relevance of valve anatomy, body size and age

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Purpose: Current guidelines recommend that an ascending aorta wider than 45 mm should be replaced in patients with bicuspid aortic valve (BAV), but limited knowledge exists regarding the appropriate management of a moderately dilated ascending aorta, which is more common in BAV patients. This study aimed to clarify the factors affecting ascending aortic dilatation with regard to BAV anatomy, body size, and age, to allow the development of an appropriate treatment strategy.
Methods: A total of 130 consecutive patients with BAV (87 male, 43 female; mean age, 59.9±16.1 years; mean body surface area (BSA), 1.58±0.20 m^2) who underwent aortic valve surgery between 1993 and 2010 were evaluated. Cusp configuration was classified according to the presence or location of raphe and direction of the cusps. Ascending aortic diameter index (AADI) was calculated using multidetector computed tomography and BSA. The relationships between AADI and age or valve anatomy were evaluated.
Results: (1) Sixty-four patients had vertical BAV (50 with raphe between left and right coronary cusps, 14 without raphe) while 66 patients had horizontal BAV (33 with raphe between right and non-coronary cusps, 9 between left and

non-coronary cusps, 24 without raphe). (2) Mean ascending aortic diameter was 42.6±6.7 mm and mean AADI was 27.1±5.6 mm/m^2. AADI was significantly greater in patients with horizontal BAV than in those with vertical BAV (28.3±6.0 mm/m^2 vs. 25.8±4.9 mm/m^2, p<0.05). However, actual mean ascending aortic diameter did not differ between these groups. (3) In elderly patients (>70 years old), AADIs greater than 28 mm/m^2 occurred more frequently in patients with horizontal BAV than in those with vertical BAV. (4) Among 20 patients with AADIs greater than 28 mm/m^2, ascending aortic replacement was performed ten years later in two patients with horizontal BAV. No patients with vertical BAV required ascending aortic replacement after initial operations.
Conclusions: Relative ascending aortic diameter and valve anatomy were helpful for identifying patients with BAV who were at risk of dilatation, thus enabling appropriate surgical decision-making. Replacement of a moderately dilated ascending aorta in patients with BAV should be considered in patients with horizontal BAV. It is possible to avoid ascending aortic replacement in elderly patients with vertical BAV.

P627 Impact of the introduction of a TAVI program on characteristics of patients undergoing conventional aortic valve replacement

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Background: The adoption of transcatheter aortic valve implantation (TAVI) by a rapidly increasing number of clinical sites is accompanied by concerns that a significant number of patients who would be suitable candidates for conventional surgery are now shifted to TAVI. We therefore compared the clinical characteristics of patients undergoing surgical aortic valve replacement in 12-month periods before and after establishing a joint TAVI program of the cardiology and cardiac surgery departments in our institution.
Methods: A TAVI program was introduced in 2008. Clinical characteristics of all patients undergoing surgical aortic valve replacement (AVR) for atherosclerotic valvular stenosis either in an isolated procedure or in combination with coronary bypass grafting (ACB) between January and December 2007 were compared to data between January and December 2009. In addition, patients who underwent TAVI between January and December 2009 were reviewed.
Results: In 2007 and 2009, a similar number of patients received surgical aortic valve replacement. Clinical characteristics were similar in these groups. Between January and December 2009 55 patients underwent TAVI. The mean age and indicators of surgical risk such as log. EuroScore were significantly higher than in the surgical cohort. The details of the patient data are displayed in table 1.

Table 1

	Surgery 2007	Surgery 2009	Surgery 2007 vs. Surgery 2009	TAVI	TAVI vs. Surgery 2007	TAVI vs. Surgery 2009
AVR+ACB (n)	166	172		55		
PCI prior to TAVI (%)				31		
Age (years)	72±10	73±9	n.s.	81±5	p<0,001	p<0,001
Log. EuroScore	10±10	10±9	n.s.	37±14	p<0,001	p<0,001
LV-EF pre-OP (%)	55±14	56±12	n.s.	47±15	p=0,002	p<0,001
Procedural time (min)	193±85	202±75	n.s.	117±69	p< 0,001	p<0,001
30-day-mortality (%)	9,6	7,5		11		
TIA/Stroke post-OP (%)	1,8	4,6		5,6		
Pacemaker post-OP (%)	4	2		7		

Conclusion: The introduction of a joint TAVI program does not change the number or clinical characteristics of patients undergoing surgical aortic valve replacement. TAVI is offered to additional patients who would not be considered suitable candidates for surgery.

P628 Treating anemia prior to cardiac surgery reduces in-hospital mortality and complications

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Introduction: Anemia is a risk factor for complications and mortality in patients undergoing cardiac surgery. The aim of our study was to evaluate whether correction of hemoglobin (Hb) levels with iron plus erythropoietin (rhEPO) improve in-hospital outcomes and decrease post-operative complications in anemic patients undergoing cardiac valve surgery.
Methods: We compared a historic (1998-2005) cohort of anemic patients undergoing valve replacement (group A; n=63) with a recent (2006-2010) cohort of anemic patients receiving multiple doses of intravenous iron plus rhEPO beginning one month before surgery (Group B; n=64).
Results: Patient's mean age was 72±9 years (68% females). There was no difference in basal hemoglobin between groups (11.1±0.9 g/dl). The only pre-surgery differences between both groups were logistic Euroscore (13 in A vs 18 in B, p=0.009) and pre-operative HB (10.9 g/dl in A vs 12.6 g/dl in B, p=0.001). Aortic valve replacement was the main surgical procedure (56% in A vs 73% in B, p=0.04), with no difference in coronary bypass between groups. Group A had shorter aortic occlusion time and extracorporeal bypass time than group B (62 vs 75 minutes, p=0.008 and 102 vs 110 minutes, p=0.28, respectively). Group A received more blood transfusion (median 3 concentrates in A vs 1 in B, p<0.001). In-hospital mortality was reduced from 22% in group A to 9% in group B (p=0.04). There was a reduction in all post-operative complications (78% in A vs 39% in B, p<0.001). Renal failure was reduced from 52% in A to 23% in B (p=0.001). Severe infection and heart failure were also reduced (23% in A vs 8% in B, p=0.02 and 44% vs 27%, p=0.04, respectively). After adjusting for year of the surgery, logistic Euroscore and extracorporeal bypass time, the use of rhEPO plus iron was identified as an independent predictor of in-hospital mortality (OR 0.15, 95% CI 0.02-0.94; p=0.04) and post-operative morbidity (OR 0.20, 95% CI 0.49-0.86, p=0.03). Length of hospitalization was also reduced in group B (median 14 days in group A vs 9 days in group B, p=0.01).
Conclusions: Treating anemic patients undergoing cardiac surgery with iron plus rhEPO reduces in-hospital mortality, complications and length of hospitalization.

P629 Low cardiac/hypotension syndrome after aortic valve replacement for aortic stenosis: independent predictors and its impact on perioperative mortality

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Objectives: To identify the preoperative predictors of low cardiac output/hypotension syndrome (LCOHS) and its impact in perioperative mortality after aortic valve replacement (AVR) for severe symptomatic aortic stenosis (AS).
Methods: 614 patients who underwent AVR in our institution between 1997 and 2008 for AS were analyzed. LCOHS was defined as a sustained cardiac index < 2.2 L/min and/or hypotension requiring any intervention such volume loading, inotropic-vasoactive drugs support or the need of intra-aortic-balloon counter pulsation. Multivariable logistic regression analyses were performed to identify independent predictors of LCOHS and its impact on perioperative mortality.
Results: LCOHS occurred in 160 patients (26%) of AS patients and was associated with increasing age (p<0.01), female sex (p<0.05), lower EF (p<0.01), absence of preoperative sinus rhythm (p<0.05), higher NYHA class (p<0.01), preoperative pulmonary hypertension (p<0.05) and patient prosthesis mismatch (p<0.05). Perioperative mortality was higher in those patients who presented LCOHS compared with those without it (26% vs. 5%, p<0.01, OR=7.10, CI 95% 4.04-12.48). In multivariable analysis, the risk of LCOHS was independently associated with increasing age, lower EF, NYHA class and PPM. LCOHS was independently associated with an almost 5-fold increase in the risk of perioperative death (OR=5.84, CI 95% 3.02-11.30).
Conclusion: Our data suggest that LCOHS is a frequent complication after AVR for AS and is a strong and independent predictor of the risk of perioperative death.

P630 Emergency extra-corporeal membrane oxygenation in cardiac shock and cardiac arrest in hospital without on-site cardiac surgical facilities

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Purpose: Emergency extra-corporeal membrane oxygenation (ECMO) implantation for severe cardiac shock or refractory cardiac arrest (under cardiac massage), conducted in hospitals with on-site cardiac surgical facilities, has been reported as both safe and effective. We report the feasibility, in-hospital complications and outcomes of ECMO implantation in pts in severe cardiac shock or refractory cardiac arrest in a local hospital without on-site cardiac surgical facilities.
Methods: This single-centre, prospective, consecutive cohort study involved 50 pts who had ECMO implantation (Sept 06-Sept 10). Of these pts, 26 were in severe cardiac shock and 24 in refractory cardiac arrest (16 admitted with refractory out-of-hospital cardiac arrest and 8 developed refractory in-hospital cardiac arrest). Implantations were done via a percutaneous femoral approach by an interventional cardiologist team available 24/7, and in collaboration with the nearest cardiac surgical institution, located 100 km away, to which patients were transferred subsequently.
Results: Patients' mean age was 51±15 yr; 31 (62%) were men. Stable ECMO implantation was achieved in 89% of pts in severe cardiac shock and in 79% in

Patients undergoing ECMO implantation

Outcome	Severe cardiac shock (n=26)	Refractory cardiac arrest (n=24)
Stable EMCO implantation achieved (%)	23 (89)	19 (79)
Median duration of external cardiac massage, min (IQR)	–	90 (43–57)
In-hospital complications (%)	20/23 (87)	18/19 (95)
In-hospital death	10/23 (44)	18/19 (95)

refractory cardiac arrest. In-hospital complications occurred in 20/23 pts in cardiac shock; 13/23 were discharged alive. In-hospital complications occurred in 18/19 pts in refractory cardiac arrest, 15/19 pts were disconnected from ECMO because of brain death or multiorgan failure within 12-36 h, only 1 of whom was discharged alive.
Conclusion: In a hospital with no cardiac surgical facilities, rates of implantation failure, initial complications, and hospital outcomes in pts who had ECMO implantation for severe cardiac shock or refractory cardiac arrest were concordant with previous reports from hospitals with cardiac surgical facilities. We observed a low rate of survival among implanted pts in refractory cardiac arrest.

P631 Intermacs score predicts post-implant survival and resource utilization

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Objectives: Risk stratification of candidates for left ventricular assist device (LVAD) implantation has emerged as an important tool in patient selection and outcomes assessment. The purpose of this study was to determine if a relationship exists between pre-implant INTERMACS score (ITMS) and clinical and economic outcomes among patients implanted with continuous flow LVADs.
Methods: The study included 91 BTT and DT LVAD patients implanted after 7/1/2008. Each patient was categorized according to their ITMS classification at the time of implant, where lower numerical score is associated with increasing acuity. Analysis was stratified by ITMS. Outcomes of interest included survival while on mechanical circulatory support, implant hospitalization length of stay (LOS), and cost of implant hospitalization (Cost). Survival at 30 and 180 days was based on actuarial survival on VAD support where the outcome of interest was dead on support and patients were censored at transplant or loss of follow-up.
Results: Days at risk totaled 21,892 days with a mean follow-up of 251.6 days. Implant hospitalization survival, actuarial survival at 30 and 180 days, LOS, and cost each had an indirect relationship with ITMS (table). Actuarial survival at 180 days was 100%, 97%, 75%, and 63% in the ITMS 4+, 3, 2, and 1 groups.
Conclusions: The INTERMACS classification system is a useful metric for risk stratifying candidates for LVAD implantation. Less acutely ill but functionally impaired heart failure patients receiving continuous flow LVADs as BTT or DT experienced superior outcomes compared to more acutely-ill recipients. These findings suggest that it is necessary to explore the safety and effectiveness of LVADs in the less acutely ill but functionally impaired heart failure population.

P632 Does left ventricular assist device implantation modulate the cardiac cell apoptosis in end-stage heart failure?

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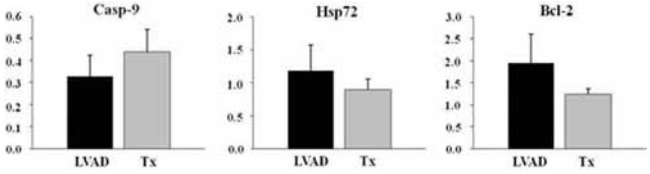
Purpose: In heart failure (HF), the balance between pro- and anti-apoptotic factors has a key role in cardiac cell apoptosis. Appropriate treatments, such as Left Ventricular Assist Devices (LVAD) implantation, could be able to modulate the apoptotic process. Aim of this study was to assess the expression of apoptosis biomarkers in cardiac tissue of severe HF patients with mechanical ventricular support compared to patients submitted to cardiac transplant.
Methods: Seven end-stage HF patients (NYHA class III-IV; age 57±11 yrs; LVEF<20) undergoing LVAD implantation, as bridge to heart transplantation, and seven patients directly driven towards heart transplantation (Tx) were studied. Cardiac tissue biopsies were collected both from left (LV) and right ventricle (RV) and mRNA expression of Caspase (Casp)-3, Casp-9 and their regulatory systems, Bcl-2 and Hsp72, were determined by semi-quantitative RT-PCR analysis. Nitric oxide (NO) expression was also studied. The eEF1A was used as reference gene.
Results: Lower expression levels of Casp-9, associated to higher expression of Hsp72 and Bcl-2, were observed in LVAD compared to Tx, both in RV and LV. The figure shows data relative to LV. In RV Casp-9 0.49±0.12 vs 0.73±0.07, p=ns; Hsp72 2.01±0.72 vs 1.08±0.04 p=ns; Bcl-2 2.88±0.74 vs 1.13±0.42 *p=0.02, LVAD vs Tx. No significant difference in Casp-3 and NO expression was found in all situations.



Pro- and anti-apoptotic factors in LV

Conclusions: These findings suggest that, in end-stage HF, LVAD implant may modulate the apoptotic pathway. The lower expression of Casp-9 and the higher expression of the apoptosis control systems found in LVAD compared to transplant hearts suggest a more favourable balance between pro-apoptotic and anti-apoptotic factors in this condition.

P633 Bench repair of donor mitral valve: common procedure

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Objective: The imbalance between the rising numbers in cardiac transplant candidates, the scarce number of ideal heart donors and the diagnosis of heart disease in some of the previously considered ideal donors stimulated us to adopt pre-implantation heart optimization procedures.
Material and methods: Nine donor hearts (5%), of 189 patients submitted to heart transplantation between Nov/2003 and Dec/2010, in which mitral insufficiency was detected in the pre-transplant echocardiogram or in the pre-implantation test, were submitted to bench mitral valve repair. Mitral annuloplasty was the most common procedure (7 cases, 78%). The heart donors had a median age of 38 years (17-51) and 67% were female. The transplanted patients were 67% male and had a median age of 59 years (51-71).
Results: The median follow-up period was 3.6 years (0.2-7 years). All patients are in NYHA class I and present minimal or mild mitral regurgitation in the echocardiogram, with good left ventricle function. No operative or late cardiac mortality was registered. The median hospital stay was 13 days. Two late mortalities were due to hemorrhagic cerebral event and endocarditis, one case each.
Conclusion: The reduced number of donors is the most limiting factor in heart transplant programs. The good results of bench mitral valve repair in the donor heart, a common procedure in our centre, allowed the inclusion of marginal donors which expanded the pool of possible heart donors, reducing the mortality in patients waiting for transplant.

P634 Higher incidence of gastrointestinal angiodysplasia and bleeding in patients with continuous flow left ventricular assist device

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Background: Continuous flow left ventricular assist devices (LVADs) require combination anticoagulation and antiplatelet therapy. LVAD use has been associated with gastrointestinal tract bleeding. The purpose of this study is to determine the incidence and cause for gastrointestinal bleeding in addition to bleeding risks associated with antiplatelet/anti-thrombotic use.
Methods: A retrospective analysis of 55 patients implanted with Ventrassist 3 (n=33) and HeartWare (n=22) referred for gastrointestinal review was performed. 11 patients underwent endoscopy to investigate active bleeding or anaemia. Incidence was compared against age-standardized population rates. All patients were on warfarin, aspirin and/or clopidogrel.
Results: Of the 55 patients with LVADS implanted, gastrointestinal bleeding was demonstrated in 5 patients (9% of all LVADs). Of these, gastrointestinal angiodysplasia was demonstrated in 4 (80%). 2 patients had gastric antral vascular ectasia (GAVE). 2 patients had colonic angiodysplasia of which one patient required placement of coils to treat haemorrhage. The quoted incidence for angiodysplasia in healthy asymptomatic adults with a mean age of 62 years is 0.8%, of which only 20% actively bleed. We have thus found an increased incidence of angiodysplasia in our LVAD cohort in addition to increased rates of bleeding from these lesions.
Conclusion: To our knowledge, this is the first study to show increased rates of angiodysplasia in patients with continuous flow LVADs. We postulate that this could be due to abnormal gastric tonometry due to lack of blood pressure pulsatility. Increased expression of vascular endothelial growth factor (VEGF) which

Abstract P627 – Table 1. Outcomes and cost by ITMS Class

ITMS	N	Survival			Hospital LOS (days)	ICU LOS (days)	Cost ($)
		Implant Survival (%)	30 Actuarial Survival (%)	180 Actuarial Survival (%)	Mean±SD	Mean± SD	Mean ± SD
4+	6	100	100	100	15.3±4.6	3.0±3.2	175,772.00±21,712.53
3	33	93.9	100	96.9	18.4±9.9	4.5±6.3	274,795.63±71,538.88
2	29	79.3	92.6	74.5	29.8±21.9	6.7±6.3	318,799.19±118,512.63
1	23	65.2	72.7	63.3	19.9±14.7	7.5±6.3	330,361.32±104,159.59
Total	91	82.4	90.8	81.9	22.1±16.2	5.9±10.9	295,673.78±102,022.38

contributes to remodelling of the supported ventricle could also contribute to the pathogenesis of angiodysplasia. Increased rates of bleeding from these lesions could be due to acquired von Willebrand syndrome due to break-down of the large vWB multimers, recently described in literature.

NEW TECHNICAL APPROACHES IN STENTING

P635 Pathology of second- versus first-generation drug-eluting stents in humans: does safety issue still exist?

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Purpose: First-generation sirolimus- (SES) and paclitaxel- (PES) drug-eluting stents (1st-gen DES) have dramatically reduced restenosis, whereas concern still exists about the long-term safety with reference to late stent thrombosis (LST). Second-generation zotarolimus- (ZES) and everolimus-eluting stents (EES) (2nd-gen DES) have been developed as safer stenting, and several clinical studies have reported a lower incidence of LST in 2nd-gen than 1st-gen DES. The primary pathologic substrate underlying LST in 1st-gen DES is a lack of complete endothelialization; however, little is known about the pathologic findings of 2nd-gen DES in humans. We sought to evaluate the vascular response to 2nd-gen DES as compared to 1st-gen DES in human coronary arteries.
Methods: The overall analysis included 256 DES lesions (174 cases) with duration of implant >30 days (1st-gen DES=233 [115 SES, 118 PES] and 2nd-gen DES=23 [6 ZES, 17 EES]). Histomorphometric findings in 2nd-gen DES were compared to those in 1st-gen DES with similar duration of implant to 2nd-gen DES (≤2 years, n=136).
Results: Age, sex, and risk factors were similar between 1st-gen vs. 2nd-gen DES. Although 1st-gen DES had longer duration of implant than 2nd-gen DES (330 [137-540] vs. 180 [99-360] days, p=0.04), LST was more frequent in 1st-gen than 2nd-gen DES (21% vs. 4%, p=0.05). Only 1 lesion with LST in 2nd-gen DES was EES implanted over an underlying PES. The results of histomorphometric analysis are shown in Table. The percentage of uncovered struts were significantly lower in 2nd-gen DES, while mean neointimal thickness was similar between 1st- and 2nd-gen DES. Fibrin deposition was also less in 2nd-gen as compared to 1st-gen DES.

Morphometry of 1st- versus 2nd-gen DES

	1st-gen DES (n=136) (median; 7.0 months)	2nd-gen DES (n=23) (median; 6.0 months)	P value
Uncovered struts (%)	20.0 (6.7, 50.0)	2.0 (0.0, 5.2)	<0.001
Mean neointimal thickness (mm)	0.11 (0.05, 0.18)	0.17 (0.08, 0.30)	0.158
Inflammation score	1.0 (0.5, 1.5)	0.5 (0.2, 1.8)	0.335
Struts with fibrin (%)	48 (21, 65)	15 (0, 28)	<0.001
Maximum number of eosinophils per strut	4.1±11.1	0.8±2.4	0.154

Values are expressed as median (interquartile range) or mean ± SD.

Conclusions: Second-gen DES shows a lower incidence of LST and substantially less uncovered struts with similar neointimal thickness as compared to 1st-gen DES in humans. The current pathologic findings are predictive of greater clinical safety of 2nd-gen DES.

P636 Latest results from the pooled RESOLUTE clinical program

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Purpose: We will present results from a novel zotarolimus-eluting stent (R-ZES), a new-generation drug-eluting stent consisting of a thin-strut cobalt alloy bare-metal stent (BMS) and a novel biocompatible, non-inflammatory, durable polymer. Since individual trials are often underpowered to show real differences in rare adverse clinical events, the R-ZES is being studied in a series of clinical trials prospectively planned to allow pooled analysis of clinical endpoints. This clinical program comprises 5 trials prospectively designed with similar data collection procedures; adverse event definitions and adjudication procedures; statistical programming algorithms; and datasets.
Methods: Over 5,000 patients treated with the R-ZES were pooled from 5 trials: the RESOLUTE first-in-human study (N = 139); the RESOLUTE All Comers randomised, non-inferiority trial, comparing R-ZES (N = 1140) with the XIENCE V everolimus-eluting stent (N=1152); the confirmatory, open label, RESOLUTE International study (N=2349); RESOLUTE Japan (N=100); and RESOLUTE United States (N=1402). We will present the pooled safety and efficacy outcomes for the latest follow-up from each trial overall and for important clinical subgroups such as patients with diabetes mellitus. All trials recommended a minimum of six months dual antiplatelet therapy.
We will also compare 596 BMS patients from the control arm of the ENDEAVOR II randomised trial to a subset of the pooled R-ZES patients (n = 2455) with the same inclusion criteria as the ENDEAVOR II study. We will adjust for patient and between-trial variations using the propensity score method.
Results: We plan to report pooled patient-level long-term safety results for all-cause mortality, as well as cardiac death, myocardial infarction and stent thrombosis; and efficacy including ischemia-driven target lesion and target vessel revascularization. Rates of dual antiplatelet therapy compliance will be reported.
Conclusion: In August 2011, we will report pooled safety and efficacy of this novel zotarolimus-eluting stent in over 5000 patients followed to one year and over 3000 patients followed to two years.

P637 Clinical benefits of zotarolimus-eluting stents compared with paclitaxel-eluting stents: a meta-analysis of randomised controlled trials

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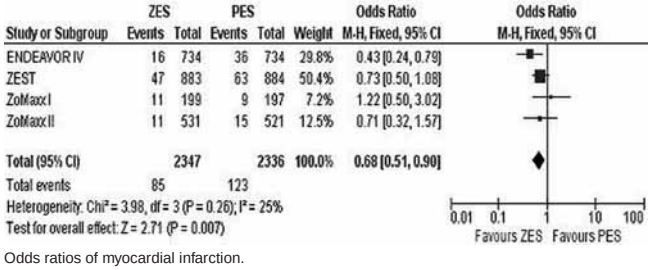
Purpose: Zotarolimus-eluting stent (ZES) is a second generation drug-eluting stent. However, its efficacy and safety compared with first generation drug-eluting stents, for example paclitaxel-eluting stents (PES), are controversial according to several clinical trials. The purpose of this study was to evaluate the efficacy and safety of ZES comparing with PES.
Methods: A meta-analysis was performed on randomised controlled trials (RCT) comparing ZES with PES in patients with coronary artery disease undergoing percutaneous coronary intervention. The databases searched for RCT included PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, the U.S. National Institute of Health, and TCTMD.
Results: A total of 4 RCT were included in this meta-analysis, involving 4693 patients (2347 patients were randomised to ZES and 2346 patients were randomised to PES). At 9 months to 3 years, the rate of target lesion revascularisation in ZES was similar to that in PES (odds ratio: 1.16, 95% confidence interval: 0.71-1.88, p=0.56) On the other hand, ZES showed a significant reduction in myocardial infarction compared with PES (Figure), even though there was no difference in death (odds ratio: 0.98, 95% confidence interval: 0.66-1.46, p=0.91) between the 2 groups.



Odds ratios of myocardial infarction.

Conclusions: In this meta-analysis, ZES was associated with similar efficacy and decreased incidence of myocardial infarction compared to PES during up to 3 years.

P638 Long term tissue coverage of a bioresorbable polylactide polymer-coated biolimus-eluting stent: comparative sequential assessment with optical coherence tomography till complete resorption of the poly

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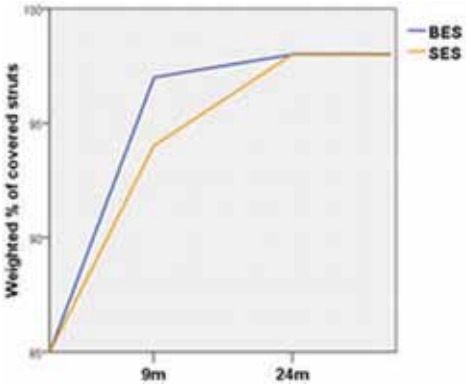
Purpose: To assess the tissue coverage of a biolimus-eluting stent (BES) with bioresorbable polymer in abluminal coating at 24 months, when the polymer has been completely resorbed, as compared to a control sirolimus-eluting stent (SES) with durable polymer, using optical coherence tomography (OCT).
Methods: The LEADERS randomized trial (NCT00389220) compared the performance of BES vs. SES in a non-selected population of patients with coronary heart disease. Patients recruited for the angiographic substudy of this trial at prespecified OCT sites were enrolled in the OCT substudy, with strut coverage at 9 and 24 months as primary outcome. The results in both study groups were compared using a bayesian hierarchical model, to overcome the problem of clustering at the levels of patient and lesion.
Results: 56 patients (26 BES, 30 SES) were enrolled in the OCT substudy. At 24 months 21 patients (10 BES, 11 SES) agreed to perform a second OCT follow-up. Eleven lesions, 12 stents were sequentially analyzed in the BES group (2455 struts at 9 months, 2131 struts at 24 months) and 11 lesions, 18 stents in the SES group (3421 struts at 9 months, 4170 struts at 24 months). Initial advantage of BES over SES in terms of better strut coverage at 9 months was followed by improvement in coverage of the SES between 9 and 24 months, resulting in



Trend of coverage at 9-24 months.

identical coverage in both BES and SES at 24 months: 1.5 vs. 1.8%, difference -0.2%, 95% Credibility Interval -3.2 to 2.6%, p=0.84.
Conclusions: More complete strut coverage of BES as compared with SES at 9 months was followed by improvement of coverage in SES between 9-24 months and similar long-term OCT coverage in both stent types at 24 months.

P640 Long-term local inflammatory and coagulative responses after coronary artery stenting with drug-eluting stent

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Purpose: The long-term effects of drug-eluting stent (DES) on coronary local inflammation and coagulative response are not known. We evaluated the local release of pentraxin3 (PTX3) and prothorombin fragment F1+2 (frF1+2) as a local inflammatory and coagulative marker respectively in nonrestenotic coronary arteries more than six months following DES and bare metal stent (BMS) implantation.
Methods: Eighty-seven patients treated six months earlier with a coronary stenting for isolated proximal left anterior descending arterial stenosis, with no evidence of restenosis, were studied. Forty patients had been stented with BMS, 47 with sirolimus-eluting stent (SES). We measured serum PTX3 and frF1+2 levels sampled in coronary sinus (CS) and sinus of Valsalva (V). The translesional PTX3 and frF1+2 gradients (Δ) were defined as CS level minus V level.
Results: There were no significant differences in coronary risk factors between the two groups. The ΔPTX3 and ΔfrF1+2 were larger in the SES group than in the BMS group (0.14$\pm$0.09 vs 0.01$\pm$0.06 ng/ml, $p<0.01$ and 29$\pm$19 vs 5$\pm$14 pmol/l, $p<0.05$, respectively). The ΔPTX3 correlated positively with the ΔfrF1+2 ($r=0.56$, $p<0.01$) in the SES group, whereas there were no significant correlation in the BMS group.
Conclusions: More increased local inflammatory response was observed and related with local hypercoagulability long term after DES implantation. These findings may be associated with late catch-up phenomenon and further progression of coronary atherosclerosis.

P641 Long-term follow-up after coronary stenting with the sirolimus-eluting stent in clinical practice. Results from a substudy of the prospective multi-centre German cypher stent registry

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Background: In April 2002 the Sirolimus-eluting stent (SES) was introduced for percutaneaous coronary interventions (PCI). Meanwhile there is accumulating data on short and midterm results with this stent. However, long-term follow-up data from unselected patients treated with the SES in clinical practice is still sparse.
Methods: We analysed data from a substudy of the German prospective multicentre Cypher Registry.
Results: Between April 2002 and September 2005 5946 patients at 16 hospitals were treated with at least one SES. A follow-up after a median of 4.1 years (Q1 3.2, Q3 4.9 Jahre) was obtained in 5247 patients.
Mean age was 65.4 Jahre with a male gender in 75.8% of patients. Indications for SES implantation were: stable angina pectoris in 46.9%, unstable angina in 17.5%, NSTEMI in 10.7% and STEMI in 10.7% of patients. Clinical events until the end of follow-up are given in the table.
Multivariate analyses showed clinical characteristics to be the leading predictors for clinical events (age, diabetes, indikation AMI, 3-VD, renal failure, prior MI), whereas interventional characteristics were the main predictors for TVR (target vessel = venous bypass graft, 3-VD, treatment of >1 stenosis during the index PCI).

Events during follow-up	Rates (%)
Death	9.2% (486/5269)
Myocardial infarction (in survivors)	5.9% (282/4756)
Stroke (in survivors)	2.2% (106/4753)
MACCE (Death/myocardial infarction/stroke)	16.3% (861/5269)
Any revascularisation (PCI/CABG)	34.9% (1745/4997)
Any TVR	20.3% (977/4820)
Target vessel revascularization by PCI	15.7% (756/4820)
Target vessel revascularization by CABG	4.6% (221/4820)
MACCE or TVR	32.6% (1701/5269)

Conclusions: Clinical event rate (MACCE) after SES in clinical practise after a median follow-up of 4.1 years was 16.3%. TVR rate was 20.3%, consisting predominatly of further PCIs (15.7%).

P642 Frequency and predictors of drug eluting stents implantation in patients with acute myocardial infarction - analysis from the PL-ACS Registry

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Drug eluting stents (DES) use in patients with acute myocardial infarction (AMI) is still under debate. The purpose of this study was to assess the frequency and predictors of DES use in patients with AMI.
Methods: All patients with NSTEMI (N=25005) and STEMI (N=52854) treated by PCI with stenting, registered in the Polish Registry of Acute Coronary Syndromes (PL-ACS) from 10.2003 to 11.2009, were included.
Results: The frequency of DES use in AMI raised from 0.4% in 2003 to 5.9% in 2009. The predictors of DES use are shown in the table. 12-months mortality was significantly lower in patients who received DES compared to bare-metal stent (6.7% vs. 9.9%, $p<0.0001$). However, after multivariate adjustment for differences in baseline characteristics implantation of DES was not associated with lower 12-month mortality (relative risk = 0.85, 95%CI = 0.67-1.08, p=0.19).

Table 1

	Odds ratio (95% confidence interval)	P value
AMI due to restenosis or reocclusion	3.97 (3.29–4.78)	<0.0001
Infarct related artery - LM	2.68 (2.07–3.47)	<0.0001
NSTEMI (vs. STEMI)	2.10 (1.91–2.31)	<0.0001
Initial TIMI flow grade > 0	1.84 (1.68–2.03)	<0.0001
Diabetes mellitus	1.61 (1.47–1.77)	<0.0001
Prior myocardial infarction	1.46 (1.30–1.63)	<0.0001
Age (per 10 years less)	1.31 (1.26–1.36)	<0.0001
Females	1.18 (1.07–1.30)	0.0006
Prior bypass surgery	1.18 (0.98–1.42)	0.080
Infarct related artery - bypass	1.09 (0.77–1.57)	0.62
Left ventricle ejection fraction ≤ 40%	0.94 (0.79–1.13)	0.52
Infarct related artery - LAD	0.89 (0.81–0.99)	0.027
Cardiogenic shock on admission	0.88 (0.67–1.15)	0.36
Infarct related artery - RCA	0.47 (0.41–0.53)	<0.0001
Bypass surgery planned after PCI	0.45 (0.34–0.59)	<0.0001

LAD = left anterior descending, LM = left main, RCA = right coronary artery.

Conclusion: The use of DES in selected patients with AMI seems to be safe. DES are more frequently use in restenosis or reocclusion, LM, NSTEMI, open arteries, diabetics, younger patients, and females, being avoided in patients being referred to bypass surgery.

P643 Facilitated culottes in coronary artery bifurcation stenting using a dedicated side branch stent: two years clinical outcome

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Objectives: Treatment of coronary bifurcation lesions with stenting has been associated with increased complication rate and remains a major challenge in intervention cardiology. Introduction of DES reduced restenosis in the main branch. However, restenosis at the ostium of the side branch remains a problem. As part of an international registry we evaluated the clinical safety and efficacy of Tryton a dedicated side branch stent. In this study we sought to determine the clinical

outcome of facilitated culottes in coronary artery bifurcation stenting using Tryton stent.
Methods and results: We prospectively looked at 157 consecutive patients who had bifurcation lesion and treated with Tryton stent. Males constitute 80% with mean age of 68 and 33.7% were age above 70 years. The target lesion was LAD/Diagonal bifurcation in 54.0%, LCX/OM in 30.5% and RCA bifurcation in 15.5%. All were de novo lesions and cases of CTO, graft lesions and ISR were not included. Stent was successfully implanted in 98.6% and there was one case of proximal migration of stent after fully deployed. Dissection at distal edge of Tryton occurred in 8 cases and treated with DES. Clinical follow up was completed in all patients and all stayed on aspirin and clopidogrel. Over a period of 12-24 months follow up, there was no cardiac death, emergency CABG or acute/sub-acute stent thrombosis. Over all incidence of major adverse cardiac event (MACE) was 14.4% and target vessel revascularisation was encountered in 5.8%. There were 18 admissions for non-related medical conditions and 12 cases for elective PCI to a different coronary artery.
Conclusion: Dedicated side branch stent allows easy access into side branch and in this early clinical study it appears to be safe and effective. The risk of late stent thrombosis, instent restenosis and long term clinical outcome is yet to be seen.

P644 Inter-strut distance is a significant predictor of restenosis in human coronary drug-eluting stent implants

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Purpose: Drug-eluting stents (DES) continue to present restenosis, yet the mechanisms of which remain poorly understood.
Methods: From 244 stented coronary segments implanted for >30 days in the CVPath autopsy registry, 51 segments from 42 patients were selected for histologic review with exclusion criteria of left main or saphenous vein graft disease, late stent thrombosis, the ratio of uncovered to total struts >30% at any sections, and chronic total occlusion. The stented lesions were stratified into 3 categories based on the most severe cross-sectional stenosis, and designated as: i) Patent (<50%, n=21), ii) Intermediate (50-75%, n=18), and iii) Restenosis (>75%, n=12). Area measurements were performed for EEL, stent, lumen, with further attention to neointimal thickness, and inter-strut distances. Known predictors of restenosis for BMS such as medial disruption and strut penetration into necrotic core was also accessed (Circulation. 2002;105:2974-80).
Results: There were no differences in overall underlying plaque morphologies among study groups. Of the measured parameters, notable differences were only observed for the normalized maximum inter-strut distance (Patent: 1.52±0.23, Intermediate: 1.61±0.23, Restenosis: 1.85±0.40, p=0.009). Medial disruption was more frequent for stents with restenosis and intermediate stenosis albeit without statistical significance. Strut penetration into the necrotic core was observed solely in patent and intermediate groups.

Table. Histomorphometric analysis of DES stratified by cross-sectional stenosis

	Restenosis (>75%)	Intermediate (50-75%)	Patent (<50%)	P value
Total stented length, mm	27.0±15.4	25.0±10.7	17.6±8.4	0.04
EEL area, mm²	10.8±3.6	9.0±4.0	11.0±3.7	0.21
Stented area, mm²	5.0±1.3	5.1±1.9	6.1±2.1	0.06
Lumen area, mm²	0.6±0.2	1.8±0.7	3.8±1.8	<0.0001
Underlying plaque, mm²	5.8±3.2	3.8±2.8	5.0±2.5	0.13
Neointimal area, mm²	4.4±1.3	3.3±1.3	2.2±0.6	<0.0001
Stenosis, %	87±4	64±7	38±8	<0.0001
Neointimal thickness, mm	0.69±0.17	0.37±0.08	0.19±0.07	<0.0001
Inter-strut distance				
Mean, mm	0.99±0.32	0.92±0.21	1.03±0.27	0.46
Maximum, mm	1.76±0.40	1.49±0.39	1.53±0.31	0.15
Normalized maximum*	1.85±0.40	1.61±0.21	1.52±0.23	0.009
Media disruption, %	50	56	24	0.10
Strut penetration into necrotic core, %	0	17	19	0.13

*Normalization was performed by following formula: maximum / mean distance per section.

Conclusions: Unlike BMS, restenosis of DES appears to be independent of strut penetration into necrotic core however, the extent of medial injury and the distribution of the anti-proliferative drug (dependent on inter-strut distance) is the best predictors of restenosis.

P645 Very long-term clinical outcomes of sirolimus-eluting stents in an unselected real-world population

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Background: It has been shown that sirolimus-eluting stents (SES) are highly effective in preventing angiographic and clinical restenosis, and therefore target vessel revascularisation (TVR). However, there are very few published data concerning the very long-term (>5-year) efficacy and safety of SES. The aim of this prospective cohort study was to examine the clinical outcomes of the first consecutive patients who underwent SES implantation at our institution.
Methods: We prospectively followed up all of the consecutive patients who were treated with SES during the first 24 months of its use at our centre.
The incidence of major adverse cardiac events (MACE, including cardiac death, myocardial infarction [MI] and TVR) was evaluated, as well as target lesion revascularisation (TLR) and stent thrombosis.
Results: Between April 2002 and March 2004, 300 patients (75% males; mean age 65±11 years) underwent percutaneous coronary angioplasty with the implantation of 382 SES. High risk features were common and included diabetes (23%), acute coronary syndromes and ST-elevation MI (50%), three-vessel coronary disease (23%), a reduced ejection fraction (32%), and complex coronary lesions (69%).
The 6- and 7-year follow-up was completed by respectively 298 (99%) and 145 patients (48%), for a mean duration of 1886±640 days.

Study results

	Number of events (N)	Incidence (%)
MACE	76	25.0
Cardiac Death	29	9.6
Myocardial infaction	46	15.3
TVR	46	15.3
TLR	23	7.6
Definite Stent Thrombosis	9	3.0
Definite + probable stent thrombosis	12	4.0
Total mortality	57	19.0

Conclusions: This analysis of an unselected real-world population confirms the efficacy and safety of SES after very long-term follow-up, with a very limited need for repeat revascularisation and an acceptable rate of stent thrombosis.
The rather high incidence of adverse events and their constant rate throughout the follow-up period can be attributed to the patients' high clinical risk.

P646 The association between stent fracture and peri-stent contrast staining after drug-eluting stent implantation

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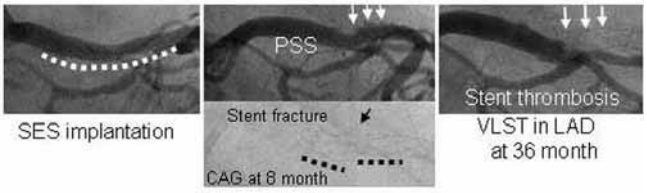
Purpose: Stent fracture (SF) is sometimes observed after drug-eluting stent (DES) implantation and known as one of risk factor for stent thrombosis. Peri-stent contrast staining (PSS) is an angiographical finding that contrast medium stain outside the stent and is also thought to be one of the risk factor for very late stent thrombosis (VLST). However the association between SF and PSS after drug-eluting stent (DES) implantation is little known. The aim of this study is to clarify the the association between SF and PSS after drug-eluting stent (DES) implantation.
Methods: We retrospectively analyzed 6526 lesions after DES implantation including sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), and zotarolimus-eluting stent (ZES). SF is defined as the separation of stent segments or stent struts. PSS is defined as vessel enlargement, with contrast medium staining outside the stent, over 20% of stent diameter.
Results: Figure shows a case of SF coexisting with PSS after SES implantation. This patient occurred VLST at 36 month after SES implantation. SF were observed in 291 of 5275 SES lesions (5.5%), 35 of 872 PES (4.0%), and 8 of 379 ZES (2.2%). PSS were found in 40 of 291 SES lesions with SF (13.7%), 5 of 35 PES (14.2%), and 0 of 8 ZES (0%). In SES and PES lesions, we observed PSS more frequently in lesions with SF than did in those without SF (P<0.001).



Stent fracture coexisting with PSS

Conclusion: There is a clear association between SF and PSS in lesions after SES and PES implantation, not ZES. Further examination about the association among SF, PSS, and VLST is needed.

P647 Scanning electron microscopic observation of coating irregularities and their precursors in unexpanded durable polymer-based drug-eluting stents

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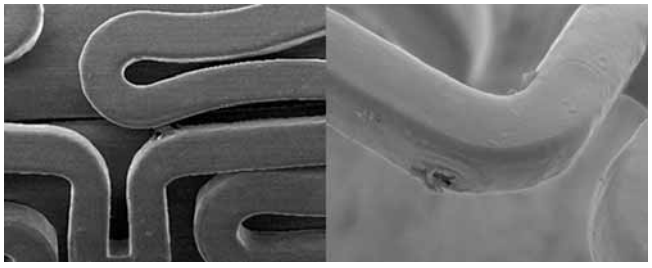
Purpose: To assess coating irregularities on unexpanded and expanded durable polymer-based drug-eluting stents (DES) with the purpose of gaining insights into the potential origin of coating irregularities.
Background: Previous scanning electron microscopy (SEM) studies in various expanded DES revealed differences in the incidence and size of coating irregularities between DES types and specific distribution patterns.
Methods: We assessed at bench-side a total of 600 SEM images obtained in 20 DES samples (expanded and unexpanded) of Cypher Select Plus, Taxus Liberté, Endeavor Sprint, Xience V, and Endeavor Resolute.
Results: For most types of coating irregularity seen in expanded DES (66%; 21/32), a matching irregularity (n=14/21) and/or its precursor (n=13/21) was observed in unexpanded samples of corresponding DES. Only few individual coating irregularities (13%; 4/32) could not be accessed in unexpanded samples, as these irregularities were typically located on the (invisible) luminal side. Unexpanded Cypher Select showed (small) crater lesions and cracks together with precursors of "peeling of polymer". Thinning of polymer and wrinkles were found on unexpanded Taxus Liberté together with one type of precursor. Unexpanded phosphorylcholine-based Endeavor stents showed cracks and crater lesions as well as precursors of the latter, while unexpanded Xience V and Endeacor Resolute samples revealed only crater lesions and their precursors.



Crater (right) and its precursor (left).

Conclusions: Scanning electron microscopic assessment demonstrated the presence of various coating irregularities and/or their precursors on unexpanded durable polymer-based DES. These findings provide some insights into the origin of DES coating irregularities, suggesting that coating irregularities may arise during both DES manufacturing and stent expansion.

P649 Duration of dual antiplatelet therapy after coronary stenting with the genous Bio-engineered R stent in patients from the e-HEALING registry

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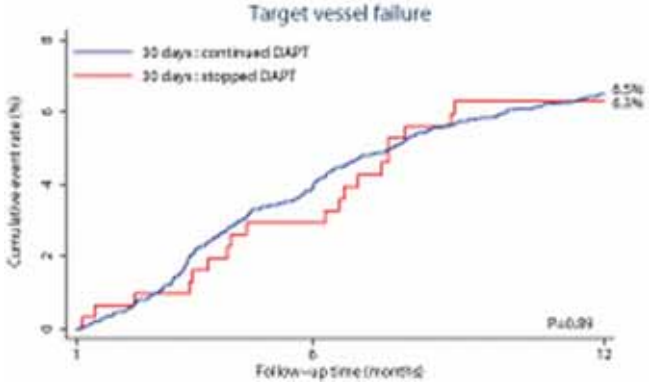
Purpose: Investigate the relation between duration of dual antiplatelet therapy (DAPT) and 1-year outcomes after Genous™ Endothelial Progenitor Cell capturing R stent™ placement in the e-HEALING registry
Methods: Patients were analyzed according to continuation or discontinuation of DAPT at a 30-day (n=4249 & 309) and 6-month (n=2654 & 1408) landmark,



excluding patients with events occurring prior to the landmark. Each landmark was used as a new baseline, and outcomes were followed up to 12 months after index procedure. The main outcome for our current analysis was Target Vessel Failure (TVF), defined as target vessel-related cardiac death or myocardial infarction and target vessel revascularization. Secondary outcomesincluded stent thrombosis (ST). (Un)adjusted hazard ratios (HR) for TVF were calculated with Cox regression models.
Results: No difference was observed in the incidence of the main outcome TVF (HR 1.03 [95% CI: 0.65-1.65, p=0.89] in patients continuing DAPT at 30 days versus patients stopped, and HR 0.82 [95%CI: 0.55-1.23, p=0.34] in patients continuing DAPT at 6 months versus patients who stopped DAPT). Furthermore, no statistical differences were observed in ST. The adjusted TVF hazard was comparable in patients continuing or who stopped DAPT at 1 or 6 months, after addition of identified independent predictors for TVF.
Conclusion: In the e-HEALING registry, duration of DAPT was not associated with the occurrence of theoutcomes TVF or ST. The Genous stent may be an attractive treatment especially in patients at increased risk for (temporary) cessation of DAPT or with anincreased bleeding risk.

P650 Sustained clinical safety and efficacy of a biodegradable-polymer coated sirolimus-eluting stent in real-world practice: 4-year outcomes of the CREATE study

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Background: The CREATE is a post-marketing surveillance multicenter registry that demonstrated satisfactory angiographic and clinical (at 18 months) outcomes of a biodegradable polymer based sirolimus-eluting stent (EXCEL, JW Medical System, Weihai, China) for the treatment of patients in routine clinical practice. The aim of this study was to evaluate the 4-year clinical safety and efficacy outcomes in patients enrolled in the CREATE study.
Methods: A total of 2077 all comers have been enrolled in the CREATE study at 59 centers from 4 countries. Recommended antiplatelet regimen was clopidogrel and aspirin for 6 months followed by chronic aspirin therapy. The primary outcome of this study was the rate of major adverse cardiac events (MACE) at 4 years.
Results: Clinical follow-up was completed in 2008 (96.7%) patients at 4 years. The mean duration of dual antiplatelet therapy was 199.8±52.7 days. The 4-year cumulative rates of all-cause death, cardiac death, myocardial infarction, target lesion revascularization and MACE were 4.6%, 2.0%, 0.8%, 2.8% and 5.0%, respectively. Stent thrombosis had developed in 34 patients (1.69%), including 2 (0.1%) acute, 8 (0.39%) subacute, 7 (0.34%) late, and 17 (0.85%) very late stent thrombosis. The occurrence of definite or probable stent thrombosis was 1.2%. A landmark analysis showed that the cumulative primary events-free survival rate during 6-month to 48-month were not significantly different between patients had clopidogrel treatment 6 months and >6 months (94.1% vs 94.0%,P=0.933)
Conclusions: This study demonstrates sustained 4-year clinical safety and efficacy of biodegradable polymer based sirolimus-eluting stents when used with 6 months of dual antiplatelet therapy in a "real-world" setting.

P651 Comparison of peri-stent vascular response after sirolimus and paclitaxel-eluting stent implantation

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Objectives: Peri-stent vascular responses to DES have been incompletely understood with different DESs. Serial intravascular ultrasound was used to study chronic arterial responses and edge effects after implantation of Sirolimus-eluting stent (SES) or Paclitaxel-eluting stent (PES).
Methods: Two hundred-two angina patients (123 men; 61.5±9.2 years of age) were assigned to SES (n=91) or PES (n=111) implantation. Intravascular ultra-

sound of 5-mm long segments immediately proximal and distal to the stent was performed to determine volume and area of Vessel, Plaque, Lumen after the procedure and at the 9-month follow-up. The change (Δ) of each parameters between postprocedure and follow-up was calculated
Results: In proximal reference segment, the Δ Vessel, Δ Plaque and Δ Lumen volume were not different between two groups. The Δ Plaque volume, however, increased more in PES than SES in distal reference segment (6.6±15.7 vs 1.0±13.1 mm^3, P=0.016). In proximal 1mm and distal 1mm reference segments, mean Lumen area decreased because of negative remodeling (proximal, 9.9±2.4 to 9.4±2.6 mm^2, P=0.004; distal, 7.6±2.4 to 7.2±2.4 mm^2, P=0.052) with plaque progression (proximal, 1.9±1.5 to 2.2±2.0 mm^2, P=0.095; distal, 0.6±1.1 to 1.0±1.4 mm^2, P=0.018) in the PES group. Conversely, mean Lumen area increased because of plaque regression (proximal, 3.2±1.8 to 2.1±1.6 mm^2, P=0.000; distal, 1.5±1.4 to 0.9±1.3 mm^2, P=0.000) even though there was negative remodeling in the SES group (proximal, 10.1±2.4 to 9.6±2.3 mm^2, P=0.019; distal, 7.8±2.3 to 7.5±2.3 mm^2, P=0.074). The Δ Plaque and Δ Lumen at proximal and distal reference segment were more prominent in the PES group than the SES group (table).

Area (mm^2)	Proximal 1 mm to Stent		P	Distal 1 mm to Stent		P
	SES	PES		SES	PES	
ΔEEM	–0.5±1.8	–0.5±1.6	0.967	–0.3±1.2	–0.3±1.6	0.748
ΔPlaque	–1.1±1.9	0.4±2.0	0.000	–0.7±1.4	0.3±1.4	0.000
ΔLumen	0.7±1.6	–0.6±2.1	0.000	0.6±1.4	–0.6±1.5	0.000

Conclusions: The PES implantation was associated with luminal reduction accompanied by negative remodeling with plaque progression. These findings, however, were not noted in the SES group.

P652 Incidence, risk factors, and clinical sequelae of angiographic peri-stent contrast staining after sirolimus-eluting stent implantation

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Background: We have noted abnormal angiographic findings at the site of drug-eluting stents implantation suggesting contrast staining outside the stent struts that do not fulfill the classical definition of coronary artery aneurysm. We propose a new term, namely peri-stent contrast staining (PSS), for these abnormal angiographic findings and assess their incidence, risk factors and clinical sequelae.
Methods and results: PSS was defined as contrast staining outside the stent contour extending to >20% of the stent diameter. The study population consisted of 3081 lesions (1998 patients) that were treated exclusively with sirolimus-eluting stents (SES) and were evaluated by follow-up angiography within 12 months after SES implantation in a single center. Late acquired PSS was observed in 58 lesions (1.9%) in 49 patients (2.5%). Independent risk factors of PSS was chronic total occlusion, while negative risk factors for PSS were left circumflex coronary artery lesion and in-stent restenosis lesion. Stent fracture was more frequently observed in lesions with PSS than in lesions without PSS (43.1% vs. 5.4%, p<0.0001). Excluding 269 lesions with target-lesion revascularization (TLR) within 12 months, the study population for long-term follow-up consisted of 51 lesions (42 patients) with PSS and 2761 lesions (1751 patients) without PSS. Cumulative incidence of TLR and definite very late stent thrombosis (VLST) at 3 years in the PSS group was higher than that in the non-PSS group (15.0% versus 6.5%, and 8.2% versus 0.2%, respectively).
Conclusions: PSS found within 12 months after SES implantation appeared to be associated with subsequent TLR and VLST.

P653 Sequential side-main-side vessels balloon dilation (SMS technique) for bifurcation lesions treated with provisional stenting

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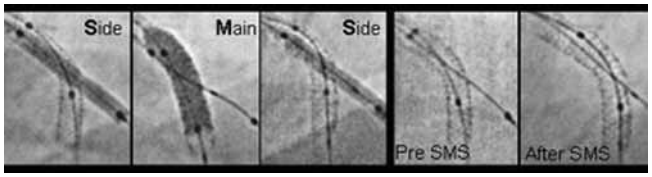
Final kissing balloon is often used in provisional stenting of bifurcation lesions but it may induce an asymmetry in the proximal stent, being recently questioned. Objective.To evaluate the scaffolding and changes in stent geometry with a new sequential balloon dilation technique which we called SMS-technique with IVUS.
Methods: 57 patients (pts) with a true bifurcation coronary lesion (LM 3,LAD 43,LCx 10,RCA 1) were treated with the SMS-technique (figure).Stent diameter was selected using the distal main branch (MB) reference, then side branch (SB) balloon angioplasty (S) was performed with a balloon selected according to its diameter.Another balloon, selected according to the proximal MB reference diameter, was inflated proximally and at the carinal region (M).Final balloon angioplasty of the SB was again performed (S).IVUS study was performed at each step.
Results: Primary success was obtained in all lesions.Two pts needed a second stent (3%).Table shows the IVUS data at each step.No MACE were recorded during the follow-up (9±4 months).

Quantitative IVUS findings (*p<0,01)

	In-stent proximal (mm^2)	Under the SB origin (mm^2)	In-stent distal (mm^2)
Baseline MB stent	7,13±1,44	6,67±1,75	6,70±1,53
(S) SB angioplasty	7,19±1,52	5,79±1,67*	6,78±1,47
(M) MB dilation	8,86±1,14*	7,57±1,88*	7,06±1,51
(S) Final SB angioplasty	8,97±1,45	6,70±1,57*	7,02±1,50

MB, main branch; SB, side branch; S, side; M, main.



SMS technique.

Conclusion: SMS technique is feasible and provides optimal stent apposition at the proximal segment of the MB and correction of the stent deformation under the SB origin.

P654 Time-dependent changes of local coagulative response up to five years after sirolimus-eluting and bare-metal stent implantation in patients with stable angina

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Purpose: We have previously demonstrated increased local coagulative response six months after sirolimus-eluting stent (SES) implantation by measuring plasma prothrombin fragment F1+2 (frF1+2) levels. The aim of this study is to examine time-dependent changes of local hypercoagulability following SES and bare-metal stent (BMS) implantation.
Methods: Twenty-nine consecutive patients treated five years earlier with a coronary stenting for isolated left anterior descending (LAD) stenosis, with no evidence of restenosis, were studied. Thirteen patients had been stented with BMS, and 16 with SES. We measured the levels of frF1+2 from the coronary sinus (CS) and sinus of Valsalva (V) 6 months (6M) and 5 years (5Y) after stent implantation. The transcardiac gradient (Δ) was defined as the CS levels minus V levels. In a separate analysis, quantitative coronary analyses in lesion characteristics were also performed.
Results: There were no significant differences in coronary risk factors between the BMS and SES group at both stages. The ΔfrF1+2 six months after stent implantation [ΔfrF1+2 (6M)] was significantly greater in the SES group than in the BMS group (21.1±13.4 vs 6.3±9.6 pmol/l, p<0.01). The ΔfrF1+2 five years after stent implantation [ΔfrF1+2 (5Y)] had no significant differences between the two groups (7.1±9.4 vs 5.0±8.8 pmol/l, NS). The time-dependent changes of ΔfrF1+2 [ΔfrF1+2 (5Y) minus ΔfrF1+2 (6M)] was significantly greater in the SES group than in the BMS group (-12.9±10.8 vs -0.9±8.9 pmol/l, p<0.01). A larger percent diameter stenosis was observed at 5 years than at 6 months after stent implantation in the SES group (25.3±15.4 vs 7.1±16.5%, p=0.02), whereas no significant changes were observed in the BMS group.
Conclusions: More time-dependent decrease of local coagulative response was observed after SES implantation as compared to BMS. In the SES group, sufficient neointimal regrowth in very late chronic phase might be associated with our findings.

RISK FACTOR, BIOMARKERS AND COMORBIDITIES IN THE MANAGEMENT OF ACUTE AND CHRONIC ISCHAEMIC HEART DISEASE

P655 Histological assessment of chronic total occlusion in coronary arteries in sudden death cases

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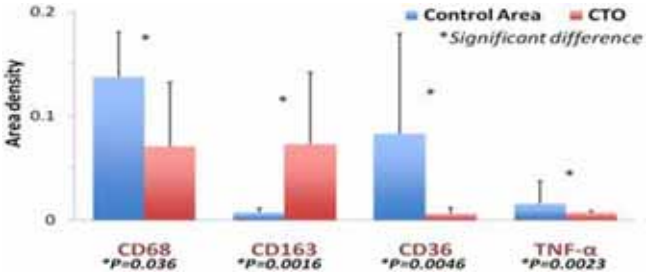
Purpose: Chronic total (coronary) occlusion (CTO) remains a significant obstacle to effective revascularization. Data from autopsy study on the prevalence of CTO is scarce and the histopathology of CTO still requires exploration.
Methods: 940 sudden death autopsy hearts were received and examined in consultation with the Maryland Medical Examiners between 2005 and 2010, where coronary artery disease (CAD) was the cause of death in 351 cases. All major coronary arteries were sectioned at 3-4 mm intervals and processed for histologic examination. The left ventricle myocardium was serially cut at 1.5cm intervals parallel to the base of heart for the presence of myocardial infarction.
Results: Of 351 sudden coronary death cases, 81 cases (23%) had chronic total

occlusion. Males accounted for the majority of CTO. Transmural healed infarction accompanied CTO in 67% (n=54), subendocardial infarction in 14% (n=11), and no infarction in 20% (n=16) whereas the majority of non-CTO cases did not show evidence of infarction (79%). Occluded vessels were identified predominantly in RCA (53%), followed by LAD (23%) and LCx (23%), and the least in left main (1%). Macrophages (Mac) were identified in 60% of cases in the presence or absence hemosiderin suggesting that episode of CTO was recent. Most of the Mac were non-foamy, demonstrated M2 phenotype (CD163 positive), and were associated with "mature" microvessels consisting of perivascular smooth muscle cells (SMC).



Conclusions: CTO occurred predominantly in males with high prevalence of M2 Mac phenotype with iron and are accompanied by mature vessels, which will allow easier antegrade recanalization, especially of <1 year duration.

P656 Insulin therapy at discharge in diabetic patients with acute myocardial infarction is associated with poorer survival: the FAST-MI registry

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Following the two DIGAMI trials, the role of insulin therapy after AMI is debated. We assessed 3-year survival in 1228 hospital survivors of AMI with diabetes, according to the prescription of insulin therapy at discharge. All patients were included in the FAST-MI registry, a French nationwide registry including patients with recent AMI hospitalized at the end of 2005 in 223 institutions.
Of the 1228 diabetic patients, 751 (61%) received insulin during the first 48 hours and 467 (38%) were prescribed insulin at discharge. Patients with insulin at discharge were older (70±12 vs 69±12 years, p=0.004), had a higher GRACE risk score (156±33 vs 147±35, p<0.001), higher admission glycemia (232±110 vs 190±85 mg/dL, p<0.001), higher HbA1c (8.1±1.6 vs 7.2±1.4, p<0.001) and had a longer evolution of diabetes (diabetes Hx >10 years: 35% vs 18.5%, p<0.001). Type of MI did not differ (STEMI: 39% vs 44%, p=0.11) Fewer patients in the insulin group underwent coronary angiography (78% vs 88%, p<0.001) or PCI (53% vs 67%, p<0.001) during the hospital stay. Optimal medical therapy at discharge was prescribed in 51% vs 47% of the patients, respectively (P=0.12). Finally, other antidiabetic medications at discharge were prescribed less frequently in the insulin group (metformin: 8% vs 25%, p<0.001; sulfonylureas: 9% vs 36%, p<0.001; glitazones: 0.2% vs 3.4%, p<0.001).
Three-year survival was 66% in insulin-treated versus 80% in patients without insulin (p<0.001). Subgroup analyses confirmed a higher mortality in patients with insulin at discharge in both STEMI and NSTEMI patients, in those aged 75 years or less, or in those with or without PCI.
Cox multivariate analysis was used to determine predictors of 3-year mortality and covariates included age, sex, risk factors, comorbidities, type of AMI, CAD extent, use of PCI, use of CABG, HbA1c and admission glycemia levels, duration of diabetes, in-hospital complications, and other discharge medications. The adjusted HR for 3-year death was 1.56 (1.15-2.10), p=0.004, for patients treated with insulin at discharge; when treatment with insulin within 48 hours of admission was added to the model, the HR was 1.40 (1.06-1.84), p<0.02. Finally, in propensity score matched cohorts (n=240 in each group), HR for death at 3 years was 1.41 (1.01-1.98), p=0.04 for patients on insulin at discharge.
Conclusion: In this real-world nationwide AMI registry, the prescription of insulin at discharge in diabetic patients was associated with poorer long-term survival, even after extensive multivariate adjustment for confounders.

P657 Copeptin as a predictor of cardiovascular events in patients with coronary artery disease

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Purpose: Besides clinical features and biomarkers, the identification of patients at high risk of adverse outcome after acute coronary syndrome (ACS) remains still a challenge. [Arg8]-vasopressin, an essential neurohypophyseal hormone, modulates the cardiovascular (CV) system as a potent vasoconstrictor and maintains osmotic homeostasis. In the population-based, observational single-center Gutenberg Heart study and in two prospective studies, the StenoCardia for short (26.1 weeks) and the AtheroGene for long-term (3.8 years) outcome in patients with documented coronary artery disease, the C-terminal arginine vasopressin precursor fragment, copeptin, was measured.
Methods: Copeptin and other biomarkers such as troponin I, N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein, creatine kinase, and myoglobin were analyzed. The StenoCardia study cohort comprised 899 patients with non-coronary chest pain (NCCP) and 483 with ACS whereas the AtheroGene study cohort comprised 1330 patients with stable angina pectoris (SAP) and 863 with ACS.
Results: Patients presenting with NCCP and SAP had lower copeptin levels than those with ACS and the highest levels of copeptin was seen in patients with ST-segment elevation myocardial infarction (STEMI) (SAP vs. STEMI, 7.03 vs. 14.2 pmol/L, p<0.001). In the short term prospective analysis, an increase in one standard deviation of logarithmically transformed copeptin was significantly increased in an age, sex and GRACE score adjusted model in patients with a risk for future CV mortality (1.75-fold (98.8% CI: 1.07–2.89; p=0.019)) and even after additionally adjustment for troponin I (1.70-fold (98.8% CI: 1.04-2.79; p=0.028)). In the long term cohort, copeptin was significantly increased in an age, sex and classical risk factor adjusted model in patients with a risk for future CV events (1.36-fold (98.8% CI: 1.15-1.61; p<0.0001)) and mortality (1.71-fold (98.8% CI: 1.39-2.09; p<0.0001)) and in a model additionally adjusted for NT-proBNP for CV events (1.26-fold (98.8% CI: 1.05-1.51; p=0.0063)) and mortality (1.50-fold (98.8% CI: 1.19-1.89; p<0.0001)). Compared to other biomarkers, copeptin was the strongest predictor for CV mortality in both cohorts and for CV events in patients with a long follow-up period.
Conclusions: For future CV events and mortality, copeptin is a powerful predictor and provides additional information to established biomarkers to predict independently short and long term CV risk.

P658 'The lower, the better' was proven in Japanese subjects for primary prevention even with one year treatment; the first evidence of superiority of intensive lipid-lowering with highly potent statin

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Purpose: The aim of the JART (Justification for Atherosclerosis Regression Treatment) study is to demonstrate the efficacy of intensive lipid-lowering therapy in Japan. "The lower, the better" is a well-accepted concept of LDL-C management for prevention of atherosclerosis and cardiovascular events in the West. However, since Asians including Japanese have been at lower cardiovascular risk due to dietary habit, ethnic difference and so on, the Japan Atherosclerosis Society (JAS) guideline is conservative for primary prevention compared with AHA/ACC/ESC guideline. We thus examined whether the efficacy of highly potent statin on atherosclerosis and the superiority to conventional statin treatment are demonstrated even in Japanese.
Methods: The JART study is a prospective, randomized, multi-center, open-label, blinded endpoint evaluation, parallel-group comparative study. Subjects with LDL-C ≥140 mg/dL and maximum IMT ≥1.1 mm, without CVD were enrolled for 2-year treatment either intensively with rosuvastatin (ROS: target LDL-C level <80 mg/dL) or conventionally with pravastatin (PRA: target LDL-C level <120 mg/dL according to JAS 2007 guideline). The primary endpoint is percent change of carotid mean-IMT, a surrogate marker of cardiovascular events, after 2-year treatment. We report the interim one-year results of this study.
Results: A total of 295 subjects were randomized to ROS (147 patients: 63.0±8.9 (SD) yrs; male 47%) or PRA (148 patients: aged 62.6±9.0 yrs; male 47%), where no differences existed in baseline characteristics. After one year, in ROS, LDL-C decreased from 163.4±31.1 to 85.0±23.7 mg/dL, LDL-C/HDL-C ratio changed from 3.1±0.8 to 1.5±0.6, and HDL-C increased from 55.3±11.6 to 59.3±14.2 mg/dL. In PRA, LDL-C decreased from 166.2±29.7 to 117.8±22.6 mg/dL, LDL-C/HDL-C ratio changed from 3.1±1.0 to 2.1±0.7, and HDL-C increased from 56.1±12.8 to 59.9±15.3 mg/dL. The percent of change of mean-IMT was 2.0±10.7% (n.s. from baseline) in ROS and mean-IMT increased by 5.5±11.5% in PRA (p<0.001 from baseline, p=0.0155 vs ROS; unpaired t test).
Conclusions: This is the first evidence clearly demonstrating the superiority of intensive lipid-lowering therapy with highly potent stain on development of atherosclerosis compared to conventional therapy with the first generation statin. Although the study was planned to treat subjects for 2 years, the clinical advan-

tage of intensive lipid-lowering was clearly proven at one-year interim analysis. The concept "The lower, the better" should also be applied to primary prevention of atherosclerotic diseases in Asian population.

P659 Increased visceral adipose tissue is associated with increased resting heart rate in patients with clinical manifest vascular diseases

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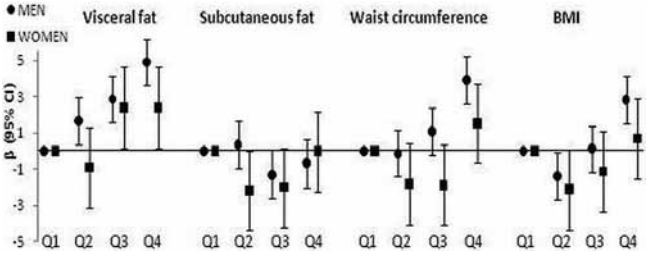
Purpose: Abdominal obesity is characterized by sympathetic nerve activation (SNA), mediated by elevated insulin and leptin levels. Resting heart rate (RHR) is a marker of SNA, and independently associated with cardiovascular events and death. We investigated and quantified the relation between visceral adipose tissue (VAT) and RHR in patients with cardiovascular disease.
Methods: In 3724 patients with cardiovascular disease, VAT was measured with ultrasonography. RHR was obtained from an electrocardiogram. The association between quartiles of VAT and RHR was quantified using linear regression analysis. Results are expressed as beta (β) coefficients with 95% confidence intervals (95%CI). Adjustments were made for potential confounding factors. Separate analyses were performed for men and women and for location of vascular disease.
Results: VAT was categorized into sex-pooled quartiles (Q) ranging from 2.7-8.0 cm in Q1 (reference) to 9.4-20.6 cm in Q4. High visceral fat thickness was associated with increased RHR, in men (Q4 versus Q1, β 4.89; 95%CI 3.61-6.18) and women (β 2.40; 95%CI 0.15-4.66), adjusted for age. Further, multiple, adjustment did not markedly change the results, and in men the relation between VAT and RHR even remained significant after adjusting for BMI (Q4 versus Q1, β 3.89; 95%CI 2.33-5.44). Waist circumference and BMI were also significantly related with RHR in men (β 3.91; 95%CI 2.58-5.23 and β 2.83; 95%CI 1.53-4.13 respectively) but not in women (β 1.51; 95%CI -0.67-3.69 and β 0.68; 95%CI -1.53-2.88 respectively). Subcutaneous fat was not related tot RHR. These relations were similar in patients with different locations of cardiovascular disease.



Adiposity measures related to heartrate.

Conclusions: VAT is associated with RHR in male and female patients with cardiovascular disease, independent of the location.

P660 Characteristics and in-hospital outcomes of women with a history of breast cancer and acute myocardial infarction

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Background: In European women, Breast Cancer (BC) is currently the most frequent cancer, whereas CV diseases such as myocardial infarction (MI) are the leading cause of death. BC and MI share common major risk factors such as obesity. We aimed to analyse the characteristics and outcomes of women with a history of BC in the setting of acute MI.
Patients and methods: Among the 2087 consecutive women included between 01/01/2001and 31/12/2009 in the French regional RICO survey database, 104 (5%) had a history of BC. Each woman with prior BC (n=104) was matched, with respect to age, with 5 women without prior BC (n=520).
Results: Women with prior BC were 75 (65-80) year old. Time from BC diagnosis to acute MI was 10 (3-16) years. Most BC had been treated by surgery and/or radiation therapy, and 37% had also received hormone therapy. CV risk factors, in particular smoking or obesity, type of MI, as well as acute management and in-hospital complications were similar for the 2 groups. Chronic statin use and admission blood lipids were also identical for the 2 groups (LDL-cholest: non BC group: 1.27 (0.99-1.57) vs. BC group: 1.24 (0.92-1.48) g/l, p=0.375). However, median admission CRP levels showed a trend toward a lower level in women with a history of BC (8.0 (3.3-28.6 vs 60.(2.9-19.6) mg/l, respectively, p0.082). Strikingly, peak CK as a reflect of infarct size, was dramatically reduced in the BC group (495 (167-1314) vs 287 (135-786) UI/l, p=0.021). History of BC was associated with increased rate of in-hospital major cardiac events, combining CV death, stroke, ventricular arrhythmias, recurrent MI, AV block, major bleeding events and atrial fibrillation (51.0% vs 34.8%, p=0.002). By multivariate analysis, BC remains an independent predictor of worse outcome (OR (95%CI: 1.90 (1.02-3.53)).
Conclusions: In women currently admitted for acute MI, a non-negligible proportion had prior BC. Women with prior BC had a similar risk profile and lipid levels to those in women without prior BC. In spite of their lower level of inflammation and reduced infarct size than their counterparts without BC, their were strikingly associated with worse in-hospital prognosis. Further investigations are ongoing to determine whether hormone therapy such as oestrogen receptor modulators could account for the observed effects in this population.

P661 The value of routine screening for diffuse vascular disease in the Canadian post-ACS/ischemic stroke/TIA general practice population with no previously documented peripheral arterial disease

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Introduction: Coronary artery disease (CAD) and cerebrovascular disease (CVD) patients frequently have peripheral arterial disease (PAD) of the lower limbs. Presence of PAD powerfully predicts cerebrovascular and cardiovascular events, yet it is under diagnosed and under treated compared to other types of atherothrombosis. The measurement of the ankle brachial index (ABI) is an effective, objective and non-invasive screening tool, which is able to identify the presence of PAD and measure its severity. Edinburgh Claudication Questionnaire (ECQ) has been used to identify the presence of symptomatic PAD.
Objective: This survey's primary objective was to investigate the value of the ECQ against the ABI in patients with CAD and/or CVD who were not known to have PAD. The secondary objective was to estimate the percentage of patients with CAD and/or CVD who also have PAD as measured by ABI.
Design: DIVA was a Canadian, multicenter, non-interventional, prospective, primary care survey in 130 sites which enrolled 2235 patients with previous CAD and/or CVD and no previously documented PAD. ABIs were performed on 478 randomly selected ECQ negative patients (25%) and all 337 ECQ positive patients (100%). The ABI measurement was completed within 12 weeks of the patient's enrollment in the study. ABIs were calculated using the ratios of the higher of the limb systolic blood pressures (SDP) (conventional) and the lower of the limb SDP (alternative). Descriptive statistics, validity measures and kappa coefficient have been used to describe the results.
Results: For the 815 patients with ABI results, the mean (SD) age was 67 (11), the percentage of males and Caucasians were 70% and 74%, respectively.71% had CAD, 21% had CVD and 8% had both. The degree of agreement between ECQ and ABI measured by the kappa coefficient was 0.24, but the negative predictive value was 88% (conventional). Based on ABI <0.90, 18% and 26% of patients with manifest vascular disease were noted to have PAD using the conventional or alternative method, respectively. Higher rates were noted in the diabetic population.
Conclusion: Patients with negative ECQ are unlikely to have PAD. PAD is underestimated, especially in diabetics. Consideration should be given to the alternative method of calculating ABI.

P662 Impact of chronic obstructive pulmonary disease on long term prognosis in coronary artery disease

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Purpose: Chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in coronary artery disease (CAD) patients (pts) but its impact on long term prognosis has been little investigated so far in CAD pts. We aimed to assess the long term prognosis associated with COPD in a contemporary large cohort of pts with established CAD.
Methods: 783 consecutive male pts hospitalized in 2001-2004 for coronary artery disease were considered. The median follow-up was 7.17 years. Total mortality was predicted with a Cox proportional hazard model.
Results: Mean age (SD) was 60.2 (8.1), 144 pts (18.4%) were diabetic, mean glycaemia was 5.9 mmol/l (2.1), 155 pts (19.8%) were smokers, mean blood pressure was 139 (20)/84 (11) mmHg and median heart rate was 61 bpm [Interquatile range (IQR)] [57 – 70]. Mean HDL cholesterol was 43 mg/dl (11), mean LDL cholesterol 124 mg/dl (39) and median triglycerides were 147 mg/dl IQR [109 – 197]. Mean Cockcroft-Gault creatinine clearance was 87 ml/min and 11 pts (1.4%) had a severe chronic renal failure (lower than 30 ml/min). Mean left

ventricular ejection fraction was 0.53 (0.13). 88.5% were on antiplatelet therapy, 75.2% on beta-blocker, 66% on statin therapy and 54.8% on ACE inhibitors or ARB.
A previous history of COPD was present in 3.5% of pts; 37% of them had a beta-blocker therapy. The cumulative seven-year total mortality rate was 17.9% in the whole sample (51.8% in pts with COPD and 16.7% in those without, $p<0.001$). Among COPD pts with beta-blocker therapy, the mortality rate was 30% while mortality reached 64.7% in COPD pts without beta-blocker (p=0.08).
After multivariate adjustment for age, diabetes, tobacco consumption (none, $\leq$40 pack-years, $>$40 pack-years), heart rate, left ventricular ejection fraction (>0.5; ≤0.5 and >0.35; ≤0.35), duration of CAD, ankle-brachial index (>0.9; ≤0.9 and >0.6; ≤0.6), history of stroke, statin therapy and coronary revascularization, hazard ratio for all-cause death was 2.22 (95% CI [1.15; 4.26] p=0.016) in pts with COPD compared to those without.
Conclusion: Presence of a chronic obstructive pulmonary disease is associated with a doubling risk of all-cause death in CAD pts. Systematic screening of COPD should be promoted in all CAD pts.

P663 Multicentre OPTIMA carbostent use in patients treated with two-month dual antiplatelet therapy after index procedure - MATRIX II study

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Purpose: A twelve-month dual antiplatelet therapy (DAT) period is currently recommended after drug-eluting stents (DES) implantation. In this respect, DES use might represent a limit, especially in patients with several comorbidities, with contraindications to long term DAT or requiring major surgery within 1 year after DES deployment or living in the "low-income countries" where, given the lack of reimbursements, DAT costs are not sustainable for all patients. We aimed to evaluate safety and efficacy of a 2-month DAT after percutaneous coronary intervention (PCI) with OPTIMA Carbostent (CID, Saluggia, Italy), a Tacrolimus-eluting, Carbofilm-coated, coronary stent, with polymer-free drug elution through abluminal reservoir technology.
Methods: A multicentre, prospective, non-randomized registry has been designed. Primary endpoint was Major Adverse Cardiac Events (MACE) incidence at 30 days, 6, 12 and 24-month follow-up after PCI. MACE included: cardiac death, myocardial infarction (MI), target lesion revascularization (TLR). Secondary endpoint was stent thrombosis (ST) rate within 30 days, 6, 12 and 24-month follow-up after stenting, according to Academic Research Consortium (ARC) criteria.
Results: From May 2008 to December 2009, 392 patients (81.1% males; mean age 65.3$\pm$11.3 years) were enrolled (25% diabetics; 55.1% acute coronary syndrome; 57.4% multivessel disease) with 440 lesions treated (65.4% B2/C; 16.4$\pm$6.6 mm lesion length; 24.8% bifurcations). After successful stenting, complete 6-month follow-up reported a 4.3% MACE rate (0.3% cardiac death, 0.3% MI, 3.6% TLR, 0.3% acute ST, due to device undersizing). An interim twelve-month follow-up analysis (292/392 patients) showed low (7%) overall MACE rate (0.3% cardiac death, 1.2% MI, 5.7% TLR), without ST occurrence, despite the short DAT time window.
Conclusions: At 12-month follow-up, OPTIMA Carbostent implantation, followed by only 2-month DAT, was safe and feasible in patients undergoing coronary stenting. A randomized trial, with longer follow-up, evaluating OPTIMA Carbostent as an alternative for patients, suitable for DES implantation, at high-risk for bleedings or with long-term DAT contraindications, is warranted.

P664 Influence of comorbidities on one-year outcomes in non-ST-segment elevation acute coronary syndrome

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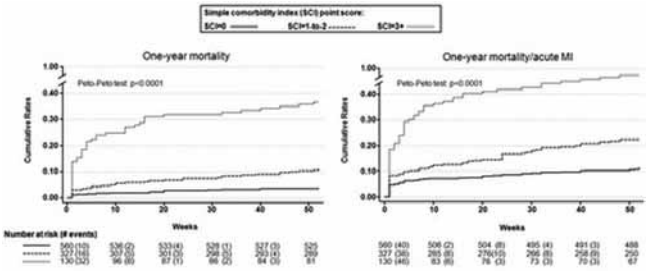
Purpose: To investigate the comorbidities with prognostic influence in non-ST elevation acute coronary syndrome (NSTEACS).
Patients and methods: The study group consisted of 1017 (derivation cohort, Hospital Clínic) and 652 (external validation cohort, Hospital Clínic) patients. Comorbid conditions, including risk factors and components of the Charlson comorbidity (ChCI) and coronary artery disease (CAD) specific indices, were collected. The main outcome was 1-year mortality.
Results: During follow-up, 103 patients died. After adjusting for variables related to NSTEACS characteristics (base model), 5 comorbidities predicted mortality: severe (HR=2.9) or mild (HR=1.6) renal failure, dementia (HR=3.1), peripheral artery disease (HR=2.0), prior heart failure (HR=2.6) and prior myocardial infarction (HR=1.4). A simple comorbidity index (SCI) was developed using these variables, (per point, HR= 1.6, 95% CI 1.4 to 1.8, p=0.0001). Adding the SCI, ChCI or CAD-specific index to the base model resulted in 6.58%, 5.0% and 4.04% gain in the discrimination ability respectively (p=0.001), without differences among them. In comorbid patients, the highest risk period was observed within the first weeks after NSTEACS. The strength of the association between the SCI and mortality was similar in the external validation cohort (HR=1.3, 95% CI 1.1 to 1.6, p=0.001).



One-year mortality and death or acute MI.

Conclusions: Renal dysfunction, dementia, peripheral artery disease, prior heart failure and prior myocardial infarction are the comorbidity predictors of mortality in NSTEACS. A simple index using these variables proved to be as accurate as the more complex comorbidity indices for risk stratification. In-hospital management of comorbid patients merits further investigation.

P665 Glucose metabolism and acute coronary syndromes: diabetes determines the index event, admission glycaemia the prognosis

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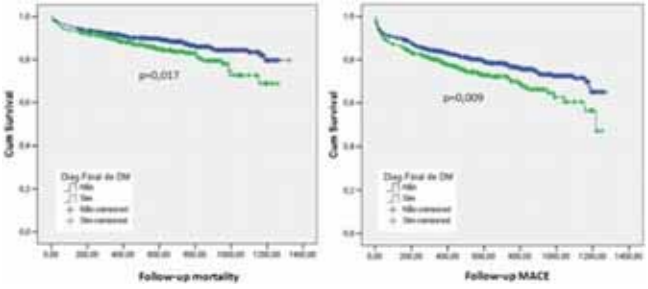
Introduction: Diabetic patients have high incidence of acute coronary syndromes (ACS) and worse prognosis than those without diabetes.
Aim: To evaluate the impact of diabetes on short and long-term prognosis in patients admitted for ACS and to identify independent predictors of post-ACS mortality.
Population and methods: This study included 3716 patients, diabetics (n=1243) and non-diabetics (n=2473), admitted for ACS between May 2004 and November 2010. Mean follow-up was three years.
Results: Diabetics were older, had higher rates of hypertension, dyslipidemia, prior vascular disease (coronary or other territories), severe coronary anatomy, NSTEMI and more frequently treated with ACE inhibitors, nitrates and diuretics. This group showed higher levels of troponin I and triglycerides, lower LDL, HDL and hemoglobin levels, lower creatinine clearance and ejection fraction (EF).
In-hospital (IH) (1.7% vs 2.8%, p=0.019) and follow-up (FUP) (12.7% vs 16.2%, p=0.017) mortality was significantly higher in diabetics. There was a trend towards to increase IH complications (2.8% vs 3.9%, p=0.059), which became significant in the FUP (22.5% vs 27.4%, p=0.009).
Age, troponin and admission glycaemia levels were independent predictors of IH death, while age, admission glycaemia, hemoglobin, Killip class and EF were predictors of FUP mortality. Diabetes was not an independent predictor of death or complications.



Long-term prognosis.

Conclusion: Our data provides further evidence that diabetics have a worse prognosis in ACS, although diabetes per se was not an independent predictor of poor prognosis.
The dismal prognosis of these patients may be related to higher prevalence of risk factors, co-morbidities and sub-optimal therapy, reinforcing the need for an early and aggressive treatment of both diabetes and other ACS risk factors.

P666 Evaluation for predicting the risk of in-hospital mortality in patients with acute myocardial infarction using multicenter registry database in Japan

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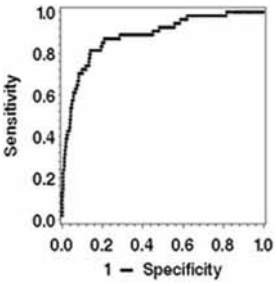
Objectives: There was no established measurement of in-hospital mortality for

acute myocardial infarction (AMI) in Japan. We investigate to develop and validate the risk adjustment in-hospital mortality model in the patients with AMI.
Methods: We established the multicenter registry to collect data of the patients with AMI. As the derivation cohort (16A-1), 1897 patients with AMI were enrolled into a registry from 27 hospitals during 2005 and 2006. As the validation cohort (19A-2), 1826 patients with AMI enrolled from the same hospitals during 2008 and 2009. Logistic regression was used for risk model. The accuracy of the model was measured using the c-index with the validation cohort (19A-2).
Results: In the derivation cohort, multivariate analysis showed independent predictors of in-hospital death which were age (odds ratios 1.84), female gender (1.67), smoking (0.69), hyperlipidemia (0.50), peak Log CPK (1.78), Killip classification more than 2 (3.06), time from onset to hospitalization (1.03) and anterior of infarct location (1.63). The risk model of in-hospital mortality was estimated as 1/(1 + exp(-βx)); in-hospital mortality = 1/(1 + (11.902 – 0.607×age – 0.512×gender + 0.37×smoking + 0.696×hyperlipidemia – 0.579×Log peak CPK – 1.12 × Killip classification – 0.03 × time from onset to hospitalization – 0.491 × anterior of infarct location, these clinical or statistical relevant factors were finalized by checking goodness-of-fit and calibration. Using the validation cohort, C-index for in-hospital mortality prediction for patients with AMI was 0.89 (95%CI: 0.84-0.93). There was no clear relation between hospital factors and in-hospital mortality.



C-Index.

Conclusion: This is a first report, the risk adjustment in-hospital mortality model in the patients with AMI and showed good discrimination in Japan.

P667 Effects of omega-3 fatty acids on post-prandial triglyceride tolerance and monocyte activation

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Background: Omega-3 fatty acids (ω-3 FAs) are known to lower fasting triglyceride (TG) levels. Epidemiologic studies suggest that post-prandial triglycerides (ppTG) are associated with cardiovascular events. Monocyte activation plays an important role in lipid-mediated vascular diseases. The effects of ω-3 FAs on ppTG metabolism and the role of ppTG for monocyte activation have not been studied in detail. We employed a standardized oral triglyceride tolerance test (OTTT) which tested TG concentrations at various time points following application of 75g cream fat in patients with angiographically documented stable coronary artery disease (CAD).
Methods and results: 514 CAD patients were metabolically characterized, and 126 patients showed a normal glucose tolerance. Of these, 30 patients with a ppTG increase above the median were treated with 4g ω-3 FAs/day or placebo in a randomized, placebo-controlled, double-blind, crossover study. OTTT was performed at baseline and after 21 days of treatment. Following a three-week washout period, patients were switched to the other treatment group and treated for another 21 days. Relative TG increase reached its maximum 4h after fat intake with 185.1±10.9% of baseline levels. ω-3 FAs reduced fasting TG from 137.1±12.9 to 112.2±8.6mg/dl ($p<0.05$), while placebo had no effect. Maximal ppTG concentrations were decreased from 243.6±24.6 to 205.8±17.1mg/dl ($p<0.05$), while relative TG increase after treatment with ω-3 FAs (192.8±12.7%) was comparable to placebo. The area under the curve of TG during OTTT was reduced from 1042±99 to 873±60mg/dl ($p<0.05$) by ω-3 FAs and did not change after placebo (988±71 vs. 1033±88mg/dl, p=ns). Differential blood count showed relative monocytopenia and neutrophilia following fat intake, which was unaffected by ω-3 FAs. Monocyte adhesion molecule CD11b and LPS–co-receptor CD14, investigated by flow cytometry during OTTT, were unchanged by ω-3 FAs. OTTT induced a decrease of the MCP1-receptor CCR2 from 31.8±1.6 to 27.1±1.7 mean fluorescence/monocyte ($p<0.05$) which was not influenced by treatment with ω-3 FAs. Monocyte subpopulations CD16+CD14high and CD16+CD14low were not affected by OTTT or ω-3 FAs.
Conclusion: ω-3 FAs lower fasting TG and potently attenuate the post-prandial TG increase. The post-prandial TG raise did not induce a pronounced activation of monocytes. Further analyses need to show whether post-prandial TG kinetics identify specific subgroups of patients with CAD that show increased risk and could potentially benefit from TG lowering by ω-3 FAs.

P668 Routine laboratory tests: independent and incremental prognostic value in chronic coronary heart disease

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Purpose: We aimed to investigate whether routine laboratory tests provide prognostic information additional to a complete diagnostic work-up in patients with chronic coronary heart disease (CHD).
Methods: We prospectively examined a cohort of 2370 consecutive patients with chronic CHD, as shown by the evidence of a >50% coronary stenosis or a previous myocardial infarction (MI). We tested the ability of clinical and laboratory variables to predict future cardiac events (cardiac death and non-fatal MI). The laboratory variables explored were hematocrit, white blood cell count, platelet count, fasting glucose, serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and C-reactive protein.
Results: During follow-up (median, 46 months), 147 of 2370 patients (6.2%) died from cardiac causes and 81 (3.4%) experienced a non-fatal MI. After adjustment for age, sex, history of diabetes mellitus, left ventricular ejection fraction by echocardiography and angiographic extent of coronary stenoses, an HDL cholesterol level < 35 mg/dL ($p<0.0001$), an fT3 serum level < 2.1 pg/mL with normal TSH (low-T3 syndrome, p=0.010), and serum creatinine levels >1.4 mg/dL (p=0.021) showed an independent and incremental prognostic value. The global chi-square increased from 157.01 (clinical variables) to 181.00 (clinical variables + laboratory tests). Low HDL cholesterol, elevated serum creatinine level, and low T3 syndrome were associated with an increase in the rate of cardiac events of 94%, 47%, and 53%, respectively.
Conclusions: Routine laboratory tests provide prognostic information that is independent and incremental to the main clinical, echocardiographic and angiographic variables.

P669 Hyperglycemia at admission and during hospital stay are independent risk factors for mortality in a high risk population admitted to the intensive cardiac care unit

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Hyperglycemia in patients with acute medical conditions has been associated with increased mortality compared to normoglycemia in patients with the same condition. However, the prognostic implications of initial (admission) and/or sustained hyperglycemia in high risk patients admitted to an Intensive Cardiac Care Unit (ICCU) have not been described.
This study describes the predictive value of admission- and average glucose levels in patients admitted to the ICCU of a tertiary medical center.
Over a 19 month period, 1713 patients that were admitted to the ICCU had glucose measured and were included in the analysis. Mean age was 63±14 years, 72% (1227) were male, 17% (288) had known diabetes. Median (interquartile) glucose concentration at admission was 7.9 (6.5 - 10.1) mmol/L; median average glucose during hospitalization at the ICCU (available in 873 patients with 3 or more measurements) was 7.3 (6.7 - 8.3) mmol/L. Cox-regression analysis, including the variables age, gender, admission diagnosis, length of stay, prior (cardio)vascular disease and diabetes, revealed that a 1 mmol/l increase in admission glucose (above 9 mmol/l) was associated with a 10% (95% CI: 7% - 13%) increased risk for all cause mortality. A 1 mmol/l higher average glucose (above 8 mmol/l) was an additional independent predictor of mortality (HR 1.11, 95%CI: 1.03 - 1.20). At 30 days, 16.8% (97/579) of the patients with an admission glucose in the highest tertile (>9.8 mmol/L) had died vs. 5.2% (59/1134) of those with a lower admission glucose.
Conclusions: In a high risk ICCU population both a high admission glucose as well as a high average glucose during hospitalization at the ICCU were associated with an increased mortality, even when accounting for other risk factors and parameters of disease severity.

P670 Copeptin and sensitive cardiac troponin in the early diagnosis of acute myocardial infarction in patients with preexisting coronary artery disease

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Introduction: Chronically elevated levels of cardiac troponin (cTn) were found in more than 10% of patients with pre-existing coronary artery disease (CAD). These patients often suffer from acute chest pain and the early diagnosis of acute myocardial infarction (AMI) is particularly challenging. It is unknown whether

copeptin, a novel marker quantifying endogenous stress, has additional value in patients with pre-existing CAD for the diagnosis of AMI.
Methods: We conducted a multicenter study to examine the incremental value of copeptin in 1067 consecutive patients presenting with symptoms suggestive of acute myocardial infarction (AMI), of whom 385 (36%) had pre-existing CAD. Measurement of copeptin, the Roche 4th generation standard assay (TnT) and the Siemens sensitive cTnI-Ultra (TnI Ultra) assay were performed in a blinded fashion.
Results: AMI was the final diagnosis in 76 patients with CAD (20%). Copeptin levels were significantly higher in AMI patients compared with patients having other diagnoses (26 pmol/l [IQR 9-75] vs. 7 pmol/l [IQR 4-16], p< 0.001). The combination of TnT and copeptin resulted in an area under the receiver-operating characteristic curve (AUC) of 0.94 (95% CI: 0.92 - 0.97), which was significantly higher than 0.87 (95% CI: 0.82 - 0.93) for cTnT alone (p<0.001). The AUC for the diagnosis of AMI was significantly higher for the TnI Ultra assay than for the standard assay TnT and Copeptin (AUC for TnI Ultra, 0.94 vs. 0.87 for TnT and 0.75 for Copeptin; p=0.002 and p<0.001 respectively). Among the patients with an initial sensitive TnI Ultra level below the 99th percentile (0.04ug/l), copeptin was significantly higher in patients with AMI than in patients with other causes of chest pain (40pmol/l [21-122] vs. 7pmol/l [4-15], p=0.001). The combination of Copeptin and TnI Ultra was able to improve the negative predictive value from 97% to 100% to rule out AMI. In patients with elevated TnI levels above the 99th percentile, Copeptin was significantly higher in patients with AMI (26pmol/l [8-72] vs. 13pmol/l [5-36], p=0.024).
Conclusion: Copeptin together with the standard TnT assay improves the diagnostic accuracy to diagnose AMI in patients with pre-existing CAD. In the era of upcoming sensitive cTn, Copeptin could be an ideal partner in patients with initially negative sensitive cTn levels, providing a very high negative predicting value to rule out AMI. In patients with elevated sensitive cTn levels, Copeptin shows only a low diagnostic accuracy for the diagnosis of AMI.

P671 Elevated resting heart rate is associated with increased all-cause mortality in patients with different locations of clinical manifest vascular disease

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[1]University Medical Center Utrecht, Department of Vascular Medicine, Utrecht, Netherlands; [2]University Medical Center Utrecht - Julius Centre for Health Sciences and Primary Care, Utrecht, Netherlands; [3]University Medical Center Utrecht, Department of Cardiology, Utrecht, Netherlands

Purpose: Resting heart rate (RHR) is a reflection of sympathetic nerve activity and is an independent risk factor for the occurrence of cardiovascular events and death. We investigated the relation between RHR and risk for subsequent vascular events and death in patients with coronary artery disease (CAD), cerebro vascular disease (CVD), peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA).
Methods: Data were used from a prospective cohort study (SMART) of patients with clinical manifest vascular disease. RHR was obtained from an electrocardiogram. Patients were followed for the occurrence of non-fatal stroke, non-fatal myocardial infarction, all-cause mortality and vascular mortality. The relation between RHR and the occurrence of outcome events was estimated by Cox proportional hazard analyses adjusted for age, gender, smoking, location of vascular disease and use of medication.
Results: 4272 patients were included in the current analysis: CAD (n=2244), CVD (n=930), PAD (n=823) and AAA (n=275). In the whole cohort, an increase in RHR of 10 beats/minute (bpm)independently increased the risk on all-cause mortality (HR 1.14; 95%CI 1.07-1.21) and vascular mortality (HR 1.15; 1.05-1.25), but not of myocardial infarction (HR 1.03; 0.94-1.13) or ischemic stroke (HR 1.05; 0.92-1.20). There is a potential for reverse causality and therefore analyses were performed excluding all patients with an event in the first year of follow-up, which did not change the results. After stratification for location of disease, RHR was independently associated with vascular mortality and all-cause mortality (table).

Hazard ratios per 10 bpm increase in RHR

	CAD (n=2244)		CVD (n=930)		PAD and AAA (n=1098)	
	‡	HR (95% CI)	‡	HR (95% CI)	‡	HR (95% CI)
Myocardial infarction	117	0.96 (0.81–1.15)	54	1.09 (0.89–1.34)	108	1.03 (0.90–1.18)
Ischemic stroke	23	0.82 (0.53–1.25)	76	1.10 (0.93–1.31)	32	1.05 (0.81–1.36)
Vascular death	60	1.20 (0.97–1.49)	82	1.17 (1.00–1.38)	150	1.14 (1.02–1.28)
All–cause mortality	116	1.23 (1.05–1.44)	144	1.19 (1.06–1.35)	245	1.09 (1.00–1.19)

‡ = number of events.

Conclusions: An increase in RHR is associated with increased vascular mortality and all-cause mortality, but not with myocardial infarction or ischemic stroke, in patients with CAD, CVD, PAD and AAA, indicating a role for sympathetic nerve activity in the prognosis in patients with various vascular diseases.

P672 Impact of renal insufficiency on safety and efficacy of drug-eluting stents compared to bare-metal stents at 6-years

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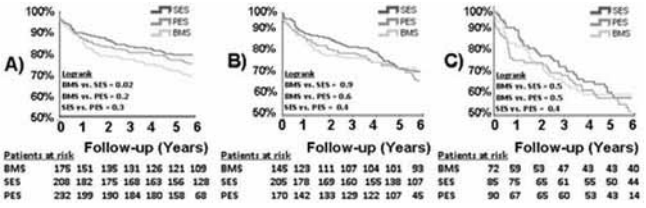
Purpose: Whether sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) enhance long-term safety and efficacy parameters in patients with coronary artery disease and renal insufficiency (RI) compared to bare-metal stents (BMS) in the "real world" remains unknown. Our aim was to assess the 6-year clinical outcome of percutaneous coronary intervention (PCI)-patients with RI treated exclusively with BMS, SES or PES.
Methods: A total of 1382 patients, included in three PCI-cohorts (BMS=392; SES=498; PES=492), were categorized by creatinine clearance calculated by the Cockroft-Gault formula (normal≥90; mild RI=60-89; moderate RI<60) and systematically followed for the occurrence of major adverse cardiac events (MACE).
Results: Mortality rates were significantly higher for patients with moderate RI compared to mild RI and normal kidney function at 6-years post-PCI (Kaplan-Meier estimate: Moderate RI (34%) vs. mild RI (12%), p<0.001; Moderate RI (34%) vs. normal kidney function (8%), p<0.001). After multivariate Cox regression analysis, SES and PES decreased the occurrence of TVR and MACE at 6-years in patients with a normal creatinine clearance compared to BMS (aHR=0.48, 95%CI:0.28-0.84; aHR=0.75, 95%CI:0.57-0.97; respectively) with no significant effect on mortality. Safety- and efficacy end points remained similar for the three stent types in patients with mild- and moderate renal function.



KM-curve.

Conclusion: Patients with a normal creatinine clearance had a significant improvement in TVR and MACE rates after SES- or PES implantation compared to BMS at 6-years. However, there was no superiority of drug-eluting stents over BMS in safety and efficacy end points for patients with impaired renal function.

P673 The presence of retinal microvascular dysfunction is a predictor of underlying coronary artery disease

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Purpose: Endothelial dysfunction (ED) is a key early feature of systemic atherosclerosis. Early identification of ED may lead to targeted screening and increased preventive therapies. Retinal endothelial function can be assessed by real time non-invasive assessment of retinal microvascular dilatation to flicker light which is a nitric oxide dependent phenomenon. We sought to determine if retinal microvascular function is impaired in patients with coronary artery disease (CAD).
Methods: Stable patients from a clinic setting with or without clinically evident CAD were prospectively recruited (n=194). CAD was defined as chest pain with a positive functional study and /or a coronary angiographic stenosis of >50%. Retinal vascular reactivity in response to diffuse luminance flicker light was measured in both eyes after pupil dilatation using the Digital Vessel Analyzer (IMEDOS, Germany). Retinal arteriolar diameter change is expressed as percentage increase over baseline diameter and an average of both eyes per patient was recorded. Baseline characteristics were analysed with Chi-square and t-test and logistic regression analysis was performed to determine predictors of CAD.
Results: Subjects with CAD (n=75) were older (63±9 versus 55±12 years; P<0.01), more likely to be male (83% versus 55%; P<0.01) and have dyslipidaemia (96% versus 74%; P<0.01), but less likely to be current smokers (16% versus 30%; P=0.04) than subjects without CAD. Retinal arteriolar dilatation was attenuated in patients with CAD (1.5±0.2% versus 2.4±0.2%, mean±SEM; p=0.003). When predictors of CAD were examined, each 1% decrease in retinal arteriolar dilatation was associated with a 33% higher risk of having CAD after adjustment for age, gender, body-mass index, smoking, hypertension and dyslipidaemia (OR 1.33, 95% CI 1.05 – 1.67, p=0.017).
Conclusion: Retinal arteriolar dilatation to a flicker light stimulus is attenuated in stable CAD patients. The capacity of retinal arterioles to dilate is an independent predictor of the presence of CAD and suggests that endothelial dysfunction in the retinal microcirculation is a marker for underlying CAD. Further evaluation

is warranted to determine the utility of dynamic retinal vascular assessment in predicting cardiovascular events.

P674 A combination of urine NGAL and IL-18 identifies contrast induced nephropathy early in patients with diabetes and CKD undergoing coronary angiography and PCI

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Background: The incidence of contrast nephropathy (CIN) post coronary angiography (CA) or PCI in patients with diabetes mellitus (DM) may be up to 30% and is associated with increased long term morbidity/mortality. Patients with chronic kidney disease (CKD) are excluded from the majority of cardiology trials and are at high risk for development of CIN. We aimed to identify if a panel of novel biomarkers could predict CIN early post procedure allowing earlier identification of patients and if severity of coronary disease influenced the development of CIN.
Methods: We recruited 208 consecutive patients undergoing angiography or PCI with known DM and CKD (eGFR <60ml/min). CIN was defined as a rise in creatinine (Cr) at day 3 >25% from baseline/absolute rise of 44.5μmol/l, severity of coronary disease by the SYNTAX Score and risk of CIN by the Mehran score. We evaluated neutrophil gelatinase-associated lipocalin (NGAL) and Interleukin-18 (Il-18) and albuminuria for additional information about CIN risk. NAC and iv hydration were given in accordance with local guidelines.
Results: 116 patients underwent CA and 92 PCI. 39 (18.8%) developed CIN. Contrast dose was similar in the 2 groups (p=0.249). The SYNTAX score did not differ between the 2 groups (p=0.188). The mean Mehran score was significantly higher in the CIN arm (13.7 vs 11.1 p<0.001) and gave an AUC (Area Under Curve) on ROC analysis of 0.69. A 20% or greater increase in urine IL-18 and NGAL at 2h increased the AUC to 0.78. Neither alb:Cr ratio (p=0.149) or protein:Cr ratio (p=0.635) predicted CIN development.

Table 1. Baseline characteristics

	No CIN outcome (n=169)	CIN outcome (n=39)	p value
Age (Mean, SD)	70.8 (8.5)	71.5 (9.5)	0.642
Hypertension (%)	155 (91.7)	33 (86.8)	0.347
Hyperlipidaemia (%)	165 (97.6)	37 (97.4)	0.923
Heart Failure (%)	32 (19.1)	7 (18.4)	0.929
BMI (Mean, SD)	28.6 (5.4)	29.2 (6.1)	0.541

Conclusions: The current gold standard for measuring CIN is a rise in serum Cr but is of limited value as it does not increase until 48-72 hours post renal injury. A 20% rise in urine NGAL and Il-18 within 2 h of procedure allows earlier diagnosis of CIN and improves the diagnostic ability of a well validated risk score for both clinical and investigational purposes.

P675 ACUITY, CRUSADE and GRACE bleeding risk scores: comparative performance in patients with acute coronary syndrome

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Background: Bleeding events in patients with acute coronary syndromes (ACS) are common and associated with poorer prognosis. The identification of patients at risk of bleeding is a clinical priority.
Objectives: To compare the performance of ACUITY, CRUSADE and GRACE Bleeding Risk scores for predicting in-hospital major and moderate bleeding in patients with ACS.
Population and methods: We studied 692 consecutive patients admitted for ACS, mean age 64±11 years, 80% male and 66% with non-ST segment elevation (NSTE) ACS. Bleeding during hospitalization was classified using major TIMI and GUSTO criteria and any major+moderate. The predictive accuracy for TIMI and GUSTO major and any major+moderate bleeding was calculated by ROC curves for each score and compared using the Hosmer-Lemeshow statistic.
Results: The incidence of TIMI major bleeding was 1.3%, GUSTO major was 0.9% and any major+moderate was 4.5%. All bleeding risk scores showed good discriminatory capacity for predicting GUSTO major bleeding and reasonable for TIMI major and any major+moderate bleedings. There were no statistically significant differences for comparisons between risk scores.

Comparative performance

Score	Any Major + Moderate		TIMI major		GUSTO major	
	AUC	P	AUC	P	AUC	P
ACUITY	0.627	0.016	0.656	0.109	0.851	0.003
CRUSADE	0.639	0.009	0.659	0.102	0.785	0.016
GRACE	0.615	0.030	0.611	0.252	0.726	0.057

Conclusions: Risk scores developed for predicting the risk of bleeding in ACS showed a good discriminatory capacity for the events defined by clinical criteria (GUSTO) and reasonable for events defined by laboratory criteria (TIMI).

P676 The coronary angiographic analysis of 16573 patients for coronaro-cameral communications

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Purpose: The coronaro-cameral communications (CCC) includes coronary fistulae and coronaro-cameral microcommunications. Small CCC are usually benign and do not cause clinical symptoms. However, large coronary fistulae are usually symptomatic and cause symptoms of ischemia usually due to coronary steal. Coronary fistulae might even cause sudden cardiac death. Many of the CCC are small and found incidentally during coronary angiography. In this study, we aimed to analyze the coronary angiograms performed from 2001 to 2011 to determine the frequency and types of CCC in our centre.
Methods: The coronary angiographies of 16573 patients (11273 male, mean age 60 years) with symptomatic heart disease from November 2001 to January 2011 were analyzed by two cardiologists. The diagnosis of coronary fistula was made according to criteria defined by Angelini. The rest of the connections were defined as coronaro-cameral microcommunications.
Results: Among the 16573 patients who underwent coronary angiography, 15 (0.09%) patients had CCC. The mean age of these 15 patients were 62,9 years and 8 (53%) were male. Coronary fistulae were identified in 2 (13,3%) patients. The coronary fistula arises from branches of left anterior descending (LAD) and right coronary artery (RCA) and drains into right ventricle in the first and fistula originates from branches of LAD, circumflex (Cx) and RCA and drains into left ventricle in the second patient. In 7 (46,6%) patients, coronaro-cameral microcommunications originated from LAD. In 3 (20%) patients, Cx artery was the origin. The coronaro-cameral microcommunications arised from RCA in 2 (13,3%) patients. In 1 (6,6%) patient coronary-cameral microcommunication arise from RCA and Cx artery. Also in 2 patients coronaro-cameral microcommunications were associated with intracardiac masses. There was a right atrial myxoma that was resected surgically in first patient and a large left atrial thrombus also removed surgically in the second patient.
Conclusion: In our study, we found CCC in 0,09% of the patients. However large coronary fistulae were found only in 2 (0,01%) patients. Coronary fistulae with large intracardiac shunts are very rare in adult patients, because the majority of them are detected and repaired during childhood. Surgical and catheter based interventions in large coronary fistulae are not recommended in adult patients because of frequent peri- and postoperative complications. Even after surgical correction, remaining risk of coronary thromboembolic disease in the excessively ectatic coronary segments is at least equal that of patients treated medically.

P677 Renal dysfunction and cardiovascular outcome after acute myocardial infarction: results from Korea acute myocardial infarction registry

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Objectives: Few studies have defined how the renal dysfunction impact on adverse outcome after acute myocardial infarction (AMI). Renal failure is associated with one of the highest risks, but relation between chronic kidney disease (CKD) stage and cardiovascular outcome after AMI is not well defined.
Methods: As a part of the Korea Acute Myocardial Infarction Registry (KAMIR), we identified 12,636 patients with AMI between November 2005 and July 2008. The glomerular filatration rate (GFR) was estimated by means of the four-component Modification of Diet in renal Disease equation, and the patients were grouped according to CKD stage. Primary end points were death and complication in hospital courses. Secondary end points were major adverse cardiac event (MACE) during follow-up.
Results: The median follow-up was 404±61 days, the mean age was 64±13 years, and 70.4 percent of the group were men. A graded association was observed between stage of CKD and clinical outcomes. CKD stage 4 (hazard ratio, 1.869; 95% CI, 1.360 to 2.569, p<0.001) and CKD stage 5 (hazard ratio, 4.789; 95% CI, 3.228 to 7.103, p<0.001) independently predicted in-hospital death and MACE. Diabetes mellitus (DM) does not associated with in-hospital MACE (hazard ratio, 1.183; 95% CI, 0.978 to 1.431, p=NS), while was an independent risk factor for MACE during one year follow up (hazard ratio, 1.191; 95% CI, 1.051 to 1.351, p=0.006). Use of beta blocker, angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and statin were associated with reduced risk for MACE.
Conclusion: Severe renal dysfunction and DM were an independent risk factor for the mortality and complications of AMI, while use of beta-blockers, ACEIs or ARBs and statins were associated with reduced risk.

P678 Epicardial obesity as a possible marker of metabolic syndrome in patient with coronary artery disease

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Objective: To study the correlation between thickness of epicardial fat with neurohumoral and proatherogeneic activity of visceral fat.
Materials and methods: The study included 100 patients with angina II-III functional class. All patients were measured with waist circumference (WC), level of leptin, adiponectin, resistin and also coronaroangiografy. Thickness of epicardial fat was assessed by echocardiography - determined by the amount of adipose tissue in the right ventricle in the atrioventricular groove. Have been identified 2 groups of patients in terms of the thickness of epicardial fat. Group 1 - (48 attendees) with a thickness of epicardial fat more than 7 mm, Group 2 - (52 attendees) with a thickness of epicardial fat less than 7 mm. The groups were comparable in terms of the ratio of men and women in groups mean age (52,4±8,1 and 50,3±7,6 years).
Results: Thickness of epicardial fat in group 1 was 9,5±1,3 mm and WC 106±4,3 cm; in group 2 epicardial fat was 5,4±0,5 mm and WC 99±5,1 cm. In group 1, resistin levels were 78,3±3,1, while in group 2 - 61,3±2,1 ng/ml, the levels of resistin - 11,8±1,6 and 8,2±0,6 ng/ml, respectively, and levels of adiponectin - 4,1±0,2 and 7,1±0,5 μkg/mmol. All differences are significant with $p<0,05$. Correlation analysis showed that epicardial fat thickness in group 1 had a close, positive statistically significant correlation with the levels of leptin and resistin ($r=0,68$; $p<0,01$ and $r=0,61$; $p<0,01$ respectively) and negative with adiponectin ($r= -0,56$; $p<0,01$). In this case, correlation of these indices with waist circumference were less close, and not always reliable ($r=0,23$; $p<0,05$; $r=0,18$; $p>0,05$; $r= -0,27$; $p<0,05$ respectively). Also was studied the thickness of epicardial fat in patients with varying severity of coronary atherosclerosis. Revealed that patients with damage to a single coronary artery thickness of epicardial fat was 5,6±0,3 mm, two arteries - 7,8±0,5 mm, and three of the arteries - 10,1±0,4 mm (between all indicators $p<0,05$). Average of waist circumference in the group with a 3-coronary vascular lesions was 104±8,1 cm, patients with a 2-vascular lesions 102±7,8 cm, with 1-vascular 101±5,5 cm, no significant differences between these parameters were detected ($p>0,05$).
Thus, epicardial obesity has a closer relationship with the level of adipokines and with the severity of coronary atherosclerosis than the WC. Perhaps the thickness of the epicardial fat may be an additional marker of metabolic syndrome.

P679 Age differences in clinical presentation and management of outpatients with stable coronary artery disease: baseline characteristics of the CLARIFY registry

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Purpose: Age is one of the most powerful characteristics associated with cardiovascular event rates, but limited contemporary data are available in patients with stable CAD of different age groups from routine practice and diverse regions. We sought to assess age-specific differences in clinical characteristics and management of patients enrolled in CLARIFY.
Methods: CLARIFY is an international, prospective, longitudinal registry in outpatients with proven stable CAD. Patients will be followed up annually for 5 years. Of >33,000 pts enrolled from 46 countries (Nov09–July10), >15,000 are ≥65 years.
Results: Compared with those <65 yrs, older pts had lower heart rates, higher systolic BP, more commonly diabetes, and were less likely to be current smokers.

Patient characteristics and treatments

Variable	≤65 yr (n=17,212)	65-74 yr (n=10,789)	≥75 yr (n=5164)
Men	82	74	71
Age, years	56 (7)	70 (3)	80 (4)
Heart rate (palpation) bpm	69 (11)	67 (11)	68 (11)
Blood pressure (mmHg)	129 (17)/79 (10)	132 (17)/77 (10)	134 (17)/75 (10)
Current smoker	18	7	4
Diabetes	28	31	29
Treated hypertension	66	76	77
Myocardial infarction	65	55	53
Angina	25	20	18
Aspirin	91	86	80
β-Blocker	78	73	69
Ivabradine	11	8	9
Calcium antagonist	23	31	32
ACE inhibitor or ARB	77	80	77
Lipid-lowering drug	94	91	90
Diuretic	24	33	40

Data are given as % or mean (SD). All p-values are less than 0.0001.

There were significant differences in the current medications among different age groups, including less common use of β-blockers in older pts.
Conclusion: Age-related differences exist in baseline characteristics and management of this contemporary population of patients with stable CAD. Patients ≥65 years had lower heart rates and were treated less frequently with β-blockers.

P680 Acute kidney injury and outcomes in ischemic cardiomyopathy: evaluation of the RIFLE criteria

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Purpose: There is little information about acute kidney injury (AKI) in patients (P) with acute coronary syndromes (ACS). The Risk, Injury, Failure, Loss, End stage (RIFLE) criteria have recently been established as the standard method for evaluating AKI in critically ill P, but have not been tested in the setting of ACS. We therefore investigated the association between ACS outcomes and AKI evaluated by this method.
Methods: Retrospective study of 506 P (68% male, age 67.2±13.7 years), consecutively admitted for ACS to a Coronary Unit. AKI was classified according to RIFLE criteria. Mortality (M) was assessed at follow-up (FU) (7.5±5.2months). Uni and multivariate analysis was performed using SPSS 17.0.
Results: AKI occurred in 184 P (36.4%), with the following RIFLE class distribution: 137 (74.5%) Risk, 25 (13.6%) Injury and 22 (11.9%) Failure. The factors at admission associated with AKI were: female gender ($p=0.003$); older ages (72±12 vs 65±14; $p<0.001$); diabetes mellitus ($p<0.001$); high blood pressure ($p<0.001$); chronic heart failure (HF) ($p=0.018$); chronic renal disease ($p=0.022$); acute HF (KK≥2) (41.3% vs 16.1%; $p<0.001$); cardiogenic shock (11.4% vs 2.2%; $p<0.001$); higher levels of BUN ($p<0.001$), creatinine (115±63 vs 93±44; $p<0.001$) and NT-pro-BNP ($p=0.003$); lower glomerular filtration rate (MDRD) (62±28 vs 80±26; $p<0.001$) and haemoglobin ($p<0.001$). There were no differences in the incidence of coronariography or angioplasty. P with AKI had more extensive coronary artery disease (number of segments evolved); higher incidence of diastolic dysfunction ($p<0.001$), mitral regurgitation ($p=0.031$) and a trend towards higher incidence of left ventricular dysfunction (EF < 40%; $p=0.087$). They also had longer hospitalizations (6.7±5.6 vs 4.7±2.1; $p<0.001$); more frequently were discharged with the diagnosis of new HF (38.7% vs 16.9%; $p<0.001$); had higher M both in-hospital (13% vs 2.5%; $p<0.001$) and during FU (17.6% vs 3.9%; $p<0.001$). In P with AKI there was an association between RIFLE class (Risk vs Injury vs Failure) and the duration of hospitalization (5.8±4.8 vs 8.4±6.4 vs 10.2±7.4; $p=0.001$), in-hospital M (4.4% vs 28% vs 50%; $p<0.001$) and M in the FU (14.1% vs 33.3% vs 42.9%; $p=0.027$). In multivariate analysis, AKI stratified by RIFLE adds prognostic value to Grace Score regarding M both in-hospital and during FU.
Conclusions: AKI is common in P with ACS and as expected has negative impact on prognosis. Its stratification according to RIFLE allows us a more accurate determination of its prognostic importance, showing that the severity of AKI is even more important than its mere occurrence, being an independent predictor of M.

P681 The highest risk patients with coronary heart disease treated in primary health care - evaluation of the efficiency of treatment

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Background: Patients (pts) with history of coronary heart disease (CHD) and comorbidities are at the supreme priority for cardiology. Therefore, under the auspices of the Ministry of Health in Poland, POLKARD-SPOK survey was performed to distinguish risk factors and describe their current management.
Aim: The aim of the study was to determine whether the diabetes, chronic renal failure (RF) defined as GFR<60 ml/min, older age defined as ≥ 75 years influence on treatment in pts with CHD in primary care practice.
Methods: The study was based on questionnaires addressed to physicians working in primary health care. The randomization was performed by the Studio of Social Researches. Finally data of 13514 pts with CHD treated in Polish primary health care were analyzed: 4027 subjects with diabetes; 3477 with RF determined by glomerular filtration rate (GFR<60 ml/min) and 1889 patients aged ≥ 75 years. The control group included 6435 pts with CHD but with age<75 years, without diabetes and without RF who were treated by the same physicians.
Results: Beta-blockers were prescribed to: 66.4% of pts who had one of the risk factors (age≥75 years or diabetes or RF); 63.3% of pts with those two risk factors; 56.3% of pts with all three risk factors in comparison to 72.5% of pts from control group (p for the change tendency <0.001). Similarly, statin therapy was administered less often with the increasing amount of risk factors in analyzed groups (respectively: 72.2% vs. 66.1% vs. 61.1% in comparison to 75.5% in the control group, p for the change tendency <0.001). With the increase of the number of risk factors the angiography of coronary arteries was performed more rarely (in pts with one optional risk factor – 29.7%; two optional risk factors – 24.9%; all three risk factors – 16.9% in comparison to 39.1% of pts from control group; p for change tendency < 0.001). The revascularization: CABG (Coronary Artery Bypass Graft) and PCI (Percutaneous Coronary Intervention) were performed more

rarely with increasing the number of risk factors (7.7% vs 5.4% vs 2.7% in comparison to 9.1% for control group respectively for CABG; p for change tendency < 0.001 and 11.2% vs 9.0% vs 6.1% in comparison to 16.2% respectively for PCI; p for change tendency <0.001).
Conclusions: Among pts with CHD, who are treated by primary Polish health care physicians, 29.8% are pts with diabetes, 25.7% with RF estimated by GFR and 14,0% are ≥75 years old. People with additional risk factors (diabetes, RF, age ≥ 75 years) are diagnosed and treated worse than those without any risk factors and it is despite the higher risk of cardiovascular events.

P682 Association of the apolipoprotein(a) genomic region with myocardial infarction

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Purpose: An increased level of lipoprotein(a) has been identified as a risk factor for coronary artery disease (CAD) that is highly heritable. The genetic determinants of the lipoprotein(a) level and their relevance for the risk of CAD and myocardial infarction (MI) are incompletely understood. We conducted a case-control study to investigate the association between the apolipoprotein(a) gene region and MI.
Methods: The study population consisted of patients with MI and controls free of CAD and MI, together almost 5000 individuals, all of whom were examined with angiography of coronary arteries. Genotyping was performed with the use of nine single nucleotide polymorphisms, covering the common variation in and near the apolipoprotein(a) gene on chromosome 6.
Results: One (rs3127599) of the polymorphisms examined was associated with MI, with its minor allele (T allele; frequency 29% in the study sample) showing an elevated risk effect (OR 1.14, 95% CI 1.03-1.26, P=0.013). Nine haplotypes with frequencies >1% were inferred from the genotype data, none of which showed convincing evidence of association with MI. Following a prior report, haplotypes with a TxCxxxxTC pattern were merged (n=3; combined frequency 47%) and the composite haplotype (TCTC haplotype) was used as a reference for risk estimations. As a result, the relatively frequent (14%) CCTTGTGTG haplotype (OR 1.18, 95% CI 1.02-1.36, P=0.025) and the rare (2%) CCCTGGATC haplotype (OR 1.61, 95% CI 1.13-2.29, P=0.0075) were associated with elevated risks of MI. Pooling of the haplotypes with a xxTTGTGTx pattern (n=3; combined frequency 28%) yielded a significant risk effect, when compared with the TCTC haplotype (OR 1.16, 95% CI 1.04-1.29, P=0.0086).
Conclusions: This study provides supportive evidence for an association between the apolipoprotein(a) gene region and MI. The haplotypes involved in disease risk are independent from other variations at the apolipoprotein(a) locus, specifically a pentanucleotide polymorphism and the kringle 4 repeat polymorphism, that were associated with MI in prior reports.

P683 The "General Cardiovascular Disease Risk Score" underestimates the risk of cardiovascular events in patients with end-stage renal disease

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Background: The cardiovascular disease (CVD) risk model based on the Framingham Heart Study estimates the risk of any cardiovascular (CV) event in a primary care setting. We compared the predicted CVD risk with the observed rate of events in a large cohort of pt with end-stage renal disease (ESRD).
Methods: 542 pt with ESRD (53±10 years; 58% men; 25% with diabetes, 19% smokers) without CVD at baseline were prospectively followed-up for 5 years. The CV risk was calculated for each participant based on age, gender, diabetes and smoking status, treated/untreated systolic blood pressure, total and HDL-cholesterol. The rate of the primary outcome (CV death, myocardial infarction, unstable angina, stroke, peripheral artery disease, or heart failure) was recorded for each risk category [low (<1%/year); intermediate (1-2%/year); high (≥2%/year)].

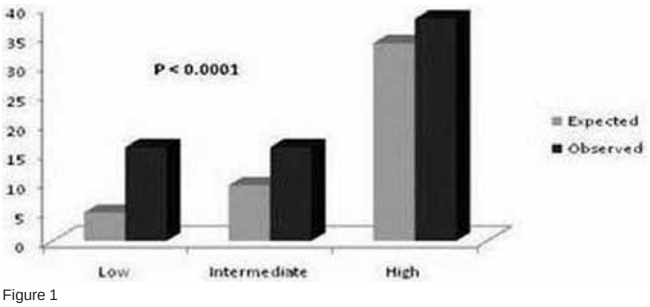

Figure 1

We compared the expected rate of events (based on the CVD risk score) with the observed rate of events, using the Fisher's exact test.
Results: 70 pt (13%) had a first CV event. We found that for each CVD risk category, the observed rate of events was consistently higher than that predicted by the CVD risk score (P<0.0001), particularly in the low- and intermediate-risk categories (see Figure 1).
Conclusions: Pt with ESRD have a greater than predicted risk for CV events. Not only cardiologists should be aware of the underestimated risk but also new models for risk assessment should be developed taking into account renal function as a predictor of CV events in pt with chronic kidney disease without CVD.

P684 Long term prognostic effect of cardiac troponin T in hospitalised patients

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Purpose: Cardiac troponins are increasingly measured in conditions other than acute coronary syndrome (ACS). We investigate the prognostic effect of cardiac troponin T (TnT) and other comorbid factors in affecting 6-year all-cause mortality in an unselected cohort of hospitalised patients.
Methods: Consecutive patients admitted to a university teaching hospital between 02/01/04 – 29/02/04 who had TnT measurement were included. Measurement of TnT was entirely at the discretion of the clinicians and not influenced by the study. Serum TnT level was routinely measured at 12 hours from onset of symptoms in accordance with a hospital wide policy. TnT level was measured by the Elecsys TnT electrochemiluminescence immunoassay ECLIA (4th generation). Patients were separated into those with normal (<0.01 ug/L) or raised TnT levels (≥0.01 μg/l), and further categorised into four groups: (1) unstable angina with normal TnT; (2) non-ACS with normal TnT; (3) ACS with raised TnT; and (4) non-ACS with raised TnT. All survival data were complete.
Results: Of 1,021 patients, 313 patients had raised TnT (195 ACS, 118 non-ACS), and 708 had normal TnT (80 unstable angina, 628 non-ACS). Patients with raised TnT were older (mean age 74.1 years SD (12.4) v 65.6 (16.7); P<0.001), more likely to have previous myocardial infarction (30.4% v 20.3%; P<0.001), diabetes mellitus (20.4% v 10.9%; P<0.001), cerebrovascular disease (19.8% v 12.0%; P=0.001), renal disease (7.0% v 2.8%; P=0.002), hypertension (49.8% v 42.8%; P=0.037), higher Charlson's comorbidity score (mean score 2.0 SD (1.9) v 1.7 (1.9); P=0.021), and were less likely to have coronary revascularisation (5.1% v 10.6%; P=0.005) than those with normal TnT. 6-year all-cause mortality was significantly higher in patients with raised TnT than those with normal level (66.8% v 38.3%; P<0.001). Among 313 patients with raised TnT, 6-year mortality was significantly higher in those with non-ACS than ACS (78.8% v 59.5%; P<0.001). Multivariate logistic regression with backward elimination identified increasing age (OR 1.09, CI (1.07, 1.10); P<0.001), higher Charlson's comorbidity score (OR 1.57, CI (1.41, 1.74); P<0.001), and raised TnT (OR 2.61, CI (1.85, 3.67); P<0.001) as independent predictors for 6-year all-cause mortality. Both ACS with raised TnT (OR 1.85, CI (1.26, 2.73); P=0.002) and non-ACS with raised TnT (OR 4.11, CI (2.40, 7.06); P<0.001) were independent predictors for 6-year mortality.
Conclusions: Hospitalised patients with a raised troponin T level from any cause predicted an excess increase in 6-year mortality than those with normal troponin T level.

P685 Myocardial scar differences between polymorphic and monomorphic ventricular events in ischemic cardiomyopathy: a contrast-enhanced magnetic resonance imaging

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Background: Patients with ischemic cardiomyopathy have an increased risk for ventricular arrhythmia, since myocardial infarction can be the substrate for re-entrant arrhythmias. Contrast-enhanced cardiac magnetic resonance imaging (CMR) has proven to reliably quantify myocardial infarction. Aim of our study was to evaluate correlations between functional and contrast-enhanced CMR findings and spontaneous ventricular tachy-arrhythmias in patients with ischemic cardiomyopathy who underwent implantable cardioverter-defibrillator (ICD) therapy.
Methods: Forty-one patients with ischemic cardiomyopathy and indication for ICD therapy were examined in a 1.5-T whole-body CMR system. Cine images for quantification of left ventricular volumes and function and late gadolinium enhancement images for quantification of myocardial scar extent were acquired in all patients covering the entire left ventricle.
Results: During a follow-up period of 1184±442 days 68 monomorphic and 14 polymorphic types of ventricular tachycardia (VT) could be observed in 12 patients. Patients with monomorphic VT had larger scar volumes (25.3±11.3 vs. 11.8±7.5% of myocardial mass, p<0.05) than patients with polymorphic VT. Moreover myocardial infarction involved more segments in the LAD perfusion territory (86% vs. 20%, p<0.05) than in patients with polymorphic VT.
Conclusion: Patients with spontaneous monomorphic VT during the long-term

follow-up period had more infarcted tissue, which was more often present in the LAD perfusion territory than patients with polymorphic events. These data strengthen the diagnostic benefit of CMR in patients with ischemic cardiomyopathy. CMR may be used for comprehensive risk stratification in patients with ischemic cardiomyopathy undergoing ICD therapy.

P686 Plasma aldosterone and atherosclerotic burden in a population with stable coronary artery disease

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Aims: Aldosterone is associated with clinical events in patients with stable coronary artery disease (CAD) and preclinical studies suggest involvement in atherogenesis. In patients, the relationship of aldosterone with the atherosclerotic process is largely unexplored. We investigated the association of aldosterone levels with markers of atherosclerotic burden in patients with established CAD.
Methods and results: Plasma aldosterone levels (median 96 pg/mL, IQR 69-138 pg/mL) were measured in 2758 ambulatory patients with stable CAD, included in the SMART prospective cohort study. Involvement of multiple vascular territories (CAD plus at least one other manifestation of atherosclerosis), presence of carotid artery stenosis >50%, ankle brachial index (ABI) and carotid intima-media thickness (CIMT) were considered as markers of atherosclerotic burden. Univariate regression analysis showed aldosterone levels to be positively associated with involvement of multiple vascular territories, presence of carotid artery stenosis and negatively with ABI. After correction for possible confounders in multivariable regression analysis, the associations were attenuated. Nevertheless, aldosterone was still significantly associated with involvement of multiple vascular territories.

Table 1. Aldosterone in relation to indicators of atherosclerotic burden

	Univariable			Multivariable		
	OR/β	95%CI	p-value	OR/β	95%CI	p-value
Involvement of multiple vascular territories	1.78	1.36 to 2.33	0.000	1.42	1.05 to 1.92	0.022
Carotid stenosis (>50%)	1.49	1.060 to 02.11	0.023	1.12	0.76 to 1.64	0.575
ABI	–0.043	–0.046 to –0.023	0.000	–0.017	–0.037 to +0.004	0.110
CIMT	0.022	–0.008 to +0.052	0.150	0.002	–0.027 to +0.032	0.882

Odds ratios (OR), for logistic regression, or beta regression coefficients (β), for linear regression, as appropriate, are depicted for aldosterone Quartile 4 vs Quartile 1. Multivariable models are adjusted for age, sex, systolic BP, DM, BMI, creatinine clearance, LDL, hsCRP and smoking.

Conclusion: Our results show an independent relationship of aldosterone with extent of manifest atherosclerosis, although the association with other markers of atherosclerotic burden appeared to be influenced by confounding factors. These result may indeed suggest a relationship of aldosterone with the atherosclerotic process, but the exact mechanisms remain to be elucidated.

P687 Impact of creatinine clearance on coronary artery disease extent and cardiovascular events in patients with normal or mildly impaired renal function

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Purpose: The purpose of this study was to examine the relation between estimated creatinine clearance, coronary artery disease extent, and the risk of major adverse cardiovascular events (MACE), among individuals with normal or mildly impaired renal function.
Estimated creatinine clearance (CrCl) < 60 ml/min is an independent predictor of cardiovascular mortality. However, little is known about the association between CrCl and coronary artery disease (CAD) extent or cardiovascular event rates among individuals without chronic kidney disease (CKD).
Methods: The impact of CrCl on CAD extent and future MACE rates was studied in 1535 consecutive patients with angiographically-proven CAD with mildly reduced or normal renal function, and without history of CKD (CrCl >60 ml/min) as well as in a subgroup of patients (n=606) with normal renal function (CrCl >90 ml/min).
Results: After adjusting for potential clinical and laboratory confounders, CrCl was found to be independently associated with CAD extent in the entire study cohort. The odds ratio per 10ml/min decrement in CrCl was 1.43 (95% CI 1.16-1.74, p=0.001). In patients with CrCl >90 ml/min, the odds ratio per 10ml/min decrement in CrCl was 1.26 (95% CI 1.04-1.52, p=0.017). By Cox regression analysis, CrCl was the strongest independent predictor (HR=1.96 (95% CI 1.23-3.1, p=0.005) of 30-day and 1-year MACE.
Conclusions: Estimated CrCl is a powerful independent predictor of CAD extent and adverse clinical outcomes in patients with normal or mildly impaired renal function.

P688 The value of cystatin C in predicting contrast-induced acute kidney injury in patients with chronic kidney disease undergoing percutaneous coronary intervention

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Background: Contrast-induced acute kidney injury (CI-AKI) is associated with a prolonged in-hospital stay and represents a powerful predictor of unfavorable early and late outcome. Therefore, it has been recommended to monitor renal function in all patients at risk with serial measurements of serum creatinine (sCr) after contrast media (CM) exposure. However, the delayed increase in sCr is a potential reason for overlooking CI-AKI
Purpose: Cystatin C (CyC) is more sensitive than serum creatinine (sCr) to rapidly detect acute changes in renal function. The purposes of the study were to assess whether changes in CyC levels at 24 hours after CM exposure anticipate the occurrence of CI-AKI, defined as an increase in sCr concentration of 0.3 mg/dL from the baseline value at 24-48 hours after administration of the CM and predict the occurrence of 12-month mortality (cardiac death, repeat revascularization, acute stroke).
Methods: We studied 120 patients who underwent elective percutaneous coronary intervention (PCI). The risk factors for CIAKI were measured before and 24-48 hours, 1 month, 3 months and 6 months after PCI. We were observed during the 12months follow-up survey in the group with and without CIAKI.
Results: The frequency of CIAKI occurred in 12 patients (10.0%) with all and 10 patients (17.8%) with moderate renal insufficiency (eGFR 30-59ml/min/1.73m^2) after PCI. A CyC increase concentration ≥20% at 24-48 hours after contrast media exposure was detected in 10 patients (83.3%) with moderate renal insufficiency (p=0.003).
δCystatin C levels with moderate renal insufficiency were significantly higher in CI-AKI patients than in those without CI-AKI (0.217±0.090 vs. 0.138±0.049 mg/L, p=0.007). However, in the patients with moderate renal insufficiency, there were no differences the other factors for CI-AKI as age, anemia, diabetes, congestive heart failure, shock, myocardial infarction, contrast volume, baseline sCr and CyC between the group with and without CI-AKI. Multivariate logistic regression analysis peformed for the patients with moderate renal insufficiency revealed that δcystatin C levels was independently predictive of mortality during 12 months (Odd ratio[95% confidence interval] 0.311 [0.058 to 0.538; p=0.026].
Conclusions: In patients with moderate renal insufficiency, CyC seems to be a reliable marker for the early diagnosis and prognosis of contrast-induced acute kidney injury.

P689 The nature of coronary artery ectasia may differ from coronary atherosclerosis; an evidence from cardiovascular risk factors

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Introduction: Coronary Artery Ectasia (CAE) is defined as localized coronary dilatation that exceeds the diameter of normal adjacent segments or the patient's largest coronary vessel by 1.5 times. Atherosclerosis is a common association with CAE in the western world but not uniformly in all cases.
Purpose: We hypothesize that CAE may have a different pathology to atherosclerosis, and therefore aimed to study the conventional cardiovascular risk factors for coronary atherosclerosis in non atherosclerotic CAE.
Methods: Two independent cardiologists reviewed a total of 18,464 coronary angiograms performed between January 2003 and December 2009 in two European centers. Sixty six patients (age 66.3±10 years, 46 male) were identified as having CAE based on conventional criteria (above). Patients with any coronary lesions (>10% luminal narrowing) or previous coronary intervention were excluded. Another group of 37 patients (age 64.9±8 years, 13 male) with seemingly normal coronary arteries were also examined for comparison. Cardiovascular risk factors were critically studied in the two patient groups.
Results: Pure form of CAE prevalence was slightly less than 0.04%. A univariate analysis showed male gender and smoking as two predictors of CAE (p=0.001 and p=0.04, respectively). On multivariate analysis, gender was the independent risk factor for CAE. In a sub analysis, only 15/66 patients had CAE with no evidence for any coronary irregularity, a prevalence of <0.01%, compared with the remaining 51/66 CAE patients (with minor coronary irregularities of less than 10% narrowing), prevalence of 0.03%. Patients with CAE with no evidence for any coronary irregularity proved to be younger and tended to have all coronary vessels involved compared to the others (P = 0.007, OR =0.9 and 95% CI = 0.83-0.98) and (P=0.003, OR = 8.55 and 95% CI= 1.79-40.9), respectively.
Conclusion: Coronary Ectasia does not seem to be directly related to conventional coronary risks of atherosclerosis. Despite potential similar clinical outcome, coronary ectasia has unique anatomical features which suggest different underlying pathphysiology and disease nature. This early findings remain to be confirmed.

P690 Impact of previous medications and cardiovascular disease on in-hospital mortality in acute myocardial infarction from the Korean acute myocardial infarction registry

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Purpose: Little is known about the impact of previous medications and cardiovascular disease on in-hospital mortality in patients with acute myocardial infarction (AMI) including ST-segment elevation myocardial infarction (STEMI) and non-STEMI.
Methods: Between November 2005 and January 2008, 13,211 eligible patients (9,289 males; mean age=63.1±12.6 year-old) were included from the Korean AMI Registry.
Results: Of these patients, the previous history of taking anti-platelet drugs, beta-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, and statins before admission were present in 14.8%, 8.6%, 10.3%, 10.2%, 5.5%, and 7.1%, respectively. Previous history of coronary heart disease, cerebrovascualr disease, and peripheral vascular disease were present in 16.2%, 7.1%, and 1.1%, respectively. The in-hospital mortality was significantly higher in patients with STEMI compared with non-STEMI (6.3% versus 3.8%, $p<0.001$). Previous anti-platelet drugs, beta-blockers, and diuretics therapy increased the risk of in-hospital mortality. However, there were no significant associations between previous medication and in-hospital mortality after adjustment for confounding variables. Among previous cardiovascular disease, previous cerebrovascular disease was independently associated with increased risk of in-hospital mortality in overall (odds ratio [OR] 1.938, 95% confidence interval [CI] 1.295 to 2.899, p=0.001), and in patients with STEMI (OR 1.906, 95% CI 1.090 to 3.333, p=0.024) and non-STEMI (OR 2.156, 95% CI 1.195 to 3.893, p=0.011) after adjustment for confounding variables.
Conclusion: Previous cardiovascular disease rather than previous medications affect in-hospital mortality in post-MI patients including STEMI and non-STEMI.

P691 The impact of revascularization and optimal medical therapy on six-month clinical outcome in patients with and without congestive heart failure after acute myocardial infarction

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Purpose: Revascularization and optimal medical therapy (OMT) is mainstay of contemporary management of coronary artery disease in modern era. The aims of this study were to determine the interactive effect of revascularization and OMT in patients with acute myocardial infarction (AMI) complicated by congestive heart failure (CHF) on 6-month major adverse cardiac events (MACE).
Methods: Between November 2005 and January 2008, 14,871 patients suspected AMI were included from the Korea AMI Registry, and 9,470 patients (6,649 men; mean age = 63.0±12.5 years-old) followed up 6-month were finally analyzed. Of these patients, 2,595 (27.4%) patients had CHF (Killip class II-IV) at presentation. The 6-month MACE was defined as death, nonfatal MI, and revascularization.
Results: Overall, 8,146 (86.0%) patients underwent revascularization and 4,657 (49.2%) patients received OMT. Patients were categorized into 4 groups based on treatment modalities; revascularization and OMT. Kaplan-Meier survival curves showed the patients underwent revascularization and received OMT had the lowest 6-month MACE (6.1%) and mortality (3.1%), whereas non-revascularized and non-OMT patients had the highest 6-month MACE (33.4%) and mortality (29.9%). The revascularized and non-OMT patients had significantly lower 6-month MACE (14.0% versus 24.3%, $p<0.001$) and mortality (11.4% versus 18.0%, $p<0.001$) compared with the non-revascularized and OMT patients. Among non-CHF, compared with revascularized and OMT group, there was no significant difference in 6-month MACE in revascularized and non-OMT group (adjusted hazard ratio [HR] 1.235, 95% confidence interval [CI] 0.967 to 1.578, p=0.091), whereas non-revascularized and OMT group had significantly higher 6-month MACE (adjusted HR 2.437, 95% CI 1.416 to 4.197, p=0.001) after adjustment for confounding variables in Cox proportional hazard model. Among CHF patients, compared with revascularized and OMT group, there was no significant difference in 6-month MACE in non-revascularized and OMT group (adjusted HR 1.721, 95% CI 0.953 to 3.111, p=0.072), whereas revascularized and non-OMT group had significantly higher 6-month MACE (adjusted HR 1.408, 95% CI 1.026 to 1.931, p=0.034) after adjustment for confounding variables.
Conclusions: This observational study suggest that less use of revascularization in non-CHF patients and less use of OMT in CHF patients are associated with 6-month MACE in post-MI patients. More assertive revascularization in non-CHF patients and more use of OMT in CHF patients are required for reducing 6-month MACE in post-MI patients.

P692 Effects of prediabetes and diabetes on coronary microvascular circulation

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Purpose: Abnormalities of coronary microcirculation have been reported in diabetic patients even in the presence of normal coronary arteries, suggesting the existence of a distinct coronary microvascular dysfunction. It is yet unknown when the microvascular effects on coronary arteries begin to appear in the DM disease course. Coronary flow reserve (CFR), determined by pharmacological stress transthoracic Doppler echocardiography (TTDE), is a reliable and reproducible indicator of coronary microvascular function. We sought to determine the coronary microvascular function of prediabetic patients compared to DM patients and normal population.
Methods: A hundred and thirteen subjects who underwent coronary angiography and who were found to have normal coronary arteries were included in the study. DM and prediabetes were diagnosed according to American Diabetes Association criteria. Transthorasic echocardiography for CFR was performed within 24-48 hours of coronary angiography. All subjects had Doppler recordings of the LAD with adenosine infusion at a rate of 0.014 mg/kg/min.
Results: The clinical and demographical characteristics and laboratory findings of the 3 groups were similar (DM group: n=37, mean age 59.0±8.4 years, 27 females; Prediabetic group: n=38, mean age 62.0±11.3 years, 34 females; Control group: n=38, mean age 60.3±9.1 years, 26 females) except fasting glucose levels. CFR values of the 3 groups were significantly different (DM group CFR=1.7±0.5, prediabetes group CFR=2.1±0.6, control group CFR=2.1±0.4, $p<0.001$). In posthoc analysis, CFR values of the DM group were significantly lower than the prediabetic and control groups (DM vs.prediabetic: $p<0.001$, DM vs. control: $p<0.001$). However CFR levels of prediabetic group were not different from the control group (p=0.287).
Conclusion: We demonstrated that coronary microvascular dysfunction doesn't start in the prediabetic state but it appears after DM becomes overt.

P693 Acute hospital-acquired anemia in patients with acute coronary syndromes

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Purpose: Anemia (A) is common among patients (P) with acute coronary syndromes (ACS) and is associated with poor outcomes. Less is known about acute, hospital-acquired anemia (HAA). Our purpose was to determine the incidence, correlates and prognostic implications of HAA in P with ACS.
Methods: From a population of 519 P consecutively admitted for ACS to a Coronary Unit, we studied 348 P (71% male, age 65±14years) with normal hemoglobin (Hb) at admission. HAA was defined according to criteria proposed by Beutler and Waalen. Mortality (M) was assessed at follow-up (FU) (7.5±5.1months). Uni and multivariate analysis was performed using SPSS 17.0.
Results: HAA occurred in 151 P (43.4%). Hb declined by a mean of 2.1±1.4g/dL. 27 P (17.9%) developed moderate-severe A (Hb<11g/dL). The factors associated with HAA were: female gender (p=0.008), older ages ($p<0.001$), diabetes mellitus (p=0.017), chronic renal disease ($p<0.001$), STEMI (p=0.022), acute heart failure (HF) (p=0.003); lower Hb (14±1.0 vs 15±1.2; $p<0.001$), haematocrit (42±3.4 vs 45±3.9; $p<0.001$) and glomerular filtration rate ($p<0.001$). P with HAA had higher GRACE Score ($p<0.001$), CRUSADE Bleeding Score (32±15 vs 24±12; $p<0.001$) and Outpatient Bleeding Risk (1.6±0.6 vs 1.4±0.7; p=0.001). There were no differences in the incidence of coronariography, angioplasty or use of antiplatelet agents (including Gp IIb/IIIa inhibitors – 32% vs 29%). P with HAA more often had a femoral access (45% vs 28%) or were submitted to crossover (p=0.002), a larger catheter sheath (p=0.014) and longer treatment with enoxaparine (p=0.006). P with HAA had longer hospital stay ($p<0.001$); higher incidence of cardiorenal syndrome (p=0.002) and left ventricular dysfunction (p=0.011). No differences were found in documented bleeding (7.9% in P with HAA; p=0.126). 3.3% of P with HAA were transfused (p=0.01). 112 P (80%) were discharged with A criteria. Mortality was parallel to A severity (p=0.003): mild (5.6%) vs moderate (9.1%) vs severe (40%). In FU there was higher M in P with HAA (p=0.003). After adjustment for GRACE score, P with moderate-severe A had higher M in FU (p=0.048; HR 3.426).
Conclusions: Nearly half of ACS P developed HAA in the absence of documented bleeding. Bleeding scores correctly predicted these P. HAA was only partially explained by the use of drugs with bleeding potential. The vascular access for coronariography was crucial. We confirmed that HAA is associated with worse prognosis, being an independent predictor of mortality even after adjustment for Grace Score and therefore is an important target for prevention efforts.

P694 Acute kidney injury is a stronger predictor of one-year mortality than chronic kidney disease in patients with acute myocardial infarction. The HEROES study

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Purpose: We investigated the incidence, clinical predictors and prognostic value of acute kidney injury (AKI) regarding 1-year mortality in acute myocardial infarction (AMI) patients with and without chronic kidney disease (CKD).
Methods: We collected in-hospital data from 447 patients hospitalized for AMI in our institute within 12 hours of symptoms' onset. From blood samples obtained on admission and throughout hospitalization hemoglobin, white blood cell count, C-reactive protein, B-type natriuretic peptide, plasma glucose, troponin I and baseline and peak creatinine levels were measured. MDRD equation was used to estimate glomerural filtration rate (GFR). AKI was defined as a 25% or more decrease in GFR during hospital stay. CKD was defined as an estimated GFR between 15 and 59 ml/min/1.73m^2. Ejection fraction was calculated on admission with 2D echocardiography. All patients underwent coronary arteriography and the revascularization status (complete or not) was also recorded. The end-point was all-cause mortality after one year of follow-up.
Results: AKI was detected in 63 pts (16.7%). Age (OR 1.074; 95%CI 1.041-1.109), ejection fraction (OR 0.951; 95%CI 0.923-0.980) and white blood cell count (OR 1.089; 95%CI 1.004-1.181) were the only independent predictors of AKI. The incidence of 1-year mortality was 10.7% (48 deaths). Patients with AKI exhibited higher 1-year mortality (37.5% vs. 6.3%, log rank $p<0.001$). AMI patients with AKI and CKD (n=28, 6.3%) had a 17.8-fold greater incidence of mortality compared to those without either AKI or CKD (n=278, 62.2%) (log-rank $p<0.001$). Moreover, patients with AKI but not CKD (n=36, 8.1%) exhibited a 5.3-fold greater incidence of mortality compared to those without AKI and CKD (log-rank $p<0.001$) while the 2.3-fold increased mortality rate in patients with AKI but not WRF (n=105, 23.5%) reached marginal statistical significance (log-rank p=0.041). Finally, AMI patients with AKI but not CKD compared to those with CKD but not AKI had 2.4-fold greater incidence of one-year mortality (log-rank p=0.06). By applying multivariate Cox regression analysis AKI (adjHR 5.024, $p<0.001$), BNP (adjHR 2.859, p=0.004), ejection fraction (adjHR 0.943, p=0.003) and admission diastolic blood pressure (adjHR 0.971, p=0.017) remained the only predictors of death.
Conclusions: AMI patients with AKI and normal baseline renal function appear to have a worse prognosis than patients with CKD but not AKI, while co-existence of both AKI and CKD acts synergistically and further increases one-year mortality.

P695 Relative hyperandrogenemia in central obesity as possible predictor of coronary artery disease in postmenopausal women

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Objectives: Hypoestrogenemia is an established metabolic risk factor for cardiovascular diseases in women. After menopause 34-45% of women show extensive abdominal fat deposition, therefore aromatizing of estrogens continues particularly in fat tissue. Development of central obesity impairs normal process of estradiol conversion and benefits the predominance of inactive estrone therefore leading to relative hyperandrogenemia. The purpose of our study was to establish the role of hyperandrogenemia and central obesity for coronary artery disease development in postmenopausal women by means of determining the peculiarities of the pituitary activity, dehydroepiandrosterone sulfate level and blood lipoproteins levels.
Methods: 63 females in postmenopause were evaluated. The patients were randomized into 2 groups comparable by age and postmenopause duration. 1st group included 32 women with signs ofcentral obesity, 2nd – 31 women with normal body mass index and waist/hip ratio. All patients were assessed by Kupperman menopausal index for climacteric symptoms evaluation, blood lipids level, levels of follicle stimulating & luteinizing hormones, dehydroepiandrosterone by means of radioimmune assay.
Results: Gonadotropins in all patients reflected the postmenopausal changes: high levels gonadotropins were equivocal in 2 groups. The mean value of Kupperman index in 1st group was 45,2±6,7, in 2nd - 34,7±2,3 what evidenced more severe climacteric symptoms in women withcentral obesity. There was significant predominance of women with hyperandrogenemia among those with elevated body mass index (28,7±1,8 kg/cm^2) and signs of central obesity. Atherogenic changes of blood lipids were registered in both groups: increased levels of total cholesterol and low density lipoproteins were found in women with hyperandrogenemia ($p>0,05$); increased levels of triglycerides and low levels of high density lipoproteins were noted in women with central obesity ($p<0,05$). Level of dehydroepiandrosterone sulfate showed positive correlation with triglycerides and negative – with high density lipoproteins levels.
Conclusions: Postmenopausal women with central obesity have relative hyperandrogenemia and develop more severe symptoms of climacteric syndrome than women with normal waist/hip ratio. Levels of dehydroepiandrosterone have positive correlation with triglycerides and negative – with high density lipoproteins levels. Evaluation of the waist/hip ratio and consequentially serum levels of dehydroepiandrosterone should be included for screening patients in postmenopuse for individual coronary artery disease risk evaluation.

P696 CETP polymorphism adds to the characterisation of premature coronary heart disease and multiple vessel disease

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Patients with premature coronary syndromes impose an enormous challenge of diagnosis and long-term management. Traditional markers can be ephemeral or unespecific and may fail to identify patients who are at high risk for cardiovascular disease, to develop severe disease or have poorer outcomes. Traditional risk factors do not explain all of the risk for CHD, and emerging risk factors have the potential to improve global risk assessment.
Aim: We analysed a common polymorphism in the Cholesteryl Ester Transfer Protein (CETP) gene (Taq1B) related to lipid profiles.
Method: An atypical model was designed to compare a set of 570 male Canarian patients (P) with early onset acute coronary syndromes (under 55 years old) with 199 healthy, aged controls (c), far beyond the age of premature CHD (over 65 y-o). PCR-RFLP techniques rendered similar B1B1-B1B2/B2B2 allele distribution in both groups.
Results: The mean age was 46 for patients (P) and 71 for controls (c); $p<0.000$. The case/control analysis showed significant differences ($p<0.000$) in the prevalence of family history of CHD (61 P/39% c), family premature CHD (35 P/7% c), dyslipidemia (71 P/53% c), hypertension (48 P/74% c), mean atherogenic index (log triglycerides/HDL-cholesterol: 0.63 P/0.47 c) and exercise tolerance (METS: 10 P/7 c). The first ACS was myocardial infarction in 64% and angina in 46%; multivessel disease was present in 55%, 63% underwent revascularisation (PCI 62, CABG 7%; restenosis rate 9%) and 33% had recurred ACS. B2B2 genotype was more common among patients (15 P/10% c; $p<0.045$); while variant homozygous genotype was associated with multivessel disease (47/37%; $p<0.013$). Our model predicted 74.1% of premature CHD with family history of CHD and common CEPT genotype. A logistic regression model built with risk factors, genotypes, clinical features and atherogenic index: depicted dyslipidemia ($p<0.019$) and variant CETP genotype ($p<0.031$) to explain 72.5% of multivessel disease in patients with angina.
Conclusions: Despite an unusual model with a considerable age gap our young patients had a very high prevalence of risk factors. Variant CETP genotype is an inexpensive suitable marker for premature CHD and multivessel disease, thus contributing to characterise individual variability.

P697 Ivabradine impact on heart rate in patients with chronic obstructive lung disease and coronary heart disease after the inhalation of salbutamol

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Background: Tachycardia is a frequent display of chronic obstructive pulmonary disease (COPD) which complicates accompanying coronary heart (CHD).
Aim: To assess an effect of salbutamol 400 μg and ivabradine 5 mg on heart rate in patient with COPD combined with CHD.
Methods: Cross-randomized controlled study. Study included twenty patients (18 males and 2 females) with COPD combined with CAD, NYHA I-III. Average age was 62±8.5 yrs, FEV1 - 49.1±25.3. 55% of patients had pulmonary arterial hypertension at a level more than 30 mm. Hg estimated echocardiographycally. On six minutes walking test the average distance was 447±63.5 m. Standard inhalation test with about 400 mkg of salbutamol within two consecutive days was performed. In one of the days, the patient accepted ivabradine 5 mg per os certain under the table of random numbers and 3 hours prior to inhalation.
Results: Results of this study have been divided into groups: "salbutamol 400 mkg" (S) and "salbutamol 400 mkg+ivabradine 5 mg" (S+I). The positive gain of heart rate frequency was marked in group S after salbutamol inhalation, in average on 5.5±10.5 impacts in a minute ($p<0.03$). Gain of heart rate frequency was - 2.4±10.5 in S+I group (p=0.9). The gain of heart rate frequency in S-group markedly exceeded the gain in S+I-group ($p<0.05$). Salbutamol inhalation caused the positive gain of FEV1 in S-group 6±7.4% and in S+I-group on 7.7±10.9% from due ($p<0.01$). The gain between two groups did not differ statistically.
Conclusion: Ivabradine prevent tachycardia after inhalation of high doses of salbutamol and has no impact on lung function in patients with COPD and CAD.

P698 Prognostic value of N-terminal pro-brain natriuretic peptide in patients with acute myocardial infarction and chronic kidney disease

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Purpose: Renal dysfunction has been shown to affect N-terminal pro–brain natriuretic peptide (NT-proBNP) levels and the prognostic value of NT-proBNP levels in patients with chronic kidney disease has been questioned. The purpose of this study was to evaluate prognostic value of NT-proBNP in patients with acute myocardial infarction (AMI) and chronic kidney disease (CKD).
Methods: Between November 2005 and January 2008, 834 post-MI patients (560 males; mean age = 64.7±11.7 year-old) followed up more than six-month were included. Glomerular filtration rate was estimated (eGFR) using the abbreviated Modification of Diet in Renal Disease Study equation. Patients were categorized into two groups according to the level of eGFR at baseline; Group 1 (eGFR <60 ml/min/1.73 m^2) and Group 2 (eGFR ≥60 ml/min/1.73 m^2). The 6-month major adverse cardiac events (MACEs) were defined as a composite of death, non-fatal MI, and revascularizations.
Results: During the follow-up, 57 (11.4%) MACEs occurred. Log-transformed NT-proBNP levels increased significantly with increasing eGFR grades and inversely correlated with eGFR in patients with (r = - 0.544, p<0.001) or without CKD (r = - 0.158, p<0.001). In multivariate Cox regression analysis, log-transformed NT-proBNP (hazard ratio [HR] 1.342, 95% confidence interval [CI] 1.013–1.778; p=0.040) in addition to systolic blood pressure (HR 0.988, 95%CI 0.979–0.997; p=0.010), eGFR <60 ml/min/1.73m^2 (HR 2.776, 95%CI 1.238–6.244; p=0.013), percutaneous coronary intervention (HR 0.349, 95%CI 0.155–0.786; p=0.011), and multi-vessel disease (HR 2.431, 95%CI 1.188–4.973; p=0.015) were independent predictors for 6-month MACEs after adjustment for clinical characteristics, angiographic findings, and procedural data. In receiver-operator characteristic curve, the area under curve (AUC) of the NT-proBNP for predicting 6-month MACEs was 0.681±0.040 (sensitivity 58.7%, specificity 72.3%; p<0.001), and optimum cut-off value was 10,816 pg/mL in Group 1, whereas the AUC of NT-proBNP was 0.732±0.036 (sensitivity 72.9%, specificity 68.5%; p<0.001), and optimum cut-off value was 691 pg/mL in Group 2. Kaplan-Meier survival curve showed patients with NT-proBNP ≥10,816 pg/mL in Group 1 (52.9% versus 23.2%; log-rank test p<0.001) and patients with NT-proBNP ≥691 pg/mL in Group 2 (15.6% versus 3.0%; log-rank test p<0.001) had significantly higher 6-month MACEs.
Conclusions: Although renal function is a significant confounder of NT-proBNP level, elevated NT-proBNP levels have clinical significance even in post-MI patients with CKD.

P699 Myeloperoxidase levels predict progression of coronary atherosclerosis in diabetic patients

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Purpose: While inflammation has been proposed to contribute to the adverse cardiovascular outcome in diabetic patients, the specific pathways involved have not been elucidated. The leukocyte derived product, myeloperoxidase (MPO), has been implicated in all stages of atherosclerosis. The relationship between MPO and accelerated disease progression observed in diabetic patients has not been studied.
Methods: 881 patients with angiographic coronary artery disease underwent serial evaluation of atherosclerotic burden with intravascular ultrasound. Disease progression in patients with (n=199) and without (n=682) diabetes, stratified by baseline MPO levels was investigated.
Results: MPO levels were similar in patients with and without diabetes (1255 v 1362 pmol/L, p=0.44). No relationship was observed between increasing quartiles of MPO and either baseline or serial changes in levels of percent atheroma volume (PAV) in patients without diabetes. In contrast, increasing MPO quartiles were associated with accelerated PAV progression in diabetic patients (Table). While achieving LDL cholesterol levels < 80 mg/dL was associated with less disease progression, a greater benefit was observed in diabetic patients with lower (-0.59±0.57 v 1.20±0.50%, p=0.008) compared with higher (1.59±0.57 v 2.47±0.47%, p=0.73) MPO levels at baseline.
Conclusions: Increasing MPO levels are associated with greater progression of atherosclerosis in diabetic patients. This highlights the importance of MPO pathways in promoting diabetic cardiovascular disease and identifies patients who require more intensive modification of risk factors.

Atheroma Volume and baseline MPO

Parameter	MPO Quartiles				P Value
	<780 pmol/L	780-1369 pmol/L	1374-2278 pmol/L	>2278 pmol/L	
Patients Without Diabetes (n=682)					
Baseline PAV	39.2±9.5	38.4±10.6	38.3±9.2	39.4±10.3	0.48
Change PAV	0.28±0.36	0.88±0.35	0.60±0.34	0.67±0.34	0.53
Parameter	MPO Quartiles				P Value
	<553 pmol/L	553-1213 pmol/L	1216-2251 pmol/L	>2251 pmol/L	
Patients With Diabetes (n=199)					
Baseline PAV	40.9±9.5	41.2±9.6	40.2±9.8	41.7±9.99	0.55
Change PAV	0.34±0.58	0.78±0.56	2.16±0.55	2.21±0.56	0.007

P700 In hospital deterioration of glomerular filtration rate - prognostic predictor in acute coronary syndromes

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Introduction: The relationship between renal dysfunction and cardiovascular risk is well established. In patients (pts) with acute coronary syndrome (ACS), the presence of renal dysfunction on admission is associated with a worse prognosis. However, the role of in-hospital deterioration of renal function (DRF) is not well established.
Purpose: To determine the prognostic impact of the DRF in pts admitted with ACS.
Methods: We studied 2435 pts admitted to a coronary care unit with ACS over 7 years (2004-2010). For each patient, plasma creatinine on admission and during hospital stay was determined. Then, the glomerular filtration rate (GFR) was calculated both for plasma creatinine value on admission and for its lowest value using Cockroft-Gualt equation. The DRF was considered to be significant if reduction of GFR was greater than 25% of the admission value (definition of acute renal failure according to the Acute Dialysis Quality Initiative). Primary outcome was 6-month mortality.
Results: The significant DRF was detected in 366 (15%) pts. These pts were older (p<0.001), more often women (p<0.001), had higher prevalence of diabetes (p<0.05), hypertension (p<0.05) and renal failure (p<0.001) and a lower prevalence of smoking (p<0.001). At admission, these pts were more often in Killip class (KK)>1 (p<0.001) and had lower mean hemoglobin levels (p<0.001). During the hospital stay they had more often KK maximum>1 (p<0.001). In-hospital mortality (15.5% vs 3.3%; p<0.001), in-hospital reinfarction (4.9% vs 2.3%; p<0.05) and 6-month mortality (12.3% vs 4.1%; p<0.001) were higher in pts with DRF. After adjustment for potential confounding variables in a logistic regression model, the DFR remained as a significant independent predictor of 6-month mortality [Odds Ratio (OR) = 2.5, 95% confidence interval (CI):1.7-3.6; p<0.001]. The other independent predictors of 6-month mortality were age (OR = 1.03, 95% CI: 1.01-1.05; p=0.001), preexisting renal failure (OR =1.6, 95% CI: 1.1-2.5; p=0.025), KK at admission>1 (OR=1.6, 95% CI: 1.1-2.5; p=0.035) and KK maximum> 1 (OR = 3.8, 95% CI: 2.3-6.3; p<0.001).
Conclusion: In this population, the DRF was a powerful independent predictor of 6-month mortality. It should be considered in risk stratification of pts with ACS and in the implementation of aggressive therapeutic measures in the short and long term.

P701 Videodensitometric myocardial perfusion abnormalities in diabetic patients with normal epicardial coronary arteries

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Background: Disturbances of coronary circulation with presumed microvascular complications but no significant coronary artery obstruction (macrovascular disease) have been reported in patients with diabetes mellitus (DM). The present study was designed to evaluate regional myocardial perfusion abnormalities by a novel computerized videodensitometric method in patients with versus without DM and normal epicardial coronary arteries.
Methods: The study comprised 11 diabetic patients who underwent coronary angiography with a negative result (<50% intraluminal diameter stenosis). Their results were compared to 62 non-diabetic matched controls with normal epicardial coronary arteries. The computerized method for myocardial perfusion assessment was based on the analysis of time-density curves (TDC) measured over the coronary artery-related myocardial region of interest. During assessments, maximal density of the TDC (Gmax) and time to reach maximal density (Tmax) were measured on the filtered curve. Gmax/Tmax of the TDCs in left anterior descending- (LAD), left circumflex (CX)- and right coronary (RC)-related myocardial regions on X-ray coronary angiograms were used as quantitative myocardial perfusion parameters. Arteries were masked out from regions of measurement improving sensitivity of measurements.
Results: Gmax/Tmax values were decreased in diabetic patients compared to non-diabetic subjects in LAD-, CX-, and RC-related coronary artery territories on coronary angiograms (Gmax/Tmax–LAD: 2.69±0.38 vs. 3.23±1.39, p<0.05, Gmax/Tmax–CX: 2.13±0.92 vs. 2.96±1.19, p<0.05, Gmax/Tmax–RC: 1.87±0.64 vs. 2.49±1.06, p<0.05).
Conclusions: Reduced Gmax/Tmax values of the TDCs assessed on coronary angiograms by a recently developed computerized videodensitometric method could be measured suggesting myocardial perfusion abnormalities in diabetic pa-

tients compared to non-diabetic subjects with normal epicardial coronary arteries.

P702 Acute coronary syndrome and sleep apnea syndrome, a surprising association?

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Preamble: The Sleep Apnea Syndrome (SAS) is related to cardiovascular events. The prevalence of SAS among Acute Coronary Syndrome (ACS) patients (P) is higher than in the general population. Unfortunately, the screening of SAS is rarely performed in ACS patients.
Purpose: To evaluate: 1) the prevalence of SAS in P admitted with ACS in our coronary care unit (CCU) 2) which are the predictors of SAS in P with ACS.
Methods: Prospective study including P consecutively admitted in our CCU with ACS with coronary disease confirmed by angiography. P not living in our hospital's reference area or with previous diagnosis of SAS were excluded. We assessed demographic data; anthropomorphic data such as neck circumference, waist circumference and body mass index (BMI); personal history of: hypertension, type II diabetes, smoking, dyslipidemia, chronic angina or ACS; and Epworth Sleepiness Scale to evaluate daytime sleepiness. The sleep study was conducted with the Apnea Link device during hospitalization or after discharge. It was considered diagnosis of SAS for an apnea-hypopnea index (AHI): number of apneas and hypopneas per hour of sleep $\geq$5. The SAS was considered mild for AHI $<$15, moderate for AHI between 15 and 29 and severe for AHI $\geq$ 30. The study was conducted with the permission of the Ethics Committee and with informed consent of all P. The data were treated statistically with Medcalc 9.3.
Results: In a period of 4 months were admitted 91 P with ACS. We excluded 33 P (24 not residents, 7 not cooperative, 1 died and 1 had a previous diagnosis of SAS). The study included 58 P, 43 (74%) were male, the average age was 62$\pm$12 years and the mean BMI was 27$\pm$3 kg/m^2. The median time to perform the study was of 17.5 days. The SAS was diagnosed in 36 cases (62%), and was classified as mild in 20 (34.5%), moderate in 9 (15%) and severe in 7 (12%). When comparing the SAS group with the group without SAS there was significantly statistical difference among the male P group (P=0,011), among P with history of chronic angina (P=0,043) and among P with daytime sleepiness (P=0,019). The P were sent to a pneumology appointment to confirm the SAS by polysomnography and to initiate therapy with continuous positive airway pressure or servo-ventilation according to the clinical situation.
Conclusions: 1- In our study we found a high prevalence of SAS in P hospitalized with ACS (62%), and of these 44% presented moderate or severe SAS. 2- The results support the need for a screening of SAS in P admitted with ACS. 3- The male P, those with chronic angina or with daytime sleepiness should be the primary target of screening.

P703 Cystatin C: a predictor of outcome in patients with acute coronary syndrome and normal GFR

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Purpose: Evaluate the prognostic value of cystatin C in patients (pts) with acute coronary syndrome (ACS) and normal glomerular filtration rate (GFR$\geq$60ml/1,73m^2) at admission to the coronary care unit (CCU).
Methods: We evaluated retrospectively the total number of consecutive patients with ACS admitted to our CCU from June 2009 till October 2010. After excluding pts with GFR$<$60 ml/1,73m^2, the population was divided into two groups according to cystatin C level at CCU admission – Group A $<$0,95mg/dl; Grupo B $\geq$0,95mg/dl. All pts were followed for a minimum of one month (mean follow up of 7,1$\pm$5,2 months) and major adverse cardiac events (MACE) were assessed – cardiovascular death (CVD), myocardial infarction (MI), stroke, heart failure hospitalization (HFH) and composite MACE.
Results: A total of 519 pts were admitted to the CCU during the previously mentioned period, 242 of which had normal GFR (63$\pm$13,4 years; 29,8% women; 43,8% with ST elevation MI). At follow up, composite MACE was significantly lower in Group A (188 pts) than in Group B (OR 2,5; p=0,014), mainly due to lower HFH (OR 3,8; p$<$0,04) e and CVD (OR 24; p$<$0,0001). There were no differences between the two groups regarding MI and stroke (p=ns).
Conclusions: In pts with ACS and normal GFR at hospital admission, high levels of cystatin C seem to predict a worse prognosis at follow up. Routine cystatin C determination can therefore contribute to an early identification of higher risk ACS pts.

P704 Echocardiogarphic epicardial fat thickness on one-year clinical outcomes in patients with coronary stenting

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Background: Several studies identified independent clinical predictors of restenosis after percutaneous coronary intervention (PCI) including female gender, diabetes, hypertension, smoking, BMI, multivessel disease and multiple stenting.
The aim of this study is to assess the relationship of epicardial adipose tissue (EAT) and clinical outcomes after PCI.
Methods: We consecutively enrolled 399 patients with significant coronary artery disease, who received successful PCI. One year angiographic follow-up was obtained and angiographic outcomes were compared with EAT thickness by echocardiography. Clinical restenosis was defined as target lesion revascularization (TLR). TLR was defined as clinically indicated revascularization of the index lesion during follow-up. Revascularization was decided clinically indicated if there was $>$70% diameter stenosis on angiography or $>$50% stenosis with a positive stress test or ischemic symptoms. The target lesion was considered to be the area covered by the previous stent site plus a 5-mm margin proximal and distal to the stent edges.
Results: Mean EAT of 399 patients was 3.3$\pm$1.9mm. The mean follow-up interval was 12$\pm$5months. Mean EAT was increased in patients undergoing TLR than those without clinical restenosis (3.2$\pm$1.9 vs. 3.8$\pm$1.8mm, p=0.003). Table shows the multiple logistic analysis of the clinical predictors for restenosis. In addition to the well-known restenosis predictors, EAT was an independent factor associated with clinical restenosis in this study population.

Risk factors	Odds ratio (95% CI)	p
Hypertension	1.361 (0.787–2.353)	0.271
Diabetes mellitus	1.519 (0.847–2.724)	0.161
Smoking	2.253 (1.091–4.650)	0.028
Gender	1.197(0.649–2.210)	0.564
Body Mass Index	1.022 (0.702–1.488)	0.908
Multi-vessel disease	1.878 (1.053–3.348)	0.033
Multiple stenting	2.022 (1.156–3.536)	0.014
EAT thickness	1.019 (1.005–1.034)	0.008

Conclusion: This study demonstrates that the EAT thickness is related with clinical restenosis in patients who underwent PCI. The EAT thickness might provide additional information for future restenosis after PCI.

P705 Prevalence and determinants of elevated high-sensitive cardiac troponin T levels among patients with non-cardiac cause of chest pain

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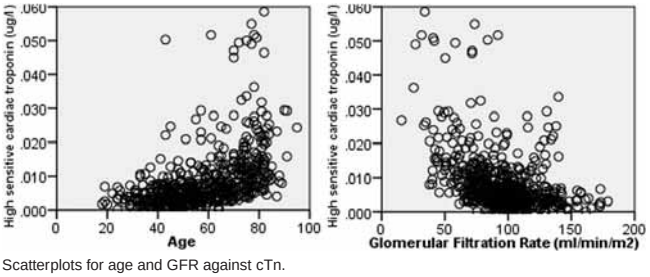
Purpose: To evaluate the prevalence of high-sensitive cardiac troponin T (hs-cTnT) elevation and determine its association with cardiovascular risk factors among patients diagnosed with non-cardiac cause of chest pain. We were particularly interested in age and and renal function quantified by glomerular filtration rate (GFR).
Methods: In a prospective observational international multicenter study, we enrolled consecutive patients presenting to the emergency department with symptoms suggestive of AMI. Of 1181 patients enrolled, 572 patients were diagnosed with a non-cardiac cause of chest pain. Final diagnoses were adjudicated by 2 independent cardiologists. Multiple linear regression analyses were used to determine the important predictors of hs-cTnT. Different curve estimation regression statistics were used to determine the best relation of age and GFR with hs-cTnT.
Results: 88 patients (15%) had hs-cTnT $>$0.014 ug/l ($>$99th percentile for healthy population). When data was input using enter method for linear regression analysis to predict hs-cTnT; age, GFR, coronary artery disease, previous percutaneous coronary intervention, pulmonary embolism, peripheral artery disease, renal insufficiency, use of Aspirin and Diuretic on admission emerged as significant factors (Adjusted R square=0.40). When only age and GFR were entered in the equation (Adjusted R square=0.27), age was the more important covariate. Hs-cTnT increased exponentially with age and had a linear relationship up-to 0.014 ug/l. However an inverse curve best explained the relationship between GFR and hs-cTnT.



Scatterplots for age and GFR against cTn.

Conclusion: Unknown chronic cardiac disease and/or acute cardiac involvement

in non-cardiac conditions and NOT renal dysfunction are the cause of most of the increased hs-cTnT levels in patients with non-cardiac cause of chest pain.

P706 Is contrast echocardiography safe and useful for the assessment of the left ventricular function in the perioperative period after cardiac surgery? A pilot study

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Background: Myocardial contrast echocardiography (CE) improves quality of standard echocardiography. Value of CE during early postoperative period after CABG has not yet been well established.
Aim: We aimed to evaluate the accuracy and safety of CE applied for the assessment of LV function in patients after CABG in the setting of cardiosurgery postoperative unit (CPU) in comparison with conventional transthoracic echocardiography (TTE).
Methods: Echocardiographic contrast agent Sono-Vue (Bracco, Italy) was administered in 30 consecutive patients with technically difficult TTE, after CABG treated at CPU. Improvement of the quality of echocardiographic imaging was assessed by the number of LV segments possible to evaluate. LVEDV, LVESV and LVEF were calculated before and after contrast administration.
Results: There were no side effects after contrast administration. Number of LV segments visualised after CE increased from 8,0±4 to 16,9 segments in all patients (52,4% of improvement). 272 (52,3%). out of 510 segments were described as poorly visible, while only 4 (0,8%) segments were not visible after contrast administration. 63 (12%) segments from visible hypokinetic, akinetic and dyskinetics segments were classified in a wrong way. LV volumes were smaller and EF significantly higher after CE in comparison to standard TTE (EDV 127 ml vs. 98 ml; ESV 65 ml vs. 45; p=0,0002 and p=0,0016, respectively). In all methods used: visual, Simpson's method and biplane method EF was significantly higher in comparison to standard TTE (p=0,012, p=0,0088, p=0,00065, respectively). In patients after surgical LV restoration CE enabled to assess LV geometry, patch localization and excluded the presence of LV thrombus.
Conclusions: CE is a rapid, simple, and safe technique when performed at bedside in the cardiosurgery postoperative unit setting, with positive impacts on the results of both segmental and global wall motion analysis. Application of contrast echocardiography may help differentiate conditions of LV systolic dysfunction immediately after CABG surgery.

P707 Links between sleep apnoea syndrome, coronary atherosclerotic burden and cardiac biomarkers in patients with stable coronary artery disease

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Objectives: This study sought to evaluate the links between sleep apnoea syndrome (SAS), coronary atherosclerotic burden, and cardiac biomarkers in patients with stable coronary artery disease (CAD).
Background: SAS is highly prevalent in the population with cardiovascular diseases, although it is not clear whether SAS has any link to coronary atherosclerotic burden, nor is there any information about its pathophysiology in patients wtih stable CAD.
Methods: We prospectively studied 83 consecutive patients who underwent diagnostic coronary angiography or scheduled percutaneous coronary intervention in 2008. SAS was evaluated by an ambulatory polygraphic monitoring device during sleep. Coronary atherosclerotic burden was evaluated by the Gensini score, and myocardial stress/injury were assessed by measuring plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high sensitivity troponin T (hs-TnT).
Results: Patients with an apnoea hypopnea index (AHI) above 15/hour (n = 32) showed a significantly higher Gensini score (35.7±38.0 vs. 20.1±19.7, p=0.033) than those with an index below 15/hour (n = 37). The higher AHI group revealed significantly higher NT-proBNP levels (275.8±402.6 pg/ml vs 131.9±146.3 pg/ml, p=0.047) and hs-TnT levels (0.011±0.005 vs 0.008±0.003 ng/ml, p=0.015). AHI had significant correlations with the Gensini score (r = 0.253, p=0.036), NT-proBNP (r = 0.266, p=0.027) and hs-TnT (r = 0.274, p=0.023).
Conclusions: Severe SAS has a profound link to the severity of coronary atherosclerotic burden, and silent minute myocardial ischemia and injury with elevated NT-proBNP and hs-TnT.

P708 Influence of diabetes mellitus type 2 and type D personality on the incidence of multifocal atherosclerosis

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Objective: To study the effect of diabetes mellitus (DM) type 2 and type D personality in the incidence of multifocal atherosclerosis (MFA) among patients of cardiovascular surgery clinic.
Patients and methods: 942 patients (774 men and 169 women), median age 58,6 yrs (range 34 to 82 yrs), assessed in cardiovascular surgery clinic before the coronary bypass (CABG), carotid and major vascular surgery. Type D personality was determined by DS-14 scale. The simultaneous presence of hemodynamically significant stenoses in two or more arterial basins was considered as MFA. Hemodynamically significant stenosis were considered in case of plague narrow 50% or more of the lumen.
Results: 71.3% of patients underwent CABG, elective percutaneous coronary intervention was performed in 4.7%, 10.3% of patients underwent carotid surgery, and 12% and 5.8% peripheral and abdominal aortic reconstruction. Patients with DM accounted for 15.2% of all patients. Type D was detected in 19.2% of patients. Prevalence of MFA was 39.3% among all patients. Using logistic regression analysis of factors influencing the prevalence of the MFA. In the univariate logistic regression model the following variables are included: gender, age, smoking, obesity, body-weigt index, presence of DM, serum fibrinogen and creatinine level, glomerular filtration rate (GFR) by MDRD, lipid profile: the level of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, the value of left ventricle ejection fraction and left atrium size, measured by echocardiography and the presence of type D personality. In univariate analysis such factors as age, serum creatinine, GFR MDRD and presence of type D personality are revealed as the predictors of MFA. The next step was multivariate logistic regression analysis, including variables for which values of the criterion of statistical significance in univariate analysis were less than 0.2. In multivariate analysis only DM and type D influenced on the prevalence of the MFA, regardless of age, renal function and systolic function. Moreover, the presence of DM almost doubled the prevalence of MFA (OR 1.948, CI 1.012-3.749, p=0.04), and the presence of type D personality led to 15-fold increase the likelihood of MFA (OR 15.042, CI 6.984-32.396, $p<0.001$).
Conclusions: The presence of DM and type D personality have a significant impact on the development of the MFA, regardless of age, renal function and systolic function.

P709 Prognostic implications of acute gastrointestinal bleeding in acute coronary syndrome: intrahospital follow up

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Purpose: The use of multiple antithrombotic drugs and aggressive invasive strategies has increased the risk of major bleeding in acute coronary syndrome (ACS) patients. It is not known to what extent bleeding determines clinical outcome. The aim of this study was to assess the role of gastrointestinal bleeding on intrahospital prognosis in patients with acute coronary syndrome.
Methods: Between January 2008 and December 2008, 300 patients, with acute coronary syndrome, were randomized to either oral pantoprazole (20 mg/day during hospital stay) or no therapy. The primary study end point was mortality and the secondary end points were recurrent myocardial infarction and stroke) during short term follow up.
Results: Follow-up was completed in all 300 (100%) of patients. In the pantoprazole group, the drug was well tolerated (without any side effects) and was maintained in 100% of patients. 3/150 (2.%) pts in the pantoprazole group died and 7/150 (4.7%) died in the control group og patients ($p<0.05$). 1/150 pts suffered re-infarction in the pantoprazole group and were no reinfarctions in the controle group of pts. In total, 9/300 (3.0%) of patients had gastrointestinal bleeding; 2/150 (1.3%) in pantoprazole group – without any major bleeding and 7/149 (4.7%) in the control group, ($\chi 2 = 2.899$; p=0.08) - 4/149 (2.7%) were major; ($\chi 2 = 4.081$; p=0.06) for major bleeding. Transfusion was required in 1/150 (0.7%) in the pantoprazole group and in 6/149 (4.0%) in the control group of patients ($\chi 2 = 3.691$; p=0.05).
Conclusions: This randomized, controlled, and unblinded study showed that the administration of the oral pantoprazole, during hospital stay, in pts with acute coronary syndrome was associated with a trend towards lower mortality rate, lower bleeding rate and lower need for blood transfusion.

P710 Pattern of culprit coronary atheroma formation among young patients presented with ST elevation myocardial infarction undergoing coronary angiography and its association with conventional risk factors

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Background: Large epidemiology studies such as INTERHEART have shown that cardiac risk factors play more significant role in young patients with myocardial infarction. Other studies suggested each risk factor carries different weight in atheroma formation and acute coronary syndrome. In addition to the distinctive risk factors distribution, young people with myocardial infarction also appear to have unique coronary involvements. We designed a study to look at the distribution of the culprit coronary plaque in young ST elevation MI patients and analysed their risk factors.
Methods: Retrospective analysis of young patients with ST segment elevation myocardial infarction referred to a tertiary cardiac centre in Canada over a two year period for coronary angiography. Young patients defined as male $<$55 years or female $<$65 years. Data was analysed by a professional statistician.
Results: Medical charts and coronary angiography images of 286 males and 141 females were analysed. 39% of patients had anterior MI, 58% had inferior MI and 0.5% had high-lateral MI. Analysis by gender showed more males had anterior MI, 43% Vs 31% (p=0.024) and more females had diabetes, 28% Vs 13% ($p<0.001$). No difference in the mean body mass index between male, 29.76, and female, 29.39. Simple and complex lesions (AHA class A,B1 and B2,C) were found in comparable frequency, 51% Vs 41%. Culprit atheroma was located in the straight part of the vessel in 61% of cases and around bend in 30%. Detailed analysis of atheroma around the bend showed the pattern of plaque formation where atheroma on lesser curve $>$ greater curve was higher than lesser curve = greater (14.8% Vs 7.7%, $p<0.001$); and greater curve $>$ lesser curve (14.8% Vs 4%, $p<0.001$). Of the right coronary artery infarct (RCA), 42% of culprit atheroma located on a bend Vs 25% of the left coronary artery infarct (LCA) - ($p<0.001$). More diabetics on insulin has culprit plaque in the LCA Vs RCA (10% Vs 4%, p=0.03).
Conclusions: There are unique patterns of atheroma formation and subsequent plaque rupture within coronary tree. Individual risk factors appear to influence the distribution of these atheroma. Even though the stretch and shear stress resulting from circulatory pressure and flow may partly explain this observation, further study on intra-vascular flow dynamics will be needed.

P711 Acute coronary syndrome after noncardiac surgery: similar pathophysiology deserves similar medical approach

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Purpose: The pathophysiology of acute coronary syndrome (ACS) in the perioperative setting may involve thrombosis over a vulnerable plaque or decreased oxygen demand secondary to anemia or hypotension. Depending on the predominant mechanism, prognosis and treatment may be different. The purpose of this study was to compare the angiographic characteristics between ACS in the perioperative setting (PACS), and in the emergency room - spontaneous ACS (SACS).
Methods: Between February 2006 and June 2010 clinical and angiographic data were prospectively recorded into a database for consecutive patients that had PACS after noncardiac surgery (n=120), and for 120 patients with SACS. We also collected data for a control group of 240 patients with stable coronary artery disease (CAD). All angiographies were analyzed by a single expert observer who was unaware of the patients' clinical diagnosis. The number and location of coronary lesions with obstructions greater than 50% were recorded. Each lesion was classified based on Ambrose's classification. The presence of Ambrose's type II lesions was compared between the three groups.
Results: Four hundred and eighty patients and 1470 lesions were analyzed. There were no differences between the three groups in the prevalence of male sex (p=0.521), hypertension (p=0.837) or diabetes (p=0.230). Patients in PACS were older than patients of SACS or CAD groups (mean age 67.8$\pm$10.2 years x 64.5$\pm$12.4years x 61.9$\pm$9.7years, respectively; $p<0.001$). In PACS 45% of patients had Ambrose's type II lesions x 56.7% in SACS group and 16.4% in CAD group ($p<0.001$). Overall, the independent predictors of Ambrose's type II lesions were PACS (OR 3.2; 95%CI, 1.93-5.32), SACS (OR 5.35; 95%CI, 3.24-8.62) and EKG changes (OR 1.79;95% CI, 1.06-3.02).
Conclusions: Patients with perioperative ACS have slightly less Ambrose's type II lesions than patients with spontaneous ACS, but much more than patients with stable CAD. These findings support the concept that coronary thrombosis is an important mechanism in the genesis of perioperative myocardial infarction and must have clinical relevance.

P712 Prevalence of coronary artery disease among males with poor sexual performance and increased arterial stiffness

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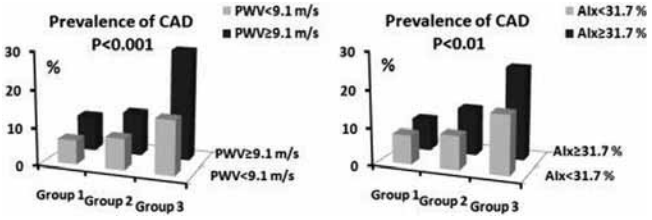
Purpose: Erectile dysfunction (ED) may carry an incremental predictive value for future cardiovascular events. Arterial stiffness is a prognosticator of cardiovascular risk. We investigated whether evaluation of ED severity and measurement of arterial stiffness can be used for detecting underlying coronary artery disease (CAD) in ED patients.
Methods: Carotid-femoral Pulse Wave Velocity (PWV) as an index of aortic stiffness and Augmentation Index (AIx) as a measure of wave reflections were measured in 369 consecutive ED patients. ED was diagnosed according to history and score of the 5-item Sexual Health Inventory for Men (SHIM, cut-off value $<$21). Lower scores indicate poorer erectile function.
Results: Subjects were categorized according to tertiles of ED severity [Group 1: first tertile (mild ED, SHIM score: 15-20, n=123), Group 2: second tertile (moderate ED, SHIM score: 10-14, n=123), Group 3: third tertile (severe ED, SHIM score: $<$9, n=123)]. PWV and AIx were significantly different between Groups 2 and 3 (by 0.72 m/s, $p<0.001$ and by 2.3%, p=0.02, respectively) and between Groups 1 and 2 (by 0.59 m/s, $p<0.001$ and by 2.9%, $p<0.01$, respectively) after adjustment for age and risk factors. The prevalence of CAD and multi-vessel CAD tended to being significantly higher among males with severe ED ($p<0.01$ and $p<0.001$, respectively). ED patients categorized by SHIM score were further subdivided according to PWV and AIx values $\geq$75th percentile. Compared with the other subgroups, the subgroup of patients with severe ED and high PWV or AIx values (PWV$\geq$9.1m/s, AIx$\geq$31.7%) exhibits the higher CAD prevalence (figure).



ED severity, arterial stiffness and CAD

Conclusions: Our findings suggest that determination of degree of ED and arterial stiffness may help to identify underlying CAD in ED patients.

P713 Acute myocardial infarction in young adults of Singapore: clinical characteristics, risk factors and outcomes

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Purpose: There is limited data on the clinical features of young adults (age $\leq$45) with acute myocardial infarction (AMI) in Singapore. We evaluated the clinical characteristics, risk factors and in-hospital outcomes of young adults with AMI in Singapore. As Singapore is a multi-racial society, we analyzed whether ethnic differences exist between the three dominant races, Malay, Chinese and Indian with regards to the clinical features.
Methods: From October 2004 to September 2010, 352 consecutive patients aged between 25-45 years were diagnosed to have AMI at our centre. Clinical data was collected retrospectively on demographic characteristics, presenting symptoms and signs, blood investigation, hospital course and in-hospital mortality.
Results: For the overall study group, the mean age of presentation was 49.8$\pm$4.1 years with male predominance (93.5%). The majority of patients were Chinese (48.6%) followed by Indians (29.2%), Malays (16.8%) and others (5.4%). The most common risk factor was smoking (73.0%) followed by hypertension (28.7%), dyslipidemia (20.2%) and diabetes mellitus (16.2%). 85.2% of patients were considered obese (BMI $>$23 kg/m^2). The mean total cholesterol, low-density lipoprotein and high-density lipoprotein levels were 5.6$\pm$1.2 mmol/L, 3.8$\pm$1.1 mmol/L and 0.93$\pm$0.25 mmol/L respectively The mean left ventricular function was 43.6$\pm$9.9% with the incidence of heart failure 3.1% and cardiogenic shock 4.8%. Overall in-hospital mortality was low with 4 deaths (1.1%). For ethnic subgroup analysis, Indians has a highest age adjusted risk of developing young AMI (3-fold), compared with Malays (1.4-fold risk) and Chinese (0.7-fold risk). There was no significant difference between the 3 races with regards to traditional cardiovascular risk factors and lipid profile. However, Indians have the strongest family history of ischaemic heart disease and were more likely to be diagnosed with new-onset diabetes mellitus at presentation. The incidence of in-hospital major complications and in-hospital mortality did not differ between the 3 races. For angiographic analysis, left main stem artery involvement was 6.5%. The majority of patients were single vessel involvement (39.8%) followed by triple vessel (30.1%) and double vessel (28.4%).

Conclusions: Young adults with AMI in Singapore are characterized by male predominance, high incidence of smoking and obesity in Singapore population. Overall in-hospital clinical outcomes are favorable. Among the 3 races, Indians have the highest risk of developing young AMI.

P714 Myocardial injury in septic diseases - correlations between troponin and inflammatory status

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Background: Elevated concentrations of cardiac troponin I (cTnI) are frequently observed in patients with severe sepsis and septic shock even in the absence of an acute coronary syndrome. Objective: The aim of this study was to detect myocardial damage in severe septic disease, to assess the relationship between troponin and inflammatory status and to evaluate the use of troponin as a prognostic risk factor in septic disease.
Methods: 30 patients with septic diseases: 20 with bronchopneumonia and 10 with other infections, without known coronary arterial disease. They underwent clinical examination, routine laboratory and inflammatory tests, serial determinations of troponin, ECG, echocardiography. PORT score was used to asses the disease severity in patients with bronchopneumonia.
Results: 22 patients (73%) showed elevated cTnI (median 0.57 ng/ml; 0.17-15.4). Coronary angiography ruled out significant coronary artery disease in 17 cTnI-positive patients (57%). There is a positive correlation, statistically significant between cTnI and C reactive protein ($p<0.0001$), between cTnI and PORT score (Pearson correlation= 0,434), between cTnI and E/tissue Doppler imaging E' ratio (Pearson correlation= 0,534). Contrary to expectation, the value of cTnI did not correlate well with left ventricular longitudinal systolic function -tissue Doppler imaging S wave (r = 0.260, r2= 0.063, P=0.015).
Conclusions: Although the mechanisms of troponin release into plasma during sepsis are not clearly established, cardiac troponin I is an indicator of myocardial injury in septic patients and is potentially associated with left ventricular diastolic dysfunction and poor outcome. Therefore, troponin should be proposed as a biomarker that accurately detects myocardial dysfunction and provides prognostic information in septic patients.

P715 Cardiac scintigraphy fails to add prognostic value in patients with end-stage renal disease and significant coronary artery disease

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Background: Patients (pt) with end-stage renal disease (ESRD) have an increased risk of major adverse cardiovascular events (MACE), particularly due to coronary artery disease (CAD). Therefore, it is imperative for pt with ESRD to undergo cardiovascular assessment before their inclusion on waiting lists for renal transplantation. Current guidelines recommend non-invasive testing for risk stratification, and coronary angiography only in those with positive results. There is controversial data regarding the appropriateness of this strategy.
Objective: To investigate the value of cardiac scintigraphy in addition to coronary angiography in predicting the occurrence of MACE in pt with ESRD.
Methods: 479 pt with ESRD on dialysis (56±9 years-old, 69% men, 45% with diabetes) at high-risk for CAD were prospectively enrolled. All pt underwent myocardial perfusion assessment by cardiac scintigraphy (SPECT with 99mTc-Sestamibi) with dipyridamole, and coronary angiography, regardless of symptoms or results of non-invasive tests. The median follow-up was 25 months (range=1 to 107). Kaplan-Meier curves were constructed for the primary endpoint (probability of survival free of fatal/non-fatal MACE) based on the combined results of cardiac scintigraphy and coronary angiography.
Results: There were 130 (27.0%) fatal/non-fatal MACE; 234 (48.8%) pt had at least one vessel with stenosis $\geq$ 70%. In pt with significant CAD, the relative risk of MACE was 2.4 (1.6 – 3.7) compared with pt without significant CAD ($P<0.001$). In pt with significant CAD, there was no additional increment in the incidence of MACE in pt with myocardial perfusion defects (n=54/151 or 35.8%) compared with pt with normal myocardial scans (n=30/83 or 36.1%) [RR = 0.98; 95%CI 0.56 – 1.72; P=1.00). On the other hand, in pt without significant CAD (n=245), any myocardial perfusion defect significantly increased the risk of MACE (2.6 [1.4 – 5.0]; P=0.006).
Conclusions: In pt with ESRD and high-risk for CAD, cardiac scintigraphy fails to add prognostic value to pt who have significant CAD by coronary angiography assessment. In this special group of pt, the coronary atherosclerotic burden seems to be a stronger predictor of MACE than myocardial ischemia. This information might be useful when cardiologists are called upon to assess the risk of MACE in pt with ESRD.

P716 Incidence, clinical feature and Long-term outcomes of insignificant abnormal coronary spasm during ergonovine provoked coronary angiography

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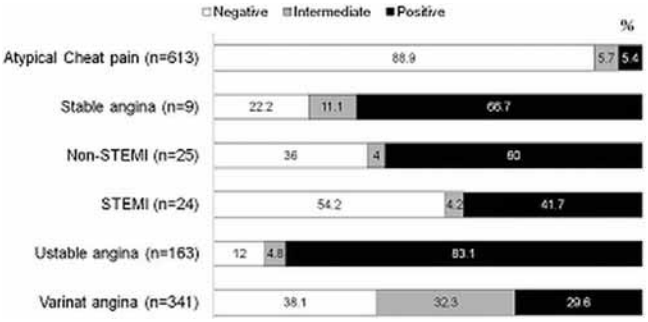
Background: Although the sensitivity and specificity of ergonovine provoked coronary angiography (ErgCAG) were reported to both high in patients with variant angina and high disease activity, it is not well known about the patients who have abnormal coronary spasm but not positive for ErgCAG.
Methods: 1,178 consecutive patients who underwent ErgCAG were included (754 men, 55±11 years). We divided the patients with three groups according to the result of ErgCAG; negative (group 1, n=719), intermediate (group 2, n=156, and positive (group 3, n=303), and compared the risk factors, angiographic findings, and MACEs between three groups. Angiographically insignificant abnormal coronary spasms were defined as an "intermediate spasm"; diffuse or focal intermediate spasm. MACEs were defined as cardiac death, MI and revascularization.
Results: More than one-third of suspected cases of variant angina by history taking had negative results of ErgCAG, and about one-third patients showed the intermediate spasm (Figure). The male gender, and calcium-channel blocker and/or nitrate use during 30 months follow-up were more prevalent in group 2 and group 3 than group 1 ($p<0.001$). The rate of MACEs were not different between groups. Cox regression analysis showed the more than intermediate organic stenosis to be the only independent predictor of MACEs-free survival in all three groups (OR 4.143; 95% CI 1.966 – 8.731; $p<0.001$).



Results of provocation test.

Conclusion: The patients who have intermediate spasm during ErgCAG were frequently observed, and they have been treated with calcium channel blockers or nitrates for symptom or risk factor control considerably. Long-term clinical outcome of the patients with intermediate spasm was favorable and more than intermediate disease was the only independent risk factors for MACEs-free survival.

P717 Differential prognostic effect of revascularization according to cardiovascular comorbidity in high-risk non ST-segment elevation acute coronary syndrome

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Aim: Data on the effect of revascularization on outcome in patients presenting with non ST-segment elevation acute coronary syndrome (NSTEACS) and significant comorbidities are scarce due to underrepresentation of these patients in available trials.
Methods: We included 1014 consecutive patients with high-risk NSTEACS (i.e. elevated troponin and/or ST-segment depression). Cardiovascular comorbidity, other than ischemic heart disease (CV-Co), was defined as the presence of at least one of the following: history of stroke, heart failure, peripheral arterial disease or renal failure. The effect of revascularization on a combined endpoint of long-term all-cause cause mortality or non-fatal myocardial infarction according to the presence of comorbidities was evaluated using Cox regression analysis.
Results: 245 (24.2%) of the study group had history of CV-Co. A coronariogra-

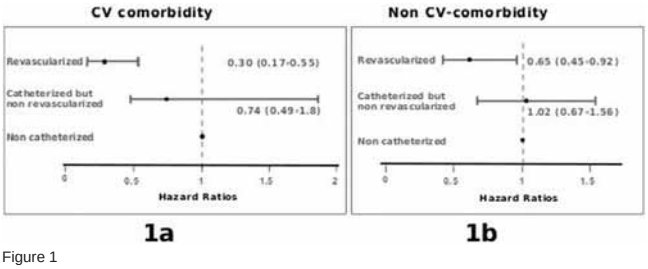

Figure 1

phy and a revascularization procedure was performed in 627 (61.8%) and 382 (37.7%) patients, respectively. During a median follow-up of 3 years (IQR: 1-6), 393 (38.8%) patients reached the combined endpoint [273 deaths (26.9%) and 206 myocardial infarctions (20.3%)]. Under a multivariate context, a differential prognostic effect attributable to revascularization was observed according CV-Co (p for interaction = 0.006); thus, revascularization was associated with a greater prognostic benefit in patients with CV-Co (HR=0.32; CI 95%: 0-18-0.56, p<0.001) - figure 1a, compared to those with no CV-Co (HR=0.75; CI 95%: 0.56-1.01, p=0.054) - figure1b.
Conclusions: In patients with high-risk NSTEACS, revascularized subjects with CV-Co display a significant larger long-term death/MI risk reduction compared to patients without CV-Co.

HYPERTENSION ETHNIC GROUP AND DIET

P719 Hypertension control in a large cohort of patients in Poland - preliminary results of the Pol-Fokus study

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Purpose: In surveys performed in the past decade hypertension control in Poland was below the average control in the EU countries. Therefore the aim of the study was to establish the current hypertension control rate in pharmacologically treated patients in Poland.
Methods: In the ongoing, cross-sectional questionnaire-based observational study (the Pol-Fokus study) we have included 5556 hypertensive patients (54,1% females, mean age 63,1±12,9 years) attending a routine visit in primary (4122 patients) or specialist care (1434 patients). Physicians participating in the study were selected in a way providing representative sample of doctors and patients for each of Poland's provinces and each size of town. The included patients had to be ≥ 18 years old and had to be treated for at least 12 months with antihypertensive drugs. Blood pressure (BP) was measured twice in a seated position according to ESH/ESC guidelines and mean value was calculated. The hypertension control was defined as BP level below 140/90 mm Hg. Selected demographical and clinical data were evaluated.
Results: In the studied group mean BP was 140±17/84±10 mm Hg, and the hypertension control rate was 53,2%. There were no significant differences in control rates between primary care and specialist care patients. Patients with diabetes as well as patients with coronary artery disease (CAD) had higher hypertension control rate in comparison with patients without these diseases (63,9% vs. 49,0%; p<0,001 and 56,5% vs. 51,7%; p=0,001 for diabetes and CAD respectively). There were no differences in gender and age between patients with or without good BP control. Patients with obesity (BMI ≥ 30 kg/m^2) were characterized by higher rate of BP control as compared with patients without obesity (56,0% vs 50,6%; p<0,001).
Conclusion: Our results show that 53,2% of hypertensive patients treated for at least one year achieved blood pressure control. Among them higher control rate was observed in patients at higher cardiovascular risk.

P720 Factors influencing awareness, treatment and control of hypertension in urban Thai population

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Background: Lowering high blood pressure to recommended values is crucial in reducing cardiovascular risk. Despite knowing that, several studies have reported a substantial amount of unawareness, untreated and uncontrolled hypertension (HTN) in real world situation. Age, gender and socioeconomic status (SES) are among the risk factors for disparity in treatment of hypertension. We use the baseline data from two waves of a longitudinal cohort study in 1985 and 2009 to evaluate the disparity and evolution of risk association.
Objective: To explore factors influencing awareness, treatment and control of hypertension in a cohort of urban Thai population.
Methods: Participants from the electricity generating authority of Thailand (EGAT) 1 and EGAT 3 study who completed the questionnaire, physical examination and blood tests in 1985 and 2009 were enrolled (n = 3,499 and 2,070 respectively). Prevalence of HTN, HTN awareness, treatment and control were analyzed. Age, gender, presence of co-morbidity, educational attainment and income level were considered as confounding factors for awareness and treatment. While in controlled HTN, body mass index, alcohol consumption and exercise were added. Statistical analysis was performed using multiple logistic regression and Chi-square.
Results: Prevalence of hypertension was rising from 22% in 1985 to 27% in 2009 (p 0.03). Prevalence of unawareness dropped from 59% to 51% (p 0.004), accompanying by a substantial rise in the proportion of subjects receiving treatment (from 32% in 1985 to 40% in 2009, p 0.002). Despite the improvements in disease awareness and treatment, the percentage of controlled HTN remained low (43% and 40%, p 0.50). Older age and presence of co-morbidity significantly related to higher awareness of hypertension (Odd ratio (OR) 2.1 and 2.0 in 1985 and OR 1.8 and 6.1 in 2009 respectively, all p<0.005). Education and income were not related to disparity in awareness, treatment and controlled of hypertension in both years (all p ns).
Conclusions: Hypertension awareness and treatment have been improving over 24-year period. Controlled hypertension remains below half. Older age and presence of co-morbidity significantly increase awareness of hypertension in both years. There is no new emerging risk for disparity in treatment detected. High-intensity health promotion in this workforce may overcome the effect of socioeconomic status on awareness and treatment inequality in this population.

P721 Prevalence of hypertension in Brazil over the past three decades: a systematic review with meta-analysis

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Background: Hypertension has become a major public health concern among developing countries with ever growing prevalence of the disease over the past few decades. Nevertheless, emerging nations, such as Brazil, lack data on national prevalence of hypertension obtained on well designed population-based studies.
Purpose: To estimate the prevalence of hypertension among the adult Brazilian population.
Methods: Published cross-sectional and cohort studies conducted from 1980 to 2010 were independently identified by two reviewers, with no language restriction, in the PubMed, Embase, LILACS, and Scielo electronic databases. Unpublished studies were searched in the CAPES electronic thesis database. Hypertension was defined by 7-JNC criteria of blood pressure ≥140/90 mmHg or use of blood pressure lowering medication, and self-reported hypertension through home or telephone surveys.
Results: Database searches retrieved 710 results, 57 PhD thesis, and relevant articles, adding 599 results after duplicated publications were removed. Screening of titles and abstracts excluded 444 articles, and full-text screening, additional 108, leaving 47 eligible studies. A third party excluded another 5 results based on studies with poor execution or design flaws, leaving 42 final articles comprising over 124 thousand individuals. In the 1980's, national prevalence of hypertension, defined by blood pressure measurement or use of lowering medication, was 35.9% (95% CI 28.4 – 44.2%); 45.1% (95% CI 40.0 – 50.4%) and 34.6% (95% CI 23.7 – 47.5%) among men and women, respectively. In the 1990's the prevalence was 28.5% (95%CI 21.4 – 36.9%); 24.6% (95% CI 15.5 – 36.6%) among men and 23.0% (95% CI 14.5 – 34.3%) among women. In the 2000's, the prevalence rates were 29,6% (95% CI 26,3 – 32,9%); 29.4 (95% CI 24.1 – 35.3%) in men and 25.8% (95% CI 20.5 – 31.9%) in women. On the other side, in the 2000's, the prevalence of self-reported hypertension on telephone surveys was 20.6% (95% CI 19.0 – 22.4%); 18.6% (95% CI 17.4 – 19.9%) in men and 23.2% (95% CI 21.1 – 25.4%) in women, while self-reported prevalence on home surveys was 25.2% (95% CI 23.3 – 27.2%); 15.8% (95% CI 11.7 – 21.0%) in men and 23.4% (95% CI 16.6 – 31.9%) in women.
Conclusions: This meta-analysis was the first to summarize prevalence rates of hypertension for all Brazilian regions over time. Steady estimates were detected over three decades in accordance with international data on hypertension prevalence.

P722 Renin-angiotensin-aldosterone system polymorphisms in resistant arterial hypertension: a genetic risk score for adverse cardiovascular events - GENHART-RIO study

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Introduction: Renin-angiotensin-aldosterone system (RAAS) regulates circadian arterial pressure fluctuation and may influence end organ damage in resistant arterial hypertension (RAH). The aim of this study was to investigate, in subjects with RAH in a South American city: 1) Adverse cardiovascular events defined as a composite of fatal and non-fatal stroke and/or acute myocardial infarction (AMI); and 2) to develop a RAAS polymorphism-based risk score for adverse cardiovascular events.
Methods: From 2000 to 2006, two hundred and twelve subjects under investigation for RAH were admitted. All received standard drug therapy aiming at achieving office BP <140/90mmHg, and were re-evaluated one month later, including 24h ambulatory arterial pressure monitoring. In this group, 65% were found to have RAH and 35% pseudo-RAH. Secondary causes of RAH were excluded. Subjects were followed at scheduled clinical visits. Eighty eight subjects (age 58±10 y.o, 58 women) underwent RAAS polymorphism genotyping: renin (G1051A), angiotensinogen (M235T), angiotensin II type 1 receptor (A1166C) and aldosterone synthase (C344T). Hypertension onset and cardiovascular events prior to admission were investigated by interview and review of medical records. During follow-up, a composite of fatal and nonfatal stroke and/or

AMI was assessed. Hypertension burden time (HBT) was defined as time from hypertension onset to end of follow-up. A polygenic score (GEN) based on allele risk was composed for each polymorphism (zero [low risk homozygosis], 1 [heterozygosis] to 2 [high risk homozygosis]), and summed up. Cox proportional-hazard model assessed both RAH and RAAS polymorphisms for adverse events. ($\alpha<0.05$)
Results: During a median HBT of 26 years, 40 subjects reached endpoint. Hardy-Weinberg equilibrium was observed in all polymorphism. In univariate model, all polymorphisms were predictors for end point and entered GEN. Optimal cutoff for GEN was >3 (AUC=0.66; p=0.006). In multivariate model, RAH and GEN>3 were independent predictors for composite endpoint (RAH: Hazard ratio [HR] 2.3; 95%CI [1.1-5.0]; p=0.027; and GEN>3: HR 3.4; 95%CI [1.2-9.6]; p=0.020). No significant interaction was found (p=0.92). No significant differences according to age, gender, HBT, Framingham score, 24hsystolic and 24hdiastolic blood pressures were found for GEN >3 or ≤3. In 1,000 bootstraps, HR for RAH and GEN were, respectively, (mean±SD) 2.2±0.2 and 3.2±0.2 (both p<0.001).
Conclusion: RAH determines an increased risk for stroke and AMI. Polygenic RAAS-based score independently identifies hypertensive subjects at higher risk for adverse cardiovascular events.

P723 In-hospital complications and one-year outcome of acute coronary syndrome in hypertensive subjects; findings from the 2nd Gulf Registry of Acute Cardiac Events (Gulf-RACE 2)

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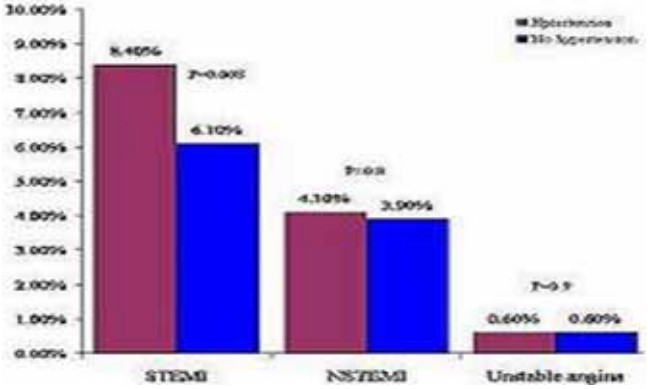
Aims: This study to investigate the in-hospital complications and one-year outcome of systemic hypertension (HTN) in patients with acute coronary syndrome (ACS).
Methods and results: Data was collected from October 2008 to June 2009 from 6 Middle Eastern adjusted countries, 7,847 consecutive patients admitted with ACS were enrolled in this study. HTN patients represented 47.7% of the recruited patients. HTN was more prevalent in women than in men (66.5% vs. 42.7), among Arabs when compared to Asians and with advancing age. HTN patients were older and more likely to have other cardiovascular risk factors, prior history of coronary artery disease and prior episodes of heart failure when compared to non-HTN patients. Patients with HTN were more likely to present with dyspnoea and advanced killip class when compared to non-HTN patients. Overall in ACS, patients with HTN were more likely to develop heart failure, recurrent ischemia, stroke and atrial fibrillation when compared to non-HTN patients. Among HTN patients, the mortality rate was increased only among those who were admitted with ST-elevation myocardial infarction (STEMI) when compared to non-HTN patients. After adjustment for baseline variables; HTN was an independent factor for heart failure (OR=1.314, 95%CI: 1.045-1.652, p=0.02) and stroke (OR= 2.467, 95%CI: 1.114-5.467, p=0.02). After adjustment for baseline variables, there were no significant differences in mortality rates in HTN ACS patients when stratified according to gender, age or ethnicity.



In-hospital mortality rates by ACS types.

Conclusion: HTN is highly prevalent among Middle-Eastern patients with ACS particularly in women, Arab ethnicity and older age. HTN was independently associated with increased risk of heart failure and stroke. In STEMI, HTN was associated with higher risk of in-hospital mortality and stroke.

P724 Communuty based analysis of the genetic risk factors for essential hypertension in Japanese

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Purpose: Essential hypertension (HT) is considered to be a multifactorial disease resulting from the combined influence of environmental and genetic factors, especially single nucleotide polymorphisms (SNPs). There are gender, ethnic/racial and geographic differences in the frequency of SNPs. The aim of this study was to identify SNPs responsible for HT in a case-control study of community-based patients in Japan.
Methods: Genotyping of 30 SNPs on different candidate genes was performed in Jichi Medical University. We genotyped 189 HT patients (94 males) and 245 healthy controls (79 males) who live in town of Wakuya, agricultural area, Japan. Diagnosis of HT was based on blood pressure≧140/90 mmHg. All subjects were divided into groups stratified by gender and age (≦49 or ≧50). In each group, case-control study was performed. The effect of each SNP on HT was analyzed by logistic regression model. Odds of minor homozygote and heterozygote were compared with that of major homozygote as reference genotype.
Results: In men aged 50 years and over, genotypes having minor alleles of ALDH2, PON1, UCP2, EDN1, PRKAA2 and RETN were related to decreased risk of HT. In women aged 50 years and over, genotype having minor allele of AGT was related to decreased risk of HT, but that of TNFRSF1B was related to increased risk of HT. In women under age 49 years, genotype having minor allele of UCP2 was related to decreased risk of HT, but that of NPY was related to increased risk of HT.
Conclusions: Our findings show that the genetic risk factors associated with essential hypertension vary based on gender and age. In a Japanese population, minor alleles of NPY and TNFRSFIB may be risk alleles.

P725 Angiotensin converting enzyme I/D polymorphism impacts left ventricular remodeling in resistant arterial hypertension - GENHART-RIO study

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Introduction: Angiotensin converting enzyme (ACE) I/D polymorphism influences circadian arterial pressure control and has impact on myocardial hypertrophy. Resistant arterial hypertension (RAH) is a clinical setting likely to develop end-organ damage. The aim of this study was to investigate the association between ACE I/D polymorphism and left ventricular remodeling in RAH.
Methods: Two hundred and twelve subjects under investigation for RAH were admitted. All received standard drug therapy aiming at achieving <140/90mmHg, and were re-evaluated one month later, including 24h ambulatory arterial pressure monitoring (mean 24hsystolic BP and systolic nocturnal fall), 1D/2D TT echocardiogram (left ventricular mass index[LVMI]), serum creatinine, plasmatic B-type natriuretic peptide (BNP), body mass index (BMI) and Keith-Wagener-Baker fundoscopy classification (KWB). In this group, 65% were found to have RAH and 35% pseudo-RAH. Secondary causes of RAH were excluded. Eighty eight subjects (age 58±10 y.o, 58 women) underwent ACE I/D genotyping by extracting DNA from peripheral leukocytes and applying PCR technique. Hypertension burden time (HBT) was defined as time from hypertension onset to admission. Kruskal-Wallis analyzed continuous and chi-squared test analyzed discrete variables. ANCOVA tested for factors interaction. Data is presented as mean±SD or percentage. ($\alpha<0.05$)
Results: Hardy-Weinberg equilibrium was confirmed in ACE I/D polymorphism (observed vs expected genotype absolute frequency [n]: II:16 vs 15.8; ID:42 vs 43.1; DD:30 vs 29.1; p=0.73). According to II, ID and DD genotypes, LVMI was 183±39 g/m^2, 168±53 g/m^2 and 207±68 g/m^2 (p=0.03), respectively. No differences regarding to mean 24hsystolic BP (II:140±26 mmHg; ID:144±23 mmHg; DD:142±27mmHg; p=0.80), nocturnal fall (II:6.2±7.5 mmHg; ID:6.9±7.1 mmHg; DD:5.1±5.9mmHg; p=0.66), HBT (II:14±8 years; ID:14±7 years; DD:13±9 years; p=0.74), serum creatinine (II:89±14 μmol/L; ID:84±27 μmol/L; DD:80±23 μmol/L; p=0.23), plasmatic BNP (II:89±58 ng/L; ID:40±40 ng/L; DD:47±44 ng/L; p=0.12), BMI (II:30±4 kg/m^2; ID:31±5 kg/m^2; DD:31±5 kg/m^2; p=0.74) and KWB (class III: II:43%; ID:52%; DD:42%; p=0.50) were found. No significant interaction between LVMI and each analyzed factor (LVMI vs: 24hsystolic BP p=0.07; nocturnal fall p=0.27; HBT p=0.76; serum creatinine p=0.78; BNP p=0.99; BMI p=0.07; KWB p=0.20) was found.
Conclusion: ACE I/D polymorphism impacts left ventricular remodeling in subjects with RAH independently of mean 24h systolic blood pressure, nocturnal fall, hypertension burden time, cardiac and kidney functions, BMI and retinal vascular damage.

P726 Cardiac, vascular and renal damage as predictors for the incidence of new-onset atrial fibrillation in essential hypertensives. A Greek 6-year prospective study

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Purpose: Evaluation of hypertension-related organ damage is considered a very important tool in order to assess total cardiovascular (CV) risk, because asymptomatic alterations of the CV system and the kidney are crucial intermediate stages in the disease continuum that links hypertension to CV events and death. In the present study, we investigated the predictive value of CV and renal damage for the incidence of new-onset atrial fibrillation (AF) in essential hypertensives.
Methods: We prospectively followed up for a median period of 6 years (IQ 5-6.6 years) 782 uncomplicated hypertensives without history of AF episodes (aged 58.1±10 years). All subjects had at least one visit annually and at entry underwent complete echocardiographic study, including left ventricular diastolic function evaluation by means of transmitral flow (E, A, E/A ratio) and tissue Doppler imaging (Em, Am), as well as carotid – femoral PWV measurement by a computerized device (Complior SP). Metabolic profile, serum creatinine levels (sCr) and estimated creatinine clearance (CrCl) (according to Cockroft-Gault formula) were assessed from a morning blood sample. CKD was defined based on estimated CrCl between 15 and 59 ml/min.
Results: The incidence of new-onset AF over the whole follow-up period was 5% (22 patients with paroxysmal AF and 17 patients with permanent AF). Patients with new-onset AF compared to those without were older (by 9 years, $p<0.001$) and exhibited at baseline higher office pulse pressure (by 7.4mmHg, p=0.002), waist circumference (by 3cm, p=0.048), left ventricular mass index (by 13.8 g/m^2, p=0.002), left atrium diameter (by 4.2mm, $p<0.001$) and E/Em ratio (13±6.3 vs. 10.6±4.6, p=0.037), while no difference was observed with respect to gender, baseline diabetes status and body mass index. Moreover, hypertensives with new-onset AF compared with those without had at baseline increased PWV (by 0.85m/s, p=0.014) and decreased CrCl (by 13.7ml/min, p=0.006) along with higher prevalence of CKD (27.8% vs. 12.8%, p=0.01). By applying multivariate Cox regression analysis age (HR 1.076, $p<0.001$), left ventricular mass index (HR 1.015, p=0.013) and LA diameter (HR 1.201, $p<0.001$) turned out to be independently associated with the incidence of new-onset AF.
Conclusions: Uncomplicated hypertensives with new-onset AF are characterized adverse structural and functional cardiac adaptations, aortic stiffening and impaired renal function. Alterations in cardiac structure are considered the more powerful predictors of new-onset AF in the setting of essential hypertension.

P727 Increasing prevalence of hypertension and myocardial infarction amongst young patients in the UK

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Introduction-Hypertension is a major risk factor for Myocardial Infarctionwhich account for over 3 million deaths in Europeevery year. Over the past few years,Clinical practice in the UK has focused on the diagnosis and control of risk factors such as Hypertensionto reduce the risk of Myocardial Infarction. Recent evidence suggests thatMyocardial Infarction is affecting younger patients often with no or singlefactors. We hypothesised an increasing prevalenceof Hypertension and Myocardial Infarction amongst young patients in the UK.
Methods-Anonymous information on patients with Hypertension attending alarge multi-ethnic general hospital in Birmingham, UK in theperiod 2000-2007 was obtained from the local health authority computerisedhospital activity analysis register. We looked at the change in the prevalence ofhypertension according to demographics and co-morbidities including myocardialinfarction were diagnosed according to national guidelines.
Results-Between 2000-2007, of 101836 patients below the age of 50,there were2762 (2.71%) patients with hypertension and showed year-on-year increases (2000/01-1.52% to 2006/07-4.45%). Therewere increases amongst all ethnic groups; Caucasians - 1.31% (2000/01) to 4.38% (2006/07); South-Asian - 2.81% (2000/01) to 6.84% (2006/07); Afro-Caribbean - 2.1% (2000/01) to 8.09% (2006/07). 162 out of 2762 (5.8%) hypertensive patients developed myocardialinfarction, also showing year-on-year increases (2000/01-5.3% to 2006/07-6.5%).
Conclusion-The prevalence of young patients below the age of 50 havingHypertension has significantly increased over the last decade, corresponding toan increase in myocardial infarction. This increase could be secondary to improveddiagnosis and/or other contributing lifestyle and environmental factors such asincreased stress, sedentary lifestyle, and unhealthy eating behaviours leadingto the development of hypertension in young people. Further research is required to delineate thecauses of hypertension amongst young people in the UK.

P728 Association between adiponectin T94G polymorphism and resistant hypertension in the young-onset hypertensives Chinese

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Background: The young-onset primary hypertensives (YPHs) with resistant hypertension (RH) would have higher long-term cardiovascular risk. Adiponectin is a major adipocytokine and associated with level of blood pressure (BP). The present study examined whether functional adiponectin T94G polymorphism is associated with RH in the YPHs.
Method: We had carried out an association study (Academia Sinica Collaborative Study on Hypertension Genetics in Non-Aboriginal Taiwanese) to compare genotype information between YPHs (≦50 years old) and normotensive controls. Finally 1131 YPHs were enrolled. Among them, 861 subjects with detailed genetic data were enrolled in the present study. The resistant hypertension was defined as need of at least 3 drugs including a diuretic to control BP. Gene polymorphisms were analyzed by polymerase chain reaction.
Result: The YPHs with RH (n = 54) were older and had higher waist, triglyceride, BUN, creatinine, uric acid, aldosterone, C-reactive protein (CRP) and fibrinogen. For the adiponectin T94G polymorphism in the allelic model, the odds ratio (OR) of RH was 2.45 (p=0.001) and there is a linear relationship between allele numbers and presence of RH (p=0.001). The binary regression analysis indicated that T94G polymorphism (OR = 2.766, 95% CI = 1.434-5.338, p=0.002), age (OR = 1.103, CI = 1.040-1.169, p=0.001), uric acid (OR = 1.322, 95% CI = 1.126-1.552, p=0.001), CRP (OR = 2.769, 95% CI = 1.535-4.992, p=0.001) and aldosterone (OR = 1.004, 95% CI = 1.002-1.006, $p<0.001$) were independently associated with the presence of RH.
Conclusion: In the Chinese population we found adiponectin T94G polymorphism is associated with RH in the YPHs.

P729 Regional differences in hypertension and obesity among France overseas territories

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Methods: A prospective population-based survey of 2418 adults from Guadeloupe, Martinique, French-Guiana, and French-Polynesia, four FOT. Hypertension was defined as BP >140/90 mmHg or current use of anti-hypertensive medications. Obesity was defined as body mass index >30kg/m^2.
Results: The prevalence of hypertension was lower in French-Guyana (18%) than in the other territories: Guadeloupe (29%), Martinique (28%), and French-Polynesia (24%). With Guadeloupe as the reference group, age and gender-adjusted odds-ratio of hypertension in French-Guyana was 0.6 [0.5-0.8]. Awareness was lower in French-Polynesia (50%, adjusted odds-ratio 0.6 [0.3-0.9]), as was treatment of hypertension (32%, adjusted odds-ratio 0.3 [0.2-0.6]). Control of hypertension was lower in French-Polynesia (9%, adjusted odds-ratio 0.3 [0.2-0.6]) compared to the other territories (30 to 32%). French-Polynesia had the highest prevalence of obesity (33%, adjusted odds-ratio 2.0 [1.5–2.6]), compared to the other territories (18 to 23%), and the largest Population Attributable Fraction of hypertension due to obesity (36%), compared to Guadeloupe (18%), Martinique (20%), and French-Guyana (28%)
Conclusion: Wide differences are found in the prevalence of obesity and hypertension, and in management of hypertension. Obesity appears a key target to reduce hypertension

P730 Young and middle-aged hungarians have much higher blood pressure compared to Canadians - a potential contributor to the high CV mortality and stroke risk in hungary

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Purpose: Hungary has one of the highest cardiovascular (CV) mortality and stroke rates in Europe. Data from two recent blood pressure (BP) screening projects in Hungary and Canada provided us with the opportunity to compare potential differences in the prevalence of hypertension and other key CV risk factors between these countries.
Methods: The cross-sectional Ontario blood pressure (ON-BP) study examined a randomly selected population sample of 2551 residents of Ontario. In Hungary, a total of 1000 bank employees were screened for the presence of CV risk factors. BP measurements were performed identically in both cohorts using BpTRU-instruments. For this inter-country analysis, we selected 880 white Caucasian Canadians between the age of 20-60 years, who had a 'white collar' occupa-

tion and, thus, were comparable to the Hungarian bank employees. Hypertension was defined by elevated BP measurement (systolic BP ≥140 and/or diastolic BP ≥90mmHg) or current intake of antihypertensive medication.
Results: The Ontario study population was on average 10 years older with a higher rate of obesity, diabetes and high cholesterol. Smoking was more prevalent among Hungarians (29.4% vs. 22.5%, P<0.001). Despite being younger, Hungarians exhibited significantly higher SBP (mean±SD: 121.3±14.3 vs. 111.6±14.1, P<0.001) and DBP (78.5±10.5 vs. 70.8±9.5, P<0.001), which remained significant after adjustment for age and use of antihypertensives as well as sex and CV risk factors. At any age group, hypertension prevalence was significantly higher among Hungarians (see Table, P=0.03 with adjustment for sex, BMI, smoking, high cholesterol, diabetes, heart rate).

Hypertension prevalence according to age

Age group	Hungarian study	ON-BP study
20–29y	55 (12.6%)	1 (0.9%)
30–39y	57 (15.0%)	7 (3.5%)
40–49y	41 (31.1%)	43 (15.0%)
50–62y	20 (40.8%)	89 (32.0%)

Conclusion: The increased prevalence of hypertension among young and middle-aged Hungarians compared to Canadians could represent an essential contributor to the high CV mortality and stroke rates in Hungary. These differences suggest that in Hungary, BP awareness, treatment and control require improved medical attention and should be addressed early among young Hungarians.

P731 Salt sensitivity and elevated aldosterone/renin ratio are additive risk factors for cardiovascular disease

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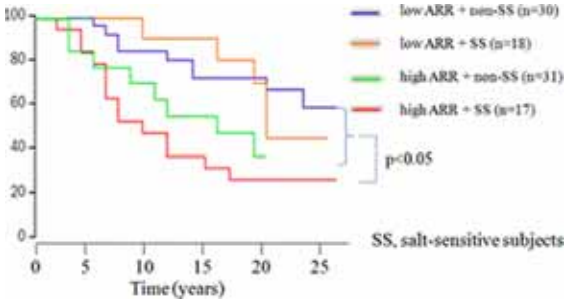
Background: We recently found that increased plasma aldosterone/renin ratio (ARR) is associated with future cardiovascular (CV) events. In the present study, we investigated the interrelationship between salt sensitivity of blood pressure (SS) and ARR in Japanese patients with essential hypertension (EH).
Methods: Study design is a retrospective cohort study. The cohort consist of 96 EH patients whose ARR and SS were determined between 1984 and 1993 in a hospitalized condition. SS was defined as elevation of mean blood pressure >10 mmHg after switching dietary NaCl from 3g to 20g/day for 1 week. Patients were divided into 4 groups by fifty-percentile (ARR=55) and the presence of SS. The incidence of major CV events were observed for 14 years in average.
Results: The numbers of patients classified as high ARR/SS (n=17), high ARR/non-SS (n=31), low ARR/SS (n=18), and low ARR/non-SS (n=30), respectively. The mean ARR values were significantly higher in SS than in non-SS patients (109±16 vs. 77±19, p<0.05). The morbidity of fatal and non-fatal CV events were high in a order of high ARR/SS, high ARR/non-SS, low ARR/SS, and low ARR/non-SS.(figure)



Cumulative survival rates of CV events.

Conclusions: SS and high ARR are additive risk factor for CV disease.

P732 Predictors of adequate control of hypertension among chronic kidney disease patients

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Objectives: We performed this study to describe the clinical profile of adult patients with hypertension and CKD seen at the Nephrology Out-patient Clinic of our institution, specifically, to compare the clinical characteristics of patients with controlled (<130/<80) versus uncontrolled (> or =130/> or = 80) hypertension and to correlate the clinical characteristics with adequate BP control.
Design: Cross-Sectional Study
Participants: All patients with CKD seen in November 2010 were included. CKD was defined as estimated glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2 or proteinuria (protein ≥ +1 on standard dipstick test for urine), for ≥ 3 months.
Primary outcome measure: Disease-specific BP Control (<130/80 mmHg)
Results: There were 142 patients included in this study. The proportion of patients with controlled BP by general definition (<140/90) and disease-specific definition (<130/80) are 47.9% and 19.01%, respectively. The mean systolic blood pressure was 134.37 (+18.31) mmHg and a mean diastolic blood pressure of 80.63 (+9.9). The most common etiology of the underlying renal disease was hypertensive nephropathy (42.3%) and diabetic nephropathy (30.3%). Diabetes mellitus was the most common associated co-morbid illness (41.5%). Most patients were at stage 5 CKD (31.7%). The mean serum creatinine was 342.95 mmol/L (+328.25). Mean lipid profiles show elevated triglycerides, acceptable HDL, and high LDL. Univariate analysis revealed that, female gender (OR 0.41, 95% CI 0.17-0.99, p=0.049) was significantly associated with better BP control while the use of dihydropyridine calcium-channel blockers (CCB) (OR 2.36, 95% CI 1.00-5.54, p=0.040) and the presence of LVH (OR 6.21, 95% CI 1.69-22.78, p=0.048) by 2DE were significantly associated with poor BP control. On multivariate analysis, none of the above mentioned clinical characteristics were significantly associated with BP control.
Conclusion: We have presented the clinical profile of out-patient adult hypertensives with CKD at our institution. The disease-specific proportion of patients with adequate BP control is 19.01%. Univariate analysis showed that the female gender is associated with good BP control while LVH by 2DE, and the use of dihydropyridine CCB were significantly associated with poor BP control. On multivariate analysis, no significant predictor of adequate BP control was identified among the population studied.

P733 Current prescription of blood pressure lowering drugs and adherence to treatment in Russian outpatients with arterial hypertension

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Purpose: To assess the current use of blood pressure lowering drugs and adherence to treatment in outpatients with arterial hypertension (AH) in the Russian Federation.
Methods: A multicenter study RELIF (REgularnoe Lechenie I proFilaktika) has been performed in 20 big cities of Russia: in each city were randomly selected 5 polyclinics, in each policlinic – 5 general practitioners (GPs), each GP enrolled 5 consecutive pts with AH who came for a visit. Both pts and GP's filled out questionnaires containing information on risk factors, their targets achievement, current drug regimen, adherence to treatment.
Results: A total of 2517 pts were enrolled. 1510 pts (59.99%) reported themselves to be adherent with their drug regimen which was defined as agreement with 3 statements: "I take my drugs every day"; "I take drugs strictly in doses recommended by my physician"; "I do not miss any intake of my drugs". Angiotensin-converting enzyme (ACE) inhibitors were the most frequently used class of antihypertensive drugs. They were prescribed in 73.37% of pts; almost equally in patients reporting themselves to be compliant or not compliant with their regimen (respectively 74.83% and 71.40%, p<0.1). Second most used class were diuretics (61.46% of pts), which were prescribed to adherent pts more often (65.13% vs 56.36%, p<0.001). Beta-blockers were prescribed in 44.71% pts (45.87% adherent and 42.58% not adherent, ns). 25.06% of AH pts were on calcium antagonists, which were associated with better compliance (28.13% vs 20.76%, p<0.001). Angiotensin II receptors antagonists were used only in 6.49% of pts (respectively 6.88% and 5.93%, ns). 21.59% of pts received fixed-dose combinations of antihypertensive drugs (23.38% of adherent and 18.86% of not adherent pts, p<0.01). The efficacy of antihypertensive treatment was low: 70.39% of non-adherent pts and 70.90% of adherent pts didn't reach the blood pressure goals (ns).
Conclusions: Present study has shown a gap between general practice and National (and European) standards for AH treatment. Poor adherence of patients seems to be of concern, but it may be improved by certain drug choices as well as by use of fixed-dose combinations.

P734 Snoring and obstructive sleep apnoea syndrome among hypertensive Nigerians: prevalence and clinical correlates

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Purpose: Association between hypertension and sleep apnoea and/or snoring has been described. The study aim to describe the prevalence of snoring and OSA among hypertensive subjects in South Western, Nigeria.
Materials and methods: This was a descriptive study conducted at the Cardiology clinic, South West Nigeria. One hundred consecutive hypertensive patients were recruited from the clinic. The Berlin questionnaire and the Epworth sleepiness scale (ESS) were used to determine excessive daytime sleepiness and the risk of having OSA. Statistical analysis was done using SPSS 16.0. Data were summarized as means ± S.D and percentages.
Results: The study participants consisted of 40 males (40.0%). The demographic data were similar between both genders except that females had higher mean body mass index than males. The prevalence of snoring was 50.0%. 52% were categorized as being at high risk of having OSA. Snorers were more likely to be older, males and to have a higher fasting blood sugar than non-snorers.96% of

snorers reported excessive daytime somnolence as predicted by the ESS score compared to 4% of non snorers. Prevalence of snoring was also higher among overweight and obese hypertensive subjects than normal body mass index hypertensive subjects.

Clinical and demographic characteristics

Variable	Snorers (50)	Non snorers (50)	p
Age (years)	59.4±12.1	56.1±11.9	0.041*
SBP(mmHg)	141.9±21.2	134.9±14.1	0.0369*
DBP (mmHg)	82.2±13.4	83.4±10.7	0.778
FBS(mmol/l)	5.90±1.0	4.9±1.8	0.021*
ESS	8.74±3.9	7.1±4.7	0.0429*
BMI (kg/m^2)	27.6±5.8	25.6±5.2	0.184
WHR	0.93±0.07	0.91±0.06	0.107
Proportion with ESS high risk of OSA	48 (96.0%)	2(4.0%)	0.000**

Key to table: SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose; ESS, Epworth sleepiness score; BMI, body mass index; WHR, waist hip ratio; OSA, obstructive sleep apnoea.

Conclusion: Snoring is common among hypertensive subjects in South Western Nigeria. Clinically suspected OSA was similarly high in prevalence among them. Early identification and management may reduce the cardiovascular risk of hypertensive subjects.

P735 Coffee consumption has a less potent acute-on-chronic effect on aortic stiffness and wave reflections than caffeine

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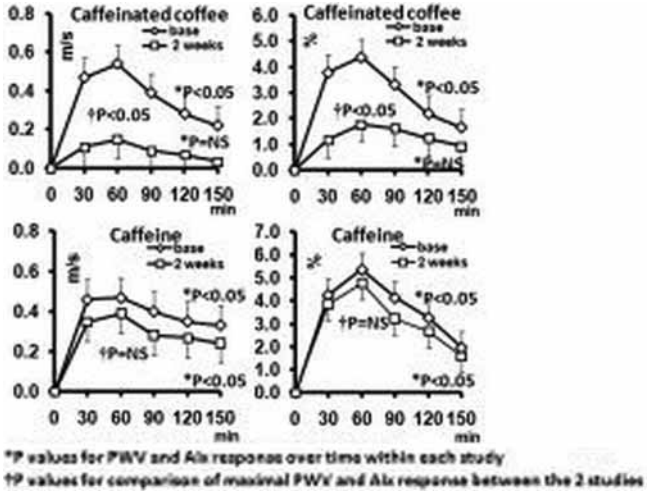
Purpose: Both coffee and caffeine have an acute effect on arterial stiffness; however their acute-on-chronic effect has not been investigated.
Methods: The acute-on-chronic effect of a 2-week long, daily coffee or caffeine was studied in 11 healthy volunteers receiving on 4 separate occasions: a) triple espresso, b) decaffeinated triple espresso, c) 240mg of caffeine alone (amount contained in a triple espresso) and d) placebo. Repeated measurements were taken 30, 60, 90, 120 and 150 min. after drug administration at the first day (acute study) and at the end of each treatment arm (acute-on-chronic study). Aortic stiffness was evaluated with carotid-femoral pulse wave velocity (PWV) and wave reflections with augmentation index (AIx) of the aortic pressure waveform.
Results: PWV and AIx did not change after the 2-week long daily consumption of either coffee or decaffeinated coffee whereas, caffeine significantly increased both PWV and AIx (maximal responses by 0.51 m/sec and 4.3%, respectively, $p<0.05$ at the end of the treatment arm). The acute and acute-on-chronic effect of decaffeinated coffee on arterial stiffness was not significant. Coffee with caffeine induced a significant change in PWV and AIx values at the first day, however, the acute-on-chronic effect was proportionally less significant (upper panel). On the contrary there were not differences in PWV and AIx responses by caffeine between the acute and acute-on-chronic study (lower panel).



Conclusions: Coffee consumption has a less potent acute-on-chronic effect on aortic stiffness and wave reflections than caffeine. This finding indicates that substances other caffeine may partially counterbalance the active effect of caffeine on the intrinsic properties of the elastic arteries already modified by a two-week daily coffee administration.

P736 Adherence to the mediterranean diet and albuminuria levels in adolescents: emerging data from the lyceum leontio albuminuria (3L) study

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Purpose: Mediterranean diet has favorable effects on the cardiovascular system, while albuminuria is associated with atherosclerosis progression. The aim of the study was to investigate the relationship of dietary habits with urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR), in a cohort of adolescents.
Methods: A total of 365 adolescents 12-17 years of age [212 males, aged 13.9 years, office blood pressure (BP)=115/67 mmHg] that were included in the Lyceum Leontio Albuminuria (3L) study were considered for analysis. In all participants ACR values were determined in a morning spot urine and for each adolescent a questionnaire was completed on lifestyle and socio-economic characteristics. Moreover, the Mediterranean Diet Quality Index for children and adolescents (KIDMED) was estimated and accordingly subjects were divided into those with optimal ($\geq$7), average (4-7) and low ($<$4) score.
Results: Only 6.8% of the participants had optimal KIDMED score, whereas 51.2% had an average and 42% had a low score. Participants with at least average KIDMED score (n=187) compared to those with low KIDMED score (n=153) had higher body mass index (22.2 vs 21.4 kg/m^2, p=0.043) and waist circumference (77.6 vs 75.4 cm, p=0.044), spent more frequently time for sports activities outside school (75.2% vs 58%, p=0.001), reported less consumption of foods outside home (3% vs 14%, $p<0.001$) and less hours of watching television (1.75 vs 2.05 hours, p=0.013). Moreover, those with at least average compared to those with low KIDMED score exhibited higher systolic BP (117 vs 114 mmHg, p=0.039), whereas had lower heart rate (84 vs 87 bpm, p=0.014) and ACR levels (12.6 vs 20.5 mg/g, p=0.015). In the total population, ACR was associated with age (r= -0.11, p=0.044), body mass index (r= -0.131, p=0.016), systolic BP (r= -0.144, p=0.008) and KIDMED score (r= -0.111, p=0.041).
Conclusion: In adolescents there is an inverse relation of KIDMED score with albuminuria and those who adhere to the Mediterranean diet exhibit lower levels of ACR. However, the paradoxical associations of both ACR and KIDMED score with obesity markers and BP levels suggest distinct mechanisms of albuminuria development in adolescents.

P737 Binge drinking and blood pressure: cross-sectional results of the HAPIEE study

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Purpose: Current evidence on the effect of binge drinking on blood pressure is sparse and inconsistent. We investigated whether binge drinking pattern influences blood pressure independently from drinking volume or whether it modifies the effect of volume of drinking.
Methods: We used cross-sectional data from random urban population samples of 7559 men and 7471 women aged 45-69 years, and not taking antihypertensive medication, from Russia, Poland and Czech Republic. Annual alcohol intake, drinking frequency and binge drinking ($\geq$100 g in men and $\geq$60 g in women in one session at least once a month) were estimated from graduated frequency questionnaire. Blood pressure was analysed as continuous variables (systolic and diastolic pressure) and a binary outcome of high blood pressure ($\geq$140/90 mm Hg).
Results: The prevalence rates of binge drinking ranged from 12% in Poland to 32% in Russia in men, and from 1.2% in Russia to 3.4% in the Czech Republic in women. In men, the odds ratio of high blood pressure for binge drinking was 1.62 (95% CI 1.45-1.82) after controlling for age, country, body mass index, education and smoking; additional adjustment for annual alcohol intake reduced it to 1.20 (1.03-1.39). Both annual alcohol intake and drinking frequency were strongly associated with blood pressure in men. In women, the adjusted OR of high blood pressure for binge drinking was 1.35 (1.12-1.62) and 1.31 (1.05-1.63) after additional adjustment for annual intake. The effects of annual alcohol intake and drinking frequency in women were less consistent than in men. Binge drinking did not modify the effect of annual alcohol intake in either sex. Further adjustment for day of week (to indirectly account for recent alcohol consumption) or for past drinking did not change the results. Consuming alcohol as wine, beer or spirits had similar effects. Results were similar across countries and in analyses using systolic and diastolic blood pressure as continuous variables.
Conclusions: The independent effects of binge drinking were modest, binge drinking did not modify the effect of the overall alcohol intake, and different alcoholic beverages had similar effects on blood pressure. By contrast, blood pressure was associated with the annual volume and frequency of drinking; the relationship was particularly strong in men.

P738 Blood pressure control in patients with coronary heart disease is facilitated by fruit and vegetable intake

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Purpose: The aim of this study was to determine if there was a relationship between fruit and vegetable (FV) consumption and blood pressure (BP) outcomes as continuous variables as well as the mean quantum of daily FV consumption required to achieve BP targets.
Methods: This post-hoc analysis of the EUROACTION cluster randomised controlled intervention trial concerned patients with coronary heart disease (CHD) (n=942) enrolled in the intervention arm. The trial involved a multidisciplinary cardiovascular disease prevention programme in 6 European countries, addressing lifestyle and medical risk factor management. These patients were assessed after 12 months as to daily FV consumption (g per day) and BP outcomes. The desirable BP target to be achieved was 140/90 mm Hg (or 130/85 in people with diabetes) and FV target >400 g per day. An analysis was also performed with reference to the individual study centre.
Results: A negative linear relationship was obtained for daily FV consumption and diastolic (r -0.0797, p=0.0145) and systolic (r -0.0582, p=0.074) blood pressures. Mean daily FV consumption in those achieving BP target was 583 g per day, compared to 536 g per day in those not achieving BP target (mean difference -47 g per day, CI -83,-12, p=0.009). In patients with uncontrolled systolic BP (>140), mean daily FV intake was 541 g per day, compared to 577 g per day in those with systolic BP <140 (mean difference 36 g per day, CI -2,73, p=0.064). Similarly for uncontrolled diastolic BP (>90), mean daily FV intake was 485 g per day, compared to 576 g per day with controlled diastolic BP (mean difference 91 g per day, CI 35,148, p=0.002). Furthermore, countries demonstrating higher FV target achievement also generally had higher prevalence of BP target achievement (p<0.001).
Conclusions: FV intake appears to favourably improve BP outcomes in a linear fashion. BP target achievement in this patient group is associated with a mean FV intake of around 580 g per day.

P739 (W)

WITHDRAWN

P740 Does obesity influence target organ damage and outcomes in patients with malignant phase hypertension?

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Purpose: To investigate the impact of baseline body mass index (BMI) at presentation on the primary outcome (death or dialysis) in patients with malignant phase hypertension (MHT).
Methods: 184 patients [overall mean (SD) age 48 (13) years; 61% male; 62% White-European; 20% African-Caribbean, 18% South-Asian] from the West Birmingham MHT Register were included. The patients were grouped according their BMI (Table). 93 primary outcomes occurred during a median (IQR) follow-up of 10.7 (5.8-18.6) years.
Results: There was no significant difference in baseline BMI by age or ethnicity (Table). Overweight and obese patients included a larger proportion of females and a lower proportion of smokers than those underweight or of normal weight. Retinopathy (p=0.25), proteinuria (p=0.08), haematuria (p=0.56) and left ventricular hypertrophy (p=0.14) were not significantly related to BMI (data not shown). BMI was predictive of death or dialysis in univariate analyses [0.95 (0.90-1.00), p=0.046] but multivariate analyses revealed that only baseline age [odds ratio (95% confidence intervals) 1.06 (1.03-1.09), p<0.001], smoking [2.89 (1.40-5.92), p=0.004], and creatinine level [1.011 (1.005-1.017), p=0.001] independently predicted death or dialysis.

Baseline characteristics by BMI in MHT

Mean (SD); n (%)	Underweight [BMI <21] (n=16)	Normal [BMI 21.1-25.0] (n=50)	Overweight [BMI 25.1-29.9] (n=66)	Obese [BMI ≥30.0] (n=52)	p-value
Age, years	46±13	51±15	49±11	45±13	0.20
Male	10 (63)	37 (74)	43 (65)	23 (44)	0.017
White-European	10 (62)	34 (68)	41 (62)	29 (56)	For ethnicity 0.14
African-Caribbean	0 (0)	11 (22)	14 (21)	12 (23)	
South-Asian	6 (38)	5(10)	11 (17)	11 (21)	
Smokers (at baseline)	10 (67)	29 (58)	26 (39)	16 (31)	0.01
SBP, mmHg	226±44	230±30	233±30	231±34	0.91
DPB, mmHg	147±15	144±20	141±19	146±19	0.42
Creatinine, mmol/L	150 (121-213)	133 (109-198)	127 (97-173)	118 (88-168)	0.044
Death or dialysis	9 (56)	31 (62)	33 (50)	20 (38)	0.12

BMI, body mass index in kg/m^2; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

Conclusions: BMI at presentation is not related to BP at presentation or target organ damage, and does not independently predict death or dialysis in patients with MHT.

P741 Longitudinal change in blood pressure in relation to 5 candidate genes and urinary sodium excretion in 1405 subjects from 5 European populations

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Purpose: The genes encoding angiotensin converting enzyme (ACE), adducin subunits (ADD1, ADD2 and ADD3) and aldosterone synthase (CYP11B2) share the potential of influencing blood pressure (BP) via sodium homeostasis. In this analysis we aimed to investigate longitudinal changes in BP in relation to polymorphisms in aforementioned genes (ACE I/D, ADD1 Gly460Trp, ADD2 C1797T, ADD3 A386G, and CYP11B2 C-344T) in White Europeans recruited from 5 populations.
Methods: At baseline and after median (IQR) 6.3 (5.2-8.3) years of follow-up, we measured conventional BP and 24-h urinary sodium excretion (24-h UVNa) as index of salt intake, in 1405 never treated subjects recruited using a family-based random sampling frame from Hechtel-Eksel (Belgium, n=1038), Kraków (Poland, n=106), Novosibirsk (Russian Federation, n=64), Padova (Italy, n=138) and Pilsen (Czech Republic, n=59). The analyses of genotype-phenotype relations were adjusted for covariables and relatedness of study participants.
Results: In analyses not accounting for urinary sodium, ACE DD homozygosity was associated with a greater increase in diastolic BP during follow-up (DD vs DI+II (adjusted mean±SE): 5.40±0.50 vs 4.40±0.39 mmHg; P=0.036), but not in systolic BP (5.72±0.69 vs 4.72±0.54 mmHg; P=0.14) as compared to I-allele carriers. We have not observed any association between polymorphisms in CYP11B2 and 3 adducin subunits and follow-up changes in blood pressure. The relation between ACE genotype and change in BP depended on baseline sodium excretion (P for interaction between baseline 24-h UVNa and change in systolic

BP=0.059). In subjects with higher than sex- and country-specific median of baseline 24hUVNa (≈167 mmol/24h), carriers of D allele had higher increase in systolic (4.36±0.72 vs 2.34±1.10 mmHg; P=0.049) and diastolic BP (4.53±0.52 vs 3.08±0.78 mmHg; P=0.044) as compared to II homozygotes. Such relation was not observed in subjects with lower than median baseline 24hUVNa (P≥0.37). We did not observe any gene-gene interactions among polymorphisms under study.
Conclusions: The I/D polymorphisms of the ACE gene influences longitudinal BP change. However, sodium intake seems to modulate this genetic effect.

P742 Difference of central hemodynamic parameters according to the sex in hypertensive patients

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Purpose: Central BP is pathophysiologically more relevant than peripheral BP for the pathogenesis of cardiovascular disease. Central hemodynamic parameters have been shown to be independently associated with organ damage and incident cardiovascular disease. But sex differences of the central hemodynamic parameters in hypertensive patients were not well defined.
Methods: We recruited serial 547 hypertensive subjects with sinus rhythm who came to our cardiovascular outpatient facility from June, 1st, to June, 30th, 2010. They were taking antihypertensive drugs. Radial artery waveforms were recorded with the radial tonometry (HEM 9000-AI). Systolic BP1 (SBP1; peripheral BP), SBP2 (central BP), peripheral augmentation index (pAI), pAI corrected at pulse rate 75/min (pAI75), ΔSBP1-SBP2, and central pulse pressure (cPP) were obtained.
Results: Women were older than men (n=247, 66.7±11.2 yrs vs. n=300, 64.6±11.5 yrs, p=0.037). Men were more smokers (23.4% vs. 0.4%, p<0.001), and had coronary heart disease (34.0% vs. 21.9%, p=0.002) and chronic kidney disease (9.3% vs. 2.0%, p<0.001). There was no difference of the classes of anti-hypertensive medication. SBP2, pAI, pAI75 and cPP were significantly higher and ΔSBP1-SBP2 was significantly lower in women. In multivariate analysis including age, SBP2 (p=0.028), pAI (p<0.001), and ΔSBP1-SBP2 (p<0.001) were independently different according to the sex.

	Men (n=300)	Women (n=247)	p value
SBP1 (mmHg)	130.3±17.5	131.6±18.2	0.399
SBP2 (mmHg)	117.5±20.1	124.9±18.4	<0.001
pAI (%)	79.3±12.9	91.2±11.6	<0.001
ΔSBP1-SBP2 (mmHg)	12.8±10.7	6.7±4.7	<0.001
cPP (mmHg)	44.5±16.4	50.0±14.9	<0.001

SBP1, peripheral BP; SBP2, central BP; pAI, peripheral augmentation index; cPP, central pulse pressure.

Conclusions: Although female hypertensive patients had less cardiovascular risk factors such as smoking, coronary heart disease or chronic kidney disease, they showed the more increased arterial stiffness parameters of central hemodynamics.

ACUTE PULMONARY EMBOLISM

P743 Predictive variables for in-hospital bleeding in patients presenting with objectively confirmed pulmonary embolism

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Background: Several predictors of bleeding have been identified in patients with venous thromboembolism. There are no studies reporting predictive variables for bleeding in patients with pulmonary embolism (PE) as a primary disease.
Purpose: To identify predictors of in-hospital bleeding in patients with objectively confirmed PE according to validated diagnostic criteria.
Methods: 2015 patients with suspicion of PE admitted to 80 cardiology departments across Poland from January 2007 to September 2008 were included in national ZATPOL registry. Results of in-hospital evaluation and risk factors for bleeding were reported through web-based questionnaire and revised by central reviewers. Additional questionnaires were sent to centers, which reported bleeding.
Results: PE was diagnosed locally in 1216 patients, but validated diagnostic criteria according to ESC guidelines were implemented in 1112 patients (mean age 66±15 yrs, 42% males). In this group 67 (6%) bleeding complications were reported, including 6 (0.5%) fatal bleedings. Vascular access area was the most common site of bleeding (n=24; 35.8%), followed by gastrointestinal tract (n=13; 19.4%), respiratory system (n=9; 13.4%), urogenital tract (n=8; 12%), intracranial (n=7; 10.4%), retroperitoneal area (n=4; 6%) and postsurgical wound (n=2; 3%). 25 (37%) patients who bled received antiplatelet agents. Independent predictors of in-hospital bleeding and proposed risk score are presented in the Table.

ZATPOL Bleeding Risk Score

Bleeding predicting factor	OR [95% CI], P	β	Points
Thrombolytic therapy	7.24 [4.07, 12.9], P<0.001	1.98	+2
Peptic ulcer disease or inflammatory bowel disease	3.92 [1.83, 8.36], P<0.001	1.37	+1.5
≥1 In-hospital intervention (i.v. access, pulmonary angiography, surgical or transcutaneous embolectomy, vena cava filter implantation)	2.4 [1.08, 5.32], P=0.032	0.88	+1
Sequential use of UFH and LMWH or UFH and pentasacharide	1.76 [0.98, 3.17], P=0.06	0.56	+0.5
Age >71 yrs	1.73 [1.0, 3.02], P=0.051	0.55	+0.5

Based on prognostic index, estimated probability of in-hospital bleeding is 1.8–4.7% for ≤1 point category, 7.6–18.2% for the 1.5–2.5 point, 26.9–37.8% for the 3.0–3.5 point category and ≥50% for the ≥4 point category. In the derivation sample there were no patients for whom the model based risk of in-hospital bleeding exceeded 64.6%.

Conclusion: Predictors of in-hospital bleeding in patients with objectively confirmed PE were identified. Useful tool to assess bleeding risk was proposed. Further validation is required.

P744 The italian pulmonary embolism registry: in-hospital course results

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Purpose: Pulmonary embolism (PE) is a common potentially fatal disease. Recent advances in the diagnosis (CT angiography) and risk stratification (serum biomarkers) have changed the clinical management of patients with acute PE. Whether these advances have led to an improvement of clinical course is still undefined.
Methods: The IPER Registry is a web-based registry, started in 2006, that allows cardiologists, emergency physicians, pneumologists and internal medicine physicians to collect data regarding the in-hospital and long term clinical course of consecutive patients with acute PE. Data regarding instrumental and laboratory exams are collected at admission, during the hospital stay, at discharge and during follow-up until four years from the index PE episode.
Results: As for September 2010, data from 1719 patients included in the registry have been analysed (mean age 70±15, 30% of patients >80 years, 57% females, 58% admitted to cardiology divisions). Diagnosis of PE was achieved by MDCT angiography in 81% and lung scan in 8.4%; in no cases pulmonary angiography was used. According to ESC guidelines, PE was considered at high risk for mortality in 202 (11.8%). Out of 1514 patients with non-high risk for mortality, 1105 (73%) had echocardiography performed within 48 hours of PE onset. Based on echocardiographic results 755 (44%) and 350 (20.4%) patients were categorized as intermediate or low risk, respectively, while 409 of non-high risk patients could not be further categorised. In-hospital all-cause mortality occurred in 116 (6.7%) of the patients. Causes for death were PE in 68 (3.9%), intracerebral haemorrhage in 6 (0.4%) and cancer in 5 patients. Death occurred in 33.5% and 3.6% of high risk or non-high risk patients, respectively. When echocardiographic data were taken into account, in-hospital death occurred in 4.4% and 1.5% of patients at intermediate and low risk for mortality, respectively. Overall, 185 cases (10.8%) received thrombolysis. Troponin levels were measured at admission in 1091 (72%) of non-high risk cases and resulted elevated in 462 (42.3%); mortality was 5.2% and 1.7% in non-high risk patients with elevated or normal troponin, respectively, in these patients categories PE-related death occurred in 1.3% and 1%, respectively.
Conclusions: The IPER Registry is a contribute to the knowledge of the real-life management and course of pulmonary embolism.

P745 Independent prognostic value of plasma lactate in acute pulmonary embolism

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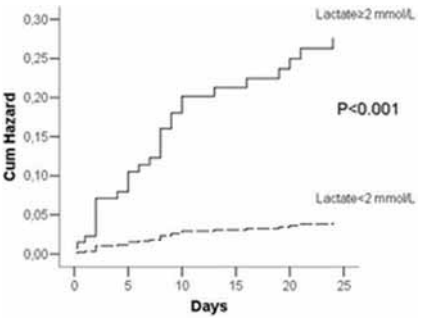
Purpose: To investigate the prognostic value of plasma lactate in patients with acute pulmonary embolism (PE).
Methods: Consecutive adult patients with symptomatic and objectively confirmed acute pulmonary embolism were prospectively included in the study. Diagnosis of acute PE was established in our emergency department (ED) by computed tomographic pulmonary angiography or perfusion lung scan. Plasma lactate values ≥ 2mmol/L and troponin I values ≥ 0.10 ng/ml were considered abnormal. Rightventricular dysfunction (RVD) was assessed by echocardiography. Primary endpoint was the composite of death related to PE or any of the following within 30 days from presentation: sustained hypotension, shock, endotracheal intubation, cardiopulmonary resuscitation or recurrent PE.
Results: From January 2007 to January 2010, 235 patients were included, 129 were females (55%), with a mean age of 72±12 years. Seventeen (7%) showed shock/hypotension at presentation, 85 (36%) had RVD, 75 (31%) had troponin I ≥ 0.10 ng/ml and 72 (31%) had plasma lactate ≥ 2 mmol/L. During 30 days follow-



up, 11 patients (5%) died due to PE and 29 (12%) experienced other adverse events. Six patients out of 163 (3%)with serum lactate $<$ 2 mmol/l and 23 out of 72 (31%) with serum lactate $\geq$ 2 experienced the primary endpoint (OR 12.3, CI 95% 4.7-31.9). At multivariate Cox proportional hazards regression analysis plasma lactate$\geq$2 mmol/L was associated with primary endpoint (HR 6.9, 95% CI 2.7-17.6) and with PE-related death (HR 25, CI 95%3.2-196) independent of shock/hypotension, RVD or elevation of troponin I.

Conclusions: Patients with plasma lactate values$\geq$2 mmol/L are at high risk of PE-related adverse events independent of shock/hypotension and of markers of rightventricular dysfunction/injury.

P746 Novel assessment of vortex formation time of the right ventricle: comparison with left ventricular fluid dynamics in pulmonary embolism

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Background: We have previously shown that vortex formation time (VFT) is a useful and sensitive index in left ventricular (LV) heart failure and after-load states. Right ventricular (RV) VFT has not been previously measured. We aim to quantify echocardiographic-derived LV and RV VFT in patients (pts) with pulmonary embolism (PE), comparing these with controls.

Methods: Pts with clinically suspected PE underwent pulmonary artery computed tomography and were divided into Group A (n=24, age 54$\pm$18 yrs, confirmed pulmonary artery occlusion) and Group B (n=34, age 61$\pm$13 yrs, negative scan). Conventional echocardiography, tissue Doppler imaging (mitral and tricuspid annular velocities, (including ratio of transmitral E velocity to annular E' velocity), RV and LV functions were assessed. RV and LV VFTs were obtained using time-velocity integrals of tricuspid or mitral in-flows divided by their respective annular dimensions during early diastole.

Results: In controls (Group B), RV VFT is lower than LV VFT (paired t-test P=0.035). RV fractional area change (FAC) was lower in pts with PE (32$\pm$11 vs 44$\pm$10%, P$<$0.001) but RV VFT was not significantly reduced (1.96$\pm$1.18 vs. 2.04$\pm$1.16, P=0.84). VFT of RV correlated inversely with myocardial performance index, MPI (rho= -0.35, P=0.047) and pulmonary artery systolic pressure (rho= -0.40, P=0.031).

In contrast, LV ejection fraction (EF) was not different between the 2 groups though cardiac index (CI) was reduced (2.6$\pm$0.7 vs 3.2$\pm$1.1L/min, P=0.012) in Group A. LV VFT was significantly attenuated in the PE Group (2.48$\pm$1.03 vs 3.13$\pm$1.18, P=0.038). It correlated to indices of diastolic LV function (transmitral E/A ratio, rho=0.37, P=0.006; lateral annular E'/A', rho=0.35, P=0.018) and LV filling pressure (E/E'; septal, rho=0.49, P=0.001; lateral, rho=0.42, P=0.004).

There was moderate correlations between RV and LV VFT (rho=0.36, P=0.039).

Conclusion: In PE, there appears to be reduced RV FAC and reduced LV CI. RV pressure overload from acute pulmonary embolism results in alter fluid dynamics, paradoxically in the LV but was preserved in the RV. Though VFTs of the LV and RV correlated moderately with each other, they were affected differently, predicted by diastole LV and overall RV dysfunctions respectively.

P747 Lower levels of the adipocytokine leptin are associated with poor short- and long-term outcome in patients with acute pulmonary embolism

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High leptin levels as found in obesity are a risk factor for coronary artery disease (CAD) and a predictor for future cardiovascular events. In addition, obesity is a risk factor for venous thromboembolism. We therefore postulated that circulating leptin levels might be elevated in patients with pulmonary embolism (PE) and high concentrations are associated with poor prognosis.

We prospectively studied 264 patients (63$\pm$17 yrs; BMI 28$\pm$5.8 kg/m^2) with acute PE. Leptin levels determined by ELISA were compared to a control group of 38 patients with acute chest pain or dyspnoea (58$\pm$11 yrs [p=0.007 vs. PE group]; BMI 26.9$\pm$5 kg/m^2 [p=0.383]), in whom PE and CAD were excluded. In the entire PE population, leptin levels were 19.7$\pm$29.4 ng/ml and thus not significantly different from those in the control group (20.6$\pm$27.5; p=0.449). However, patients (n=49; 18.6%) with a complicated 30-day course, i.e. death, need for catecholamines, intubation or resuscitation, had significantly lower leptin levels (16.2$\pm$23.8 ng/ml) compared to PE patients without complications (20.6$\pm$30.5 ng/ml; p=0.02) and also compared to controls (p=0.035). Of note, BMI levels did not differ between the groups. Univariable logistic regression indicated that higher leptin levels were associated with a lower risk of 30-day complications with an odds ratio (OR) of 0.73 (95% confidence intervall [CI], 0.57-0.95; p=0.017) for each increase by one standard deviation of ln leptin. When leptin was corrected for BMI, it remained a significant predictor for an uneventful course (OR, 0.66 (95% CI, 0.49-0.89; p=0.006). Over a follow-up period of 803$\pm$682 days, 73 (28%) patients died. Cox regression analysis revealed that higher leptin levels on admission were associated with better long-term survival (hazard ratio (HR), 0.77 (95% CI, 0.63-0.93; p=0.006), and again, independently of BMI levels (adjusted HR for ln leptin, 0.74; 95% CI, 0.59-0.92; p=0.008). When leptin was analysed as a categorical variable split into tertiles, a similar association was seen between higher leptin levels and better prognosis, with a HR of 0.55 (95% CI, 0.32-0.94; p=0.03) for the highest tertile. Accordingly, the probability of survival assessed by the Kaplan-Meier method was worse for the lower baseline leptin tertiles (p=0.018).

In conclusion, lower leptin levels were unexpectedly associated with poor short- and long-term outcome in patients with acute PE. The underlying mechanisms of the BMI-independent effect of the adipocytokine are unknown, but as previously shown in the case of acute severe sepsis, low leptin levels might impair the body's capacity to fight acute disease.

P748 Left ventricular regional non-uniformity quantified by displacement and strain imaging in the radial, longitudinal, and circumferential directions in patients with acute pulmonary embolism

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Objective: We aimed to investigate the impact of acute right ventricular (RV) pressure overload (RVPO) on left ventricular (LV) function and regional uniformity using speckle-tracking displacement and strain analyses in patients with acute pulmonary embolism (PE).

Methods: Twenty-five patients with acute PE (mean age, 59$\pm$16 years) and 25 normal subjects were enrolled. Radial, longitudinal, and circumferential LV wall motion and myocardial deformation were analyzed using speckle-tracking displacement and strain imaging echocardiography respectively from the mid-LV short axis and apical 4-chamber views. The standard deviation of regional time-to-peak systolic displacement (PSD) and strain (PSS) from QRS onset for the 6 segments was used to quantify LV systolic dyssynchrony. The standard deviation of regional PSD and PSS divided by their global values was used to quantify LV systolic heterogeneity. Mechanical discoordination of regional LV wall motion and myocardial deformation was assessed by averaging the frame–by-frame percent discordance between segmental and global signal changes in the 6 segments.

Results: Patients with acute PE had reduced radial wall motion and large extent of non-uniformities assessed using displacement imaging (global radial PSD, 5.1$\pm$1.4 vs. 7.6$\pm$1.2 mm; dyssynchrony, 74$\pm$32 vs. 40$\pm$20 msec; heterogeneity, 0.39$\pm$0.13 vs. 0.17$\pm$0.08; and discoordination, 23$\pm$2 vs. 15$\pm$3%, p$<$0.05 vs. normal subjects for all comparisons). In contrast, all three indices of radial LV uniformities assessed using strain imaging were not altered by acute RVPO in patients with acute PE. Patients with acute PE also had impaired LV systolic function and uniformities in the longitudinal and circumferential directions. After the amelioration of acute RVPO by primary treatment, most of the indices of LV function and regional uniformity were restored to normal values. Multiple regression analysis indicated that only radial LV wall motion discoordination was a significant determinant of cardiac index.

Conclusion: Acute RVPO impairs LV regional uniformities in all three contractile directions except radial strain-derived uniformities, and radial displacement-derived discoordination is closely associated with impairment of LV performance and plays a key role in the short-term regulation of cardiac output in patients with acute PE.

P749 Risk of recurrence in patients with pulmonary embolism: predictive role of d-dimer and of residual perfusion defects on lung scintigraphy

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Purpose: The stratification of recurrence risk after a first episode of venous

thromboembolism (VTE) is an important topic of recent research. This is of particular clinical relevance in patients who experienced pulmonary embolism (PE) for the risk of developing chronic thromboembolic pulmonary hypertension and for the mortality related to PE. Elevated D-dimer levels after withdrawing oral anticoagulant treatment (OAT) are predictive of recurrence, but it is still unknown if residual perfusion defects (PD) on lung scintigraphy are related to recurrent PE. Aim of our study was to evaluate whether PD are associated with the risk of recurrence.

Methods: We prospectively followed 102 consecutive patients who survived a first episode of objectively confirmed PE, with or without deep vein thrombosis. After at least 3 months of OAT, treatment was withdrawn and the patients followed to detect VTE recurrences. D-dimer levels were evaluated 1 months after OA withdrawal and perfusion lung scan (P-scan) was performed. PD affecting 10% of the pulmonary vascular bed or greater were considered relevant.

Results: Elevated D-dimer levels were significantly associated with VTE recurrence (p=0.002), but no association was found between PD and recurrences (p=0.5).

Table 1. Patients characteristics

	N (percent, or range)
Follow-up (patient-years)	237.3
Median follow-up (mo)	22 (1-120)
Unprovoked PE	74 (65.5)
Isolated PE	46 (41.1)
Oral contraceptives (for females)	17 (26.6)
Congenital Thrombophilia	20/100 (20)
Median OAT duration (mo)	12 (4-72)
Recurrent VTE (1 fatal)	13/102 (12.7)
Rate of VTE recurrence (×100 pt-yrs)	5.4
Median time of recurrent VTE (mo)	6 (1-81)
PD on P-scan	21 (19.4)
Elevated D-dimer levels	31 (27)

Conclusions: We confirmed the positive predictive value of elevated D-dimer levels for recurrent VTE. Residual PD on lung scintigraphy are not predictive of recurrence.

P750 Prevalence and time course of ECG-detected right ventricle strain in patients with acute pulmonary embolism: results from the IPER registry

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Purpose: In patients with acute pulmonary embolism (PE) signs of right ventricle strain can be found at electrocardiography (ECG). The prevalence and time-course of these findings in different risk categories of patients is not well established.

Methods: The IPER Registry is a web-based registry on the in-hospital and long term clinical course of consecutive patients with acute PE. Data regarding ECG findings at baseline (within 24 hours from the index episode), at day 3 and at discharge were collected and signs of RV strain, namely right bundle branch block (RBBB), Qr pattern in V1 or negative T waves in V1-V4 were evaluated. The time course of these ECG abnormalities in patients with PE at high-intermediate and low-risk according to ESC guidelines was assessed.

Results: Data from 1719 patients included in the registry have been evaluated as for September 2010. ECG findings were reported at baseline in 1643 (95.6%) patients and at serial ECG (baseline, day 3 and discharge) in 687 (40%). Apart from sinus tachycardia, the most common ECG finding at baseline was T-wave inversion V1-V4 (28% in the overall population, 33% in high-, 33% in intermediate and 16% in low-risk patients, respectively); complete or incomplete RBBB was present in 20% of patients (44%, 20%, 9% of high-intermediate and low-risk patients, respectively); Qr pattern in lead V1 was detected in 6% of cases (12%, 6%, 3% of high-intermediate and low-risk patients, respectively). In low-risk patients, the prevalence of ECG signs of RV strain remained steadily low during the hospital stay, while in intermediate and high-risk patients a reduction of RBBB as well as Qr in V1 was observed. In intermediate-risk patients, a moderate increase in T-wave inversion V1-V4 was observed at day 3 from the index PE event and this finding was more pronounced in high-risk population

	Low risk			Intermediate risk			High risk		
	ECG1	ECG2	ECG3	ECG1	ECG2	ECG3	ECG1	ECG2	ECG3
RBBB, %	9	7	7	20	12	9	44	25	15
Qr in V1, %	3	4	3	6	4	4	12	8	4
T wave inversion V1-4, %	16	19	14	33	46	33	33	57	40

Conclusions: Individual ECG signs of right ventricle strain have a different prevalence and time course in patients with acute PE at different risk for in-hospital death.

P751 Improvement of renal function indicates better prognosis in acute pulmonary embolism

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Objective: Risk stratification of patients with acute pulmonary embolism (APE) is based on clinical status, presence of right ventricle (RV) dysfunction or injury indicted by echocardiography or biomarkers. However, there were studies suggesting important role of renal dysfunction in mortality of APE. Therefore we evaluated changes of the renal function in APE.

Material and method: We evaluated 117 consecutive pts (56M, aged 66±18 years) with APE proven by spiral CT. On admission and 72hrs later blood samples were collected for creatinine assays, GFR was estimated using Modification of Diet in Renal Disease (MDRD) formula.

Results: On admission GFR below 60ml/min was noted in 58 (50%) pts and in 11 (9%) pts it was <30ml/min. Seventy two hours later GFR was below 60ml/min in 48 (45%) pts, while GFR<30ml/min was found in 4 (4%) pts. There were 7 pts with high-risk APE, 69 pts with moderate risk APE and 36 pts with low-risk APE. Patients with high-, moderate- and low-risk APE did not differ GFR on admission (median 51.8ml/min (range:20.1-103.4) vs. 60.4ml/min (19.2-153.5) vs. 56.9ml/min (17.1-151.3), p=NS), while GFR was significantly lower in low-risk group after 72hrs (98.9ml/min (41.6-156.1) vs. 70.0ml/min (18.6-153.5) vs. 56.4ml/min (17.9-129.7), p<0.05). Interestingly, during 72hrs after admission due to APE, GFR increased in high- and moderate-risk groups (p=0.07 and p=0.03), while in low-risk group difference of GFRs was not significant. Nineteen pts died during 30-day observation (10pts during first 72hrs). Two (29%) patients died in high-risk group, 4 (6%) with moderate-risk APE and 1 (3%) with low-risk APE. The difference of GFR levels between survivors and nonsurviors on admission (61.3ml/min (17.1-169.3) vs 50.1ml/min (9.6-118.8), p<0.14) and on third day (66.9ml/min (17.9-156.1) vs. 55.2ml/min (30.3-101.9), p<0.26) did not reached significance. Interestingly, GFR increased in survivors (61.3ml/min (17.1-169.3) vs. 66.9ml/min (17.9-156.1), p=0.02), while in group of pts, who died after third day increase was no significant (50.1ml/min (19.2-118.8) vs. 55.2ml/min (30.3-101.9), p<0.26). GFR after 72 hrs correlated with age (r= -0.45, p<0.001), presence of RV dysfunction (r= -0.30, p<0.01) and GFR (r=0.76, p<0.001) on admission.

Conclusion: About 50% of patients with APE has at least moderately impaired renal function on admission. Renal function improves within 72hrs in patients with good prognosis and RV overload in acute period. Moreover, renal function correlates with age, presence of RV dysfunction and GFR on admission.

P752 Predictors of clinical outcome in patients with acute pulmonary embolism

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We sought to determine predictors of mortality in patients with acute pulmonary embolism (PE).

Methods: 243 patients (132 M,mean age 55.4±15.4 years) were treated at our centre for acute PE. 35 various parameters from clinical assessment, ECG, transthorasic echocardiography, blood gases, biochemistry and coagulation were tested as risk factors for in-hospital and follow-up mortality.

Results: In- and post-hospital mortality rates were 9.5% (n=23) and 15.9% (n=35, follow-up 15.6±17.5 months).bOn univariate analysis right ventricular anteroposterior diameter [OR 1.17 (1.04-1.31) p=0.01], left ventricular ejection fraction (EF) [OR 0.93 (0.87-0,98) p=0.01], heart rate [OR 1.04 (1.01-1.08) p=0.006], pH [OR 0.008 (0.001-0.488) p=0.02], pO2 [OR 1.03 (1.0-1.07) p=0.05], APTT [OR 1.02 (1.0-1.03) p=0.01] were associated with increased in-hospital mortality. Age [OR 1.05 (1.02-1.08) p=0.002], history of neoplasm [OR 10.9 (3.5-33,5) p<0.001], BMI [OR 1.09 (1.0-1.18) 0=0.04], creatinine[OR 1.03 (1.0-1.07) p=0.04]; peak pulmonary artery pressure (PAP) at discharge [OR 1.05 (1.01-1.08) p=0.01] and EF [OR 0.92 (0.87-0.97) p=0.003] were defined as risk factors for follow-up mortality. On multivariate analysis EF (p=0.009) was identified as an independent predictor of in-hospital mortality (EF<45%, sensitivity 50%, specificity 80.8%) and

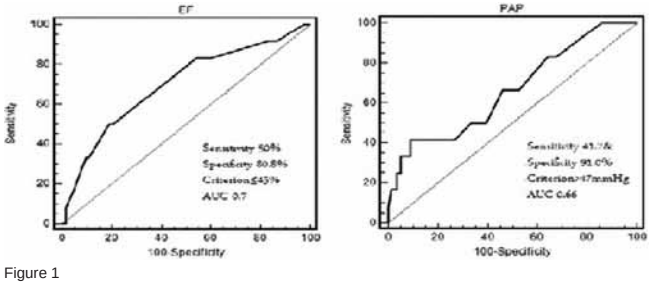

Figure 1

PAP (p=0.026) was found as an independent predictor of follow-up mortality (PAP >47%%, sensitivity 41.7%, specificity 91%).
Conclusions: Simple bedsite clinical and echocardiographic assessment as well as basic blood tests may serve as markers of mortality in patients with acute pulmonary embolism. Left ventricular ejection fraction was identified as an independent predictor of in-hospital mortality and peak pulmonary artery pressure at discharge was found as a risk factor for post-hospital mortality.

P753 Mean platelet volume as a predictor of mortality in acute pulmonary embolism

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Purpose: Acute pulmonary embolism (APE) is a life threatening disease and one of the main causes of in-hospital mortality. Mean platelet volume (MPV), which is widely available in clinical practice, is a potentially useful biomarker of platelet activity in APE. The purpose of this study was to determine the prognostic value of MPV for in-hospital mortality in patients with APE.
Methods: We conducted a prospective, cohort study, between 1 January 2004 and 31 December 2009. The patients with APE, admitted in the Ist Medical Cardiology Clinic, were included. The blood samples for MPV meassurements were collected. Data analysis used chi-square test or the independent samples t-test for patients groups comparisons, to test the statistical significance of differences (p value < 0.05 considered significant).
Results: During the study period, we enrolled 326 patients with APE. Mean age of the patients was 62.3 years (range 16 - 95 years), 197 (60%) were females, 30 (9%) were in shock at admission. The cases were classified in: high-risk APE 89 patients (27%), intermediary-risk APE 40 patients (12%) and low-risk APE 197 subjects (61%). Fifty seven patients died during hospital stay (17%). As compared with low-risk and intermediary-risk group, the high-risk APE group had significantly higher MPV values ($p<0.05$). Moreover, we found that the MPV values were higher in patients with shock at admision. MPV was higher in non-survivors than survivors ($p<0.05$). Multivariable analysis showed that MPV was an independent mortality predictor for in-hospital mortality ($p<0.05$).
Conclusion: MPV is an independent predictor for in-hospital mortality in APE. Moreover, MPV in APE is associated with shock or high-risk patients.

P754 Pulmonary embolism and GRACE score: a new potent outcome predictor

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Acute Pulmonary Embolism (PE) is associatedwith high early and medium term mortality and risk stratification is mainlybased in heart failure assessment. However more sensible risk stratification isneeded before clinical decline occurs, to better manage these patients andimprove outcomes. We aim to study possible new independent mortality predictorsto evaluate risk assessment in patients admitted with PE.
Methods: Retrospectiveanalysis of 199 patients admitted with PE, during 4 years and with a 6-monthfollow-up (68.8±13.4 years, 40.7% men, 48% HTN, DM 20.1%, CCF 26.1%, AF 22.1%).Demographic, cardiovascular and PE risk factors, clinical, laboratorial andimagiological parameters were investigated. Potential predictors for earlyintra-hospital (IHMo) (N=33) and 6 month mortality (6Mo) (N=42) were evaluated.
Results: The following predictors for 6Mo were found:shock (OR 10.4, $p<0.001$), troponin rise (OR 2.95, p=0.05), creatinineclearance (MDRD)< 60 mL (OR 2.47, p=0.012), CHADS2 $\geq$3 (OR 2.6, p=0.015), Geneva score >11 (OR 3.9, p=0.003), history of chronic cardiac failure (CCF) (OR 2.16, p=0.046), history of active malignancy (OR 2.6, p=0.015). Heartrate, CRP and haemoglobin on admission revelled also prognostic value. In a multivariate analysis, 6-month Grace score proved to be the mostpotent independent predictor of the studied variables (OR: 1.029, $p<0.001$). 6-monthGrace score = 128.5 presents 70.5% sensibility and 65% specificity for 6Mo.
Conclusions: Asexpected shock on admission is the variable associated with the worstprognosis. However for hemodynamic stable patients admitted for PE, variableslike creatinine clearance < 60, troponin, haemoglobin and heart rate areuseful in risk stratification for IHMo and at 6 months of follow-up. Even Genevascore, usually used for evaluation of PE likelihood, has proven impact onprognosis, which interestingly widens its clinical utility. Yet from all thevariables Grace score was the most potent independent mortality predictor inthe 6-month follow-up. According to these results new parameters can be used tobetter assessed patient's risk and management before clinical deterioration and/ormarkers of heart failure subsides

PULMONARY HYPERTENSION IN CONGENITAL HEART DISEASE

P755 Pulmonary arterial hypertension associated with congenital heart disease: what is new with the currently proposed clinical classification? insights from the Spanish registry of pulmonary hypertension

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There is a lack of data regarding epidemiology, clinical management and survival in adult patients (pts) with Pulmonary Arterial Hypertension associated with Congenital Heart Disease (PAH/CHD). The Spanish Registry on Pulmonary Arterial Hypertension (REHAP) is a prospective registry initiated in 2007 that is including patients of groups I and IV of the PH classification. A new clinical classification for PAH/CHD has been recently proposed, but there are still scant data about the differences between groups. The aim of this study is to analyze the epidemiological, clinical and survival data regarding each of the subgroups of adult CHD/PAH population.
Methods: Voluntary reporting of adult (>14y) pts. diagnosed of PAH/CHD from Jan/1998 to Dec/2010. Diagnosis of PAH was performed with cardiac catheterization, based on current guidelines. Physicians from 38 centers reported cases, although 75% of the data were collected from the 4 largest referral centers for CHD and for PAH. Demographic, functional, hemodynamic, and follow-up data were recorded. Patients were divided into 4 groups according to the new clinical classification for PAH/CHD: 1) Eisenmenger; 2) PAH with systemic to pulmonary shunt 3) PAH with restrictive shunt and 4) PAH with previously corrected and no residual shunt.
Results: A total of 239 pts have been registered (18% of all PAH population in REHAP registry). Differences between clinical classification groups are shown in the table. Mean follow-up since diagnosis was 8.1±10 years.
Conclusion: 1) Eisenmenger physiology is the most frequent clinical PAH/CHD group, being those pts younger, with more severe hemodynamics and $\frac{1}{4}$ have Down syndrome. 2) Patients with corrected shunt have a trend towards a worse survival and die more frequently of heart failure. 3) In our clinical setting, 79% of pts with PAH/CHD, independently from the group, receive specific treatment for PAH.

P756 Iron deficiency is associated with adverse outcome in Eisenmenger patients

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Background: Iron deficiency is common in patients with Eisenmenger's syndrome (ES). This study aimed at evaluating (1) whether iron deficiency is related with adverse outcome, (2) the determinants of iron deficiency and (3) the relation between iron reserves and haemoglobin level in a contemporary cohort of ES patients.
Methods and results: All ES patients, older than 18 years, selected from the Belgian Eisenmenger registry, were prospectively followed using a web-based registry. Univariate Cox-regression analysis was performed to evaluate the relation with outcome, defined as all-cause mortality, transplantation and hospitalisation due to cardiopulmonary causes. Bivariate analysis was performed where applicable.
A total of 68 patients with a complete dataset (mean age 36.9±14.2 years; 30.9% male) were included. During a median follow-up time of 3.1 years, 21 patients (30.9%) reached the predefined endpoint. NYHA class≥III (HR 4.76; 95%CI 1.84-12.30; P=0.001), iron-deficiency (HR 5.29; 95%CI 2.04-13.76; P=0.001), mean

Abstract P751 – Table 1. Differences between PAH/CHD groups

	Age (yrs) / % female / %Down S	NYHA III-IV	PVR (WU)	mPAP (mmHg)	Specific PAH-Tx	Survival 1, 3, 5 y (%)	Death HF / SCD / other
Eisenmenger (n=159)	30±17 / 67% / 26%*	58%	15±7*	73±16*	77%	91 / 87 / 83%	22 / 41 / 27%
S-P shunt (n=13)	37±18 / 77% / 7%	84%	13±9	57±16	77%	100 / 87 / 87%	50 / 0 / 50%
Restrictive shunt (n=14)	37±14 / 64% / 0%	57%	8±3	55±16	79%	100 /100 / 80%	0 / 0 / 100%
Corrected shunt (n=53)	33±15 / 71% / 7%	55%	12±6	58±17	89%	96 / 86 / 71%$	58 / 25 / 17%

*$p<0.05$; $p=0.08; S-P: systemic to pulmonary; PVR: pulmonary vascular resistance; Tx: treatment; HF: heart failure; SCD: sudden cardiac death.

corpuscular volume (HR 0.94; 95%CI 0.90-0.99; P=0.021) and mean corpuscular haemoglobin (HR 0.87; 95%CI 0.76-0.98; P=0.027) were related with adverse outcome. The use of oral anticoagulation and frequent phlebotomies were independently related with iron deficiency (P=0.005 and P=0.008). In iron-deplete patients, mean corpuscular volume (R= -0.408; P=0.014) and mean corpuscular haemoglobin (R= -0.437; P=0.026) were inversely related with hematocrit. In patients with low oxygen saturation, iron reserves were related with haemoglobin levels (R=0.587; P=0.001).
Conclusions: Iron-deficiency was associated with a higher risk of adverse outcome. Moreover, the use of OAC was related with iron deficiency. Patients under anticoagulation should be monitored rigorously for iron deficiency. However, in patients with low oxygen saturations, careful iron substitution to avoid too high haemoglobin levels is suggested.

P757 Liver dysfunction and hypoalbuminemia predict adverse outcome in Eisenmenger syndrome

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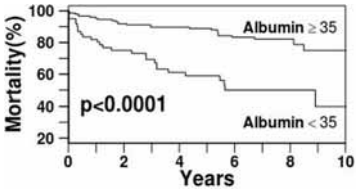
Purpose: There is a significant ongoing morbidity and mortality associated with Eisenmenger syndrome (ES), even in this era of advanced therapies. However, the tools to effectively determine prognosis remain limited and the significance of multi-system involvement is unclear. We assessed the prevalence of liver dysfunction and its relation to outcome in ES.
Methods: Data on all ES patients who underwent liver function assessment in our centre over the last 10 years were studied retrospectively. The oldest albumin, alkaline phosphatase, bilirubin and ALT/AST concentration was analysed and its relation to all-cause mortality assessed by Cox regression.
Results: A total of 210 ES patients were included. Mean age was 40.8±12.4y; 38% were male. Mean albumin concentration was 37.0±6.1g/l (29%<35g/l), bilirubin 21.2±10.0mg/l (13%>30mg/l), ALP 76.3±26.U/l (44%>100U/l). An abnormal AST or ALT concentration (>34/40U/l) was present in 13%.
During a median follow-up of 5.8 years, 54 pts died. Abnormal albumin (HR 3.62, 95% CI:2.11-6.23, p<0.0001, see Figure) and bilirubin concentration (HR 2.50 95% CI:1.27-4.92, p=0.008) were strong predictors of outcome in ES. An abnormal AST/ALT concentration (HR 2.14 95% CI: 1.07-4.28, p=0.03) and ALP (HR 1.85 95% CI:1.04-3.30, p=0.04) were also predictive of outcome. On multivariable analysis, albumin, bilirubin and ALP remained in the model.



Conclusion: Liver dysfunction and hypoalbuminemia are common in ES and relate to outcome. This underscores the systemic nature of ES affecting many organs including the liver and gut. Caution should be executed when medication with hepatotoxic potential is prescribed.

P758 Safety, tolerability, clinical and haemodynamic impact of oral bosentan in patients with congenital heart disease related pulmonary hypertension or Eisenmenger syndrome and PWP >15 mmHg

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Objective: Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) is included in group 1 of the pulmonary hypertension clinical classification. However, patients with CHD-related PAH or Eisenmenger syndrome may rarely have pulmonary wedge pressure (PWP) >15 mmHg, that theoretically exclude the diagnosis of PAH and the use of specific therapy. Aim of this study was to evaluate safety, tolerability, clinical and haemodynamic impact of oral bosentan in patients with CHD-related PAH or Eisenmenger syndrome and PWP >15 mmHg.
Methods: Clinical status, liver enzymes, WHO functional class, resting oxygen saturations, 6-min walk test (6MWT) and haemodynamics were assessed at baseline and after six month of oral bosentan therapy in patients with Eisenmenger syndrome and PWP >15 mmHg.
Results: At baseline right heart catheterization, 9/62 (14%) patients (3 male, age 48±13 y) with CHD-related PAH and Eisenmenger syndrome showed PWP >15 mmHg (18.0±1.7 mmHg, range 16-20 mmHg). Transpulmonary pressure gradient (TPG) was 46±22 mmHg. All 9 patients were in WHO functional class 3. Two patients had complete AV canal, 4 ventricular septal defect and 3 single ventricle. All patients well tolerated oral bosentan at common doses. No major side effects were observed during the follow-up. After 6 months therapy was observed a significant improvement in WHO functional class (2.5±0.4 vs 3.0±0.0; p<0.005), distance travelled in the 6MWT (365±74 vs 304±109 m; p<0.05), pulmonary vascular resistances index (15±4 vs 21±9 WU m^2; p<0.01) and pulmonary cardiac index (3.9±1.7 vs 2.9±1.0 l/min/m^2; p<0.005). In contrast, PWP (17.2±2.3 vs 18.0±1.7 mmHg; p=ns) and TPG (41±18 vs 46±22 mmHg; p=ns) did not significantly change. Finally, bosentan did not worsen oxygen saturation (83±6 vs 82±7%; p=ns).
Conclusion: Bosentan was safe and well tolerated in adults with CHD-related PAH or Eisenmenger syndrome and PWP >15 mmHg during 6 months of treatment. Clinical status, exercise tolerance and pulmonary haemodynamics significantly improved without compromising peripheral oxygen saturation.

P759 Clinical and haemodynamic effects of sidenafil in pulmonary hypertension secondary congenital systemic-to-pulmonary shunts and RV disfunction

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Purpose: Pulmonary hypertension (PH) resulting from congenital heart disease (CHD) remains one of the most difficult childhood illness to treat. Furthermore PH leads in evolution to RV remodelling and dysfunction. Sildenafil, a selective inhibitor of phosphodiesterase-5, is known as an effective and promising pulmonary vasodilator.
Methods: We have evaluated the efficacy and the tolerability of sildenafil in children with advanced PH secondary CHD with shunts (simple (18 pts), mixed (28 pts) and complex (27 pts). In this monocentric, double-blind, placebo-controlled study we randomly assigned 69 pts with advanced PH (39 with repaired shunts, 21 with palliative procedure and 9 inoperable pts) to placebo or sildenafil orally, with the dose of 0,5-2 mg/kg/day each 6 h for 12-24 weeks. The sildenafil group was consisted of 34 pts (mean age 26,3±7,1 months) and the placebo group – 35 pts (mean age 23,5±7,8 months). The study protocol included: functional class (FC) NYHA/Ross;O2 saturation; 6-min walk test; transthoracic echocardiogram (mean PAP, tricuspid annular plane systolic excursion (TAPSE), myocardial performance index (MPI or Tei index), right cardiac catheterisation, measuring pulmonary vascular resistance (PVR). In addition a special questionnaire of evidence of adverse reactions was available.The quality-of-life (QL) was studied using the questionnaire PedsQL, cardiac module.
Results: At the patients treated with Sildenafil was observed an improvement of FC NYHA/Ross from 3,2±0,1 to 1,6±0,1 (p<0,001); O2 sat from 92, 9±0,7 to 96,7±0,5% (p<0,001); an effort tolerance estimated by 6-minute walk test from 286,7±17,4 to 486,7±14,9 m (p<0,001); the decreasing of mean PAP from 53,8±2,2 to 34,2±1,9 mmHg (p<0,01) and PVR from 6,56±0,3 to 3,8±0,3 UW/m^2 (p<0,01); the improvement of the systolic function, TAPSE from 16,8±0,4 to 23,4±0,5 mm (p<0,01) and global function of RV (Tei index) from 0,48±0,01 to 0,32±0,01 (p<0,001), QL total score from 54,2±3,1 to 26,3±2,5. In placebo group the respective signs have slightly changed and only PVR diminished from 6,4±0,1 to 5,7±0,3 UW/m^2 (p<0,05). There was no death in the sildenafil-treated cases, contrary to 4 pts in the placebo group.
Conclusions: Sildenafil is efficient in treating PH secondary to congenital systemic-to-pulmonary shunts and RV disfunction, but even more effective in corrected surgical shunts. Sildenafil improves FC, tolerability at effort,O2 sat, systolic and global function of RV, diminishing PAPm and PVR comparing with placebo. This remedy has good tolerability, with minors and insignificant adverse reactions and favourable impact on the quality of life.

PULMONARY HYPERTENSION – MISCELLANEOUS

P760 Phenotype of patients with pulmonary hypertension as a complication of dilated cardiomyopathy

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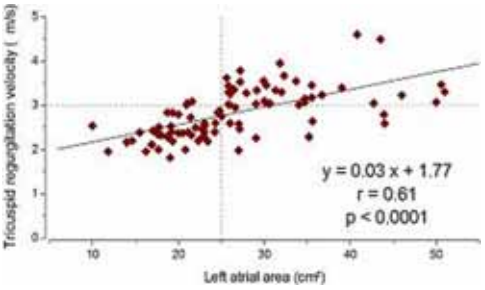
Background: Because pulmonary hypertension (PH) seriously worsens prognosis of patients with EF < 35%, new drugs are currently being tested to improve hemodynamic and outcomes. The purpose of this work is to establish the prevalence and determinants of PH in an echo core lab.
Methods: Between 01/01/2009 and 31/12/2009, all patients scanned in our echo core lab were divided into 2 groups on the basis of EF and then dichotomized based on the tricuspid regurgitation velocity (TRV >3m/s, i.e. high prevalence of PH). In the subset group of patients with EF <35%, we randomly selected 97 patients for left ventricular systolic and diastolic function measurement, mitral regurgitation quantification, left atrial volume calculation as well as TRV and right ventricular function assessment.
Results: From 5658 echocardiography studies, 731 patients (13%) had EF < 35%. Among these 731 patients, TRV was undetectable in 34%, < 3m/s in 38% and >3m/s in 28% of patients. Of the 97 patients carefully investigated, left atrial area (p<0.0001), E velocity (p<0.0001), A velocity (p=0.0004), E/A

ratio ($p<0.0001$), S longitudinal velocity at mitral valve level (p=0.007), E/E' ratio ($p<0.0001$), mitral regurgitation severity ($p<0.0001$) and left ventricular preejection time (p=0.0002) were univarietely but not independently correlated to TRV. Left ventricular dimensions and EF were not correlated to TVR. From multiple regression analysis, the 2 residual determinants of TVR were left atrial area (p=0.02, figure) and mitral regurgitation severity (p=0.02).



Left atrial and tricuspid regurgitation.

Conclusion: Pulmonary hypertension is prevalent in patients with EF < 35%. Both mitral regurgitation severity and left atrial dilation were the strongest determinants of pulmonary hypertension. They should be considered in the future for specific therapeutic approach.

P761 Pulmonary arterial hypertension in patients with chronic kidney disease on dialysis and without dialysis: results of the PEPPER-study

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Background: Pulmonary hypertension (PH) is common in patients with dialysis-dependent chronic kidney disease (CKD) and is an independent predictor of mortality. However, specific hemodynamics of the pulmonary circulation, changes induced by hemodialysis and prevalence of pulmonary arterial hypertension (PAH) have not been evaluated in patients with CKD.
Methods and results: We assessed consecutive patients with CKD on hemodialysis (group 1, n=31) or without dialysis (group 2, n=31), in World Health Organization functional class >II with dyspnea unexplained by other causes, using right heart catheterization (RHC). In group 1 RHC was performed before and after dialysis. PAH was diagnosed if mean pulmonary arterial pressure (mPAP) was >25 mmHg and pulmonary capillary wedge pressure (PCWP) <15 mmHg (after dialysis in group 1) and if other causes of PH were excluded. In CKD patients after dialysis, prevalence of PH was 24/31 (77%; 20/31 postcapillary PH, 4/31 precapillary PH); prevalence of PAH was 3/31 (10%). After dialysis, there were significant decreases in mPAP (from 62±18 to 55±17 mmHg) and PCWP (from 25±8 to 20±6 mmHg); all four cases of precapillary PH were unmasked by dialysis. In group 2, postcapillary PH was diagnosed in 22 cases (71%); no cases of PAH were detected.
Conclusions: The finding that the prevalence of PAH was 10% in CKD patients on hemodialysis who have unexplained dyspnea suggests careful screening for P(A)H in this patient population is warranted. The possibility that dialysis might be a trigger for the development of PAH is plausible given that there were no instances of PAH in the nondialysis CKD patient group. RHC should be performed after dialysis to unmask precapillary P(A)H.

P762 Cardiac hemodynamics and 6-minute walk distance in patients with chronic obstructive pulmonary disease

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Aim: To evaluate the association between cardiac hemodynamics determined by right heart catheterization (RHC) and 6-minute walk distance (6MWD) in patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension (PH).
Methods: RHC with measurements of mean pulmonary artery pressure (mPAP), mean pulmonary capillary wedge pressure (mPCWP), mean right atrial pressure (mRAP), and 6MWD were performed in 98 COPD patients without left sided heart diseases, age 64 (7) years, 50% men. PH was defined as mPAP at rest ≥ 25mmHg and mPCWP ≤15 mmHg. Right ventricle stroke work index (RVSWI) was calculated as stroke volume index (SVI) x (mPAP-mRAP) x 0.0136. Indexed pulmonary artery compliance (PACI) was calculated as SVI/PP (PP=pulse pressure).
Results: RVSWI was significantly increased ($p<0.01$) in the group of COPD patients with PH compared to the group with no PH (10.9±3.2 vs. 6.9±2.1), and PACI was significantly ($p<0.01$) decreased (1.7±0.6 vs. 2.2±0.7). For those with PH (n=26), 6MWD was significant reduced (343±149 m) compared to no PH (489±113 m) ($p<0.01$). Moreover, 6MWD correlated with RVSWI, r=0.5 ($p<0.01$), PACI, r=0, 3 ($p<0.01$) and mPAP, r=0.5 ($p<0.01$) (fig.1). Significant differences ($p<0.01$) in following parameters in PH group, mPAP, mPCWP, mRAP, 29±4, 11±3, 7±3 mmHg vs. no PH group, 18±3, 8±4, 5±3 mmHg, respectively. No significant differences in SVI.

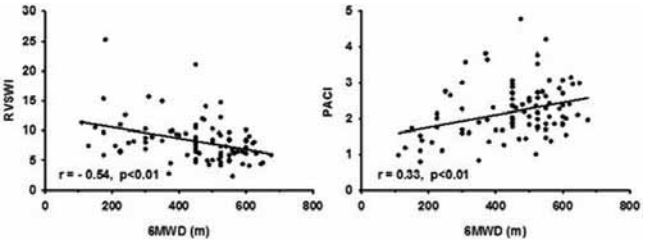

Figure 1

Conclusion: Exercise capacity as evaluated by 6MWD in COPD with PH is reduced. In these patients we observed increased RVSWI and reduced PACI. The increased RVSWI is caused by PH, since there is no difference in SVI between COPD patients with or without PH. Reduced compliance contributes to deterioration in RV-PA coupling and increases RV afterload in PH group, and likely generates a higher workload at the right ventricle.

P763 Persistent pulmonary hypertension in patients with severe mitral regurgitation undergoing mitral valve replacement

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Mitral valve disease is frequently associated with pulmonary hypertension (PH), where in most cases, secondary to increased pulmonary venous pressure and therefore reversible after surgery. However there is a subgroup of patients in whom there is no such regression of PH and in whom it may even progress in time despite the proper correction of the valvular lesion. There are no known factors associated with this condition, but it carries an impact on functional capacity and prognosis.
Our goal is to determine the clinical and echocardiographic factors associated with the development of persistent PH in patients with severe mitral regurgitation undergoing mitral valve replacement.
Results: 98 consecutive patients undergoing mitral valve replacement for severe mitral insufficiency with clinical and echocardiographic follow-up exceeding 12 months and normally functioning mitral prosthesis. The follow-up was 58±22 months, median 62 months. 31 patients developed PH at follow-up. Mortality in this subgroup was significantly above patients without PH. We analyzed preoperative clinical and echocardiographic variables. Factors that were significantly associated ($p<0,05$) with the development of PH were: a)clinical: age, hypertension, permanent atrial fibrillation and degree of Parsonnet b) echocardiographic: preoperative left atrium transverse diameter and grade of tricuspid regurgitation. In multivariate analysis, preoperative atrial fibrillation (p=0,01, CI 0,1-0,5) and the Parsonnet index (p=0,01, CI 1,02-1,2) were significantly associated to the development of PH. There was no association with the area of the prosthesis/body surface, left ventricular function parameters or previous lung disease.
We conclude that persistent PH in patients with severe mitral insufficiency after mitral valve replacement carries a bad prognosis and is related to preoperative permanent atrial fibrillation and not to prosthesis area or left ventricular function.

P764 Prevalence of established and exercise induced pulmonary hypertension in moderate to severe chronic obstructive pulmonary disease

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Purpose: The prevalence of pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD) is uncertain. This inconsistency can be explained by dissimilarities in definitions of PH as patient population studied and mixing of pre and post-capillary reasons for PH. We aimed to describe prevalence of precapillary PH at rest and exercise induced pulmonary hypertension (EIPH) in a population of stable smoke associated COPD without left sided heart diseases.
Methods: 98 patients, 64±7 yrs and 50% men, were prospectively recruited and classified according to GOLD (Global initiative for Obstructive Lung Disease) cri-

teria. Right heart catheterization with exercise protocol was done with the following pressure measurements: Mean pulmonary artery pressure (mPAP) and capillary wedge pressure (mPCWP), and pulmonary vascular resistance (PVR) were calculated. Pulmonary artery compliance (PAC) was defined as stroke volume/puls pressure (PP). Pre-capillary PH at rest was defined as mPAP $\geq$25 mmHg and PCWP $\leq$15 mmHg. Pre-capillary EIPH was defined as an increase in mPAP combined with abnormal exercise responses both in PVR (unchanged or increased value from rest to exercise) and PAC (reduced value from rest to exercise) with an increase in mPCWP $\leq$20 mmHg.
Results: 26 (27%) patients, mPAP 29±4 mmHg, had pre-capillary PH at rest. Categorized by GOLD stages, PH at rest was found in 2 (5%) in GOLD II, 8 (28%) in GOLD III, and 16 (52%) patients in GOLD IV. PCWP was normal at rest, 11±3 mmHg. During maximum effort 60 of 72 (83%) patients showed normal response in mPCWP, and 12 (17%) showed pathological increase in mPCWP (23±2 mmHg) at maximum effort. Among the 60 patients with normal rise in mPCWP, EIPH was found in 30 (50%). In this group of patients mPAP at rest and exercise were 18±3 and 38±7mmHg, respectively; 15 patients were allocated to GOLD II, 11 to GOLD III, and 4 to GOLD IV. Accumulated prevalence of pathological response of the pulmonary artery pressure (PH at rest with normal PCWP and EIPH with normal rise in PCWP) was found in 56 (58%) of all the 98 patients.
Conclusion: There was a high prevalence, even in patients with GOLD 2, of PH and EIPH of pre-capillary type in this COPD population. In lack of upper normal limit for mPAP during exercise we suggest a combined evaluation of PAC and PVR to determine if increase in mPAP is a pathologic or an expected physiologic response to exercise.

P765 Increase in pulmonary vascular resistance during exercise: a frequent but neglected problem in advanced heart failure

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Introduction: Left heart failure is the most common cause of pulmonary hypertension (PH) and there is firm evidence that left-sided PH carries a poor outcome. However, data on incidence, pathophysiology and functional importance of PH are sparse. Exercise testing has the advantage to put stress on the pulmonary circulation and to allow data collection when symptoms really occur.
Methods and results: 51 consecutive patients with NYHA class II-III and a reduced ejection fraction were prospectively enrolled for hemodynamic exercise testing. The study was focused on an accurate measurement of patients cardiac output and the corresponding transpulmonal gradient at different exercise levels. All parameters correlating with peak cardiac output were introduced into a multivariate regression model (MRM).
At peak incremental exercise 43 patients experienced an increase in pulmonary artery mean pressure (PAM) above 30 mmHg and 25 patients had an elevated pulmonary vascular resistance (PVR) above 130 dyn s cm^{-5}. Interestingly, PVR showed a stronger correlation with peak cardiac output ($r = 0.51$; $p<0.01$) than right ventricular ejection fraction ($r = 0.29$; $p=0.02$) and PAM ($r = 0.3$; $p=0.04$). PVR was identified as the sole independent predictor of peak cardiac output in this patient group.
Conclusion: In heart failure with reduced ejection fraction pulmonary vascular distensibility is an important determinant of limited exercise capacity and promissing target for specific therapy.

P766 Pulmonary artery pressure rise during exercise in COPD with normal pressure at rest is accompanied by pathologic responses in pulmonary artery compliance and in pulmonary vascular resistance

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Background: The majority of COPD patients have normal resting mean pulmonary artery pressure (mPAP). The aim of the present study was to investigate if these patients showed abnormal pulmonary pressure rise during exercise.
Methods: 112 patients (47% male), in age 63±7 (mean ± SD) years with smoke associated COPD, and normal LV function, were included. Right heart catheterization at rest and during supine bicycle exercise was performed to exhaustion. End expiratory mPAP, mean pulmonary arterial wedge pressure (mPCWP) and cardiac output (CO) were measured. Pulmonary vascular resistance (PVR) was calculated as (mPAP-mPCWP)/CO. Pulmonary artery compliance (PAC) was calculated as stroke volume /pulse pressure.
Results: 74 patients had normal mPAP at rest (18±3 mmHg), which increased to 37±7 mmHg ($p<0.01$) during max effort (Wattmax 35±21). CO increased from 5.2±1.0 to 10.8±3.0 L/min ($p<0.01$) and stroke volume increased from 71.2±16.7 to 98.7±24.2 ml/beat ($p<0.01$). There was a significant decrease in PAC from rest 4.0±1.5 to exercise 3.0±1.2 ($p= <0.01$). There was no significant change in PVR (exercise 2.1±1.1 vs. 1.9±0.9 wu at rest). There was a significant correlation between PACmax and PVRmax, $r=0.7$ ($p<0.01$) and between PACmax and mPAPmax, $r= 0.5$ ($p<0.01$).
Conclusion: We have demonstrated a significant increase in pulmonary artery pressure on exercise at low workload, which was accompanied by a reduction in PAC and a lack of reduction in PVR. These findings might support the existence of an early clinical phase of pulmonary hypertension in patients with COPD and normal mPAP at rest.

P767 Manifest connective tissue diseases often develops in patients with idiopathic pulmonary arterial hypertension

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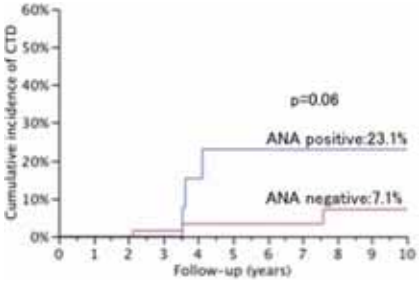
Purpose: The aim of this study is the frequency and the relation between idiopathic pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension associated with CTD (PAH-CTD).
Methods: We retrospectively studied 120 patients who had been diagnosed with IPAH at the first visit in our hospital. Six patients without ANA data and three patients with CTD-specific symptoms at first visit without confirmed diagnosis of CTD were excluded. Thus the data were available in 111 patients with IPAH, we divided them in two groups based on the titer of ANA: We defined that ANA positive (ANA$\geq \times$160) and ANA negative (ANA$< \times$160).At first We examined the cumulative incidence of definite CTD using Kaplan-Meier method. Secondly we examined the cumulative incidence of diagnosed-CTD + strongly suggested-CTD. In this study we found the patients who developed to CTD-specific symptoms as time advances, but did not fulfilled the criterion for diagnosis of CTD. We defined these patients as strongly suggested-CTD.
Results: Manifest CTD developed in ANA-negative group was 0, 1.5, 3.4,7.1% in 1,3,5,10 years later. And in ANA-positive group was 0, 0, 23.1,23.1% (Log-rank test; P=0.06). The cumulative incidence of diagnosed-CTD + strongly suggested-CTD in ANA-negative group was 1.2, 4.0, 5.8,9.4% in 1,3,5,10 years later. And in ANA-positive group was 0,6.7,43.5,51.5%(Log-rank test; $P<0.0001$).



Cumulative incidence of CTD

Conclusion: CTD developed as time advances with high frequency in the patients initially diagnosed with IPAH. Revised classification of PAH-CTD may be needed not only in ANA-positive groups but also in ANA-negative groups.

P768 Diagnostic accuracy of transthoracic contrast echocardiography as a screening method for pulmonary arteriovenous malformations

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Purpose: Patients with hereditary hemorrhagic telangiectasias (HHT) are routinely screened for pulmonary arteriovenous complications (PAVMs) because of the associated neurological complications. We compared the detection of intrapulmonary shunting on transthoracic contrast echocardiography (TTCE) with the presence of PAVMs on high-resolution chest computed tomography (HRCT) in a large series of screened persons.
Methods: In the period from May 2004 till December 2010, 626 persons with possible HHT were screened with both a TTCE and chest HRCT. TTCE was judged positive or negative for a pulmonary shunt, or indeterminate when intracardiac and intrapulmonary shunting could not be discriminated. Chest HRCT was interpreted as positive, negative or indeterminate for the presence of PAVMs.
Results: TTCE was positive for a pulmonary shunt in 252 patients (40.3%), negative in 369 patients, and in 5 patients the origin of the shunt could not be discerned. Chest HRCT showed PAVMs in 122 patients (19.5%), and in 18 patients the presence of a PAVM was uncertain. The negative predictive value of TTCE for the absence of PAVMs on chest HRCT was 99.4%, and sensitivity was 98.3%. In two patients with PAVMs on chest HRCT but no shunt on TTCE, PAVMs were very small and far beyond possibility for treatment. The positive predictive value of TTCE for the presence of PAVMs was 48.4%, and specificity 73.9%.
Conclusion: In this large series directly comparing TTCE with chest HRCT, TTCE appears to have an excellent negative predictive value. When used as a first-

line screening tool, no PAVMs amenable for embolisation were missed. Intrapulmonary shunting on TTCE is frequently present in patients without macroscopic PAVMs on chest HRCT.

P769 Prevalence of pulmonary arterial hypertension in the HIV cohort of the University Bonn: results of the PAHIBO study

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Background: PAH (pulmonary arterial hypertension) is a rare and life-threatening complication of HIV (human immunodeficiency virus) infection. An investigation of the presence of HIV infection is a standard diagnosis in patients with unexplained PAH. Previous studies suggest a prevalence of PAH in HIV patients close to about 0.5%, but are limited in the study design. Therefore the exact prevalence is unclear.
Methods: The PAHIBO study is investigating all HIV patients (n=700) in a prospective cross-sectional study. If systolic pulmonary arterial pressure (sPAP) is >35 mmHg in Doppler echocardiography, right heart catheterization is followed. The findings are correlated with a dyspnea questionnaire (Shortness of breath, SOB).
Results: To date, 340 patients were enrolled (age: 23-74 years, average 45±10, 81% men). 44/340 (13%) had an echocardiographic sPAP >35 mm Hg (average 42±4 mmHg). Severe dyspnea (SOB >50 points) was found in 33/340 (10%) of all examined HIV-patients and in 11/44 (25%) patients with pulmonary hypertension (PH). The right heart catheterization was carried out so far in 22/44 patients with echocardiographically proven PH. In 4 cases, a precapillary PAH (including a complete work-up and exclusion of other causes of PAH) was diagnosed, of which 1 case was already known, in 13 cases postcapillary PH and in the remaining 5 cases, the exclusion of a manifest PH. Thus, the PAHIBO study reveals a prevalence of HIV-associated PAH of at least 4/340 cases (1.2%). In addition, the study showed many comorbidities: coronary heart disease (7%), heart failure (8%), diastolic dysfunction (29%), valvular defects (2%) and COPD (11%).
Conclusion: The prevalence of HIV-associated PAH is probably higher than previously described. Severe cardiac and respiratory comorbidities are very frequent in the examined HIV cohort. If these results should be confirmed in the extended cohort of 700 patients, a regular echocardiographic screening in asymptomatic HIV patients is to discuss.

P770 Unmasked pulmonary venous hypertension during vasodilator challenge predicts poor outcomes with medical therapy

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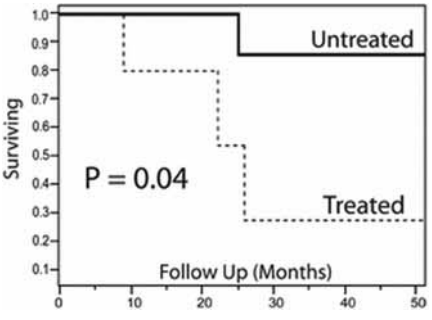
Purpose: Pulmonary arterial hypertension (PAH) is defined by a resting mean pulmonary arterial pressure (PAP) of ≥25 mmHg and a pulmonary capillary wedge pressure (PCWP) <15 mmHg. Vasodilator challenge to identify patients for possible calcium blocker therapy is part of the routine hemodynamic evaluation in PAH. Occasionally PCWP increases during testing, suggesting a component of pulmonary venous hypertension. Whether this finding should limit the use of outpatient PAH-specific therapy (endothelin antagonists, PDE-5 inhibitors and prostanoids) is currently unknown.
Methods: We performed a two-center prospective cohort study of 270 PH patients referred for invasive evaluation. Among the 175 patients meeting hemodynamic criteria for PAH, 14 patients (8%) increased PCWP to ≥15mmHg during inhalation of 40 ppm nitric oxide (iNO). All patients were prospectively followed and mortality confirmed using the Social Security Death Index.
Results: Mean age of the cohort was 55±15 years, 66% were women and 78% Caucasian. WHO function class was 2.8±0.7, mean PAP was 45±17 mmHg and mean PCWP 10±3 mmHg. No significant differences among these characteristics were seen between the 14 patients with iNO-induced PCWP elevation and those without. 36% of patients with iNO-induced PCWP elevation were treated with PAH-specific therapy. These patients experienced increased mortality compared to those who remained untreated (p=0.04).
Conclusions: In patients with pulmonary arterial hypertension, nitric oxide inhalation may unmask a pulmonary venous component, which appears to worsen clinical outcome when treated with PAH-specific therapy.



P771 Two easily obtainable echocardiography variables can identify patients with increased total and vascular pulmonary resistance

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Background and aim: The total pulmonary resistance [TPR, pulmonary artery mean pressure (PAMP)/cardiac output (CO)] and the pulmonary vascular resistance [PVR, (PAMP-capillary wedge pressure (PCWP))/CO] describe the right ventricular afterload and the vascular component. A comprehensive echocardiography (Echo) study can provide calculation of TPR and PVR, however, these are cumbersome. In the present study we hypothesised that the ratio between PA systolic pressure and the velocity time integral in the left ventricular out-flow (PASP/VTI) can be used as a surrogate for TPR. Further we examined the previously described augmented pressure (AP) as a surrogate for PVR. The aim of the study was to evaluate the diagnostic accuracy of the Echo derived TPR, PVR and their surrogate variables.
Methods: Echocardiography and right heart catheterization were performed within 24 hours in 97 patients. PASP, right atrial pressure and CO were assessed using standard Echo methods. The PAMP was estimated using a regression equation (PAMP=0.65PASP-1.2). The PCWP was estimated semi-quantitatively from mitral and pulmonary vein data. The timing of peak velocity in the PA (pulsed Doppler) was determined and the corresponding pressure estimated (PAPV). AP was calculated as PASP-PAPV. Increased TPR and PVR was defined as >5 and >3 WU. Cut-off values were generated to determine increased TPR and PVR using receiver-operating characteristics curve analysis.
Results: The mean± SD age was 54±15 years, 59% were female. Thirty-seven patients had left heart disease, 39 had pulmonary vascular disease, 15 chronic tromboembolism and 6 were normal. Seventy-four patients had increased TPR and 66 increased PVR at catheterization. There were no significant differences between Echo derived TPR, PVR and their surrogate variables (Table).

Variables	AUC (95% CI)	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	NPV	PPV
Echo TPR (WU, n=89)	0.93 (0.88–0.98)	>7.4	90 (80–95)	86 (67–95)	73	95
PASP/VTI (mmHg/cm, n=95)	0.94 (0.89–0.99)	>2.9	92 (83–96)	88 (69–96)	78	96
Echo PVR (WU, n=80)	0.88 (0.80–0.96)	>4.2	86 (74–93)	83 (64–93)	71	92
AP (mmHg, n=97)	0.96 (0.93–1.00)	>8	89 (80–95)	90 (75–97)	80	95

NPV, negative prdictiv value; PPV, positive predictive value.

Conclusions: Echo can be used to identify patients with increased TPR and PVR. The more simple surrogate variables have the same diagnostic accuracy as direct Echo estimation of TPR and PVR.

P772 Improved pulmonary endothelial function after 24 weeks of bosentan therapy in 60 patients with Eisenmenger physiology: study HP 3.2 of the German network of competence for congenital heart disease

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Introduction: Therapy aimed at reducing pulmonary vascular resistance in patients with Eisenmenger physiology may be beneficial in some while the precise mechanisms of such therapy remain incompletely understood. We studied in detail, in the largest patient cohort with Eisenmenger physiology to date, clinical, hemodynamic and pulmonary endothelial function before and after 24 weeks of Bosentan therapy.
Methods: 60 patients (16-51ys, 25m/35f) with shunting defects and Rp/Rs>0.75 were recruited to receive therapy for 24 weeks with Bosentan, an endothelin receptor ETA/ETB antagonist. Cardiac catheterisation to asses pulmonary vascular resistance (PVR) together with acute pulmonary vasoreactivity test (AVT), magnetic resonance imaging, echocardiography, and laboratory markers of cell function (VEGF, BNP, endothelins), were performed before and after therapy, which was followed up with 6-MWT, ECHO and clinical status at 5 outpatient appointments in the interim.
Results: After therapy, clinical status improved (average NYHA 2.66±0.59 to 2.32±0.51, p<0.005) as well as 6-MWD (65.1±14.3m, p<0.001). Hemodynamics after therapy showed a lowered baseline PVR, while minimum PVR with NO/O2 remained statistically unchanged. There was a significant reduction of pro-BNP (p=0.0011), whereas mid region-ANP, selectins and cell adhesion molecules re-

mained unchanged. Levels of big endothelin and endothelin increased, as did plasma nitrite, nitrate and ADMA, showing enhanced NO production in response to therapy.
Conclusion: 24 weeks of Bosentan-Therapy in patients with Eisenmenger physiology was safe and improved clinical, exercise, hemodynamic, and pulmonary endothelial biology parameters. Specifically, the data suggest better pulmonary endothelial function with improved vasodilating capacity and endothelin handling of the pulmonary vascular system, thus demonstrating the beneficial effects of bosentan for the first time in these complex patients both at the clinical, cardiac and at the pulmonary vasculocellular level.

P773 Intensive immunosuppressive therapy improves pulmonary hemodynamics and prognosis in patients with pulmonary arterial hypertension associated with connective tissue disease

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Background: Pulmonary arterial hypertension (PAH) still remains a serious disease characterized by elevated pulmonary artery pressure (PAP) and increased pulmonary vascular resistance (PVR), leading to right-sided heart failure and death. Among the several forms of PAH, PAH associated with connective tissue disease (CPAH) has the worse prognosis due to resistance to conventional vasodilator therapy. Since immunological mechanisms may be involved in the pathogenesis of CPAH, we hypothesized that intensive immunosuppressive therapy could improve pulmonary hemodynamics and prognosis in CPAH.
Methods: In our PAH cohort with 136 PH patients, we evaluated the clinical characteristics of 13 patients with CPAH, who received the intensive immunosuppressive therapy (IIT) with cyclophosphamide (500 mg/month IV for more than 6 months) and glucocorticosteroids (1 mg/kg/day PO for more than a month) (IIT group, mean age 44.8±7.7 [SD] years, 12 females and 1 male). The underlying collagen disease included systemic lupus erythematosus in 7, Sjogren syndrome in 4, mixed connective tissue disease in 1 and systemic sclerosis in 1. We compared them with 8 historical controls (Control group: mean age 52±18 [SD] years, 8 females, SLE in 1, MCTD in 3, systemic sclerosis in 2, rheumatoid arthritis in 1, and dermatomyositis in 1) in terms of pulmonary hemodynamics and prognosis. Both groups were treated with the conventional vasodilator therapy with calcium channel blocker, prostacyclin, bosentan and/or phosphodiesterase-5 inhibitors.
Results: We have closely followed up all patients every half to one year by cardiac catheterization. The control group had slightly increased mean PAP (mPAP, from 43.5±17.4 to 50.3±18.8 mmHg, P=0.08). In the IIT group, the intensive immunosuppressive therapy significantly decreased mPAP (from 39.5±9.1 to 28.9±11.0 mmHg, $P<0.01$) and tended to decrease PVR (from 700±434 to 481±418 dyn sec/cm^5, P=0.07), while cardiac index was well maintained (from 2.8±0.7 to 2.9±1.4 L/min/m^2, n.s.). Importantly, in 6 out of the 13 patients of the IIT group (46%), mPAP was almost normalized (<25 mmHg) and was stabilized within normal range for more than a year (353±308 days). Furthermore, the IIT group showed significantly better prognosis compared with the control group (Log-rank Test P=0.01; follow-up period, 740±398 days).
Conclusion: These results suggest that the intensive immunosuppressive therapy with the combination of cyclophosphamide and glucocorticosteroids significantly improves pulmonary hemodynamics and prognosis in patients with CPAH.

P774 Quality of life in patients with pulmonary arterial hypertension

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Background: Pulmonary arterial hypertension (PAH) has an impact on all aspects of quality of life (QoL). QoL score is commonly used as an endpoint in the evaluation of treatment effect in left heart failure patients (pts).
Aim: To validate the applicability of the Minnesota Living with Heart Failure Questionnaire (MLHFQ) in pts with PAH and to find out which QoL aspects are most important in PAH pts. To assess the relationship of QoL score and WHO functional class (FC), 6-minute walk distance (6MWD), and intensity of depression.
Patients and methods: 26 pts (mean age 57.7±13.6 years, 20 female) with diagnosed PAH (23 idiopathic PAH) were evaluated. All of them were diagnosed and treated according to the recent ESC PH management guidelines. 13 pts were in FC III, 11 in FC II, and 2 in FC I. Mean 6MWD was 379.2±145.0 m. Mean MLHFQ Global score (GS) was 29.2±18.6, Soma score (SS) was 25.6±12.6 and Psycho Score (PS) was 7.18±9.3 Mean Beck Depression Inventory (BDI) score was 8.2±8.0. Mild degree of depression was present in 6 pts, moderate in 1, and severe in 1 patient. General Linear Model and univariate analysis were used for statistical evaluation.
Results: Univariate MLHFQ analysis showed that the most significant limitations of QoL in PAH pts are low walking and stair climbing capacity (70%), walking longer distance (65%), reduction of daily activities (54%), sleep disturbances (39%), fatigue and anenergy (35%), anxiety (27%), and depression (23%). A significant difference between FC III vs FC I+II in both GS (45.1 vs 32.8, p=0.008) and SS (22 vs 11.5, p=0.001) was present. Women showed higher PS than men (12.1 vs 5.2, p=0.005). Correlation analysis revealed a significant relation between PS and BDI (r=0.842, $p<0.0001$) as well as GS and BDI (r=0.493, $p<0.001$). A significant linear relationship between SS and 6MWD (r= -0.408, $p<0.001$) as well as GS and 6MWT (r= -0.362, $p<0.001$) was also found. Age correlated with 6MWTD (r= - 0.305, $p<0.003$) but not with the QoL score.
Conclusion: Lower walking capacity and reduced daily living activities are the most significant factors limiting the QoL in PAH pts. Soma Score tightly correlated with 6MWD and Psycho Score with depression intensity. QoL score is not influenced by age which is its essential advantage in comparison to 6MWD and could be considered as a clinical trial study endpoint.

P775 Longitudinal strain curves of the RV free wall differ in morphology in patients with pulmonary hypertension compared with controls

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Purpose: Right ventricular (RV) function is an important determinant of clinical status and prognosis of patients with pulmonary hypertension. Therefore, central to the management of those patients is an accurate measurement of RV function. Previous studies that have used speckle tracking-derived strain for quantification of RV function have focused on magnitude of global and regional peak longitudinal systolic strain (PLSS) and systolic strain-related indices of dyssynchrony. Aim of our study was to investigate whether the contour of strain curves described by the time to PLSS (SST) and the time from PLSS to 50% of PLSS (systolic strain half time-SSHT) differ between patients with pulmonary hypertension (PH) and controls.
Methods: Twenty five patients with PH (15 with pulmonary arterial hypertension and 10 with left-sided valvular heart disease) without right bundle branch block (mean age 45±18 years, 13 women) and 20 normal subjects (mean age 42±15 years, 5 women) were evaluated. A complete two-dimensional echo with speckle-tracking-derived longitudinal strain of the basal right ventricular free wall and interventricular septum was performed and the cycle length-corrected SST and SSHT intervals in both regions were calculated.
Results: Patients with PH had significantly reduced PLSS (-24.9±2.0% vs -43.2±3.0%, $p<0.001$) and increased SST (0.47±0.02 vs 0.39±0.02, p=0.043) and SSHT (0.22±0.02 vs 0.16±0.02, p=0.047) in the basal RV free wall compared with controls. There was no statistically significant difference between patients and controls regarding PLSS (-15.4±2.0% vs -14.7±2.7%, p=843), SST and SSHT in the interventricular septum. No significant correlations were found between SST or SSHT and PLSS, as well as between SST or SSHT and RV systolic pressure.
Conclusions: Longitudinal strain curves in the RV free wall differ in morphology in patients with PH compared with controls reaching peak values later in the cardiac cycle and returning slower towards baseline. Therefore, they can effectively illustrate changes in RV contraction and relaxation caused by PH.

P776 Evaluation of left ventricular diastolic dysfunction by Doppler and 2d speckle-tracking imaging in patients with primary pulmonary hypertension

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Background: In patients with Primary Pulmonary hypertension (PPH), RV pressure overload causes right ventricular dilation and left ventricular (LV) cavity reduction.
Objects: We sought to investigate the LV diastolic dysfunction using Doppler and 2D speckle- tracking imaging (2DSTI) in patients with PPH.
Methods: We performed Doppler and speckle-tracking imaging in 38 patents with PPH (Group PH) and 18 control subjects (Group N:30.6±4.6 years). Fifteen (Group PH-HF) of 38 patients in Group PH were complicated with right heart failure, and other 23 patients (Group PH-N) were not complicated. We measured early and late diastolic peak velocities of mitral inflow (E and A), and deceleration time (DT), and the mitral annular velocities (e') in two sites by tissue Doppler imaging, and the ratio of early mitral inflow to mitral annular velocity (E/e'). Global LV peak relaxation strain rate (RSR) during early diastole were analyzed by 2DSTI in the longitudinal direction.
Results: E (60.5±3.5 vs. 84.3±3.5 cm/s: $p<0.0001$) and E/A (0.8±0.07 vs. 1.8±0.7: $p<0.0001$) were significantly lower in Group PH than in Group N. DT (181.2±43.7 vs. 152.8±31.5 ms: p=0.0203) was longer in Group PH. e' (14.3±0.6 vs. 8.8±0.5 cm/s: $p<0.0001$) was lower and E/e' (7.8±0.4 vs. 5.9±0.4: p=0.0108) was higher in Group PH than in Group N. RSR was significantly lower in Group PH (0.9±0.1 vs. 1.4±0.1: p=0.0217).
Conclusion: LV diastolic dysfunction appeared in patients with PPH. RV pressure overload and reduction of RV output caused impaired LV filling.

P777 Efficacy of imatinib in patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis

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Background: Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension. Its prognosis is reported to be worse than other types of pulmonary arterial hypertension (PAH). None of the PAH-targeted therapy is proved to be effective in patients with PVOD/PCH. Especially, vasodilators that are effective in most cases of PAH sometimes cause fatal pulmonary edema. This is why the prognosis of PVOD/PCH has not been improved despite the progress of therapeutic options. Lung transplantation is the only cure for patients with PVOD/PCH. The average waiting time is as long as about 3 years in Japan. Considering the poor prognosis, many patients cannot survive until suitable organs become available. Imatinib is a tyrosine kinase inhibitor, which is one of the molecular target drugs and expected to be effective in patients with PAH. We hypothesized that imatinib might also be efficacious in patients with PVOD/PCH.
Methods: We applied imatinib on patients with PVOD/PCH after approval of our protocol by the Institutional Review Board. Written informed consent was obtained from all patients. Survival was retrospectively compared with that of patients with PVOD/PCH who were not on imatinib therapy.
Results: There are 17 patients clinically suspected as PVOD/PCH. In 7 of them, the diagnoses were confirmed by pathological studies. The average age was 42.3±17.6 years old and 76.5% were male. We applied imatinib (200-400mg/day) on 8 patients. Five out of 8 patients (62.5%) on imatinib therapy died. In 9 patients without imatinib therapy, 6 patients (66.7%) died and 2 patients (22.2%) underwent living-donor lobar lung transplantation. Mean survival time in patients treated with imatinib therapy was significantly longer than those without imatinib treatment (3.3±0.6 vs. 1.5±0.4 years, $p<0.05$).
Conclusions: In patients with PVOD/PCH, who have no effective medical therapy, imatinib might be a potential therapeutic option to improve their survival and work as a bridge to lung transplantation.

ADULT CONGENITAL HEART DISEASE – MISCELLANEOUS I

P778 Chromosome 22q11.2 microdeletion and congenital heart defects: impact of the genetic abnormality on the surgical outcome and perioperative complications

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Purpose: The impact of congenital heart defects (CHD) in children with chromosome 22q11.2 microdeletion (del22q11.2+) is relevant: about 75-80% of cases are affected by conotruncal defects. The treatment of cardiac anomalies is primarily surgical and must be performed early after birth in most cases. Aim of this study was to evaluate the surgical outcome and perioperative complications in children with CHD and with del22q11.2, compared to a control group.
Methods: Anamnestic, clinical and diagnostic findings of 49 children with CHD and del22q11.2 (CHD+/del22q11.2+) were retrospectively reviewed and compared with those of a control group of patients with contruncal CHD and without del22q11.2. The postoperative course and related complications (cardiac, infectious, respiratory and neurological) were assessed in patients who underwent corrective surgery. Absolute CD4 count and percentage were considered in the CHD+/del22q11.2+.
Results: 44/49 patients with CHD+/del22q11.2+ underwent corrective surgery at a mean age of 117days. Mean age at operation of the controls was 114 days. Two operative deaths (4,5%) occurred, and 2 cardiac death after hospital discharge (respectively after 90 and 740 days). There is a statistically significant association between del22q11.2+ and total surgical time (302 vs 269 minutes, p=0,0332) and extra corporeal circulation duration (174 vs 142 minutes, p=0,0140); no association between del22q11.2+ and duration of aortic cross clamp (62 vs 57 minutes, p=0,1845). Cardiac and respiratory complications were equally present in the two groups (50% vs 48% and 28% vs 27% respectively); while infectious and neurological complications were more frequent in patients with del22q11.2+ (38% vs 27% and 21% vs 9% respectively). Total absolute CD4 count $<$ 500/ mm^3 and a percentage $<$20% were not associated with infective complications.
Conclusion: Children with CHD+/del22q11.2+ who underwent corrective surgery had longer surgical and extra corporeal circulation time, and higher frequency of infectious and neurological complications than control group. The absolute CD4 count and percentage were not associated with infectious complications. A more complex cardiovascular anatomy, typically associated with the syndrome, more than the extra-cardiac co-morbidities may influence the surgical prognosis in these children.

P779 Low body mass index predicts outcome in adult congenital heart disease: the role of cachexia

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Purpose: Abnormal body mass index (BMI), whether high or low, has been shown to be detrimental on morbidity and mortality in various types of cardiovascular disease, also affecting the risk of cardiac interventions and surgery. Despite advances in surgery, adult patients with congenital heart disease (ACHD) are likely to require further interventions during their lifetime and many develop heart failure. Our goal was to evaluate the impact of BMI on survival in adults with moderate or severe types of congenital heart disease.
Methods: BMI was calculated for 1248 patients who were categorised in groups of cardiac complexity according to the Bethesda classification system (classes 2 and 3). BMI groups were defined as follows: $<$17 underweight, 17-25 normal weight, $>$25 overweight. The relation between BMI and all-cause mortality was evaluated using Cox regression.
Results: Mean age was 41±17 years, 44% female. ACHD was defined as moderate in 699 patients (56%) and severe in 549 (44%). Mean BMI was 24.6±4.7; 78 (6%) of patients were underweight and 548 (43%) overweight. After a median follow-up of 2.95 years (IQR: 2.6y), 114 (9%) patients died. Patients who were underweight were at significantly higher risk of death compare to those with a normal BMI (HR 3.07, 95%CI: 1.50-6.27, p=0.002, Figure 1, left). There appears to be an inverse linear relation between BMI and the risk of death for BMIs below 18.5 (Figure 1, right). No relation could be identified between overweight/obesity and survival.

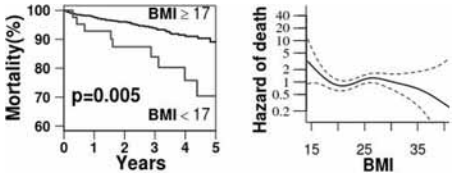

Figure 1

Conclusion: The relation of low BMI to survival underscores the role of cachexia in defining outcome in patients with moderate-severe ACHD. Body weight should therefore be closely monitored in their follow-up and taken into account in any decisions on their management.

P780 Onset of cardiac iron loading in a large and homogenous cohort of thalassemia major pediatric patients

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Purpose: Heart failure remains the main cause of mortality in thalassemia major (TM). Magnetic Resonance Imaging (MRI) by the T2* approach is the unique non invasive technique for highly reproducible quantifications of myocardial iron burden and is the gold standard for quantifying biventricular function parameters. It is important to determine the appropriate age to start MRI screening, because its high cost and no large availability. Few data are available in the literature. So the aim of this study was to address this issue in a cohort of paediatric patients selected from a large TM population homogenous for geographical origin and treatment approach.
Methods: We studied retrospectively 72 TM patients enrolled in the MIOT (Myocardial Iron Overload in Thalassemia) network with an age $<$ 18 years (47 males, 4.2-17.9 years old, mean age 13.0±3.7 years). Myocardial iron overload (MIO) was measured by T2* multislice multiecho technique. Biventricular function parameters were quantitatively evaluated by cine images.
Results: The global heart T2* value was 29±11 ms. No MIO was detected in the 33% of the patients; 44% of the patients showed a heterogeneous MIO with a global T2*value $\geq$ 20 ms; 10% showed a heterogeneous MIO with a T2* global value $<$ 20 ms and 13% had a homogeneous MIO. No significant correlation was found between global heart T2* value and age. OR for a global heart T2* $<$ 20 ms was 1.13 (P=0.18) per year. The global heart T2* value did not show significant differences according to the sex (male 30.2±11.0 ms versus female 28.7±11.8 ms, P=0.568). None of patients with an abnormal global heart T2* value ($<$20 ms) was under 8 years of age. Global heart T2* value was negatively correlated with mean serum ferritin levels. OR for high serum ferritin levels ($\geq$ 1500 ng/ml) was 8.4 (1.01-69.37 OR 95%CI) for abnormal global heart T2* values ($<$20 ms). The global heart T2* value did not show a significant difference with respect to the chelation therapy (P=0.322). No significant correlations were found between the

global heart T2* values and the bi-atrial areas or the left ventricular (LV) and right ventricular (RV) morphological and functional parameters. Five patients showed a LV ejection fraction (EF) < 57% and one patient showed a RV EF < 52%. None of them was under 8 years of age.
Conclusion: The MRI screening for both iron overload and function assessment can be started for TM patients at the age of 8 years. At this age not sedation is generally needed. If the availability of cardiac MRI is low, the serum ferritin levels can be used as a discriminating factor.

P781 The fate of complex congenital heart disease: prediction of mortality in adulthood

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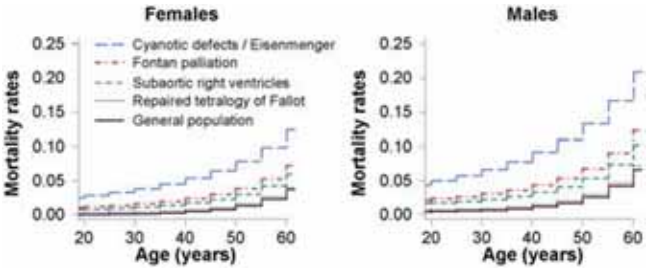
Introduction: Most patients with complex congenital heart disease now survive childhood; thus there is increasing interest in their outcomes as adults. The extent to which survivors of complex congenital heart disease remain at risk for premature death as adults is not well understood.
Methods: From our clinic database, we identified all deaths among adults with congenital heart disease between 1980 and 2009. For cardiac lesions of >/=moderate complexity for which at least 25 deaths were identified, a mathematical model was created to predict annual mortality rates of congenital heart disease patients compared to the general population.
Results: Among 12,599 patients in our database, we identified 506 deaths (4%). Of those who died (60% male, mean age at death 40±15 years), 438 (87%) had lesions >/= moderate complexity. The most prevalent cardiac defects among deceased patients were: cyanotic lesions (149 patients), transposition complexes with subaortic right ventricles (64patients), Fontan procedures for single ventricle physiology (44 patients) and repaired tetralogy of Fallot (54 patients). While patients with these lesions account for only 13% of all patients followed at our centre, these 311 deaths account for 61% of all deaths. Our model predicts that annual mortality rates in adulthood for patients with these defects will be 3 to 10-fold higher than in the general population, except for adults with repaired tetralogy of Fallot for whom predicted mortality rates are only mildly higher than in the general population (Figure).



Conclusion: Adult survivors with common forms of complex congenital heart disease are predicted to have a far higher risk of premature death than the general population. Increasing resources will be needed to care for this emerging high-risk population of young adults.

P782 Univentricular hearts in denmark 1977-2009: incidence and survival

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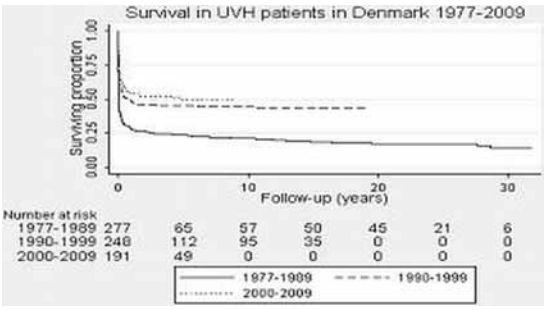
Purpose: Over the past four decades outcome has improved in children born with a functionally univentricular heart (UVH). This study describes incidence and survival among UVH patients born in Denmark from 1977 to 2009.
Methods: Using nationwide registries we identified UVH patients and induced abortions due to UVH in the fetus. All diagnoses were confirmed through different local registries. If UVH could not be confirmed the patient was excluded.
Results: 822 cases were identified. The incidence of UVH (including induced abortions) was evenly distributed in the period (mean 0.400 per 1000 births, SD 0.056). Outcome of birth groups is shown in the table. The Kaplan-Meier curves (abortions excluded) show an increase in survival between 1977-89 and 1990-99 (log-rank, P<0.0001) and between 1990-99 and 2000-09 (although not statistically significant, log-rank, P=0.20).

Birth group	Born with UVH, n	Abortion, n	Alive 2009, n	Fontan/TCPC, n (dead)	Type of Fontan, n (dead)		
					1	2	3
1977–1989	277	0	43	42 (10)	13 (4)	19 (6)	10 (0)
1990–1999	248	6	106	99 (4)	1 (0)	66 (4)	32 (0)
2000–2009	191	100	99	74 (4)	0	5 (2)	69 (2)

Fontan 1: Atriopulmonary connection; Fontan 2: Lateral tunnel; Fontan 3: Extracardiac tunnel.



Conclusions: The incidence of UVH was constant throughout the period. The incidence of liveborn UVH patients was falling after 2000 due to introduction of fetal ultrasound. Survival has improved from the 1980ies but has not significantly improved in the last 20 years.

P783 Cardiac outcomes in adults with supravalvar aortic stenosis

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Introduction: Supravalvar aortic stenosis (SVAS) felt to be a progressive disease in childhood and is often associated to the Williams-Beuren-Syndrome (WBS). While the natural history in childhood has been well described, outcomes in adults have not been studied.
Methods: We conducted a multicenter retrospective analysis of adults (>18 years) seen in adult congenital cardiac clinics. We studied cardiac outcomes and predictors of reoperations and cardiac complications (death, myocardial infarction, stroke, heart failure and arrhythmias) in the adult population. Cox survival analysis was used to assess determinants of cardiac complications and reoperations.
Results: A total of 113 patients were identified (68% males; median age at first visit 19 years, 62 with WBS) of whom 76 (67%) had undergone surgical repair of SVAS in childhood. At the first visit to an adult clinic, residual SVAS was more common in patients with WBS (71% versus 53%, p=0.048). In constrast, patients with WBS were less likely to have co-existent aortic valve disease (3% versus 37%, p<0.001). For 96 patients (85%) follow-up information was available (median follow-up time of 6.0 years, range 0.1-30.0 years). Twelve patients (13%) had a total of 18 cardiovascular complications (2 deaths, 7 heart failure, 8 arrhythmias, 1 stroke) and 12 patients (13%) underwent reoperations. Reoperations varied and included: resection of supravalvar aortic stenosis at first visit in adulthood (n=4), aortic valve replacement (n=5), pulmonary valve replacement (n=1), tricuspid valve repair (n=1) and implantation of a left ventricular assist device (n=1). The diffuse form of SVAS (HR 7.2, CI 1.4-35.8, p=0.017) was associated with late cardiovascular complications. Residual SVAS in adulthood was not predictive for cardiovascular complications. Predictors of reoperations in adulthood included SVAS without WBS (HR 5.7, CI 1.2-26.8, p=0.03) and those with right bundle branch block (HR 4.1, CI 1.1-15.4, p=0.04).
Conclusion: A significant portion of adults with supravalvar aortic stenosis develop late cardiac complications such as heart failure and arrhythmias. These complications are more common in patients with the diffuse form of SVAS. Reoperations are also required in adulthood for a variety of reasons and are more common in those patients who do not have Williams-Beuren-Syndrome.

P784 QRS and QTc intervals on 12-lead surface ECG predict survival in adults late of atrial switch palliation of transposition of the great arteries

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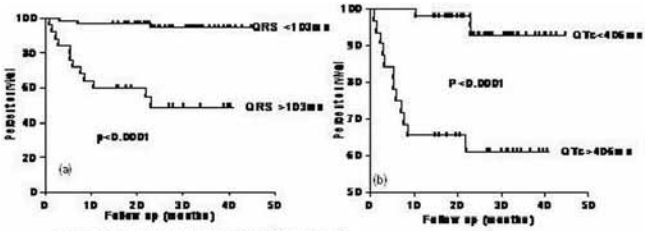
Introduction: QRS duration and QTc interval are strong predictors of survival in acquired left ventricular dysfunction; equivalent data in those with a systemic right ventricle is lacking. This study investigated the relationship between ECG parameters and outcome in adults with transposition ofthe great arteries (TGA) late after atrial switch palliation.
Methods: 69 adults with Senning or Mustard palliation of TGA under follow up at a dedicated congenital heart failure clinic and 15 similar adults who suffered a cardiac death (n=14) or underwent cardiac transplantation (n=1) were included for study. 12 lead ECG was analysed and time to follow up/death calculated.

ROC curves, Cox regression analysis and Kaplan Meier survival analysis were used.
Results: Mean follow up for the cohort was 25 months. Mean age 28±7years at follow up and 28±9 years at death. 27 (32%) were female and 44 (52%) underwent Senning palliation. Operative method was not associated with adverse outcome.
Median QRS for the whole cohort was 90ms (64-184); median QTc interval400ms (301-536). Both QRS>103ms andQTc>406ms were independently associated with increased risk of death (p<0.001 for both; figure). Adjusting for age and gender, those with QRS>103ms have an OR 13.26 (CI 3.60 to 48.85, p<0.001) compared to those with QRS <103ms of death, and QTc>406ms have 13.27 (CI 2.97 to 59.36, p=0.001) higher odds to die compared to those below the QTc cutoff.



Kaplan Meier survival curves for QRS (a) and QTc (b).

Conclusions: This is the first study of surface ECG predictors in adults with either Mustard or Senning palliation of TGA. We find that QRS width and corrected QTc interval are associated with increased risk of death. Given that a QRS of only 104ms defines a high risk population, careful examination of the ECG is indicated in all patients.

P785 Systemic right ventricular longitudinal strain is reduced in adults with transposition of the great arteries, relates to subpulmonary ventricular function and predicts adverse outcome

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Background: Impairment of systemic right ventricular (RV) function is common in pts with transposition of the great arteries (TGA) who underwent atrial switch operation and those with congenitally corrected TGA (ccTGA). We investigated the value of novel indices of myocardial deformation on speckle-tracking echocardiography for quantifying ventricular function, for assessing ventricular-ventricular interaction and for predicting outcome.
Methods and results: In 129 patients (TGA with atrial switch, 87; ccTGA, 42; male, 71; age 35±12 years) biventricular myocardial deformation was measured and compared with findings in normal subjects (n = 38, age 36±10 years). Systemic (RV) ventricular longitudinal 2D- peak systolic strain (2D-LS) was significantly reduced compared to controls (-12.9±3.6 vs. -15.4±5.1 and - 21.0±5.5 in TGAs, ccTGAs and controls; p<0.0001). Systemic and subpulmonary 2D-LS were correlated in TGA (r=0.46, p<0.0001) and ccTGA patients (r=0.64, p<0.0001), suggesting interventricular interaction, and this was confirmed when ejection fraction on MRI was assessed (r=0.53, p<0.0001). In addition, systemic 2D-LS (OR=1.11, p=0.025) and subpulmonary 2D-LS (OR=1.11, p=0.002) were significantly related to adverse outcome (NYHA class>2, history of clinically relevant arrhythmia, ventricular tachycardia or death) independently of diagnosis or functional class.
Conclusions: Systemic ventricular global systolic strain is significantly reduced in patients with TGA. Similar to patients with tetralogy of Fallot, systemic and subpulmonary myocardial function are interrelated in patients with TGA and this is likely due to an adverse ventriculo-ventricular interaction. Most importantly, biventricular dysfunction on speckle tracking echocardiography was significantly related to adverse outcome in this cohort of adults with TGA and systemic right ventricles.

ADULT CONGENITAL HEART DISEASE – MISCELLANEOUS II

P786 Patient registry of the competence network for congenital heart defects in Germany

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Introduction: Many CHD patients remain chronically ill throughout their lives and require lifelong care. Since patient numbers are small and due to the high variability of disease patterns, there is a lack of sufficient data for the development of adequate treatment and care. Therefore in 2003 the German cardiac associations have initiated a patient registry that collects data and (since 2008) biomaterial samples from patients of all ages and from all over Germany on a long-term basis in a central database & biobank facility.
Methods: Patients (or parents of underage patients) enrol on their own account via a registration form that is distributed by most German heart centres and parents' associations. On registration and entry of personal data (IDAT-database), a unique patient identifier (PID) is generated. The PID applies for all databases within the Competence Network (including a clinical study- and image database) and ensures a correct assignment of data sets. Health-related and medical data are based on patient questionnaires and physician's medical reports and are stored in a separate database (MDAT-database) to ensure data privacy. Diagnoses and procedures are classified using the EPC-Code/Short List. EDTA-blood samples are collected via (i) direct contact to registry patients and their families, and (ii) cooperation with several involved clinical centres in Germany. DNA isolated from EDTA-blood is stored in a central facility.
Results: Presently (January 2011) the registry comprises a total of 40,013 patients. The large majority (84%) of participants are underage, sex is evenly distributed. Simple heart lesions (VSD, ASD, PDA) represent 51%, moderate (TOF, ISTA, AoV, TGA, AVSD, PaV, DORV, PAPVC, TAPVC, HRST) 42%, and severe/complex (DIV, CMP, PA, CCT, TAC, HLHS, Marfan) 7%. Based on registry data and directed recruitment of participants numerous studies have been initiated regarding quality of life, social situation, patient communication, genetic causes, as well as clinical studies. The DNA collection presently comprises 712 samples covering a wide range of CHD phenotypes. The sample collection will be extended to include also cardiac tissue, a pilot phase has started in autumn 2010.
Conclusions: The patient registry and biobank facilitates collaborative and translational research on congenital heart defects.

P787 Clinical advantage of real-time three dimensional transesophageal echocardiography in transcatheter closure of multiple atrial septal defects

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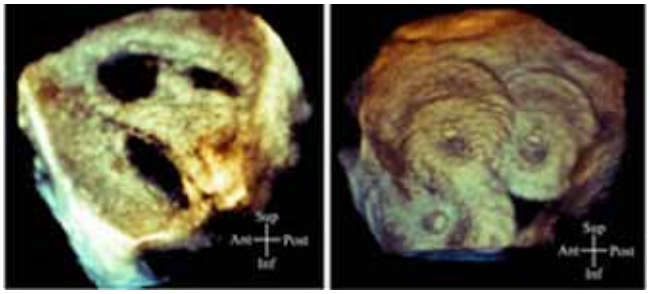
Purpose: The aim of this study was to evaluate the usefulness of real-time (RT) three-dimensional (3D) transesophageal echocardiography (TEE) compared to two-dimensional (2D) TEE in patients with multiple atrial septal defects (ASDs) undergoing transcatheter closure.
Methods: Consecutive 212 patients with ASDs (mean age 45.2±21.7 years) who were scheduled for transcatheter closure of ASDs using the AMPLATZER Septal Occluder under 2D TEE and RT3D TEE guidance were enrolled in this study. Patients were divided into multiple ASDs group (n=27) and a single ASD group (n=185).
Results: In multiple ASDs group, 13 patients were required multiple devices to close their defects. Procedural success was obtained in 26 patients (96.3%) with multiple ASDs and 182 patients (98.4%) with a single ASD. There were no significant differences in the feasibility of obtaining optimal 3D zoom images (85% vs. 94%, p=0.11) and 3D full-volume images (83% vs. 92%, p=0.19) between multiple ASDs and a single ASD group. The distance between two major defects measured with RT3D TEE was significantly smaller than that measured with 2D TEE (6.1±5.9 mm vs. 8.1±6.4 mm, p<0.001). RT3D TEE could provide useful information on the morphology of multiple ASDs and guidance of the procedure, especially in patients required multiple devices.



Left atrium en face image.

Conclusions: RT3D TEE has a clinical advantage over 2D TEE in transcatheter closure of multiple ASDs in terms of morphological evaluation and development of a successful treatment strategy. And it provides variable information for interventionalists in the catheterization laboratory.

P788 Predictive model for late atrial arrhythmia after closure of an atrial septal defect

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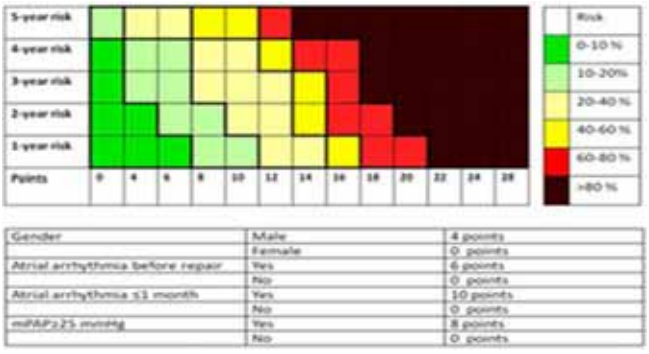
Background: The clinical management of atrial septal defect (ASD) is driven by risk factors that determine the occurrence of late atrial arrhythmia. However, a quantitative event-free prediction model has not yet been established for clinical use or research aims.
Methods: Data from ASD type secundum patients in the Belgian Congenital Heart Disease Registry were analyzed to build a model for arrhythmia free survival. Based on review of the literature, age at repair, gender, pulmonary hypertension, atrial arrhythmia before and within one month after repair were considered for inclusion in the model. Using Cox-regression analysis a weighted risk score was derived. Validation of the model was performed using the Brier score.
Results: A total of 155 patients (38 men, 117 women) having 349 follow-up years was included. Twenty-four patients (median age at follow-up 48.3 years, range 19.9–79.8) underwent surgical and 131 (median age at follow-up 57.6 years, range 18.2–86.9) transcatheter closure of the ASD. Thirty-nine patients (25.2%) presented with late atrial arrhythmia. Multivariate analysis showed that a mPAP ≥25mmHg (HR 4.39; 95%CI 2.17-9.09; P<0.0001), the presence of atrial arrhythmia before (HR 3.52; 95%CI 1.75-7.14; P=0.002) and ≤1 month after repair (HR 6.62; 95%CI 2.38-20.00; P<0.0001) and gender (HR 2.18 95%CI 1.11-4.35) were associated with late atrial arrhythmia. A risk score (0 to 28 points) to predict atrial arrhythmia free survival was derived for follow-up times ranging from 1 to 5 years. Mean Brier score for the model was 0.10.



Gender	Male	4 points
	Female	0 points
Atrial arrhythmia before repair	Yes	6 points
	No	0 points
Atrial arrhythmia ≤1 month	Yes	10 points
	No	0 points
mPAP≥25 mmHg	Yes	8 points
	No	0 points

Predictive score.

Conclusions: We could formulate a well validated risk model to predict arrhythmia-free survival in ASD patients undergoing ASD repair. Further research is needed whether this model can be used for individual clinical risk stratification.

P789 Cardiac function assessment in adult post autograft implantation patients (the ross procedure) by cardiac magnetic resonance imaging, echocardiography and N-terminal B-type natriuretic peptide

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Purpose: Pulmonary homograft and/or pulmonary autograft dysfunction can occurr after the Ross procedure. The aim of this study was to assess homograft and autograft function and relate it to biventricular function in post Ross operation patients.
Methods: Included in this study were 66 adult patients (M 41, 34,4±10,1 years, range 16-57years) after the Ross procedure (root replacement technique) who were operated between 1994-2005 (9,1±2,7 years post Ross surgery, range 3,5-15,3 years). Twelve of this patients had already undergone the reoperation (homograft n=5, autograft n=7).
Autograft, homograft, ventricular systolic and diastolic function as well as the presence of myocardial scar were assessed with a combination of cardiovascular magnetic resonance (CMR), echocardiography (2D,Doppler,TDI) and plasma NT– pro BNP level.
Results: Mean autograft diameters were: at the sinuses level= 39,9±5,2 mm, at the sinotubular junction level = 39,5±6,5mm and at the ascending part level = 39,8±7,7 mm. Mean autograft regurgitation was 9,5±10,2% (trivial). In six patients severe autograft dilatation occurred (55,5±5,6 mm).
Mean homograft peak velocity was 2,7±0,9 m/s (mild stenosis) and regurgitation was 4,3±6,5% (trivial regurgitation). Three patients had severe homograft stenosis (Vmax 5,2±0,6 m/s.)
Left ventricular systolic and diastolic function were in the normal range (EF 60,6±5,8%, MAPSE 17,8±3,2 mm, SV/BSA 59,1±11,5 ml/m^2, s' 9,7±2,2 cm/s, LV mass/BSA 66,8±16,0g/ m^2, E/A 1,6±1,6, E/e' 6,2±2,4)
Right ventricular systolic and diastolic function were normal (EF 58,4±9%, TAPSE 19,4±4,1mm, SV/BSA 57,7±14,3 ml/m^2, s'11,8±2,4cm/s, RVmass/BSA24,5±6,6 g/m^2, E/A 1,5±0,4 E/e' 5,2±1,7). Trivial myocardial scar was observed in 16,6% of patients studied.
Median NT-pro BNP value was 78,3 pg/ml (normal).
Conclusions: This study indicates minor autograft and homograft dysfunction associated with good biventricular function in majority of patients after the Ross operation.

P790 Is ADMA a better biomarker for heart failure in adults with congenital heart disease than NT-proBNP?

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Purpose: Chronic heart failure is an important cause for morbidity and mortality in adults with congenital heart disease (ACHD). While NT-proBNP is an established biomarker for heart failure of non-congenital origin, its value in ACHD has limitations. Asymmetrical dimethylarginin (ADMA) correlates with disease severity and independently predicts adverse clinical events in heart failure of non-congenital origin. Its role in ACHD has not been investigated.
Methods: In 97 patients (female n=40, male n=57; mean age 30.2±10.4 years; n=68 left systemic ventricle (LV), n=13 right systemic (RV), n=16 univentricular (UV)) ADMA and NT-proBNP were measured and related to NYHA class, systemic ventricular function and parameters of cardiopulmonary exercise testing.
Results: 56 patients (p.) were in NYHA class I, 21 in NYHA II and 20 in NYHA ≥ III. While ADMA is elevated in p. with NYHA class ≥III (0.55±0.10 mol/l) compared to p. with NYHA class II (0.48±0.08 mol/l, p=0.007) and NYHA class I (0.44±0.06 mol/l, p<0.001), NT-proBNP is not significantly elevated in p. with NYHA class ≥ III compared to p. with NYHA class II (915±1337 pg/ml vs. 432±517 pg/ml, n.s.) but to p. with NYHA class I (128±202 pg/ml, p<0.001).
NT-proBNP and ADMA both correlated with peak oxygen update (r= -0.438; p<0.001/ r= -0.356; p=0.002) and VE/VO2 slope (r=0.455, p<0.001/ r=0.419; p<0.001).
In 52 p. systemic ventricular function was normal, while in 36 p. it was moderately and in 9 p. severly impaired. ADMA was not significant different in p. with normal function compared to p. with moderate and severe ventricular dysfunction (0.46±0.07 μmol/l vs. 0.47±0.08 μmol/l vs. 0.53±0.14 μmol/l). NT-proBNP was elevated in severe ventricular dysfunction compared to moderately impaired ventricular function (1541±1834 pg/ml vs. 377±459 pg/ml, p<0.001) and normal ventricular function (142±177 pg/ml, p<0.001) but not between the later two.
NT-proBNP is elevated in p. with LV compared to RV (969±1383 pg/ml vs. 181±247 pg/ml, p=0.001), but not to UV (606±1026 pg/ml). ADMA is elevated in p. with UV compared to LV (0.53±0.11 μmol/l vs. 0.46±0.07 μmol/l; p=0.008), but not compared to RV (0.50±0.09 μmol/l) and also not between RV and LV.
Conclusions: ADMA is a better biomarker than NT-proBNP for the assessment of NYHA class and as a good as NT-proBNP for the estimation of maximum exercise capacity in adults with congenital heart disease. ADMA acts as an endogenous inhibitor of eNOS thereby promoting endothelial dysfunction. It may therefore not only act as a biomarker, but contribute to systemic endothelial dysfunction in ACHD.

BASIC SCIENCES AND FETAL CARDIOLOGY

P791 Birth prevalence of congenital heart disease; meta-analysis on changes during the last 80 years

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Purpose: Congenital heart disease (CHD) is the most common form of congenital abnormalities, with an estimated birth prevalence of 8 per 1000 live births. To obtain insight into birth prevalence of CHD worldwide and temporal changes in the past century we conducted a systematic review and meta-analysis of published reports.
Methods: On September 23rd 2010 a PubMed literature search was conducted with the search terms: "heart defects, congenital/epidemiology" and "incidence" or "prevalence". Weighted averages of CHD birth prevalence per 5-year time period were calculated using the generic inverse variance method. Time trends were plotted by the Savitzky-Golay Smoother.
Results: Including 131 articles, a total study population of 25,172,760 live births was formed of which 166,899 were diagnosed with CHD. Over time, the reported birth prevalence of CHD increased substantially (Figure 1); from 0.6 per 1000 live births (95%CI 0.39-0.93) in 1930-1934 to 9.0 per 1000 (95%CI 8.76-9.04) after 1995. The reported birth prevalence of VSD, ASD and open ductus increased

over time, especially after the 1970s when echocardiography was widely introduced in clinical practice. The birth prevalence of pulmonary stenosis, Fallot, coarctation, transposition and aortic stenosis was stable over time.

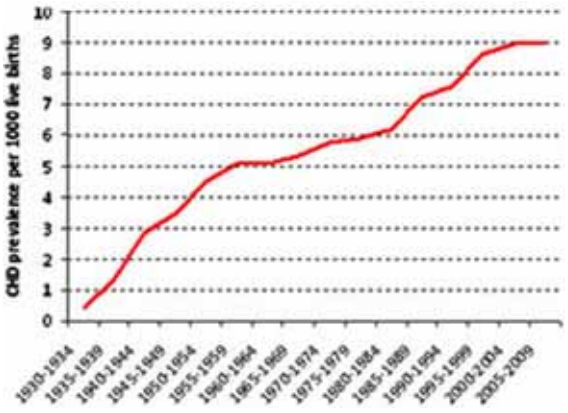

Figure 1. CHD birth prevalence over time.

Conclusion: The reported birth prevalence of CHD increased substantially during the last century with improvement of diagnostic methods and more population wide screening, eventually reaching a stable number of 9 per 1000 live births over the last 15 years. This corresponds to 1.35 million live births with CHD worldwide every year, representing a major global health problem. Although the reported prevalence increased over time, it remains unclear if true prevalence has changed.

P792 Investigation of germline and somatic GATA4 and NKX2.5 mutations in congenital heart defects: is it not all in the DNA?

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Background: Congenital heart disease (CHD) is the most common type of birth malformation. Recently, somatic mutations in the GATA4 and NKX2.5 transcription factor genes have been reported in the diseased heart tissues of patients. However, the "somatic mutation hypothesis" awaits further evidence.
Aim: To assess the presence of germline and somatic mutations the GATA4 and NKX2.5 genes in familial and sporadic cases.
Methods: We studied 12 patients with familial CHD (7 males; 12.3±7 years) with septal defect (n=8), conotruncal defects (n=3) and hypoplastic right ventricle (n=1). Sporadic cohort included 6 (2 males; 15.3±4.6 years) with septal defect (n=4) and conotruncal defects (n=2). From all patients we collected peripheral blood and a sample of cardiac diseased tissue located within or in close proximity (1-3 mm) of the cardiac defect from sporadic patients. All coding regions and exon–intron boundaries, of the genes were analyzed by using a high-throughput platform (CEQ 8800 Genomelab System, Beckman).
Results: There were no GATA4 and NKX2.5 mutations in both familial and sporadic patients; 19 genetic variants were identified in GATA4 and 1 in NKX2.5 gene listed in dbSNPs. A novel deep intronic variation (IVS4 -202C>T) was identified in 2 separate patients (Table). Mostly dbSNPs were detected in the 3'-UTR of GATA4, that is emerging as critically important in regulating gene expression at post-transcriptional levels.
Conclusion: GATA4 or NKX2-5 genes mutations are uncommonly found in familial and sporadic cases of CHD, supporting the genetic heterogeneity of CHD and the limitation of genetic testing in clinical setting. Further studies are needed to define the genetic basis of CHD, including alterations and their impact upon 3'UTR-directed posttranscriptional gene regulation.

P793 Constriction of ductus arteriosus by inhibition of ATP-sensitive K-channels with antidiabetic sulfonylureas in fetal rats

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Objectives: To clarify the effect of inhibition of ATP-sensitive K channels with antidiabetic sulfonylurea drugs on the fetal ductus arteriosus (DA).
Methods: Tolbutamide, chlorpropamide and glibenclamide were administered to pregnant near-term Wistar rats on the 21st day of gestation. The fetuses were delivered by caesarean section and immediately frozen. The fetal DA was studied with a freezing microtome, a microscope and a micrometer.
Results: The inner diameter of the DA was 0.80 mm in controls. Tolbutamide and chlorpropamide, which readily crossed the placenta, constricted the DA similarly and dose-dependently. Tolbutamide constricted the fetal DA to 0.57, 0.18 and0.01 mm with 10, 100, and 1000 mg/kg, respectively by four hours later. Simultaneous glucose administration prevented maternal and fetal hypoglycemia, and did not change ductal constriction by tolbutamide. The preterm DA was less sensitive to tolbutamide. A large dose of glibenclamide (10 mg/kg equivalent to 200 times the clinical dose), with very little crossing the placenta, constricted the fetal ductus late and then only mildly.
Conclusions: In vivo inhibition of ATP sensitive K channels with sufonylureas has a potent constrictive effect on the fetal DA in rats. These results suggest that the ATP-sensitive K channel has a physiological role in fetal patency of the DA. Sulfonylureas with coadministration of glucose, may be useful in closing the PDA of premature babies.

Gene	Position	Sequence variants	Novel/Known variants	MAF
GATA4	Exon 1 (untranslated)	-543 c>t	Known	0.29
	Exon 6	c.1129 A>G (S377G)	Known	0.11
	IVS 2	-116 t>c	Known	0.2
	IVS 2	-64 g>c	Known	0.2
	IVS 4	-202 c>t	Novel	
	IVS 4	-174 t>c	Known	0.26
	IVS 5	+56 c>a	Known	0.5
	3'-UTR	+354 g>c	Known	0.3
	3'-UTR	+426 c>t	Known	0.5
	3'-UTR	+517 c>g	Known	0.44
	3'-UTR	+532 t>c	Known	0.42
	3'-UTR	+563 c>g	Known	0.34
	3'-UTR	+567 a>g	Known	1
	3'-UTR	+852 g>a	Known	0.3
	3'-UTR	+1158 c>t	Known	0.08
	3'-UTR	+1256 a>t	Known	0.3
	3'-UTR	+1355 g>a	Known	0.1
	3'-UTR	+1521 c>g	Known	0.32
NKX2.5	Exon 1	c.63 A>G (E21E)	Known	0.3

Genetic variants detected in patients.

P794 Performance of antenatal diagnosis to detect postnatal coarctation of the aorta

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The aim of this study is to assess the postnatal outcomes of fetuses diagnosed with potential aortic coarctation.
Material and methods: The records of all neonates with antenatal suspicion of coarctation of the aorta were reviewed retrospectively for clinical, echocardiographic data and treatment.
Results: Among 78 fetuses diagnosed with abnormal asymetric ventricles, 35 (44.9%) developed coarctation of the aorta, 42 did not (52.5%) and 2 had hypoplastic left heart (2.6%).
All patients were hospitalized from birth until closure of the ductus arteriosus (2 to days) or Crafoord surgery. The antenatal RV to LV ratio was 1.74 in patients with coarctation of the aorta compared to 1.39 in those without (p=0.018), and the pulmonary artery to ascending aorta ratio was respectively 1.69 versus 1.30 (p=0.0001). The frequency of left superior vena cava was not different between patients with and without postnatal coarctation (29.7 versus 25%). The 2 cases with hypoplastic left heart died postnatally. All the other patient were asymptomatic, and had no symptom of heart failure.
Mean postnatal LV diameter was 15.7mm, ascending aorta 7.2mm. None of the patients required prostaglandin infusion or preoperative mechanical ventilation. Crafoord operation was performed at median age of 11.5 days. Median hospital stay was 21.4days for operated patients.
Conclusion: The performance of antenatal diagnosis to detect postnatal coarctation of the aorta remains low. However RV to LV and PA to AO ratios may help to ameliorate sepecificity. Despite high rate of false positive, antenatal diagnosis allows to avoid postnatal acute heart failure and improve early prognosis.

P795 Right ventricular global longitudinal strain, velocity and displacement during 2nd and 3rd trimester in human fetuses: feasibility, normal values and reproducibility using 2D speckle tracking imaging

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Background: Quantitative evaluation of right ventricular (RV) performance by echocardiography/Doppler has been a challenge for fetuses at risk for heart failure due to structural and functional abnormalities. We sought to assess potential

utility of 2D speckle tracking imaging (2D STI) to assess RV systolic function during 2nd and 3rd trimester in human fetuses.
Methods: A total of 88 consecutive pregnant women (age 27.4±3.5 years, gestational age 29.6±5.4 weeks) with a normal level 2 ultrasound scan were enrolled. Voluson 730 Expert (GE Medical System) ultrasound system was used to obtain standard 4 chamber views for 2D STI analysis. Manual identification and editing of the endocardial borders was performed. The mean longitudinal peak systolic strain (PSSm), velocity (Vm) and displacement (Dm) were obtained by averaging six segments (basal, mid, apical) of the RV free wall and ventricular septum using the software by TomTec (Image Arena 4.0, TomTec, Munich, Germany). The frame rate ranged from 83 to105
Frames/sec: Results: Image analysis was feasible for 84 fetuses (95%). The PSSm was -19.0±4.4%, Vm 2.2±0.9 cm/sec and Dm 2.0±0.7 mm, respectively. There was no significant correlation between PSSm and gestational age (r= -0.07, P>0.05); but there was significant correlation between Vm and Dm with gestational age (r=0.74, P<0.05). There was significant difference in Vm and Dm with a decreasing trend but not in PSSm between basal, mid, and apical RV segments. In addition, PSSm, Vm, and Dm values were significantly higher for RV free wall segments than septal segments. The coefficient of repeatability of PSSm, Vm and Dm by Bland-Altman analysis for intraoperator was 4.69, 0.37, 0.38, and for inter-operator measurements 5.99, 0.48, 0.56, respectively.
Conclusions: Our study suggests evaluation of RV longitudinal PSSm, Vm and Dm by 2D STI is feasible and reproducible. RV PSSm is independent of gestitional age but Vm and Dm are not. This technique may provide a quantitative measure for longitudinal follow-up of fetuses at risk of RV dysfunction and for assessing therapeutic intervention.

P796 Ebstein anomaly and tricuspid valve dysplasia: prognosis after diagnosis in utero

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Aims: Tricuspid valve malformations are rare congenital heart diseases. The prenatal diagnosis of Ebstein's anomaly (EA) and Tricuspid valve dysplasia (TVD) are associated with high mortality. There are conflicting reports concerning accurate prognostication after diagnosis in utero. The aim of our study was to assess prognostic factors based on our experience.
Methods and results: We reviewed 37 fetuses between 1984 and June 2010, 26 EA and 11 TVD. There were 11 terminations, 5 intrauterine deaths, 7 neonatal deaths and 14 survivors to age over 2 years. We found that the major prognostic factor for outcome was the pattern of pulmonary valve artery flow. Retrograde pulmonary flow had a predictive positive value (PPV) for death of 83%, and when associated with significant pulmonary insufficiency, PPV was 100% for death. An anatomic pulmonary atresia was also associated with 100% of death. By contrast, cardiothoracic index, right to left ventricular ratio, Celermajer index were not useful prognostic markers. Compared with retrograde pulmonary artery flow, anterograde flow in utero predicted good outcomes with a PPV for survival of 86%. The SAS score, more complex, was less correlated to our series with 79% PPV of death when the score was ≥5 and a PPV survival of 79% when the score was < 5.
Conclusion: Pulmonary artery flow is a simple and excellent prognostic factor when major tricuspid valve disease is diagnosed in utero. Nevertheless, these fetuses should be monitored throughout the pregnancy because several hemodynamic factors may change the prognosis.

P797 Congenital heart defects in twin pregnancies: a series of 226 cases

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Background: The relative risk for congenital heart defects (CHD) is increased in monochorionic twins. The respective contribution of genetics of cardiac development and environmental risk factors such as twining per se are scarcely known.
Aim: To analyze CHDs in twin pregnancies in which one or two foetuses were diagnosed to have a CHD and to identify the role of chorionicity and amnionicity on CHD type and concordance between twins.
Methods: Over a period of 16 years, 226 twin pregnancies with one or two foetuses having a CHD were reviewed. Chorionicity, amnionicity, presence of twin-twin transfusion syndrome (TTTS), cardiac phenotypes, anatomical/CHD type (7 groups of CHD), concordance between twins and outcomes were analyzed.
Results: Pregnancies were dichorionic-diamniotic (DCDA) in 103 cases and monochorionic in 112 (diamniotic 92-MCDA, monoamniotic 20-MCMA) and the remaining 11 were unknown. 28 pregnancies were obtained after assisted reproductive technologies (12.3% vs 2.6% for all pregnancies). Overall the 2 foetuses were affected in 35 cases (15.4%) with the two CHDs belonging to the same group in 23 (65.7%). The two foetuses had a CHD in 35% of MCMA, 14.1% of MCDA and in 10.7% of DCDA. The most frequent defects were conotruncal defects (n=71) with concordance in 13/71 (8/20 MCDA, 3/5 MCMA). For other groups concordance in all pregnancies, in MCDA and in MCMA were respectively: right outflow tract obstructions 5/48, 0/33, 0/0; obstructive left heart diseases 7/42, 2/13, 1/1; laterality defects 2/36, 0/6, 2/12; ventricular septal defects 5/19, 1/9, 0/0; atrioventricular septal defects 3/9, 1/2, 0/0; functionally univentricular heart 1/15, 0/5, 0/1. MCDA pregnancies were more frequent in right outflow tract obstructions (33/48; 69%-p<0.01) and discordance between twins was constant (pulmonary stenosis in the recipient twin) and was associated with proven TTTS in 22/33. MCMA were more frequent in laterality defects (12/36; 33%-p<0.01) and discordance between twin of was observed in 10/12. The outcome of pregnancy was: termination of pregnancies 47 foetuses, intrauterine foetal deaths 20 foetuses, neonatal death 24/387 live births. 116 patients underwent cardiac surgery within the first year of life with 13% mortality.
Conclusion: Concordance for CHD between twins is low even in monochorionic (certainly monozygotic) twins. Discordance in monochorionic twins might be related to twining per se for laterality defects in MCMA and pulmonary stenosis in MCBA-TTTS. Postnatal mortality before one year is much higher than in singleton with CHD.

P798 Left ventricular dysfunction in a mouse model of marfan syndrome

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Background: Cardiovascular manifestations in Marfan syndrome (MFS) are mainly characterized by aortic root dilatation, ensuing aneurysm formation and finally (often) fatal aortic dissection. Primary cardiomyopathy with both systolic and diastolic ventricular dysfunction is clinically less pronounced in most cases, although well documented in recent literature. The underlying pathophysiology of this finding is largely unknown although it is likely that the TGFβ pathway, which is implicated in most pleiotropic findings occurring in MFS, plays a role.
One possibility to gain insight into the pathophysiology of cardiomyopathy in MFS is to study a mouse model, allowing detailed in vivo and in vitro studies.
Methods: We conducted detailed serial cardiovascular ultrasound studies in 10 MFS mice (fbn1 C1039G) and 10 control mice. Both vascular (aortic dimensions) and cardiac data (left ventricular diameters and diastolic function) were obtained with a high-frequency ultrasound apparatus (Vevo 2100, Visualsonics, Toronto, Canada) equipped with a linear array probe (MS 550D, frequency 22-55 MHz).
Results: MFS mice at 6 months had significantly larger diameters at the level of the aortic sinus (1,84mm + 0,13 vs 2,26mm + 0,33; P=0,003), ascending aorta (1,64mm + 0,14 vs 2,1 mm+ 0,5; P=0,007) and transverse aorta (1,5 + 0,2 vs 1,9 + 0,36mm; P=0,036). Pulmonary artery diameters were also significantly larger in MFS mice (1,44mm + 0,06 vs 1,63mm + 0,21; P=0,02). There was a non-significant trend towards larger aortic diameters at 1 and 3 months. Left ventricular ejection fraction was lower in MFS mice at all time points (64,5% + 6,9 vs, 58,9% + 9,4; p=0,16 at 6 months) although the number of studied animals was too small to reach significance.
Conclusion: Developing animal models that accurately recapitulate the phenotypic features that ensue as a result of mutant gene expression is essential to study underlying pathophysiological processes and ultimately develop targeted treatment. Here we provide evidence for involvement of the myocardium in a mouse model of MFS. This model may enable us not only to study the development and treatment strategies of cardiomyopathy in MFS but may ultimately also increase our insights into more common forms of cardiomyopathy.

HEART FAILURE – LEFT VENTRICULAR DYSFUNCTION

P800 Plasma Neuthrophil Gelatinase associated Lipocalin (NGAL) predict worsening renal function and rehospitalization in patients with acute decompensated heart failure

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Background: Many laboratory and new diagnostic imaging parameters have been associated with poor outcome in heart failure, however the prognosis of these patients cannot be easy predicted by traditional indexes. Neutrophl Gelatinase associated Lipocaline (NGAL) is a marker associated to early acute kidney injury that is likely to have a specific role in predicting, detecting and describing severity of tubular damage in acute and chronic HF patients.
Aims: To support this hypothesis we measured plasma NGAL levels in patients admitted to the hospital for acute decompensated HF. We compared NGAL levels with Creatinine and Glomerular filtration rate at baseline and before discharge. We evaluated the role of NGAL in predicting hospital readmission and cardiac events during a one year follow-up.
Methods and results: Plasma NGAL levels were measured in 123 patients by a research enzyme-linked immunosorbent assay within the first 48 hours from hospital admission. Patients with mild to moderate renal dysfunction at baseline demonstrated higher NGAL levels respect to subjects with normal creatinine and glomerular filtration rate values (154±68 vs 91,2±50 ng/ml p<0.01). However the subgroup that during hospitalization showed a renal function impairment had increased values respect to patients with preserved renal function (123±56 vs 88±32 ng/ml p<0.05). We also recruited a positive correlation between NGAL

and BNP level (r= 0.86 p<0.001). The ROC curve analysis showed that cut off of 150 ng/ml has been related to renal insufficiency development with good sensitivity and specificity of 84 and 75%. Follow-up analysis demonstrated that NGAL was associated to recurrent hospital admission for heart failure and cardiac death (HR 2.9 IR 1,91-4,4 for NGAL >120 ng/ml)
Conclusions: NGAL measurement is able to predict worsening renal function in patients with acute Heart failure. Patients with higher plasma NGAL levels as well as renal dysfunction, demonstrated a poor prognosis during a one-year follow up period.

P801 Potential protective effects of myeloid and plasmacytoid dendritic cells (DCs) in dilated cardiomyopathy (DCM)

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Background: DCM is frequently the result of viral infections of the myocardium leading to chronic heart failure. DCs are assumed to have an immune mediating role in heart muscle diseases. However, their potential immunomodulating effects in DCM are unknown yet. The aim of our present study was to investigate the presence of myeloid (mDCs) and plasmacytoid (pDCs), macrophages, as well as HLA-DR expression in the myocardium of patients with left ventricular (LV)-endomyocardial biopsy in DCM.
Methods: LV-endomyocardial biopsies of 52 patients with DCM were immunohistochemically analyzed for the presence of mDCs (fascin+), immature mDCs (CD209+), pDCs (CD304+), macrophages (CD68+), and HLA-DR expression. Post-mortem myocardial specimens of 18 age-matched suicide or accident victims were used as controls. Myocardial fibrosis was histologically quantified, as well as the presence of viral genome of parvovirus B19, enterovirus and adenovirus by polymerase chain reaction. Echocardiography was performed at first diagnosis and follow-up after 6 months. The difference between the ejection fraction at first diagnosis and follow-up (ΔEF) was calculated.
Results: Compared to healthy myocardium, in patients with DCM significantly lower mDCs (2,5fold, p<0.001), pDCs (1,4fold, p<0.05), immature mDCs, and HLA-DR (1,8fold, p<0.001) expression was observed, whereas macrophages did not differ significantly. Subgroup analysis showed in patients with identification of viral genome in the myocardium significantly less mDCs (1,6fold,P=0,01). The number of mDCs significantly correlated with HLA-DR expression (R=0.58,P<0.001), immature mDCs (R=0.36,P=0.01), pDCs (R=0.48, P<0.001), ΔEF (R=0.41,P=0.02), and intra-ventricular septum (IVS, R=0.37,P=0.03) at follow-up, and inversely with fibrosis (R= -0.28, P=0.05) and myocardial viruses (R= -0.43,P=0.008). HLA-DR expression correlated with pDCs (R=0.43,P=0.002), IVS (R=0.5,P=0.002) and EF at follow-up (R=0.47,P=0.005) and inversely with fibrosis (R= -0.33; P=0.02) and left ventricular enddiastolic diameter (LVED, R= -0.29,P=0.09) at follow-up. The number of pDCs tended to inversely correlate with fibrosis (R= -0.24,P=0.1) and LVED at follow-up (R= -0.31,P=0.07). The only significant correlation with macrophages was with IVS at follow-up (R=0.5,P=0.002).
Conclusions: We show significantly decreased mDCs and pDCs in the myocardium of patients with DCM, predominantly in those with pronounced LV deterioriation in terms of fibrosis and function. The reduction of mDCs in the myocardium in DCM might be due to a defective recruitment, leading to an incomplete clearance of myocardial viruses.

P802 Anemia is not a predictor of all-cause mortality in outpatients with advanced heart failure or severe renal dysfunction

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Purpose: Anemia is identified as an independent prognostic marker in patients with heart failure. The effect of anemia on mortality is assumed to decrease with increasing creatinine levels. We wanted to evaluate the prognostic impact of baseline anemia in outpatients with chronic heart failure attending their first visit at specialized heart failure clinics, and specifically investigate the prognostic utility of anemia in patients with severe renal dysfunction or advanced heart failure.
Methods: Multivariate Cox regression analyses were used to investigate the prognostic effect of baseline anemia in 4144 patients with heart failure from 21 outpatient heart failure clinics in Norway. Severe renal failure was defined as eGFR ≤45 ml/min per 1.73 m^2 and advanced heart failure as NYHA class IIIb and IV. Interaction analyses by product terms were used to test for differences in HR of anemia in paients with severe renal dysfunction and advanced heart failure compared to the rest of the population.
Results: Median age was 70 years and 71% of patients were men. Twenty-four percent had anemia at baseline as defined by WHO criteria. In the whole population anemia was a strong predictor of all-cause mortality with a crude HR of 1.87 (95% CI 1.66-2.11, p<0.001) and adjusted HR of 1.30 (95% CI 1.09-1.56, p=0.004). Anemia was not an independent predictor of all-cause mortality in the 752 patients with severe renal dysfunction (HR 1.08, 95% CI 0.77-1.51, p=0.662) or in the 528 patients with advanced heart failure (HR 0.87, 95% CI 0.56-1.34, p=0.542). HR of anemia was significantly lower in patients with severe renal dysfunction (p=0.022) and advanced heart failure (p=0.002) compared to the rest of the population.
Conclusions: Baseline anemia is an independent predictor of all-cause mortality in outpatients with heart failure. In patients with advanced heart failure or severe renal dysfunction other prognostic variables seem to be more important than anemia. These patients might benefit from different therapeutic strategies in the management of anemia.

P803 Heart failure mortality trends in Europe

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Backgroung: It is claimed that heart failure (HF) prevalence increases with time in relation with the aging of the population. In parallel, the treatment of chronic HF with low EF has improved while the management of acute HF seems not to have improved in the same manner. There may also be some outcome heterogeneity among various European countries because of differences in health systems. Therefore, impact of treatment on HF as cause of death, in Europe, is unknown.
Aim: The aim of this study was to assess the death rates related to HF as underlying cause during the last 20 years in 6 European countries.
Materials and methods: The number of deaths with HF as underlying cause was collected from national statistic organizations in 6 European countries: Greece, England-Wales, Spain, France, Finland and Sweden from 1987 to 2008. Disease coding for HF was based on international classification of diseases (ICD 9th and 10th versions). We computed age-standardized mortality rates per 100 000 inhabitants, using the direct method, on the basis of the 1976 European standard population. Mean age of death with HF as underlying cause was also calculated for the same period.
Results: In Greece, Spain and France, the age-standardized rate of death related to HF as underlying cause was above 40 deaths per 100 000 in 1987 and continuously decreased until 2008. In England and Wales, Finland and Sweden, it was below 30 per 100 000 in 1987 and remained roughly stable until 2008. During the same period, the mean age of death increased from 80.5 to 84.4 years in the total population of the 6 European countries.
Discussion: Patients die older with time in all the 6 countries. Mortality with HF as underlying cause has been reduced in Greece, France and Spain in the last 20 years, whereas it remained stable in England-Wales, Finland and Sweden at a lower level. These differences may be the consequence of differences in health care systems or in HF management among different countries. The age-standardized rate of death related to HF as underlying cause seems to converge to the same level around 25 to 35 deaths per 100 000. One possible reason for that may be the large diffusion of European guidelines on HF management.
Conclusion: Mortality with HF as underlying cause is decreasing in south Europe countries, whereas it remains stable at a low level in northern Europe.

P804 Influence of diabetes, sex, and ejection fraction on the risk of death in patients with heart failure: results from the MAGGIC individual patient meta-analysis

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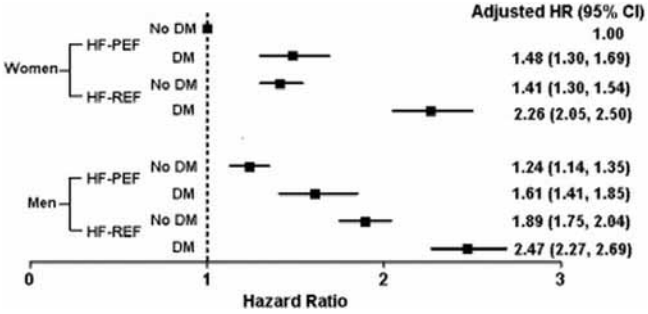
Background: Most of what is known about the impact of diabetes in heart failure (HF) comes from clinical trial populations that included a low percentage of women and fewer patients (pts) with preserved ejection fraction (EF). The aim of the current analysis was to assess the association of diabetes with long-term survival in pts with HF.
Methods: The MAGGIC meta-analysis incorporated patient-level data from 31 studies and determined outcome for pts with HF and preserved or reduced EF (PEF & REF, respectively). All-cause mortality data (3 year follow-up) were analysed using Cox proportional hazards models for pts with and without diabetes adjusted for sex, EF group, age and aetiology of HF and stratified by study.
Results: Data were available for 41,949 pts (28,052 men [67%], 13,897 women). There were 2997 deaths among 9,475 pts with (31.6%), and 7366 among 28460 pts without (25.9%), diabetes, adjusted hazard ratio HR 1.41 (95% CI 1.35-1.47). Diabetes was an independent predictor of cardiovascular mortality, HR 1.51 (95% CI 1.41-1.62). Diabetes was more common among women (25.4%) than in men

(22.8%), a difference observed in pts with REF (26.6% of women, 23.1% of men) and PEF (23.6% of women, 21.7% of men). Diabetes was an independent risk factor for death from any cause, regardless of gender and EF group (Figure). In women, the increase in mortality due to diabetes and due to reduced EF was similar, and presenting both accumulated the risk. Risk of death was higher in men, though sex difference was smaller for diabetic pts, especially for those with reduced EF.



Risk of death from any cause.

Conclusion: Diabetes commonly occurs among pts with HF and is a strong independent risk factor for death from any cause, regardless of gender and EF group.

P805 Hypo- and hyperglycaemia predict outcome in patients with heart failure after acute myocardial infarction: data from EPHESUS

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Background: Hyperglycaemia predicts death in patients with cardiovascular disease. Intensive glucose lowering strategies might increase mortality rates. The present analysis aimed to investigate the prognostic value of post-admission glucose concentration (PG) on outcome in high risk patients with heart failure after acute myocardial infarction (AMI).
Methods: 6496 patients from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) were retrospectively categorized in four groups by plasma glucose concentration ($\leq$4.5 mmol/l, 4.5-5.5 mmol/l, 5.5-8.3 mmol/l, and $>$8.3 mmol/l). We evaluated the time to death from any cause (primary end-point) and time to cardiovascular death or hospitalization (secondary end-point). Inter-groups comparisons were performed by using chi-square or analysis of variance. The association between blood glucose and the primary end-point was assessed using Cox proportional hazards regression models
Results: Hypo- (PG $\leq$4.5 mmol/l) or hyperglycaemia (PG $>$8.3 mmol/l) was prevalent in 509 (8%) and 1588 (24%) patients. PG was significantly associated to all-cause death in a U-shaped manner while cardiovascular death or hospitalization was only increased in hyperglycaemic patients (36% vs. 23% in PG 4.5-5.5 mmol/l; $p<0.0001$). Patients with hypoglycaemia were younger (62$\pm$12 vs. 65$\pm$11 years; $p<0.0001$) with a higher left ventricular ejection fraction (61% vs. 54% of patients with LVEF $\geq$35; $p<0.0001$). Proportion of diabetics was highest in patients with hyperglycaemia (78% vs. 12% in PG 4.5-5.5 mmol/l and 9% in PG $\leq$4.5 mmol/l, $p<0.0001$). In multivariate Cox regression analysis, hypo- (hazard ratio (HR) 1.41; 95% confidence interval (CI) 1.07-1.84; p=0.0131) and hyperglycaemia (HR 1.33; CI 1.07-1.64; p=0.0088) proved to be strong predictors of death of any cause. Only hyperglycaemia was an independent predictor of cardiovascular death and hospitalization (HR 1.33; CI 1.14-1.55; p=0.0003).
Conclusions: In heart failure after AMI, hypo- and hyperglycaemia identify patients with increased risk of death during long-term follow-up.

P806 Interleukin family member ST2 rapidly responds to heart failure treatment and its changes predict one-year mortality

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Background: Soluble ST2, also known as IL1RL1, signaling has been shown to be associated with death in acute heart failure. However, the response of ST2 levels to heart failure treatment and the prognostic implications of this response are largely unknown.
Methods: A total of 207 consecutive patients presenting to the emergency department with AHF were enrolled. Plasma ST2 levels were measured in a blinded fashion at presentation and serially thereafter. The potential of plasma ST2 changes from presentation to day 2 to predict 1-year mortality was assessed as the primary endpoint. Biomarker sampling at both timepoints was complete in 137 patients.
Results: Overall 37 patients (27%) patients died during the observational period (median follow up: 360 days [120-380]). These patients were more likely to suffer from pre-existing chronic cardiac or kidney disease. At presentation, ST2 levels were significantly higher in decedents than in survivors (median 121 vs. 64 ng mL^{-1}, $P<0.01$) and decreased significantly during the first two days (median change: -33%). Patients dying during the follow-up period experienced a significantly lower decrease in ST2 levels compared to survivors (median change: -18% vs -37%, $p<0.01$). In a logistic regression analysis the percentage ST2 change over the first two days significantly predicted one-year mortality in univariate analysis (p=0.007). This predictive potential remained after the adjustment for ADHERE heart failure risk factors (creatinine, urea, BNP, blood pressure) (HR for an increase of 10%: 1.11 (95%CI 1.00-1.24); p=0.04). Using a categorical division between patients successfully responding to treatment (decrease $<$50%), intermediate responders (decrease -25% - -49%) and non-responders (increase or decrease below 25%) clearly separated survivors from non-survivors in a Kaplan-Meier analysis (p log rank= 0.03). Patients responding to treatment experienced a one year mortality rate of 11% compared to a staggering 41% mortality rate in non-responders.
Conclusion: Plasma ST2 levels respond rapidly to heart failure treatment. The extent of ST2 changes within the first two days might provide an additional tool for treatment guidance.

P807 Prognostic significance of change in diastolic function defined by mitral Doppler - a prospective cohort study - the Tromsø Study 1994-2009

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Diastolic dysfunction (DD) of the left ventricle (LV) is a known risk factor for all cause death. Few have documented change in diastolic function (DF) over time and its prognostic significance.
A population sample of 1337 subjects aged $\geq$55 years with LV ejection fraction $\geq$0.5 had mitral Doppler echocardiography done in 1994 and 2001. Validated cut-off values for mitral EA-ratio and mitral E-wave deceleration time (EDT) were used to classify the subjects into five groups with increasing degree of DD from group 1 (normal) to 5. Group 1 was defined as EA-ratio 0.75-1.50 and EDT $\geq$140ms, group 2 EA-ratio$\geq$1.51 and EDT$\geq$140ms, group 3 EA-ratio $\leq$0.74 and any EDT, group 4 EA-ratio 0.75-1.50 and EDT$\leq$139ms and group 5 EA-ratio$\geq$1.51 and EDT$\leq$139ms.
1292 subjects (96.6%) could be classified according to these groups both in 1994 and 2001. Change in group from 1994 to 2001 was recorded and subjects were classified as having stable, improved or deteriorated DF.
End-point was all-cause mortality with follow-up until 31 Jan 2009. There were 191 deaths of all-causes. Cox regression analysis was used to calculate hazard ratios (HR) for change in group with 95%-confidence interval (CI) for all cause mortality and p-values for trend.

Change in group of diastolic function	n	HR (CI) Model I*	HR (CI) Model II**
Improved	142	0.76 (0.44-1.30)	1.15 (0.72-1.85)
Stable	869	1	1
Deteriorated by 1 group	58	1.19 (0.58-2.43)	0.96 (0.46-2.01)
Deteriorated by 2 groups	197	1.65 (1.13-2.41)	1.08 (0.68-1.73)
Deteriorated by 3 groups or more	26	2.56 (1.24-5.28)	1.28 (0.51-3.18)

*Model I: Adjusted for age, sex and group of diastolic function in 1994 - p-trend = 0.014. **Model II: Adjusted for age, sex and group of diastolic function in 2001 - p-trend = 0.943.

The table displays that when adjusted for age, sex and degree of DF in 1994 (model I), there was a significant trend towards increasing mortality with deterioration in DF. However, adjusted for degree of DF in 2001 (model II) this effect was absent. In conclusion, this illustrates that the degree of diastolic function has predictive power, whereas change in DF per se does not.

P808 Baseline characteristics, adverse events and hospitalizations indicate an increased risk of death in patients with heart failure. An analysis of the TIME-CHF trial

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Background: Risk factors for death in patients (pts) with heart failure (HF) have been defined but vary with populations studied. Whether death is preceded by an increased rate of clincial events has not been well characterized.

Methods: To further clarify these relations, baseline characteristics as well as adverse events (AE) and hospitalizations within 60 days preceding death were compared with those of the survivors within a similar time period in the TIME-CHF study, a randomized controlled multicenter trial comparing a standard symptom-guided with an intensified, NT-BNP guided medical therapy in 622 pts ≥60 years with symptomatic HF NYHA ≥II, a history of HF hospitalization <1 year and an elevated NT-BNP level.
Results: During the 18-month follow-up, 132 (21%) of the pts died. In multivariable analysis, coronary disease as primary cause of HF (odds-ratio [OR]=2.54 [95%-CI 1.57-4.10]), log10 of NT-BNP (2.79 per factor 10 [1.55-5.01]), presence of pacemaker (2.35 [1.35-4.10]), systemic inflammatory disease (3.13 [1.37-7.13]), anemia (1.67 [1.06-2.63]), history of cancer (1.89 [1.07-3.33]), Charlson score (1.16 per score point [1.01-1.32]) and serum creatinine (1.06 per 10μmol/l [1.00-1.13)] were the baseline characteristics associated with increased risk of death. Mode of death was found to be cardiovascular (CV) in 77% (sudden death 21%, circulatory failure 50%, vascular 6%), non-CV in 18% and unknown in 5%. Pts who died experienced a median of 4 AE (IQR 1-7) <60 days prior to death compared to 0.7 (0.4-1.4) during randomly selected 60 days in pts who survived ($p<0.0001$). This was true for HF related AE (1 [0-2] vs 0.1 [0-0.2]), CV AE (2 [1-3] vs 0.3 [0.1-0.6]), and non-CV AE (2 [0-4] vs 0.4 [0.2-0.8]); all $p<0.0001$. Pts who died were more often hospitalized <60 days prior to death (median 1 [IQR 0-1]) than those surviving (0.1 [0.0-0.2]), $p<0.0001$. Significant differences were seen for CV, cardiac and HF related hospitalizations ($p<0.0001$), but not for non-CV hospitalizations (p=0.1). Frequency of AE varied between different modes of death.
Conclusions: In TIME-CHF, simple clinical and biological variables were associated with death. In addition, pts who died were characterized by frequent AE and hospitalizations prior to death. Timely recognition of these factors might improve identification, management and outcome in pts with HF.

P809 High sensitivity troponin T serum levels and prognosis in ambulatory patients with heart failure

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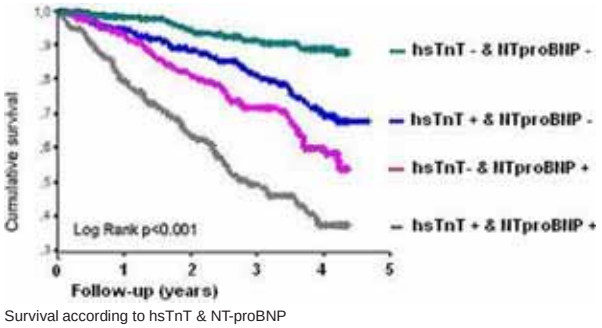
Background: Heart failure (HF) remains a clinical syndrome with high mortality and therefore is crucial to identify those patients with poorer prognosis. High sensitivity Troponin T (hsTnT) is a novel biomarker that provides prognostic information in several clinical settings.
Aim: To examine whether hsTnT levels improve risk stratification in a non-selected outpatient population with HF, and to test if the combination of hsTnT + NT-proBNP is actually better than either separately. Both hsTnT and NT-proBNP were measured from -80°C stored plasma samples via a sandwich monoclonal immunoassay.
Patients: 876 patients (71.9% men, median age 70.3 years [IQR 60.5-77.2]) were studied. Aetiology of HF was mainly ischemic heart disease (52.1%). Median LVEF was 34% [IQR 26-43%]. Most patients were in NYHA class II (65.5%) or III (26.3%). Median follow-up was 33 months [IQR 15.6-39.4].
Results: 238 patients died during follow-up. Both NT-proBNP (HR 1.00004 [1.00003-1.00005], $p<0.001$) and hsTnT (HR 1.004 [1.002-1.005], $p<0.001$) were good prognostic predictors. After adjustment for other significant clinical and therapeutic variables, both biomarkers remained as independent prognostic factors. When patients were grouped according to their NT-proBNP and hsTnT values below vs equal or above the median values, the combination of the two biomarkers increased significantly their prognostic discriminator capacity, as shown in Kaplan-Meier survival curves (figure). Considering the group of patients with both values below median as the reference, the HR for group with both NT-proBNP and hsTnT equal or above the median values was 5.50 [3.87-7.82], $p<0.001$.



Survival according to hsTnT & NT-proBNP

Conclusion: The combination of hsTnT and NT-proBNP increased significantly their long-term prognostic predictor accuracy in unselected outpatients with HF.

P810 Bioelectrical impedance-derived oedema index provides 6-month prognostic value in patients hospitalised due to acute heart failure

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Background: Bioelectrical impedance analysis (BIA) is a commercialized, noninvasive, inexpensive, and reproducible property-based modality for estimating fluid state. Yet, it has not been tested whether the oedema index (OI) derived from BIA provides 6-month prognostic values in patients hospitalised due to acute heart failure.
Methods: This study included 3 parts. Part 1: To determine the range of OI in different patient population, the distribution of OI was estimated in 5 groups: normal (CON), hypertensive (HTN), stable heart failure (SHF), acute heart failure (AHF), stable acute heart failure (SAHF). Part 2: To test whether OI differs in patients with different HF stages, the distribution of OI was estimated in patients with HF from stage A to D. Part 3 was designed to estimate the 6-month prognostic value of OI in patients hospitalised due to acute pulmonary oedema. From January 1, 2008 to January 31, 2010, 98 patients hospitalised due to acute cardiogenic pulmonary oedema were consecutively enrolled.
Results: In part 1 study (n=214), compared to the HTN group, both AHF and SAHF groups had higher OI ($p<0.0001$ and p=0.029, respectively). The OI was highest in the AHF group. In part 2 study (n=205), compared to the patients at stage A, patients at stage C or D had higher OIs (p=0.002 and $p<0.001$, respectively). In study part 3, patients were separated into OI >0.390 (n=57) and OI 0.390 were older, had lower blood albumin levels, shorter 6-min walking distance, higher BNP levels within 24h after admission, and higher incidence of diabetes mellitus and NYHA functional class. Based on the OI before discharge, univariate analysis showed that OI >0.390 predicted a higher incidence of re-hospitalisation, emergency room visits, or composite events (both HF related and all cause-related) (all $p<0.05$). Albumin and BNP levels and NYHA functional class were also associated with poor outcomes. In terms of re-hospitalisation, multivariate analysis showed that OI >0.390 before discharge was an independent predictor of events (odds ratio = 3.3, OR=1.4~7.7, p=0.005).
Conclusions: Fluid overload is the most frequently encountered aetiology of re-hospitalisation in patients with HF. BIA can sensitively discriminate the optimal fluid status at different stages of HF. Our data demonstrated that OI provides 6-month prognostic values in patients hospitalised due to acute heart failure.

P811 Baseline blood urea nitrogen as a marker for predicting cardiac events in patients hospitalized for acute heart failure syndrome - beyond other renal variables -

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Purpose: Previous studies reported elevated baseline blood urea nitrogen (BUN) value was associated with high mortality in acute heart failure syndrome (AHFS). However, there are few studies comparing BUN and other renal variables, especially regarding cardiac events. We aimed to assess the precision of BUN at admission as a predictor of in-hospital mortality for AHFS, compared with other renal variables at admission, using the data from ATTEND Registry, which is multicenter prospective observational cohort study of AHFS in Japan.
Methods: We examined 3154 patients that excluded patients on dialysis. The prognostic importance of four variables of renal function –BUN, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), and BUN-SCr ratio (BUN/Scr)- at admission was assessed using receiver operating characteristic (ROC) curve analysis, which end points were in-hospital total and cardiac death.
Results: The ROC curves for in-hospital death were shown (Figure 1). Areas under the curve (AUCs) for BUN, SCr, eGFR, and BUN/Cr at admission were 0.692 (SE 0.0193, 95%CI 0.675-0.708), 0.610 (SE 0.0211, 95%CI 0.592-0.627), 0.629 (SE 0.0208, 95%CI 0.612-0.646), and 0.622 (SE 0.0196, 95%CI 0.605-0.639) in in-hospital total death, respectively. In cardiac death, AUCs were 0.703 (SE 0.0241, 95%CI 0.686-0.719), 0.621 (SE 0.0256, 95%CI 0.603-0.637), 0.642 (SE 0.0256, 95%CI 0.625-0.658), and 0.637 (SE 0.0235, 95%CI 0.620-0.656),

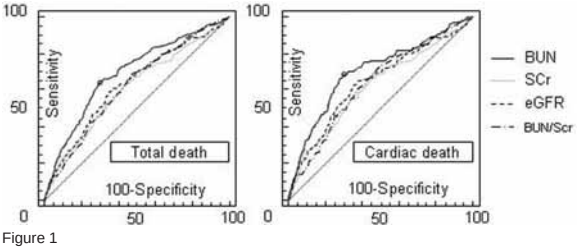

Figure 1

respectively. The optimal cut-off point for BUN value was 27.3mg/dl (Sensitivity 63.9%, Specificity 70.3%).
Conclusion: Baseline BUN value was the most useful prognostic marker for in-hospital mortality, especially cardiac events, in AHFS patients, compared with other variables of renal function, suggesting that BUN should be used more for the better management in AHFS.

P812 Is left ventricular mechanical dyssynchrony independently associated with outcome? A follow-up study of 631 patients undergoing gated positron emission tomography

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Background: The prognostic value of LV mechanical dyssynchrony independent of other determinants such as EF and defect size remains undefined.
Methods: Consecutive patients with LVEF≤35% who underwent stress/rest Rb82 gated PET between March 2006 and November 2010 were followed for cardiac death (primary endpoint) and all-cause mortality (secondary endpoint) over of 1.3±0.7 years. Patients with cardiac resynchronization therapy were excluded. PET images were analyzed for LV volumes, EF, perfusion defects, and dyssynchrony index (standard deviation (SD)) using Corridor4DM software.
Results: Of 631 pts with LVEF ≤35% (age 61±13 y, 56% men), 86% had ischemic cardiomyopathy, 11% had LBBB, and fixed perfusion defect size (PDS) was 20±20%. The mean SD was significantly higher than normal (defined from 110 pts with LVEF ≥50%, normal perfusion and QRS<120 ms) (49°±20° vs. 13°±4.0°, P<0.0001). Of 81 cardiac deaths (13%), 67% were from pump failure, 22% from arrhythmias and 11% from coronary artery disease. Using a SD cut-off of 43° to define significant dyssynchrony, patients with SD ≥43° (N= 362) had worse outcome than those with SD<43° with (cardiac death 16% vs. 9%, log rank P=0.03). However, Cox analysis showed survival to be independently associated with age (HR [95%CI] of 1.05 [1.03-1.07]), EF (0.95[0.92-0.98]), fixed PDS (1.02 [1.00-1.03]) and history of SCD (2.20 [1.00-4.84]), but not SD. Similarly, although SD showed a univariate association with the 121 (19%) pts who died from any cause (23% vs. 14%, log rank P=0.015), only age, EF and fixed PDS were independently associated with all-cause death.

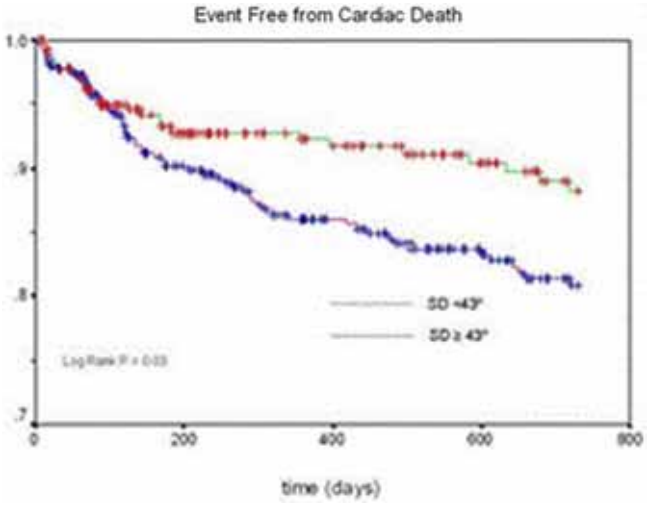

Figure 1

Conclusion: In this group with predominant ischemic cardiomyopathy, the association of LV mechanical dyssynchrony with worse outcome was mainly driven by advanced age, worse LVEF and scar burden.

P813 Short and long-term outcome of impedance-guided preemptive therapy provided to prevent acute heart failure in the course of acute myocardial infarction

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Background: Patients sustaining an acute myocardial infarction (AMI) frequently develop acute heart failure (AHF) during their hospitalization. Currently, treatment is initiated only after the appearance of overt signs of lung fluid overload. Ongoing monitoring of the status of lung fluid content (LFC) in AMI patients may enable the prediction of impending AHF and prompt early therapy, thus precluding AHF and improving outcomes.
Aims: We sought to find out whether non-invasive lung impedance (LI) guided preemptive treatment of AMI patients improves clinical outcomes.
Methods: LI was determined by using a new method to measure the electrical resistance of the lungs based on detection of transverse propagation of electromagnetic energy through chest. Any increase in LFC results in LI decrease. Previously we have found that a decrease of 12-14% from normal LI value reflects the transition from interstitial to alveolar edema. In the present study we randomized 213 patients (2:1 ratio) admitted for their first AMI with no chronic heart failure (CHF) who expressed a >12% LI decrease to conventional therapy or LI-guided preemptive treatment.
Results: 142 patients were treated conventionally (Group1) and 71 preemptively according LI (Group2). Groups were compatible with regard to clinical and laboratory parameters, (age: 61.3±14.1 vs 59.9±11.5, LVEF: 45.9±12.4% vs 47.1±11.8%, CPKmax: 2078±1938 vs 1927±1622). In Group1, AHF treatment was begun only at symptom onset. As a result, all patients developed some degree of AHF. In Group 2, preemptive treatment halted AHF development in 92% of patients. Hospital stay in Group1patients was longer 1.4-fold (p<0.0001). Readmissions for cardiovascular causes within the first year after discharge was 1.5 times more common in Group1 (p<0.01). During 6 years mean follow-up progression to CHF was 2-fold and mortality 2.8-fold higher in Group1 (p<0.01). Multivariate logistic regression analysis with age, LVEF and CPKmax as non dependent variables was performed. All differences between Group1 and 2 remained significant. LI-guided therapy in Group2 reduced progression to CHF during a 6-year period, OR=0.37 [CI: 0.17-0.8, p=0.01] and mortality OR=0.34 [CI: 0.12-0.92, p<0.0001]. Factors that prolonged hospital stay in both groups were age (F=18.5), CPKmax (F=10.7), LVEF (F=9.6) while preemptive therapy reduced it (F=15.8).
Conclusions: LI-guided preemptive therapy halts progression to AHF in 92% of patients, and significantly reduces hospital stay, recurrent admissions, evolution of CHF and mortality. Age determined hospital stay in both groups.

P814 Prognostic impact of pulmonary function in systolic heart failure

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Purpose: We investigated the prognostic impact of pulmonary function on mortality in systolic heart failure (SHF).
Methods: Consecutive outpatients were evaluated six months after hospitalization for congestive SHF (left ventricular ejection fraction (LVEF) ≤40%). Evaluation six months after discharge included clinical assessment of heart failure symptoms and performance of echocardiography and pulmonary function testing (PFT). Obstructive ventilatory disorder (OVD) was diagnosed if forced expiratory volume in the first second (FEV1) divided by forced vital capacity (FVC) was <0.7.
Results: We included 635 patients, mean age 65±12 years, and 76% male. During mean follow-up time of 23±11 months, 138 patients died (22%). Death was associated with age (70±11 vs 64±12 years), higher NYHA functional class (III/IV: 44 vs 16%) and lower LVEF (38±12 vs 43±11%). Furthermore, mortality was associated with lower FEV1 (79±24 vs 92±22% of predicted), FVC (80±20 vs 92±32% of predicted), FEV1/FVC (0.75±0.11 vs 0.79±0.09) and total lung capacity (TLC, 91±15 vs 95±16% of predicted), all p<0.01. Adjusted for age and sex, decade increase of percent predicted in FEV1, FVC and TLC was associated with lower mortality (all HR 0.7, 95%CI 0.6-0.9, p<0.01 for all) but not FEV1/FVC (HR 0.7, 95%CI 0.7-1.1). Nevertheless, presence of OVD was predictive for negative outcome (HR 1.6, 95%CI 1.1-2.4, p=0.016) and was more pronounced if combined with reduced TLC (Figure) which almost triples the risk of mortality (HR 2.8, 95%CI 1.5-5.1, p=0.001).
Conclusion: Reduced airflow and lung volumes in PFT are associated with increased mortality in SHF patients. Patients with OVD are at special risk if combined with restriction.

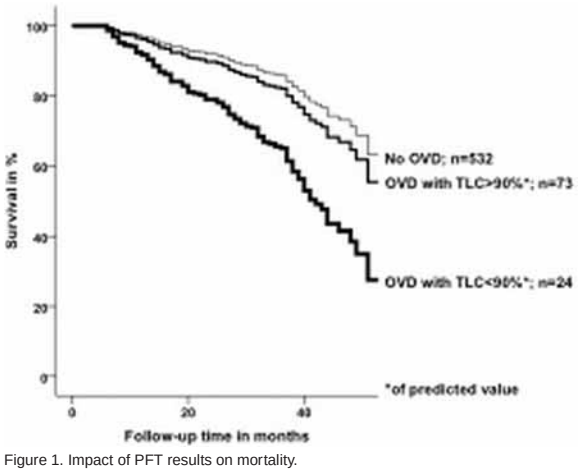

Figure 1. Impact of PFT results on mortality.

P815 Albuminuria as prevalence and predictor in chronic heart failure patients

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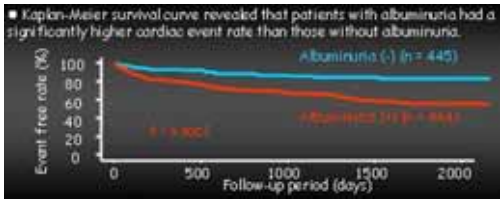
Background: Albuminuria is associated with increased risk for cardiovascular morbidity and mortality. Albuminuria might be a marker of the various pathophysiological changes that arise in chronic heart failure (CHF) patients. However, the relation between albuminuria and CHF has not been well described yet. Therefore, the purpose of this study was to assess the prevalence and predictor of albuminuria in CHF patients.
Methods and results: We measured albuminuria in 889 CHF patients. As a result, 445 (50%) patients had normoalbuminuria, 316 (36%) had microalbuminuria, and 128 (14%) had macroalbuminuria. The prevalence of microalbminuria and macroalbuminuria was similar in patients with reduced and preserved left ventricular ejection fractions. Patients with albuminuria were older, had more severe NYHA functional class, and worse renal function than those with normoalbuminuria. There were 168 cardiac events during follow-up period. Urine albumin level was higher in patients with cardiac events than those in event free patients. Kaplan-Meier analysis clearly demonstrated that the albuminuria group had a significantly higher incidence of cardiac events than the normoalbuminuria group. Albuminuria was significantly associated with increased risk of cardiac events even after adjustment for other prognostic variables including renal function, diabetes, and hemoglobin A1c. The adjusted hazard ratio for the cardiac events in patients with microalbuminuria versus normoalbuminuria was 3.73 ($P<0.0001$) and for macroalbuminuria versus normoalbuminuria was 4.15 ($P<0.0001$).



Kaplan-Meier analysis.

Conclusions: Albuminuria is a powerful and independent predictor of prognosis in CHF patients and may be useful for risk stratification of CHF patients.

P816 Gender-related differences in patients with acute heart failure: clinical characteristics and predictors of in-hospital mortality

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Purpose: We sought to investigate the gender-related differences in clinical phenotype, in-hospital management and prognosis of acute heart failure (AHF) patients included in ALARM-HF survey.
Methods: The ALARM-HF was a retrospective observational survey that included a total of 4953 patients hospitalized for AHF in 666 hospitals (cardiology deparments:66%; intensive care units: 33%) in 6 European countries, Mexico and Australia.
Results: Men (n=3128) with AHF had at admission lower left ventricular ejection fraction (LVEF) (36±13% vs 41±14%, $p<0.001$), lower systolic blood pressure (SBP) ($p<0.05$), higher creatinine levels ($p<0.001$) and exhibited more frequently positive plasma troponin levels (31% vs 27%, $p<0.001$) than women (n=1825). Regarding the comorbidities, women had more frequently diabetes (47% vs 43%, p=0.02), obesity ((30% vs 25%, $p<0.001$), anemia (17% vs 13%, $p<0.001$) and depression (11% vs 7%, $p<0.05$). Women exhibited higher rates of atrial fibrillation episodes as precipitating factor of AHF (45% for women vs 38% for men, $p<0.001$), while men exhibited more frequently an acute coronary syndrome as a cause of AHF hospitalization (41% for men vs 30% for women, $p<0.001$). Men received more frequently iv nitrates ($p<0.01$), dobutamine (p=0.06), vasoconstricting agents ($p<0.05$) and levosimendan ($p<0.05$) as well as interventional treatment with intra-aortic balloon counterpulsation (6% vs 3%, $p<0.001$), PCI (16% vs 8%, $p<0.001$) and CABG ($p<0.05$). In-hospital mortality was higher in women but not statistically significant (10.5% for men vs 11.1% for women, p=NS), while men exhibited shorter ICU length stay ($p<0.05$). The multivariate analysis revealed that age ($p<0.001$), LVEF (p=0.004), SBP at admission ($p<0.001$), serum creatinine >1.5 (p=0.023) and existence of diabetes (p=0.02) and anemia (p=0.04) were independent predictors of in-hospital mortality in males. SBP at admission ($p<0.001$) and serum creatinine>1.5 (p=0.012) were also independent factors of adverse outcomes in females, while SPO2 (p=00.7), history of hypertension (p=0.02) and smoking p=0.015), and the existence of an acute coronary syndrome (p=0.008) as precipitating factor were some additional prognostic factors.
Conclusion: There were different clinical characteristics as well as in-hospital management between males and females with AHF in ALARM-HF survey, although their in-hospital mortality did not significantly differ. Females had more frequently preserved systolic function and multiple co-morbidities than males. Finally, SBP and renal function at admission seem to be common prognostic factors in males and females.

P817 Depressed stress-corrected midwall fractional shortening as independent predictors of 1-year mortality in patients with heart failure and preserved ejection fraction: a population-based study

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Background and aims: Impairment of myocardial contractility may not be evident on left ventricular (LV) ejection fraction (EF) assessment as fractional shortening based on endocardial contours may be amplified by concomitant longitudinal and transverse myofiber contraction. This shortcoming may be rectified by using LV stress-corrected midwall fractional shortening (sc-mFS) for assessment of myocardial contractility in cases where EF appears preserved. We aimed to determine correlation between sc-mFS and 1-year mortality in patients with heart failure and preserved ejection fraction (HFPEF).
Methods: We conducted a prospective study with 526 patients hospitalized due to HF [199 HFPEF; 327 HFREF (HF with reduced EF)] who underwent echocardiography. M-mode LV end-diastolic (d) and end-systolic (s) LV internal diameters (LVID), septal (IVST) and posterior wall (PWT) thicknesses, as well as Doppler and tissue Doppler measurements were assessed. mFS was calculated as {(LVIDd + IVSTd/2 + PWTd/2) – (LVIDs + Hs/2)}/(LVIDd + IVSTd/2 + PWTd/2) × 100%; Hs/2 denotes the mean mid-myocardial to endocardial wall thickness such that both resultant inner and outer LV shell volumes remain constant during the cardiac cycle. sc-mFS was determined as a percentage of that predicted for any given circumferential end-systolic wall stress (cESS) using the regression derived from a normal control population (mFS(pre) = 19.42 – 0.004 × cESS). cESS was calculated as SBP × $(LVIDs/2)^2$ × [1 + $(LVIDs/2 + PWT)^2$/$(LVIDs/2 + PWTs/2)^2$]/{[$(LVIDs/2 + PWTs)^2$ – $(LVIDs/2)^2$]}, where SBP is systolic blood pressure.
Results: Patients with HFNEF were older and more likely to be female compared to HFREF (median age (IQR): 75 (69-82) years vs 69 (63 - 76) years; $P<0.0001$; male/female: 84/118 vs 225/107, $P<0.0001$). 81 patients (15.4%) died at 1-year follow up; 1-year mortality rates were similar in HFPEF and HFREF (14.1% vs. 16.2%; P=0.51). sc-mFS was impaired in HFPEF and HFREF (80.27±20.99% vs 55.01±20.68, $P<0.0001$). Multivariable cox-regression analysis identified sc-mFS (<76%) (Hazard ratio [HR]: 2.25; 95% confidence interval [CI]: 1.0-5.08, P=0.04) and creatinine (>120 umol/L) (HR:3.06; 95% CI:1.30-7.21, P=0.01) as independent predictors of 1 year mortality in HFPEF after adjusting demographic, concomitant medical conditions, echo Doppler and tissue Doppler indices. In contrast. sc-mFS is not associated with adverse outcome in HFREF.
Conclusion: In HFPEF, Depressed sc-mFS, and not other echo-Doppler and tissue Doppler indices is strongly associated with 1-year mortality in HFPEF.

P818 Anaemia independently predicts outcome in patients with heart failure with preserved and reduced ejection fraction: a MAGGIC sub-group analysis

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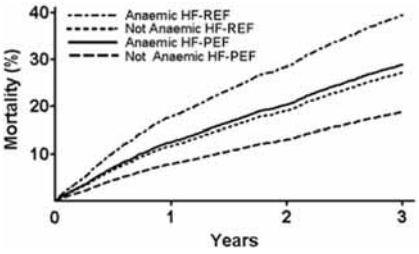
Background: Anaemia is common in heart failure (HF). A recent meta-analysis showed that anaemia predicts mortality in patients (pts) with HF and preserved (HF-PEF) and reduced (HF-REF) ejection fraction. But it did not include patient-level data excluding the possibility of covariate analysis; had heterogeneity of entry criteria and definition of anaemia; and precluded investigation of other prognostic factors. We evaluated the prognostic role of anaemia alongside other covariates, especially in HF-PEF.
Methods: MAGGIC has collated patient-level data from prospective studies of HF that recruited both pts with HF-PEF and HF-REF. This sub-group analysis included pts with haemoglobin (Hb) data. Cox proportional hazards analysis derived adjusted mortality curves and the multivariable hazard ratio (HR).
Results: Among 7814 pts (26% HF-PEF, mean age 67yrs, 35% female) for whom Hb data were available, 2600 (33%) had anaemia (Hb<130g/L men, <120g/L women). There were 1549 deaths. Anaemia was associated with higher all cause mortality (adjusted by age & gender) in both the HF-PEF and HF-REF pt groups (Figure). Multivariable analysis showed mortality was independently related to anaemia (HR 1.41 (95%CI:1.26,1.57)), age (HR 1.03 (1.03,1.04)), gender (HR 1.30 (1.17,1.46)), atrial fibrillation (HR 1.19 (1.05,1.35)), ischaemic aetiology (HR

1.22 (1.09,1.36)), diabetes (HR 1.19 (1.06,1.35)), REF (HR 1.47 (1.29,1.68)), and eGFR (HR 0.63 (0.56,0.71)), but not hypertension. Similar results were found for cardiovascular (CV) death (HR 1.28 (1.06,1.55)). No significant interaction of eGFR & anaemia with all cause mortality.



Conclusion: Anaemia is an independent predictor of all cause (and CV) 3-year mortality in pts with HF-PEF and HF-REF. Importantly, this relationship is independent of the impact of other covariates.

P819 Additive prognostic value of diastolic dysfunction and coronary flow reserve in non-ischemic dilated cardiomyopathy

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Background: Coronary flow reserve (CFR) on left anterior descending (LAD) can be reduced in non-ischemic dilated cardiomyopathy (DCM).
Aim: To assess the additive prognostic value of CFR in LAD and resting severe diastolic dysfunction to identify responders to CRT.
Methods: One hundred twenty-nine DCM patients (pts, 87 men, 62±12 years, ejection fraction: 33±7%) underwent dipyridamole (0.84 mg/kg in 6') stress echo. CFR was defined as the ratio between maximal vasodilation and rest peak diastolic flow velocity in LAD, and diastolic dysfunction as the presence of resting irreversible restrictive transmitral pattern.
Results: We divided DCM pts in 4 groups, according to normal (>2 56 pts) or abnormal (≤2 73 pts) CFR on LAD and absence (88 pts) or presence (41 pts) of restrictive transmitral pattern. In pts with abnormal CFR on LAD, the additional presence of restrictive patterns was associated to lower ejection fraction at rest (26±5% vs 31±7% p=0.007) and at peak stress (30±5% vs 36±8% p=0.03) and larger end-systolic volume at rest (149±55 ml vs 185±48, p=0.030). During median follow-up of 30 months, 19 deaths, and 33 cardiac adverse events. Abnormal CFR on LAD and diastolic dysfunction were associated with poorer event-free survival (Log Rank: 33.1, p<0.0001, Figure), with additive negative prognostic value in pts with CFR on LAD <2 and the presence of restrictive pattern.

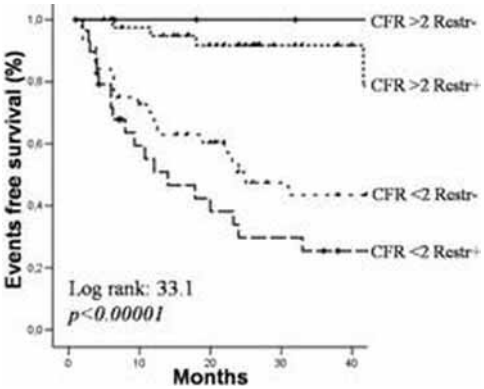

Figure 1

Conclusions: In DCM patients with reduced CFR left anterior descending territory during vasodilator stress, the associate presence of restrictive transmitral pattern is an additive independent prognostic marker of bad prognosis.

P820 Subclinical thyroid dysfunction in heart failure: always prognostically relevant?

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Purpose: Therapeutic and prognostic implications of subclinical thyroid dysfunction in patients with heart failure (HF) are unclear. We investigated the differential prognostic impact of euthyroidism, euthyroid sick syndrome (ESS) and subclinical thyroid dysfunction in patients with systolic HF.
Methods: Thyroid function was evaluated in 865 patients participating in a randomized trial on the effects of a HF disease management program. Subjects were recruited in-hospital after recompensation. All subjects exhibited left ventricular ejection fraction (LVEF) <45%, and were characterized in detail with regard to HF history and status, medication, comorbidities and routine laboratory. 103 subjects were excluded from analysis due to overt clinical thyroid dysfunction (n=14), or intake of thyreostatic agents or amiodarone (n=89). Remaining 762 patients were divided into 4 groups: euthyroidism (thyroid hormones within normal ranges); ESS (fT3<2.7pmol/l & TSH<4.0mU/l); subclinical hyperthyroidism (scHyper; TSH<0.3mU/l & normal fT3/fT4); subclinical hypothyroidism (scHypo; TSH>4.0mU/l & normal fT3/fT4). Survival analysis was performed using Cox regression.
Results: The table shows group sizes with age and outcome information. Subclinical thyroid dysfunction was present in 108 (14%) of patients at baseline. No differences were found between groups regarding NYHA class (P=0.38), LVEF (P=0.69), heart rate (P=0.34), LDL (P=0.51) and triglycerides (P=0.43). Patients with ESS had lower hemoglobin (P<0.001) and higher creatinine (P=0.023). Compared to euthyroid subjects, risk of death was 3-fold and 1.5 increased in patients with ESS or scHyper, respectively, whereas no risk increase was observed in scHypo.

Group characteristics

Group	N (%)	Mean (SD) age at baseline (y)	Median follow-up (y)	All-cause death (%)	HR (95% CI)	P
Euthyroidism	641 (84)	70 (13)	2.0	33	Referent	
Euthyroid sick syndrome	13 (2)	75 (10)	1.2	62	3.2 (1.6–6.4)	0.001
Subclinical hyperthyroidism	74 (10)	74 (9)	2.5	53	1.5 (1.1–2.2)	0.016
Subclinical hypothyroidism	34 (4)	64 (12)	1.6	32	0.9 (0.5–1.7)	0.840

HR, hazard ratio; 95% CI, 95% confidence intervals.

Conclusion: In this large well-characterized HF cohort, ESS was infrequent but a strong indicator of a grave prognosis. ScHyper, but not scHypo, also indicated an increased mortality risk. Whether this is (partially) due to genuine thyroid disease and its potential therapeutic implications need to be addressed by future studies.

P821 Fluid restriction improves cardiac function and survival in rats with chronic heart failure

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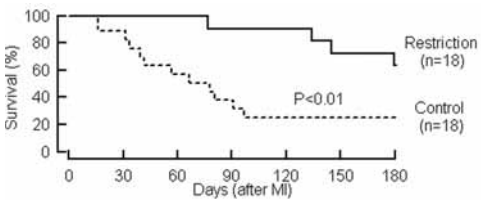
Patients with chronic heart failure (CHF) are often prescribed a fluid restriction of 1-1.5L/day, but there is no scientific evidence that based on neither clinical nor animal study for this prescription. This study was aim to investigate the effects of fluid restriction on cardiac function and survival in the rat model of CHF.
Methods: Myocardial infarction was induced in male rats by ligation the proximal left coronary artery. Survived rats were randomly assigned to control and fluid restriction group. The drinking flow was monitored and controlled by a feedback computer program. The intake volume was individualized by the body weight (3.75mL/kg·30min). Cardiac function was evaluated by the approved telemetry technique for artery pressure recording and echocardiography in anesthesia follow with blood sampling for BNP assay.
Results: By modulating the drinking rate, daily fluid consumption decreased by 37% (97±26 vs. 61±5.9 ml/kg/day, n=10, p<0.01). After 4-weeks fluid restriction, left ventricular ejection fraction increased (24.5±6.1 vs. 30.3±6.6%, n=8; p<0.05); plasma BNP level decreased (481±64 vs. 375±34 pg/ml, n=8; p<0.05). Meanwhile hemodynamics significantly improved in the conscious rats that characterized by increased systolic pressure (99±4.3 vs. 107±4.4 mmHg, n=8; p<0.01); associated with slowdown of heart rate (361±19 vs. 319±7bpm; p<0.01). Chronic fluid restriction markedly suppressed the mortality rate of CHF rats (Fig).



Conclusion: This is the first study designed to mimic the clinical condition of human CHF for assessing the outcomes of fluid restriction in the rat model of CHF. The results showed that simple controlling the volume of drink a time led to decrease daily fluid consumption, then improved cardiac function and survival rate in CHF rats.

P822 Nampt/Visfatin expression is protective in chronic heart failure

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Background: Nampt (Nicotinamide-Phosphoribosyltransferase)/Visfatin is an intra-and extracellular enzyme in the NAD+ salvage pathway that recently has been shown to critically regulate NAD+ and ATP contents, thereby playing an essential role in mediating cell survival by inhibiting apoptosis and stimulating autophagic flux in cardiac myocytes in vitro. Preventing downregulation of Nampt inhibits myocardial injury in response to myocardial ischemia and reperfusion in mice. Therefore, Nampt is an essential gatekeeper of energy status and survival in cardiac myocytes. Here, we investigated for the first time whether Nampt/Visfatin plays a role in patients with chronic heart failure (CHF).
Methods and results: 100 patients were enrolled in our study and divided into a control (n=15), a dilated cardiomyopathy (DCM, n=40) and an inflammatory cardiomyopathy (DCMi, n=45) group according to their hemodynamic and cardiac inflammatory parameters. Plasma Nampt/Visfatin levels were measured at enrollment. A follow up examination was performed after 6 months to elucidate the changes in hemodynamics and inflammation. Nampt/Visfatin plasma concentrations were not different between the DCM and DCMi groups (DCM: 1.53±1.29 ng/mL; DCMi: 1.4±1.22 ng/mL, $p>0.05$), indicating that cardiac mononuclear inflammation does not regulate the expression of the cytokine. However, patients with DCM and DCMi had significantly increased plasma Nampt/Visfatin levels at enrollment (control: 0.55±0.29 ng/mL, $p<0.05$). Moreover, patients with DCM and DCMi that showed increased Nampt/Visfatin levels at the beginning of the study developed a significant better improvement of hemodynamic parameters as measured by LVEF (DCM: 28.7±4.3% vs 9.2±0.9%; DCMi: 30.3±5.1% vs -0.9±0.5%) and LVEDD at 6 months follow up. Moreover, a multivariate regression analysis confirmed the positive predictive value of Nampt/Visfatin on prognosis in these patients.
Conclusion: This is the first human study to demonstrate a protective effect of high extracellular Nampt/Visfatin concentrations on outcome in patients with CHF. Protection of Nampt/Visfatin is independent of cardiac inflammation and might be mediated by increasing stress resistance and improvement of energy status within the heart.

P823 Does hypertension affect outcome of patients with acute decompensated heart failure (data from the AHEAD registry)?

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Purpose: Although higher blood pressure (BP) on hospital admission in patients hospitalized for acute heart failure (AHF) is associated with better outcome, the association between longstanding hypertension (HT) (antedating development of AHF regardless of BP values on admission) and mortailty has not been well studied.
Methods: We used data from AHEAD (Acute HEArt failure Database) – Czech national multicentric prospective AHF registry. 2421 patients with acute decompensated heart failure (with "mild" signs of AHF) were enrolled at 7 centres during the years 2005-09. Patients with pulmonary oedema, cardiogenic shock or hypertensive crisis at hospital admission were excluded from the analysis. We provided comparative analysis between HT and non-HT patients (previous history, hospital course and mortality rates were assessed). The association between HT and all-cause mortality was tested using univariate and finally multivariate Cox regression analysis.
Results: Patients with longstanding HT (N=1731) were older (73,6 years, non-HT 66,6, $p<0.001$), more women (45%, non-HT 33%, $p<0.001$), frequently with history of diabetes mellitus (48%, non-HT 22%, $p<0.001$), previous myocardial infarction (35%, non-HT 21%, $p<0.001$), with higher BMI (29,2 kg/m^2, non-HT 27,5, $p<0.001$), left ventricular ejection fraction (LVEF) (40%, non-HT 33%, $p<0.001$), entry serum creatinine (109 μmol/l, non-HT 98, $p<0.001$) and lower hemoglobin level (131 g/l, non-HT 137, $p<0.001$). In-hospital all-cause mortality was similar (2,6%, NS), 3-year mortality was higher in HT group (41,3%, non-HT 30,2%, $p<0.001$). Although HT influenced long-term mortality in univariate analysis with OR 1,36 (95% CI 1,14;1,62, p=0.001), in multivariate model stronger independent mortality predictors were found: age >70 years with OR 1,86 ($p<0.001$), BMI ≥ 25 kg/m^2 OR 0,68 ($p<0.001$), de-novo AHF OR 0,617 ($p<0.001$), diabetes mellitus OR 1,46 ($p<0.001$), admission serum creatinine ≥ 120 μmol/l OR 1,63 ($p<0.001$), hemoglobin level < 120 g/l, OR 1,4 ($p<0.001$), LVEF ≤30% OR 1,3 (p=0.017), hyponatremia ≤130 mmol/l, OR 1,78 (p=0.004) and systolic BP at hospital admission ≤100 mmHg, OR 1,54 (p=0.005).
Conclusions: HT is a frequent comorbidity of patients with acute decompensated AHF. Patients with HT have worse long-term mortality rates, but HT was not found as an independent predictor of all-cause mortality in multivariate analysis. Higher age, new onset AHF, diabetes, renal insufficiency, anemia, low LVEF, higher BMI, hyponatremia and hypotension at hospital admission were factors strongly associated with mortality.

P824 INTERMACS profiles predict postoperative outcomes in critically ill patients undergoing urgent heart transplantation. Data from the Spanish national heart transplant registry

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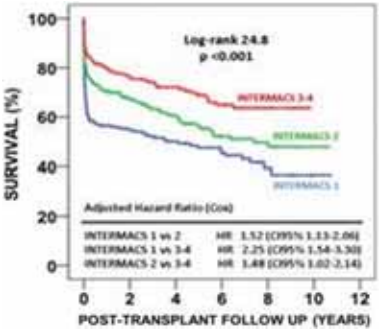
Purpose: Several studies demonstrated the usefulness of the INTERMACS scale to predict outcomes in patients with advanced heart failure (AHF) undergoing VAD implantation. We aimed to determine if this classification is also useful to predict outcomes in critical AHF patients treated with urgent heart transplantation (UHT).
Methods: We conducted a multicenter registry including 704 adult patients who underwent UHT in 15 Spanish institutions between 2000-2009. All had inotrope-dependent or VAD-dependent AHF or life-threatening arrhythmias. Post-UHT outcomes were compared according to patient's preoperative INTERMACS profile, which was assigned retrospectively by two independent cardiologists in each center after reviewing clinical records.
Results: Patients at pre-UHT INTERMACS 1 profile ("critical cardiogenic shock", n=207) were younger, required higher doses of inotropes and showed a lower cardiac index and higher preoperative serum levels of creatinin, AST and ALT (all $p<0.05$) than INTERMACS 2 ("sliding fast", n=291) and INTERMACS 3-4 ("inotropic dependent", n=206) patients. Pre-UHT rates of infection and need for VAD support, ventilator, IABP and dialysis were also higher among INTERMACS 1 and 2 patients (all $p<0.05$). No differences were observed regarding donor age or gender or cold ischemia times. Post-UHT rates of primary graft failure (1: 31%, 2: 22%, 3-4: 22%, p=0.03), need for dialysis (1: 33%, 2: 19%, 3-4: 22%, p=0.001) and in-hospital mortality (1: 43%, 2: 27%, 3-4: 18%; $p<0.001$) significantly varied across INTERMACS profiles, without differences in other major outcomes. Non-adjusted and adjusted long-term survival rates were also significantly influenced by patient's preoperative INTERMACS profile (figure).



Conclusions: The INTERMACS scale is useful to predict outcomes after UHT.

P825 Elevated troponin is associated with increased mortality in patients with acute dyspnea

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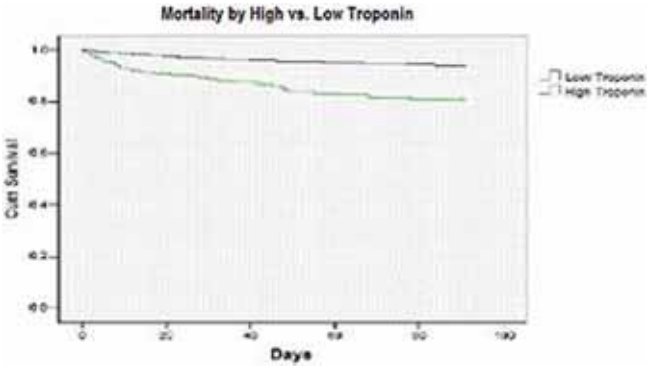
Introduction: Troponin is a well known prognostic biomarker in patients with heart disease. However, its prognostic utility may extend well beyond cardiac diseases. This analysis of the Biomarkers in Acute Heart Failure (BACH) study aims to evaluate troponin as a prognostic biomarker in patients with acute dyspnea.
Methods: The BACH trial was a 15-center study of 1641 patients with acute dyspnea. All biomarkers were measured during the initial visit. Patients were followed for up to 90 days for all-cause mortality. Elevated troponin was defined as levels above the upper limit of normal at each enrolling site.
Results: 1162 patients with troponin measurements were included in this analysis. Elevated tropoinin was associated with significantly increased mortality ($p<0.001$). (Figure) In multivariate analysis, troponin and mid-region proadrenolmedullin (MR-proADM) were statistically significant predictors of mortality (troponin: p=0.009; MR-proADM: $p<0.001$), while heart failure, chronic obstruc-

tive pulmonary disease, and B-type natriuretic peptide (BNP) were not. Furthermore, troponin elevation was a significant predictor of mortality in both cardiac (n=691, p<0.001) and pulmonary (n=255, p=0.003) diagnosis in this cohort. In bivariate analysis of BNP >400pg/L and elevated troponin, among patients with cardiac diagnosis, both troponin and BNP were statistically significant predictors of mortality (BNP: p=0.001; troponin: p<0.001) while only troponin was statistically significant among patients with pulmonary diagnosis (BNP: p=0.41; troponin: p=0.015).



Conclusion: Troponin elevation was a significant predictor of mortality in patients with acute dypnea due to both cardiac and pulmonary etiologies. Troponin was better than BNP in predicting mortality in patients with pulmonary diagnosis.

P826 Left bundle branch block and prognosis in patients with reduced and preserved ejection fraction: results from the MAGGIC meta-analysis

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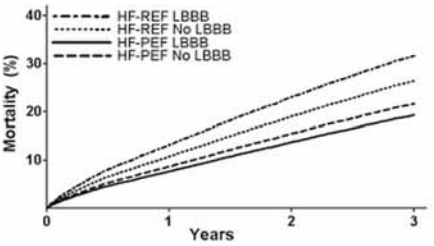
Purpose: Left bundle branch block (LBBB) has been associated with adverse prognosis in patients with chronic heart failure (HF). Progressive ventricular dysfunction increases the risk and degree of LBBB, and there have been inconclusive findings whether LBBB is an independent predictor of mortality. Further, most studies have concerned patients with reduced ejection fraction (HF-REF), and the influence of LBBB in HF with preserved EF (HF-PEF) is less well known. LBBB is of particular interest, as it might indicate benefit of cardiac resynchronisation therapy.
Methods: The Meta-Analysis Global Group In Chronic Heart Failure (MAGGIC) individual patient meta-analysis included data from 31 studies that recruited patients without EF inclusion criterion. Cox proportional hazards survival analysis was undertaken for presence or absence of LBBB, adjusted for age, gender, aetiology, hypertension, diabetes and stratified by study for the overall group and within HF-REF and HF-PEF groups. The primary outcome was 3-year all-cause mortality.
Results: Data on presence or absence of LBBB were available in 19,444 patients, 14,861 without LBBB and 4,583 with LBBB. Among patients with HF-REF and HF-PEF, 4,096 (27.7%) and 442 (9.6%) had LBBB, respectively. LBBB was an independent predictor of death from any cause in the whole group, HR 1.32, 95% CI [1.24-1.41]. LBBB was an independent predictor of death among patients with HF-REF, HR 1.29 [1.20-1.39], but not among patients with HF-PEF, HR 0.98 [0.81-1.20]. LBBB*EF interaction p=0.005. LBBB appeared to be of additive prognostic importance at a cut-off level of EF below 40%.



Conclusion: LBBB is common among patients with HF-REF but less so in HF-PEF. LBBB has an independent impact on an adverse outcome in patients with HF-REF but not in HF-PEF.

P827 Impact of functional tricuspid regurgitation on long-term survival and heart failure in patients with functional mitral regurgitation and left ventricular dysfunction

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Background: The prognostic implications of functional mitral regurgitation (FMR) in the patients with ischemic and non ischemic left ventricular dysfunction is certain as well as the prognostic role of residual tricuspid regurgitation (TR) associated to organic left side valvular heart disease. However, no data are available about the prognostic value of associated TR in patients with FMR and left ventricular dysfunction.
Aims: We designed this study to examine mortality and morbidity associated with TR after controlling for left ventricular ejection fraction (EF), right ventricular (RV) dysfunction, and pulmonary artery systolic pressure (PASP) and degree of MR in patients with FMR.
Methods and results: We prospectively enrolled 374 consecutive patients (mean age 68.3±11.2 years), 249 ischemic and 123 non-ischemic etiology, ejection fraction 34.7±9.4%, and at least mild FMR. During follow-up 97 deaths occurred, of these, 65 (67%) were cardiac deaths and 32 (33%) non-cardiac deaths. At 6 years, the survival free of all-cause mortality and cardiac death were 57% (95% CI 45% to 70%) and 68% (95% CI 55% to 78%) respectively. At 6 years, survival free of all-cause mortality was 69% (95% CI 59% to 78%) for patients without ITR, 67% (95% CI 61% to 74%) for patients with mild ITR, 51% (95% CI 48% to 66%) for patients with moderate ITR, 40% (95% CI 36% to 57%) for patients with severe ITR (p=0.004), and the survival free of cardiac death was 78% (95% CI 71% to 98%) for patients without ITR, 79% (95% CI 68% to 79%) for patients with mild ITR, 58% (95% CI 54% to 72%) for patients with moderate ITR, 55% (95% CI 43% to 65%) for patients with severe ITR (p=0.003). Moderate-severe TR was a predictor of cardiac death (HR= 1.6, 95% CI 1 to 4.4, p=0.02) and all-cause mortality (HR= 1.8, 95% CI 1.2 to 3.7, p=0.005) independent of age, FE, pulmonary pressure, MR severity and TAPSE. At 6 years, survival free of HF in overall population was 44% (95% CI 37% to 69%). The moderate-severe TR (HR= 1.7, 95% CI 1.2 to 4, p=0.02) was an independent predictor of HF independent of age, FE, pulmonary pressure, MR severity and TAPSE.
Conclusions: We conclude that increasing TR severity is associated with worse survival and incidence of HF episodes in patients with FMR regardless of age, EF, pulmonary artery pressure or right ventricular function.

P828 The combined impact of TNF-alpha, cTnI and BNP on mortality in patients with acute heart failure

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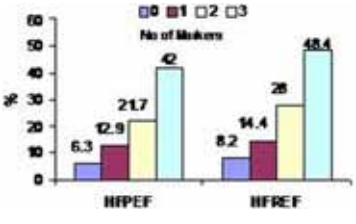
Purpose: To evaluate the combined impact of circulating levels of tumor necrosis factor alpha (TNF-α), cardiac troponin I (cTnI) and brain natriuretic peptide (BNP) for the prediction of 1-year mortality in patients with acute decompensated heart failure and preserved (HFPEF) or reduced ejection fraction (HFREF).
Methods: A total of 414 and 697 consecutive pts, who were hospitalized for acute decompensated HFPEF (LVEF≥50%; mean LVEF:60%) and HFREF (LVEF<50% mean LVEF:35%) respectively, were studied. Biochemical markers were measured upon admission. The incidence of 1-year death was the prespecified primary endpoint.
Results: The incidence of the primary endpoint was 18.7% and 20.4% in pts with HFPEF and HFREF, respectively. By separate multivariate Cox analysis in the study cohorts, elevated circulating levels of TNF-α (p<0.001and p<0.001 in pts with HFPEF and HFREF, respectively), BNP (p<0.001and p=0.002 in pts with HFPEF and HFREF, respectively) and cTnI (p=0.001 and p<0.001 in pts with HFPEF and HFREF, respectively) were independently associated with the primary endpoint. When the pts were divided according to the number of elevated biomarkers (estimated by ROC analysis) there was a significant gradual increase in the rate of the primary endpoint with increasing of the number of the positive biomarkers in both cohorts (p for trend<0.001 for both cohorts) (figure).



Conclusions: The present results suggest that serum levels of TNF-α, BNP and

cTnI can be used in combination for enhanced early risk stratification in patients who hospitalized due to either acute decompensated HFPEF or HFREF.

P829 New onset left bundle branch block independently predicts long-term mortality in patients with idiopathic dilated cardiomyopathy. Data from Trieste heart muscle disease registry

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Background: The data regarding and prognostic role of LBBB in pts with HF conflicting. Most of analyses specifically exploring this issue in patients with DCM are outdated.
Objectives: To evaluate the prevalence, incidence, and long-term prognostic implications of LBBB in patients with Idiopathic Dilated Cardiomyopathy (DCM) on optimal medical treatment with ACE inhibitors and beta blockers.
Methods: Were analyzed the data of 608 pts with DCM enrolled in the Heart Muscle Disease Registry of Trieste from January 1988 to December 2007.
Results: One hundred eighty nine patients (31%) out of 608 patients with DCM had LBBB at baseline. During the median follow-up of 116 months (65-180 months) was observed significantly higher mortality rate among patients with LBBB at baseline in comparison to patients without LBBB (p=0.007). However, LBBB at baseline was not independent predictor of mortality.
Forty-seven patients (11.2%) developed new LBBB, 19 (40.4%) of them in the first year of follow-up. At multivariable analysis incident LBBB considered as time dependent variable was a strong and independent predictor of all cause mortality (HR 2.89, 95% CI 1.7-4.8, $p<0.001$).
Conclusions: LBBB is frequent among patients with DCM and its presence at baseline was not an independent marker of poorer survival. Incident LBBB in patients on optimal medical treatment with ACE inhibitors and beta blockers is independently associated with an adverse outcome. Thus, the management of these patients should be more aggressive and possibly to include device therapy.

P830 Brain natiuretic neptide in patients with type 2 diabetes and normal ejection fractions predicts all-cause mortality

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Introduction: The use of brain naturetic peptide (BNP) to predict outcome in patients with normal ejection fractions (EF) and type 2 diabetes (T2DM) is understudied. Only three previous studies have specifically addressed the question as to whether BNP adds prognostic information in T2DM. There appears to be a link between survival and BNP in T2DM, however these studies included small numbers of patients and did not fully exclude left ventricular systolic dysfunction (LVSD). We therefore studied the five year survival in a cohort of 500 T2DM patients prospectively phenotyped with echocardiography.
Methods: 500 patients with T2DM where studied with echocardiography between April 2002 and October 2003. Patients were recruited from the diabetes clinics. Transthoracic echocardiography was performed by one trained operator and left ventricular (LV) assessment was performed using modified biplane Simpson's method over three cycles. We excluded individuals with EF of $<55\%$. Follow up data was linked via the Health Informatics Centre (HIC), to mortality data, laboratory test data, hospitalisation, and prescribing via the community health index (CHI) number. Cox proportional hazards model was used to examine the effects of BNP (bedside stick measurement) measure on all-cause mortality using age, sex, smoking status, hypertension, IHD, duration of diabetes, and diabetic drug prescription as co-variants. Outcome was all cause mortality.
Results: In total we followed 316 patients over eight years. 56 patients died over this time. After adjusting for confounding factors we have shown that for every 10 unit increase in BNP there is a 6% increased risk of death. HR 1.06 [95%CI 1.02–1.10] ($p=<0.01$).
Conclusions: In patients with normal EF, BNP is an independent predictor of death in a cohort of T2DM patients. Although more research is needed, BNP may become an important tool in risk stratifying T2DM patients in the future.

P831 Impact of tricuspid regurgitation on survival in patients with chronic heart failure - a long-term observational study

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Purpose: Tricuspid regurgitation (TR) is common in patients with chronic heart failure (CHF). However, data about the prognostic value of significant TR in CHF patients are sparse.
Methods: 575 consecutive patients with CHF were prospectively included. Patients represent an unscreened contemporary cohort of CHR patients treated according to current guidelines in a tertiary heart failure clinic. At study entry detailed clinical and echocardiographic data were collected. The prognostic impact of significant TR was assessed and compared with established risk factors.
Results: Patients were followed for 69.18±50.24 months. TR was common in the study population. 10.6% of patients had severe, 24.0% moderate, and 65.4% of patients had no or mild TR. Kaplan Meier analysis showed a considerably increased mortality rate of patients with moderate and severe TR ($p<0.0001$). However, by multivariable analysis NTpro-BNP (p=0.0054), systolic blood pressure (p=0.0012), heart rate (p=0.0152), age ($p<0.0001$), serum creatinine, ($p<0.0001$), serum sodium (p=0.0449) and left ventricular function (p=0.0130), but not TR independently predicted mortality.
These independent predictors of mortality were used to define disease severity to analyse the predictive value of TR at different stages of CHF. In patients with mild and moderate CHF, characterized by NT-proBNP concentrations <500 mg/pg, serum-creatinine levels <1.5mg/dl, sustained systolic blood-pressure >100mmHg, heart rate <90/min, severe TR was highly predictive of mortality ($p<0.0001$ for all, except NTproBNP p=0.00175). In patients with advanced disease, however, significant TR did not add additional information.
Conclusion: The prognostic impact of TR strongly depends on the severity of heart failure. Whereas TR excellently predicts excess mortality in mild to moderate CHF, it has no additive value in advanced CHF when compared with established risk factors. Since it is only in mild to moderate CHF that severe TR is associated with adverse outcome it is this group of patients that might benefit from tailored pharmacological or surgical interventions.

P832 The obesity paradox in heart failure: is aetiology the key?

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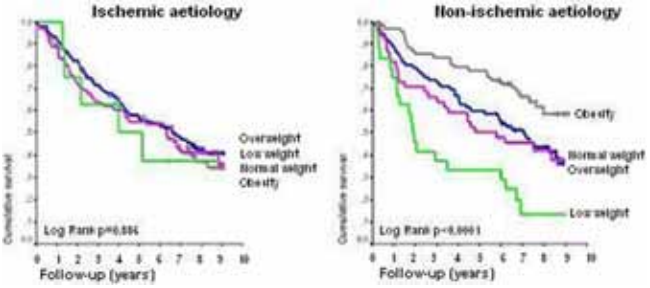
Background: Obesity is paradoxically associated with survival in heart failure (HF). The role of HF aetiology in obese HF patients is incompletely characterized.
Objective: To assess whether the relationship between body mass index (BMI) and long-term mortality in an ambulatory HF cohort was associated with HF aetiology (ischemic vs. non-ischemic).
Patients and method: BMI and survival status after a median follow-up of 6.1 years [IQR 2.2-7.8] were available in 504 patients (73% men; median age 68 years [IQR 58-74]). Aetiology of HF was ischemic heart disease in 59% and non-ischemic in 41% of patients. Median LVEF was 30% [IQR 23-39.7%]. Most patients were in NYHA class II (51%) or III (42%). According to BMI patients were divided in 4 groups (WHO 1999 classification): low weight (BMI $<$ 20.5 kg/m^2), normal weight (BMI 20.5 to $<$25.5 kg/m^2), overweight (BMI 25.5 to $<$30 kg/m^2) and obesity (BMI $\geq$30 kg/m^2).
Results: Mortality differed significantly across BMI strata in non-ischemic patients (Log rank $p<0.0001$) but not in patients of ischemic aetiology (figure). Taking as reference normal weight patients, hazard ratios (HR) for low-weight, overweight and obesity were: 2.08 [1.16-3.75] p=0.014; 0.88 [0.54-1.43], p=0.60; and 0.49 [0.28-0.86], p=0.01; respectively for patients of non-ischemic aetiology; and 1.19 [0.48-2.97] p=0.71; 0.88 [0.61-1.27], p=0.48; and 0.96 [0.66-1.41], p=0.85 for those of ischemic aetiology. After adjustment for age, sex, aetiology, NYHA class, LVEF, hypertension, and diabetes, BMI remained an independent predictor of survival in non-ischemic patients.



Survival by BMI groups and aetiology.

Conclusion: In a long-term follow-up, the obesity paradox was only found in HF patients of non-ischemic origin.

P834 Prognostic value of atrial fibrillation pattern in heart failure in a large real life community based cohort study

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Atrial fibrillation (AF) and heart failure (HF) frequently coexist and are associated with an increased mortality. The aim of the study was to evaluate the prognostic value of AF pattern in patients with both AF and HF.

Methods: All patients with AF seen in the cardiology department in our institution between 2000 and 2007 were identified in a database and followed up for mortality and cardiac events. The patients were identified by a search in the hospital discharge records of our computerized codification system which include information on diagnoses and co-existing conditions.

Results: Among 6517 patients with AF, 1999 patients had both AF and HF (age 73±13, 1232 men [62%]): 818 had paroxysmal AF, 207 had persistent AF and 974 had permanent AF. Left ventricular ejection fraction (LVEF) was 48±17% and 47% of the patients had LVEF≤45%.

During a follow up of 920±761 days, 389 patients died (177 cardiac deaths) and 506 had HF rehospitalisation. Patients with permanent AF had the highest mortality rate. Compared with persistent AF, paroxysmal AF was associated with an increased risk of mortality, both for all cause mortality and for cardiovascular mortality. The independent predictors of cardiac death were older age ($p<0.0001$), paroxysmal AF and permanent AF compared to persistent AF (RR=2.21, p=0.03 and RR=2.02, p=0.05 respectively), renal insufficiency (p=0.009), valvular disease (p=0.02), lack of use of oral anticoagulation (p=0.02) and alcohol abuse (RR=2.22, p=0.01). The rate of readmission for HF was lower in non permanent AF (paroxysmal and persistent) than in permanent AF. The proportion of patients who required hospitalisation for HF was higher in patients with persistent AF than in those with paroxysmal AF. The independent predictors for rehospitalisation related to HF were older age (p=0.01), permanent AF and persistent AF compared to paroxysmal AF (RR=1.42, p=0.002 and RR=1.56, p=0.03, respectively), renal insufficiency (p=0.0001), decreased LVEF (p=0.0001), valvular disease (p=0.0001) and use of diuretic (p=0.008).

Conclusions: In patients with both AF and HF, permanent AF was independently associated with a worse prognosis. Persistent AF was associated with a better survival but more frequently required rehospitalisation for HF than paroxysmal AF. Moreover, this would suggest that maintaining sinus rhythm might bring a benefit in terms of mortality or morbidity in AF patients with HF if one uses a therapy which is sufficiently safe on the long term.

P835 No impact of revascularization on short term mortality in ischemic acute heart failure; a report from ATTEND registry

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Purpose: Revascularization therapy (RT) is the most useful strategy in acute coronary syndrome (ACS) patients and recommended in several guidelines. However, there is no study about the procedure timing or indication of RT in ischemic acute heart failure syndrome (IAHFS). Therefore, we examined the effect of RT on short-term mortality in IAHFS using the data from acute decompensated heart failure syndromes (ATTEND) registry, which is the ongoing multicenter prospective observational cohortstudy of AHF in Japan.

Methods: The ATTEND registry enrollment took place at 48 hospitals between March 1st 2007 and Dec 30th 2010. Patients greater than 20 years of age with a primary discharge diagnosis of heart failure were enrolled, which admitted with a diagnosis of ACS were excluded. The study involved 949 patients who were admitted with IAHFS, defined by the American College of Cardiology/American Heart Association clinical data standards. Patients were classified as treatment with RT and treated medically (MED) and clinical characteristic were compared. The primary study endpoint was in-hospital all cause mortality.

Results: In IAHFS patients, median hospital stay duration was 22 days [Interquartile range (IQR) 14-35] and primary endpoint occurred in 85 (9.0%) patients. RT was performed in 243 (25.6%) patients, who were younger (72±11 vs. 76±10, $p<0.001$) than MED groups, but there was no gender difference between two groups. The patients with RT had less history of HF admission and atrial fibrillation (28.4 vs. 49.3%, 18.9 vs. 29.9%, respectively $p<0.001$), admitted with higher heartrate (103±27 vs. 96±25 bpm, $p<0.001$), systolic blood pressure (152±38 vs. 147±36 mmHg, $p<0.029$) and estimated glomerular filtration rate (52.7±29.1 vs. 44.9±34.0 ml/min/1.73m^2, p=0.001) compared with MED. The percentage of preserved left ventricular systolic function and brain natriuretic peptide level had no significant differences between two groups (30.5 vs. 31.7%, 824 [IQR458-1330] vs. 792 [IQR 435-1380] pg/dl). Despite these differences, all cause in-hospital death in the RT patients were similar to MED patients (9.5% vs. 8.8%; p=0.758).

Conclusion: The present study demonstrated that RT for IAHFS, even in younger patients, did not improve in-hospital mortality during hospitalization. Impact of RT in IAHFS on long-term mortality should be clarified in AHFS.

P836 CXCL16 is associated with both death and hospitalization due to worsening of heart failure in patients with chronic heart failure

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Purpose: Both experimental and clinical studies indicate a role for inflammation in the development of myocardial failure. Thus, we recently demonstrated increased production of CXCL16 in experimental and clinical heart failure indicating a role in vascular remodeling and development of HF. We hypothesized that soluble CXCL16 concentrations are associated with long-term outcome in patients with HF.

Methods: The importance of plasma CXCL16 as a risk factor for the primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; n= 318 events) and for all-cause mortality (n= 329) and all-cause mortality and hospitalization for worsening of heart failure (WHF; n= 475) was investigated in a total of 1464 patients at least 60 years of age [mean age 72±7 (SD), 341 (23%) women], in NYHA class II-IV, with ischaemic systolic HF receiving optimal pharmacological therapy in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) population, randomly assigned to receive 10 mg rosuvastatin or placebo once daily and followed for a median 32.8 months.

Results: In multi-variable analyses, baseline CXCL16 as a continuous variable, added no significant predictive information for the risk estimation of the primary endpoint, all-cause or CV-mortality, or hospitalization due to WHF beyond demographic, clinical and biochemical variables (left ventricular ejection fraction, NYHA class, age, body mass index, diabetes, sex, intermittent claudication, heart rate, serum creatinine, apoA1 and NT-proBNP). However, the change in CXCL16 from baseline to 3 months, added independent predictive information for CV-mortality [HR 1.19 (1.04-1.35), p=0.009] and in particular death due to WHF [HR 1.34 (1.08-1.66), p=0.008] when adjusting for the variables mentioned above, including NT-proBNP. Finally, the change in CXCL16 was associated with hospitalization due to WHF [HR 1.10 (1.00-1.20), p=0.046) after adjustment for all variables excluding NT-proBNP.

Conclusion: Baseline CXCL16 levels was poorly associated with long-term outcome. However, the change in CXCL16 during follow-up was associated with both death and hospitalization due to WHF in patients with advanced chronic systolic HF of ischemic etiology supporting a role for CXCL16 the pathogenesis and progression of chronic myocardial failure.

P837 Determinants and prognostic impact of improvement in left ventricular ejection fraction after hospitalisation for systolic heart failure

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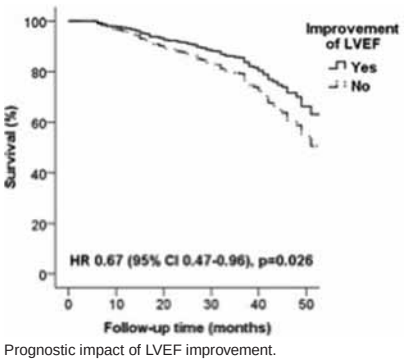
Background and aims: The potential of improvement in left ventricular ejection fraction (LVEF) afterhospitalization for systolic heart failure (SHF) is unknown. Therefore, we aimed to identify determinants of LVEF improvement after discharge and investigated its prognostic significance.

Methods: Patients hospitalized for acute SHF with LVEF≤40% prior to discharge were included and re-evaluated six months later. LVEF was quantified using Simpson biplane method; an increase of >8.5% was considered a significant improvement, and a decrease of >8.5% a significant deterioration.

Results: We included 654 patients (mean age 66±12 years, and 75% male). After six months, LVEF had improved in 386 (59%), remained unchanged in 238 (36%) and decreased in 30 (5%) patients. Logistic regression revealed that higher LVEF, left ventricular end-diastolic diameter and leukocytes were negative predictors of LVEF improvement, but the effects were small (HR 0.9, 95%CI: 0.9-1.0 for all; $p<0.05$ for all). Absences of coronary artery disease and of left bundle branch block were both predictors of LVEF improvement (HR 0.5, 95%CI: 0.3-0.8 and HR 0.4, 95%CI: 0.3-0.7, respectively; both $p<0.01$). Improvement of LVEF was asso-



Prognostic impact of LVEF improvement.

ciated with better survival (81 vs 70%; p=0.003) in a mean (median) follow-up time of 32 (36) months. After adjustment for potential confounders, improvement of LVEF remained an independent predictor of long-term survival (Figure).
Conclusion: Significant LVEF improvement is frequent in survivors six months after hospitalization for SHF. Non-ischemic etiology and absence of left bundle branch block render improvement more likely, which is a relevant predictor of long-term survival after hospitalization for SHF.

P838 Red cell distribution width relates to exercise capacity in chronic heart failure but provides prognostic information incremental to peak oxygen consumption

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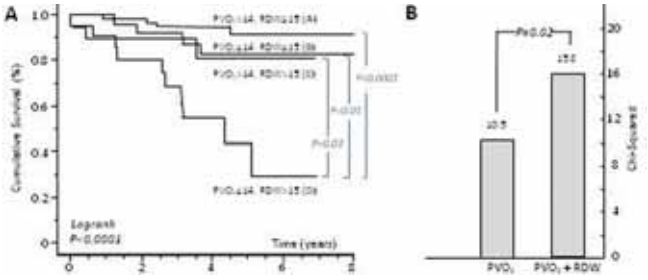
Background: Red cell distribution width (RDW), an index of the variability in size of circulating erythrocytes, is a surrogate of many aberrations (iron deficiency, inflammation, oxidative stress) that may drive chronic heart failure (CHF) progression. Whilst an elevated RDW powerfully predicts mortality in CHF, little is known about its relation to exercise performance and its ability to prognosticate when adjusted for peak oxygen consumption (PVO2).
Methods: We analysed the relation between red cell indices, exercise capacity, and survival in 136 patients with systolic CHF (mean [±SD] age 67±13y, RDW 14.4±1.5%, PVO2 18±8 mL/kg/min, 71% male, 68% with ≥ moderate LV impairment).
Results: Higher RDWs correlated to lower PVO2 (R= -0.3, P=0.0002) levels and oxygen uptake efficiency slopes (P<0.01), and higher VE/VCO2 slopes (P<0.001). On multiple regression, RDW related to PVO2 independently of age, haemoglobin, and peak heart rate (R2=0.49, P<0.0001). Over a median (±IQR) follow-up of 3.8±3 years, 22 (16%) patients died. Both RDW (HR 1.39, P=0.001) and PVO2 (HR 0.87, P=0.001) independently predicted mortality. An RDW>15% (ROC AUC 0.71, P=0.002) and PVO2≤14mL/kg/min (ROC AUC 0.74, P<0.0001) were optimally predictive with each conferring 4-fold escalated risks for death. In incremental prognostic models, the addition of RDW to PVO2 increased hazard ratio (Fig A) and chi-squared (Fig B) values significantly, with the combination of an RDW>15% and PVO2<14mL/kg/min identifying those at a 6-fold enhanced risk of mortality.



Incremental Prognostic Utility of RDW

Conclusions: An increased RDW relates to exercise intolerance in CHF but provides prognostic information incremental to PVO2. Ameliorating drivers of RDW expansion such as iron deficiency might durably improve functional capacity and survival in this cohort.

P839 The independent prognostic value of hyponatremia in a cohort of heart failure patients: analysis from the Duke databank for cardiovascular disease

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Background: Hyponatremia (serum sodium<135mmol/l) is a well-known predictor of short-term outcomes in chronic heart failure (HF); however, its impact on long-term survival has not been well established.
Methods: Using the Duke Databank for Cardiovascular Diseases, we identified 1,045 patients with diagnosis of HF due to systolic dysfunction (EF<40%) undergoing cardiac catheterization from January 2000 through December 2008. The effect of hyponatremia as an independent predictor of all-cause death was examined using a multivariable Cox model.
Results: Hyponatremia at the time of catheterization was present in 107/1,045 patients (10.2%). The maximum patient follow-up was 10.7 years with an average of 4.5 years. Using an unadjusted analysis, hyponatremia was associated with higher risk of all-cause death (p<0.0001; HR 1.89, 95% CI 1.44-2.49). When entered into a multivariable Cox model, hyponatremia remained a significant predictor for all-cause death (HR 1.42, 95% CI 1.07-1.88; c-index 0.71). Variables used for adjustment in the multivariable setting were age, BUN, CHF Class, extent of coronary disease (reflected by the number of diseased vessels), renal disease, hemoglobin, history of peripheral vascular disease, ejection fraction (Table 1).

Table 1. Multivariable cox model for all cause de

Parameter	Comparison	HR (95% CI)
Hyponatremia (<135)	Yes vs No	1.418 (1.069–1.881)
Age	5 years increase	1.139 (1.086–1.195)
BUN	5 U increase	1.131 (1.085–1.180)
CHF Severity	Class IV vs Class II/III	1.313 (1.068–1.615)
Number of Diseased Vessels [1]	1 vs 0 vessels	1.780 (1.271–2.492)
[2]	2 vs 0 vessels	1.724 (1.256–2.367)
[3]	3 vs 0 vessels	2.212 (1.677–2.917)
Renal Disease	Yes vs No	2.423 (1.293–4.542)
Hemoglobin [11.5–14.0]	1 U increase	0.872 (0.788–0.965)
Peripheral Vascular Disease	Yes vs No	1.506 (1.108–2.047)
Ejection Fraction	5 U increase	0.926 (0.871–0.983)

Conclusions: Hyponatremia is common in patients with chronic HF, and is independently associated with increased risk of all-cause mortality. Hyponatremia remained a significant predictor in the multivariable Cox model for all-cause mortality.

P840 Factors independently associated with mid- and long-term prognosis differ from each other

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Aim: To investigate predictors of mid- (1-year) and long-term (5-year) mortality after hospitalization for acute heart failure (AHF).
Methods: Patients hospitalized for AHF (n=620) from the multicentre FINN-AKVA study were followed prospectively and all-cause mortality at 1 and 5 years assessed. Clinical variables predicting mortality were identified by logistic regression.
Results: Mean age was 75 years at hospitalization. Half of the patients were women and 51% had acutely decompensated chronic heart failure [ADCHF]. All-cause mortality was 27,4% (170 deaths) at 1 year and 60,5% (375 deaths) at 5 years. Age and impaired kidney function had prognostic impact both on mid- and long-term prognosis, whereas male gender, hypertension, systolic blood pressure (BP) and inflammation predicted mid-term mortality, and previous HF, cerebrovascular disease (CVD) and chronic obstructive pulmonary disease (COPD) affected only long-term mortality (Table 1).

Independent predictors of mortality

Variable	0 to 1 year	From 1 to 5 years
Age (/year)	1.06 (1.04–1.09)†	1.11 (1.08–1.15)†
Male gender	1.9 (1.2–3.1)†	–
Previous HF	–	2.7 (1.6–4.6)†
Hypertension	0.6 (0.4–1.0)‡	–
CVD	–	2.3 (1.1–4.5)‡
COPD	–	2.8 (1.3–6.3)‡
Systolic BP	0.86 (0.78–0.95)†	–
Creatinine (/10 μmol/L)	1.04 (1.01–1.08)‡	1.10 (1.03–1.19)†
CRP > 10 mg/l	2.2 (1.4–3.3)†	–

Adjusted for history of coronary artery disease, myocardial infarction, atrial fibrillation, valvular disease and diabetes. ‡p<0.05, †p<0.01.

Conclusions: Both mid- and long-term mortality after hospitalization for AHF are high. Factors independently associated with prognosis before and after one year from hospitalization differ from each other. For patients surviving the first year after AHF hospitalization, age, history of HF, kidney function and co-morbidities are important determinants of subsequent mortality. Interestingly, hypertension and systolic BP did not improve survival after first year of follow-up.

P841 Prognostic role of red cell distribution width (RDW) variations among patients with chronic heart failure

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Purpose: We assessed the possible prognostic role of: 1- red cell distribution width (RDW) serial follow-up evaluations, 2- RDW variations from baseline values (deltaRDW), in a group of ambulatory patients with chronic heart failure. The endpoints was death for cardiovascular causes+ HF hospitalizations.
Methods: The patients underwent routine clinical and instrumental assessment with follow-up visits, echocardiography, cardiopulmonary exercise stress test, laboratory exams and were reassessed after 202±78 days after baseline. Follow-up was performed.
Results: We studied 304 ambulatory patients with chronic heart failure due to left ventricular systolic dysfunction (LVEF 36±9%, age 67±12 years, 42% idiopathic dilated cardiomyopathy, 58% ischemic dilated cardiomyopathy), on op-

timal medical therapy (89% ACE-inhibitors-ARBs, 97% beta-blockade, 45% aldosterone antagonists, 79% loop diuretics, 32% amiodarone). The clinical characteristics were evenly distributed among the patients subdivided according to RDW2 and deltaRDW ≤ or > median, except for a higher incidence of atrial fibrillation among patients with RDW2 and deltaRDW > median value and for a worse LVEF among subjects with RDW2 > median value. Cumulative event-free survival for cardiovascular death+heart failure hospitalizations was worse among patients with RDW2> median value (HR 2.95, 95% IC 1.78-4.88, p<0.0001) and deltaRDW > median value (HR 2.61, 95% IC 1.58-4.29, p=0.0002). At multivariable cox proportional hazards regression analysis, age (HR 1.04 for one unit increase, 95% IC 1.01 - 1.07, p=0.01), LVEF (HR 0.93 for one unit increase, 95% IC 0.90 - 0.96, p<0.0001, diabetes (HR 2.3 for presence vs absence, 95% IC 1.29 - 4.09, p=0.005), deltaBUN (HR 1 for one unit increase, 95% IC 0.98 – 1.01, p=0.06), deltaRDW (HR 1.21 for one unit increase, 95% IC 1.03 - 1.42, p=0.02) were independent prognostic factors for cardiovascular death + HF hospitalizations.
Conclusions: Among patients with chronic heart failure (HF), the variations of RDW values (deltaRDW) have prognostic significance and identify patients with increased mortality for CV causes and HF hospitalizations.

P842 Predicting mortality in heart failure patients by echocardiographic parameters; looking beyond the ventricles

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Background: Traditionally, the left ventricle function and dimension are considered as the most important predictors for mortality in heart failure (HF).
In the current study we evaluated the importance of left atrial diameter as a predictor for mortality.
Methods: We studied baseline echocardiography parameters in 702 patients followed at our HF clinic and reordered their mortality over 4.5 years. Mean age was 67±13 years, 500 (71.2%) patients were males, mean LVEF of 35%±16 and mean NYHA class of 2.7±0.9. During the follow-up period, 203 (29%) patients died.
Based on the echocardiographic data available at the first clinic visit, we defined enlarged left atrium diameter as LAD>44 mm, reduced left ventriclefunction as LVEF<30%, enlarged left ventricle diameter as EDD>55 mm and significant mitral regurgitation as MR of at least mild to moderate. We analyzed these echocardiographic parameters in regarding to our patients mortality, focusing specifically at the left atrial diameter.
Results: Comparing to patients with lower LAD, patients with enlarge LAD had significantly lower LVEF, larger EDD and more significant MR. In univariate analysis for mortality prediction, the LAD, LVEF and MR severity were significant (p<0.001). In further logistic regression analysis, patients with enlarged LAD almost doubled their risk of dying. In addition to age >70 years and advanced NYHA class, an enlarged LAD was the most predictive parameters for HF patients death, followed by significant MR and reduced LVEF {OR and 95% CI were: 2.5, 1.7-3.6, p<0.001;2.52, 1.7-3.6, p<0.001; 1.97, 1.3-2.8, p<0.001; 1.73,1.2-2.5, p<0.03; 1.54, 1.1-2.2, p<0.02, respectively}.
Conclusion: In HF patients, enlarged left atrial size is highly predictive of mortality, as these patients almost doubled their risk of dying. Moreover, left atrial diameter seems to be a stronger predictive parameter for mortality in HF patients than the traditional prognostic parameters of LV function and size.

P843 Prognostic value of blood pressure variability daytime in chronic heart failure

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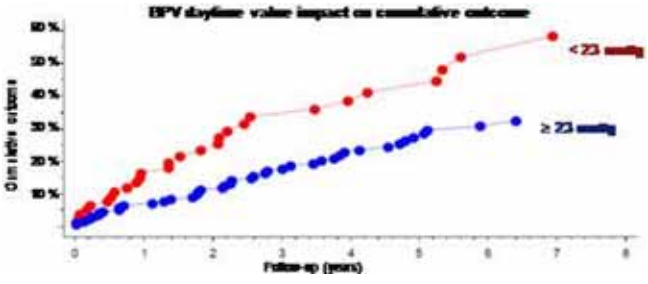
Purpose: Systolic blood pressure (SBP) level is positively correlated with survival in chronic systolic heart failure (CHF) and negatively with arterial hypertension disease. A high level of blood pressure variability (BPV) represents, especially in arterial hypertension disease, a stronger cardiovascular risk. The aim of our study was to evaluate the prognostic impact of BPV level in CHF.
Methods: We prospectively collected ambulatory monitoring blood pressure (AMBP) of 288 patients hospitalized for CHF in the department of Cardiology of the University Hospital, between 1999 and 2006. Follow up was realized retrospectively using physician, patient or family phone contact during 2010. The composite outcome was defined by all causes of death and/or heart transplant.
Results: Mean age was 59±12 years with 227 (79%) men. Mean left ventricular ejection fraction was 28±9% and mean arterial blood pressure was 110±15/68±9 mmHg. During a mean follow up of 7 years, the composite outcome was observed for 71 (32.2%) patients. After multivariate analysis, NYHA class (I/II vs. III/IV) and BPV daytime (≥ vs. < 23 mmHg – mean median value) were found to be the two independent factors of survival with a hazard ratio of 5.1 (95% IC: 3 - 8.8; p<0.01) and 1.8 (95% IC 1.1 - 2.9; p<0.02) respectively.
Conclusion: In a population of CHF, high level of BPV daytime (≥23 mmHg) is a positive prognostic value for survival.



P844 Red cell distribution width is better for predicting short-term and long-term outcomes than hemoglobin in acute onset of congestive heart failure

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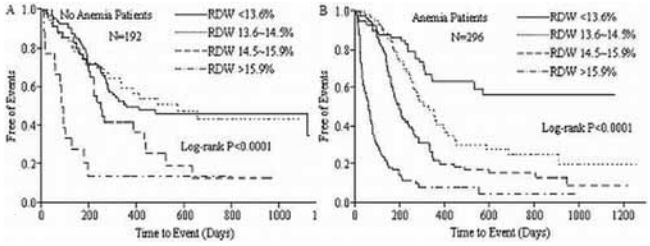
Purpose: The goal of this study was to assess whether red cell distribution width (RDW) determine the short-term and long-term outcomes in congestive heart failure (CHF) patients hospitalized in cardiac care unit.
Methods: In a cross-sectional observation study, patients with acute onset of CHF and admitted to cardiac care unit were enrolled from Jan 2007 to Dec 2009 and were followed for a median of 24 months (range 6 to 42 months). We measured RDW, hemoglobin and other biomarkers at admission. Short and long-term prognosis were investigated in 521 patients.
Results: A median (IQR) age was 72 (64, 80) years (66.6% male). The mean level of hemoglobin in in-hospital-death group was similar to that in alive group (11.0±1.8 g/dl versus 11.8±2.6 g/dl, P>0.05). The median value of RDW was significantly higher in death group than that in alive group [16.2% (15.1%, 17.6%) versus 14.4% (13.5%, 15.8%), P<0.0001]. Through a median of 24 months follow up, the median (IQR) value of RDW was also higher in events group compared to that in events-free group [14.9% (13.9%, 16.5%) versus 13.8% (13.3%, 14.4%), P<0.0001]. In Cox proportional hazard models, RDW (per SD increase, HR 2.19, 95% CI 1.92-2.50, P<0.0001), left ventricular ejection fraction (per SD increase, HR 0.81, 95% CI 0.71-0.92, P=0.0016), age (10 years increase, HR 1.19, 95% CI 1.07-1.34, P=0.0017) and NYHA III/IV (HR 1.52, 95% CI 1.15-2.03, P=0.0029) remained independent predictors of long-term outcomes after adjustment, while hemoglobin did not add prediction value (per SD increase, HR 1.01, 95% CI 0.96-1.13, P=0.86).



Kaplan-Meier survival curves.

Conclusions: Higher RDW values at admission in congestive heart failure patients were associated with worse short-term and long-term outcomes, with more prognostic value than hemoglobin.

P845 Combined assessment of a novel virtual analyte NT-proXNP and pro-inflammatory cytokines in the prognostic evaluation of patients with acute heart failure

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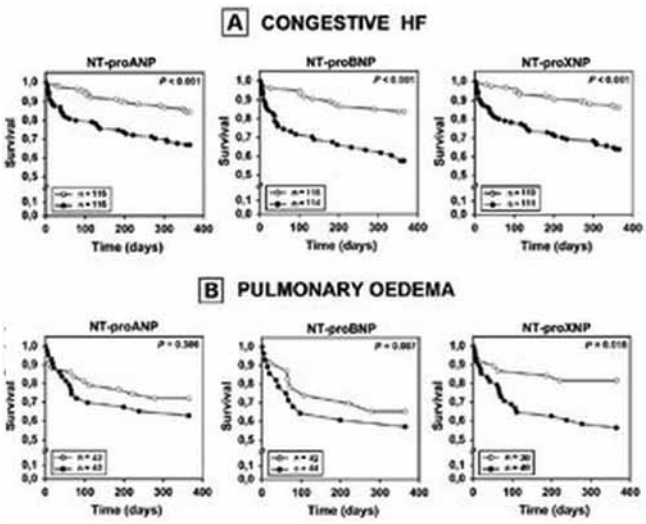
Purpose: To assess the prognostic value (12 months) of a novel virtual analyte, NT-proXNP, which combines the information provided by the individual assays for N-terminal pro-atrial natriuretic peptide (NT-proANP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), in patients with acute heart failure (AHF).
Methods: Circulating levels of both neurohumoral (NT-proANP, NT-proBNP, NT-proXNP) and inflammatory (interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α)) markers were measured from patients with congestive HF (n=230) or pulmonary oedema (n=86) at the time of their hospital admission. The prognostic

utility of (1) each of the peptides alone and (2) in combination with markers of inflammation was then assessed by comparing the survival of patients stratified according to the median values of the biomarkers.
Results: Whereas all the natriuretic peptides were somewhat equal in predicting 12-month survival in patients with congestive HF (P<0.001 for all; Fig. 1A), only NT-proXNP retained its prognostic power also among patients with pulmonary oedema (P=0.018; Fig. 1B). The dual biomarker analyses enabled even more comprehensive risk stratification of patients with congestive HF (P<0.001 for all); in patients with pulmonary oedema a combination of NT-proXNP and TNF-α was the only one to identify patients at high risk of death within 12 months from discharge (P=0.010).



Survival curves for patients with AHF

Conclusions: Although the NT-proANP and NT-proBNP assays identified AHF patients with poor prognosis, the novel NT-proXNP assay was able to discriminate patients with different outcomes regardless of the clinical manifestation of the disease. Furthermore, the prognostic power of natriuretic peptides was significantly accentuated when combined with measures of inflammation.

P846 Right ventricular function predicts chronic kidney disease and survival in patients with chronic systolic heart failure

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Objective: Examine the association between right ventricular (RV) dysfunction and chronic kidney disease (CKD) and whether CKD might be a causal intermediate linking RV dysfunction and survival in chronic systolic heart failure (HF).
Background: The association between RV dysfunction and CKD has not been addressed previously.
Methods: Consecutive outpatients (n=390) with chronic HF and LV ejection fraction ≤45% underwent clinical and echocardiographic evaluations and were followed on average for 31±24 months. Tricuspid annular plane systolic excursion (TAPSE) assessed RV dysfunction. Estimated glomerular filtration rate (eGFR) was measured using the Cockroff-Gault formula. The odds ratios (OR) for CKD and hazard ratios (HR) for all-cause mortality were assessed using multivariable logistic or proportional hazards regression models.
Results: TAPSE≤14mm was associated with elevated right atrial pressure (RAP) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Patients with TAPSE≤14mm had an increased odds of eGFR<30ml/min, OR (95%CI)=5.97 (2.58,13.80), p<0.0001. Increased age, male gender, lower body surface area, and NT-proBNP were also independently associated with eGFR<30 ml/min. TAPSE≤14mm was also associated with an increased odds eGFR<60 ml/min: OR (95%CI)=2.48 (1.44,4.28), p<0.0001. TAPSE≤14mm predicted all-cause mortality, HR (95%CI)=1.76 (1.18,2.62), independent of age, gender, LV end-diastolic volume index, Framingham HF score, and NT-proBNP, which were also predictors of mortality in the multivariable model. The addition of estimated GFR<30 ml/min to the model attenuated the association between TAPSE and mortality by 23%.
Conclusions: RV dysfunction predicts CKD and survival in outpatients with chronic systolic HF. Our results also suggest severe CKD to be a possible causal intermediate linking RV dysfunction and death in this population.

P847 When chronic heart failure intersects chronic obstructive pulmonary disease: impact on long-term prognosis

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Purpose: Chronic obstructive pulmonary disease (COPD) frequently occurs in chronic heart failure (HF) and impacts on clinical status. We aimed to identify the prognostic value of COPD on long-term survival in HF patients.
Methods: We enrolled 446 consecutive patients with systolic HF (age: 65±13 years, 352 males, left ventricular ejection fraction -EF- <50%, mean±SD), on up-to-date drug and device treatment. All patients underwent a comprehensive clinical and neurohormonal assessment, as well as a complete spirometry for COPD staging (Global Initiative for Chronic Obstructive Lung Disease, GOLD). The prognostic value of COPD for all-cause and cardiac death was tested by multivariate Cox proportional hazard regression model.
Results: COPD was diagnosed in 127 patients (29% of total), who were assigned to mild (25%), moderate (55%), severe (17%) and very severe (3%) COPD stage, respectively. Patients with COPD were older (70±9 vs 64±12 years, p<0.0001), more symptomatic (NYHA class III/IV 50%vs 36%, p<0.005), were more likely to be smokers or ex-smokers (36 vs 14%, p<0.001). Furthermore, COPD patients showed higher plasma norepinephrine [631 (422-932) vs 489 (321-721) ng/L, median (interquartile range), p<0.0001] and NT-proBNP [1838 (830-4466) vs 1391 (503-3039) ng/L, p<0.001]. No difference was found for EF, haemoglobin, renin activity, aldosterone, cortisol, C-reactive protein and use of beta-blockers.
On a median 36-month follow-up (14-64) a total of 136 patients died, n = 85 for cardiac death. All-cause mortality was higher in COPD group (39% vs 27%, p<0.05) with a significant trend toward COPD stage and NYHA class (for both, p<0.001). Notably, 15 deaths (30% of total COPD deaths) were mainly related to COPD exacerbations leading to respiratory failure, which occurred more frequently as the severity of COPD increased (p<0.05). At univariate analysis, predictors of death resulted EF (odds ratio 0.97; 95% CI 0.94 to 0.99; p<0.01), NT-proBNP (odds ratio 1.4; 95% CI 1.09 to 1.9; p<0.01), NYHA class (odds ratio 2.5; 95% CI 1.4 to 4.5; p<0.01), as well as smoking habit (odds ratio 3.05; 95% CI 1.1 to 8.5; p<0.05), whereas at multivariate analysis, only NYHA class (odds ratio 2.4; 95% CI 1.3 to 4.4; p<0.01) and smoking (odds ratio 4; 95% CI 1.4 to 11.3; p<0.01) resulted independently related to the outcome.
Conclusions: HF patients with associated COPD have worse prognosis compared to HF patients without COPD. A more integrated strategy, namely to manage COPD exacerbations and to promote pulmonary rehabilitation, as well as smoking cessation, could improve clinical outcome of these patients.

P848 Comparison of mode of death among Chagas' disease, ischemic cardiomiopathy and other etiologies

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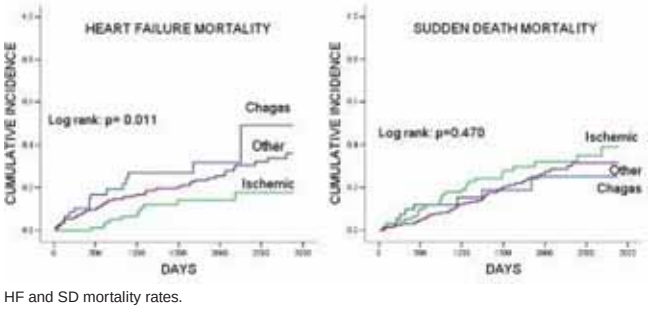
Purpose: Evaluate the mode of death (MD) in outpatients of a brazilian heart failure (HF) clinic focusing in the role of different etiologies.
Methods: 390 pts included from oct-1999 to feb-2006 and followed for 1475±903 days.
Results: There were 207 deaths (46.9%), which included 178 (86%) from cardiovascular causes (40.1% sudden death (SD) and 38.6% HF progression). There was significant difference in the incidence of HF progression death rates among

Multivariate predictors of mode of death

Mode of Death	Variable	p	HR	95% CI
Heart failure	Chagas' disease	0.002	4.758	1.771–12.788
	LVEDD (mm)	<0.001	1.08	1.047–1.106
	CrCl (ml/min/1.73 m^2)	0.023	0.988	0.977–0.998
Sudden death	LVEDD (mm)	<0.001	1.057	1.022–1.076
	β-Blockers use	0.016	1.913	1.130–3.239
	Age	0.027	1.026	1.003–1.050

LVEDD: left ventricular end diastolic diameter; CrCl: creatinine clearance.



HF and SD mortality rates.

different etiologies (p=0.011), but not in SD rates. Independent variables associated with death from HF progression were Chagas' disease, LVEDD and creatinine clearance and with sudden death were LVEDD, β-Blockers use and age.
Conclusion: Despite the general concept that deaths of Chagas' disease pts are mainly sudden they had a significant incidence of HF progression death. These results should be taken into account to a therapeutic approach based on HF etiology.

P849 Patterns of acute heart failure in nonagenarians

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Background: Since heart failure (HF) often occurs in >70y old subjects and the population of Western countries is getting older, the incidence of HF is expected to dramatically increase in the future. However, limited information is available on HF in the extreme elderly.
Methods: Using local and national French HF registries, we retrospectively studied 227 cases of >90y old patients admitted for acute HF. Patients with incomplete clinical records were excluded. Main areas of focus were: epidemiological data, initial presentation, biological results, imaging tests and clinical outcome.
Results: 77% of the patients were female. The mean age was 94 [range 91-97] and the main cardiovascular risk factors were hypertension (72%), hypercholesterolemia (18%) and diabetes (10%). 36% of patients had no known underlying cardiomyopathy at admission while 23% were ischemic, 21% hypertensive and 11% valvular (others 9%). In 10% of the patients, the cardiomyopathy had a mixed origin. The 3 main precipitating factors of acute HF were infection (37%), atrial fibrillation (22%) and acute coronary syndrome (13%). No factor could be identified in 15%. At admission, 31% of the patients were admitted to the ICU, 20% required breathing assistance and 5% inotropic drugs. Mean creatinine was 126±66μmol/L, BNP 1185 pg/mL [631-2359], and ejection fraction 49±15%. In-hospital mortality was 12% and significantly associated with female sex, a known cardiomyopathy at admission and breathing assistance in cox proportional hazard model (HR respectively of 13.4 [1.7-108.6], 5.3 [1.2-23.0], and 3.9 [1.4-11.0], P<0.05). For survivors, medical treatment at discharge included diuretics (85%), ACE inhibitors (60%) and beta-blockers (40%). Mean length of stay was 12 days [2-22] and almost half (46%) were not able to be discharged home directly but were dischaged to nursing homes.
Conclusion: Acute HF in nonagenarians is mainly triggered by infection and atrial fibrillation and associated with a high mortality, especially for female patients. Optimal medical therapy is often achieved at discharge. A significant proportion of patients need additional nursing care upon discharge.

P850 Right ventricular ejection fraction is an independent prognostic predictor in patients with ischemic heart disease

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Purpose: The number of studies on the prognostic value of the right ventricular ejection fraction (RVEF) in patients with ischemic heart disease (IHD) is limited. In a retrospective study we analyzed whether RVEF is an independent prognostic factor for mortality and morbidity in patients with IHD.
Methods: Between 2004 and 2008, 347 consecutive patients underwent a gated-equilibrium radionuclide ventriculography to determine the LVEF. With this technique the RVEF is also provided. RVEF was categorized in ≥40%(n=240) and <40% (n=107). Outcome parameters were all-cause mortality, cardiac mortality and cardiac hospitalization. Univariate analyses of potential prognostic factors (age, gender, LVEF, medication) was performed. Cox regression analysis was then conducted with significant univariate predictors added to the model.
Results: Mean RVEF was 44.7% (±11.0%). Median follow up was 826 days (range 3-2400). All-cause mortality rates were 12.1% and 29.0% in patients with an RVEF ≥40% and <40%, respectively (p<0.001) (figure 1). When comparing patients with an RVEF ≥40% to those with <40%, unadjusted hazard ratio (95% CI) for all-cause mortality was 3.45 (2.07-5.74). When adjusting for confounders, respective hazard ratios were 2.80 (1.60-4.90) for all-cause mortality, 4.15 (1.88-9.17) for cardiac mortality and 1.96 (1.20-3.19) for cardiac hospitalization.
Conclusion: RVEF assessed by gated-equilibrium radionuclide ventriculography is a significant independent predictor of all-cause mortality, cardiac mortality and cardiac hospitalization in patients with ischemic heart disease.

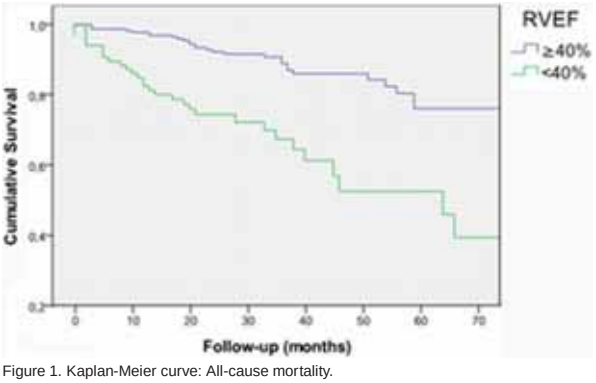

Figure 1. Kaplan-Meier curve: All-cause mortality.

P851 The six-minute walking test is still an excellent tool for ongoing monitoring of a population of elderly patients with chronic heart failure

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Background: Exercise intolerance is an outstanding feature of chronic heart failure (HF). The six-minute walk test (6MWT) and the cardiopulmonary exercise testing (CPx) provide a valid assessment of functional performance in patients (pts) with HF but in elederly pts a comparison on prognostic validity of the 2 techniques has not been yet performed.
Aims: We sought to compare the prognostic ability of the two functional tests in risk stratification of elderly CHF pts.
Methods: We prospectively followed-up 170 stable HF outpatients on optimized medical therapy by using a thorough clinical, laboratory and instrumental evaluation, including the 6MWT and the CPX. The composite end–point of was death or hospitalizations for cardiovascular causes.
Results: Mean age was 71±11 years, 28% were female, 43% had ischemic heart disease, 18% were in NYHA class III, 70% were on beta-blockers, 13% had an advanced diastolic disfunction, echocardiographic left ventricular ejection franction (LVEF) was 44±13%, mean BNP was 358±482 pg /ml. The mean distance covered during the 6MWT was 329±104 m. Peak workload was 71±11 watts, peak oxygen consumption (PVO2) was 13.2±4 ml/kg/min, the slope of the regression line relating ventilation to CO2 output, (VE/VCO2 slope) was 34±7. Exercise oscillatory breathing was found in 79 pts (46%). During a median follow-up of 13 months, 18 patients died of cardiovascular causes and overall 51 met the combined end point of death or cardiovascular hospitalization. Distance walked correlated significantly correlated to P VO2 (r=0.47, p<0.0001). By Cox multivariable analysis, independent predictors of outcome were mean distance covered during the 6MWT (HR 0.996, CI 95% 0.992-0.999), LVEF (HR 0.962, CI 95% 0.938 – 0.985) and PVO2 (HR 0.883, CI 95% 0.790-0.987).
Conclusions: Among elderly CHF pts 6MWT is not only a simple and reliable first – line test for quantification of exercise intolerance but retains a prognostic value independent of CPX derived PVO2. This is a cornerstone in functional assessment because the 6MWT is widely diffused, safe and may be more feasible than CPX in a population of elderly HF pts.

P852 Anemia and renal insufficiency in the different AHA/ACC stages of heart failure

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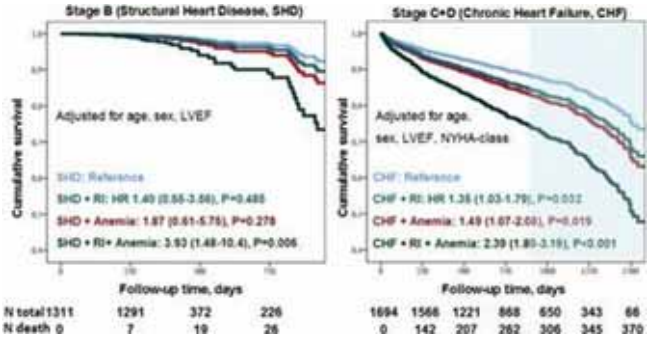
Background: Both anemia and renal insufficiency correlate with adverse outcomes in heart failure (HF). Data regarding the prognostic impact in the early asymptomatic stages of HF are scarce. In the present analysis we compared prevalence and prognostic impact of these frequent comorbidities in the different stages of heart failure.
Methods: Patients were selected from 4 CNHF cohorts, if they had complete standardized data sets including echo/Doppler obtained at baseline and at least one complete follow-up examination. 3260 patients allocated to ACC/AHA stages A (n=255), B (n=1311), C1 (NYHA I+II; n=1080), C2+D (NYHA III+IV, n=614) were according to clinical and echocardiographic findings. Anemia was defined as hemoglobin <13/12 g/dl in men/women (WHO criteria), and RI as a glomerular filtration rate <60 ml/min/1.73m^2.
Results: Average patient age in A/B/C1/C2+D was 64/67/65/68 yrs (P trend <0.001); 52/53/37/36% were female. Mean hemoglobin and GFR decreased with increasing HF severity (14.2±1.3/14.0±1.2/14.0±1.8/13.4±2 g/dl, P<0.001, and

76±18/74±18/74±24/64±26, P<0.001), while prevalence of anemia and RI increased (5/8/18/31%, P<0.001, and 19/21/27/48%, P<0.001). In Cox Regression adjusted for age, sex, ejection fraction, NYHA-class coincidence of anemia und RI was incrementally associated with mortality both in asymptomatic (stage B) and symptomatic patients (stage C+D).



Prognostic impact of anemia and RI

Conclusions: Significant prevalence rates of both, anemia and RI were found already in patients at risk to develop HF (stage A) and in patients with asymptomatic structural heart disease (stage B). Prevalence increases further with HF severity. The prognostic impact of anemia and RI is cumulative and equally adverse in early and advanced HF stages.

P853 Rapidly progressive coronary artery vasculopathy in heart transplant recipients: a volumetric intravascular ultrasound evaluation

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Purpose: Coronary artery vasculopathy (CAV) remains a leading cause of morbidity in heart transplant recipients. While intravascular ultrasound (IVUS) is used to monitor focal changes to detect CAV, volumetric changes have not been well characterized. The current study characterized factors associated with volumetric features of CAV in heart transplant recipients.
Methods: 76 patients underwent IVUS imaging within a coronary artery following transplantation and at 12-month follow-up between 2000 and 2009. Volumetric changes in vascular dimension and patient demographics were characterised. Patients received standard immunosuppression with a calcineurin inhibitor, mycophenolic acid moefitl and steroids.
Results: Recipients were treated with statins routinely (78.7%). Rapidly progressive CAV (increase maximum intimal thickness [MIT] ≥0.5 mm in one year) was observed in 23% and associated with greater disease burden and lumen reduction. (Table) Volumetric analysis showed remarkable progression in percent atheroma volume (PAV, +3.2±0.6%, p<0.001) and total atheroma volume (+13.5±3.3 mm^3, p<0.001), with reductions in the external elastic membrane (EEM, -17.1±8.8 mm^3, p=0.06) and lumen (-30.5±7.8 mm^3, p<0.001) volumes. Aggressive disease progression was correlated with contraction of lumen volumes (r= -0.59, p=0.006), but no changes in EEM dimensions (r= -0.34, p=0.14). Aggressive disease burden was observed in the recipients who were more likely to be treated with insulin (57.9 v 26.8%, p=0.01), and with donors who were older (37.5±13.1 v 29.6±13.5 years, p=0.03), had a higher BMI (28.8±5.1 v 25.8±4.7 kg/m^2, p=0.04), and more likely to be hypertensive (31.6 v 5.3%, p=0.006) and smokers (26.3 v 3.5%, p=0.009).

Change in parameter	ΔMIT <0.5 mm (n=66)	ΔMIT ≥0.5 mm (n=20)	P Value
Percent atheroma volume (%)	0.8±0.4	11.3±0.7	<0.001
Total atheroma volume (mm^3)	2.6±2.9	50.3±5.3	<0.001
EEM volume (mm^3)	–14.1±10.1	–26.9±18.6	0.55
Lumen volume (mm^3)	–15.8±8.3	–80.4±15.3	<0.001

Conclusion: Profound atheroma accumulation is observed in heart transplant recipients on volumetric analysis, associated with a constrictive form of arterial wall remodeling. There is an ongoing unmet opportunity to reduce the development of CAV despite use of contemporary therapies following heart transplantation.

P854 Clinical outcomes in advanced acute heart failure (AHF) patients stratified by INTERMACS classification

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Purpose: Risk stratification in patients presenting severe heart failure in the Intensive Care Unit (ICU) with acute decompensation is difficult. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) had defined seven clinical Profiles to describe patients included in its registry. We assessed the INTERMACS (IMCS) classification in patients admitted in an ICU with cardiogenic shock.
Methods: Consecutive patients with cardiogenic shock on admission who were admitted in a tertiary hospital ICU. IMCS status was assessed at within the first 24 hours and 96 hours after admission. Outcomes (bi-ventricular assist device (BiVAD), heart transplantation (HT) and mortality) were recorded in hospital and at 3 and 12 months.
Results: The study included 87 patients (median age 60 [IQR:54-69] years). 41 (47%) patients had IABP and 27 (31%) were on mechanical ventilation. At 24 hours after admission, 7 patients (8.04%) with IMCS Profile 1 (critical cardiogenic shock), 18 (20.6%) with IMCS Profile 2 (sliding on inotropes) and 62 (71.3%) with IMCS Profile 3 (dependant on inotropes). Results are presented in the table.

Best IMCS Profile within the first 24 hours	IMCS Profile1 (n=7)	IMCS Profile2 (n=18)	IMCS Profile3 (n=62)
Ischemic myocardiopathy	3 (42.9%)	12 (66.7%)	28 (45.2%)
Median age (yr-IQ)	57 (5.5)	62 (16)	58 (7)
Evolution 24-96 hours: Died	5	4	1
Evolution 24-96 hours: BiVAD or HT	1	2	3
Alive without BiVAD or HT at the 96th hour	1 (14%)	12 (66.6%)	58 (93.5%)
Evolution in ICU after the 96th hour			
Died		4	4
BiVAD or HT		4	7
Discharged from ICU without BiVAD or HT	1 (14%)	4 (22%)	47 (75.8%)
3-months mortality	n=5 (71%)	n=12 (67%)	n=21 (34%)*
1-year mortality	n=6 (86%)	n=12 (67%)	n=27 (44%)*

*p values <0,05 Profile3 vs 2, Profile3 vs 1.

Conclusion: In patients with cardiogenic shock, the INTERMACS classification is an easy way to classify patient's risk during the first 24 hours. Evolution of IMCS profiles allows to assess response to treatment over time. It may present as a useful tool in the ICU to discuss early the best strategies to manage cardiogenic shocks.

LONG TERM FOLLOW UP IN CARDIAC RESYNCHRONISATION THERAPY. IS THERE ROOM FOR A CRYSTAL BOWL?

P855 Seattle heart failure model predicts survival in patients with cardiac resynchronization therapy: a validation study

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Purpose: The aim of our study was to validate the Seattle Heart Failure Model (SHFM) in patients with cardiac resynchronization therapy (CRT).
Methods: Prospectively collected registry data of 402 patients with CRT (either pacemaker or defibrillator) was used for the evaluation of the discrimination and calibration performance of the SHFM. The primary end point was all-cause mortality. Expected probabilities of mortality at 1, 2, and 5 years into follow-up were calculated from SHFM scores and were used as explanatory variables in logistic regression models with corresponding observed vital status as outcome to assess classification performance. Calibration profile was assessed using Hosmer-Lemeshow tests. Discrimination was assessed by calculating areas under receiver-operating characteristic curves (AUC) derived from the models. Analyses stratified by type of device were also carried out, including testing for significance of differences.
Results: Mean (SD) age of the study population was 61.0 (11.1) years (male: 73.6%), 53.7% (216/402) of the patients received a biventricular pacemaker while 46.3% (186/402) got a biventricular defibrillator. During a median follow-up of 17.9 months, 17.2% (69/402) of patients reached the primary end point, with observed outcomes of 34/283, 54/217, and 69/91 at years 1, 2, and 5, respectively. No evidence of insufficient fit was found in any calibration tests. AUC estimates in all subjects were 0.7165 (95%CI 0.6313 to 0.8017) at year 1, 0.7743 (95%CI 0.7075 to 0.8410) at year 2, and 0.7628 (95%CI 0.6425 to 0.8832) at year 5. In pacemaker vs defibrillator recipients, AUC estimates were 0.7344 vs 0.7042 (p=0.734), 0.7940 vs 0.7636 (p=0.660), and 0.7599 vs 0.7623 (p=0.985) at years 1, 2, and 5, respectively.
Conclusions: SHFM offers an accurate prediction of survival in patients with CRT with good observed calibration and AUC estimates indicating discrimination performance similar to those found by earlier validation studies in different heart failure populations. No evidence of classification performance heterogeneity over device type was found.

P856 Intermacs level 2-3 class iv patients have worse outcome after cardiac resynchronization therapy than stable class IV patients

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Introduction: Cardiac resynchronization therapy (CRT) is a well established treatment for advanced heart failure (HF). However, its use in patients with NYHA Class IV is still controversial. We aimed to investigate the impact of CRT on survival and identify predictors of response in Class IV drug-refractory HF patients.
Methods: Retrospective analysis of a prospective register of 486 patients treated with CRT between 2000 and 2009 in one centre. We identified 42 NYHA Class IV patients, 23 (55%) of whom were inotrope-dependent, mean age 64±12 years, BMI 25±5, FE 20±6%, QRS width 172±31 msc. Basal measurement and 6- and 12-month follow-up included clinical assessment, echocardiography, 6 minutes walk test (6MWT), quality of life assessment (QoL), and biochemistry.
Results: During a mean follow-up of 13.9±11.8 months, 21 patients (50%) died or underwent heart transplantation (15 [36%] pump failure events, 3 [7%] sudden death events, 3 [7%] transplants). Kaplan-Meier analysis showed reduced survival for patients on inotropic support (INTERMACS 2-3, log rank p=0.026). Cox regression analysis showed increased mortality for inotrope-dependent patients (HR 2.8, 95% CI 1.0-7.5, p=0.03), with a high number of hospitalizations in previous months (HR 1.4, 95% CI:1.0-1.9, p=0.014) and low sodium levels (HR 0.8, 95% CI: 0.8-0.9, p=0.002).

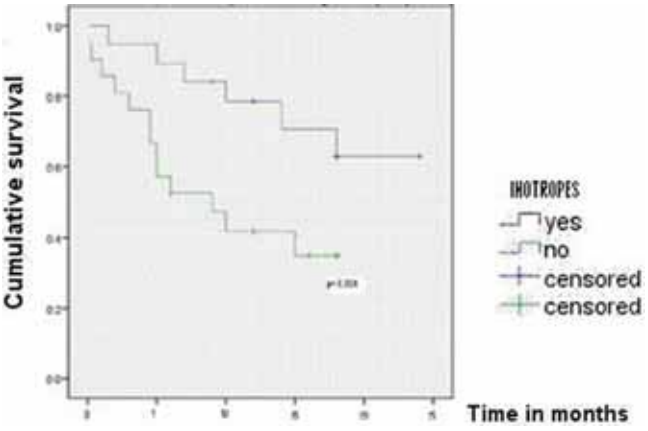

Figure 1. Survival of CRT patients according to inotrope dependency.

Conclusions: Class IV inotrope-dependent patients have very high mortality despite CRT. In our series this set of patients did not receive a survival benefit from CRT.

P857 Long-term outcome of eligible CRT-D candidates versus patients treated with CRT-D according to degree of clinical and echocardiographic response

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Purpose: To determine event-free survival of eligible CRT-D candidates who only received ICD in comparison to patients receiving CRT-D with either good or poor clinical and echocardiographic response to CRT.
Methods and patients: We analyzed 193 consecutive heart failure patients on optimal medical therapy who were eligible candidates for CRT-D implantation, of whom 164 received implantation of CRT-D (mean age 61±11 years, 81% male) and 29 patients (mean age 56±13 years, 83% male) only underwent ICD implantation between the years 1998 and 2009. All patients were followed up at our outpatient device clinic and heart failure clinic after implant. Clinical improvement was defined as either as improvement of NYHA class ≥1 or extension of ≥ 50m in 6-min-walk-test. Echocardiographic improvement was defined as either a categorical increase of systolic LV-function ≥1 category (EF<30% to 30-40% or 30-40% to 41-51%) or a reduction of LVEDD ≥ 10mm. Response to CRT was only considered existent when at least one clinical and one echocardiographic improvement was demonstrated in follow up. Clinical outcome (shock therapy, heart transplantation (HTx) and death) was compared between patients who responded to CRT-D (responders), patients without clinical/echocardiographic response (non-responders) and those who only received ICD.
Results: During follow-up (mean 2.7, max. 8.9 years; in total 445.1 patientyears), 28/164 (17%) patients responded to CRT-D per definition. No confounding differences were found between the groups in regards to gender or cardiovascular risk factors. Appropriate shock delivery in follow up occurred in 3.6% of patients who responded to CRT, in 3.7% of non-responders and in 20.7% of patients with ICD only (p<0.01), equaling to 1.1, 1.4 and 8.9 patients receiving ≥ 1 appropriate shock per 100 patientyears, respectively. Estimated five-year survival was highest among patients who showed good clinical and echocardiographic response to CRT and lowest among those with ICD only (log rank test p<0.05). Event-free survival from death/HTx did not significantly differ between the 3 groups (log rank test p=NS).
Conclusions: Evidence of clinical and echocardiographic response to CRT identifies patients who are at lower risk of death, yet not at lower risk of appropriate shock delivery or HTx. In overall comparison, implantation of ICD only in patients who are eligible for CRT-D is associated with higher all-cause mortality and risk of appropriate shock delivery in long-term follow up. Enhanced patient selection criteria for CRT-D may improve the rate of response to CRT.

P858 Long term outcomes in patients receiving cardiac resynchronization therapy: a 10-year single center Irish registry

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Background: Internationally, data on long term follow up of patients treated with Cardiac Resynchronization Therapy (CRT) is scarce. To our knowledge, there are no registries in the Republic of Ireland that have followed up patients implanted with CRT, assessing improvement of symptoms, mechanical and electrical dyssynchrony, and mortality benefit. The aim of this registry is to characterize our patient population that are treated with CRT with view to quantifying the long-term effect of CRT on clinical status, improvement of echocardiographic parameters, and survival benefit.
Methods: This is a retrospective observational study that looked at consecutive patients that have been implanted with CRT in a single center in Dublin over the past 10 years. We registered their baseline demographics and assessed their indication for implantation. We then looked at their most current office visit to establish their most recent NYHA status, QRS duration, and their most recent EF. All mortalities were noted along with documentation of the interval between time of death and date of CRT implant.
Study results: 202 CRTs were implanted between 2001 and 2011 in our center.Average age of our patient population was 71 years of age. 87% of the patients were male. 21 of the implanted devices were CRT-Ps and the rest were CRT-Ds. 69% of the patients had an underlying ischemic cardiomyopathy. Mean follow up was 5 years.With view to indications of CRT implantation: average EF at time of implant was 28.8% with a LV end systolic dimensions of 6.1 cm, the average QRS duration was 164.8 milliseconds, the average NYHA functional classification at time of implant was 3.1. The EF rose to 34.6% on average after CRT therapy and the QRS duration was shortened to 131.2 milliseconds. In terms of functional classification, thepatients' NYHA status improved by an average of 1.2 classes.
71% of the patients were on Aspirin, 82% on beta-blocker therapy, 74% on ACE-inhibitor or ARB's, and 84% were on diuretics prior to and post implantation. However, a trend was noted that the required diuretic dosages were reduced after implantation due to improvement in symptoms.
Out of the 202 patients, 45 died (22%). 8 of those had their devices implanted within 1 year of their mortality.
Conclusion: This is observational retrospective analysis of our center's experience in CRT implantation over the past 10 years. It shows trends in improvement in EF, NYHA status, and electrical dyssynchrony with this therapyin our patient population with mortality benefit and long term outcomes that are comparable to the international data.

P859 Impact of mitral regurgitation on the outcome of heart failure patients treated with a biventricular defibrillator: real world data from the InSync ICD Italian Registry

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Purpose: To assess the influence of presence/absence of a clinically significant mitral regurgitation (MR) at baseline on the clinical- echocardiographic response and the outcome in heart failure (HF) patients treated with a biventricular defibrillator (CRT-D device).
Methods: A total of 659 HF patients underwent successful implantation of a CRT-D device and were enrolled in a multicenter prospective registry (median follow up of 15 months). According to baseline echocardiographic evaluation, patients were stratified in two groups according to the MR severity at baseline: 232 patients with more than mild MR (Group MR+: grade 2, 3 and 4 MR) versus 427 patients with mild (grade 1) or no functional MR at baseline (Group MR-).
Results: At 6 and 12-month echocardiographic evaluation MR improved in the vast majority of MR+ patients, while remained unchanged in most of MR- patients. At 12 months of follow up comparable response to CRT was observed in the two groups in terms of extent of LV reverse remodeling and combined clinical and echocardiographic response. During long-term follow-up, event-free survival did not differ between MR+ and MR- patients, even when the subpopulations of

patients with ischemic heart disease with dilated cardiomyopathy were analysed separately. At multivariate analysis the only independent predictor of death from any cause was the lack of β-Blockers use.
Conclusions: In "real world" practice the presence of a clinically significant mitral regurgitation should not limit the indication to CRT-D in HF patients and no major influence on patients' outcome has to be expected.

P860 Predictive role of QRS hieroglyphic morphology for response to cardiac resynchronization therapy

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Purpose: Nearly a third of patients with advanced systolic heart failure complicated by ventricular conduction delay fail to derive benefit from cardiac resynchronization therapy (CRT). We hypothesized that response to CRT is predicted by QRS hieroglyphic morphology on surface electrocardiogram (ECG).
Methods: Twelve-lead ECGs before cardiac resynchronization therapy were analyzed in 78 consecutive patients [44 patients with ischemic heart disease and 34 with dilated cardiomyopathy, aged = 67.4yrs old, New York Heart Association class III to IV heart failure, mean ejection fraction = 25%, mean QRS duration = 156.7ms (120ms-228ms)]. Based on conventional ECG criteria patients were divided into those with LBBB morphology (n=56), RBBB morphology (n=11) and nonspecific intraventricular conduction disturbance (IVCD) (n=11). In addition, among patients with conventional LBBB we separated those with typical LBBB activation which is registered as right to left (frontal plane), anterior to posterior (horizontal plane), and variable axis. Typical LBBB is characterized by a QRS hieroglyphic signature with dominant positive forces in I, aVL (R, Rs); negative forces in aVR (QS); variable forces in II, III, AVF; dominant negative forces in V1 through V2 (QS, rS); transition V3 through V5; and dominant positive forces in V5 through V6 (R, Rs). Response to CRT was defined as reduction in NYHA class ≥1 and/or increase in LV ejection fraction ≥5% 6 months after CRT.
Results: Response to CRT was observed in 56 patients (71.8%). Typical LBBB morphology was present in 31 patients (55.4%). In the whole study population the incidence of response to CRT did not differ between patients with conventional LBBB compared to those with either RBBB (76.8% vs. 54.5%, log rank p=0.13) or IVCD (76.8% vs. 63.6%, log rank p=0.36). Presence at baseline of conventional LBBB did not predict response to CRT (OR=2.29, CI 0.8-6.55, p=0.12). Among patients with conventional LBBB the presence at baseline of typical LBBB hieroglyphic morphology predicted significantly response to CRT (OR=3.8, CI 1.005-14.4, p=0.049). Similarly, response rates were significantly higher in patients with typical LBBB compared to those without (87.1% vs. 64%, log rank p=0.044).
Conclusions: Presence at baseline of LBBB hieroglyphic morphology predicted significantly response to CRT. Use of 12-lead surface ECG might improve CRT patient selection.

P861 QRS voltage predicts response to CRT in patients with left bundle branch block

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Background: The QRS complex is a reflection of the summation of instantaneous electrical forces within the heart. In left bundle branch block (LBBB), the propagation of the electrical wavefront is dyssynchronous and unopposed, and is thereby associated with an increase in the QRS voltage in the precordial leads.The aim of this study was to assess the impact of cardiac resynchronizationtherapy (CRT) on QRS voltage and its ability to predict response.
Methods: Twelve-lead EKGs were analyzed in 105 consecutive patients with LBBB (age 67±12 years, 81 men, LVEF 22±6%, QRS width 159±22ms) who received CRT for a median duration of 29 months.
Results: Fourteen patients reached the composite endpoint of death (N=12) and cardiac transplant (N=2). Total QRS amplitude in leads V2-V4 decreased significantly with CRT (values preimplant/immediately postimplant, P<0.001 for all changes): lead V2 2.5±0.9mV/1.2±0.7mV, lead V3 2.6±0.7mV/1.4±0.8mV, and lead V4 1.7±0.7mV/1.3±0.6mV. Patients in whom the total QRS amplitude in lead V3 decreased with CRT had significantly better survival that patients in whom it increased or did not change (Figure). Changes in QRS amplitude in lead V3 correlated with changes in LVEF over a period of 6 months post implant (r= -0.301, p=0.039). Total QRS amplitude in lead V3 and its change with CRT independently predicted event free survival in multivariate Cox models that included age, gender, baseline LVEF and the change in QRS duration.
Conclusion: A reduction in the QRS voltage in the precordial lead V3 is predictive of response to CRT in patients with LBBB.

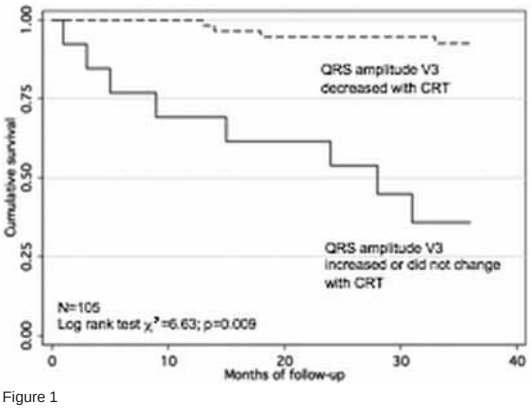

Figure 1

P862 QRS decomposition using the morlet wavelet transformation as a novel tool for predicting response to cardiac resynchronization therapy

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Purpose: Among eligible patients for cardiac resynchronization therapy, those with QRS ≥150 ms and left bundle branch block (LBBB) are more likely to respond. According to recent reports not all LBBBs are created equal and the wavefront pattern of myocardial ventricular activation may differ between responders and non responders. Aim of the present study was to explore the differences in the QRS complex components between responders and non-responders to CRT.
Methods: We conducted a pilot prospective study in consecutive patients with heart failure and LBBB treated with CRT according to established guidelines. Signal averaged electrocardiograms were recorded before implantation and QRS decomposition was performed by dedicated software using the Morlet wavelet transformation. Wavelet parameters expressing the mean and maximal (max) energy were calculated in three orthogonal axes (x,y,z) and in the vector magnitude (vm), in each of three frequency bands (200-160 Hz, 150-100 Hz, 90-50 Hz). Patients were followed up for 6 months. Response was defined as clinical improvement by one or more NYHA classes or decrease in left ventricular end systolic volume (LVESV) by 15%.
Results: A total of 24 patients (age 64±9 years, 20 males) were studied. At baseline mean QRS duration was 162±26 ms, left ventricular ejection fraction (LVEF) 24±6% and LVESV 156±36 ml. At month 6 LVEF had increased to 31±9% (p=0.028) and LVESV had decreased to 132±67 ml (p=0.046). Eighteen patients (75%) were identified as responders. Responders had wider baseline QRS (169±26 vs 142±10ms, p=0.002) and lower mean and max energies in all frequency bands on x axis as compared to non-responders. Multivariate analysis identified max energy of the QRS complex recorded in the higher frequency band (200-160 Hz) on x axis as an independent predictor of response (p=0.002). A cut-off value of ≤35.18 μV had 94% sensitivity and 83% specificity in predicting response to CRT (AUC, 0.935, p=0.002).
Conclusions: This pilot study showed that wavelet transformation of the amplified QRS complex may contribute in discriminating among patients who are more likely to benefit from CRT. A larger prospective study is deemed necessary to validate our findings.

P863 Prognostic value of fragmented QRS in CRT-D patients

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Purpose: Fragmented QRS on electrocardiogram (ECG) can suggest a myocardial scar. It is a marker of depolarization abnormality that can be correlated with higher risk of sudden cardiac death. The purpose of this study is to analyze the responsiveness to CRT-D and cardiac event rate in patients with fragmented QRS in spontaneous and stimulated heartbeat.
Methods: 58 consecutive patients, candidated to CRT-D, were included in this study (mean age 70.8±6.8 years, mean EF 24±9%, NYHA III). They performed an echocardiogram and 12-lead ECG before and after CRT implant. The ECG were analyzed by 3 independent readers blinded to clinical outcome during 6 month follow-up. Fragmented QRS in patients without left bundle branch block (LBBB) were defined as: presence of an additional R wave, notching in the nadir of the R wave or the S wave or one fragmentation of R wave in two or more contiguous leads. Fragmented QRS complexes in patients with LBBB were defined as more than 2 notches in the R or the S wave. The arrhythmic events were reviewed in all patients. Non responders were defined as patients with no improvement of NYHA class and increase of ejection fraction (EF) at 3 months <10% than baseline. Interventricular dyssynchrony was measured considered an aorto-pulmonary pre-ejection delay >40 msec.
Results: Spontaneous fragmented QRS prevalence was 66% in all patients; stimulated fragmented QRS prevalence was 52% in ischemic and 59% in non-ischemic patients. Elderly (≥65 years) have a 2.8-fold higher risk to have a stimulated fragmented QRS (p=0.005). At 6 months follow-up, the incidence of non responders to CRT is higher in patients with stimulated fragmented QRS (88% vs 45%; p=0.031). Patients with spontaneous non-fragmented QRS have a greater reduction of left ventricular dyssynchrony (-34.9±11.7 ms vs -11.3±26.0 ms,

p=0.030) and an increase of mean systolic arterial blood pressure (6.7±18.1 mmHg vs -7.2±14.5 mmHg, p=0.024); patients without stimulated fragmented QRS showed a greater increase of left-ventricular EF than baseline (12.9±12.3% vs 6.23±9.7%, p=0.009) at 6 months. We did not found any difference in arrhythmic events.
Conclusions: Non-fragmented QRS is associated with an improvement of echocardiographic parameters in CRT patients, thus it could be a good marker in identifying responders. Instead, the persistence of stimulated fragmented QRS is associated with lack of response to CRT making this subgroup of patients less likely to benefit from CRT. In our study fragmented QRS is not predictive of arrhythmic events in CRT patients; this aspect should be assessed with longer follow-up.

P864 The benefit of cardiac resynchronization therapy and QRS duration: a meta-analysis

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Purpose: Cardiac resynchronization therapy (CRT) improves outcomes in patients with left ventricular systolic dysfunction and a wide QRS complex. Whether this benefit is consistent across all degrees of QRS widening is unclear. We performed a meta-analysis of subgroup data from randomized clinical trials to evaluate the impact of QRS duration on the efficacy of CRT.
Methods: We searched MEDLINE and EMBASE databases for studies evaluating the efficacy of CRT with or without implantable cardioverter defibrillator (ICD) in patients with heart failure. Only trials which reported subgroup data according to QRS duration were included. Hazard ratios (HR) with 95% confidence interval (CI) were calculated using a random effects modeling approach.
Results: Five trials involving 6,501 patients (4,437 with QRS>150ms and 2,064 with QRS<150ms) were included. Three trials, enrolling patients with mild to moderate heart failure, compared CRT-ICD with CRT, whereas CRT vs. medical therapy was compared in the other 2 trials, which included patients with advanced heart failure. The QRS duration cut-off varied from 148ms to 160ms (median 150ms). Based on the pooled estimate across the 5 studies, CRT significantly decreased the primary endpoint of death or hospitalization for heart failure in patients with QRS>150ms (HR=0.58, 95% CI 0.50 to 0.68; p<0.00001, Figure), but not in patients with narrower QRS (HR=0.95, 95% CI 0.83 to 1.10; p=0.51, Figure). These results were consistent across all degrees of heart failure severity.

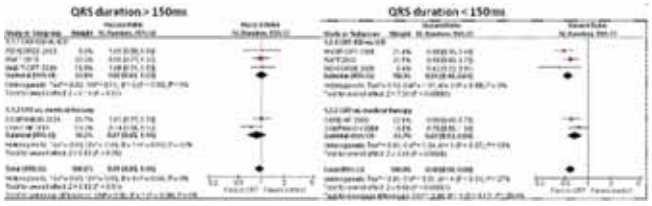

Figure 1

Conclusions: The benefit of CRT appears to be dependent on QRS duration. Available data suggest a significant benefit associated with CRT in patients with QRS>150ms, but do not conclusively show that CRT improves outcomes in patients with QRS<150ms.

P865 Chronic RV pacing prior to CRT decrease hemodynamic responds and long term survival

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The growing number of chronic RV paced patients (pts) course an increased part of CRT in the hole CRT population. The ESC* recommends CRT in pts with concomitant pacemaker indication, NYHA III and LVEF≤35%. It is not clear if the well proved effect of CRT to hemodynamic and mortality in classic CRT pts can translate to prior chronic RV paced pts.
Methods: We investigated 142 pts who received a CRT device from 2005 to 2008 in our center. Following the implantation AV and VV delay were optimized using invasive pulse pressure and dp/dt. Further a Kaplan Meier survival analyses was investigated for long term survival in a mean of 3.6±1.1 years.
Results: 25 of 142 pts were chronic RV paced prior to CRT. There were no differences in baseline characteristics. The pts with prior paced RV had a significant lower VO2max, but lower NT-proBNP level. The acute hemodynamic responds was significant lower and a trend to a higher mortality in prior RV paced pts.

	All (n=142)	No RV pacing (n=117)	RV pacing prior CRT (n=25)	p
Age (years)	66±9	67±9	65±8	ns
NT-proBNP (pg/ml)	4261±5898	4629±6212	1592±225	0,001
VO2max (ml/min/kg)	13±4	13±5	11±3	0,01
% dp/dt max	31±79	33±86	18±14	0,01

Conclusion: RV pacing prior CRT upgrade reduces the acute hemodynamic responds and may reduced the long term survival in contrast to classic CRT pts. Further studies should investigate this type of CRT pts for a better understanding.
*EHJ (2010) 31, 2677–2687

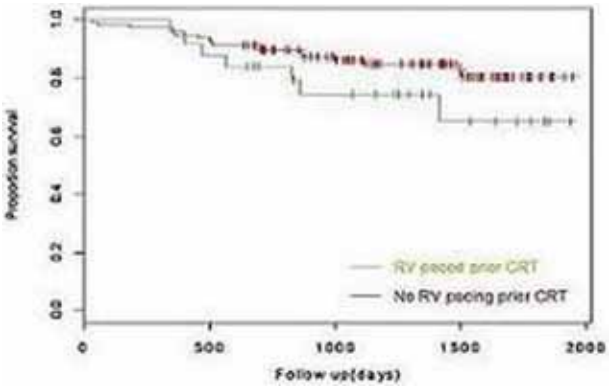

Figure 1

P866 Effects of long-term resynchronization therapy in pacemaker patients upgraded to biventricular pacing, a single-center, long-term follow-up study

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Backgound: Cardiac resynchronisation therapy (CRT) is an effective, non-pharmacological treatment modality in patients with severe symptomatic, therapy-refractory heart failure, wide QRS and a severe left ventricular systolic dysfunction. There is only a few data on the long-term effects of CRT upgrade in pacemaker patients.
Objective: To assess the effects of cardiac resynchronization therapy in pacemaker patients upgraded to CRT between 2005-2010 in a single-center experience.
Methods: 62 pacemaker and 59 ICD patients with a device implanted for 60,4±58,6 months were upgraded to CRT therapy. Clinical, echocardiographic and electrocardiographic data were evaluated before the device implantation and during the follow-up visit. The quality of life was assessed using the EQ-5D questionnaire.
Results: 77 of 119 patients had ischaemic cardiomyopathy (mean age 70±10 years, 97 male). During the mean follow-up duration of 19±15 month, 36 patients died of cardiac and non-cardiac causes. QRS duration (175±31,1 vs. 140±32,2 ms; p<0,001), the degree of mitral insufficiency (2,4±0,9 vs. 2,0±0,9; p=0,032), and the pulmonary artery pressure (48,3±13,8 vs. 41,3±11,2 Hgmm; p<0,001) decreased significantly during the follow-up. The decrease in QRS duration was associated with a significant improvement of the left ventricular systolic ejection fraction (29,8±7,6 vs. 35,9±8,4%; p<0,001) and improvement of the clinical status (NYHA functional class 3,0±0,8, vs. 2,4±0,8; p<0,001). The beneficial clinical effects were associated with the improvement of the quality of life, as assessed both by visual analog scale (46,5±22,1 vs. 60,6±21,1; p<0,001) and by the clinical composite score (0,59±0,29 vs. 0,75±0,23; p<0,001). Multivariate survival analysis using Cox's regression model showed previous PCI (p=0,047), deep vein thrombosis (p=0,03), pulmonary embolism (p=0,008), pulmonary artery pressure (p=0,026) and baseline urea level (p=0,021) to be an independent predictor of mortality.
Conclusions: CRT upgrade in pacemaker and ICD patients resulted in significant improvement of clinical and echocardiographic parameters as well as in improvement of the quality of life. In our study population, renal dysfunction, ischaemic cardiomyopathy and the function of the right ventricle were independent predictors of mortality.

P867 Long-term adverse effect of right ventricular pacing on ICD patient survival: Is it mitigated by cardiac resynchronization?

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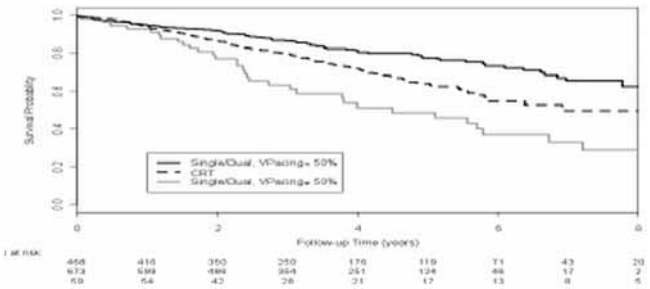
Purpose: Chronic right ventricular pacing (RVP) increases the risk of death and heart failure (HF) in ICD patients with left ventricular dysfunction (LVD), and it decreases survival (SURV) of MADIT II patients without left bundle branch block. Our aim was to assess the long-term adverse effect of RVP on SURV in the overall ICD population with LVD, and to determine if it is mitigated by cardiac resynchronization (CRT).
Methods: The study included all ICD patients at our center ≥18 years with ejection fraction (EF) ≤35%. Excluded were 145 patients upgraded to CRT after single

or dual chamber (S or D) ICD. SURV were estimated by the Kaplan-Meier method and compared by the logrank test. A Cox proportional hazards model assessed the effects of clinical variables on SURV.
Results: Between 2000 and 2009 we followed 1200 patients: 673 had ICD-CRT (avg age 69.2±11.7 years; EF=22.3%±7.2; paced avg 93.3%±18.2, median 99%), 468 had S or D ICDs and were paced less than 50% (avg age 64.2±12.0years; EF=25.5%±6.8; paced avg 2.2%±6.6, median 0%) and 59 had S or D ICDs and were paced ≥50% (avg age 69.7±12.3 years; EF= 25.6±6.1; paced avg 87.8%±15.8, median 96%). The SURV of the 3 groups are shown in the graph (global p<0.0001; p<0.005 for all pairwise comparisons). After adjusting for variables, including age, HF, EF, diabetes, chronic kidney, lung, and vascular disease, and cardiac surgery, the SURV difference remained significant (global p=0.0116),but the SURV of CRT patients was similar to S+D patients paced <50% (HR=1.2[95%CI 0.9-1.7]; p=0.182).



Survival After ICD Implant.

Conclusion: The adverse effect of RVP on SURV is sustained long-term, but the impact appears to be mitigated by CRT. This finding suggests that biventricular synchronization may improve the survival of ICD patients who have LVD and require chronic ventricular pacing.

P868 Biventricular pacing in patients with bradycardia and normal ejection fraction: Tugendhat study

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Objectives: Observational studies suggest that long-term conventional right ventricular (RV) pacing may have a deleterious effect on left ventricular (LV) function. The aim of the TUGENDHAT Study was whether biventricular (BiV) pacing is superior to right vntricular (RV) apical pacing in preventing deterioration of LV systolic function, cardiac remodeling and atrial fibrillation (AF) onset.
Methods: 151 consecutive patients with AV block and standard indication for permanent ventricular pacing were included. In all the standard biventricular pacemaker was implanted. Using a multicenter, prospective, randomized crossover design, after a run-in phase (6 week after implant) 6 month of RV pacing were compared with 6 month of BV pacing with regard to LV ejection fraction (EF), N-terminal pro-B-typu natriuretic peptide (NT-proBNP) plasmatic concentration, 6 min walk test, and quality of life in this.
Results: At 12 month, the mean LVEF was significantly lower in the RV pacing group than in the BiV pacing group (52±8% x 61.8±9%, p<0.001), BiV pacing reduced LV end-diastolic (- 8.2%, p<0.23 and end-systolic volumes (-17.2%, p<0.001), the Minnesota Living with Heart failure score was lower in BiV pacing group (52±12 x 76±17 in RV pacing group, p<0.001), there was no significant NT-proBNP level difference in both pacing modes (1128±521 in RV x 721±386 pg/ml in BiV). There was 1 death in the BiV pacing phase and 11 in during the RV pacing phase.
Conclusions: In patients with normal systolic function, conventional permanent right ventricular apical pacing resulted in LV remodeling and reduction in the LV ejection fraction. These effects were prevented by biventricular pacing. The patient population will be observed for totaly 5 years. It was an investigator-driven trial by IGA grant NR 9190-2007.

P869 Super-responders after cardiac resynchronization therapy implants: results of a single center study

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Purpose: The aim of this study is to assess the characteristics of CRT super-responders patients based on echocardiography evaluation.
Methods: 149 patients implanted from 2004 to 2009 with CRT, with or without defibrillator back-up, were considered for the analysis. Echocardiographic parameters were collected at baseline and during scheduled follow-up. We defined as super-responders all patients alive, without heart failure hospitalizations and with a left ventricle ejection fraction (LVEF) ≥45% at follow-up.
Results: The main characteristics of enrolled population were: male 75%, age 68±9 years,
III NYHA class 81%, ischemic heart disease (IHD) 48%, sinus rhythm 81%, QRS duration 162±28 ms, LVEF 26.2±7.4% and CRT-ICD 69%.
At a mean follow-up of 24±15 months, 66% of patients have improved LVEF of at least 25% respect baseline and 57% of patients have reduced LV end systolic volume of at least 15%. We reported the following echocardiographic parameters variations from baseline to follow-up: LV end diastolic diameter from 69±10 mm to 62±10 mm, LV end systolic diameter from 59±11 mm to 49±11 mm, LV end diastolic volume from 228±88 ml to 180±75 ml, LV end systolic volume from 170±71 ml to 118±65 ml and LVEF from 26.2±7.4% to 38.8±12.8% (for all differences p<0.0001).
In the whole population we had 33% of super-responders with the following major baseline differences respect the no super-responders group: IHD 32% vs 57% (p=0.027), LV end systolic diameter 66±10 mm vs 70±11 mm (p=0.032) and LV ejection fraction 29.6±8.9% vs 25.1±7.0% (p=0.010).
Conclusion: In our experience, in a consistent part of implanted population (33%), we reported a LV ejection fraction at follow-up of more than 45% with a nearly complete recovery of LV function. No IHD, higher LV ejection fraction and lower LV end systolic diameter at implant are the major characteristics of super-responders patients.

P870 Super-responders to CRT: the golden hour could be the right question

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Aims: Despite the current selection criteria, individual response to cardiac resynchronization therapy (CRT) varies significantly. A minority of patients show an excellent clinical and functional improvement after CRT. These patients have been called super-responders. The aim of our study was to identify predictors of becoming a super-responder after CRT and to assess the survival benefit associated with this response.
Methods and results: Eighty-nine consecutive patients in optimized medical therapy (mean age 69±9years, male 71%, NYHA 3.1±0.6, LVEF 26.8±6.3%) who underwent CRT were prospectively studied. Before CRT and 6-12-24-48 months after, clinical and echocardiographic evaluation were performed. Patients with a 12-months decrease in NYHA functional class ≥1 and an absolute increase of LVEF ≥5 were classified as clinical (CR) and functional responders (FR), respectively; an absolute improvement in LVEF >10 was used to define super-responders (SR). We observed 74, 43 and 26% of CR, FR and SR, respectively. In SR group the 85% was also CR, while in CR group only 29% was also SR. At baseline SR showed an higher prevalence of primitive etiology (39 vs 17%, p<0.01), a smaller mitral regurgitation degree (p 0.04), a less advanced diastolic dysfunction (p<0.01), smaller end-diastolic and end-systolic diameter (p 0.03), a lower pulmonary hypertension (p 0.01) and a shorter duration of heart failure symptoms (50±43 vs 129±85months, p<0.01). By logistic regression mitral regurgitation degree (OR 0.8, p 0.03), diastolic dysfunction (OR 0.9, p 0.05) and duration of heart failure symptoms (OR 0.5, p 0.01) were correlated with this super-response. During all follow-up SR group showed significant sustained symptomatic (48-months change in NYHA class from baseline -1.2±0.6, p<0.01) and functional improvement (48-moths LVEF change from baseline +22±6%, p<0.0001). Overall 48-months cardiac mortality was 14.7%; in responders subgroup we observed a 48-months cardiac mortality of 7.6% in CR, 9.1% in FR and 0% in SR.
Conclusion: Patients in earlier phases of the cardiomyopathy, with a less altered ventricular geometry and a more preserved diastolic filling, seem to have a greater probability of becoming SR. The SR long-term prognosis is strongly better than all other CRT responders patients, either CR either RF.

P871 Age in cardiac resynchronization therapy: should it stop mattering?

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Introduction: Even though prevalence of heart failure increases with age and with it the eventual indication for cardiac resynchronization therapy (CRT), little is known about its long term efficacy in the elderly, most of the time sub-represented or even excluded from the majority of clinical trials.
Purpose: Compare the long term response to CRT, evaluating clinical and echocardiographic parameters, in old patients (≥ 75 years) and in patients < 75 years old.
Methods: Prospective study including all patients submitted to CRT between November 2002 and December 2008, with a minimum follow up period of 2 years. The clinical and echocardiographic response, in terms of mortality from cardiovascular cause, NYHA functional class, left ventricular end-diastolic dimension (LVtd)

and ejection fraction (EF) were evaluated and compared in patients $\geq$ 75 and $<$ 75 years old.
Results: Of the 56 patients included, 13 (23%) were in the elderly group, 10 (77%) of them being male. There was no significant difference regarding clinical baseline characteristics or type of structural cardiopathy. In the elderly group, there was a significantly improvement in NYHA functional class, mean left ventricular EF (EF1 26% (sd 6,25); EF2 39,7% (sd 13,43) p=0,008, and a significant decrease in LVtd: LVtd1 65,1mm (sd 8,89); LVtd2 57,4 (sd 8,86) p=0,042. When compared, there was no significant difference regarding the increase in LV ejection fraction: EF ($\geq$ 75): 14,1% (sd 10,8) vs 16,9% (sd 14,5), p=0,57 or in the mean reduction of LVtd: LVtd ($\geq$ 75) - 5,5 mm (sd 5,9) vs - 7,1 mm (sd 8,8), p=0,63 in the two groups. Mortality from cardiovascular cause and improvement in NYHA functional was also similar in the two groups, with improvement of at least one score in NYHA functional class in 92% of patients in the elderly group vs 89% in patients aged $<$ 75 years (p=0,15).
Conclusion: In our series, the benefit of CRT was consistent independently of age, even in a long term follow-up, suggesting that age should not be exclusion criteria in patients otherwise candidates to this type of therapy.

P872 Implantation failure occurs more often in patients receiving an upgrade to CRT ICD versus those receiving a CRT ICD as the first device

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Indications of CRT ICD therapy have expanded. Implantation failure and complications are important adverse outcomes and patients with pre-existing devices may be at higher risk. The purpose of this study was to compare implantation failure and complications in patients undergoing an uprgrade to CRT ICD with those receiving a CRT ICD as the first device.
Methods: Consecutive patients undergoing an implantation procedure via an endocardial approach for a new CRT ICD or an upgrade to CRT ICD from a pre-existing device were assessed. Procedures were considered implantation failures if the device and all necessary leads for normal CRT ICD function could not be implanted at the time of the procedure. All complications occurring up to 90 days post-operatively were also identified.
Results: One hundred and four patients (104), mean age 67.5$\pm$1.14 SEM, undergoing 106 consecutive procedures were assessed. Eighty eight (84%) patients were male. Sixty four patients (61%) had an ischemic cardiomyopathy while 40 (39%) had a dilated cardiomyopathy. There were 45 upgrade procedures and 61 procedures performed as first implants. Implantation failure occurred in 4 patients (6.6%) undergoing a new implant and in 12 patients (26.7%) undergoing an upgrade ($p<0.05$). Four patients in the upgrade group were undergoing a second attempt procedure, of which three were successful. Venoplasty was performed in 4 patients (8.9%) undergoing an upgrade versus none receiving a first device. Two patients undergoing an upgrade to CRT ICD had failed implants due to total venous occlusion, requiring subsequent attempts from the contralateral side, which were successful. Eight of the upgrade failures occurred in one of 25 patients with at least 2 pre-existing ipsilateral leads (32%) versus 4 of 20 patients (20%) with $<$ 2 pre-exisiting ipsilateral leads. Complications occurred in 7 of 61 patients undergoing a new implant (11.4%) versus 5 patients (11.1%) receiving an upgrade (p=NS).
Conclusion: Implantation failure occurs more often in patients receiving an upgrade to CRT ICD versus those receiving a CRT ICD as the first device. Pre-existing hardware and/or venous thrombus obstructing vascular access may affect procedural success.

P873 (W) Avoidance of diaphragmatic pacing in CRT systems

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Introduction: Diaphragmatic pacing (DP) is a common complication of cardiac resynchronisation therapy (CRT) and occurs when the threshold for DP is close to that for LV pacing. When DP occurs reoperation for LV lead repositioning may be necessary. To avoid this, we investigated two reprogramming strategies: alternate pacing configuration and exploitation of strength-duration characteristics for LV and DP within each configuration.
Methods: In patients with spontaneous or inducible DP in implanted devices over a two year period, all programmable pacing configurations were investigated. Strength duration curves were determined for both LV and DP at pulse widths (PW) between 0.1 and 1.5ms over 2 respiratory cycles. Rheobase and chronaxie were calculated by the method of Lapique. The optimum setting was defined as the pacing configuration and PW with the greatest separation between LV and DP voltage threshold. The output was programmed to double the LV threshold, or where this was above the DP threshold, mid-way between LV and DP thresholds.
Results: 73 out of 94 pacing configurations in 31 patients out of 120 CRT devices implanted during the period were associated with DP. DP was less common with cathodal stimulation of the LV ring compared to tip (17 vs 56 configurations, $p<0.05$). In 15 patients, DP was inducible with every pacing configuration. The optimum PW was 0.4ms in 5, $>$0.4ms in 5 and $<$0.4ms in 5. DP was eliminated in 12 patients by device programming, 2 experienced DP rarely and only 1 patient required LV lead repositioning. The mean rheobase for DP was higher than LV rheobase ($p<0.01$) and DP chronaxie was lower than LV chronaxie ($p<0.01$).

Rheobase and Chronaxie for LV & DP

Pacing Configuration*	Mean LV rheobase (V)	Mean DP rheobase (V)	Mean LV chronaxie (ms)	Mean DP chronaxie (ms)
LV tip to LV ring (n=23)	0.62	3.61	0.47	0.12
LV tip to RV (n=24)	0.66	3.01	0.34	0.14
LV tip to can (n=9)	0.72	2.88	0.48	0.18
LV ring to RV (n=14)	0.97	3.05	0.42	0.16
LV ring to can (n=2)	1.7	3.52	0.3	0.12
LV ring to LV tip (n=1)	2.8	7.5	0.39	0.01

*n = number of patients with DP in this PC.

Conclusions: In most patients with DP at follow up, the problem can be eliminated by reprogramming pacing configuration and/or exploration of different pulse widths.

P874 Four years follow-up of left ventricular endocardial lead implantation in resynchronization therapy via transseptal puncture of right jugular vein

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Introduction: Epicardial lead implantation in coronary venous system fails in 30% of candidates for cardiac resynchronization therapy (CRT). We evaluated left ventricular ejection fraction (LVEF) and six minute exercise capacity before and after CRT using left ventricular endocardial approach (LVEA) via interatrial septum puncture.
Methods: From 2002 to 2010, LVEA was carried out in eighty patients (aged 63$\pm$13 years) with ischemic or idiopathic dilated cardiomyopathy in NYHA class III-IV, left bundle branch block and QRS duration of $>$150 ms and LVEF assessed by 1D/2D echocardiogram $<$ 35%. Ten patients (14.4%) presented permanent atrial fibrillation (AF) and underwent concomitant His bundle ablation.
Results: CRT via atrial transseptal puncture directly from right jugular vein allowed the implantation of active bipolar lead in the left ventricular endocardial site at the posterior-lateral wall. Long-term anti-coagulation therapy was used only in AF patients. In patients without AF, anti-platelet therapy was prescribed. Three patients (3.7%) presented pericardial effusion with spontaneous resolution. Acute and chronic threshold were (mean$\pm$SD) 0.47$\pm$0.08 volt and 0.89$\pm$0.53 volt, respectively. No fatal outcomes occurred either during the procedure or within first 24h post-procedure. During average follow-up pf 48 months, 12 pts died (15%): 6pts (7.5%) from CHF, 3pts (3.7%) from renal failure, 1pts (1.2%) of infection not related to the CRT procedure, and two others (2.5%) of sudden cardiac death. One pt had aborted sudden death and received ICD+CRT. Three pts (3.75%), two survivors and one nonsurvivor, presented transient ischemic neurologic deficit during follow-up, and none them were in the group of AF. The LVEF before and at six months were, respectively, 0.29$\pm$0.08 to 0.49$\pm$0.11 ($p<0.001$). Fifty pts were submitted to six minute walking test. There was a significant improvement in covered distance, from 267$\pm$132m before to 455$\pm$94m at six months ($p<0.001$).
Conclusions: 1-LVEA via interatrial septal puncture exhibits a safe procedure profile; 2-There was a significant improvement in left ventricular function and exercise capacity in resynchronized patients using LVEA in the posterior-lateral wall; 3- LVEA may be an alternative for non-responders to conventional CRT and due to coronary veins anatomy restrictions, limiting lead progression to reach the appropriate resynchronization target region.

P875 Left ventricular lead survival rate; insight from a long-term analysis in a large patient population

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Introduction: New Left Ventricular (LV) leads with different lead tip geometry, fixation and pacing configuration options combined with increasing implanter experience may change LV lead performance and reduce post-operative lead modifications. Limited data is published on long-term performance of LV leads. The data from the prospective world-wide System Longevity Study (SLS) was analyzed to assess long-term performance of Medtronic's LV leads.
Methods: The analysis included all model 2187, 4193, 4194, 4195 and 4196 LV leads enrolled in SLS since 1999. The Kaplan-Meier method was used to estimate the probability of lead survival from confirmed lead complications. The log-rank test was used to compare lead survival probably as a function of the lead model, implanting experience (earlier vs. more recent), implant introduction site, subject gender and age.
Results: The average follow-up time of 1997 leads was 27.5$\pm$24 months. Table 1 shows that LV lead survival probabilities across 6-years follow-up varied

from 94.2% - 99.1%. The most common complication was lead dislodgement (18/1997). The lead models, 4196 followed by 4195 and 2187, achieved the highest survival probability (2 years post implant data: 100%, 99.6% and 99.1%, respectively). There was no effect of gender (p=0.27) or implant introduction site (p=0.26) on survival probability. Lead complications decreased as age increased (HR ratio 0.98 for 1-year increase in age, p=0.02). More complications were observed in earlier LV lead implanting experience (1999 – 2004 vs. 2005 – 2010, p=0.01), showing a survival rate of 95.4 vs. 97.3% at 4 years, respectively.

Lead Model	# Complications/Total	2 years survival (%)	4 years survival (%)	6 years survival (%)	8 years survival (%)
2187	1/134	99.1	99.1	99.1	99.1
4193	34/680	94.9	94.2	94.2	94.2
4194	8/708	98.6	98.0	98.0	
4195	2/256	99.6	96.6		
4196	0/219	100.0			

Conclusions: In this large multi-center study, long-term LV lead survival is excellent. The risk of lead complications has decreased in the last 5 years and is lower for older patients. Lead dislodgement remains one of the main challenges for CRT lead retention.

P876 Suboptimal CRT reimplantation caused by CS vein thrombosis after CRT device infection and explantation

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Background: There are a growing number of device infections with or without endocarditis or generator pocket perforation caused by rising CRT implantation, upgrades and revision. The unavoidable complete CRT device removal often leads to a progress of heart failure. After the rehabilitation of infection the CRT reimplantation is a challenge of every experienced cardiologist caused by frequent thrombosis of posterolateral CS vein.
Methods: From 2007 to 2010 in 29 patient (age 68.3±9.4 years; 14 CAD/15 DCM, LVEF 25.6±7.2%; LBBB 162±13ms; 12 patients with chronic AF) CRT device removal was initialized in our center caused by endocarditis and/or pocket infection or perforation. A CRT reimplantation procedure was plant after 99±123 days in all these patients. The aim of this study was the evaluation of thrombosis in the already used posterolateral CS vein in all patients.
Results: Only 13 (45%) of 29 patients were successful implanted in posterolateral CS vein again. In 16 (55%) of 29 patients a complete thrombosis of posterolateral CS vein and in 2 of these 16 patients a partly thrombosis of posterolateral CS vein were examined. 14 (48%) of these 16 patients were suboptimal implanted in posterior or lateral vein and 2 CRT reimplantation procedures failed. In only 3 of 15 patients underlying oral anticoagulants with coumadin derivative thromboses in posterolateral CS veins were examined (exact fisher test p=0.009; OR 0.12; 95% CI: 0.013-0.78).

Coronary vein thrombosis	Coumadine	No coumadine	Sum
Yes	3 (9%)	13 (45%)	16 (55%)
No	12 (41%)	1 (3%)	13 (45%)
Sum	15 (52%)	14 (48%)	29 (100%)

Conclusion: After CRT device removal a CS vein thrombosis is very common and the reason of suboptimal CRT reimplantation. The oral anticoagulants with coumadine derivative significant reduce the risk of CS vein thrombosis. There is a need of alternative LV pacing devices independent of CS vein particular for these patients.

P877 Transseptal endocardial left ventricular lead implantation, a highly effective alternative method for resynchronization in selected cases

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Left ventricular (LV) lead positioning might be challenging or in some instances it can not be carried out via the tributary of the coronary sinus (CS). In these cases alternative methods might be necessary. The aim of our study was to investigate the effectiveness and safety of transseptal endocardial left ventricular lead implantation.
Transseptal endocardial left ventricular lead implantation was performed in 12 patients (9 men, age: 62±11 years, NYHA III-IV stage) Transseptal puncture was done via the femoral vein, and the site of the puncture was dilated with a 6mm, later an 8 mm balloon. After the puncture of the left subclavian vein, steerable CS (8 pts) or ablation catheter (4 pts) was introduced into the CS sheath. The CS catheter was used to reach the left atrium and the left ventricle through the dilated transseptal puncture gap. In the left ventricle the region of latest activation (RLA) was searched. In 4 cases CARTO electroanatomical mapping system was used to help to find the septal gap and RLA. Active fixation bipolar electrode was fixed in the lateral wall of the left ventricle through the sheath.
The lead was fixed in the left ventricle in all cases with good pacing threshold values (0.65±0.2 V;0,4 ms). Puncture complication, pericardial effusion was not detected. Because of anticoagulation therapy started immediately after the procedure, pocket haematoma was found in three cases, one of them needed evacuation. Follow-up is longer than one month in 8 patients (12,4±12 months). Significant improvement was observed in all but one case, on the first month control left ventricular ejection fraction was (27±4% vs 37±9%). Patient's NYHA class improved at least one class on the last visit. Early lead dislocation was noticed in one case, the lead dislodged into the right atrium, reposition was performed using the originally punctured transseptal opening. Explantation of the system was necessary because of pocket infection in one case, it was performed with traction only, no complication was noticed during and after the operation.
Conclusion: If transvenous and surgical epicardial method can not be applied, left ventricular endocardial electrode implantation might be an alternative for implanting the left ventricular lead.

P878 Left ventricular pacing with a new quadripolar lead for CRT: is it useful?

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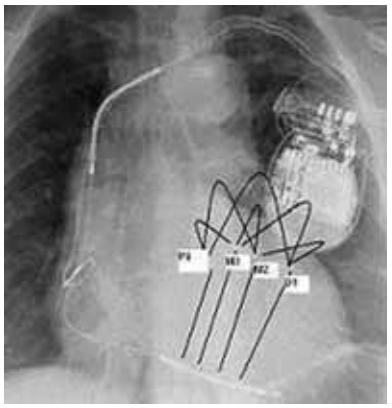
Background: Placement of the coronary sinus (CS) lead in Cardiac resynchronisation therapy (CRT) devices is a challenging procedure with the need of reoperation for lead dislodgement or phrenic nerve stimulation (PNS) in about 8% of the patients (pts). We report the first results of 39 patients with a new quadripolar lead (Quartet, St. Jude Medical) in a single center, prospective study. With this lead, 9 different stimulation vectors can be programmed (see picture 1).
Objective: To verify the effectiveness of the quadripolar lead concerning LV lead failure.
Methods: 39 patients were implanted with the quadripolar lead from 11/2009 until 12/2010. Operative and follow-up data were prospectively noted.
Results: Implantation success rate of the Quartet lead was 92% with an initial mean stimulation threshold of 1.2V (0.6-3.0V at 0.5msec). Two lead dislodgements requiring reoperation occurred during a mean follow up period of 190 (10-398 days). Reprogramming the stimulation vector of the quadripolar lead was necessary in 5 patients: 4 had a significant increase of stimulation threshold, which could be solved by reprogramming the device, so that last stimulation threshold was 1.1 (0.6-2.5V at 0.5msec) in mean. One patient had phrenic nerve stimulation which could be successfully managed by reprogramming the stimulation vector.



Vectors by Quartet electrode.

Conclusion: This prospective study provides strong evidence that the quadripolar LV lead is a useful tool in CRT therapy to prevent reoperation for phrenic nerve stimulation and for prolonging battery lifetime by achieving low stimulation thresholds.

P879 The stimulation site of quadripolar left ventricular pacing affects hemodynamics

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Purpose: To investigate acute hemodynamic effects of different pacing configurations of a novel quadripolar left ventricular pacing lead (SJM Quartet).
Methods: Left ventricular (LV) dP/dt was invasively assessed in a total of 76 pacing configurations using a pressure wire (PressureWire Certus, SJM) in 9 patients (7 male, 65.3±9.8 years) with standard indication for cardiac resynchronization therapy (CRT) (3 ischemic, 6 non-ischemic cardiomyopathy, LV EF 22.0±4.5%, QRS 157±22.5ms, NYHA class III) on the day following CRT-D implantation (Promote Quadra, SJM). All measurements were performed at individually optimized AV delays without VV delay, with each pacing configuration active for 120s and each followed by a baseline period of 120s without pacing.

Results: Overall, biventricular stimulation acutely increased LV dP/dt from 895.6±95.2 to 1058.4±178.3mmHg/s (p<0.005). Interindividually,LV dP/dt increased compared to baseline between 4.1% to 47.2%. Intra individually, the mean difference ofLV dP/dt increase depending on stimulation site (best-worst vector) was 11.7%(4.4-22.8%).
Possibly due to individual patient characteristics, different LV lead locations and the low number of patients, wedid not find systematic inter individual similarities in optimal pacing configurations.
Conclusion: The choice of the pacing configuration of a quadripolar LV lead significantly affects acute hemodynamics.This should thus be taken into account upon individual device programming.

P880 An endocardial bi ventricular resynchronization (EBVR) with transeptal puncture (TP) optimized by transesophageal parametric 3D (TEE3D) decision

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The study presents the ventricular parametric analysis using TEE3D during EBVR with transeptal techniques (TT). The transeptal EBVR is an alternative technique to the coronary venous sinus, which is the most commonly used option nowadays having 30% of nonrespondent patients.TEE3D exam is a new method with parametric analysis increasing the capability to individualize each one of 17 ventricular cardiac segments. The study's goal was to perform an EBVR using TT choosing the pacemaker lead position in the left ventricle with TEE3D help.
The study had 15 patients, All individuals were with non ischemic dilated cardiomiopathy.The heart functional classes were between III and IV. All individuals presented left block branch, desynchronized inter and intra ventricular, QRS >150 msec and EF < 35%. The right jugular vein was the main access to introduce the pacemaker leads and all the pacemaker lead location in the left ventricle was chosen with agreement between the echocardiographer and the interventionist, according to the best parametric 3D resynchronization reference.

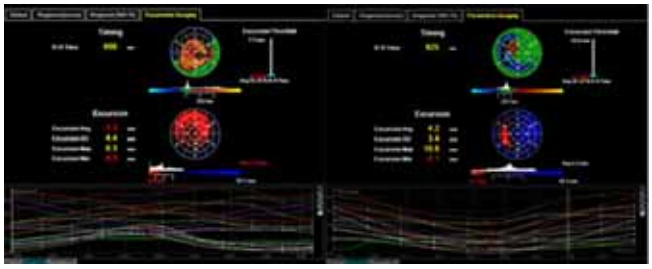

Figure 1. Pre and post EBVR.

All patients improved the functional class to I or II. The EF was performed before surgery, and 3 and 6 months later, with changes from 0,29+0,08 to 0,49+0,11 (p<0.001). All were submitted to a 6-min test. There was a significant improvement (p=0.0001) in the distance covered, from 266.7±131.7 to 454.7±93.8m, which improved the average in 58% at 3 and 6-months, demonstrating that these two new techniques together can help the interventionist haemodinamicist in the TP as much as in finding the best position to place the pacemaker lead in the left ventricle. Even though this study didn't count with a significant amount of individuals, it would be interesting to see other studies with this focus once there were no nonresponsive pacients.

P881 Triple-site cardiac resynchronization therapy in patients with heart failure - the prospective, randomized trial

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Purpose: We hypothesized that triple-site (double-left single-right) stimulation will result in a higher response-rate than conventional biventricular pacing in candidates for cardiac resynchronization therapy (CRT).
Methods: This prospective, single-center, single-blinded, parallel, controlled trial randomized a hundred consecutive patients with moderate to severe heart failure (HF-NYHA III-IV), LV ejection fraction ≤35%, electrical and mechanical dyssynchrony and sinus rhythm in a 1:1 fashion to triple-site or conventional CRT-D. In the triple-site group two LV leads were implanted into two separate coronary sinus branches and connected in parallel to the LV port of the device. Patients were followed 1 week, 1, 3 and 6 months after randomization during the blinded phase. All potential adverse events were adjudicated by a blinded committee to verify if the criteria for major adverse cardiovascular event (MACE-any-cause death/heart transplant/hospitalization for HF) were fulfilled. The primary objective evaluated response-rate, defined as the 6-month's combined endpoint of alive status, freedom from hospitalization for HF or heart transplantation, relative≥10% increase in LV ejection fraction, ≥10% in peak oxygen consumption, and ≥10% in 6-minute walking distance.
Results: Data suitable for per-protocol analysis were available for 98 patients, 98% of those in conventional and 93.8% in triple-site group were implanted successfully with the target device (P=NS). Intention-to-treat analysis revealed higher response-rate in triple-site than conventional CRT group (51.1 vs. 26.5%, P=0.014). The proportion of triple-site patients who achieved ≥10% increase in 6-minute walking distance was higher with borderline significance (74 vs 54%, P=0.05), proportions of subjects with ≥10% increase in peak oxygen consumption (67 vs. 59% in triple-site and conventional group, respectively) and in LV ejection fraction (77 vs. 78%, both P=NS) were similar. In the triple-site group two patients underwent HF hospitalization, in conventional group 1 patient died from progressive HF and 7 underwent HF hospitalization. MACE-rate was higher in conventional than triple-site group with the borderline significance (16 vs. 4.2%, P=0.05).
Conclusions: Triple-site resynchronization results in a higher response-rate than conventional CRT. This effect can be attributed mainly to the more pronounced functional improvement and greater reduction of MACE events mediated by triple-site pacing.

P882 Comparison of classic biventricular pacing with other combinations of multiple pacing sites. Experimental study

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Purpose: Classic biventricular pacing (BiP) in heart failure presents a high proportion of non-responders patients. The purpose of this study is to compare the effect of alternative pacing (P) combinations with BiP on left ventricular (LV) haemodynamic and rotational deformation parameters.
Methods: In 7 healthy pigs atrio-ventricular epicardial P in multiple P sites was performed simultaneously. Classic right ventricular apical (RVap) P was combined with: 1) LVapex lateral 2) LV basal posterior 3) LV basal anterior 4) LV basal anterior +LV basal posterior. Moreover, 5) LV basal posterior+LVapex lateral, 6) LV basal posterior+ LV basal anterior and 7) LV basal anterior + LV apex lateral P in a random order were performed. LV torsion was calculated by measuring LV basal and apical rotation from basal and apical short-axis epicardial planes with speckle-tracking technique using EchoPac software. LV torsion, ejection fraction (EF), cardiac output (CO), apical rotation (rotap), basal rotation (rotbas) in RVap+ LV basal posterior P were compared to every P combination.
Results: see Table 1.
Conclusions: In intact myocardium, every combination used (except LV basal anterior+posterior P) showed an increase of EF in comparison to classic BiP.

Abstract P878 – Table 1

	RVap + LV basal posterior	LV basal anterior + LV apex lateral	RVap + LV apex lateral	RVap + LV basal anterior	RVap + LV basal anterior + LV basal posterior	LV basal posterior + LV apex lateral	LV basal posterior + LV basal anterior
CO (ml/min)	2390,6±507	2896,9±655 P<0,02	2632,2±844,2 NS	2489,2±667,8 NS	2311±104,9 NS	2670±320,4 P<0,001	2167±560,5 NS
EF (%)	37,2±6,6	46,1±6,6 P<0,001	41±8,6 P<0,042	40,9±5 P<0,05	41,1±5,5 P<0,03	42,5±3,5 P<0,001	35,4±7,4 NS
Rotbas (°)	–4,2±1,8	–3,3±1,6 NS	–3,53±1,9 P<0,01	–4,32±1,5 NS	–4±1,8 NS	–3,5±1,8 NS	–2,7±3 NS
Rotap (°)	2,8±1,4	3,4±2,3 NS	3,2±1,8 NS	1,8±2,3 NS	2,8±1,8 NS	3,1±1,6 NS	3,6±2,3 NS
Torsion (°)	6,35±1,8	5,8±2,4 NS	6,6±1,9 NS	5,2±3 NS	6,2±3 NS	6,3±2,8 NS	5,9±3,4 NS
Heart rate (b/min)	114,1±14,69	117,7±17 NS	114,9±13,7 NS	112,8±14,8 P<0,02	114,9±15,2 NS	119±15,4 P<0,05	116,5±15,7 NS
QRS (ms)	96,5±11,33	90,1±9,1 NS	98,2±9,8 NS	102,8±9,5 NS	90,1±13,5 NS	96,9±17,8 NS	96,3±16,4 NS

Further studies are needed to confirm the above findings in cases with heart failure.

P883 LV pacing vs. BiV pacing in patients with a QRS duration greater than 120 ms: Efficacy analysis of the GREATER-EARTH trial

B. Thibault, A. Ducharme, F. Harel, M. White, E. O'Meara, M. Talajic, D. Roy, P. Khairy. *Montreal Heart Institute, Montreal, Canada*

The objective of GREATER-EARTH was to determine whether cardiac resynchronization therapy (CRT) with pacing the left ventricle (LV) alone provides a superior clinical response to biventricular (BiV) pacing. Design: A prospective double-blind randomized crossover trial was conducted in 11 sites across Canada. The primary outcome consisted of exercise tolerance determined by a constant-load sub-maximal exercise test performed at 75% of VO2max. Secondary outcomes included detailed echocardiographic and radionuclide ventriculographic assessment of LV size and function.
Population: A total of 121 patients were randomized, with a mean age of 61±9 years, 75% male and 51% ischemic cardiomyopathy. The previously reported primary intention-to-treat analysis on all patients, including those with incomplete follow-up and/or suboptimal CRT systems, found no significant differences inthe primary and secondary outcomes listed above. The current efficacy analysis excluded the 7 patients who died, 11 who withdrew after randomization, and 28 with suboptimal systems (<90% effective DDD-V pacing) due to AF (N=5) or major pacing problems including lead dislodgement, high thresholds, or phrenic nerve stimulation (N=23).
Results: The remaining 75 patients had optimal systems and complete follow-up. At baseline 68% had NYHA class II-III symptoms, a mean LVEF of 24±6% (echo), and a QRS duration of 155±23 ms. Exercise duration in patients with LV and BiV pacing were 13.8±11.6 min vs.16.3±13.0 (P=0.02). The proportion of echocardiographic responders (≥15% reduction of LVESVol) was 48.6% (in comparison to 42.0% in the intention-to-treat analysis and 26.7% in excluded patients), with a trend favoring BiV over LV pacing (51% vs. 38%, P=0.057). However, LVEF was comparable in patients with LV vs BiV pacing (30%±10% vs. 31%±9%, P=0.58).
Conclusions: This efficacy analysis confirms the non-superiority of LV vs. BiV pacing, and suggests an advantage of BiV over LVpacing in patients with optimal CRT systems. Notably, a substantial proportion of randomized patients experienced adverse conditions that prevented the consistent delivery of CRT, resulting in an inferior remodeling response. These data underscore the importance of careful attention to maximizing potential benefits of CRT.

P884 Defining response to cardiac resynchronization therapy: insights from the evaluation of resynchronization therapy for heart failure in patients with a QRS duration GREATER than 120 ms

B. Thibault, A. Ducharme, F. Harel, M. White, E. O'Meara, D. Roy, M. Talajic, P. Khairy. *Montreal Heart Institute, Montreal, Canada*

The purpose of GREATER-EARTH was to determine whether cardiac resynchronization therapy (CRT) with pacing the left ventricle (LV) alone provides a superior clinical response to biventricular (BiV) pacing. G-E was a prospective double-blind randomized crossover trial that was conducted in 11 sites across Canada. The primary outcome consisted of exercise tolerance determined by a constant-load sub-maximal exercise test performed at 75% of VO2max. Secondary outcomes included detailed echocardiographic and radionuclide ventriculographic assessment of LV size and function. Population: A total of121 patients were randomized, mean age 61±9 years, 75% male. At baseline, 95% had NYHA class II-IIIsymptoms, with a mean LVEF of 24±7% (echo), ischemic heart disease in 51%, and mean QRS duration of 155±23 ms. Seven patients died, 11 were withdrawn after randomization, and the remaining 103 patients completed a 12-month follow-up. Two definitions for CRT responders were pre-specified. Clinical response was defined as ≥20% improvement in exercise duration. Remodeling response was defined as ≥15% reduction in LVESVol.
Results: The clinical response rate was 49.1% for LV and 46.2% for BiV. The remodeling response rates were 34.0% (LV) and 50% (BiV) by echocardiography and 28.6% (LV) and 48.1% (BiV) by MUGA. Changes in NYHA functional class over time are summarized in the table, with the greatest improvement noted after device implantation but prior to activating CRT (*P<0.0001 pre-implant vs.baseline visit).
Conclusions: In GREATER-EARTH clinical response rates were slightly superior to LV remodeling response rates (especially for the LV group). The marked improvement in NYHA class after device implantation but preceding implementation of CRT may reflect a measurable placebo effect.

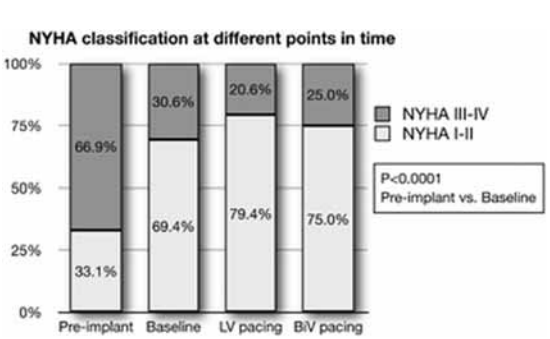

Figure 1

P885 Automatic adjustment of stimulation output in resynchronization therapy: impact and effectiveness in clinical practice

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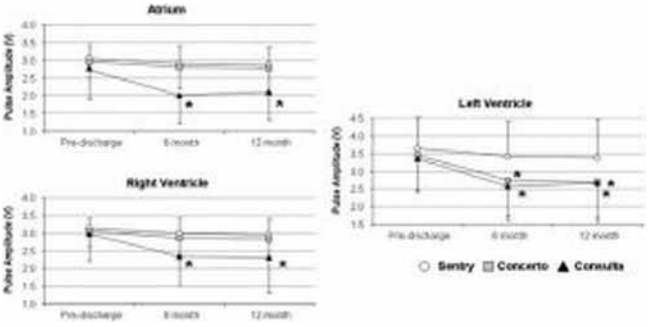
Purpose: Algorithms for automatic pacing output adjustment have been implemented in pacemakers and implantable defibrillators (ICD) and recently in resynchronization therapy ICD (CRT-D). We assessed the impact and effectiveness of these automatic features.
Methods: We prospectively enrolled patients successfully implanted with the following Medtronic CRT-D: Concerto (with automatic left ventricular (LV) output management algorithm), Consulta (automatic management of atrial, right ventricular (RV) and LV voltage) and Sentry (only manual voltage adjustments). Patients with complete device data available for at least 12 months were included in the analysis.
Results: We analyzed data from 739 patients (360 Sentry, 335 Concerto, 44 Consulta). During the first 6 months, pacing amplitudes were more frequently adjusted in Concerto and Consulta than in Sentry patients. The LV pulse amplitude for Concerto and the voltages in the three chambers of Consulta were significantly lower than the corresponding values programmed in Sentry at 6 and 12 months (figure). The proportion of ICD interrogations involving manual reprogramming was 97±8% for Sentry, 79±20% for Concerto and 56±16% for Consulta (all p<0.001).



Conclusions: Algorithms for the automatic management of the pacing output reduced pacing output in comparison with the standard manual management approach, with potential optimization of battery longevity. Moreover, they reduced the need to manually reprogram ICD, suggesting the possibility to simplify ICD management and facilitate remote monitoring.

NEW INSIGHTS IN CARDIAC RESYNCHRONISATION THERAPY

P886 Influence of ventricular pacing sites on QRS duration after CRT: results from REVERSE

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Background: The influence of left (LV) and right ventricular (RV) lead-tip position on QRS duration after CRT is unclear. As the change in QRS duration after CRT is generally assumed to influence outcome, lead tip position is of clinical importance.
Methods: We report the results of a pre-specified analysis of REVERSE in which pre-hospital discharge chest X-ray in frontal and lateral view were recorded and centrally analyzed. LV tip-position was classified as lateral or non-lateral, apical or non-apical and superior or non-superior. RV tip position was classified as apex

or non-apex. QRS duration was measured at baseline (B) during intrinsic conduction, before hospital discharge (D) and after 12-month (12m) whether in CRT ON or CRT OFF depending on randomization.
Results: All patients randomized to CRT ON with a complete data set entered the analysis (N=285). Results are shown below (see table).

QRS (ms)	Baseline (B)	Discharge (D)	Change D-B	12-month	Change 12m-B
LV Lateral	151.9±21.9	141.8±21.2	–9.4±24.8	144.5±22.0	–8.4±26.0
Non-lateral	148.5±23.2	158.8±26.1	9.2±25.7	163.1±23.8	14.3±24.0
P-value	0.32	<0.001	<0.0001	<0.0001	<0.0001
LV apical	149.3±24.3	151.7±25.8	2.7±29.3	161.6±23.4	11.3±28.3
Non-Apical	151.5±21.9	143.8±22.8	–7.4±25.2	146.3±23.0	–5.9±26.3
P-value	0.57	0.063	0.037	<0.001	<0.001
LV superior	151.0±21.5	148.4±22.1	–2.3±27.4	151.1±25.3	0.2±29.7
Non-superior	151.4±22.6	143.3±23.4	–7.7±25.2	147.2±22.7	–5.3±25.7
P-value	0.90	0.11	0.14	0.24	0.15
RV apex	151.9±22.0	142.3±21.8	–9.2±26.3	147.4±23.5	–5.3±27.3
Non-apex	150.6±23.2	149.0±23.1	–0.2±23.6	149.0±22.5	–1.5±25.5
P-value	0.63	0.022	0.007	0.60	0.29

Conclusion: In REVERSE, the LV lead-tip position had a strong influence on the acute and long-term change in QRS duration after CRT. As compared to baseline, the greater reduction was observed in patients with the LV lead placed at lateral and non-apical positions. RV lead-tip position had a short but no long term influence.

P887 Long-term risk reduction of misdetection or delayed detection of adverse events with a daily remote control system in patients with cardiac resynchronization therapy defibrillators

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Purpose: A high rate of clinical and device-related adverse events (AE) has been reported in patients with cardiac resynchronization therapy defibrillators (CRT-D). A follow-up program based on 3-6 month in-hospital visits may be associated to an increased risk of AE misdetection or delayed detection. A daily remote control system may help reducing such risk.
Methods: We analysed 2-year follow-up data from 136 CRT-D patients (102 male; age 70±8; ischemic dilated cardiomyopathies in 62 and non-ischemic in 74; ejection fraction 26%±6%; 9 patients in NYHA Class II, 121 in III, 6 in IV; primary indication for sudden cardiac death in all patients). All the patients were visited in hospital every 3 months; seventy patients (51%) were additionally controlled remotely with the Home Monitoring (HM) system (Biotronik, Berlin, Germany). The two groups had similar baseline characteristics and optimal drug therapy. AEs were classified as clinical or device-related. Kaplan-Meier curves of AE free rates were obtained.
Results: Clinical AEs were: ventricular and atrial arrhythmias in 34 and 28 patients respectively, low CRT pacing in 11, heart failure or death in 43, stroke in 3. Device-related AEs were: insufficient pacing/sensing performances in 25 patients, lead dislodgement in 10, and out-of-range impedance in 7. As comparing the HM group with the remaining patients, Kaplan-Meier curves of clinical AE free rates significantly diverged: 19.3% (95%CI 6.2%-32.4%) in the HM group and 28.5% (12.8%-44.2%) in the remaining patients (p=0.0008), with a hazard ratio (no-HM vs. HM group) of 0.41 (95%CI 0.26-0.65). Divergent Kaplan-Meier curves were also observed for device-related AE free rates: 50.7% (35.8%-65.6%) for the HM group; 82.6% (73.2%-92.0%) for the remaining patients (p=0.0008), with a hazard ratio of 0.32 (0.17-0.61).
Conclusions: CRT-D patients not remotely controlled had 59% and 68% 2-year higher risks of misdetection or delayed detection of clinical and device-related AEs respectively, despite a follow-up program of quarterly in-hospital visits.

P888 Incidence and clinical relevance of uncontrolled ventricular rate during atrial fibrillation in heart failure patients treated with cardiac resynchronization therapy

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Purpose: Uncontrolled ventricular rate (VR) during atrial fibrillation (AF) may cause clinical deterioration in a population of heart failure (HF) patients who need continuous biventricular pacing to achieve cardiac resynchronization therapy (CRT). We aimed to evaluate the association between AF, uncontrolled VR and sub-optimal CRT, defined as low biventricular pacing percentage (BIVP%).
Methods: All 1404 patients had HF, NYHA≥II, LVEF≤35% and QRS complex≥120ms and received a CRT implantable defibrillator (CRT-D). AF occurrence, VR during AF and lifetime BIVP% were estimated from device data. VR during AF was defined as uncontrolled in patients with mean VR>80 bpm and maximum VR>110bpm.
Results: In a median follow-up of 18 months, AF was detected in 443/1404 (32%) patients. In this sub-group of AF patients, VR during AF was uncontrolled in 150/443 (34%). Multivariate Cox regression analysis showed that age [HR=1.03, 95% confidence interval (CI=1.00-1.06), p=0.028] and uncontrolled VR [HR=1.69 (CI=1.01-2.83), p=0.046] were the only independent predictors of a clinical outcome, composed by HF hospitalizations and deaths. The median lifetime BIVP% was 95% (25th-75th percentile range 91%-99%). BIVP% was significantly and inversely correlated to VR, decreasing by 7% for each 10 bpm increase in VR. Sub-optimal CRT, defined as BIVP%<95%, was predicted by occurrence of persistent or permanent AF [OR=3.77, CI=2.44-5.82, p<0.001] and uncontrolled VR [OR=2.25, CI=1.35-3.73, p=0.002].
Conclusions: Ventricular rate during AF is uncontrolled in one third of patients with CRT-D and is associated with HF hospitalizations and deaths and with sub-optimal CRT (lifetime BIVP%<95%).

P889 Determinants of atrial fibrillation free survival after cardiac resynchronization therapy

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Purpose: Limited data support that atrial fibrillation (AF) is reduced after cardiac resynchronization therapy (CRT). We investigated the factors associated with freedom from persistent or permanent AF in patients after CRT.
Method: Before and 6 months after CRT, mitral regurgitant volume, diastolic mean mitral annular velocity, left atrial (LA) volume, ejection fraction and emptying fraction were measured in 62 consecutive patients with sinus rhythm at baseline. Regional peak strain in systole (Epsilon S) and late diastole (Epsilon D) from the interatrial septum, lateral, inferior and posterior walls of the LA and from the right atrial (RA) free wall were also measured. Standart deviation of LA regional time delays (Ts-SD) and inter-atrial delay from time to peak strain of the LA and RA free walls were calculated. Volume response was defined as a reduction ≥15% in LV end systolic volume.
Results: Over 4 years of follow-up, 21 (34%) patients had persistent or permanent AF. AF incidence was 21% in volume responders versus 50% in non-responders (p=0.015). Occurrence of AF was more closely related to post-CRT parameters than the baseline characteristics (Table). From these, LA active emptying fraction (p=0.02 [95%CI: 0.59 – 0.97]) and Epsilon D (p=0.03 [95%CI: 0.04 – 0.85]) were independent predictors of AF free survival after CRT.

Parameters associated with AF occurence

	Baseline			After CRT		
	No AF	AF	P value	No AF	AF	P Value
LA volume index (ml/m^2)	36±11	43±11	0.048	32±11	45±12	0.000
LA EF (%)	45±13	35±15	0.01	50±15	30±13	0.000
LA active emptying (%)	25±10	15±12	0.01	32±13	11±6	0.000
Ts-SD (ms)	43±24	63±32	0.01	34±19	55±26	0.001
LA mean Epsilon S (%)	17±8	13±6	NS	21±8	11±6	0.000
LA mean Epsilon D (%)	9±4	7±4	NS	11±3	6±3	0.000
RA Epsilon S (%)	34±14	31±14	NS	45±16	28±12	0.016
RA Epsilon D (%)	17±7	17±8	NS	24±11	16±8	0.016
Mitral regurgitant volume (ml)	23±14	30±16	NS	20±15	33±15	0.002
E/Ea	14±7	16±6	NS	12±4	18±7	0.001

Conclusion: Although AF is less frequent in volume responders, improvement in LA function after CRT seems to be essential for AF free survival during long term follow up.

P891 Ventricular rate profiles during atrial fibrillation in heart failure patients

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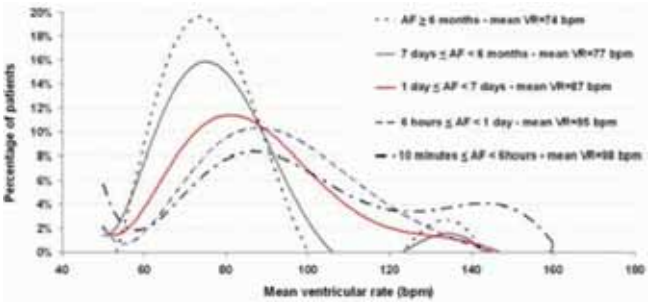
Purpose: Atrial fibrillation (AF) is a frequent comorbidity in patients with heart failure (HF). We aimed to evaluate the association between different profiles of AF and uncontrolled ventricular rate (VR) in a population of HF patients who need continuous biventricular pacing to achieve cardiac resynchronization therapy (CRT).
Methods: All 1404 patients had HF, NYHA≥II, LVEF≤35% and QRS complex≥120 ms and received a CRT implantable defibrillator (CRT-D). AF occurrence and VR during AF were estimated from device data.
Results: In a median follow-up of 18 months, AF was detected in 443/1404 (32%) patients. The mean VR during AF, calculated as the average of each patient mean VR, was 86±10bpm; while the maximum VR during AF, calculated as the average of each patient maximum VR, was 115±15bpm. Patients were classified accord-

ing to 5 AF profiles; 115 patients had an AF duration comprised between 10 minutes and 6 hours, 70 patients between 6 hours and 1 day, 57 patients between 1 day and 7 days, 154 patients between 7 days and 6 months and 47 patients suffered AF episodes longer than 6 months. Attached figure shows the distribution of mean VR during AF as a function of AF type.



Conclusions: In the studied population of patients suffering from AF and HF, the distribution of VR tends to be wider and shifted toward high rates for paroxysmal forms of AF while persistent or permanent AF patients have a Gaussian-like distribution of VR ranging between 50 and 100 bpm.

P892 Resynchronization therapy does not help heart failure patients with a QRS duration <120 ms

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Cardiac resynchronization therapy (CRT) is widely used in patients with heart failure (HF) and a QRS ≥120 ms. We assessed whether patients with HF and a QRS ≤120 ms may benefit from CRT.
Methods: A multicenter randomized double-blind clinical trial was performed. Inclusion criteria consisted of standard indications for implantable defibrillators, LVEF ≤35%, QRS ≤120 ms, and a 6-minute walk distance (6-MWD)≤400 meters. Patients were randomized to biventricular (CRT-ON) or back-up pacing (CRT-OFF). The primary outcome was exercise capacity determined by a constant-load sub-maximal test performed at 75% of VO2 max. Secondary outcomes consisted of LV size, function, and indices of dyssynchrony. A comprehensive assessment was performed at baseline, 6, and 12 months. Adverse events were adjudicated by a blinded committee and safety was overseen by an independent monitoring board. The study was powered to detect a 20%improvement in the primary endpoint.
Results: The DSMB met in November 2010 when 85 (of 120 planned) patients were randomized and recommended to prematurely terminate the study due to futility and potential harm. At 6 months, exercise duration had increased by 47±387 seconds with CRT-OFF vs. 9±364 seconds with CRT-ON (P=0.49). By 12 months, exercise duration had increased by 32±359 seconds with CRT-OFF whereas it had decrease dby 17±588 seconds with CRT-ON (P=0.70). A consistent pattern was noted with 6-MWD [i.e. 12±44 (ON) vs. 0±54meters (OFF) at 6 months (P=0.20) and 22±45 (ON) vs. -11±74 meters (OFF) at 12 months (P=0.044)]. No difference in the change in LVEF from baseline was noted with CRT-OFF versus ON [3±8% vs. 2±4% at 6months (P=0.28) and 1±7% vs. 5±8% at 12 months (P=0.19)]. Similarly, changes in LV end-systolic volumes were no different at 6 (P=0.52) and 12 (P=0.15) months. Moreover, a non-significant trend in time to worsening heart failure suggested potentially greater risk with CRT-ON (log-rank P=0.11).
Conclusions: The LESSER-EARTH trial was prematurely interrupted due to futility. In patients with HF and a QRS≤120 ms, CRT does not improve functional capacity nor reverse LV remodelling parameters. Moreover, CRT may be associated with worsening heart failure in this population of patients.

P893 Detrimental effect of biventricular and left ventricular pacing in acute heart failure with narrow QRS and mechanical dyssynchrony

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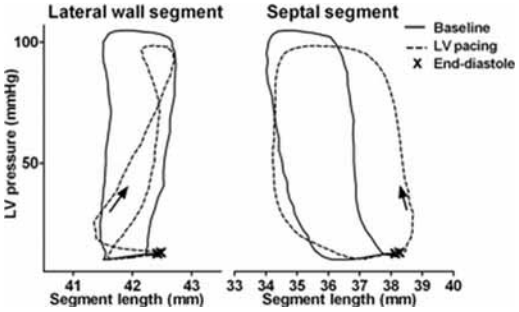
Purpose: Pacing therapy for heart failure (HF) patients with narrow QRS has gained increasing interest. We investigated responses to biventricular pacing (BVPace) and left ventricular lateral wall pacing (LVPace) in a dog model.
Methods: In 6 anaesthetised dogs with micromanometers, acute HF was induced by microembolisation of the left main coronary artery. Segment lengths were recorded by sonomicrometry and timing of peak systolic strain (PSS) was measured. Electrical and mechanical dyssynchrony was assessed by intersegmental time delay (ITD) calculated by subtracting the latest from the earliest regional measurement in each individual for intramyocardial electromyograms (IM-EMG) and PSS, respectively. Stroke work (SW) and regional work were calculated from pressure-volume and pressure-segment length loops. Measurements were performed during baseline, HF and HF with BVPace and LVPace.
Results: Coronary microembolisation decreased SW by 37±14% (p<0.01). No electrical dyssynchrony appeared, as ITD for IM-EMG remained unchanged. However, ITD for PSS increased by 56±13 ms (p<0.01), indicating mechanical dyssynchrony. During HF, LVPace and BVPace decreased SW by 18±16% and 10±8.5%, respectively (p<0.05). LVPace increased ITD for IM-EMGs by 28±15 ms (p<0.01), indicating electrical dyssynchrony. This caused a redistribution of segmental work with a reduction in lateral wall work (smaller loop area in the figure), and an increase in septal work (larger loop area).



Conclusion: In acute HF with normal electrical conduction and mechanical dyssynchrony, LVPace and to a lesser degree BVPace, reduced systolic function due to dispersion in electrical activation and a non-uniform distribution of segmental work. This emphasises the importance of caution when considering CRT for HF patients with narrow QRS.

P894 CRT does not completely reverse activation time and sequence after acute left bundle branch block. Insights from an experimental swine model

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Background:.The extent, pattern and changes in myocardial activation after Resynchronization Therapy (CRT) have been scarcely studied. Aim: To evaluate changes in activation time and sequence in healthy swine at baseline, after left bundle branch block (LBBB) and after CRT.
Methods: 7 Landrace x Large White pigs (34±2kg) with healthy hearts were anesthetized and underwent a radiofrequency LBB ablation. An electroanatomical mapping system was used to identify the LBB. A CRT device was implanted. Contact electroanatomical mapping was performed in all animals at baseline, after LBBB and CRT during simultaneous biventricular pacing. QRS width, endocardial activation time and activation sequence were analyzed.
Results: QRS width and activation time increased after LBBB (48±5ms Vs 69±6ms and 48±6ms Vs 61±6ms, P<0.05). After CRT, QRS and activation time decreased (69±6ms Vs 56±6ms and 61±6ms Vs 53±7ms, P<0.05). Activation sequence was also modified. At baseline, the breakthrough was septo-basal and time to reach lateral wall was 16±6ms.

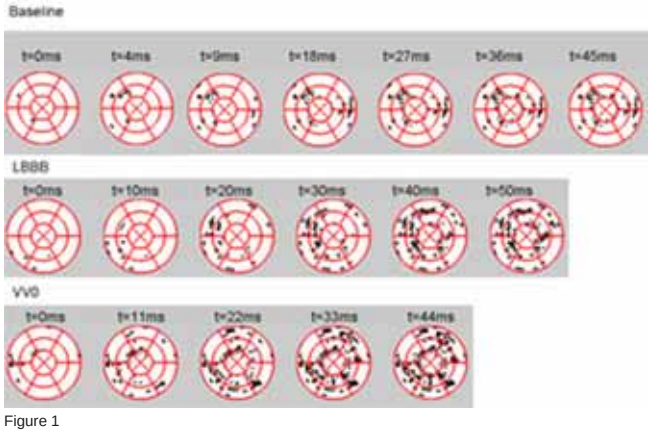

Figure 1

After LBBB, the breakthrough remained septo-basal with a significant prolongation in conduction time (28±6ms). The activation pattern was homegenously modified in 5 hearts and only one did not show any change. After CRT, all hearts showed similar patterns with the breakthroughs moved to a septal and anterolateral position. (Figure 1) Conclusions: Acute LBBB leads to changes in activation time and sequence that cannot be completely reversed by conventional biventricular pacing.

P895 Induction of left bundle branch block results in a septal flash which is corrected with cardiac resynchronization therapy in a swine model

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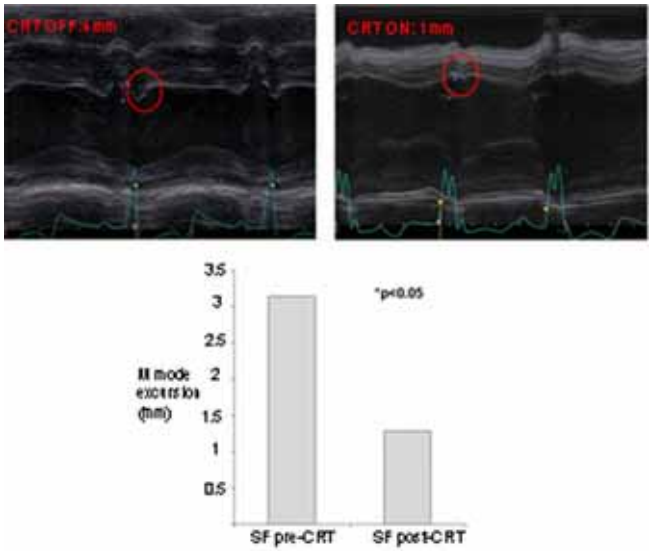
Purpose: The presence of an abnormal septal motion known as septal flash (SF) has been linked to a higher probability of response to cardiac resynchronization therapy (CRT) provided this abnormal motion is corrected. Our aim has been to study the effect induced by an acute left bundle branch block (LBBB) on interventricular septum mechanics in an experimental model, as well as its acute response to resynchronization.
Methods: 7 healthy Landrace x Largewhite pigs of 30 kgs were studied. In each animal a LBBB was induced by radiofrequency ablation of the left bundle branch. A CRT device was implanted. Echocardiography was performed in each animal prior to and immediately after LBBB induction and after the onset of CRT. The presence of SF was defined as the presence of a fast inward/outward motion of the septum occurring during the isovolumic contraction period and its excursion was quantified in M-mode (Figure).
Results: After ablation, a significant widening of the QRS was noted (48±5ms vs 69±6ms at baseline, $p<0.05$) along with a ECG pattern concordant with LBBB. Echo also revealed the appearance of a SF, not present in the baseline study. The onset of CRT partially corrected this abnormal motion (SF excursion 3.14±0.8 mm pre-CRT vs 1.29±0.39 post-CRT, $p<0.05$).



Conclusions: We have developed a swine model in which LBBB acutely induces a SF, similar to what is observed in some humans with LBBB, and which can be partially corrected with CRT. Identification of a SF in patients with heart failure might be a useful parameter to predict response to CRT.

P896 The effects of CRT on the endothelial dysfunction in heart failure

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The CRT induces reduction of mortality with a significant functional improvement in heart failure,involving most of the selected enrolment criteria, as NYHA functional class, the ECG, echocardiographic parameters or the quality of the life.
We aimed to study the role of the endothelial dysfunction in heart failure, in order to assess the effects of the CRT on the underlying endothelial dysfunction and to evaluate the relationships between the changes of the endothelial function and the other usual endpoints of this treatment.
We evaluated the endothelial function by measuring with ultrasound the brachial artery response to the flow mediated vasodilation (FMD) in 35 patients, aged 67.6±9.2yrs., with advanced heart failure, ischemic (53%) or non-ischemic (47%) in origin; the patients showed a poor NYHA class (2.6±0.6), a reduced LVEF (22.3±10.1), awidedQRS (160±31 msec), with increased BNP values (407±328 pg/dl) and Minnesota QoL scores (30.4±17). Thepatients showed an impaired FMD (3.3±2.4 vs 13.7±5.3, $p<0.05$), with an high prevalence of endothelial dysfunction (74%), without significant differences between ischemic or non-ischemic heart failure (3.4±2.2 vs 3.1±2.4, p = ns). The CRT induced an overt increase of the FMD at 3 months (6.3±4.2 vs 3.3±2.4, $p<0.05$) andat 6 months (7.2±4.9 vs 3.3±2.4, $p<0.05$); 21 pts (58,3%) were classified as CRT-responders and showed an increase of the FMD, that was significantly related with the recorded changes in other endpoints, as the LVEF (31.0±6.1 vs 22.3±10.1, $p<0.05$), NYHA class (2.0±0.7 vs 2.6±0.6, $p<0.05$), but not with the 6 minutes walking distance (254±43 vs 237±60mt, p = ns) or the QoL scores (26.6±12.3 vs 30.4±17, p = ns). A normal pre-treatment value of FMD or a normal endothelial dysfunction after CRT is usually associated to a sustained response to the treatment, as assessed according to the usual combined end points; on the contrary, a marked endothelial dysfunction, especially if characterized by basal FMD values ≤1.9%,were associated with a persistent functional impairment and were predictive for a poor response to the CRT treatment.
In conclusion, endothelial dysfunction is a marker of systemic disease, able to integrate the other endpoints of the CRT treatment; in particular, an overt endothelial dysfunction characterizes most of the patients with heart failure and is potentially reverted by the CRT; most of the non-responders show the persistence or an early recurrence of endothelial dysfunction, that is usually predictive for a poor response to the treatment.

P897 Optimization of the systolic and diastolic regional functions of the ischemic heart, by stimulating various sites, in sheep

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Purpose: The benefit of Resynchronization Therapy in treatment of heart failure is widely recognized. However many patients with inhomogeneous heart do not exhibit improvement. We hypothesize that the optimal excitation sites should be defined based on energetic considerations/matching the mechanical demands with the local energetic ability. Pacing can redistribute the workload in the heart; it decreases the regional work at the pacing site and increases the loads of remote sites. The study investigates the local and global mechanical and energetic effects of opposing strategies: pacing in the vicinity of the ischemic zone and at a remote site.
Methods: Myocardial infarction was created in the anteroseptal region in open chest anesthetized sheep (n=8) by ligation of a largest marginal coronary artery. LV volume and the ischemic region shortening were measured by sonocrystals (Sonometrics). LV Elastance was measured by utilizing the transient vena-cava occlusion technique. LAD and circumflex arteries flow (Transonics) and the arterial and coronary sinus oxygen contents (Avox) were measured to assess the oxygen consumption. Regional (pressure-segment length loops) and global LV functions were assessed at baseline and after reaching a steady state with overt myocardial infarction, during three pacing modes: normal sinus activation, anteroseptal and remote lateral pacing.
Results: Pacing on either site didn't significantly affect the stroke work, at baseline and ischemia. However, a vast decrease in the anteroseptal work was observed during local pacing (-43.5%) at baseline. The anteroseptal infarction extended the local end-diastolic length (+8%), stretched the weak region during systole, decreased the local work (-49.6%), and yielded overt post-systolic shortening (PSS) in which the ischemic region generated active work during diastole. In ischemia, anteroseptal pacing presented three favorable effects; it eliminated the systolic stretch, significantly decreased the work of the ischemic region (-26.4%) and diminished the PSS work (-38.6%). In contrast the remote lateral pacing had no marked effect on the ischemic region work while increasing PSS work.
Conclusions: Pacing the weak region redistributes the workload and presents two advantages that may promote reverse remodeling: (1) It improves the balance between regional demands and energetic capabilities, and (2) it improves the diastolic function by reducing the wasted PSS work. The study introduces the energetic concept of "workload redistribution" rather than the conventional electrical or mechanical synchronization.

P898 Mechanical dyssynchrony deconvoluted by speckle tracking in ischemic heart failure model

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Purpose: Inhomogeneous contraction aggravates heart failure outcome, and is treatable by cardiac resynchronization therapy (CRT). High rates of non-responders to CRT warrant development of surrogate models to enhance understanding of cardiac dyssynchrony evolution. Current pacing or block-induced cardiac dyssynchrony models reproduce conduction abnormalities without however recapitulating the primary substrate of cardiomyopathy. Accordingly, we here developed a mechanical dyssynchrony model where myocardial injury was introduced to deconvolute pathogenic paradigms in the context of ischemic heart failure.
Methods: Nude mice (male, 8-12 weeks, n=48) underwent left coronary ligation, microsurgically positioned at various sites to generate cohorts with or without cardiac remodeling. Remodeling was diagnosed based on dilatation with wall thinning, aneurysm formation, reduced contractility, and heart failure symptoms. Beyond electrocardiography, mechanical dyssynchrony was monitored prospectively post myocardial infraction (MI) by speckle-tracking echocardiography (30-MHz probe, 478±10 bpm, 295±13 fps).

Results: Speckle-based strain assessment of hearts with induced aneurysmal remodeling demonstrated hypo/akinesis in infarcted areas and paradoxical hypercontractility in non-infarcted areas 1 day post MI, in conjunction with QRS prolongation (pre MI 10.3±0.2 ms, post MI 13.5±0.7 ms, P<0.01). Systolic stretch in infarcted areas and reduced contractility in remote areas were detectable within 10 days, and progressed into severe dysfunctional stretch and akinesis throughout the ventricle within 1 month. As discoordinated wall motion provoked delayed and/or premature contraction, mechanical dyssynchrony calculated as standard deviation of time-to-peak systolic strain progressively increased through post MI follow-up in remodeled hearts (pre MI 5.6±1.0 ms, 1-month post MI 24.8±1.8 ms, P<0.01). In contrast, infarcted ventricles without aneurysmal remodeling displayed limited QRS prolongation (11.8±0.4 ms), hypo/akinesis in focal area, absence of systolic stretch in infarcted areas, and no paradoxical motion in remote areas, yielding modest dyssynchrony (10.4±1.5 ms) when compared with aneurysmal hearts.
Conclusions: Speckle tracking offers a sensitive tool to stratify the origin and progression of mechanical dyssynchrony in a mouse infarction model in which pathological cardiac remodeling and wall stretch with QRS prolongation were selectively induced. The validated model now provides a platform to investigate disease mechanisms, improve selection for CRT, and evaluate therapeutic modalities.

P899 Periodic W and AV delays optimization in cardiac resynchronization therapy improves patients' clinical outcome: results from the clear study

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Background: Individual and repeated programming adjustments are required to improve patients (pts) response to Cardiac Resynchronization Therapy (CRT). The CLEAR study investigated pts' response rate to CRT according to optimization procedure through a 1 year Follow Up (FU). This sub analysis focused on the impact of CRT optimization periodicity on pts' response rate, regardless of the procedure.
Methods: 268 severe HF pts in sinus rhythm with left ventricular ejection fraction <35%, LV end-diastolic diameter ≥30 mm/m^2, QRS interval >150 ms or >120 ms with ≥2 echocardiographic indications of mechanical dyssynchrony, were implanted with a device featuring Peak Endocardial Acceleration (PEA) sensor (73.1±9.9 years, Male 63%, NYHA 3.0±0.3, LVEF 27.1±8.1%, Idiopathic/ischemic/valvular/other: 46%/39%/8%/8%). They were randomly assigned to CRT optimized either automatically with PEA (providing automatic VV configuration, VV and AV delays optimization) or with standard medical practice for a 1 year FU. Pts' clinical status was defined as improved or worsened/stable, based on a composite criterion (death, hospitalization for HF, NYHA class and Quality of Life (QOL)). This sub-analysis focused on pts periodically optimized at each visit (discharge, 3 and 6 months) versus the others.
Results: The analysis included 66 pts with periodically optimized therapy (Group 1) and 66 matched patients whose CRT was insufficiently optimized (Group 2). The average length of FU was 367±50 days in Group 1 and 355±92 days in Group 2. Significantly more pts (85%) responded to CRT in Group 1 than in Group 2 according to the composite endpoint (62%; p=0.0031). Event rates for combined death and hospitalization for HF were significantly lower in Group 1 than in Group 2 (9% vs. 29%; p=0.0039). Periodically optimized CRT led to significantly greater improvements in NYHA class (p=0.0043) than non-periodically optimized therapy. There were no significant differences between the groups in the degree of improvements in QOL.
Conclusions: Periodically optimized CRT was associated with significantly improved clinical outcome in pts than non-periodically optimized therapy. This confirms the need for an automatic CRT optimization procedure, which would remain operator independent, time saving and cost effective.

P900 Understanding CRT effects: 2D speckle tracking imaging to monitor the changes in LV systolic activation patterns in responders and non-responders to CRT

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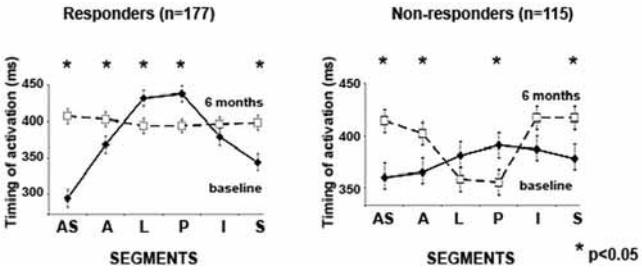
Purpose: Cardiac resynchronization therapy (CRT) induces left ventricular (LV) reverse remodeling by synchronizing LV segmental mechanical activation. We investigated the changes in segmental LV activation after CRT and related them to CRT response.
Methods: A total of 292 severe heart failure patients (mean age 65±10 years, 77% male) underwent baseline echocardiographic assessment of LV volumes and LV ejection fraction (LVEF). Time-to-peak systolic radial strain was measured for each 6 midventricular LV segments with speckle tracking strain imaging. Moreover, the time difference between the peak radial strain of the anteroseptal and the posterior segments was calculated to obtain LV dyssynchrony. After 6 months of CRT, LV volumes, segmental LV mechanical activation timings and LV dyssynchrony were re-assessed. Response to CRT was defined as a ≥15% decrease in LV end-systolic volume at 6 months follow-up.
Results: Responders (n=177) experienced LV resynchronization (LV dyssynchrony from 200±127ms before CRT to 85±86ms 6 months after CRT; P<0.001) by earlier activation of the posterior segment (438±141ms to 394±132ms; P=0.001) and delayed activation of the anteroseptal segment (295±155ms to 407±138ms; P<0.001). On the contrary, non-responders (n=115) experienced worsening of LV dyssynchrony (from 106±86ms before CRT to 155±112ms 6 months after CRT; P=0.001) with an earlier activation of posterior wall (391±139ms to 355±136ms; P=0.039) that did not match the delayed anteroseptal activation (360±148ms to 415±122ms; P=0.001).



Conclusion: Responders to CRT experienced LV resynchronization through balanced lateral and anteroseptal activations. Non-responders showed induction of LV dyssynchrony by earlier lateral wall activation and non-compensatory delayed septal wall activation.

P901 Intrinsic properties of echocardiographic dyssynchrony parameters determine their (in)ability to predict response to cardiac resynchronization therapy

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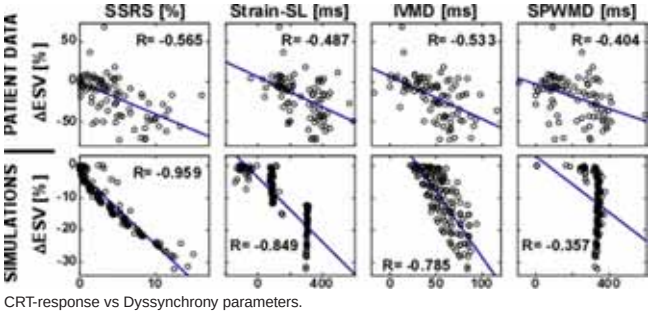
Background: Multicentre studies highlight the lack of predictive power of traditional echocardiographic dyssynchrony (DYS) parameters to predict response to cardiac resynchronization therapy (CRT) and attribute it mostly to measurement variability.
Purpose: Investigate whether intrinsic properties can also explain the inability of echocardiographic DYS parameters to predict CRT-response.
Methods: In 90 CRT-candidates (LVEF 19±6%; QRS 170±22ms), traditional DYS parameters (septal-to-lateral peak shortening delay [Strain-SL], interventricular mechanical dyssynchrony [IVMD] and septal-to-posterior wall motion delay [SPWMD]) and one novel parameter (septal systolic rebound stretch [SSRS]) were quantified using their original definitions. CRT-response was quantified as 6-months %-change of left ventricular (LV) end-systolic volume (ESV). A multiscale computer model of the cardiovascular system (CircAdapt) was used to simulate cardiac mechanics under a wide range of pathophysiological conditions: 153 simulations with random variation of ventricular dyssynchrony (delayed septal and LV free wall activation) and contractility. CRT was simulated by restoring synchronous ventricular activation. Simulated DYS parameters and CRT-response were obtained as in patients.
Results: In patients and simulations (Figure), traditional DYS parameters showed impaired relations with CRT-response due to either data clustering (Strain-SL), a broad relation spectrum (IVMD), or insensitivity to dyssynchrony (SPWMD). In contrast, SSRS showed an almost perfect linear relation in simulations and the best prediction in patients.



CRT-response vs Dyssynchrony parameters.

Conclusion: Besides measurement variability, intrinsic properties explain poor predictive performance of traditional DYS parameters. SSRS is an attractive alternative with favourable inherent behaviour.

P902 Impact of systolic dyssynchrony on left anterior descending coronary artery flow in patients receiving cardiac resynchronization therapy

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Purpose: Cardiac resynchronization therapy (CRT) re-coordinates the timing of left ventricular (LV) contraction in the failing heart. However, it is not clarified whether this is related to the improvement of myocardial blood flow. The aim of this study is to examine the impact of systolic dyssynchrony on coronary artery flow in patients receiving CRT.
Methods: Twenty-nine CRT responders (defined as 10% reduction in LV end-systolic volume at 3-month follow up) were studied. Echocardiography was performed at 3 randomly programmed pacing modes (sinus rhythm, right ventricular [RV] pacing and biventricular [BiV] pacing). Coronary flow velocity was recorded with transthoracic Doppler echocardiography at the distal-portion of left anterior descending coronary artery (LAD) and diastolic velocity time integral (VTI) and duration were measured. Myocardial systolic (LV-Sm) and early diastolic (LV-Em) velocities were measured and systolic dyssynchrony was assessed by the standard deviation of time to peak systolic velocity of the 12 LV segments (Ts-SD).
Results: Coronary flow velocity can be obtained in all patients. Both LAD coronary VTI and flow duration were significantly greater during BiV pacing when compared with either sinus rhythm or RV pacing (all $p<0.05$) (Table). Systolic dyssynchrony was decreased during BiV pacing while myocardial systolic (LV-Sm) and diastolic (LV-Em) function were improved during BiV pacing. The LAD-VTI correlated with Ts-SD (r= -0.53, $p<0.05$), LV-Sm (r=0.41, $p<0.05$) and LV-Em (r=0.38, $p<0.05$).

Parameters	Sinus rhythm	RV pacing	BiV pacing
Heart rate, beat/minute	69±11	70±11	66±11
LAD VTI, cm	11.6±4.3	9.7±3.8*	14.9±4.3*†
LAD duration, ms	491±106	447±114*	560±95*†
Ts-SD, ms	45±17	59±19*	36±20*†
LV-Sm, cm/s	3.25±0.91	2.48±0.79*	3.91±0.62*†
LV-Em, cm/s	2.84±0.75	1.87±0.78*	3.15±0.81*†

*$p<0.05$ vs. sinus rhythm; †$p<0.05$ vs. RV pacing.

Conclusion: Improvement of coronary flow was observed during BiV pacing. This is correlated with systolic dyssynchrony.

P903 The effect of cardiac resynchronization therapy and of atrioventricular delay optimization on mechanoenergetic efficiency: simply, a better value for money

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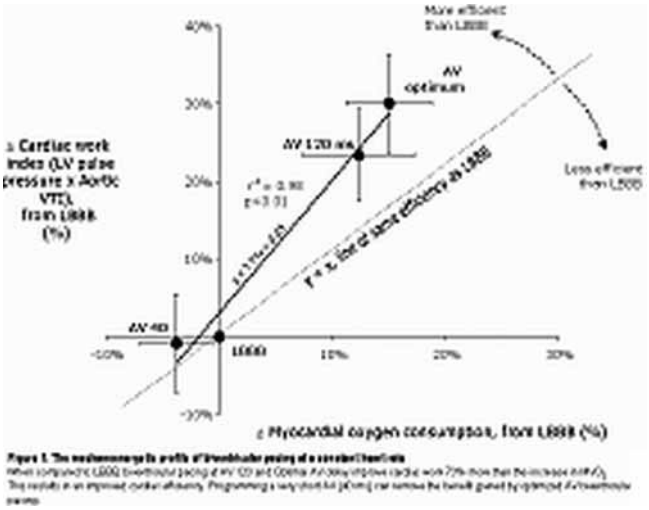
Background: The acute mechanoenergetic effects of optimization of atrioventricular (AV) delay of cardiac resynchronization therapy (CRT) are not known. We studied these invasively, in a contemporary cohort of patients.
Methods: Eleven patients with systolic heart failure (EF 26±6%) and left bundle branch block (LBBB, QRS 175±17 ms) underwent measurements of left ventricular (LV) pulse pressure, aortic flow velocity and myocardial oxygen consumption (MVO2) at four pacing states: biventricular pacing at AV 40ms (BiV-40), AV 120 ms (BiV-120) and at the individualised haemodynamic AV optimum (BiV-Opt; and at LBBB. Heart rate was fixed by atrial pacing.
Results: BiV-120, relative to LBBB, increased LV pulse pressure (11±2%, p=0.001) and aortic flow (11±3%, p=0.004), but increased MVO2 (12±5%, p=0.03).
BiV-Opt, relative to AV120, further increased LV pulse pressure (2±1%, p=0.034) and aortic flow (3±1%, p=0.019). MVO2 trended up by 3±3% (p=NS).
Mechanoenergetics at BiV-40 were no different from LBBB (p=NS).
The 4 pacing states lay on a straight line for Δpressure against Δflow, r=0.99 ($p<0.01$). Moreover, Δexternal work (Δpressure × Δflow) correlated with Δ MVO2, r=0.99 ($p<0.01$), with slope 1.71±0.03, significantly greater than 1 ($p<0.05$).
Conclusions: During acute biventricular pacing, optimisation of AV delay increases in both external cardiac work done and myocardial oxygen consumption. However, the increase in cardiac work is ~70% greater than the increase in oxygen consumption, signifying an improvement in cardiac efficiency.



P904 Prospective evaluation of echocardiographic dyssynchrony parameters for prediction of reverse remodeling in cardiac resynchronization therapy

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Purpose: The aim of this study was to prospectively study the role of various echocardiographic measures of mechanical dyssynchrony in predicting reverse remodeling in patients with heart failure indicated for cardiac resynchronization therapy (CRT).
Methods: Between 2006 and 2010, 118 consecutive candidates of CRT (60 with ischemic dilated cardiomyopathy – IDCM, and 58 with nonischemic dilated cardiomyopathy – NIDCM) were examined by a single experienced operator using a complex echocardiographic protocol, including diastolic filling time, interventricular delay (IVD), septal flash (SF), apical and whole heart rocking, time from onset of QRS to peak systolic velocity in four basal segments by tissue Doppler imaging (TDI), and evidence of restrictive filling. A change in left ventricular end-diastolic diameter (LVEDD) at one year of follow-up was used as a parameter of reverse remodeling. Positive response to CRT at one year was defined as a composite endpoint of echocardiographic reverse remodeling, improvement in NYHA class, reduction of mitral regurgitation, and freedom from major cardiovascular adverse events.
Results: The mean reduction of LVEDD was 2.7±4.7 mm, $p<0.001$ (2.0±4.36 mm in IDCM and 3.59±5.3 mm in NIDCM, p=0.09 for difference between the subroups). A total of 75% of patients were classified as responders based on the composite endpoint. In the whole study cohort, reduction of LVEDD was predicted by the magnitude of IVD ($p<0.0001$) and the presence of SF (p=0.007), but not by diastolic filling time, TDI, or by apical and whole heart rocking. In contrast, LVEDD was negatively influenced by restrictive filling (p=0.008). In the IDCM subgroup, only IVD remained a significant predictor of reverse remodeling (p=0.008). In the NIDCM subgroup, SF and IVD remained highly predictive of reverse remodeling (p=0.006, and p=0.005, 'respectively). However, all dyssynchrony parameters had poor test statistics (e.g., ROC AUC 0.76; sensitivity 0.70; specificity 0.75 for IVD).
Conclusion: In a consecutive population of CRT candidates, the likelihood of reverse remodeling was associated with the presence of SF and with increasing IVD. This association was more pronounced in the NIDCM subgroup. Conversely, restrictive filling reduced the likelihood of reverse remodeling. However, these echocardiographic parameters would fail as valid diagnostic tests in predicting presence or absence of reverse remodeling in patients treated with CRT.

P905 A mechanism-based approach results in better identification of responders to cardiac resynchronization therapy: a multivariate comparison

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Purpose: A mechanism based approach based on identifying parameters amenable to be corrected with cardiac resynchronization therapy (CRT) (the presence of a Septal Flash (SF), abnormal ventricular filling (AVF) or exagerated interventricular dependence) has been reported as a useful method for a better selection of candidates. The aim of our study is to test this approach against other proposed parameters for prediction of response in a multivariate analysis.
Methods: We included 140 CRT patients (age 68±9, mean QRS 165±35, mean ejection fraction (EF) 24±6%). Patients were clinically and echocardiographically evaluated at baseline and after 12 months follow-up (FU). Response to CRT was defined as reduction of LV end-systolic volume (LVESV) ≥ 15%. Uni and multivariate analysis were performed.
Results: The variables included in the univariate analysis are summarized in Table. At multivariate analysis, the only variable that was independently related to response was the presence of a mechanism amenable to be corrected with CRT (RR 22.95 (95% CI: 7.6-69.6). Neither QRS, NYHA functional class IV, baseline

Table 1

	Responders N=73 (52.1%)	Non-responders N=67 (47.9%)	P (univariate)
NYHA FC IV N (%)	4 (5.5%)	12 (17.9%)	<0.05
Minnesotta QoL score	40±18	45.3±20.4	n.s.
Creatinine (mg/ml)	1.2±0.4	1.4±0.6	<0.05
QRS (ms)	170±36.5	159.4±31.6	n.s.
AF N (%)	20 (27.4%)	25 (37.3%)	n.s.
LVEDV (ml)	265.1±91.6	274.2±84.7	n.s.
LVESV (ml)	203.9±78	217.3±83.5	n.s.
LVEF (%)	23.9±6.2	23.3±6.1	n.s.
Septal-to-lateral delay (ms)	65.4±47.2	70±50.5	n.s.
Any mechanism N (%)*	69 (94.5%)	30 (44.8%)	<0.05

*Independent predictor at multivariate analysis. FC: functional class; QoL: quality of life; LVEDV: LV end-diastolic volume.

creatinine level, the presence of atrial fibrillation (AF), LV volumes or LVEF were independent predictors of response in our population.
Conclusions: The presence of a mechanism amenable to be corrected with CRT is associated with a high likelihood of response to this therapy. A selection of candidates to CRT based in this parameter could have better results than the current recommended criteria.

P906 Septal strain patterns reveal ventricular asynchrony and regional differences in contractility in cardiac resynchronization therapy candidates

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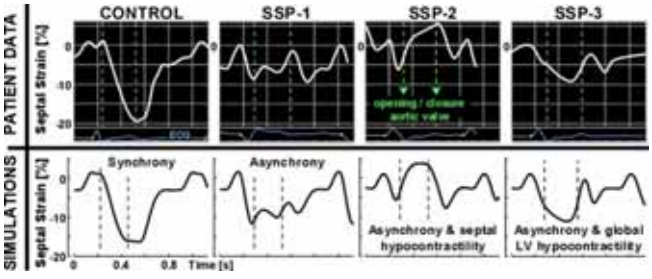
Introduction: Response to cardiac resynchronization therapy (CRT) is believed to depend both on asynchrony and (regional) contractility. Asynchronous heart failure is associated with a complicated sequence of systolic shortening and stretching of the interventricular septum.
Purpose: Investigate whether this septal strain pattern (SSP) can delineate asynchrony and additional differences in regional contractility and thereby predict CRT response.
Methods: In 132 CRT-candidates, SSP was assessed by speckle tracking echocardiography. CRT response was quantified by 6-months left ventricular (LV) ejection fraction (LVEF) improvement. To investigate the effects of asynchrony and (regional) myocardial contractility on SSP, we utilized the CircAdapt computer model of the human heart and circulation.
Results: In the patients (LVEF 19±6%; QRS 170±23ms), three characteristic SSPs were identified (Fig: upper panels): SSP-1=double-peaked shortening (n=28); SSP-2=early systolic shortening followed by prominent stretching (n=34); and SSP-3=pseudonormal shortening with subtle late systolic stretch (n=70). SSP-3 revealed more scar (2 [2-5] segments) compared to SSP-1 and SSP-2 (both 0 [0-1], p<0.05). Similar SSPs were obtained with the model (Fig: lower panels). Imposing asynchrony alone (i.e., time of activation of right ventricular free wall- septum-LV free wall: 0-25-75 ms) resulted in SSP-1. This transformed into SSP-2 by simulating septal hypocontractility and into SSP-3 by imposing global LV hypocontractility. Improvement of LVEF was most pronounced in SSP-1 (13±9%) followed by SSP-2 (8±7%) and SSP-3 (3±7%), all p<0.05.



Conclusions: Septal strain patterns reveal the presence of ventricular asynchrony and regional differences in contractility in CRT candidates and thereby predict CRT response.

P907 Effect of cardiac resynchronization therapy on phasic coronary flow pattern and microvascular resistance in patients with non-ischemic cardiomyopathy

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Purpose: Left bundle branch block (LBBB) and permanent right ventricular pacing induce mechanical dyssynchrony, which leads to deterioration of coronary flow dynamics. This study sought to examine the effect of cardiac resynchronization therapy (CRT) on coronary circulation.
Methods: 17 patients with non-ischemic cardiomyopathy (67.1±10.3 years old, 14 males, NHYA class 3.1±0.3, QRS duration 175±22ms and EF 30.2±10.5%, LBBB in 9 and complete AV block (CAVB) in 8) were enrolled. One week after CRT, coronary flow velocity and pressure in left anterior descending coronary artery were measured invasively, before and after adenosine triphosphate administration, during 2 programming modes: atrial pacing in patients with LBBB or sequential atrial and right ventricular pacing in patients with CAVB (Control), and sequential atrial and biventricular pacing (BiV). We measured hyperemic microvascular resistance index (HMR, coronary pressure divided by hyperemic average peak velocity (APV)) and phasic coronary flow pattern.
Result: Baseline APV were significantly higher at BiV compared with Control (26.4±8.8 cm/s vs. 23.1±6.4 cm/s; P=0.01). And HMR was lower at BiV compared with Control (1.51±0.42 vs. 1.75±0.35; P=0.007). Phasic coronary flow parameters were significantly higher at BiV compared with Control (33.0±12.0 cm/s vs. 27.3±7.5 cm/s for diastolic velocity, 19.4±6.8 cm/s vs. 15.9±3.7 cm/s for diastolic VTI, 20.4±9.9 cm/s vs. 14.8±9.4 cm/s for acceleration; P<0.05).In contrast, no significant changes were observed in systolic velocity, systolic VTI, systolic time, diastolic time, and deceleration.

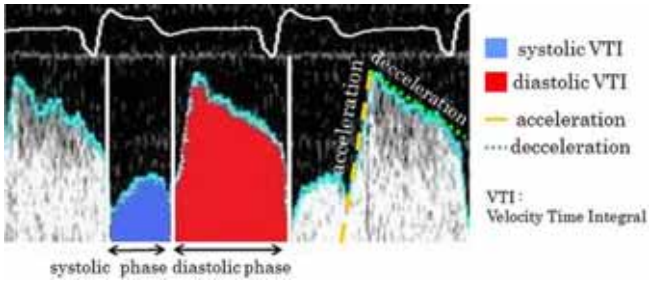

Figure 1. Method to measure coronary flow pattern.

Conclusion: CRT has a beneficial effect on phasic coronary flow circulation through reduction in microvascular resistance.

P908 Prognostic index derived from clinical and contrast-enhanced cardiovascular magnetic resonance after cardiac resynchronization therapy

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Purpose: Cardiac resynchronization therapy (CRT) reduces long-term morbidity and mortality in patients with moderate or severe heart failure and markers of cardiac dyssynchrony, but not all patients respond to a similar extent. Many baseline characteristics associated with heart failure may influence prognosis after CRT. We aimed to develop a prognostic risk index of cardiovascular events after CRT.
Methods and results: We included in a prospective cohort study 131 patients with heart failure (New York Heart Association class III or IV, LVEF<35% and QRS>120ms) who underwent CRT. All patients underwent assessment of risk factors, echocardiography variables including dyssynchrony, and cardiovascular magnetic resonance (CMR) measures of myocardial scarring (late gadolinium-enhancement (LGE) before implantation. Clinical events were assessed after a median follow-up of 842 (interquartile range 541-1265) days. At follow-up, 16/131 (12%) of patients died from cardiovascular causes, 67/131 had any cardiovascular events (cardiovascular mortality, heart failure hospitalization or arrhythmic event). In Cox proportional hazards analyses, presence of atrial fibrillation, non-optimized treatment (p<0.0001) and both- ischemic-type and nonischemic-type patterns of LGE emerged as independent predictors of cardiovascular events. The prognosis index (PI), derived from these variables combined, emerged as a powerful predictor of cardiovascular events. Cardiovascular events in patients with the high PI were 17.3 times higher (95% CI 10.11-34.12) compared to patients with a low PI.
Conclusion: The prognostic index,derived from clinical variables, myocardial scarring by LGE-CMR and presence of atrial fibrillation before implantation, is a powerful predictor of cardiovascular events after CRT

P909 Myocardial contractile reserve and mitral insufficiency during dobutamine stress echocardiography predict response to cardiac resynchronization therapy

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Purpose: It has been suggested that left ventricular (LV) myocardial contractile reserve evaluated by means of dobutamine stress echocardiography (DSE) may be useful in the selection of responders to cardiac resynchronization therapy (CRT). Increase in LV performance and decrease in LV volume during DSE can lead to a reduction in the degree of mitral regurgitation (MR). Whether the degree of MR during DSE has a role in the identification of responders to CRT is still unsettled.
Methods: 24 pts with heart failure (age 59±10, NYHA class 2.6±0.5, LVEF 26±8%, QRS 158±16 ms, ischemic etiology 20%) underwent echocardiography at baseline, during low-dose dobutamine (5-10-20 mcg/kg/min) and 6 months after CRT. MR was graded semiquantitatively from 0 (null) to 4 (severe) with color flow Doppler images (jet area/left atrial area). The presence of septal flash was evaluated both at baseline and during DSE. LV dyssynchrony was defined as a time delay >130 msec between the anteroseptal and posterior segments at speckle tracking radial strain analysis. Response to CRT was defined as a reduction ≥15% in LV end-systolic volume (ESV) at 6 months.
Results: At 6 months after CRT 14/24 pts (58%) turned out to be responders. Compared to non responders, during DSE responders to CRT had a greater absolute increase in LVEF (10±7% vs 1±4% units, P=0.001) a greater relative reduction in LVESV (30±22% vs -0.1±13%, P<0.001) and were more likely to show septal flash (71% vs 20%, P=0.03). Of note, the degree of MR was similar at baseline in responders as compared to non-responders (1.3±1.0 vs 1.5±0.8), but it was significantly lower during DSE (0.6±0.6 vs 1.4 vs 0.5, P<0.01); such a difference in MR degree was maintained at 6 months follow-up (0.4±0.6 vs 1.4±0.8, P<0.01). Based on ROC curve analysis an absolute increase in LVEF≥5.5% and a relative decrease in LVESV≥8.5% during DSE were found to be the best predictor of response (AUC= 0.84, P<0.01 and AUC=0.88, P<0.01, respectively). At univariate analysis an absolute increase in LVEF≥5.5%, a relative reduction in LVESV≥8.5%, septal flash, and the degree of MR during DSE together with basal LV dyssynchrony were found to be significant predictors of response to CRT. At multivariate analysis an increase in LVEF≥5.5% (P=0.01), a relative reduction in LVESV≥8.5% (P=0.01) and the degree of MR during DSE (P=0.02) remained independent predictors of response to CRT.
Conclusions: In heart failure patients myocardial contractile reserve and mitral insufficiency during DSE are significant independent predictors of response to CRT.

P910 The value of dobutamine stress echocardiography in prediction of volumetric response to resynchronization therapy in chronic heart failure patients. The lessons from multicenter study-VIACRT

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Rationale: It has been hypothesized that recognition of viable left ventricular myocardium in CRT candidates is one of the major predictors of favourable response to resynchronization therapy. Low Dose Dobutamine Stress Echocardiography (LDSE) has a potential to detect contractile reserve in both paced myocardial regions as well as in remote myocardium.
Aim of the study: To determine prognostic role of LDSE in predicting outcome post CRT device implantation.
Methods: 116 (93males) patients at the age of 66 years with clinically stable chronic heart failure (NYHA class II-12,9%;III-75.9%; IV-11,1%) were enrolled prospectively into this trial. Ischemic origin of LV dysfunction was recognized in 65% of patients. Baseline EDV was 249±97 ml, EF 24±6%, QRS 164±23 ms. Low dose dobutamine (DOB) protocol (mean max DOB dose – 21,5±4,4 ug/kg/min) was used during pre implantation evaluation of patients. The end points of positive response to DOB stimulation (R+) were defined as follows: WMSI↓ by >20%, EF ↑ by 20%, improved contractility in ≥ 2 LV segments, improved contractility in ≥ 4 segments. Overall response to CRT after 6 weeks was defined as follows: EF ↑ by 10% or, ESV↓ by 15% or NYHA↓ by 1 class.
Results: The response rate in this cohort of patients was 82%. Results of LDSE are presented in Table 1.
Conclusions: Dobutamine induced improvement of contractility in 4≥ LV segments but not ΔWMSI or ΔEF turned out to be the only predictor of favourable volumetric response following CRT. Clinical response (Δ NYHA) was not predicted by LDSE.

Table 1

6 weeks fup	ΔWMSI >20%; ΔEF >20%, >2 segments		ΔWMSI >20%; ΔEF >20%, >4 segments	
	R(–)	R(+)	R(–)	R(+)
ΔEF by 10%	36,4%	63,2%	37,5%	66,7%
	p=0.16		p=0.05	
ΔESV by 15%	18%	50%	19%	54,8%
	p=0.08		p=0.01	
ΔNYHA by >1 class	73%	67%	67%	70%
	p=1.0		p=0.9	

YOUNG INVESTIGATORS AWARDS SESSION: BASIC SCIENCE

913 Selective disruption of the CD40L/Mac-1 interaction by a small peptide inhibitor mimicking the EQLKKSKTL motif attenuates inflammation and atherogenesis in mice

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Background: CD40L is an established marker and mediator of inflammatory disease, such as atherosclerosis. We recently reported that CD40L does not mediate its pro-atherogenic functions via its classic receptor CD40 and proposed the leukocyte integrin Mac-1 as alternate receptor. Here, we characterized this interaction, designed an inhibitory peptide, and tested whether this peptide limits inflammation and atherogenesis in mice.
Methods and results: CD40L concentration-dependently bound to the recombinant Mac-1 I-domain in solid phase binding assays (Kd~66nM). Employing a peptide mapping strategy, we identified the motif EQLKKSKTL, an exposed loop between the α1 helix and the β sheet B on Mac-1 as binding site for CD40L. A linear peptide mimicking this sequence, M7, inhibited the adhesion of monocytic THP-1 cells to immobilized CD40L as well as the binding of CD40L to human monocytes and the I-domain. cM7, a cyclisized version optimized for in vivo use, inhibited the adhesion of Mac-1-transfected CHO cells to immobilized CD40L, but not to the Mac-1 ligands GPIbα and ICAM-1 in the flow chamber. In vivo, cM7 significantly reduced accumulation of thioglycollate-elicited leukocytes in the peritoneal cavity in wild-type but not in CD40L-/- mice, whereas treatment with the control peptide scM7 had no effect. Also, cM7 significantly impaired inflammatory cell recruitment in vivo in intravital microscopy. Leukocyte rolling and adhesion decreased by 40±11% and 24±7% compared with scM7 (N=12 per group). Finally, LDLR-/- mice consuming a high cholesterol diet for 20 weeks treated with intraperitoneal injections of cM7 three times a week developed up to 21±6% smaller atherosclerotic lesions compared with scM7 (N=14 per group). Macrophage and lipid content of atherosclerotic plaques decreased by 39±6% and 32±5%, respectively, while numbers of smooth muscle cells and collagen content increased up to 88±26% and 38±9%, respectively, characteristics associated with more stable plaques in humans. Furthermore, cM7 did not interfere with CD40L-CD40 binding in vitro and CD40L/GPIIb/IIIa-mediated thrombus formation in vivo
Conclusions: We present the novel finding that CD40L promotes inflammation and atherogenesis by interaction with the leukocyte integrin Mac-1. cM7, a small peptide, specifically inhibiting this interaction, might represent a novel anti-inflammatory treatment for atherosclerosis.

914 A novel drug-like inhibitor of plasma membrane calcium ATPase isoform 4 (PMCA4) is efficacious in the prevention and treatment of cardiac hypertrophy in vivo

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Currently there are few effective anti-hypertrophic agents available to treat cardiac hypertrophy and failure. Recently, our group showed that PMCA4 knockout mice showed a reduced response to hypertrophic stress prompting us to hypothesise that a novel PMCA4 specific inhibitor would modify the development of cardiac hypertrophy.
A library of 1280 medically optimised compounds was screened using a novel in vitro assay which measures the Ca^{2+} dependent ATPase activity of PMCA4. The compound AP2 was identified, which inhibited PMCA4 activity with high affinity (IC50=300 nM), but not related ATPases. In isolated neonatal rat cardiomyocytes, AP2 showed dose dependent inhibition of phenylephrine-induced hypertrophy. In vivo studies showed that AP2 (5mg/kg body weight/day IP) significantly reduced the development of pressure-overload induced hypertrophy in wild type mice following 2 weeks transverse aortic constriction (TAC) (heart weight/tibia length (HW/TL) (mg/mm): sham, 5.5±0.3; vehicle treated TAC, 8.7±0.2; AP2

treated TAC, 7.0±0.5; n=10 in each group, $p<0.01$). A significant reduction in the expression of the hypertrophic markers ANP and BNP and, importantly, in the percentage of fibrosis was observed in these mice compared with controls. In addition, AP2 treatment significantly reversed pressure overload induced hypertrophy following 3 weeks TAC (HW/TL (mg/mm): sham, 5.7±0.3; vehicle treated TAC mice, 9.1±0.6; AP2 treated TAC mice, 7.09±0.3; n=5 in each group, $p<0.01$). AP2 treatment led to a significant reduction in the expression of the bona fide calcineurin target RCAN1.4 and a reduction in NFAT phosphorylation level in vivo and NFAT transcriptional activity in vitro. To determine the specificity of AP2 action, PMCA4 knockout mice were subjected to TAC and then treated with AP2; this treatment showed no additional regression of hypertrophy over and above PMCA4 knockout mice alone.

In conclusion: We have identified AP2 as a novel and specific inhibitor of PMCA4 both in vitro and in vivo. Genetic deletion and pharmacological inhibition of PMCA4 significantly reduces the hypertrophic response to pressure overload likely through inhibition of calcineurin/NFAT signalling. Importantly, AP2 has drug-like properties thus laying the basis for a novel potential approach to the treatment of cardiac hypertrophy and failure.

915 Generation of patient-specific induced pluripotent stem cells from plucked hair follicle-derived keratinocytes

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The recent discovery of reprogramming of human somatic cells to induced pluripotent stem (iPS) cells provides a unique opportunity for generation of patient-specific cells for use in regenerative medicine, heart disease model, and drug screening. However, most iPSC lines described in previous studies have been isolated from skin fibroblasts or other cell types that require surgical intervention for their isolation. Therefore, an alternative cell source is required that can be readily and noninvasively isolated from patients and efficiently reprogrammed. Here we report a reproducible method to derive iPS cells from plucked human hair follicle keratinocytes. We isolated and cultivated hair follicle keratinocytes from 41 individuals between 22-52 years with an efficiency of 90%. The procedure of deriving keratinocytes takes 10–14 d and resulted in a sufficient amount of cells for subsequent transduction using the lentivirus system. After expansion of the keratinocytes they were reprogrammed either by four separate lentivirus vectors expressing the transcription factors Oct4, Sox2, Nanog, and Lin28 (OSNL) or by a single polycistronic excisable lentiviral vector expressing the combination of Oct, Sox2, Klf4, and cMyc (OSKM) with an efficiency of nearly 40%. 2-3 weeks after transduction patient-specific iPS cell colonies appeared in culture that showed phenotypical characteristics similar to undifferentiated human embryonic stem (ES) cells. They formed colonies with a similarly compact, ES cell-like morphology when cultured on mouse embryonic fibroblasts. Until now, we established 12 different keratinocyte-derived pluripotent patient-specific iPS cell-lines with characteristics typical of human ES cells. RT-PCR analysis showed that they expressed pluripotency markers Oct4, Nanog, Sox2, and Lin28. Immunocytochemistry studies demonstrated that they were positive for markers common to pluripotent cells, including alkaline phosphatase, Nanog, Oct4, Sox2, Tra-1-60, and SSEA4. When we cultivated the cells in three dimensional cell aggregates, so called embryoid bodies, they were able to spontaneously differentiate into derivatives of all three embryonic germ layers in vitro, including functional cardiomyocytes.

These data demonstrate a reproducible method for the isolation of keratinocytes from the hair follicle of patients with heart disease, their further reprogramming into pluripotent stem cells, and finally the differentiation into functional cardiomyocytes. Thus, these differentiated patient-specific cardiomyocytes can be used for heart disease modeling and individual drug screening on a cellular level.

916 Cardiomyocyte-targeted overexpression of GTP cyclohydrolase-1 increases nNOS activity and hastens myocardial relaxation

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Background: Tetrahydrobiopterin (BH4) is an essential cofactor for nitric oxide synthases (NOS), without which NOSs become "uncoupled" and generate superoxide instead of NO. Supplementation of BH4 has been shown to restore NOS activity and reverse LV diastolic dysfunction in animal models of hypertension; however, whether this is due to a genuine increase in myocardial BH4 availability or to a systemic antioxidant effect of BH4 remains to be established. To address these issues we generated a mouse with myocyte-specific overexpression of the rate-limiting enzyme of BH4 biosynthesis, GTP cyclohydrolase-1 (GCH1).

Results: GCH1 overexpression lead to a large increase in myocardial BH4 that did not involve the non-myocyte component of the LV myocardium, suggesting that biopterin transport out of cardiomyocytes and between neighboring tissues is limited or absent. The ratio between BH4 and its oxidized products was lower in mGCH1-Tg mice, indicating that a large proportion of the myocardial biopterin pool was oxidized. Nevertheless, mGCH1-Tg mice showed a 2-fold increase myocardial NOS activity (predominantly due to nNOS) and a reduction in superoxide release, which was unaffected by NOS inhibition. The reduction in superoxide production in mGCH1-Tg mice was not mediated by direct scavenging effect of NO but resulted from a nNOS-mediated inhibition of xanthine oxidase activity. Both the speed of relaxation (in LV myocytes and Langendorff perfused hearts) and the rate of decay of the $[Ca^{2+}]_i$ transient were faster in mGCH1-Tg mice whereas cell shortening and the amplitude of the $[Ca^{2+}]_i$ transient (3 Hz, 35C)did not differ between genotypes. These findings were associated with a reduction in total PLB and an increase in the Ser16 PLB phosphorylated fraction in mGCH1-Tg myocytes. Abolition of the differences in the Ser16 PLB phosphorylated fraction between mGCH1 Tg and WT by either nNOS inhibition with SMTC (100 umol/L) or beta-adrenergic stimulation with isoproterenol (10 nmol/L) also abolished the difference in the rate of relaxation and $[Ca^{2+}]_i$ decay between genotypes.

Conclusions: Increased myocardial BH4 availability leads to an increase in nNOS activity which, in turn, hastens myocardial relaxation by increasing the Ser16 PLB phosphorylated fraction. Together these findings suggest that myocardial BH4 bioavailability plays an important role in the regulation of diastolic function in health and disease.

YOUNG INVESTIGATORS AWARDS SESSION: POPULATION SCIENCES

918 Renin predicts cardiovascular events in the general population independently of aldosterone or hemodynamic parameters

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Background: Conflicting data exist regarding the importance of renin as a risk factor for cardiovascular events in the general population. This question is important again since the discovery of the (pro-)renin receptor and the development and clinical availability of direct renin inhibitors. We evaluated the role of renin and aldosterone in a large cohort of subjects without CV disease and without use of antihypertensive drugs.

Methods: From the PREVEND cohort (a large prospective observational study initiated in 1997) all subjects without prior history of CV disease and without use of antihypertensive medication were selected. Baseline plasma renin concentration (PRC, LIAISON, Diasorin, USA) and plasma aldosterone (ELISA) were measured. Hemodynamic measures, established CV risk factors, renal function measurements, and 24 hour urinary sodium excretion were included in a multivariate linear regression analysis. Significant determinants of PRC were selected by bootstrapping techniques and included in a multivariate cox-regression analysis evaluating the prognostic significance of PRC for CV clinical outcomes.

Results: 6116 subjects were included in the analysis: mean age 47 years, 49% male, mean follow up 9.4 years and 425 cardiovascular events were observed. Median (Q1-Q3) PRC was 17.6 (11.0-27.2) mIU/l, aldosterone 119 (93-153)ng/l. In a multivariate linear regression model PRC showed a positive correlation with aldosterone, heart rate, male gender and smoking and a negative correlation with blood pressure, urinary sodium, glucose, and natriuretic peptides (adjusted R-squared 0.167, $p<0.001$). The t-statistic was strongest for aldosterone, heart rate and natriuretic peptides. There was no correlation with cholesterol or renal function. In an age and gender adjusted cox-regression analysis increased PRC was strongly associated with CV outcomes (HR of 1.24 per doubling of renin, 95% CI 1.06-1.46 p=0.008) and remained significant after adjustment for the aforementioned covariates, including aldosterone (HR 1.34, 1.12-1.60 p=0.002)

Conclusion: This is the largest study by far that investigated renin in a cohort with no cardiovascular history and not using antihypertensive drugs with a correction for sodium intake. Renin was associated with all hemodynamic parameters investigated, even natriuretic peptides in the normal range. After adjustment for these and other CV risk factors, renin remains a strong predictor of CV clinical outcomes, independently of aldosterone levels. This may imply additional benefits of renin intervention in the prevention of CVD.

919 Genetic variation in lipid response to statin therapy in 18,705 participants in the heart protection study

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Background: Statins are an effective approach to reduction of LDL cholesterol (LDL-C) and risk of vascular events. Reliable evidence of the genetic determinants of LDL-C and apolipoprotein B (apoB) response to statins is limited, and it is unclear whether there is clinically important variation in individual lipid response to statin therapy.

Methods and results: A genome-wide association analysis for LDL-C response and apoB response to 4-6 weeks of simvastatin 40 mg daily was performed in 3895 participants in the Heart Protection Study. Genotyping in a further 14,810 individuals was conducted to seek replication of the 9 strongest hits and to inves-

tigate 32 single nucleotide polymorphisms (SNPs) within candidate genes. Lipid response associations were not replicated for any of the strongest hits from the genome-wide analysis. However, novel associations with lipid response to statin therapy were identified at loci linked previously to coronary disease risk: LPA (rs10455872 and rs3798220; p-value for LDL-C response = 8.1×10^{-28}, 7.1×10^{-5}; p-value for apoB response=6.5×10^{-31}, 2.5×10^{-5} respectively) and CELSR2-PSRC1-SORT1 (rs646776 p-value for apoB response=2.8×10^{-7}). In addition, SNPs in the APOE, APOC1, BCL3, TOMM40, SLCO1B1 and ABCC2 candidate genes were significantly associated with lipid response (after correction for multiple testing). The differences in lipid response to statins were greatest for LPA and APOE variants but even these were each only about 2-3% per allele (eg an LDL-C reduction with 40 mg simvastatin daily of 39-40% versus 42%).
Conclusions: Common genetic variants appear to cause modest differences of only a few percent in the lipid response to statin therapy and thus may be of limited relevance in clinical practice. Knowledge of such effects may, however, provide useful insights into relevant biological pathways.

921 Resting heart rate (RHR), chronic obstructive pulmonary disease (COPD), and mortality. The Copenhagen City Heart Study (CCHS)

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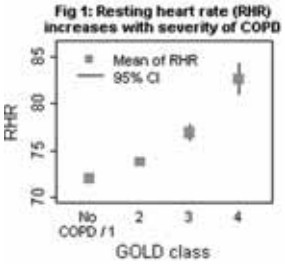
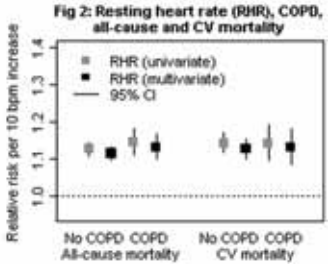
Purpose: High resting heart rate (RHR), a simple and easily obtainable clinical parameter, is associated with mortality. The cardiac and pulmonary systems are intimately connected. However, the relationship between RHR, COPD, and mortality has never been investigated.
We studied the association between RHR, severity of COPD, and association with CV -and all-cause mortality.
Methods: A prospective study of the general population initiated in 1976 with subjects participating in up to four visits during follow-up. At each visit, a full medical examination, incl EKG, was performed, and medical history obtained. Subjects with atrial fibrillation were excluded.
Severity of COPD was classified according to the GOLD classification as Mild (GOLD 1), Moderate (GOLD 2), Severe (GOLD 3), or Very Severe (GOLD 4).
Associations were studied in multivariate Cox-models with time-dependent covariates and age as underlying time-scale. Covariates included CV risk factors, comorbidities, and medication.
Results: 18593 subjects were followed for up to 34.5 years. 10903 deaths occurred.
RHR increased with severity of COPD (Fig. 1) ($p<0.001$). This relationship was unchanged by multivariate adjustments.
Within each GOLD class, RHR in the highest vs. lowest quartile predicted worse prognosis with greater mortality.
In both uni-and multivariate models RHR was associated with an increased risk of both CV and all-cause mortality in both subjects with and without COPD, (Fig. 2), all $p<0.001$.





Conclusion: In this large scale study we demonstrate that elevated RHR is related to severity of COPD.
RHR is a significant independent risk factor for mortality in subjects with COPD.
Perspective: Heart rate should be included in the clinical assessment of patients with COPD as a potentially modyfiable risk factor.

YOUNG INVESTIGATORS AWARDS SESSION: CORONARY PATHOPHYSIOLOGY AND MICROCIRCULATION

923 Intracoronary infusion of bone marrow cells and peripheral mononuclear blood cells has no influence on the recovery of myocardial perfusion after acute revascularized myocardial infarction

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Background: Several clinical and experimental studies have suggested that stem cell therapy improves functional recovery in patients with ST-elevation myocardial infarction (STEMI). These effects include the induction of neoangiogenesis in ischemic tissue and recovery of the microcirculation. In the present sub study of the HEBE trial, the effect of intracoronary infusion with bone marrow mononuclear cells (BMMCs) and peripheral blood mononuclear cells (PBMCs) on the recovery of the microcirculation after STEMI was investigated by means of cardiovascular magnetic resonance imaging (CMR).
Methods: A total of 200 patients after primary percutaneous coronary intervention (PCI) were randomly assigned to intracoronary infusion of BMMCs, PBMCs, or standard therapy (control group). All patients underwent rest first pass myocardial perfusion imaging at baseline and 4 months after primary PCI. Paired analysis was available in 157 patients with equal distribution amongst the BMMC (n=53), PBMC (n=56) and control groups (n=46). Myocardial perfusion was evaluated semi-quantitatively from signal intensity versus time curves by calculation of the relative upslope (signal intensity change per second, corrected for the time-intensity curve of the arterial input function and the baseline signal intensity) in infarct core, border infarct zone and a remote myocardial zone.
Results: Mean myocardial perfusion at baseline increased significantly from infarct core to border zone to remote (6.9 ± 3.4 in infarct core versus 9.2 ± 4.4 in border zone versus 13.8 ± 4.8 in remote zone, all p-values <0.001). At 4 months, these inter-regional differences persisted (all p-values <0.001). However, the change in perfusion per region was different. We found significant improvement in the infarct core (relative upslope at baseline 6.9 ± 3.4 versus 7.8 ± 4.3 at follow-up, $p<0.001$), whereas remote myocardium showed a significant decrease (13.8 ± 4.8 versus 12.5 ± 4.3, p=0.002). There was no change in perfusion in the infarct border zone (9.2 ± 4.4 versus 9.4 ± 4.1, p=0.57). There was no significant difference in myocardial perfusion between the treatment groups compared to control in infarct core (BMMC: 8.2 ± 3.1 versus 7.7 ± 3.7, p=0.56; PMBC: 7.6 ± 3.2 versus 7.7 ± 3.7, p=0.87), infarct border (BMMC: 10.1 ± 3.7 versus 9.5 ± 5.0, p=0.53; PBMC: 8.8 ± 3.4 versus 9.5 ± 5.0, p=0.39) and remote myocardium (BMMC: 13.1 ± 4.8 versus 12.3 ± 4.1, p=0.42; PBMC: 12.0 ± 3.9 versus 12.3 ± 4.1, p=0.70).
Conclusion: Myocardial perfusion improves in the infarct core 4 months after primary PCI. However, this was not influenced by the intracoronary infusion of mononuclear cells.

924 Significance of intramyocardial hemorrhage soon after a first reperfused ST-segment elevation myocardial infarction. Assessment by cardiovascular magnetic resonance imaging

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Purpose: In ST elevation myocardial infarction (STEMI), intramyocardial haemorrhage (IH) reflects a severe damage secondary to the ischemia-reperfusion injury. Currently, cardiovascular magnetic resonance (CMR) is the state-of-the-art technique for assessing this phenomenon. The aim of this study was to assess, using CMR, the incidence of IH, its dynamics and its implications in terms of microvascular osbtruction (MVO) and early and late left ventricle (LV) remodelling.
Methods: We prospectively studied 95 consecutive patients who were admitted in our institution for a first reperfused STEMI. CMR was performed at pre-discharge (4 ± 1 days) and at 6 months (178 ± 12 days) post-STEMI. IH (lack of enhancement in the core of a hyperenhanced area in T2-weighted sequence, % of LV mass), MVO (lack of contrast arrival in the core of a hyperenhanced area in late enhancement imaging, % of LV mass), infarct size (% of LV mass displaying late enhancement) along with traditional LV indexes in cine images were quantified. Adverse left ventricular remodelling (progressive dilation of LV end-dyastolic and end-systolic volumes indexes, ml/m^2) was determined by comparing 1-week and 6-months CMR studies.
Results: At 1-week CMR studies, the presence of IH could be accurately analyzed in 95% of cases. IH was detected in 42 patients (47%) in the core of the area at risk (with edema). All patients displaying IH exhibited MVO. A highly significant correlation existed between the extent of IH and the extent of MVO (r=0.87, $p<0.0001$). The presence of IH associated to younger age, anterior infarctions

and higher troponin peak-value ($p<0.05$ in all cases). At the 1-week CMR, IH related to more dilated LV end-dyastolic and end-systolic volumes ($p<0.0001$), more depressed ejection fraction, bigger LV mass, more extensive area at risk, infarct size and transmural extent of the necrosis, and less percentage of salvaged myocardium ($p<0.05$). At 6-months CMR, IH vanished in all cases. In the multivariate analyses, the presence of IH soon after STEMI did not add independent information to predict LV adverse remodelling from 1-week to 6 months.
Conclusions: CMR allows for an accurate assessment of IH in the vast majority of cases. This finding occurs in around 50% of patients with a first reperfused STEMI. Soon after infarction, IH is strongly associated with the presence of MVO as well as more extensive infarcts, more depressed systolic function and early and severe LV dilation. IH vanishes in all cases within the months following STEMI and it does not constitute an independent predictor of adverse LV remodeling late after STEMI.

925 Atorvastatin rapidly improves eNOS coupling in human internal mammary arteries, by stimulating GTP-cyclohydrolase I expression and improving vascular tetrahydrobiopterin bioavailability

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Background: Statins improve survival of patients with atherosclerosis, but their effects on human vessels are unclear. We examined the direct effect of atorvastatin on the mechanisms regulating endothelial nitric oxide synthase (eNOS) coupling in human internal mammary (IMA).
Methods: Segments of IMA grafts from 26 patients undergoing CABG were exposed to atorvastatin 0, 5 μmol/L for 6 hours in an LDL free environment. Then vascular O2- was measured in by lucigenin chemiluminescence in the presence of endothelial nitric oxide synthase (eNOS) inhibitor LNAME, and/or mevalonate (200μmol/L). We also quantified the changes of vascular tetrahydrobiopterin (BH4), as well as the effect of atorvastatin on GTP cyclohydrolase I (GTPCH I) activity, by using the GTPCH I inhibitor DAHP.
Results: Atorvastatin reduced vascular (O2-) and reversed LNAME-inhibitable O2- (A), suggesting a direct improvement of eNOS coupling. These effects were prevented by mevalonate (A). Atorvastatin induced a significant increase of vascular BH4 (B) by increasing GTPCHI enzymatic activity, an effect that was reversed by DAHP (B). Atorvastatin also significantly increased GCH1 mRNA (C).

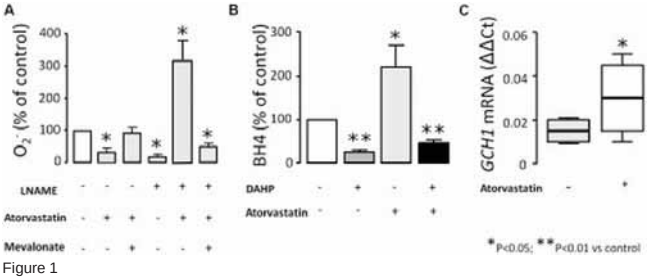

Figure 1

Conclusions: This study demonstrates for the first time in humans that atorvastatin exerts a rapid, direct effect on GCH1 expression in human arteries, leading to improved BH4 bioavailabiity and improved eNOS coupling. This results into a striking improvement of vascular redox state, documenting an additional pleiotropic effect of statins on the arterial wall of patients with advanced atherosclerosis.

926 Low endothelial shear stress upregulates atherogenic and inflammatory genes extremely early in the natural history of coronary artery disease in diabetic hyperlipidemic juvenile swine

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Purpose: The upregulation of genes responsible for the atherogenic phenotype, as well as the driving pathobiologic mechanisms, have been well studied in advanced plaques in older animals, and low ESS is known to be a critical factor responsible for the location and severity of complex lesions. The time frame for the earliest onset of such gene expression remains unknown. We investigated how early the upregulation of atherogenic genes occurs using a juvenile porcine model of human-like atherosclerosis.
Methods: In four swine (age 12 wks) diabetes and hypercholesterolemia were induced. 3D reconstruction of all major coronary arteries by angiography-IVUS was performed in vivo 4 wks later (baseline, wk 16) and again after 4 wks (followup, wk 20). Baseline local ESS was calculated using computational fluid dynamics and 3-mm segments with low ($\leq$1.2 Pa; n=21) or higher ($>$1.2 Pa; n=24) ESS were identified. Coronary arteries were harvested at wk 20. RNA was isolated from the intima-media of the segments and the expression of the following atherogenic genes was assessed by real time RT-PCR: LDL receptor, lipoprotein-associated phospholipase-A2 (LpPLA2), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1) and heme oxygenase-1 (HMOX-1).
Results: Even in the absence of significantly increased intima-media area, segments with low ESS at wk 16 had upregulated gene expression at wk 20 of LDL receptor, LpPLA2, ICAM-1, MCP-1 and HMOX-1 compared to segments with higher ESS (Figure 1). mRNA levels of VCAM-1 were not significantly different.

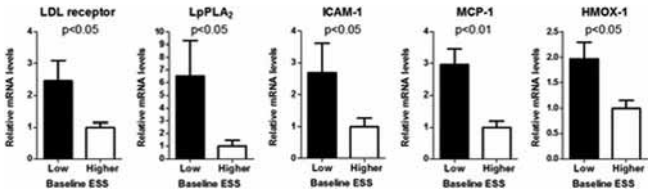

Figure 1

Conclusion: Coronary regions exposed to low ESS exhibit markedly augmented atherogenic and inflammatory activation extremely early, even in the absence of anatomic manifestations of atherosclerosis.

YOUNG INVESTIGATORS AWARDS SESSION: THROMBOSIS

928 Extracellular cyclophilin A activates platelets via EMMPRIN and PI3-kinase and enhances platelet adhesion in vitro and in vivo

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Introduction: Cyclophilin A (CyPA) is secreted under inflammatory conditions by various cell types (including platelets, leucocytes and smooth muscle cells). We have recently identified its receptor EMMPRIN (CD147) on platelets. Here we investigated the effect of extracellular CyPA on platelet activation and adhesion in vitro and in vivo.
Methods and results: Freshly isolated human platelets were stimulated with various concentrations of recombinant CyPA and analyzed after various time points by flow cytometry for the expression of p-Selectin and GPVI. In fact, p-selectin and GPVI were upregulated in a concentration- and time-dependent manner on platelets (100nM CyPA stimulation for 20min: mean Immunofluorescence P-Selectin: 23.58±0.98 vs. resting 7.16±0.32, GPVI: 38.1±2.5 vs. 28±3.0, $p<0.05$ each), which was abrogated by an EMMPRIN-blocking mAb. Moreover activation of platelets with CyPA lead to an enhanced expression of Phos-Akt (Western Blot), indicating an involvement of Phophatidylinositol-3-Kinase (PI3K). Treatment of platelets with the PI3 inhibitors Wortmannin or LY294002 abolished CyPA mediated platelet activation nearly completely measured by p-selectin expression (FACS). Perfusion of CyPA-stimulated platelets over cultivated endothelial cells under arterial shear conditions in vitro showed an enhanced rolling which could be blocked by anti-p-Selectin or anti-PSGL-1 treatment ($p<0.05$). Perfusion of CyPA-stimulated platelets over immobilized collagen (ligand for GPVI) showed enhanced adhesion (14,6±1,5 vs. 25,5±3 platelets per high powerfield), which was abrogated by mAb anti-GPVI or anti-EMMPRIN ($p<0,05$). Finally, perfusion of ex vivo CyPA-pretreated platelets into mouse carotid arteries after arterial injury showed both enhanced rolling and adhesion as assessed by intravital microscopy, which was blocked by anti-CD147.
Conclusion: Extracellular CyPA activates human platelets via EMMPRIN and PI3-kinase and thus enhances adhesion of platelets on endothelial cell and collagen in vitro and in vivo. Thus extracellular CyPA could contribute to the progress of atherosclerosis and represent a novel target for treatment of atherosclerosis.

929 MDCT-detected embolic burden and clinical outcome in patients with acute pulmonary embolism

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Purpose: In patients with acute pulmonary embolism (PE) the correlation between the embolic burden at multidetector computed tomography (MDCT) and clinical outcome remains unclear.
Methods: Consecutive patients with symptomatic acute PE diagnosed by MDCT were included in the study. The primary outcome was death or clinical deterioration at 30 days. Embolic burden was assessed by the obstruction index (OI) according to the scoring system of Qanadli and by the localization of emboli. Localization was categorised as: central (saddle or at least one main pulmonary artery), lobar or distal (segmental or subsegmental arteries). Cox regression analysis was used to assess predictors of death or clinical deterioration.
Results: Overall, 579 patients were included in the study, 60 (10.4%) died or had clinical deterioration at 30 days. No correlation was found between OI or localization of emboli and clinical outcome in the overall population. In hemodynamically stable patients central localization of emboli (HR 8.3, 95% CI 1.0-67, p=0.047), age over 75 years and right ventricle dysfunction at echocardiography were independent predictors of death or clinical deterioration.

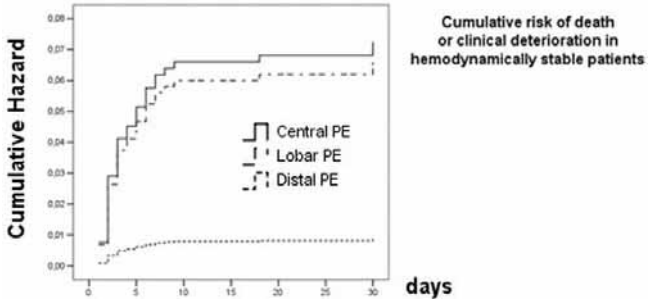

Figure 1

Conclusions: In hemodynamically stable patients with acute PE, central localization of emboli is associated with an increased risk for death or clinical deterioration.

930 A new morphologic type of Doppler-silent prosthetic valve thrombus disclosed by real-time 3 dimensional transesophageal echocardiography: definition and its relation to clinical events

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Purpose: Mechanical prosthetic heart valve thrombosis (PHVT) is a serious complication that can occur anytime during follow-up after surgery. Although 2D transesophageal echocardiography (2D TEE) has been accepted a gold standart diagnostic tool for PHVT, it may miss band-like PHVT located on the sewing ring of the prosthesis. Incremental value of real-time 3D transesophageal echocardiography (RT-3D TEE) in the evaluation of annular-type PHVT is not yet known. In this study, we aimed to investigate the utility of RT-3D TEE in PHVT, undetected by 2D TEE, and its relation to clinical events.
Methods: The study group comprised of 884 patients with mechanical prosthetic valves; all were examined by transthoracic echocardiography, 2D TEE and RT-3D TEE. During RT-3D TEE examination, annular-type PHVT which undetected by 2D TEE (i.e. non-obstructive, mounded, fixed, homogeneous and band-like appearance located over hinges and/ or valve ring) was explored. The relationship between annular-type PHVT and inadequate anticoagulation, history of thromboembolic events was analyzed.
Results: Among 884 patients (F: 580, M: 304, mean age: 48, aortic: 156, mitral: 610, aortic+ mitral: 118) PHVT has been established in 209 patients (obstructive: 30, non-obstructive: 179). Two dimensional TEE disclosed 150 (84%) of all non-obstructive PHVT (aortic: 10, mitral: 140), whereas 3D TEE examination disclosed additional 29 patients (16%), which were all annular-type PHVT in mitral position. Twenty-four patients with non-obstructive thrombosis shown by 2D TEE, also have annular-type PHVT, demonstrated by RT-3D TEE. Among these 53 patients with annular-type PHVT; 11 patients (21%) had inadequate anticoagulation, 12 patients (23%) had history of thrombolytic therapy, 14 patients (26%) had history of thromboembolic events (12 patients with transient ischemic attack and 2 patients with coronary embolism). In 11 patients with annular-type PHVT shown by RT-3D TEE, which were reoperated for other causes, thrombus was confirmed surgically. RT-3D TEE, however, was not satisfactory in evaluating annular-type aortic valve thrombosis in neither of the patients.
Conclusion: RT-3D TEE, enables us to disclose a new morphologic type of Doppler-silent, non-obstructive thrombus undetected by 2D TEE. This annular-type of thrombus may be related to thromboembolic events such as coronary, cerebral and peripheral emboli.

931 Endothelial overexpression of LOX-1 decreases arterial thrombosis and TF expression in vivo

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Background: The hallmark of the initiation of atherosclerotic lesion is foam cell formation, and oxidized LDL (OxLDL) is believed to play a key role in the initiation of the atherosclerotic process. OxLDL is internalized by several receptors, such as SR-AI/II, SR-BI, CD36, and CD68. OxLDL is also internalized by endothelial cells, but this uptake depends on receptors other than the classic scavenger receptors. In 1997, a lectin-like oxidized LDL receptor-1 (LOX-1, OLR1) was identified in bovine aortic endothelial cells. LOX-1 is a type II membrane glycoprotein with an apparent molecular weight of 50 kDa. It has a C-terminal extracellular C-type lectin-like domain. This lectin-like domain is essential for binding to OxLDL. Binding of OxLDL to LOX-1 induces several cellular events in endothelial cells, such as activation of transcription factor NF-kB, upregulation of MCP-1, and reduction in intracellular NO, which may trigger the onset of cardiovascular events or accelerate the development of atherosclerosis.
Methods and results: We generated endothelial-specific LOX-1 transgenic mice using the Tie2 promoter (LOX-1TG). 12-week-old male LOX-1TG and wild-type (WT) mice were applied for carotid artery thrombosis model. LOX-1TG mice developed carotid artery thrombosis within a mean occlusion time of 36.96±4.83 min, while WT control mice occluded within a mean time period of 22.75±3.87 min (n=10, $P<0.05$). Initial blood flow in carotid artery did not differ between both groups of mice. Decreased occlusion time in LOX-1TG mice was further associated with decreased tissue factor expression and surface activity as shown by RT PCR and ELISA. Furthermore, LOX-1TG mice showed increased mRNA expression of deacetylase SIRT1 in carotid artery, pointing out that SIRT1 may be involved in the observed downregulation of tissue factor through its known target transcription factor NF-kB.
Conclusions: Thus, our data suggest that LOX-1 plays a protective role in the arterial thrombosis and that SIRT1 may be involved. Therefore, both LOX-1 and SIRT1 may represent novel therapeutic targets for preventing arterial thrombosis.

YOUNG INVESTIGATORS AWARDS SESSION: CLINICAL SCIENCE

933 Metabolic syndrome and cardiovascular outcomes in statin-treated, stable coronary patients with low LDL cholesterol levels of the TNT and IDEAL studies

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Purpose: The usefulness of metabolic syndrome (MetS) in cardiovascular (CV) disease risk prediction among statin-treated patients has recently been challenged and it is unclear whether MetS has predictive value in patients who reach their low-density lipoprotein cholesterol (LDL-C) goal. Our objective was to investigate whether statin-treated patients with MetS reaching low LDL-C levels are at increased risk compared to those without MetS in two large randomized trials of stable coronary patients.
Methods: We used a Cox proportional hazard model adjusted for age, sex, and smoking to assess the predictive value of MetS in 8,500 patients of the TNT study and in 7,819 patients of the IDEAL study, two trials comparing the efficacy of high-dose vs. standard-dose statin therapy on cardiovascular outcomes. Individuals with diabetes were excluded. Patients with LDL-C levels <100 mg/dL (2.59 mmol/L) at baseline were considered as having low LDL-C levels. The primary endpoint was the time to the first occurrence of a major CV event (MCVE), defined as coronary heart disease death, nonfatal, non-procedure-related myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke.

Results: The prevalence of the MetS was 51.2% in TNT and 41.5% in IDEAL. A total of 744 (8.8%) and 943 (12.1%) patients had a MCVE during the follow-up, respectively in TNT and IDEAL. In TNT patients with low LDL-C levels (n=4,739), the hazard ratio (HR) for MCVE comparing those with vs. without MetS was 1.34 (95%CI, 1.09-1.63, p=0.005). In IDEAL patients with low LDL-C levels (n=1,986), the corresponding HR was 1.49 (1.13-1.96, p=0.0004). In TNT, LDL-C categories (< or >100 mg/dL) and MetS presence (yes or no) had an additive impact on CV risk (p [interaction]=0.63 and p [linear trend]=0.0002). In IDEAL, the predictive value of MetS appeared to be greater in patients with low LDL-C than in those with higher LDL-C levels (p [interaction]=0.07 and p [linear trend]=0.002). In both studies, significant trends between the number of MetS components and risk of MCVE were observed in patients with low LDL-C (p=0.0002 in TNT and p=0.01 in IDEAL) and in those with higher LDL-C levels (p=0.003 in TNT and p=0.01 in IDEAL).
Conclusions: In stable coronary patients without diabetes treated with statins, metabolic syndrome is an important predictor of CV risk, even in those with low LDL-C levels, and should be targeted accordingly.

934 Clinical implications of provocation tests of coronary vasospasm: safety, arrhythmic complication and type of spasm - a report from the multi-center registry by the Japanese coronary spasm association

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Background: Provocation tests of coronary vasospasm are useful for diagnosis of vasospastic angina (VSA). However, the prognostic impact of arrhythmic complications, including ventricular tachycardia (VT), ventricular fibrillation (VF) and brady-arrhythmias, and that of types of the spasm remain to be elucidated.
Methods: In the multicenter registry study by the Japanese Coronary Spasm Association, a total of 1429 VSA patients (M/F, 1090/339; median 66 years) were enrolled between Sept. 2007 and Dec. 2008 from 47 institutes, including 1244 patients (87%) who underwent provocation tests of the spasm. During a median follow-up of 32 months, the incidence of arrhythmic complications during provocation tests, types of vasospasm (e.g. diffuse, focal, or mixed) and the clinical outcomes of patients with provocation-related VT/VF were evaluated.
Results: The provocation tests were performed with either acetylcholine (ACh, 57.3%), ergonovine (Erg, 40.0%), both of them (1.8%) or others (e.g. hyperventilation, 0.9%). The incidence of coronary spasm of the left anterior descending artery, left circumflex artery and right coronary artery was 54%, 25% and 56%, respectively. Multivessel spasm was documented in 30% of patients. During the provocation tests, VT/VF, AV block and cardiac arrest developed at a rate of 3.2, 0.6 and 0.2%, respectively. Overall incidence of arrhythmic complications was 6.8%, a comparable incidence of those during spontaneous angina attacks (7.0%). The patients with provocation-related VT/VF, as compared with those without VT/VF, were characterized by higher proportion of female (40 vs. 24%, $P<0.05$), higher incidence of multi-vessel spasm (45 vs. 30%, $P<0.05$), diffuse-type spasm (76 vs. 50%, $P<0.01$) and clinical manifestations of typical midnight to morning attacks (55 vs. 37%, $P<0.05$). In addition, the incidence of provocation-related VT/VF was significantly higher with ACh compared with Erg (ACh 4.9 vs. Erg 0.8%, $P<0.001$). The survival rate free from composite cardiac events was comparable between patients with and those without provocation-related VT/VF (93 vs. 92% at 5 years, P=0.90). Among the 1121 patients in whom type of the spasm was characterized as focal (n=471), diffuse (n=569) and mixed (n=81), the group with mixed-type had a significantly higher incidence of 5-year composite cardiac events than the other 2 groups (mixed 16 vs. focal 7, diffuse 8%; $P<0.01$).
Conclusions: These results indicate that the provocation test for coronary vasospasm is safe with a low incidence of arrhythmic complications and that the type of the spasm may affect the prognosis of VSA patients.

935 Very late heart transplant rejection is associated with microcirculation injury, complement deposition and progression to cardiac allograft vasculopathy

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Introduction: In heart transplants, the significance of very late rejection (after 7 years post transplant, VLR) detected by routine endomyocardial biopsies (EMB) remains uncertain. Here, we assessed the prevalence, histopathological and immunological phenotype, and outcome of VLR in clinically stable patients.
Methods: Between 1985 and 2009, 10.662 protocol EMB were performed at our institution in 398 consecutive heart transplant recipients. Among the 196 patients with >7yrs follow-up, 20 (10.2%) presented subclinical ≥3A/2R-ISHLT rejection. The VLR group was compared to a matched-control group of patients without rejection. All biopsies were stained for C4d/C3d with sera screened for the presence of donor specific anti-HLA antibodies (DSAs) by sensitive technique (LUMINEX assays).
Results: In addition to cellular-infiltrates with myocyte damage, 60% of VLR patients had microcirculation inflammation with intravascular macrophages. C4d and/or C3d-capillary deposition was found in 55% VLR EMB. All cases of VLR associated with microcirculation injury had donor specific anti-HLA antibodies (mean DSAmax Mean Fluorescence Intensity =1751±583). This entity was absent from the control group ($p<0.0001$). Finally, after a similar follow-up post-reference EMB, the mean of Chronic Allograft Vasculopathy grade was 0.76±0.83 in the control group and 2.06±1.00 in the VLR group respectively, p=0.001).
Conclusion: Very late heart rejection is frequently associated with complement cascade activation in capillaries, microvascular inflammation and DSA, suggesting an antibody-mediated process. VLR in clinically stable patients is associated with subsequent progression to Chronic allograft vasculopathy. Our study provides evidence that a precise immunological characterization of asymptomatic very late heart rejection would be valuable to stratify the patients more likely to develop subsequent CAV and to propose adapted immunosuppressive therapeutic strategies.

936 The influence of a systemic inflammatory response syndrome on prognosis after transcatheter aortic valve implantation

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Purpose: Emerging data suggest that an elevated leukocyte count during the first 72 hours after transcatheter aortic valve implantation (TAVI) is an independent predictor of acute kidney injury (AKI) which is significantly associated with an unfavourable early and late outcome. The aim of this study was to elucidate the influence of a systemic inflammatory response syndrome (SIRS) on prognosis after TAVI.
Methods: TAVI was performed with the 18F-CoreValve prosthesis via transfemoral access in 101 consecutive patients (mean age of 80.7±6.4 years, logistic EuroSCORE 29.5±17.1%). Proinflammatory cytokines [Interleukin-6 (IL-6), Interleukin-8 (IL-8)] and acute-phase reactants [C-reactive protein (CRP), procalcitonin (PCT)] were measured at baseline and 1h, 4h, 24h, 48h, 72h, and 7days after TAVI.
Results: Overall procedural success rate was 97% with a 30-day mortality of 8.9% and a 1-year mortality of 27.7%. SIRS occurred in 35/101 patients of whom 17 patients (49%) died during follow-up. The incidence of SIRS was related to major vascular complications (20 vs. 3%; p=0.003), peri-prosthetic regurgitation ≥2 (26 vs. 9%; p=0.02), and AKI (49 vs. 14%; $p<0.001$). During the first 48h, patients with AKI showed a significant increase of IL-6 (P=0.004), IL-8 (P=0.04), CRP (P=0.007), and PCT levels ($P<0.001$). The occurrence of SIRS increased 30-day mortality (HR 3.9, 95% CI: 1.0-15.7; P=0.05) and 1-year mortality (HR 3.5, 95% CI: 1.6-7.4; P=0.001). Patients with a co-incidence of SIRS and AKI had the worst prognosis with a 1-year mortality rate of 76% ($P<0.001$).

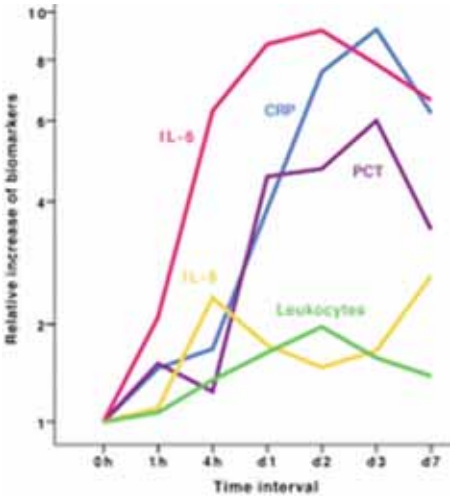

Figure 1. Inflammatory Markers in AKI after TAVI

Conclusions: Post-procedural SIRS is a strong predictor of 30-day and 1-year mortality after TAVI. Our results suggest that SIRS might be result of renal ischemia-reperfusion injury and plays a pivotal role in the pathogenesis in AKI.

NURSING / ALLIED PROFESSIONAL INVESTIGATOR AWARD

958 Socio-cultural influences of heart failure self-care among an ethnic minority population

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Since culture is central to the development of self-care, we sought to describe the self-care practices (adherence to diet, medication and symptom management behaviors) and the socio-cultural influences on self-care in an ethnic minority population with heart failure (HF).

Methods: Using mixed methods, 30 Black patients with HF (mean age 59.63±15 years; 60% Male; 65% NYHA III) participated in in-depth interviews about HF self-care, cultural beliefs (food preferences, medication beliefs, symptom meaning) and social support; and completed standardized instruments measuring self-care (SCHFI:Self-Care of Heart Failure Index) and social support (MPSS:Multidimensional social support scale). Thematic content analysis elicited themes about influences of socio-cultural factors on self-care. Qualitative and quantitative data were integrated in the final analytic phase.

Results: Self-care was very poor (standardized mean SCHFI maintenance 60.05±18.12; SCHFI management 51.19±18.98; SCHFI confidence 62.64±18.16). Few (<25%) engaged in adequate self-care (≥70% on SCHFI subscales). The overarching theme in the qualitative data analysis was that self-care is influenced by cultural beliefs, including the meaning ascribed to HF; and social norms. The common belief that HF was inevitable ("all my people have bad hearts") or attributed to "stress" influenced self-care symptom management ("when it comes...just relax, that's all I can do"). Spirituality was also linked to daily self-care ("the doctor may order it but I pray on it"). Cultural beliefs about life and family supported some self-care behaviors like medication adherence, which was deemed essential ("for a long life I take the pills"). Conversely, difficulty reconciling cultural preferences (favorite foods) with the salt-restricted diet was evident in poor self-efficacy ("our food is bad...I can't give it up"). The significant relationship of social support and self-care (r=0.45; p=0.01) was explicated by the qualitative data. Social norms interfered with willingness to access tangible resources especially when family was scattered and "selectivity" in whom individuals confided ("I don't tell them everything") that led to delay in symptom management and confounded self-care.

Conclusions: Research to develop and test culturally sensitive interventions is critically needed, especially since minority populations continue to experience poorer outcomes. Community-based interventions (cultural groups or faith-based) that facilitate self-efficacy and provide culturally acceptable resources to facilitate self-care among minority individuals with HF should be explored.

959 Older heart failure patients' preferences for cardiac rehabilitation service models

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Purpose: Recent European survey and audit data consistently demonstrate underutilisation of cardiac rehabilitation (CR). Limited participation may relate to patients' preferences for participation. We aimed to investigate older (≥65 years) heart failure (HF) patients' preferences for 3 different CR service models (hospital-based group, community-based group and home-based). Relationships between preferences and demographic factors, disease severity and co-morbidities were investigated.

Methods: Patients with confirmed HF consecutively admitted to cardiology, elderly care and general medicine wards in a London teaching hospital were screened for study inclusion in April-December 2009. A 57-item interview schedule incorporating standard measures was developed to explore preferences for attending CR. Piloting and expert review validated the schedule. Patients suitable for exercise were interviewed by a research physiotherapist. Associations between patients' preferences and categorical data (gender, living arrangements, NHYA class) were analysed using Chi^2 tests; and continuous data (age, Charlson co-morbidity score) by one-way ANOVA with post-hoc Bonferroni analysis.

Results: From 186 patients screened 106 interviews were completed (mean age 77.8±7.3, 62% male, 47% married, 47% lived alone). Most patients were NHYA class III (55%) or II (34%) and 56% had LVEF <45%. Most had co-morbidities (mean Charlson score 3.3±1.7). Median hospital stay was 15 days (IQR 9, 20). Median number of prescribed medications at discharge was 11 (IQR 9, 14). Most patients reported preferring group-based CR (40%), of which hospital classes were preferred to community classes. Home-based programmes were preferred by 30%. Fewer reported preferring not to participate (28%), often stating they performed sufficient exercise without attending CR. No associations between preferences and gender, living arrangements, NYHA class or co-morbidity were found. Age was found to be associated with certain, but not all, preferences. Those preferring to attend hospital classes were younger (mean 5.1 years, p=0.043, 95% CI -10.1 to -0.1) than those preferring not to participate. However, those preferring home programmes had the same mean age as those preferring not to participate.

Conclusions: When approached in hospital, the majority of these older HF patients with multiple co-morbidities wanted to attend CR. Older HF patients have mixed preferences towards group and home-based service models which were unrelated to their NYHA class and co-morbidities. Services should offer a variety of CR models to older HF patients to encourage participation.

960 Access to cardiac rehabilitation does not equate to attendance

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Background/aims: Timely access to appropriate cardiac care is critical for optimizing outcomes of a cardiac event. In Australia the overall attendance at cardiac rehabilitation remains less than optimal (ranging 37% - 66%). Our aim was to derive an objective, comparable, geographic measure, the Cardiac Accessibility and Remoteness Index of Australia (Cardiac ARIA) reflecting access to cardiac services for all 20,387 population locations.

Methods: An expert panel defined a single patient care pathway. Using geographic information systems (GIS) the numeric/alpha index was modeled in two phases. The acute phase (numeric) ranged from 1 (access to tertiary centre with PCI ≤1 hour) to 8 (no ambulance service, >3 hours to medical facility, air transport required). The aftercare phase was modeled into 5 alphabetic categories; A (Access to general practitioner, pharmacy, cardiac rehabilitation, pathology ≤1 hour) to E (no services available within 1 hour).

Results: Approximately 96% or 19 million people lived within 1 hour of the four basic services to support cardiac rehabilitation and secondary prevention, including 96% of older Australians and 75% of the indigenous population. Conversely, 14% (64,000) indigenous people resided in population locations that had no access to any service to support cardiac rehabilitation.

Conclusion: Results demonstrated that the majority of Australians had excellent "geographic" access to services to support cardiac rehabilitation and secondary prevention. Therefore, it appears that it is not the distance to services that affects attendance. Innovative clinical practice is needed to improve uptake of this important aspect of cardiac care.

MOLECULAR DEFECTS DRIVING CARDIAC DYSFUNCTION

1007 Genetic deletion of ARIA attenuates the doxorubicin-induced cardiomyopathy by activating the Akt pathway in cardiomyocytes

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We recently identified a novel gene, termed ARIA that is highly expressed in endothelial cells, and regulates endothelial apoptosis (PNAS 2009). In the current study, we found that ARIA is also expressed in cardiac myocytes, and plays a significant role in the doxorubicin-induced cardimyopathy by utilizing the ARIA knockout (ARIA-KO) mice. ARIA expression was detected in mouse heart as well as in rat isolated cardiac myocytes. To investigate the ARIA function in the heart in vivo, we generated ARIA-KO mice. ARIA-KO mice were viable and fertile, and no abnormality of heart was observed with respect to morphology as well as function assessed by echocardiography. We then induced cardiomyopathy by intraperitoneal administration of doxorubicin. Cardiac systolic function was significantly attenuated in WT mice by the doxorubicin-treatment, while no significant reduction in cardiac systolic function was observed in ARIA-KO mice. The left ventricular fractional shortening after doxorubicin-treatment was 38% in ARIA-KO mice, and 29% in WT mice (n=5 each, P<0.01). Doxorubicin-induced cardiomyocytes apoptosis was significantly reduced in ARIA-KO mice as compared with that in WT mice. Furthermore, we identified that Akt pathway was significantly activated in the heart of ARIA-KO mice as compared with that in WT mice heart. Akt signaling has been reported to play a crucial role in the doxorubicin-induced cardiomyopathy by reducing cardiomyocyte apoptosis and mitochondrial damage. Also, Akt plays a significant role in the transcriptional activity of GATA4, which protects cardiomyocytes against doxorubicin-induced cardiotoxicity. In consistent with the Akt activation, expression of GATA4 and its target gene Bcl-2 was significantly enhanced in the heart of ARIA-KO mice as compared with that in WT mice after doxorubicin-treatment. As a result, attenuation of mitochondrial DNA was significantly reduced in conjunction with preserved ATP level in the heart of ARIA-KO mice comparing with those in WT mice heart after doxorubicin-treatment. Taken together, ARIA plays a crucial role in the doxorubicin-induced cardiomyopathy by reducing apoptosis and mitochondrial damage in cardiomyocytes through the activation of Akt pathway. ARIA is therefore an attractive new pharmacotherapeutic target for doxorubicin-induced cardiomyopathy.

1008 S151A mutation in the delta-sarcoglycan gene causes a mild phenotype of cardiomyopathy

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So far it remains inconclusive whether mutations in the delta-sarcogylcan (Sgcd) gene can cause autosomal dominant dilated cardiomyopathy. Typically Sgcd-deficient limb girdle muscular dystrophy type 2F (LGMD2F), a progressive muscle diseases associated with dilated cardiomyopathy, is inherited in an autosomal recessive fashion. However, a S151A mutation (a single nucleotide change from thymidin to guanine in position 451 in exon 6 of the Sgcd gene changes the amino acid at codon 151 from serine to alanine) was reported to cause severe isolated autosomal dominant DCM without affecting skeletal muscle. This is controversial to previous findings in a large consanguineous family where this S151A mutation showed no relevance for cardiac disease. In the present study, the potential of the S151A mutation to cause DCM was investigated further by using two different approaches: [1] engineering and characterization of heterozygous knock-in (S151A-) mice carrying the S151A sequence variant and [2] evaluation of the potential of adeno-associated virus (AAV serotype 9)-based cardiac specific transfer of S151A-mutated Sgcd cDNA to rescue the cardiac phenotype in Sgcd-deficient (Sgcd-null) mice as it has been demonstrated for intact, wild-type Sgcd cDNA.
Heterozygous S151A knock-in mice developed a rather mild phenotype of cardiomyopathy. Increased heart to body weight suggests cardiac enlargement in 1-year-old S151A knock-in mice. However, at this age cardiac function, assessed by echocardiography, is maintained and cardiac histology and life-expectancy are completely normal. Myocardial expression of S151A cDNA, similar to intact Sgcd cDNA, restores cardiac function, although myocardial histopathology in Sgcd-null mice could not entirely be prevented. Our approach of AAV9-mediated expression of the S151A variant in the knock-out context suggests that this gene variant has a mild effect on alterations within the sarcoglycan complex.
Our results suggest that the S151A mutation causes a mild, subclinical phenotype of cardiomyopathy which may be overseen in patients carrying such sequence variants. It remains unclear whether, in general, the pathological potential of heterozygous mutations in the gene for Sgcd or the other sarcoglycans are rather mild.

1009 Impaired vacuolar H+-ATPase function causes cardiomyocyte death with extensive vacuolation and impaired autophagic degradation

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Purpose: Recent studies have demonstrated that the existence of autophagic cell death in hypertrophied failing and hibernating myocardium. Autophagic cell death is a morphological term derived from electron microscopic observations and denotes a form of cell death in which abundant autophagic vaculoles are present in the cytoplasm. However, this definition tells nothing about the pathophysiological function of autophagy in disease process. In addition, it remains unknown why abundant autophagic vaculoles are present in the failing myocardium.
Methods and results: The (pro)renin receptor [(P)RR], encoded in ATP6AP2, plays a key role in the activation of local renin-angiotensin system (RAS). A truncated form of (P)RR, termed M8.9 was also found to be associated with the vacuolar H^+-ATPase (V-ATPase), implicating a non-RAS-related function of ATP6AP2. We generated conditional knockout (CKO) mice in which exon 2 of the Atp6ap2 gene was flanked by loxP sites. Atp6ap2-floxed mice were bred with mice that expressed the Cre recombinase under the control of the cardiomyocyte-specific α-myosin heavy chain (αMHC) promoter. Cardiomyocyte-specific ablation of Atp6ap2 resulted in lethal heart failure; the cardiomyocytes contained RAB7- and lysosomal-associated membrane protein 2 (LAMP2)-positive multivesicular vacuoles, especially in the perinuclear regions. The myofibrils and mitochondria remained at the cell periphery. Cardiomyocyte death was accompanied by numerous autophagic vacuoles that contained undigested cellular constituents, as a result of impaired autophagic degradation. Notably, ablation of Atp6ap2 selectively suppressed expression of the VO subunits of V-ATPase, resulting in deacidification of the intracellular vesicles. Furthermore, the inhibition of intracellular acidification by treatment with bafilomycin A1 or chloroquine reproduced the phenotype observed for the (P)RR/ATP6AP2-deficient cardiomyocytes.
Conclusions: Ablation of Atp6ap2 created a loss-of-function model of V-ATPase. Appropriate V-ATPase function is indispensable for cardiomyocyte survival. The impairment of V-ATPase function in the failing myocardium may prevent digestion of autophagosome by the lysosomal enzyme along with the fusion between autophagosome and lysosome, which could result in the failure of survival-orientated autophagy.

1010 Roles of heat shock transcription factor 1 gene (Hsf1) expressions in cardiac remodeling in a mouse model of senile cardiac amyloidosis

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Introduction: AApoA-II protein is associatedwith mouse senile amyloidosis. Heat shock proteins function as chaperones that may preventamyloid depositions in cardiac tissues, leading to restoration of cardiacremodeling. However, whether these proteins can prevent cardiac amyloidosis is unknown.
Method andresults: One μg of mouse AApoAII amyloid fibril proteins wereinjected intravenously in wild type (WT, n = 8) and heat shock transcriptionfactor 1 gene knock out (Hsf1-KO, n =8) mice at age in 8 weeks and amyloidosis was induced. At the age of 24 weeks,systemic blood pressure (SBP) was measured from tail artery using the tail cuffmethod. Ventricular function was also investigated using two-dimensionally-directedM-mode echocardiography. Surface electrocardiogram (ECG) was measured toexamine cardiac electrophysiological remodeling. The degree of amyloid deposition was determined using an amyloidindex method on heart sections stained with Congo red. The size of ventricular muscle cells was also determinedusing digital microscopic images from left ventricular sections stained with Masson's trichrome. MSBP did not differ between WT and Hsf1-KO mice. Ventricular dysfunction determined by reduction of LVfractional shortening (32.5 ± 2.8 vs. $47.5\pm1.0\%$, $p<0.001$) was observed in Hsf1-KO but notin WT mice. Interestingly, the dimension of interventricular septum wassignificantly larger in Hsf1-KOcompared with that in WT mice (0.95 ± 0.08 vs. $0.75\pm0.04\%$, $p<0.01$). The PR interval (53 ± 1 vs. 44 ± 2 millisecond, $p<0.001$) and RR intervals (208 ± 6 vs. 163 ± 13 millisecond, $p<0.001$) of the ECG parameters were prolonged in the Hsf1-KO mice compared with those in WT mice. In contrast, theP interval, QRS complex, and collected QT interval did not differ betweenHSF-KO and WT mice. The score for amyloid index in Hsf1-KO hearts was significantly greater than that in WThearts ($p<0.01$). The size of the left ventricular muscle in Hsf1-KO mice was similar to that in WT mice. These findingsdemonstrated that HSF1 protein played an important role in preventing cardiacamyloid depositions and suggest that HSF1 is a novel therapeutic target forcardiac amyloidosis.

1011 Long-term preservation of cardiac structure and function after AAV9-mediated microdystrophin gene transfer

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Purpose: Dystrophin plays an important role in muscle contraction linking the intracellular cytoskeleton to the extracellular matrix. Mutations of dystrophin gene leading to a complete loss of the protein cause Duchenne muscular dystrophy (DMD), frequently associated with severe cardiomyopathy. Early clinical trials in DMD using gene transfer to skeletal muscle are underway, but gene transfer to dystrophic cardiac muscle has not been tested in humans yet. Aim of our study was to develop and test an optimized protocol of cardiac gene therapy in the mouse model of dystrophindeficiency (mdx) using a cardiac promoter and a microdystrophin (μDys) transgene within an adenoassociated virus (AAV) vector.
Methods: Adult mdx mice were intravenously injected with AAV9 vectors containing a cDNA encoding μDys under control of either an ubiquitously active CMV promoter (CMV) or a cardiac specific CMV-enhanced myosin light chain (MLC0.26) promoter. Mice were challenged by voluntary wheel exercise and analysed over 10 months following gene transfer.
Results: Both AAV9 vectors led to sustained μDys expression in cardiac muscle, but the MLC promoter conferred about 4-fold higher protein levels. AAV9-CMV-MLC0.26-μDys resulted in a significant protection of cardiac morphology and function as assessed by histopathology, serial echocardiograms and left ventricular catheterization/pressure volume loop measurements.
Conclusions: We established an AAV9-mediated gene transfer approach for efficient and specific longterm μDys-expression in hearts of mdx mice, resulting in a sustained therapeutic effect. Thus, this approach might be a basis for further translation into a treatment strategy for DMD-associated cardiomyopathy.

1012 A novel approach using exon array technique identifies Mtus1 as a new heart failure-related gene

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Alternative splicing plays critical roles in the pathogenesis of many diseases. Since the role of alternative splicing in heart failure is unclear, we performed global analysis of exon expression levels to identify splicing variants responsi-

ble for heart failure. We constructed exon expression profiling of murine failing hearts induced by 8-week aortic constriction using Mouse Exon 1.0 ST Array (Figure 1). We detected 133 genes with changes in splicing pattern, and we focused on 48 genes with unchanged gene expression level, because conventional 3' array could not detect them. Finally, we selected Mtus 1 (mitochondrial tumor suppressor 1) gene, because this gene is the only gene of which splicing variants are registered in public database. Total expression level of Mtus1 splicing variants was not changed in failing heart compared to non-failing hearts. However, analysis of each splicing variant confirmed that variant A and C were increased and decreased in failing heart using RT-PCR primers specific to each variant, respectively. We further investigated the splicing pattern of Mtus1 gene in rat neonatal cardiomyocytes. Knockdown of variant C using siRNA induced up-regulation of variant A both in mRNA and protein level. This result implies that variant C regulates variant A expression level. Finally, we revealed that specific knockdown of variant A increased phosphorylation level of Erk, and thus the myocyte cross-sectional area. By contrast, adenovirus-mediated expression of variant A reduced phosphorylation level of Erk, and the myocyte cross-sectional area.

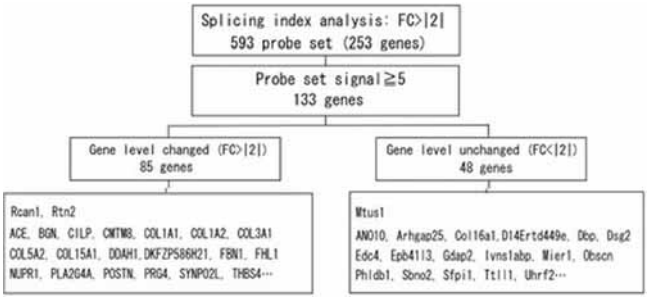

Figure 1. Exon array selection.

We conclude that Mtus 1 variant A inhibits cardiac hypertrophy, and exacerbates heart failure. Global analysis of splicing pattern using exon array is a useful approach for assessing novel targets for heart failure.

CLINICAL TRIALS IN HEART FAILURE – UPDATE 2011

1021 Cost-effectiveness of NT-proBNP-guided therapy in heart failure; results from the TIME-CHF study

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Purpose: To investigate whether NT-proBNP-guided heart failure therapy is cost-effective compared to symptom-guided therapy.
Methods: We did an 18-month cost-effectiveness analysis of the TIME-CHF study, which randomised patients to NT-proBNP-guided versus symptom-guided therapy. We used non-parametric bootstrap techniques to determine cost-effectiveness and compared prestratified groups of reduced and preserved ejection fraction (i.e LVEF≤45% and >45%). As endpoints, overall survival and quality-adjusted life-years (QALYs) assessed by SF-12 questionnaire were used (available in 528/622 patients; 434/499 with LVEF≤45%). Costs are expressed in euro's, price level 2006.
Results: In patients with reduced LVEF, NT-proBNP-guided therapy was dominant for both QALY's and life years, indicating that it is more effective (incremental effectiveness of 0.05 QALY's and 0.07 life-years) and less costly (€16,704 per patient for NT-proBNP-guided therapy and €18,853 per patient for symptom-guided therapy than symptom-guided strategy), saving €2,150 over 18 months. In patients with preserved LVEF, NT-proBNP-guided therapy was not cost-effective, being more costly (€ 38,876 per patient for NT-proBNP-guided therapy and €21,419 per patient for symptom-guided therapy, mean difference €17,457) and less effective than symptom-guided therapy (incremental effectiveness of -0.07 life-years and -0.07 QALY's). In these patients, NT-proBNP-guided therapy is inferior to standard therapy, no matter what society would pay for a QALY or life-year.
Conclusion: NT-proBNP-guided therapy is highly cost-effective in patients with reduced LVEF, in contrast to patients with preserved LVEF, where NT-proBNP-guided therapy is very unlikely more cost-effective than standard therapy.

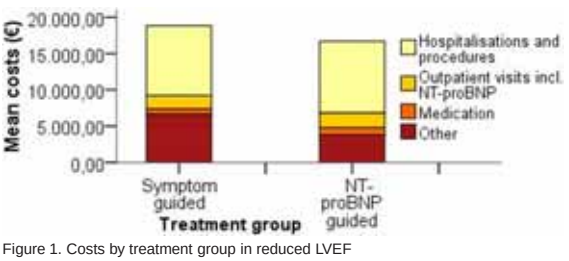

Figure 1. Costs by treatment group in reduced LVEF

1022 Adrenomedullin changes predict survival in dyspneic emergency department patients

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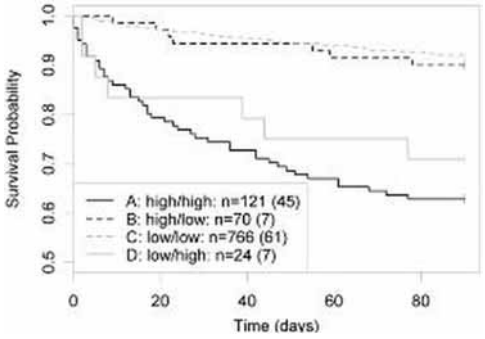
Background: Adrenomedullin (ADM), a vasodilatory peptide with potent hypotensive effects, can be measured as MRproADM. Elevated in chronic heart failure, it is increased proportionally to disease severity.
Purpose: Our purpose was to determine if ADM changes are associated with survival.
Methods: BACH was a prospective, 15-center international study of emergency department patients presenting with dyspnea. Blood was sampled at admission and repeated 14 to 48 hrs later. High or low ADM was defined by a 2.0 nmol/L cutpoint. Patients were divided into 4 groups defined by initial vs repeat ADM: high-high, high-low, low-low, and low-high.
Results: Of 1641 patients, the final diagnosis was AHF in 568 (34.6%), COPD 201 (12.2%), asthma 130 (7.0%), pneumonia 112 (6.8%), chest pain of unknown origin 106 (6.5%), bronchitis 61 (3.7%), arrhythmia 55 (3.4%), ACS 39 (2.4%), pulmonary embolism 38 (2.3%), influenza 27 (1.6%), and "other" in 304 (18.5%). At 90 days there were 130 deaths; 65 had AHF, and 65 were non-AHF. Median time to discharge was 7 days (IQR 3-12) and initial ADM levels ranged from 0.03 to 12.6 nmol/l (median 0.88 nmol/l; IQR 0.57, 1.44 nmol/l). Overall, 532 (32.4%) were discharged on the day of admission. Of the remaining 1109, 981 had >1 blood draw. At admission, 191 (19.5%) had high ADM, suggesting increased mortality. Of these, 70 (36.6%) had ADM levels that declined with therapy. The declining ADM cohort had a survival rate similar to patients who were never at risk based on the initial ADM, see figure. Including serial measurements into a time-dependent Cox model gave added value vs patients with just an admission ADM (p=0.0005).



Serial ADM changes predict survival.

Conclusion: A declining ADM identifies a cohort at low risk of 90 day mortality.

1023 Serial measurement of pentraxin-3 is a strong predictor of outcome in heart failure: results from the CORONA and GISSI-HF trials

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Purpose: Pentraxin-3 (PTX3) is an acute phase protein that, in contrast to CRP, is widely expressed under inflammatory stimuli in the heart and blood vessels.

Circulating PTX3 is a marker of severity and outcome in acute MI, but little is known in chronic HF.
Methods: PTX3 was measured in a core laboratory (ELISA, Perseus Proteomics) at baseline and 3- month follow-up in 2690 patients with chronic HF enrolled in the GISSI-HF (1233) and CORONA (1457) trials. Overall 22% were females, mean age was 69±9 y (±SD) and LVEF 32±8%. The clinical determinants of elevated logPTX3 were identified with multivariable regression analysis. The prognostic value of PTX3 at baseline or its relative changes over 3 months (%) was tested in multivariable Cox regression models that included NT-proBNP or hsCRP.
Results: The median plasma concentration of PTX3 was 5.33 [3.55-7.64] ng/mL. Advanced NYHA classes and age, low BMI, ischemic etiology and LVEF were associated with elevated PTX3. 3-month changes in PTX3, but not baseline PTX3, independently predicted incident all-cause mortality (629 events) and CV mortality (483), after adjustment for clinical risk factors, including NT-proBNP (Table) or hsCRP.

Cox proportional hazard models

Variable	All-cause mortality		CV mortality	
	Wald χ^2	p	Wald χ^2	p
3-month changes in PTX3 (%)	28	<0.0001	15	<0.0001
Baseline PTX3 (ng/mL)	0.3	0.58	1	0.27
Baseline PTX3 (ng/L)	111	<0.0001	103	<0.0001
Age (year)	23	<0.0001	11	0.001
Sex	18	<0.0001	11	0.001
BMI (kg/m^2)	4	0.04		
LVEF (%)	5	0.03	5	0.03
NYHA class	40	<0.0001	19	<0.0001
eGFR (mL/min/1.73 m^2)	16	<0.0001	19	<0.0001
Trial (CORONA vs. GISSI-HF)	0.1	0.71	0.1	0.72

Conclusions: A representative cohort of contemporary patients with HF from 2 independent trials consistently shows that (1) PTX3 is related to severity and outcomes in HF, (2) the prognostic value of 3-month changes is stronger than that of a single measurement, and (3) PTX3 emerges as a prognostic marker independent from CRP.

1024 Can the neurohormonal hypothesis be extended to patients with chronic heart failure and preserved left ventricular function?

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Background: Chronic heart failure (CHF) with low ejection fraction (HF-LEF) is characterized by increased activation of the sympathetic, renin-angiotensin-aldosterone system (RAAS) and the vasopressin axis. Although current drug management of patients with preserved ejection fraction (HF-PEF) has been extrapolated from trials evaluating the blockade of these systems in systolic CHF, there is little information about activation of these systems in patients with HF-PEF.
Aims and methods: To evaluate hypothesis that HF-PEF may have similar level of neurohormonal activation (NHA) compared to HF-LEF, the levels of norepinephrine (NE, pg/mL), plasma renin activity (PRA; ng/mL/h), serum ACE activity (SACE, U/L), aldosterone (ALD, pg/mL) and vasopressin (V, pg/mL) were determined in 637 stable consecutive CHF patients referred to our multidisciplinary heart failure program and analyzed according to 2 left ventricular ejection fraction categories: HF-PEF (LVEF>50%) and HF-LEF. Final analyses were made adjusting for significant covariates associated with NHA and LVEF using general linear models. NHA data were log-transformed to fit normal distribution. Continuous variables are reported as mean±SE.
Results: Mean age was 74±0.4 years; male gender 55%; NYHA functional class=2.0±0.1; mean LVEF was 42±0.7% (HF-PEF=35.8% of patients;HF-LEF=64.2%of patients). The unadjusted univariate analysis showed that NHA was not significantly different between HF-PEF and HF-LEF patients except from ALD levels (NE: 581±22 vs 624±24, p=ns; PRA: 6.6±0.6 vs 7.5±0.5, p=ns; SACE: 19.8±1.2 vs 17.4±0.8, p=ns; ALD: 173±44 vs ±148±8, p=0.04;V: 3.8±0.2 vs 4.2±0.2, p=ns).
In the multivariate analysis using a General Linear Model (GLM) adjusted for covariates, patients with HF-PEF compared to HF-LEF had lower adjusted levels of LnNE (5.8±0.1 vs 6.1±0.1, p=0.04). For ALD (6.6±0.2 vs 4.8±0.1, p=ns), PRA (0.8±0.3 vs 1.2±0.2, p=ns) and V (1.1±0.2 vs 1.1±0.1, p=ns) adjusted means were not significantly different between HF-PEF and HF-LEF patients, although for SACE (2.1±0.2 vs 2.5±0.1, p=0.06), this difference was marginally not-significant.
Conclusion: HF-PEF is associated with lower sympathetic activation compared to HF-LEF patients. No significant differences were observed between HF-LEF and HF-PEF patients regarding RAAS and Vasopresin activation. Further studies are warranted to elucidate the role of NHA in the physiopathology of HF-PEF and the extrapolation of NHA blockade in these patients.

1025 Use of MR-proANP and NT-proBNP in the timing of beta blocker up-titration in elderly patients with stable chronic heart failure: Data from the CIBIS-ELD study

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Purpose: Clinical parameters are usually used for beta-blocker (BB) up-titration in patients with chronic heart failure (CHF) despite known limitations. No study has evaluated the potential role of cardiac biomarkers for determination of optimal time point for initiation of BB up-titration in stable patients with CHF. Using data from the CIBIS-ELD study, we sought to investigate if the baseline value of mid-regional pro-atrial natriuretic peptide (MR-proANP), N-terminal pro B-type natriuretic peptide (NT-proBNP), and pro-vasopressin (copeptin) may help to find the optimal time point for BB up-titration, and complement patients' clinical status in every day clinical life.
Methods: We measured MR-proANP, NT-proBNP, and copeptin in 457 elderly patients (≥65 years old) with stable systolic CHF (LVEF≤45%) before initiation of BB up-titration. According to predefined cut-off values of respective biomarkers, patients were divided into three subgroups (low, intermediate, high biomarker group) and compared with each other. Additionally, New York Heart Association (NYHA) functional class and echocardiographic examination were performed at baseline and 3 months after BB up-titration.
Results: After 3 months of BB up-titration in the overall study population, we noted significant improvement of left ventricular ejection fraction (LVEF) (from 34.5±8.1 to 38.3±8.9%, p<0.001), left ventricular end-systolic diameter (from 48.2±9.7 to 47.2±9.8mm, p<0.001), and NYHA functional class (from 2.3±0.6 to 2.0±0.6, p<0.001). In all MR-proANP and NT-proBNP subgroups there was significant amelioration of LVEF and NYHA class (p<0.001 for all). However, we showed more prominent improvement of LVEF and NYHA class in patients subgroups with lower vs. higher natriuretic peptides (NP) levels (LVEF: low vs. high subgroup of MR-proANP and NT-proBNP, p=0.003 and p<0.001, respectively; NYHA: both p<0.05). Similarly, reverse left ventricular remodeling was more prominent in low NP vs. high NP subgroup (p<0.05 for both NPs). Unlike NP subgroups, copeptin subgroups did not differ in respect to studied parameters after BB up-titration.
Conclusions: We found that stable CHF patients mirrored by lower NP levels may be expected to have more benefit after initiation of BB up-titration in terms of well-being, reverse left ventricular remodeling, and left ventricular function. Thus, both MR-proANP and NT-proBNP may guide the optimal timing of BB up-titration in stable elderly patients with CHF.

1026 Prevention of renal dysfunction with hypertonic saline solution in patients with decompensated heart failure: a prospective, double blind, randomized, placebo-controlled trial

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Background: Renal dysfunction is an important risk factor in decompensated heart failure (DHF), and specific interventions are required. We tested the effects of intravenous hypertonic saline solution (NaCl 7.5%) for prevention of renal dysfunction in patients with DHF on top of guideline-oriented therapy.
Methods: 32 patients with DHF were included in a prospective, double-blind, placebo-controlled trial and randomized (2:1) to receive a three-day course of 100ml of NaCl 7.5% twice daily or placebo (100ml of NaCl 0.9%). The primary end point was a 0.3mg/dL increase in serum creatinine during intervention. The main secondary end point was change in biomarkers of renal function.
Results: The primary end point was reached by 2 (10%) patients in intervention group, and 6 (50%) patients in placebo group (RR 0.3; CI 95%: 0.09-

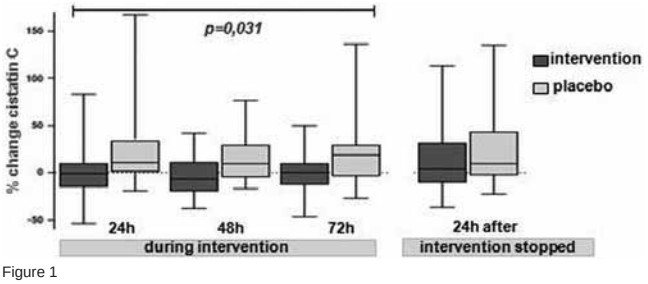

Figure 1

0.98; p=0.01). As compared with placebo, patients in intervention group had increased diuresis (p=0.03), lower serum level of creatinine (p=0.02) and c-cystatin (p=0.031), and improved renal tubular function, as measured by urinary expression of NH3 exchanger, aquaporin2 and urea transporter UTA1. Beneficial effects ceased after intervention was stopped.
Conclusions: Hypertonic saline solution is effective for prevention of renal dysfunction in DHF, as measured by markers of glomerular and tubular renal function. To the best of our knowledge this is the first trial to demostrate risk reduction in this setting, and warrants further investigation in multicenter trials.

RISK/BENEFITS OF CATHETER ABLATION FOR ATRIAL FIBRILLATION

1039 Classical and "new" complications of radiofrequency atrial fibrillation ablation

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Introduction: Over the past 10 years atrial fibrillation ablation has become a widely available procedure. Data on procedural complications are, however, mainly based on surveys or meta-analysis taking into account centers with different experience and ablation techniques. Aim of the present study is to report complications occurred in a high volume center performing radiofrequency atrial fibrillation ablation with a standard technique.
Methods and results: From 2005 to 2010, 1330 ablations were performed in 959 patients. Indication for the procedure was paroxysmal AF in 34%, persistent in 47% and atypical flutter in the remaining 19% patients. Two venous sheaths were inserted into the right femoral vein and 1 into the left. Left atrium was achieved trough single transseptal puncture or patent foramen ovale when present. Ablation was performed by an irrigated-tip catheter aiming to pulmonary vein isolation and/or creation of linear lesions in case of persistent AF. Intravenous unfractionated heparin was given during the procedure maintening an activated clotting time >300 seconds. Overall eighteen complications (1.4%) occurred: 6 (0.5%) ischemic complications (3 strokes and 3 TIA), 8 (0.6%) cardiac tamponades requiring immediate drainage, 3 (0.2%) vascular complications (2 inguinal haematomas and one AV fistula), and 1 (0.1%) symptomatic pulmonary vein stenosis. Starting from year 2009, 415 patients also underwent brain magentic resonance (MR) before and after the ablation procedure to investigate the incidence of silent cerebral ischemia. Within these patients 50 (12%) reported silent cerebral ischemia. Twenty-seven (54%) patients with positive MR scan for silent cerebral ischemia post ablation accepted to repeat brain MR after 3 months. In 3 (11%) cases the lesions remained unchanged, in 11 (41%) the diameter decreased, and finally in 13 (48%) patients the lesions resulted undetectable.
Conclusion: The overall symptomatic complication rate of radiofrequency AF ablation in a high volume center is lower than that reported in recent surveys. Cerebral ischemia, together with cardiac tamponade, is indead the most feared complication. Symptomatic patients represent only a small proportion of all cerebral ischemias, however almost half of the silent lesions seem to revert over a 3 month period. Further research in this field is mandatory to guide physicians on the actual level of safety of an AF ablation procedure.

1040 Validation of LGE-MRI based staging of atrial fibrillation structural remodeling and prediction of catheter ablation outcome

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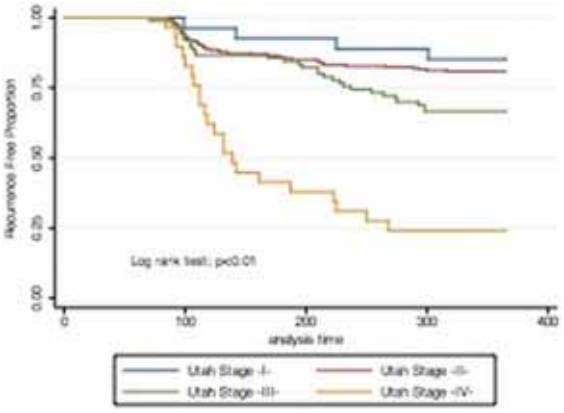
Introduction: Structural remodeling is a major determinant of catheter ablation (CA) success in atrial fibrillation (AF). We report in a large cohort of patients, the predictive value of atrial fibrosis, quantified using late gadolinium enhancement MRI (LGE-MRI), in AF recurrence post CA.
Methods: 487 patients with AF, presenting for CA underwent LGE-MRI. Left atrial (LA) fibrosis was quantified in all patients, who were divided into 4 stages of LA fibrosis (Utah Stage I: <5%, Utah Stage II: 5-20%, Utah Stage III: 20-35%, Utah Stage IV: >35%). All patients underwent CA with pulmonary vein isolation and septal and posterior wall debulking. Follow up was done with event monitoring during the blanking period, 8-day Holter monitoring every 3 months and ECGs based on reported symptoms. Recurrence was any sustained atrial arrhythmia lasting longer than 30 seconds following a 3 months blanking period.
Results: The average patient age was 66±12 years (36% female). The mean LA fibrosis was 16.3±10.8%. 31 pts (6.4%) were Utah Stage I, 317 pts (65.1%) Stage II, 107 pts (22.0%) Stage III, and 32 pts Stage IV (6.6%). The mean follow up time was 228±187 days. A Cox multivariate survival analysis identified Utah stage was the strongest predictor of recurrence (HR 2.0, p<0.001). Other predictors were prevalent diabetes (HR 1.7, p=0.02) and LA volume (HR 1.01, p<0.01). Coronary artery disease, hypertension, congestive heart failure, age, gender and AF-type were not significant.
Conclusion: In a large AF ablation cohort, atrial fibrosis quantified using LGE-MRI is the strongest predictor of AF recurrence. This validates earlier reports demonstrating the predictive value of this measure.



1041 Prevalence, characteristics and predictors of pulmonary vein narrowing after PVAC ablation

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Background: The risk and determinants of pulmonary vein narrowing (PVN) after pulmonary vein isolation (PVI) using a novel multi-electrode ablation catheter (PVAC) are unknown.
Methods and results: PV diameters (PVD) and left atrial (LA) volume were compared by computed tomography before and 3 months after PVI using duty-cycled phased RF energy (2:1 or 4:1 bipolar/unipolar ratio) in 50 patients. PVD was measured in a coronal and axial view at three levels (A=ostium, B=1cm more distal, C=2cm more distal). Moderate PVN was defined as a PVD reduction of 25-50%, severe PVN as >50%. Axial PVD shortened by 17±16%, 14±16% and 8±22% at level A, B and C respectively (p<0,001 for all); coronal PVD decreased by 16±14%, 13±17% and 7±19% (p<0,001 for all). Moderate PVN occurred in 55/200 PVs (28%) in 36 patients (72%); severe PVN occurred in 8/200PVs (4%) in 7 patients (14%). The left superior PV and the number of 2:1 applications were predictors for PVN. LA volume decreased by 10±18% (p<0,001).
Conclusions: PVAC ablation results in a consistent moderate reduction of the PVD predominantly at the ostium. PV narrowing occurred more frequently in the LSPV and was related to the number of 2:1 applications. Severe PVN in 14% of patients, raises concerns about the risk for clinical PV stenosis.

1042 Ablation of atrial fibrillation: can we achieve an additional benefit with image-integration into 3D-Maps?

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Aim: The use of 3Dimensional mapping-systems in ablation of paroxysmal and persistent atrial fibrillation results in a simplification of the ablation procedure. The additional integration of CT-/MR and ultrasound-data into these mapping-systems enables an even more accurate reconstruction of the left atrium and by that a higher rate of success of the ablation procedure. Aim of our trial was to evaluate this benefit by integration-technique based on the data of a big prospective registry (German ablation registry).
Method: From March 2007 until November 2010 3.015 patients were ablated with atrial fibrillation and by the use of a 3D mapping-system. 2.283 (75,7%) were treated only by 3D-Mapping (CARTO: 68%, NavX: 24%, other systems: 8%) (group 1), 732 (24,3%) were ablated with the additional use of image-integration (MRI: 20%, CT: 79%, ultrasound (ICE): 9%) (group 2). Patients in group 1 were 63, in group 2 61 years old. There was no difference in the incidence of cardiac disease (32% vs. 34%) and in the rate of clinical heart failure (NYHA 0/1: 87% vs. 89%).
Results: See Table 1. Follow-up: There was a more than 1 year follow-up in 1.779 patients. Within this population there were less relapses of atrial fibrillation in the group without image-integration (43,4% (group 1) vs. 51,3% (group 2); p<0,01). Also the rate of re-hospitalisation due to cardiac events was smaller in this group (74,6% vs. 85,5%; <0,01).
Conclusion: The use of image-integration in the ablation of atrial fibrillation as a routine does not seem to be reasonable. In contrast, it pretends a high amount of

Table 1. Results

	Group 1 Image-Integration: no (n=2283)	Group 2 Image-Integration: yes (n=732)	p-value
Procedure duration (min.)	180	202	<0,0001
Fluoroscopy time (min.)	24	36	<0,0001
Primary success (%)	97	98	ns
Complication rate (%)	4,4	4,2	ns
Pericardial effusion (%)	0,9	2,0	<0,05

anatomic accuracy. This fact can leed to an assumed feeling of safety particularly in investigators with less experience.

1043 Catheter ablation of atrial fibrillation using a new non-fluoroscopic sensor-guided 3D navigation tool (MediGuide)

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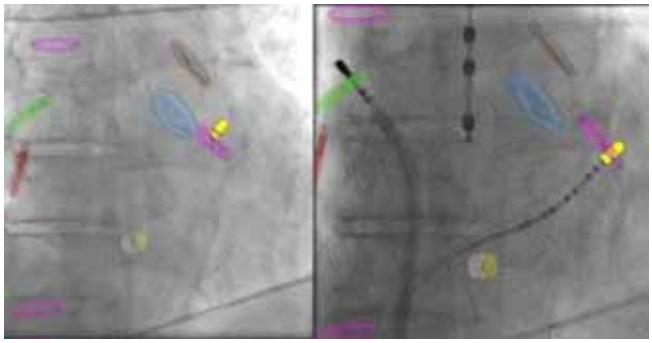
Purpose: A novel sensor-based electromagnetic 3D navigation system has been introduced that allows real-time catheter tracking in the environment of pre-recorded conventional 2D X-ray loops (MediGuide (MG) Technology, SJM). We report the first clinical experience for catheter ablation of atrial fibrillation.
Methods: 49 consecutive patients (39 male patients, age 60±10 yrs) were ablated using the new MG catheter tracking technology. Two steerable MG-enabled diagnostic EP catheters equipped with a sensor were used for CS cannulation, tagging of defined anatomical structures within the MG system, and anatomical reconstruction of the left atrium within the electro-anatomic mapping system (EAMS). Circumferential pulmonary vein isolation plus additional lines if necessary were performed with a conventional open-irrigated tip catheter. 36 patients ablated conventionally with the EAMS plus fluoroscopy served as a control group.
Results: In all 49 patients the MG-enabled catheters could be visualized and tracked non-fluoroscopically and real-time throughout the procedure. Complete circumferential pulmonary vein isolation and lesion deployment was documented in each patient. Adverse events did not occur. Usage of the MG system significantly reduced fluoroscopy time from 35±16 min to 18±10 min compared to the control group ($p<0.01$).



Fluoroscopy with MG-enabled catheters.

Conclusions: We observed for the first time a stable integration of the MG technology into the clinical application of atrial fibrillation ablation, enabling accurate non-fluoroscopic 3D catheter tracking within pre-acquired 2D cine-loops. With the system, we were able to significantly reduce fluoroscopy durations without interrupting or extending work-flow, although a sensor-equipped ablation catheter was not available yet.

1044 Is catheter ablation of atrial fibrillation safe? Experience of a high-volume centre

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Introduction: Catheter ablation has become a well-established treatment option for atrial fibrillation (AF). However, there are still safety concerns. We conducted an analysis of consecutive procedures guided by intracardiac echocardiography in a high-volume centre and assessed complication rates and possible risk factors.
Methods: A total of 1057 procedures were evaluated (393 for persistent AF; 235 robotically navigated ablations) in 857 patients (aged 58.0±9.4 yrs) referred for catheter ablation for AF between March, 2006 and August, 2010. All major complications during the procedure or within 3 months of follow-up were considered for analysis. Major complications were defined as those required prolonged hospitalization or intervention and/or resulted in long-term disability.
Results: Thirty-one major complications occurred in 1057 procedures (2.9%). Among patients with major complications, 2 pts had non-fatal stroke and 3 pts had transient ischemic attack, 2 pts had tamponade, 1 patient had pericardial effusion without the need to perform a puncture and 2 procedures were complicated by hemothorax after jugular vein puncture. The most frequent complication was vascular injury in the groin (17 cases) requiring surgical repair and/or blood transfusion. There were also 2 cases of sepsis, 1 pericarditis and 1 case of advanced atrioventricular block due to extensive ablation in the right atrium requiring pacemaker implantation. No deaths occurred periprocedurally or during the follow-up period. Among parameters such as age, body weight and height, body mass index (BMI), body surface area (BSA), AF type, and ablation technique, only body weight (83.8±13.6 vs. 90.8±15.8 kg; p=0.016), body height (172.7±9.0 vs. 176.8±9.6 cm; p=0.020), and BSA (1.97±0.18 vs. 2.07±0.21 m^2; p=0.008) were significantly different between patients with and without major complications, respectively. In a step-wise multivariate regression model with variables dichotomized at median value, the BSA was the only factor associated with major complications with incidence of 4.2% vs. 1.7% for BSA $<$ 2.07 and $>$2.07m^2 (P=0.014), respectively.
Conclusions: AF ablation procedures guided by intracardiac echocardiography in a high volume centre are associated with lower complication rate as compared with previous studies in patients undergoing AF ablation. BSA was the strongest predictor of major complications in this study and this association was mainly driven by the incidence of vascular complications.

ISCHAEMIC HEART DISEASE IN WOMEN: WHY DO WE MANAGE THEM DIFFERENTLY?

1049 Accuracy of different stress modalities for evaluation of postmenopausal women with suspected coronary artery disease

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Objective: We wanted to assess the value of different cardiovascular stress testing methods for evaluation of postmenopausal women with suspected coronary artery desease (CAD).
Background: Diagnostic procedures are less accurate in women than in men. There is compelling evidence that women with CAD experience worse outcomes than men.
Methods: We prospectively enrolled 231 consecutive postmenopausal women with chest pain or other symptoms suggestive of CAD. Each patient underwent coronary angiography and three stress testings by cardiovascular magnetic resonance (CMR), single-photon emission computed tomography (SPECT) and echocardiography (DSE) within 7±3 days. Stress was performed using Dobutamine (maximum dose of 40 μg/kg per min) and Atropine (total dose 2 mg) at the start of the 40 μg/kg per min stage if needed to augment heart rate. 197 women (mean age 61±7 years) achieved complete protocol and were followed up for 3±1 years for the occurrence of hospitalization for acute coronary syndrome, myocardial infarction and/or new-onset or worsening angina.
Results: CAD prevalence (≥50% diameter stenosis) was 64%, 79 women had 1-vessel disease (40%), 32 (16%) had 2-vessel disease and 16 (8%) had 3-vessel disease. Diagnostic sensitivity and specificity were as follows: stress electrocardiogram 66% and 70%, CMR 87% and 90%, SPECT 86% and 85%, DSE 85% and 87%. The sensitivity was lower in women with single-vessel disease compared to multivessel disease (ECG: 64% vs. 75%, p=0.04, CMR: 72% vs. 100%, p=0.002; SPECT: 70% vs. 91%, p=0.014; DSE: 75% vs. 96%, p=0.011, respectively). A combination of two modalities (CMR/SPECT, CMR/DSE or SPECT/DSE) improved the predictive power for CAD significantly. The advantage of image integration was particularly strong in those women with single vessel disease. For patients with normal results Cox survival analysis showed 3-year cumulative event-free survival rates of 59%, 98%, 95% and 96%, respectively.
Conclusion: There is high diagnostic and prognostic accuracy for CMR, SPECT and DSE stress testings in symptomatic postmenopausal women. Integration of two stress tests increases the accuracy to detect CAD even in challenging single-vessel disease.

1050 Gender differences in the treatment recommendation after diagnostic coronary angiography. Data from the prospective ALKK registry

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Background: Little is known about gender related differences in the treatment recommendation after diagnostic angiography. Therefore we evaluated a large data base to assess gender related differences in the treatment recommendation of diagnostic coronary angiography in patients with stable angina, non-ST-

elevation myocardial infarction (NSTEMI)/unstable angina and ST-elevation myocardial infarction (STEMI).
Methods: We used the data of the ongoing ALKK PCI registry. Baseline data, procedural features and in-hospital events of all consecutive diagnostic angiographies of 41 non-university hospitals were collected on standardized case record forms and centrally analysed by a institut.
Results: Between 2006 and 2009 179.362 men and 92.094 women with either stable angina, non-ST-elevation myocardial infarction or ST-elevation-myocardial infarction were included in the ALKK registry at 41 participating hospitals. Significant coronary artery stenosis was diagnosed more often in men compared to women (stable angina 57% vs. 37%, NSTEMI/unstable angina 79% vs. 66%, STEMI 87% vs. 84%). In all indications a conservative treatment was more often recommended in women.

Gender related differences

	Men			Women		
	Conservative	PCI	CABG	Conservative	PCI	CABG
Stable Angina	53%	31%	14%	63%	21%	11%
NSTEMI/Unstable Angina	31%	57%	12%	42%	48%	9%
STEMI	9%	86%	5%	14%	82%	4%

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Conclusion: In clinical practice women compared to men are treated less often with revascularization therapies, regardless of the indication for coronary angiography. However this difference is mainly due to a significant lower proportion of significant coronary artery disease in women in each indication catagory.

1051 Time trends in STEMI - improved treatment and outcome but still a gender gap

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Background: In case of ST-elevation MI [STEMI] women have received less evidence based medicine [EBM], suffered from more bleedings and had worse outcome during the fibrinolytic era. With the shift from fibrinolytics to primary percutaneous coronary intervention [PCI] we hypothesized that gender differences in STEMI management and outcome have diminished.
Material and methods: STEMI patients registered 1998–2000 (n=15697) and 2004–2006 (n=14380) in the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (today SWEDEHEART) were included.
Results: Reperfusion therapy was given to 63% vs. 71% and 64% vs. 75% women vs. men in the two groups. In the early group there were small gender differences regarding EBM. In the late group women had 14–25% less chance of receiving EBM. Gender differences in use of coronary angiography, beta-blockers, ACE-inhibitors/ARBs and statins increased between the time periodes. In-hospital mortality was 12% higher in women in the early and 24% higher in the late group. Multivariable adjusted 1-year mortality was not significantly higher in any of the groups.
Conclusion: In spite of an increased attention to gender differences in STEMI treatment, focus on adherence to guidelines and a change in predominant reperfusion strategy, differences between the genders in adherence to treatment guidelines and in early outcome actually increased from 1998-2000 to 2004-2006.

1052 STEMI and octogenarians: gender specific predictors of mortality and gender differences in reperfusion. Results from the Belgian STEMI registry

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Introduction: Gender differences in treatment options and outcome of STEMI in octogenarians are still a matter of debate.
Aims: (i) Do predictors of in-hospital mortality differ between octogenarian females and males? (ii) Does gender influence the choice of reperfusion therapy in octogenarians? Methods: The study questions were addressed in the Belgian STEMI registry, a prospective registry (2007-2010) of unselected STEMI pts from 113 hospitals. 7,922 pts were included, 950 octogenarians, with 481 male (median age 83) and 469 female octogenarians (median age 84).
Results: Octogenarian female STEMI pts had a higher Killip class (>1: 46% vs 36%), higher heart rate on admission (19% vs 13%), more often a body weight <67 kg (60% vs 21%), more arterial hypertension (66% vs 53%), less peripheral arterial disease (PAD) (16% vs 22%) and less previous coronary artery disease (21% vs 28%) than male octogenarians (all $p<0.05$). In-hospital mortality rate was 17.5% in octogenarians (13% in males, and 22% in females, p=0.01). In a logistic regression model including the above mentioned parameters, age, need for CPR, low systolic blood pressure on admission, diabetes mellitus, infarct location, reperfusion therapy, ischemic time, and door to needle/balloon time (DTNB), clinical signs on admission were independent predictors of in-hopital mortality both in the male and female group (need of CPR, low systolic blood pressure on admission, and elevated Killip class). In females additional predictors were age, high heart rate and type of reperfusion therapy chosen [thrombolysis (TL), percutaneous coronary intervention (PCI) or no-reperfusion]. In males, PAD was an independent predictor. Less PCI (73% vs 78%), less TL (8% vs 12%), and more no-reperfusion (19% vs 10%) were used in female octogenarians compared to the male group ($p<0.001$). Moreover, ischemic time was longer in females (<4h: 40% vs 52%, $p<0.001$), as was DTNB (<1h: 40% vs 46%, 1-2h: 26% vs 27%%, >2h or unknown: 34% vs 27%%, p=0.044).
Conclusions: In-hospital mortality of STEMI in octogenarians is high (18%), particularly in women. Octogenarian females have longer ischemic time and receive more no-reperfusion compared to males. Predictors of in-hospital mortality that are specific for octogenarian females are age, high heart rate on admission, and type of reperfusion therapy, while PAD is specific for octogenarian males.

1053 Higher rates of newly diagnosed abnormal glucose metabolism in females presenting with STEMI and NSTEMI in clinical practice in Germany: results of the SWEETHEART registry

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Background: Many patients with coronary artery disease suffer from diabetes or its pre-states. Joint guidelines by the ESC and the EASD recommend testing for diabetes using OGTT in patients with established CAD and without previously known diabetes.
Methods: Since 2007, 2,775 consecutive patients with STEMI or NSTEMI were enrolled into the MI-registry SWEETHEART to identify abnormal glucose metabolism and to document acute treatment and outcome. In patients with previously unknown diabetes, oral glucose tolerance test (OGTT) was performed at day 4 after acute MI. We examined gender differences in the prevalence of abnormal glucose metabolism in patients with in acute myocardial (MI).
Results: Female patients with MI were older, less often had prior MI and prior PCI as compared to males. Female patients had a higher rate of known diabetes as well as a longer duration of diabetes at the time of MI. The prevalence of

	Females (n=708)	Males (n=2067)	p-value
Age (years)	71	64	<0.01
Prior MI	13.0%	18.8%	<0.01
Prior PCI	12.2%	18.1%	<0.01
Prior CABG	6.3%	7.7%	=0.22
Prior stroke	5.7%	5.6%	=0.96
Primary PCI (STEMI), PCI (NSTEMI)	80.1%	85.3%	<0.01
Hospital mortality	2.6%	2.2%	=0.52
Known diabetes mellitus	31.3%	23.9%	<0.01
Duration of known diabetes (years)	10	7	<0.01
Results of OGTT			
Newly diagnosed diabetes	19.8%	15.3%	<0.01
IGT/IFG	33.8%	23.3%	<0.01
Pathologic glucose metabolism (known/newly diagnosed)	84.9%	62.5%	<0.01

Abstract 1048 – Table 1. Time trends in STEMI gender gaps

	Early period: Year 1998–2000 (n=15697)			Late period: Year 2004–2006 (n=14380)		
	Crude OR (95% CI)	Age adjusted OR (95% CI)	Multivariable adjusted OR (95% CI)	Crude OR (95% CI)	Age adjusted OR (95% CI)	Multivariable adjusted OR (95% CI)
Coronary angiography	0.64 (0.59–0.69)	0.86 (0.79 –0.94)	0.92 (0.83–1.01)	0.44 (0.40–0.47)	0.79(0.72–0.87)	0.79 (0.71–0.88)
Reperfusion therapy	0.70(0.66–0.75)	0.87 (0.81–0.94)	0.86 (0.78–0.94)	0.57 (0.53–0.62)	0.79 (0.73 –0.86)	0.80 (0.73–0.89)
Aspirin	0.89 (0.80–0.98)	0.96 (0.86–1.06)	0.96 (0.85–1.08)	0.71 (0.62–0.82)	0.90 (0.78–1.04)	0.86 (0.73–1.00)
Other platelet inhibitor	0.80(0.70–0.91)	0.98 (0.86–1.13)	1.01 (0.86–1.18)	0.59 (0.55–0.64)	0.83 (0.76–0.91)	0.85 (0.77–0.94)
Beta-blocker	0.78 (0.71–0.86)	0.95 (0.95–1.04)	0.96 (0.87–1.08)	0.68 (0.60–0.76)	0.80 (0.71–0.90)	0.79 (0.69–0.91)
ACE inhibitors/ARB	0.96 (0.89–1.03)	0.86 (0.80–0.92)	0.85 (0.78–0.92)	0.80 (0.74–0.86)	0.80 (0.74–0.86)	0.75 (0.68–0.81)
Statins	0.78 (0.73–0.84)	1.12 (1.03–1.21)	1.16 (1.06–1.27)	0.49 (0.45–0.53)	0.78 (0.70–0.86)	0.77 (0.69–0.86)
In-hospital mortality	1.88 (1.70–2.09)	1.19 (1.06–1.32)	1.12 (0.99–1.28)	2.24 (1.97–2.55)	1.25 (1.09–1.44)	1.24 (1.03–1.48)
1-year mortality*	1.63 (1.51–1.75)	1.05 (0.98–1.14)	0.95 (0.87–1.05)	1.97 (1.80–2.15)	1.12 (1.02–1.22)	0.96 (0.86–1.08)

Gender differences in management and outcome after multivariable adjustments. Data from logistic (*Cox) regression analyses presented as odds (*hazard) ratios with 95% confidence intervals.

newly diagnosed impaired glucose metabolism was much higher in females than in males. In females, OGTT identified another 19.8% with manifest diabetes and 33.8% with impaired glucose tolerance (IGT)/impaired fasting glucose (IFG) as compared to 15.3% and 23.3% in males respectively.
Conclusion: Although the prevalence of known diabetes was already much higher in females, the rate of newly diagnosed diabetes or IGT/IFG was significantly increased in females as compared to males. Together with known diabetes, OGTT identified 84.9% of female MI patients and 62.5% of males having impaired glucose metabolism.

1054 Gender paradox: higher incidence but lower one-year mortality with bleeding among women compared with men following fibrinolysis for acute ST-elevation myocardial infarction

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Background: Few studies have evaluated gender related differences in the incidence of bleeding and the relationship of this event to subsequent mortality in patients (pts) with ST-elevation myocardial infarction (STEMI) treated with fibrinolysis.
Methods: We studied 99379 STEMI pts receiving fibrinolysis enrolled in 7 trials-GUSTO I, IIb and III, ASSENT-2 and 3, HERO and RHAPSODY. We excluded pts with missing data on key baseline features and those treated with primary percutaneous coronary intervention (PCI). End-points included moderate or severe bleeding defined using the GUSTO criteria and adjusted 1-year death.
Results: Moderate or severe bleeding was 1.9 fold higher in women compared with men (13.3% vs. 7.1%, $p<0.0001$). Bleeding remained higher in women even after adjustment for differences in baseline confounding (adjusted OR 1.52, 95% CI 1.42-1.62, $p<0.0001$). In fact, female gender (versus male) was the second most significant prognostic factor (model χ^2 153.6) after older age (model χ^2 241.2) in the multivariate bleeding model. Bleeding was associated with significant increased risk for 1-year death. Females had higher unadjusted mortality than males in pts with and without bleeding. After adjustment for baseline confounders, bleeding was an independent predictor of 1-year death whereas female gender was not. However, while no difference was seen in the adjusted 1-year mortality between men and women without bleeding, women were significantly less likely to die at 1-year compared with men who had bleeding (p for interaction 0.0016, Figure). The highest adjusted 1-year mortality (excluding deaths $\leq$24 h) was observed in males with bleeding (hazard ratio [HR] 2.42; 95% CI, 2.20-2.66, $p =<0.0001$) followed by females with bleeding (HR 2.05; 95% CI, 1.80-2.33, p=0.0246) and females without bleeding (HR 1.08; 95% CI, 0.97-1.19, p=0.1470) (referent males without bleeding).
Conclusions: The excess in 1-year death among women compared with men with STEMI treated with fibrinolysis appears to be related to the differences in baseline confounding rather than the higher rates of bleeding observed in women as bleeding was associated less strongly with mortality in women. These data highlight the importance of understanding the factors associated with gender-related differences in bleeding and represent an opportunity for improving outcomes of all STEMI pts treated with fibrinolysis including women.

ARRHYTHMIAS, MECHANISMS AND THERAPY

1057 Left atrium size and incidence of new-onset atrial fibrillation in essential hypertensives. A 6 years prospective study

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Purpose: Left atrial (LA) enlargement is a common finding in hypertensive patients and has been identified as an independent determinant of new-onset atrial fibrillation (AF). The aim of our study was to compare the predictive role of LA size, as determined either by LA diameter or by LA volume index, for the incidence of new-onset AF.
Methods: We prospectively followed up for a median period of 6 years (IQ 5-6.6 years) 782 uncomplicated hypertensives without history of AF episodes (aged 58.1±10 years). All subjects had at least one visit annually and at entry underwent complete echocardiographic study. LA size was determined either by LA diameter or by LA volume adjusted for body surface area (LAVI).
Results: The incidence of new-onset AF over the whole follow-up period was 5% (22 patients with paroxysmal AF and 17 patients with permanent AF). Patients with new-onset AF compared to those without were older (by 9 years, $p<0.001$) and exhibited at baseline higher waist circumference (by 3cm, p=0.048), office pulse pressure (by 7.4mmHg, p=0.002), left ventricular mass index (by 13.8 g/m^2, p=0.002), LA diameter (42.4±5.3mm vs. 38±4.7mm, $p<0.001$) and LAVI (26.8±8.4mm vs. 22.7±6.7mm, $p<0.001$). No difference was observed between hypertensives with new-onset AF and those without with respect to gender, baseline diabetes status and body mass index (p=NS for all cases). In successive multivariate Cox regression models age (HR 1.076, $p<0.001$), left ventricular mass index (HR 1.015, p=0.013) and LA diameter (HR 1.201, $p<0.001$) instead of LAVI (HR 1.042, p=0.07) turned out to be independent predictors of new-onset AF.
Conclusions: Uncomplicated hypertensives with new-onset AF are characterized by significantly increased LA diameter and LA volume indexed for body surface area. Although LAVI has been generally considered a more accurate estimate of LA size, LA diameter turned out to be a more powerful predictor of new-onset AF in the setting of essential hypertension.

1058 Effectiveness of angiotensin II receptor antagonist, angiotensin-converting-enzyme inhibitor or both in patients with hypertension, type 2 diabetes mellitus and episodes of atrial fibrilation

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Objective: It has been reported that patients (pts) with arterial hypertension complicated by type 2 diabetes mellitus (DM) have a high risk of cardioivascular events.The aim of present study was to evaluate the effects of antihypertensive treatment with Valsartan (V),Perindopril (P), or both of them on prevention the recurrence of atrial fibrilation in patients with essential hypertension (EH) complicated by DM, left ventricular (LV) hypertrophy,left atrium (LA) dilatation and a history of recent atrial fibrilation (AF).
Methods: Ninety three pts with mild to moderate EH,type 2 DM,LV hypertrophy (LV mass index $\geq$ 125 g/m^2 for men and $\geq$ 110 g/m^2 for women),LA dilatation (LA dimension $>$38 mm for women and $>$42 mm for men) in synus rhythm,but with at least four ECG documented episodes of atrial fibrilation in the previous 12 months and in treatment with amiodarone were randomly assigned to V 80 mg once a day (16 males and 15 females – group A), or P 10 mg once a day (14 males and 17 females – group B),or V (80 mg) and P (10 mg) in combinatioin (17 males and 14 females – group C).The 24 hour ECG was registered every month. Echocardiography were performed at baseline and after 12 months of therapy. The parameters of LV hypertrophy and LA dimension were evaluated. LV mass index (LV mass/body surface area) was calculated according to Devereux formula. Statistical comparisons were performed by 2-tailed Student's t test for quantitative parameters.
Results: Blood pressure was lowered to less than 130/80 mm Hg in all groups. At the end of the study LV mass index reduced from 158,1±5,9 to 131,3±3,2 g/m^2 in group A, $p<0,01$, from 157,3±5,2 to 133,5±3,3 g/m^2 in group B, $p<0,01$and from 157,9±3,3 to 121,3±2,2 g/m^2 in group C, $p<0,001$. The decrease in LV mass index was essentially caused by reduction of LV end diastolic diameter and wall thickness.LA dimension reduced from 44,7±1,4 to 36,1±1,4 mm in group A, $p<0,01$,from 45,0±1,5 to 37,2±1,4 mm in group B, $p<0,01$ and from 46,6±1,2 to 30,1±1,1 mm in group C, $p<0,001$.At least one ECG documented episode of atrial fibrilation was reported in 22,6% of the patients with V, in 25,8% of the patients with P, in 12,9% of the patients with V and P in combination.
Conclusions: Blood pressure control was effective and stable in all groups.V and P in combination were significantly more effective than V or P alone in reduction of LV mass index and LA dimension.The use of amiodarone with V and P in combination seems to be significantly more effective than with these drugs alone in prevention any episode of atrial fibrilation in patients with EH,type 2 DM and recurrent AF.

1059 QT interval variability index is associated with 123I-MIBG cardiac sympathetic activity in type 2 diabetes

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Purpose: Elevated beat-to-beat QT interval variability predicts sudden cardiac death and may reflect sympathetic dysfunction. This study determined the relation of QT variability to cardiac sympathetic dysinnervation in type 2 diabetes (T2DM).
Methods: Cardiac 123I-MIBG scintigraphy and QT variability were quantified in 29 patients with T2DM (59±8y, 45% male). Early (15min) and delayed (4hr) planar images were acquired after 123I-MIBG administration. Sympathetic integrity was defined by the delayed heart-to-mediastinum ratio (HMR) and washout rate (WR; percent reduction in HMR from early to delayed image). Sympathetic dysinnervation was defined by HMR $<$1.6 (2 SD below mean normal value). Continuous 5min lead II ECGs were recorded to quantify the QT variability index (QTVI), defined by the log ratio of QT variance (QTvar; normalised to the squared mean QT interval) to RR interval variance (RRvar; normalised to the squared mean RR interval).
Results: Sympathetic dysinnervation was identified in 7 (24%) patients. Despite similar age, sex, BMI, blood pressure and HbA1c, patients with reduced HMR tended to have higher QTVI (-1.1±0.3 vs -1.4±0.4, p=0.063) compared with patients with normal HMR. In all patients, QTVI correlated negatively with HMR (r= -0.54, p=0.002) and positively with WR (r=0.49, p=0.007). Assessment of QTVI components revealed similar QTvar values in both groups and lower RRvar (-1.0±1.1 vs -0.1±0.6, p=0.058) in patients with sympathetic dysinnervation. RRvar, but not QTvar was associated with HMR (r=0.48, p=0.008) and WR (r= -0.35, p=0.07).

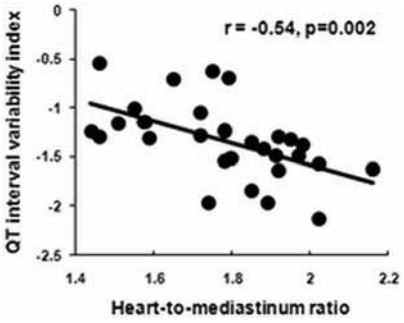

Figure 1

Conclusions: Elevated QTVI is associated with cardiac sympathetic dysinnervation in patients with T2DM. However, reduced RR variance secondary to concomitant vagal involvement may be the predominant cause for this association.

1060 Reduction in the ambulatory blood pressure favorably affects corrected QT interval and QT dispersion in essential hypertensives

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Purpose: QT interval dispersion (QTD) is increased in arterial hypertension and has been reported to be a better predictor of arrhythmic cardiac death than left ventricular hypertrophy (LVH). Our aim was to evaluate the relationship of QT and QTD changes with blood pressure (BP) changes in the setting of essential hypertension.
Methods: We prospectively followed up for a median period of 3.8 years (IQ 2.5-5 years) 155 never treated essential hypertensives who underwent ambulatory BP monitoring and ECG at entry and at follow up visit. QTD was defined as the difference between the maximum and minimum QT intervals occurring in any of the 12 leads of the ECG. The QT interval and QTD were corrected for heart rate using the Bazett's formula.
Results: At the end of follow up, 24hour systolic and diastolic BP were significantly decreased (from 132.1/82.1mmHg to 120.9/74.9mmHg, $p<0.001$ for both cases). In particular, decrease in 24hour systolic BP was observed in 127 patients (from 134.1/83.7mmHg to 118.9/74.4mmHg, $p<0.001$ for both cases) while 24hour systolic BP increased in 28 patients (from 123.6/77.4mmHg to 132.1/81.3mmHg, $p<0.001$ for both cases). Corrected QT was significantly decreased in hypertensives with BP reduction (from 415.8ms to 411ms, p=0.016), while it was increased in hypertensives with BP increase (from 410ms to 417ms, p=0.046). Similarly, corrected QTD significantly increased in hypertensives with BP increase (from 32.9ms to 38.7ms, p=0.002) while no difference occurred in those with BP reduction. In the total study population, there was a positive correlation between corrected QT change and 24hour systolic (r=0.216, p=0.007) and diastolic BP (r=0.227, p=0.005). Moreover, change in corrected QTD was positively associated with 24hour systolic (r=0.165, p=0.047) and diastolic BP (r=0.167, p=0.045), as well as with corrected QT (r=0.389, $p<0.001$).
Conclusions: Changes in ambulatory hemodynamic load in the long term are closely related with changes in corrected QT interval and QT dispersion in the setting of essential hypertension.

1061 The role of amiodarone in the development of respiratory failure early after cardiac surgery

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Purpose: To determine whether intravenous administration of amiodarone early after cardiac surgery correlates with respiratory outcome.
Methods: The study population consisted of 1963 patients that underwent on-pump cardiac surgery at one Institution from May 2004 to May 2010. Indications to give amiodarone postoperatively were: atrial fibrillation onset, prophylaxis in anti-arrhythmic surgery, ventricular arrhythmias. Respiratory failure (RF) was defined as a composite outcome of prolonged (>24 hours) mechanical ventilation, need for re-intubation, tracheotomy or non-invasive ventilation support.
Results: A total of 471/1963 (23.9%) patients received postoperative amiodarone. Overall RF incidence was 7.7% (152/1963); of those 50/471 (10.6%) were patients that received amiodarone and 102/1493 (6.8%) were patients that did not (p=0.009). A total of 29 demographic, preoperative, intraoperative and postoperative variables were tested at univariate analysis and those found correlated with postoperative RF occurrence were forced into a stepwise-fashion logistic multivariable regression. Age (OR 1.6, p=0.002), chronic pulmonary obstructive disease (OR 2.5, $p<0.0001$), extracorporeal circulation time (OR 1.5, $p<0.0001$), diabetes (OR 1.5, p=0.04), history of smoking (OR 1.6, p=0.03), non elective surgery (OR 2.5, $p<0.0001$) and postoperative amiodarone infusion (OR 1.5, p=0.04) were identified as independent predictors of RF early after surgery. Body mass index and gender (both significantly correlated with RF at univariate analysis) were not retained in the multivariate model.
Conclusions: Amiodarone infusion is associated with a statistically significant increased risk for developing RF early after on-pump cardiac surgery. Further studies are needed to confirm this finding.

1062 Atrial selectivity in sodium channel block by amiodarone

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Purpose: Sodium channel blockers are usually applied to atrial fibrillation (AF) but may sometimes cause cardiac contractile dysfunction. However, amiodarone, a multi-channel blocker with sodium channel block, does not induce cardiac dysfunction. In this study we tested the hypothesis that sodium channel block by amiodarone is selective in atrial myocytes (AM) compared to ventricular myocytes (VM).
Methods: Sodium currents and resting membrane potentials (RMPs) were measured using whole cell patch-clamp technique in isolated rabbit AM and VM. Furthermore, we evaluated the effects of amiodarone and mexiletine on conduction velocity (CV) in Langendorff-perfused rabbit hearts by optical mapping system. CV was measured during constant stimulation at basic cycle length of 200ms.
Results: Amiodarone potently inhibited sodium current in AM 20-fold more than in VM (IC50: 1.4±0.3μM [n=8] in AM versus 40.4±11.9μM [n=7] in VM; $P<0.01$). Amiodarone at 10μM dramatically shifted steady state inactivation curve to hyperpolarized direction in AM compared to VM ($V_{\frac{1}{2}}$ shift: -19.6±2.1mV [n=12] in AM versus -6.3±0.8mV [n=13] in VM; $P<0.01$). In mexiletine, there was no significant difference in sodium current inhibition between AM and VM (IC50: 3.6±0.5μM [n=7] in AM versus 6.5±1.9μM [n=7] in VM; P=0.20). The shifts of inactivation curves by mexiletine at 10μM were comparable in AM and VM ($V_{\frac{1}{2}}$ shift: -10.1±0.8mV [n=7] in AM versus -8.9±1.0mV [n=8] in VM; P=0.36). RMPs in AM were more depolarized than in VM (RMP: -75.0±1.3mV [n=4] in AM versus -82.1±1.1mV [n=9] in VM; $P<0.01$). In the absence of drugs, the half inactivation voltage in AM was 12.5 mV more negative than that of VM ($V_{\frac{1}{2}}$: -89.7±0.9mV [n=19] in AM versus -77.2±0.6mV [n=20] in VM; $P<0.01$). The decrease of CV by amiodarone at 5μM was significantly larger in atrium compared to ventricle (%change: -34.3±5.6% [n=5] in AM versus -4.8±1.0% [n=5] in VM; $P<0.01$). However, the reduction of CV by mexiletine at 5μM in atrium was smaller than in ventricle. (%change: -19.4±0.1% [n=5] in atrium versus -27.8±0.1% [n=5] in ventricle; P=0.02).
Conclusion: Amiodarone preferentially inhibits sodium current of AM compared to that of VM. This atrial-selective sodium channel block by amiodarone may contribute to treating AF without affecting ventricular contractility.

IS TAVI THE DEFINITIVE TREATMENT IN HIGH-RISK PATIENTS?

1107 Effect of concomitant coronary artery disease on early outcome after transcatheter aortic valve implantation: results from the German TAVI registry

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Background: The prevalence of coronary artery disease (CAD) in patients undergoing surgical aortic valve replacement (SAVR) is estimated at 40-50%. CAD increases procedural risk with SAVR, and revascularization is recommended at the time of surgery. In patients treated with transcatheter aortic valve implantation (TAVI), the prevalence and impact of CAD on outcome is controversial.
Methods and results: We analyzed data from 1368 patients enrolled in the German TAVI registry. The presence of coronary artery lesions with ≥50% diameter stenosis on pre-TAVI angiography was used to identify the existence of concomitant CAD.
Overall, 829 patients (60.6%) had concomitant CAD, of which 64.3% had multivessel disease and 9.9% left main disease. Patients with CAD were younger (81.5±6.1 vs. 82.1±6.3 years, $p<0.05$), more commonly males (49.9% vs. 30.1%, $p<0.0001$) and were more commonly diabetics (36.6% vs. 31.5%, $p<0.05$) compared to patients with no concomitant CAD. In addition, patients with CAD had more commonly peripheral arterial disease, had lower baseline left ventricular ejection fraction, a higher mean logistic Euroscore (23±14.6 vs. 16.9±11.1, $p<0.0001$), and a worse Canadian Cardiovascular Society (CCS)

angina class at baseline. During the TAVI procedure, patients with CAD more often required additional percutaneous coronary intervention (5.6% vs. 2.8%, $p<0.05$) and had longer procedures (92.1±52.0 vs. 85.2±46.3 minutes), but procedural success rates were similar (97.2% vs. 97.4%, p=0.84). In-hospital outcome is shown in the table.

Table 1. In-hospital outcome according to the presence or absence of CAD

	CAD (n=829)	No CAD (n=539)	p-value	OR (95% CI)
In-hospital death	81 (9.8%)	33 (6.1%)	<0.05	1.66 (1.09–2.53)
Myocardial infarction	6 (0.7%)	1 (0.2%)	0.17	3.92 (0.47–32.66)
Stroke	28 (3.5%)	14 (2.7%)	0.41	1.31 (0.68–2.52)
Major vascular complications	35 (4.3%)	15 (2.9%)	0.17	1.53 (0.83–2.82)
Reanimation	64 (7.9%)	19 (3.6%)	<0.01	2.29 (1.36–3.87)
High degree AV block	180 (22.2%)	106 (20.4%)	0.43	1.11 (0.85–1.46)

Conclusion: The prevalence of CAD in contemporary TAVI patients is high. The presence of CAD characterizes a high risk population and is associated with an increased risk of in-hospital mortality. Therefore, patients with CAD undergoing TAVI require special attention, and specific strategies to improve their outcome are needed.

1108 Impact of coronary artery disease in elderly patients undergoing transcatheter aortic valve implantation: insight the italian corevalve registry

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Aims: Coronary artery disease (CAD) in patients with degenerative aortic stenosis is a common condition. In patients candidated to surgical aortic valve replacement, myocardial revascularization and valve replacement have to be performed in same session; this strategy is not applicable recommended in the context of transcatheter aortic valve implantation (TAVI). We sought to evaluate the impact of CAD on clinical outcomes in patients undergoing TAVI.
Methods and results: Consecutive patients (N=663) who underwent TAVI with the 18-French CoreValve ReValving System (CRS) (Medtronic Inc, MN USA) from June 2007 through December 2009 at 14 institutions across Italy were included in this prospective web-based registry. Four patients were excluded from analysis due to failure to successfully release the prosthesis in the aortic annulus. Previous cardiovascular intervention or myocardial infarction, and presence of significant coronary stenosis prior to TAVI were used to identify the existence of concomitant CAD (N=359, 54%). The primary endpoint was to assess the incidence of Major Adverse Cerebrovascular and Cardiac Events (MACCE) and all-cause death across patients undergoing TAVI who presented associated CAD and who did not. A secondary analysis was employed in the CAD group, stratifying patients with treated CAD and those with untreated CAD.Overall 12-month MACCE incidence and mortality after TAVI was were 16.7% and 15%, respectively. Patients with CAD did not present more likely to develop MACCE within 12-month of the procedure than those who did not (Odds Ratio [OR] 1.14; 95% confidence interval [CI] 0.78 to 1.67; p=0.483). Consistently, after adjusting for several confounding factors, CAD was not associated to 12-month MACCE (adjusted OR 0.84; 95% CI 0.46 to 1.53; p=0.579). The 12-month mortality was 17.8% and 14.4% in CAD group and no-CAD group, respectively (adjusted OR 1.01; 95% CI 0.55 to 1.88; p=0.967). Across patients with significant CAD noticed before TAVI, 12-month mortality and MACCE incidence were not affected by the degree of revascularization, resulting a survival of 82.3%, 84.2% and 81.9% (p=0.911) and a freedom from MACCE of 81.4%, 82.5% and 79.0% (p=0.823) in patients with complete, incomplete or no revascularization, respectively.
Conclusions: This large, multicenter registry showed that coexisting CAD does not impact procedural outcomes and mid-term survival in elderly patients undergoing TAVI with CRS prosthesis. In addition, the extent of revascularization before TAVI was also not associated with different outcomes in such patients.

1109 Impact of aortic regurgitation after transcatheter aortic valve implantation on thirty-day mortality, morbidity and quality of life: an analysis from the German TAVI registry

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Background: Transcatheter aortic valve implantation (TAVI) has been shown to improve survival and symptoms in patients with severe aortic stenosis (AS) and high surgical risk. Recently, we have identified residual aortic regurgitation (AR) after TAVI as a risk factor for in-hospital mortality. It is generally believed that AR improves with time and would not impact intermediate and long term outcome after TAVI, but so far, the effect of AR on 30-day mortality, relieve of symptoms and quality of life is not known.
Methods: We analyzed data from 1365 patients enrolled in the prospective multicenter German TAVI registry. The occurrence of AR was evaluated angiographically after device deployment and removal of catheter and guidewire. Significant AR was defined as AR ≥ 2/4. Clinical endpoints were evaluated during index hospitalization and at 30 days. For survivors of the in-hospital period, symptomatic status and quality of life (using EQ-5D) were assessed 30 days after TAVI.
Results: The study population's mean age was 81.7±6.2 years and men represented 42.3%. Mean logistic Euroscore was 20.4±13.5%. Most patients (81.5%) received the Medtronic CoreValve prosthesis. Significant AR occurred in 203 patients (14.9%). In-hospital death rates were significantly higher in patients with significant AR (14.8% vs. 6.7%, OR = 2.41, 95%CI = 1.54-3.78), but rates of MI, stroke and major bleeding were similar. For patients who survived the in-hospital period and for whom a complete 30-day follow-up has been obtained (n=989, 87.4%), the New York Heart Association (NYHA) functional class was worse in patients with significant AR compared to those with no/mild AR (44.8% vs. 56.3% with NYHA I and 18.1% vs. 12% with NYHA III, $p<0.05$ and p=0.08, respectively). EQ-5D self-reported health status improved in both groups, but the degree of improvement was less pronounced in the significant AR group (from 0.63±0.28 to 0.67±0.26 vs. from 0.63±0.27 to 0.69±0.23 in patients with and without significant AR, respectively, p for delta = 0.14). Patients with significant AR more commonly described their mobility status after TAVI as "confined to bed" (6.1% vs. 2.5%, $p<0.05$), and more commonly described a worse health status after TAVI compared to before TAVI (15.8% vs. 7.2%, $p<0.01$). At 30 days, survival was 84.2% and 93.7% in patients with and without significant AR, respectively ($p<0.0001$).
Conclusion: Significant (≥2/4) AR after TAVI limits functional improvement and is associated with higher rates of mortality at 30 days. Prevention and treatment of this complication would maximize the benefit obtained from this evolving technology.

1110 Transcatheter aortic valve implantation (TAVI) - impact of paravalvular leaks (PVL) on postprocedural prognosis and NT-pro-BNP-levels

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The association of NT-pro-BNP secretion and left ventricular wallstress, particularly in patients with severe aortic valvular stenosis (AVS) has been clearly demonstrated. TAVI is a new treatment option for high-risk patients with severe AVS. Nevertheless, it has been reported that more than 25% of the implanted devices are associated with a significant degree of paravalvular leaks (PVL). The clinical impact of PVL is still insufficiently explored.
Methods: A total of 200 patients (age 80±6,8; average EURO-Score: 24,48%) with severe AVS were treated by TAVI (CoreValve n=154, EdwardsSAPIEN n=26, SAPIEN XT n=20). NT-pro-BNP and grade of PVL (angiography and echocardiography) were quantified before, directly after intervention, 6 weeks, 6 and 12 month after implantation, respectively.
Results: The procedural success was 97%. Initial angiographic assessment demonstrated a PVL ≥2+ in 92 patients (46%). Therefore, 80 patients were treated by post-ballooning and 12 patients received a snare pull back with a final result of PVL <2+ in 85%. After a transient increase in NT-pro-BNP, there was a significant progressive decline of NT-pro-BNP within 12 months (NTpro-BNP: before/1-5 days/6 weeks/6 month/12 month after TAVI: 4701±6540/ 6411±8361/ 2715±3970/1711±2123/1077±1130 ng/L). With regard to the presence (95% paraprosthetic) and grade of PVL (PVL <1+: 48%, PVL 1-2+:43%, PVL ≥2+: 9%), there was a significant relation-ship to 12-month mortality (PVL <1+: 8%; PVL 1-2+: 16%; PVL ≥2+: 47%; p=0,028). In addition, NT-pro-BNP remained elevated in patients with a PVL ≥2+ and a post-procedural increase in NT-pro-BNP by more than 2000 ng/L was associated with a significant increase in mortality.

Conclusion: TAVI is an efficient treatment option for high-risk patients with severe AVS. The incidence of paraprosthetical regurgitation is an inacceptable clinical problem and still insufficiently recognized. Serial measurements of NT-pro-BNP can be used for risk-stratification in patients with a certain degree of PVL. In general, a PVL ≥2+ is associated with a dramatically increased 6-month mortality. Therefore, any action to fight against paraprosthetical regurgitation is highly recommended.

1111 Four-year durability and patient survival with CoreValve transcatheter aortic valve

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Purpose: The durability and safety of transcatheter aortic valve (TAVI) devices have been reported through two years of follow-up. However, longer-term multicenter follow-up results have not been reported. We present four-year safety and valve durability results from an early multicenter study.
Methods: The 21-Fr TAVI prosthesis was evaluated in 52 subjects with native aortic valve disease enrolled in 2005 and 2006 at seven centers in Europe and Canada. The prosthesis materials and the design and disposition of the frame and leaflets were substantially equivalent to the current 18-Fr prosthesis, and the system was deployed in the same manner. Subject inclusion requirements included >80 years old, or surgical risk with logistic EuroSCORE >20%, or >65 years old with 1-2 high-risk co-morbidities.
Results: Implanted subjects were 81 + 5 years old, 63% female, 87% NYHA class III/IV, logistic EuroSCORE 27 + 15. At four years, follow-up status was ascertained from 20 subjects, 26 died (13 cardiac), 2 were not implanted, 2 were explanted, and 2 withdrew due to protocol noncompliance. Overall patient survival was 67.2% at 1 year, 58.5% at 2 years, 47.3% at 3 years, and 45.1% at 4 years. Cardiac survival was 77.9% at two years and 68.0% at four years. Two of the cardiac deaths, both within 3 days of the procedure, were considered study-related. No strokes occurred after three months. Through four years, no frame fractures, valve migrations, or valve endocarditis were reported. No structural valve deteriorations leading to stenosis or regurgitation were reported. Mean transvalvular gradient decreased from 41.2 + 12.4 mmHg at baseline to 10.0 + 4.5 mmHg at four years ($p<0.0001$). After four years, most patients (57%) had no aortic regurgitation, with the remainder in grade I; and, most patients were in NYHA classes I (61%) or II (22%).
Conclusion: The 21-Fr TAVI prosthesis maintained durability and an acceptable safety profile over a four-year follow-up in this first-in-man high-risk patient cohort with severe aortic stenosis. Long-term durability was indicated by the absence of structural valve deteriorations, endocarditis, frame fractures, and valve migrations, with minimal aortic regurgitation and sustained improvement in hemodynamics and NYHA.

1112 Survival after surgical aortic valve replacement in patients with logistic EuroSCORE >20; contemporary results of a high volume centre

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Purpose: In the era of upcoming percutaneaous aortic valve treatment (TAVI) of symptomatic severe aortic stenosis, we present the results of surgical aortic valve replacement (AVR) in patients with a high predicted mortality.
Methods: All consecutive patients who underwent elective isolated aortic valve replacement (IAVR; N =439) or AVR and concomitant coronary artery bypass surgery (CABG; N = 464) between January 2006 and September 2009 were identified from a prospective single centre registry. Two groups were defined: EuroSCORE <20 and >20, since this cut-off is used as selection criterion for TAVI instead of surgical valve replacement. Since a large cohort of TAVI patients are pretreated for coronary artery disease by PTCA, aortic valve surgery combined with CABG surgery was also included.

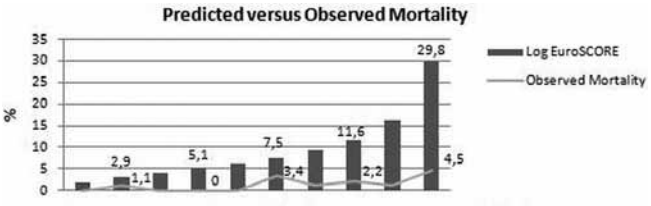

Figure shows median log EuroSCORE (bars) versus actual 30-day mortality (line) of patients undergoing AVR or AVR with concomitant CABG. Bars represent deciles of logistic EuroSCORE; N=90 per decile.

Results: In the study period, 903 patients were included. Median age was 73 (IQR 66 – 78) years, 57.5% were male, median logistic EuroSCORE was 6.6% (IQR 4.0% – 11.6%), and 27.7% of patients had a LVEF lower than 50%. Follow-up on mortality was complete in 99.3% of patients. Thirty day stroke and mortality rates were 2.1% (19/903) and 1.5% (13/896) respectively; one year mortality was 5.2% (40/770). Univariate analysis showed a trend towards a higher 1-year mortality in the combined surgery group (3.6% vs 6.5%; p=0.7). The fugure depicts predicted and observed mortality. Thirty-day mortality of the 87 patients with a logistic EuroSCORE >20 was 4.6%.
Conclusions: Our results show excellent operative survival rates after IAVR and AVR combined with CABG, even in patients with a logistic EuroSCORE over 20%. Surgical AVR should therefore be considered also for patients with very high predicted mortality.

STRESS ECHO: FROM CHEST PAIN TO MOUNTAIN SICKNESS

1117 Stress echocardiography and multidetector computed tomography in the evaluation of acute chest pain: a randomized pilot study

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Background: Acute coronary syndromes (ACS) may be misdiagnosed in up to 10% of patients with acute chest pain, negative troponins and normal ECG. Functional evaluation with stress echocardiography or an anatomical approach using Multidetector Computed Tomography (MDCT) has been proposed in the evaluation of patients with low to intermediate probability of coronary artery disease (CAD). We conducted a randomized pilot study to compare these two diagnostic strategies.
Methdos: We prospectively included 92 patients with no prior cardiac history with acute chest pain, negative serial troponins, normal ECG and intermediate probability of CAD. Patients were randomly assigned to undergo either stress echocardiography (43 patients) or MDCT (49 patients) during admission in the chest pain unit. Patients with non conclusive MDCT or showing coronary stenosis >50% and patients with inconclusive or positive stress echocardiography were admitted to the hospital for further study. The presence or absence of a final diagnosis of ACS was recorded and major cardiac events were evaluated at six months follow-up.
Results: Based on risk factors and chest pain characteristics, the mean pre-test probability of coronary artery disease in this population was 18%. Mean age was 60±11 y, 59% were males, 13% had diabetes, 51% dyslipidemia, 64% hypertension and 60% were smokers. During work up in the chest pain unit, 28.6% of patients in the MDCT group and 30.2% in the stress-echo group were admitted for further study (P=NS). No differences were found in the final diagnosis of ACS between the MDCT and stress-echo groups (12.2% vs 11.6%, respectively, P=NS). In the MDCT group, 1 patient was admitted for non-fatal infarction and another patient with heart failure during follow-up. No events occurred in the stress-echo group.
Conclusion: A functional strategy based on stress-echo is as effective as the non-invasive anatomical approach using MDCT in the diagnosis of ACS in a low to intermediate pre-test probability population. In this pilot study, both strategies appear to be equally safe as well.

1118 The additive prognostic value of myocardial perfusion defects, coronary flow reserve and wall motion abnormalities during dipyridamole contrast stress-echo: a prospective study

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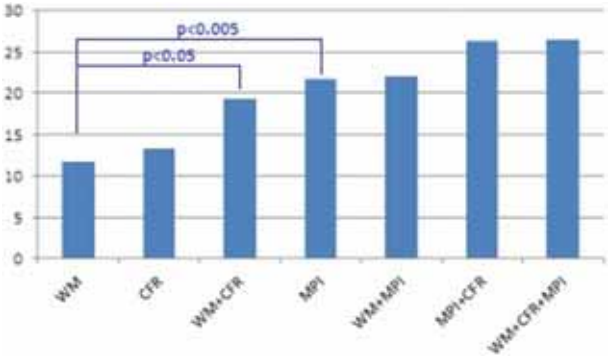
Purpose: Coronary flow reserve on the left anterior descending artery (CFR) and myocardial perfusion analysis (MPI) have individually demonstrated incremental value to predict cardiac events on top of wall motion (WM) analysis during dipyridamole stress-echo (DipSE), but there is lack of data regarding the potentially sinergistic value of WM, CFR and MPI when sequentially assessed in the same examination. The aim of this study was to assess the prognostic value of WM, CFR and MPI during contrast DipSE in patients undergoing contrast SE for suspected or known CAD.
Methods: The population consisted of 419 patients who underwent contrast DipSE for chest pain syndrome either in Parma or Mestre (Italy) echolabs. Enrollment of patients started in January 2009 and continued until March 2010. Follow-up information was obtained until December 2010.All-cause mortality, nonfatal myocardial infarction and unstable angina requiring revascularization composed the combined cardiac endpoint. Revascularized patients were excluded at the time of the procedure.
Results: 23 cardiac events (7 unstable angina, 11 non-fatal myocardial infarction and 5 deaths) were recorded (mean follow-up 483 days).At univariate analysis

WM (5-fold, p<0.001), CFR (5-fold, p<0.001) and MPI (8-fold, p<0.001) were all predictive for the study endpoint; at multivariate cox analysis only MPI (5-fold, p<0.01) and CFR (3-fold, p<0.05) remained predictive. Global chi square demonstrated additional prognostic value by adding CFR to WM (11.7 to 19.4, p<0.05) but not adding either CFR or WM, or both to MPI (see figure).



Conclusion: The addition of CFR data to WM analysis is useful for better prognostication; MPI, which as a standalone parameter significantly outperforms the other 2, does not benefit from addition of either CFR or WM or both.

1119 Direct comparison of transthoracic echocardiographic measurement of coronary flow reserve and 320-row multidetector computed tomography coronary angiography for predicting in-stent restenosis

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Purpose: Noninvasive assessment of coronary artery in-stent restenosis (ISR) would be clinically important, however, no prospective trial has compared the diagnostic accuracy of transthoracic echocardiographic measurement of coronary flow reserve (CFR) with computed tomography coronary angiography (CTCA). Therefore, we sought to determine the feasibility and diagnostic accuracy of CFR measurement using transthoracic Doppler echocardiography (TTDE) by comparing 320-row multidetector CTCA for predicting binary ISR in the three major coronary arteries.
Methods: One hundred and twenty-six patients were enrolled in this study. An invasive coronary angiography (ICA) was performed in all patients within 2 weeks after TTDE and CTCA. Coronary flow velocity was recorded in each target coronary artery by TTDE at rest and during hyperemia induced by intravenous infusion of adenosine triphosphate (0.14 mg/kg/min). CFR was calculated as the ratio of hyperemic to basal peak and mean diastolic velocity and CFR<2 was considered ≥50% stenosis. Prospectively electrocardiographically-gated CTCA was performed with the use of automatic bolus-tracking method. Stents were viewed by CTCA and narrowing of the stented segment was graded 1 to 4 according to the proportion of the vessel lumen that was poorly enhanced, and grades 3 and 4 was considered ≥50% stenosis.
Results: One hundred and twenty-six patients with 309 implanted coronary stents (90% were drug-eluting stents and 10% were bare-metal stents) in the three major coronary arteries were enrolled in this study. The mean stent diameter was 3.0±0.3 mm (range, 2.5–4.0 mm) and the mean stent length was 20±6 mm (range: 8.0–33 mm). ISR (≥50% luminal narrowing) by ICA was found in 24 (8%) of the stent segments. CFR was successfully measured in 291 of 309 coronary arteries (94%) whereas 275 of 309 stents (89%) by CTCA. CFR<2.0 had a sensitivity of 92%, a specificity of 96%, a positive predictive value (PPV) of 80%, and a negative predictive value (NPV) of 90% for predicting ISR in all three coronary arteries. CTCA grades 3 and 4 had a sensitivity of 87%, a specificity of 90%, a PPV of 64%, and a NPV of 90% for predicting ISR.
Conclusions: ISR was diagnosed with high feasibility and high accuracy using TTDE compared to CTCA, which implies a significant role for CFR measurement in identifying ISR in the three major coronary arteries.

1120 Evaluation and impact on outcome of left ventricular contractile reserve in asymptomatic degenerative mitral regurgitation

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Introduction: In degenerative mitral regurgitation (MR), the evaluation of left ventricular contractile reserve (LVCR) remains understudied. The LVCR is evaluated either with the exercise (ex)-induced changes in LV ejection fraction (LVEF) or in global longitudinal strain (GLS), as assessed by 2-D speckle-tracking imaging (2DSt). In addition, the prognostic value of LVCR in patients with asymptomatic MR is unknown. We sought to quantify LVCR and evaluate its usefulness for risk stratification in asymptomatic patient with degenerative MR.
Method and results: Comprehensive resting and exercise transthoracic echocardiography, including 2DSt quantification were performed in 112 consecutive asymptomatic patients (61±14 years, 55% of male) with moderate to severe degenerative MR (72% with severe MR) and preserved LV function. Presence of LVCR was defined as an ex-induced increase in LVEF (LVCREF) >4% or in GLS (LVCRGLS) >2%. Cardiac event was defined as cardiac-related death or hospitalization or mitral valve surgery (ESC class I or IIa). LVCREF was present in 39 (45%) and LVCRGLS in 59 (51%). BNP level was significantly correlated with ex-induced changes in GLS (r= -0.20, p=0.025), but not in LVEF (r=0.03, p=0.22) and patients with LVCRGLS had lower BNP level (39±44 vs. 73±79pg/ml, p=0.005). Patients with no LVCRGLS had significant lower 2-year cardiac event-free survival (48±7 vs. 70±7%, p=0.003). In contrast, there was no significant difference in outcome regarding to the presence or absence of LVCREF (58±8 vs. 63±8%, p=0.20). Multivariable Cox proportional hazard model showed that no LVCRGLS remained associated with lower event-free survival after adjustment for age and sex (HR=2.3, 95%CI: 1.2-4.3, p=0.008). In addition, further adjustment for BNP, indexed LV end-systolic diameter, indexed left atrial volume and resting GLS revealed that the absence of LVCRGLS is a strong independent predictor of cardiac events (HR=2.0, 95%CI: 1.0-4.1, p=0.04). LVCREF was not associated with an increase in risk of events both in uni- and multivariable analysis.
Conclusion: In asymptomatic degenerative MR, LVCR should be assessed using ex-induced changes in LV myocardial longitudinal function rather than changes in LVEF. In patients with preserved resting LV function, the absence of LVCR on exercise is independently associated with 2-fold increase in risk of cardiac events. Hence, LVCR may be useful to improve risk stratification and clinical decision making in asymptomatic patients with degenerative MR.

1121 Favorable short-term outcome of transplanted hearts selected from marginal donors by pharmacological stress echocardiography

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Background: Due to the shortage of donor hearts, the criteria for acceptance have been considerably expanded. An abnormal result at pharmacological stress echocardiography is associated with significant coronary artery disease and/or occult cardiomyopathy at verification by cardiac autopsy. The aim of this study is to establish the feasibility of an approach based on pharmacological stress echocardiography as a gatekeeper for extended heart donor criteria.
Methods: From April 2005 to December 2010, 51 marginal (>50 years old, n= 41, or <50 years with ≥3 concomitant risk factors, n=10) candidate donors (age 55±8 years, 28 male) were initially enrolled. After legal declaration of brain death, marginal donors underwent rest and, if normal, dipyridamole (0.84 mg/kg in 6', n=30) or dobutamine (up to 40 mcg/kg, n=3) stress echocardiography.
Results: We found 23 eligible hearts with normal findings. Of these, 4 were not transplanted due to lack of a matching recipient, and verification by cardiac autopsy showed absence of significant coronary artery disease or cardiomyopathy abnormalities. The remaining 19 eligible hearts were uneventfully transplanted in marginal emergency recipients. All showed normal (n=16) or nearly-normal (minor single- vessel disease, in 3) angiographic, intravascular ultrasound, hemodynamic and ventricolographic findings at 1 month. At follow-up (median 20, interquartile ranges 10-37 months), 17 patients survived and 2 died, one at 2 months from general sepsis and one at 32 months from allograft vasculopathy in recurrent multiple myeloma.

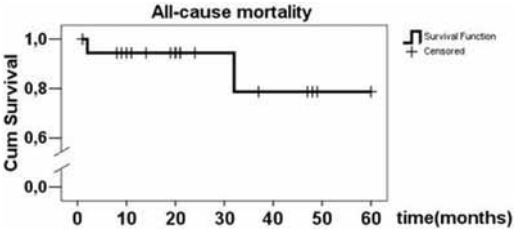

Figure 1. All cause mortality.

Conclusions: Pharmacological stress echocardiography can safely be performed in candidate heart donors with brain death, and shows potential for extending donor criteria in heart transplantation.

1122 Decreased right ventricular contractile reserve in patients with chronic mountain sickness

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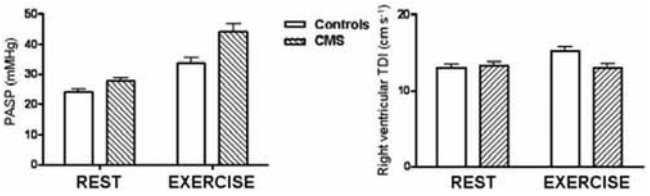
Background: Chronic Mountain Sickness (CMS) disease is characterized by increase in systolic pulmonary arterial pressure (PASP) during mild effort.
Aim: To evaluate left and right ventricular systolic function and their relationship with PASP increase during stress in CMS.
Methods: In La Paz (Bolivia, 3600 m s.l.), we evaluated 31 male CMS (age= 54±10 yrs) and 30 male healthy high-altitude dwellers (controls, C; age= 45±10 yrs) at rest and exercise. Upright bicycle exercise (up to 50 Watts) stress echo was performed with integrated 2D (Ejection Fraction, EF, Simpson rule), peak Systolic Velocity from tissue Doppler imaging at the tricuspid annulus (PSVtdi) and Doppler (PASP assessment from peak velocity of tricuspid regurgitation jet) evaluation.
Results: CMS patient showed higher PASP at rest (CMS=27.6±6 vs C=24.3±4 mmHg, p=0.02) and at peak stress (CMS=44±12 vs C=33±7 mmHg, p<0.001). Right ventricular function was similar at rest (PSVtdi: CMS=13.3±2.3 vs C=13±2.6 cm s^{-1}, p=ns) but lower in CMS at peak stress (CMS=12±1 vs C=15±3 cm s^{-1}, p<0.0001) (see figure). EF was similar in CMS at rest (CMS=63±6 vs C=66±6%, p=ns) and at peak stress (CMS=67±6 vs C=66±8%, p=ns). The exercise-induced increase in PASP was correlated with PSVtdi in C (R= 0.6, p=0.03), but not in CMS (R=0.1, p=ns).



Conclusion: When compared to controls, CMS patients show an increase in PASP during exercise associated with a preserved left ventricular and decreased right ventricular contractile reserve.

INTERFACE BETWEEN ANTIPLATELET THERAPY AND GENERAL MEDICAL CONDITIONS

1165 Acetylsalicylic acid inhibits thromboxane A2 production and thromboxane A2-dependent platelet function equally well in diabetic and non-diabetic subjects

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Background: Acetylsalicylic Acid (ASA), which inhibits platelet cyclooxygenase-1 (COX-1) dependent thromboxane A2 (TxA2) formation, decreases cardiovascular events in patients with coronary artery disease (CAD). According to some reports, patients with type-2 diabetes mellitus (DM) may be less responsive to ASA than non-DM patients. Aim. We compared the platelet production of thromboxane B2 (TxB2), a stable TxA2 metabolite, and platelet aggregation (PA) in 50 type-2 DM CAD patients and 50 non diabetic (ND) CAD patients under chronic daily treatment with 100 mg ASA. 25 healthy subjects (HS), treated with 100 mg ASA for 4 days, were also studied.
Methods: Platelet aggregation (light transmission aggregometry, LTA) induced by 1 mM arachidonic acid (AA) or 5 μg/mL collagen were measured in platelet-rich plasma (PRP), prepared from whole blood anticoagulated with sodium citrate, 2h and 24h after ASA. PA was also measured in hirudin-anticoagulated PRP and whole blood by impedance aggregometry (Multiplate) 2 h after ASA. TxB2 was measured in supernatant plasma of whole blood and PRP after stimulation with AA, and in serum.
Results: Experiments by LTA. AA-induced platelet aggregation was completely abolished in all subjects, except in 9 DM-CAD (PA between 1% and 6%), 18 ND-CAD (1-7%) and 7 HS (1-9%). Collagen-induced PA was slightly, but significantly lower in DM-CAD, compared to the other 2 groups at 24h, but not at 2h. Experiments by Multiplate. Collagen- or AA-induced platelet aggregation in whole blood or PRP was not significantly different among the 3 groups. AA-induced PA in whole blood was higher than in PRP: the in vitro addition of the thromboxane receptor antagonist SQ29458 (5 μM) to whole blood inhibited AA-induced PA in all groups by about 40%. Measurement of TxB2. No statistically significant differences in serum TxB2 were found among the 3 groups, both in the 2h (DM-CAD 3.4±3.0 ng/mL; ND-CAD 3.1±2.8; HS 2.5±1.8) and the 24h samples (3.9±6.9; 3.5±4.0; 3.0±2.9). After stimulation with AA, the levels of TxB2 in supernatant plasma from whole blood (DM-CAD 77.1±38.0 ng/mL; ND-CAD 73.8±50.3; HS 92.7±37.0) were higher than in supernatant plasma from PRP (4.2±7.1; 3.9±5.0; 3.1±2.3) without any statistically significant difference among the 3 groups of subjects.
Conclusion: We found no evidence of impaired response to ASA in DM-CAD, compared to ND-CAD and HS. ASA did not completely inhibit AA-induced platelet aggregation and thromboxane production in whole blood from all subjects,suggesting that extraplatelet sources of thromboxane may stimulate platelets even when platelet COX-1 is well inhibited by ASA.

1166 Impact of hemoglobin on residual platelet reactivity in patients undergoing percutaneous coronary intervention

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Purpose: Anemia is associated with adverse events following percutaneous coronary intervention (PCI). Experimental data suggest this excess risk may be attributable to a prothrombotic state in anemic patients. We sought to determine the association of hemoglobin (Hb) with residual platelet reactivity (RPR), a measure of blood thrombogenicity, in patients undergoing PCI.
Methods: We studied 277 clopidogrel-naïve patients who underwent platelet function testing following PCI. All patients were loaded with 600 mg of clopidogrel prior to PCI and platelet function testing was performed a minimum of 4 hours after the load. RPR to adenosine disphosphate (ADP) was assessed using the VerifyNow P2Y12 Analyzer and expressed as P2Y12 Reaction Units (PRU). Patients were categorized by levels of Hb into tertiles: low (< 12.6 g/dl), medium (12.6 to 13.9 g/dl) and high (>13.9 g/dl). As a low Hb concentration might interfere with this assay, analyses were repeating after excluding those with Hb < 10 g/dl.
Results: Patients in the lowest Hb tertile were older and more often female compared to those in higher Hb tertiles. Diabetes mellitus, chronic kidney disease and low ejection fraction were more common in those with lower versus higher Hb levels. Mean PRU values among those in the low, medium and high Hb tertiles were 261.7±108.9, 232.04±98.2 and 195.5±89.8, respectively (p<0.001, Figure). The inverse association between Hb and RPR was attenuated but remained significant after multivariable adjustment, including body mass index. Results were unchanged after excluding patients with Hb <10 g/dl.

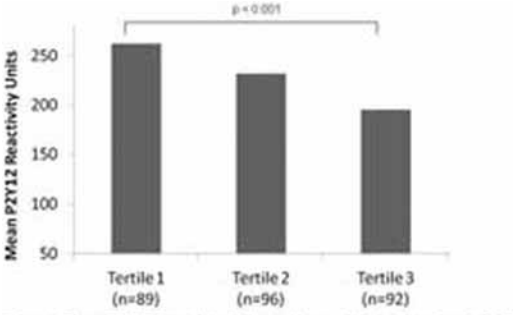

Figure. Mean P2Y12 Reactivity Units by Hemoglobin tertiles: low (< 12.6 g/dl), medium (12.6 to 13.9 g/dl), high (≥ 13.9 g/dl)

Conclusion: Hb concentration is inversely related to platelet reactivity in patients undergoing PCI. Further investigation assessing the impact of anemia on platelet function and thrombotic potential are warranted.

1167 Impact of ageing on the platelet and vascular responses in women with polycystic ovary syndrome

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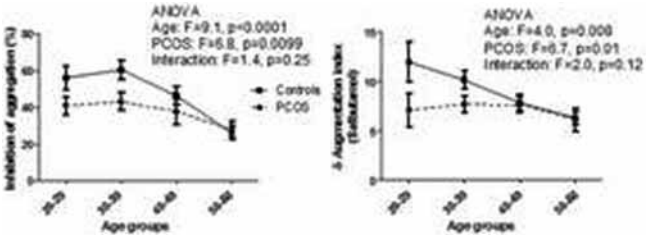
We have previously demonstrated an impairment of platelet nitric oxide (NO) responsiveness and vascular endothelial dysfunction in young polycystic ovary syndrome (PCOS) females. Impaired NO platelet responsiveness has been shown to be predictive of coronary event risk and mortality. We sought to investigate the effect of ageing on these responses in PCOS women compared to age-matched controls.
Methods: A total of 105 PCOS and 132 controls were recruited (≥20 women in age decade, age range 20-60 years). Platelet aggregation was induced by adenosine diphosphate (ADP, 2.5μM) and inhibited by sodium nitroprusside (SNP; 10μM). Vascular eNOS-dependent (salbutamol) and eNOS-independent (nitroglycerine) responsiveness were determined by applanation tonometry.
Results: In the entire study group, ageing was associated with a progressive decline in vascular endothelial function and platelet NO responsiveness (ANOVA:

p<0.01 for both), and with differential impairment of these parameters in PCOS subjects (ANOVA: p<0.05 for both). There was marked impairment of platelet NO responsiveness (p<0.01) in subjects receiving oral contraceptives: the Figure illustrates the convergence of vascular and platelet physiological data with ageing in the remainder (n=210) of the subjects.



Conclusions: (1) In normal women ageing is associated with progressive declines in both vascular endothelial function and platelet NO responsiveness
(2) PCOS is associated with marked "premature" impairment of vascular endothelial and platelet function, but differences between PCOS subjects and normals are attenuated by age 60.
The nexus between this early vascular/platelet dysfunction in PCOS and premature atherogenesis implies the potential importance of early intervention in such individuals.

1168 Phenotyping versus genotyping for prediction of adverse events in clopidogrel non-responders

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Background and aim: Although prognostic values of different tests for assessment of clopidogrel responsiveness have been shown in independent studies, no direct comparison between the assays has been made so far. Therefore, we investigated which laboratory approach has the best predictive value for adverse events in patients taking clopidogrel.
Methods: In this prospective cohort study polymorphisms of CYP2C19*2 and CYP2C19*17 genes, vasodilator-stimulated phosphoprotein phosphorylation (VASP) assay, Multiple Electrode Aggregometry (MEA; adenosine disphosphate: ADP + prostaglandine E1: PGE1 test), Cone and Platelet Analyzer (CPA; ADP test) and Platelet Function Analyzer 100 (PFA100; collagen + ADP test) were performed in 416 patients with coronary artery disease undergoing percutaneous coronary intervention. The rates of events (definite, probable or possible stent thromboses or TIMI major bleeding) were recorded during a 12-month follow-up.
Results: Receiver operator characteristic analysis showed that platelet aggregation by MEA predicted stent thrombosis better (c-index=0.90; p<0.001; sensitivity=90%; specificity=83%) than the VASP assay (c-index=0.62; p>0.05; sensitivity=70%; specificity=38%), CPA (c-index=0.62; p>0.05; sensitivity=90%; specificity=36%), PFA100 (c-index=0.66; p>0.05; sensitivity=70%; specificity=61%) or the CYP2C19*2 polymorphism (sensitivity=30%; specificity=71%). Survival analysis yielded that patients classified as non-responders by MEA had a substantially higher risk to develop stent thrombosis than clopidogrel responders (12.5% vs. 0.3%; p<0.001), whereas poor metabolisers (CYP2C19*1/*2 or *2/*2 carriers) were not on an increased risk (2.7% vs. 2.5%; p>0.05). Multiple logistic regression analysis identified clopidogrel response status assessed by MEA as an independent predictor of stent thrombosis. Although the incidence of TIMI major bleeding was higher in patients with an enhanced vs. low response to clopidogrel assessed by MEA (4% vs. 0%) or in ultra-metabolisers vs. regular-metabolisers (CYP2C19*17/*17 vs. CYP2C19*1/*1; 9.5% vs. 2%), neither test was predictive for bleeding events in clinical follow-up. The classification and regression tree analysis demonstrated that acute coronary syndrome at hospitalisation followed by diabetes mellitus were the best discriminators for clopidogrel response status assessed by MEA.
Conclusion: Phenotyping of platelet response to clopidogrel by MEA might be a better risk predictor of stent thrombosis than genotyping of the CYP2C19 allele.

1169 Safety of dental extractions during uninterrupted single or dual antiplatelet treatment

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Purpose: The optimal dental management in patients on chronic antiplatelet treatment is not clearly defined. Antiplatelet discontinuation increases the risk of thrombotic complications, whereas uninterrupted antiplatelet therapy, which is the currently recommended approach, is assumed to increase the bleeding risk following dental procedures. We sought to prospectively compare the risk of immediate and late post-extraction bleeding in patients receiving uninterrupted single or dual antiplatelet therapy.
Methods: We prospectively recruited 643 consecutive patients referred for dental extractions. One hundred and eleven patients (17.3%) were on clinically indicated antiplatelet therapy: aspirin (n=42); clopidogrel (n=36); aspirin and clopidogrel (n=33). Five hundred and thirty two controls (82.7%) were not on antiplatelet treatment. Immediate and late bleeding complications were recorded. Prolonged immediate post-extraction bleeding was determined as that which does not stop after 30 minutes of pressure pack and needs placement of haemostatic agent to be controlled. Reentry of bleeding after leaving the clinic, presence of hematoma or excessive blood loss, were recorded as late hemorrhagic events.
Results: The groups had similar clinical characteristics at baseline. Compared to controls, the risk of prolonged immediate bleeding was higher in patients on dual antiplatelet therapy (RR=177.3; 95% CI: 43.5-722; p<0.001), but not in patients on aspirin alone (RR=6.3; 95% CI: 0.6-68.4; p=0.2) or clopidogrel alone (RR=7.4; 95% CI: 0.7-79.5; p=0.18); however, all immediate bleeding complications in all treatment groups were successfully managed with local hemostatic measures. No patient experienced any late hemorrhagic complication.
Conclusions: Dental extractions may be safely performed in patients receiving single or dual antiplatelet therapy when appropriate local hemostatic measures are taken, thereby averting the thrombotic risk of temporary antiplatelet discontinuation.

1170 Coronary artery disease, aspirin, and perioperative myocardial infarction and bleeding in orthopedic surgery

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Purpose: Increasing numbers of patients with established coronary artery disease (CAD) are undergoing surgical procedures. Since patients with CAD are at increased risk for both thrombotic and bleeding complications during the perioperative state, the role of antiplatelet therapy in this setting remains elusive. We therefore sought to investigate the incidence of thrombotic and bleeding events, as well as to identify significant risk factors.
Methods: For all 3295 knee, hip, and spine surgical procedures performed November 2008 - December 2009 at a tertiary care medical care center we determined the presence or absence of CAD, CAD risk factors, and post-operative myocardial infarction or hemorrhage using ICD-9 diagnosis codes. 3083 patients were found to be eligible for the study after 212 patients less than 21 years were excluded from the study. Transfusion data were ascertained from the blood bank. Perioperative aspirin use and troponin elevation were determined through retrospective medical record review for all 327 CAD cases.
Results: Overall, the in-hospital incidence was higher in patients with CAD (n=327) versus without CAD (n=2756) for any troponin elevation (19.3% vs 4.2%, P<0.001), coded MI (2.1% vs 0.5%, P<0.001), ≥ 2 transfusions of packed red blood cells (33.6% vs 16.6%, P<0.001), and coded post-operative hemorrhage (2.1% vs 0.7%, P=0.01). Among patients with CAD, use of aspirin preoperatively was not associated with any troponin elevation (6.6% vs 13.2%, P=0.23) or ≥ 2 transfusion units (6.8% vs 9.7%, P=0.29). In fact, the use of aspirin in the preoperative state was associated with fewer coded MI's (7.5% vs 14.3%, P=0.05).
Conclusions: Patients with CAD undergoing orthopedic surgery are at a significant risk for both ischemic and bleeding complications. A lower risk of MI was seen in patients with CAD who were on preoperative aspirin, yet, there was no increase in bleeding outcomes. Future prospective studies are needed to address the potential perioperative role of aspirin and the trade-off between ischemic and bleeding complications among surgical patients with CAD.

MODERATED POSTERS
TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

P1177 Current epoprostenol use in patients with severe pulmonary hypertension (PH): data from the French PH registry

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Purpose: The management of pulmonary arterial hypertension (PAH) has evolved since the early 2000s with the introduction of oral therapies, and consequently data on the current use of i.v epoprostenol are scarce.
Methods: Data from the prospective French PAH Registry launched in November 2006 were analysed. All the newly diagnosed patients with pulmonary hypertension (PH) (i.e. incident cases: PH confirmed by right heart catheterisation < 1 year prior to enrolment) treated with i.v. epoprostenol were included in the anal-

ysis. The cut-off date was 1 September 2010. Survival analysis was calculated from the initiation of epoprostenol therapy.
Results: From November 2006 to September 2010, 177 adult patients met the inclusion criteria. The mean (±SD) age was 51±17 years and the female to male sex ratio was 1.68. The vast majority of patients (72%) had PAH (group 1 of the diagnostic classification of PH), 8% were classified as group 3 (PH with lung diseases), 12% as group 4 (chronic thromboembolic PH) and 2% as group 5 (miscellaneous PH). In addition, 11 patients (6%) received epoprostenol for pulmonary veno-occlusive disease. At the time of epoprostenol initiation, 7%, 43% and 50% of patients were in NYHA functional class II, III and IV, respectively, and 47% of patients were naïve to PAH specific therapy. The mean (±SD) 6-minute walk distance was 309±131 m. Right heart catheterisation confirmed severe haemodynamic impairment with a mean pulmonary artery pressure of 56±13 mmHg, a right atrial pressure of 10±6 mmHg, a cardiac index of 2.0±0.6 L/min/m^2 and a pulmonary vascular resistance of 1194±571 dyn s cm^{-5}. In the overall PAH population, survival estimates following epoprostenol therapy were 77%, 63% and 54% at 1, 2 and 3 years, respectively. Out of the 127 patients in group 1, 81 (64%) had idiopathic, heritable or anorexigen-associated PAH, 17 (13%) had connective tissue disease-associated PAH and 17 (13%) portopulmonary hypertension. In the subgroup of patients with idiopathic, heritable or anorexigen-associated PAH, survival estimates were 82%, 72% and 69%, respectively.
Conclusion: In a contemporary PH Registry conducted in expert PAH centers in France, epoprostenol is prescribed in 28% of the cases for non-group 1 PH, and as first line therapy in almost half of all cases. In incident patients with idiopathic, heritable or anorexigen-associated PAH, 1- and 2-year survival is similar to that of historical cohorts.

P1178 Effects of s.c. treprostinil on top of double oral combination therapy in patients with pulmonary arterial hypertensione (PAH) and inoperable chronic thromboembolic pulmonary hypertension (CTEPH)

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Purpose: Pulmonary arterial hypertension (PAH) and inoperable chronic thromboembilic pulmonary hypertension (CTEPH) are severe progressive conditions leading to right heart failure and premature death. In these patients, medical treatment is usually started with oral medications such as endothelin receptor antagonists (ERA) and/or phosphodiesterase-type 5 inhibitors (PDE5-I). The aim of this study was to evaluate the use of subcutaneous (s.c.) treprostinil, a prostacyclin analogue, as an add-on therapy to ERA and PDE5-I in patients with PAH and patients with inoperable CTEPH.
Methods: Twenty-three patients with PAH (mean age 43±12 y) and 3 with inoperable CTEPH (mean age 41±11 y) were included in the study. Among patients with PAH, 9 had idiopathic PAH, 3 PAH associated with connective tissue disease, 10 with congenital heart disease, and 1 with HIV infection. All patients were treated with an ERA drug combined with a PDE5-I. Treprostinil was initiated at a dose of 1 ng/kg/min and then increased to reach an average dose of 32±10 ng/kg/min. Six-minute walk distance (6MWD) and right-heart catheterization (RHC) data were prospectively collected at baseline and after 6 months of s.c. treprostinil.
Results: Three patients discontinued treprostinil due to pain at the site of injection before the 6-month evaluation (2 additional patients discontinued after the 6-month assessment for the same reason); 4 patients died and 1 patient received lung transplantation before the 6-month assessment. Eighteen patients completed the study. Haemodynamic and exercise capacity data at baseline and at the 6-month assessment are reported in the table.

n=18	6MWD (mt)	RAP (mmHg)	mPAP (mmHg)	CI (l/min/mq)	PVR (WU)
Baseline	401±134	11±5	67±21	2.2±0.3	17±9
Treprostinil	428±131	10±4	62±19	2.6±0.6	14±8
p	0.22	0.14	0.036	0.001	0.001

RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance.

Conclusion: S.c. administration of treprostinil on top of ERA+PDE5-I therapy improves haemodynamics in patients with PAH and inoperable CTEPH. The increase of exercise capacity is minimal and not statistically significant likely due to the reduced sample size. Five patients (19%) died or were transplanted before the 6-months assessment and five patients (19%) discontinued due to local pain.

P1179 Posthoc subgroup analysis: sildenafil (SIL) added to long-term epoprostenol therapy in patients with idiopathic and connective tissue disease (CTD)-associated pulmonary arterial hypertension (PAH)

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Purpose: In a double-blind study (PACES-1), SIL improved clinical outcomes vs placebo (PBO) in PAH patients (pts) receiving concomitant IV epoprostenol (EPO). We evaluated safety and efficacy in pts with idiopathic PAH (IPAH) and PAH-CTD.
Methods: Pts received SIL (titrated from 20 md TID [for 4 wk] to 80 mg TID, as tolerated) or PBO plus stable EPO for 16 wk. In a posthoc analysis, analysis of covariance (with etiology as a factor and baseline 6-min walk distance [6MWD] as a covariate) assessed differences vs PBO at wk 16.
Results: Baseline variables were similar among groups of pts (Table). All measured outcomes improved significantly with SIL treatment vs PBO in IPAH pts; positive trends occurred in PAH-CTD pts. (Table). Regardless of etiology, more PBO pts discontinued treatment (17.3% vs 10.3% for IPAH; 18.5% vs 3.7% for PAH-CTD); the difference significantly favored SIL in PAH-CTD ($P<0.0001$). Adverse events more common with SIL (vs PBO) included headache, flushing, and gastrointestinal effects for either etiology.
Conclusion: Sildenafil was well tolerated and significantly improved all measured outcomes in IPAH. PAH-CTD pts trended toward improvement despite low pt numbers in this posthoc analysis.

P1180 Sildenafil therapy for patients with porto-pulmonary hypertension and pulmonary arterial hypertension associated with HIV infection

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Purpose: Sildenafil, an orally active phosphodiesterase type-5 inhibitor, is effective in patients with idiopathic pulmonary arterial hypertension (PAH) and PAH associated with connective tissue diseases. We assessed the effects of sildenafil in patients with PAH associated with portal hypertension (Po-PAH) and with human immunodeficiency virus infection (HIV-PAH).
Methods: Between February 2004 and December 2010, 33 patients with Po-PAH and 22 patients with HIV-PAH received sildenafil [mean age 46±9 years; WHO functional class I (15%), II (50%), III (31%) and IV 4%)]. At baseline and after a mean treatment period of 4.6±3.2 months, patients underwent 6-minute walk distance (6MWD) assessment and right-heart catheterization.
Results: Sildenafil dose was 10 mg tid in 9 HIV-PAH patients (due to concomitant highly active antiretroviral therapy); 20 mg tid in 42 patients and 40 mg tid in 4 patients. An increase in 6MWD was observed: from 467±107 m at baseline to 516±102 m after sildenafil treatment ($p<0.001$). Mean hemodynamic parameters are presented in the table. No significant adverse events have been reported.

Hemodynamic parameters

	RAP (mmHg)	mPAP (mmHg)	mSAP (mmHg)	CI (L/min/m^2)	PVR (WU)	MVO2 (%)
Baseline	8±6	48±9	92±13	3.0±0.7	7.8±3.3	63±12
Sildenafil	6±4	41±8	91±13	3.7±0.9	5.2±2.2	71±8
p	0.004	<0.001	0.4	<0.001	<0.001	<0.001

RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; mSAP, mean systemic arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; MVO2, mixed venous oxygen saturation.

Conclusions: Sildenafil treatment of patients with Po-PAH and HIV-PAH is associated with improvements in exercise capacity and hemodynamic parameters. The effects of sildenafil in these subsets are similar to those observed in patients

Abstract P1175 – Table 1

Characteristic	IPAH			PAH-CTD		
	Baseline PBO (n=104)	Baseline SIL (n=107)	Treatment Difference at Wk 16, SIL – PBO (LOCF)	Baseline PBO (n=27)	Baseline SIL (n=27)	Treatment Difference at Wk 16, SIL – PBO (LOCF)
Women, n (%)	80 (77)	85 (79)	–	22 (81)	25 (93)	–
Age,* y	47±13	46±13	–	50±12	54±12	–
Mean (range) PAH duration, y	5.0 (0.3–37.2)	4.2 (0.3–25.8)	–	4.5 (0.5–13.1)	3.7 (0.3–8.8)	–
6MWD,* m (n)	354±72 (94)	354±65 (104)	31.1†	329±74 (25)	333±83 (27)	7.7
Functional class I / II / III / IV, %	2 / 27 / 68 / 3	1 / 26 / 65 / 8	26†§	0 / 28 / 68 / 4	0 / 23 / 69 / 8	3§
mPAP,* mmHg (n)	52±12 (81)	55±10 (93)	–4.2‡	44±10 (21)	45±10 (24)	–2.5
Pulmonary vascular resistance, dyn·s/cm^5 (n)	770±342 (55)	884±357 (75)	–187.6†	536±235 (18)	692±245 (16)	–116
Right atrial pressue, mmHg (n)	8.1±4.8 (81)	9.0±5.3 (93)	–1.7†	7.0±4.5 (21)	8.5±5.5 (24)	–3.4†
Cardiac index, L/min/m^2 (n)	2.7±0.8 (61)	2.6±0.7 (75)	0.5†	3.4±0.8 (18)	2.7±0.7 (17)	0.2

LOCF = last observation carried forward; mPAP = mean pulmonary arterial pressure. *Mean ± SD; †$P<0.05$; ‡$P<0.0001$; §Percentage of pts improving ≥1 FC vs baseline.

with other forms of PAH; no important drug related adverse events have been detected.

P1181 15 year experience in pulmonary hypertension due to congenital heart disease before and after targeted therapies: the durability of the right ventricle in this disease

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Purpose: Pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) is characterized by severe increase in pulmonary pressure and resistance with relatively preserved RV function and significantly better prognosis compared to idiopathic PAH. The purpose of this study was to examine the 15 year single-center experience in this population before and after use of PAH targeted therapies.
Methods: Between 1995 and 2011, 75 patients, aged at diagnosis 21±16 years, with PAH due to CHD were followed at our center. Diagnoses were: atrial septal defect 3 patients, ventricular/atrioventricular septal defect and/or arterial duct 30, complex CHD 37, Fontan 5. Five patients had Down syndrome while 20 had previous heart surgery. Patients were followed with clinical exam, EKG, echocardiogram, 6-min walk test and cardiorespiratory exercise test every 6 months with laboratory tests every 3 months.
Results: Over 15 years (mean follow-up 8±5 years) 96% of patients received PAH targeted therapy after 2002, initially monotherapy with second therapy added in 8 patients due to clinical worsening (3 patients improved, 5 progressed to death). Most (75%) patients remained stable clinically (WHO Class II) and in exercise capacity, while 14 (19%) deteriorated gradually to Class III. All stable patients had no clinical or echocardiographic signs of RV failure nor did they require treatment for it despite the long follow-up. There were 14 (18.6%) deaths (5 sudden, 9 due to worsening RV failure) at age 27±19 years, 2.9±2.3 years after initiation of therapy. PAH therapy was discontinued in 2 patients after surgical and interventional treatment respectively. All Fontan patients improved significantly with PAH therapy and are expected to discontinue it in the future.
Conclusions: Patients with PAH due to CHD, especially in the era of the new PAH targeted therapies, remain more stable with better prognosis than idiopathic PAH without significant RV failure over long follow-up periods, possibly because of RV adaptation since fetal life. Still, PAH due to CHD remains a complex disease with significant mortality and morbidity. Close follow-up and individualization of therapy seems critical for these patients' quality of life and long-term survival.

P1182 Current era survival of patients with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD)

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Purpose: The clinical classification of congenital heart disease (CHD) causing PAH has been updated in the recent ESC-ERS Guidelines and includes 4 different groups: Eisenmenger's syndrome (ES); PAH-CHD associated with systemic-to-pulmonary shunts (S/P); PAH with small defects (SD); PAH after corrective cardiac surgery (CS). The aim of this study is to compare the current-era survival in these different clinical sub-groups of PAH-CHD.
Methods: PAH-CHD patients followed in a single center from January 1998 to December 2010 were included. Treatment was estabilished according to the available PAH guidelines including combination therapy (CombT) of approved specific drugs. Kaplan-Meier survival curves were assessed and compared by Log-rank test according to the different clinical sub-groups of patients with PAH-CHD.
Results: 180 patients (mean age 46±15 y; 60% female) with PAH -CHD were included. According to the different clinical sub-groups 85 had ES (47±13 y); 37 S/P (47±16 y); 14 SD (38±21 y); 44 CS (42±17 y). ES patients had the higher baseline pulmonary vascular resistance and the lower exercise capacity. Seventysix percent of patients were treated with PAH approved drugs, 42% were treated with CombT. Kaplan-Maier survival rate at 1, 5 and 10 years after the diagnostic right heart catheterization is reported in the table.

Kaplan-Meier survival rate

	ES	S/P	SD	CS
1 Year	96%	100%	93%	98%
5 Years	88%	92%	80%	79%
10 Years	78%	87%	80%	68%
P vs CS	0.02	0.02	0.8	–

Conclusion: In the current era of targeted therapies for PAH, PAH-CHD patients have a better survival as compared with the other types of PAH. However, the survival of the different clinical subgroups of PAH-CHD patients appears to be heterogeneous: CS patients have a worse long term survival rate as compared to ES and S/P patients. Previous cardiac corrective surgery represents a risk factor in patients with PAH-CHD.

P1183 Survival and prognostic factors in patients with incident systemic sclerosis-associated pulmonary arterial hypertension from the French registry

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Purpose: Pulmonary arterial hypertension (PAH) is one of the leading causes of death insystemic sclerosis (SSc). Management of patients with SSc-associated PAH (SSc-PAH) is rapidly evolving and recently reported survival is better than inhistorical cohorts (albeit still unsatisfactory). This study describes thecharacteristics and outcome of SSc patients enrolled in the multicentre FrenchPAH registry.
Methods: SSc patients (according to American College of Rheumatology and/or Leroy andMedsger's criteria) enrolled in the registry between January 2006 and November2009 were prospectively included if they had PAH confirmed by right heartcatheterization <1 yr prior to enrollment (incident patients). Patients withinterstitial lung disease (ILD) on high resolution computed tomography (HRCT)were included if forced vital capacity (FVC) >70%.
Results: 91/145 SSc patients were included; 81% were women. Mean age at PAH diagnosiswas 64±12 yrs, 86% of patients had limited cutaneous SSc, 81% were in New YorkHeart Association functional class (NYHA FC) III or IV (19% in NYHA FC II), 14%had ILD on HRCT, mean FVC and the ratio of diffusing capacity of the lung forcarbon monoxide/alveolar volume (DLCO/VA) were 91±20% and 54±21% of predictedvalues, respectively. At baseline, mean 6-minute walk distance (6MWD) was 267±117m, mean pulmonary arterial pressure (mPAP) was 40±10mm Hg, mean cardiacindex was 2.6±0.8 L/min/m^2 and mean pulmonary vascular resistance (PVR) was 670±351 dyn sec cm^{-5}. Mean brain natriuretic peptide (BNP) concentration was 447±549 ng/L. Mean follow up was 1.7 years with 24 deathsobserved; overall survival was 90%, 76% and 54% at 1, 2 and 3 years, respectively. Univariate analysis identified male gender (hazard ratio [HR]:2.44), age (HR: 1.044), desaturation after 6-minute walk test (HR: 0.93), totallung capacity (HR: 0.97), PaO2 (HR: 0.96) and cardiac index (HR: 0.52) as factors prognostic of survival. Other parameters did not reachstatistical significance ($p<0.05$), including NYHA FC, PVR, SSc subtype, 6MWD, BNP, DLCO/VA and mPAP. Multivariate analysis was not performed, due tothe high number of variables and low number of events.
Conclusions: These results confirm the poor prognosis for incident SSc-PAH patients even in the modern era. As with idiopathic PAH, gender and age appear to be important prognostic factors. Cardiac index, but not mPAP, had a significant impact on survival. For the first time, PaO2 at rest and desaturation during exercise were shown to be significant prognostic factors in SSc-PAH. Longer follow up is needed to for a more complete analysis.

P1184 Long term results of ablation of arrhythmia substrate in pulmonary hypertensive patients

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Modern drug therapy improved survival of pulmonary hypertensive patients. Pulmonary hypertension (PH) leads to significant changes in right heart anatomy, which may result in increased incidence of arrhythmias. Supraventricular arrhythmias are an increasing clinical problem in PAH patients nowadays. The pharmacological treatment is very limited in this group of patients. Previous observations showed a failure of restoration and maintenance of sinus rhythm as a factor related to higher mortality in patients with PH.
The aim of the study was to present results of ablation of arrhythmia substrate in PH patients.
15 consecutive patients (3men, aged 47,8±14) with PH were qualified to radiofrequency ablation (ARF) due to recurrent symptomatic arrhythmia: atrial tachycardia (AT) -3pts, AVNRT -3pts, typical AFl -5 pts, AT coexistent with AFl – 5pts. Before ablation 2 pts presented symptoms of NYHA class II, 11pts NYHA class III and 2pts NYHA class IV. In all cases of AVNRT ARF was performed in classical way only with fluoroscopic control. Electroanatomical mapping system was used in all other cases. Transseptal puncture was abandoned due to high risk of refractory hypoxemia in course of uncontrolled right to left shunt. In 12 of 15 patients rotation of the heart was observed (approx. 20 to 30° to the left –mostly due to enlarged right atrium).
9 patients underwent ablation of all arrhythmias inducible in EP-study, in others at least one of recorded arrhytmias was ablated. In 9 of 15 patients clinical status improved immediately after ARF (defined as 1 step down in NYHA class). In others NYHA class did not change (including two patients with successful ARF). During 18,6±14,4 months of follow-up arrhythmia recurred in 8 patients. 2 pts died during follow up: 1 pt due to haemoptysis, 1 pt died suddenly. In 5pts recurrence of arrhythmia was connected with acute hemodynamic decompensation.
Conclusion: Radiofrequency ablation of arrhythmia substrate in pulmonary hypertensive patients although difficult is eligible and seems to be beneficial even without complete ablation of all arrhythmias induced during EP-study.

MODERATED POSTERS
UNDERSTANDING AND MANAGEMENT OF MYOCARDITIS: RECENT ADVANCES

P1185 Deficiencies in natural killer cell response result in a poor outcome of virus-induced inflammatory cardiomyopathy

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Purpose: Enteroviruses, such as coxsackieviruses of group B (CVB) are known to induce severe acute and chronic forms of myocarditis, leading in susceptible patients to congestive heart failure and sudden cardiac death. In a model of coxsackievirus B3 (CVB3) myocarditis we found that dependent on genetic factors mice resistant to chronic myocarditis (C57BL/6, H-2b) but not mice susceptible for ongoing myocarditis (ABY/SnJ, H-2b) can limit virus spread and cardiac damage during acute infection. To investigate the phenotype and functionality of natural killer (NK) cells and their role in virus elimination and disease progression we studied the cytotoxic potential of NK cells and various subsets in these two mouse strains.
Methods and results: The functional analysis of NK cells in the two mouse strains was studied by application of a degranulation assay. We found that compared to C57BL/6 mice, A.BY/SnJ mice (both H-2b) reveal significant lower numbers of NKp46+CD107a+ NK cells at a naïve state and day 3 post infectionem (p.i.) with CVB3, suggesting impaired cytotoxicity in ABY/SnJ mice ($p<0.001$). Interestingly, whereas both mouse strains illustrated comparable levels of NKp46+ NK cells, A.BY/SnJ mice showed significant higher levels of NKp46 expression on a per cell basis in spleen, peripheral blood and lymph nodes in FACS measurements. Also, ABY/SnJ mice revealed significantly higher numbers of CD27lowCD11blow and CD27high CD11blow NK cells at a naïve state and days 3 and 8 p.i. In contrast, resistant C57BL/6 mice showed de novo significant higher levels of mature CD27lowCD11bhigh NK cells which remained elevated until day 8 p.i. ($p<0.001$). We further compared the expression of the NKG2D receptor, one of the most potent activating natural killer cell receptors. We detected a comparably higher percentage of NKp46+NKG2D+ cells in C57BL/6 mice at a naive state as well as after infection with CVB3. In vivo neutralization of NKG2D by specific antibodies resulted in severely increased myocardial damage with enhanced infiltration of mononuclear cells, such as macrophages and T lymphocytes, and increased viral replication in C57BL/6 mice compared to CVB3-infected animals without anti-NKG2D treatment. The findings were confirmed in NKG2D deficient mice.
Conclusion: An effective functionality of NK cells is required to prevent a chronic course of myocarditis. NK cells derived from C57BL/6 mice resistant to chronic myocarditis were found to be more effective in target killing and in viral clearance – and this effect is likely to be dependent on the NKG2D receptor.

P1186 Adiponectin is a negative regulator of antigen-activated T cells

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Aim: Adiponectin (APN) is an adipocytokine exerting a variety of immunomodulatory effects. We have recently shown that high APN expression in patients with inflammatory cardiomyopathy (DCMi) and mice with autoimmune myocarditis (EAM) indicates better outcome and inflammation control. T cells play an important role in the pathophysiology of DCMi and myocarditis and the number of myocardial CD3+ cells in patients with DCMi and high APN expression is significantly diminished. Therefore, in the present study the effects of APN on T cell number and function were investigated.
Methods: T cells were isolated from healthy donors or wild-type and APN-/- mice following Coxsackie B virus infection/EAM. Costaining of Adiponectin receptors (APNRs) with clathrin and CTLA4/TIRC7 was determined by confocal fluorescence microscopy. Antigen specific T cell expansion was assessed by ex vivo expansion assays. Apotptosis was determined by Annexin V expression, proliferation of T cells was assessed by BRDU-Incorporation.
Results: Less than 10% of human peripheral T cells express APNRs on their surface. However, T cells store APNRs in intracellular compartments and react with ERK phosphorylation to APN stimulation. APN receptors in T cells co-localize with immune regulatory molecules such as CTLA-4 and TIRC7 within Clathrin-coated vesicles. After antigen-specific stimulation APNRs are rapidly transferred to the surface of antigen-specific CD137+/CD4+ and CD137+/CD8+ T cells. Incubation with APN resulted in significantly diminished expansion of antigen-specific CD137+ and cytokine (TNFα, IFNgamma, IL-2)-producing T cells following SEB as well as influenza/coxsacki-B antigen stimulation ($p<0.01$), while no effect was observed on CD137- cells. Mechanistically, APN significantly enhanced apoptosis ($p<0.05$) and inhibited proliferation following Coxsackie B and influenza antigen stimulation in CD137+ cells ($p<0.01$). Furthermore, APN directly inhibited cytokine production in response to antigen stimulation as assessed by TNFα and IFNgamma production ($p<0.01$). In line with the in vitro data, APN-/- mice had higher frequencies of antigen-specific T cells upon Coxsackie B infection. Moreover, APN gene transfer inhibited T cell expansion in EAM mice.
Conclusion: Thus, similar to CTLA-4 and TIRC7, AdipoRs are constitutively available intracellularly in T cells to be translocated to the cell surface upon TCR engagement. Our data implicate AdipoRs as novel negative T cell regulators preventing excessive T-cell activation thereby confining myocardial inflammation.

P1187 Is electron microscopy useful for analysis of endomyocardial biopsies of patients with new-onset unexplained dilated cardiomyopathy?

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Background and aim of the study: Dilated cardiomyopathy (DCM) may represent a sequela of myocardial inflammation evoked by cardiotropic viral or nonviral infection. Currently, polymerase chain reaction (PCR) is almost exclusively used to analyse endomycardial biopsy (EMB) specimens of patients with DCM in order to detect a genome of persistent infectious agent. However, PCR is usually targeted to a limited number of microorganisms. Electron microscopy (EM) is an established but laborious and rarely used method for detecting of infectious agents in examined specimens. Therefore we aimed to compare the results of PCR and EM analyses of EMB specimens obtained from the patients with new-onset unexplained DCM.
Methods: In 63 patients (52±10 years; 17 women) with new-onset unexplained DCM (LV ejection fraction 26±12%, symptoms of heart failure lasting less than 12 months), EMB specimens were studied by PCR technique as well as by EM.
Results: By using PCR, genome of infectious viral or nonviral agent was documented in 32 subjects (51%). In comparison, particles of infectious agents were found in 53 patients (84%) by using EM. Out of the PCR-negative subjects, viral agents belonging to herpesviridae family were present in 14, parvoviridae family in 12 and picornaviridae in 12 patients. Moreover, EM detected particles of mycoplasma in 4 subjects and of chlamydia and borrelia each in one patient.
Conclusions: In one third of the EMB of the patients with new-onset DCM, infectious microorganims were found only by using EM compared to PCR analysis. This finding may be of great importance regarding the possibility of specific treatment of DCM.

P1188 Therapy with granulocyte colony-stimulating factor in the chronic stage, but not in the acute stage, improves cardiac function via nitric oxide in experimental autoimmune myocarditis in rats

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Purpose: Granulocyte cology-stimuating factor (G-CSF) could mobilize multipotent progenitor cells from bone marrow into peripheral blood, and may improve ventricular function and remodeling after myocardial injury. We investigated serial efficacy of G-CSF therapy upon experimental autoimmune myocarditis in rats treated with and without the inhibition of nitric oxide (NO) with the analyses of cardiac function and tissue regeneration.
Methods: A rat model of porcine myosin-induced myocarditis was used. After the immunization of myosin, G-CSF (10 μg/kg/day) or saline was injected intraperitoneally daily on days 0-21 in Experiment I and on days 21-42 in Experiment II. Additional myosin-immunized rats were orally given with 25 mg/kg/day of NG-nitro-L-arginine methylester (L-NAME), an inhibitor of nitric oxide synthase (NOS), in each experiment. At the end of each experiment, hemodynamic study by echocardiography and pathologic study were performed (each group; n=15-20).
Results: In Experiment I, G-CSF treatment with and without L-NAME aggravated cardiac pathology associated with enhanced G-CSF receptor expression and superoxide production. Compared with saline injection in Experiment II, G-CSF treatment significantly improved not only the severity of myocarditis with enhanced von Willebrand factor and vascular endothelial growth factor expression, less myocardial macrophage infiltration, and less myocardial fibrosis but also left ventricular ejection fraction associated with lower heart weight/body weight ratio. In the rats with myocarditis treated with G-CSF associated with oral L-NAME treatment in Experiment II, the severity of myocarditis was not reduced, and the cardiac function was not improved. Myocardial c-kit+ cells were demonstrated only in G-CSF treated group in Experiment II, but not in other groups.
Conclusions: G-CSF has differential effects on experimental autoimmune myocarditis with time. The overwhelming superoxide production by G-CSF administration in the acute stage may fail to improve the condition. G-CSF therapy improved cardiac function in the chronic stage possibly through the acceleration of healing process and myocardial regeneration via NO system.

P1189 Pandemic H1N1 influenza is more commonly associated with reduced left ventricular performance than seasonal influenza infection in children

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Background: Influenza infection can affect cardiac function. Recent pandemic 2009 H1N1 influenza A virus infection (pH1N1) has been reported to be associated with severe myocardial involvement. However, there is little information whether pH1N1 is more commonly associated with left ventricular (LV) dysfunction than seasonal influenza virus infection. Myocardial performance index (MPI) combining both systolic and diastolic phases of cardiac cycle has been shown to be useful for assessing global LV function. The purpose of the study is to compare MPI in pH1N1 infected children with that in children with 2010 (November)-2011 (January) seasonal influenza A infection (H3N2).
Methods: A total of 141 children aged 5-12 years, 53 children (8.5±1.6years) with established diagnosis of 2009 pH1N1, 38 children (8.1±1.4 years) with 2010 (December)-2011 (January) H3N2, and 50 age-matched controls, was studied. Echocardiography with tissue Doppler imaging was performed at the acute stage of infection. Cardiac dimensions, LV end-diastolic volume, and LV ejection fraction were measured. Using tissue Doppler imaging, isovolumic relaxation time, isovolumic contraction time, and ejection time were measured and MPI was calculated.
Results: Cardiac dimensions and LV ejection fraction were similar among controls, pH1N1 infected children group,and H3N2 infected children group ($p>0.05$). There was no statistically significant difference in isovolumic relaxation time and MPI between controls and H3N2 infected children. However, compared with controls and H3N2 infected children, isovolumic relaxation time was significantly prolonged (45±17 msec vs. 34±12 msec and 35±11 msec, $p<0.05$) and MPI was significantly higher (0.43±0.08 vs. 0.38±0.07 and 0.37±0.09, $p<0.05$) in pH1N1 infected children.No significant valvular disease or pulmonary hypertension was found. Pericardial effusion was observed in a patient (1.9%) with pH1N1.
Conclusions: Our findings raise the possibility that pandemic H1N1 influenza ismore commonly associated with reduced LV performance than seasonal influenza A infection.

P1190 Magnetic resonance imaging or endomyocardial biopsy for the diagnosis of myocarditis and viral heart disease

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Purpose: How precise is the diagnostic yield by cardiac magnetic resonance imaging (CMRI) when compared to heart catherization and endomyocardial biopsy (EMB)?
Patients (pts): Head to head comparison of CMRI and EMB in 343 pts with clinically suspected inflammatory dilated cardiomyopathy (mean age 51,1 y, 217 m, 126 f).
Methods: CMRI criteria for (peri)myocarditis were the 3 Lake Louise Criteria 1) late gadolinium enhancement (LGE), 2) T1 gRE = gE (myocardium)/gE (skeletal muscle) >4, 3) T2-edema signal intensity(SI) comparing heart and skelettal muscle >1,9 and 4) pericardial effusion (PE). EMBs from the left ventricle were analysed for >14 cells/mm^2 (WHF) and for the genomes of entero-, cytomegalo-, Ebstein Barr, Influenza-, Parvo B19-, herpes humanus 6, herpes simplex and adeno virus, chlamydia pneumoniae, borrelia Burgdorferi in the EMB. The number of positive items (1 to 4) by CMRI was compared to the presence of inflammation and/or virus in the respective EMB (EMB1 = all inflammation; EMB 2 = inflammation + virus, EMB 3: inflammation without virus).
Results: EMB 1 was positive in 60 pts, but only 3 pts demonstrated all 4, 14 pts 3, 11 pts 2 and 24 pts 1 CMRI myocarditis criterium. EMB 2(I+v) was observed in 25 pts, but only 2 pts demonstrated all 4, 6 pts 3, 8 pts 2 and 8 pts 1 CMRI criterium of inflammation. Inflammation in EMB without virus (EMB 3) was observed in 35 pts, but positive for 4 CMRI-criteria was only 1 pt, 3 MRI-criteria were positive in 8 pts, 2 criteria in 3 pts, and one criterium in 16 pts. Viral persistence without inflammation did not correlate to CMRI.
Conclusions: CMRI according to the Lake Louise criteria + PE give a fair information on inflammation in the myocardium but is unable to correlate mere viral persistence alone. It cannot substitute EMB in the diagnosis of viral heart disease.

P1191 Adiponectin inhibits Toll-like receptor 4 mediated cardiac inflammation and injury

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Purpose: Adiponectin (APN) is an adipocytokine that is also expressed in cardiac myocytes and mediates immunomodulatory and cardioprotective effects in inflammatory cardiomyopathy. Toll-like receptor 4 (TLR4) has been shown to be a major contributor for the induction and progression of autoimmune myocarditis. Here, we investigated whether APN can inhibit cardiac inflammation and injury by interfering with TLR4 expression and TLR4 mediated signal transduction.
Methods: Effects of APN in an animal model of Experimental autoimmune myocarditis (EAM) were studied following adenoviral gene transfer. Cardiac gene expression and apoptosis at the inflammatory peak of EAM were analyzed by PCR-Array and TUNEL. In vitro gene expression was measured by RT-PCR, ELISA or FACS. NFkB activation was analyzed by ELISA. Immune cell migration was quantified by FACS. Cardiac myocyte apoptosis was measured by TUNEL.
Results: APN overexpression in EAM induced a marked downregulation of cardiac TLR4 expression associated with significantly reduced expression levels of key players of the immune response downstream of TLR4 such as TNFα, IFN gamma, IL-6, IL-17α, CCL-2 and ICAM-1. Moreover, quantification of apoptosis demonstrated that APN gene transfer reduced cardiac injury in EAM. In vitro APN significantly attenuated NFkB activation after TLR4 ligation in cardiac myocytes and fibroblasts as well as in dendritic cells and CD19+ and CD14+ immune cells. Moreover, APN markedly inhibited the expression of an inflammatory phenotype downstream from TLR4 in cardiac cells as assessed by attenuated TNFα, CCL-2 and ICAM-1 expression and in immune cells as reflected by reduced TNFα and IFN gamma expression. Consequently, APN diminished splenocyte migration towards TLR4 stimulated cardiac myocytes and fibroblasts. Finally, APN significantly inhibited apoptosis of TLR4 stimulated cardiac myocytes after cocultivation with splenocytes.
Conclusions: APN overexpression significantly interfered with TLR4 expression and TLR4 mediated signal transduction in EAM. In vitro APN attenuated the development of a TLR4 mediated proinflammatory phenotype in cardiac and immune cells resulting in reduced immune cell triggered damage to cardiac cells. Mechanistically, APN inhibits TLR4 mediated signal transduction by reducing activation of the transcription factor NFkB. Our observations comprehensively indicate that APN protects against TLR4 mediated cardiac inflammation and injury and thus represents a new therapeutic option for inflammatory myocardial diseases.

P1192 Lupus myocarditis: a contemporary case series

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Objective: Lupus myocarditis is an uncommon but serious manifestation of systemic lupus erythematosus (SLE). We describe the clinical phenotype and outcomes of treatment in a series of hospitalized patients, MN who carried a final diagnosis of lupus myocarditis between January 1st 1999 and December 31st 2009.
Methods: A diagnosis database as well as a pathology database, searched for SLE plus either myocarditis, cardiomyopathy or congestive heart failure, returned 634 patients. Chart review was performed, 24 patients were included in the study and descriptive analysis was performed.
Results: 79% of patients were female and 82% were Caucasian. The mean age was 47.6±20.4 with a mean follow up of 9.2±6.1 months. The frequency of anti-RNP was 62%, compared with 23-40% in the literature. SS-A was also higher in our series, at 69% compared to 25-40%. The most common echocardiographic findings were reduced LVEF (LVEF <45%), found in 78% and wall motion abnormalities, found in 70%. The initial mean LVEF was 33.8%, which improved to 49.5% after a mean of 7.2 months. Five of the six patients who underwent CMR had delayed gadolinium enhancement of either the myocardium or pericardium or both. Nine patients received 500mg - 1g methylprednisolone per day for 1-5 days with subsequent steroid tapering. Twelve patients received 40-80 mg methylprednisolone or equivalent for 5-10 days followed by steroid taper. One patient died of cardiogenic shock during hospitalization, with two others dying within one year of follow up, one from congestive heart failure and the other after withdrawal of care.
Conclusions: To our knowledge we present the largest series of lupus myocarditis patients described in the literature. Clinically, this study helps us to realize, that in patients with lupus, or suspected lupus, one should have a high index of suspicion for myocarditis. A higher frequency of elevated SS-A and anti-RNP in our series than is reported in the literature among patients with active SLE suggests a possible association between these antibodies and lupus myocarditis. Echocardiography is a useful initial investigation for patients suspected of lupus myocarditis, but not specific enough to confirm the diagnosis. Echo is also highly effective in monitoring subsequent response to therapy. However due to the non-specific echo findings in lupus myocarditis, cardiac MRI is the modality of choice for diagnosis, and patients should be referred early to CMR in this clinical setting. High dose steroids appeared to be as effective as pulse dose in the treatment of lupus myocarditis.

LEFT VENTRICULAR LEADS COMPLICATIONS: AN UNDERESTIMATED ISSUE?

1246 Long-term complications related to biventricular defibrillator implantation: rate of surgical revisions and impact on survival

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Purpose: Long-term data on device-related untoward events in patients receiving defibrillators for resynchronization therapy (CRT-D) are lacking. We quantified the frequency and nature of long-term complications and repeat invasive procedures in current clinical practice, and examined possible predictors of device-related events and their association with long-term patient outcome.
Methods: We analyzed data from 3253 patients who underwent successful implantation of CRT-D and were followed up for 18 months (median, interquartile range 9 to 30) in 117 Italian centers.
Results: Device-related adverse events were reported in 416 patients and, specifically, surgical interventions for system revision were described in 390 patients. Four years after the implantation procedure, about 50% of patients underwent surgical intervention for device-related events and 15% of patients had unanticipated events (e.g. device-related infections, lead dislodgments). No independent predictors of infections were identified among baseline clinical characteristics. However, more frequent infections were noticed after device replacements (1.8 per 100 patient-years) than after first implantations (0.9 per 100 patient-years, p=0.049). Left ventricular lead dislodgements were reported at a rate of 2.3 per 100 patient-years and were predicted by longer fluoroscopy time and higher pacing threshold on implantation. Device-related adverse events were not associated with a worse clinical outcome; indeed, the death rate was similar in patients with and without surgical revision (2.4 versus 4.1 events per 100 patient-years, p=0.090).
Conclusions: Long-term complications are not rare in current clinical practice of CRT-D and are frequently managed by surgical intervention for system revision. However, a worse clinical outcome does not seem to be associated with these events.

1247 Phrenic stimulation in patients with cardiac resynchronization may be resolved by electronic repositioning: the ERACE trial

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Background: Nowadays cardiac resynchronization (CRT) is an established therapy for heart failure patients. Despite the development of various sophisticated left ventricular lead technologies, phrenic nerve stimulation (PNS) remains an adverse effect observed in a substantial number of patients.
Aim of the study: Modern CRT devices provide the option to avoid PNS not only by anatomic repositioning but also by software based adaption of the pacing configuration. The ERACE study was designed to evaluate the incidence of PNS in a CRT population and to determine how often left ventricular (LV) lead relocation can be avoided by the so called "electronic repositioning" (ER).
Methods and results: In this study patients (pts) indicated for a first CRT defibrillator with a bipolar LV lead and the option of ER could be enrolled. Primary endpoint was the efficiency of ER determined by the frequency of PNS with the standard pacing configuration - LV tip to RV coil - avoidable by ER. PNS and pacing parameters were evaluated during implant, predischarge and first routine follow up (FU) using the four different pacing configurations available by ER (LV tip or ring to RV coil, LV tip to ring or inverse).
In total 305 pts (82.3% male, 65.5±9.2 years) were enrolled in 54 German and French centers. The majority of the patients was in NYHA III (84.2%) and had a LV ejection fraction ≤30% (84.1%, mean 25.6±6.2%), with a mean QRS width of 154.9 ms ± 26,9 ms (mean/SD); 43.4% of the patients had ischemic cardiomyopathy. The median follow-up (FU) period after discharge was 116 days.
In the standard pacing configuration PNS was inducible in 18.9%/25.6%/24.6% of the pts at implant/predischarge/FU respectively, resulting in 32.1% of the pts presenting at least once with inducible PNS. The safety margin between LV pacing and PNS threshold was smaller than 0.5 V at 0.5 ms in 2.4%/3.3%/3.3% of the pts, corresponding with a total rate of 6.8% during the FU period. In the finally chosen configuration clinical relevant PNS occurred in 0.7%/0.7%/0.4% when using ER. In total 5 patients required anatomical repositioning due to PNS.
Conclusion: The incidence of phrenic stimulation in CRT patients is considerable. In this study diaphragmatic irritation could be avoided in the majority of the patients by means of a non-invasive pacing reconfiguration. Therefore the use of this feature should be considered for CRT patients.

1248 Transvenous coronary sinus lead extraction: procedural outcomes and predictors of mechanical dilatation

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Purpose: Only limited experience with coronary sinus (CS) leads extraction has been reported. We aimed to evaluate procedural outcomes and implications of CS lead extraction, focusing on necessity of mechanical dilatation (MD) and predictors, in the event that manual lead traction (MT) was ineffective.
Methods: In our database, we identified 145 consecutive patients (69±10 years, 121 male), with a total of 147 CS pacing leads, who underwent transvenous removal between January 2000 and March 2010.
Results: All but one (99%) CS leads (time from implant 29±25 months) were successfully removed; MT was effective (MT group) in 106 patients (72%) and ineffective in 41 patients (28%), for whom MD was necessary (MD group). In multivariate analyses, prior cardiac surgery (OR 2.4, 95% CI 1.01-5.9, p=0.05), unipolar lead design (OR 3.7, 95% CI 1.56-8.33, p=0.003) and non infective procedural indication (OR 5.3, 95%CI 1.9-14.7, p=0.001) resulted independent predictors of MD (p<0.0001).
Five (3.4%) complex procedures occurred, requiring a transfemoral approach (TFA) or a repeated procedure. No deaths occurred. Among complications (3.4%), only one major (0.7%) was observed (i.e. cardiac tamponade treated by pericardial drainage) after MT. No predictors of complications were identified.
Conclusions: CS leads can be safely and effectively removed almost with MT alone, even if MD may be required in about 30% of cases. Preoperative predictors include a prior cardiac surgery, an unipolar lead design and a non infective indication. Complications are rare but unpredictable and may be observed also after MT alone.

1249 Left ventricular leads transvenous extraction: 6-year single-centre experience

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Purpose: In the recent years, the increasing use of cardiac resynchronization therapy (CRT) device has increased the number of device-related complications and then the need for removal. Aim of this study is to evaluate safety, efficacy and techniques of left ventricular (LV) leads extraction.
Methods: From May 2004 all consecutive patients with CRT devices (69 pts, 69.5% male, mean age 67.4 yrs, range 49-91) who underwent transvenous lead extraction were enrolled. The procedures were initially performed with traction (simple or mechanical on a locking stylet) and, in case of failure, with the use of mechanical devices or powered sheaths, whose choice was based on the first operator experience. All the procedures were performed in the EP laboratory with a surgical backup. All leads implanted for less than 6 months were excluded from the analysis. Procedural success was defined asextraction of all implanted intravascular materials.
Results: Sixty-nine patients underwent extraction of 72 LV leads. The mean time from the date of implantation to the extraction was 68.5±9.7 months. The extraction was effective in all approached leads (100%) and it was successfully made with traction method using the venous entry site for 62/72 leads (86.1%) while mechanical devices were necessary for 10/72 leads (13.9%) (p<0.01). Only in one case a femoral workstation was needed because of lead fracture. No minor complications occurred. Only one major complication was observed: a cardiac tamponade successfully treated with pericardiocentesis in a patient who underwent a challenging laser-assisted procedure consisting in the extraction of 2 LVleads, 1 ICD and 1 right atrial lead. No deaths occurred.
Conclusions: In our experience transvenous extraction of left ventricular leads is a safe, feasible and highly effective procedure. It can be successfully performed with traction method and the use of mechanical devices or powered sheaths is rarely necessary.

1250 Endocardial leads mutual abrasions - important findings among explanted leads

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Introduction: External tube of permanent lead abrasions in the crush syndrome mechanism, abrasion against the PM/ICD case in the pocket are commonly known phenomenon. Its possibility with participation of tricuspid valve apparatus were described too. Recently SJM announced the possibility of silicone ICD

lead abrasion in intracardiac region; there were no similar elaborations on PM silicone lead abrasions.
Material/method: Examination of 1212 endocardial leads removed in 700 pts. extracted transvenously by mechanical systems (Byrd dilators). Macroscopic examination presented in 192 of them (177 pts), the abrasion of external lead insulation with exposure of metal wire in intracardiac part of leads. Lead abrasion were confirmed by microscopic examination.This phenomenon was associated with infective indications for lead removal, CS electrode implanted and presence of excess of implanted electrodes. The risk of lead abrasion increased with number of leads implanted, unnecessary lead loops presence, age of leads and number of intervention prior lead explanations. In multivariate analysis following factors were associated with lead abrasion: increased number of leads, implant duration, infective indications for system removal, presence of CS lead and excess of implanted leads. Intracardiac lead abrasion may have association with LDIE and probably reflects place of vegetations.
Results: See Table 1.

Table 1

	Lead abrasion:			P*
	Absent	Probable	Certain	
Number of patients	472	50	177	
Indications for lead extraction				
Non-infective indications	256 (56,0%)	15 (30,0%)	84 (47,5%)	
Local pocket infection	152 (32,3%)	19 (38,0%	32 (18,1%)	<0,001
Lead dependent endocarditis	55 (11,6%)	16 (32,0%)	61 (34,5%)	
Number of leads in heart before lead extraction (SD)	1,82±0,74	2,56±0,95	2,46±0,87	0,02
Number of extracted leads in one patient (SD)	1,51±0,70	2,35±1,31	2,30±1,06	0,05
CS (LA, VV) lead presence	58 (12,3%)	13 (26,0%)	59 (33,3%)	< 0,001
Overmuch of lead length in right atrium – too long loops or long loop in tricuspid valve	61 (12,9%)	19 (38,0%)	75 (42,6%	< 0,0001
Average age of extracted leads (in months)	66,8±54,7	116,8±59,2	97,1±61,4	0,0432

Conclusions: 1. Mechanical abrasions of silicone lead's insulation in the heart chambers resulted from mutual friction. 2. Implant duration, number of leads, CS leads presence and overlong lead's length (looping) are factors facilitating leads' abrasions.

1251 Left ventricular lead adverse events observed at 1 year follow up in the multicenter randomized FREEDOM trial

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Introduction: FREEDOM aimed to assess benefit of frequent optimisation of AV and VV delays over 12 months post CRT-D implant using an automated algorithm developed by St Jude Medical called QuickOpt™. FREEDOM also collected data related to complications. Data from large clinical trials detailing common challenges faced at implant and follow-up is sometimes not reported.
Methods: Patients were randomized (1:1) two weeks post CRT implant to frequent optimization (OPT) or control (CON) group. Implanters could choose any commercially available LV lead. In OPT patients, AV and VV delays were programmed using values suggested by the QuickOpt™ algorithm at 3 month intervals. CON patients had AV and VV delays optimised at one month according to standard of care. Patients were followed at 3, 6, 9 and 12 months post-CRT implant. Complications and actions taken to resolve them were recorded throughout the duration of the study.
Results: A total of 1647 patients (73.6% male, 66.7±11.2 years, 92.8% NYHA class III, LVEF 24.3±7.0% and QRS duration 152±27 ms) were enrolled and randomized. 1644 patients were followed for 11±3 months. Phrenic Nerve stimulation (PNS) occurred in 6% (95) of patients. 32% (30) required an invasive procedure, withdrawal of therapy, an epicardial lead or classed as "unresolvable"; 24% (23) were reprogrammed but with compromise (defined as programming output within 1V of pace threshold) and 37% (35) could be resolved by reprogramming. Event resolution for 7% (7) was given as "other" or "Not Known". 4% (69) of LV leads displaced, 74% (51) of which required an invasive procedure to resolve, 1 was resolved by reprogramming, in 8 the resolution was not reported, 1 was unresolvable, 4 were explanted and not replaced, 3 were switched off and 1 had an epicardial lead.
Conclusions: Despite major advances recently performed in LV Lead and CRT technologies, common challenges are still encountered in clinical practice, requiring additional costly, uncomfortable and time consuming invasive procedures. This leads to the consideration of new original LV leads, designed with multiple electrodes, offering the capabilities to manage complications, such as PNS, by simple reprogramming rather than re-intervention.

CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

1252 Unusual aortic sinus of valsalva reentry circuit sites of non-ischemic ventricular outflow tract tachycardia

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Background: Reentrant ventricular outflow tract (OT) tachycardia is rare in patients with non-ischemic heart disease. The mechanism of ventricular tachycardia (VT) arising from the region of the aortic sinus of Valsalva (ASOV) is usually focal, rather than reentrant. Consequently, less is known about reentrant circuits in the OT and the aortic sinuses. The purpose of this study was to evaluate existence of reentry circuits in these areas using entrainment mapping techniques.
Methods: We performed electrophysiological study in 53 consecutive patients with idiopathic or non-ischemic symptomatic VT arising from the OT. Eight of these patients were found to have VT of reentrant mechanism with 10 VT morphologies. VT was induced by programmed stimulation, entrainment mapping, electro-anatomical mapping (in two patients) and radiofrequency catheter ablation were performed. In 2 patients, although entrainment mapping could not be performed because of non-sustained VT, an inverse relationship was identified during initiation of VT. The mechanism of these 2 VTs was thought to be reentry.
Results: Pacing entrained the VT at 93 sites, 52 of which were determined to be in the reentry circuit based on matching of the post-pacing interval and VT cycle length. However reentry circuit site was not identified in 2 non-sustained VT, ablation terminated these VTs at left coronary cusp.
Of the reentry circuit sites, 6 were in the aortic sinus, 43 were below the aortic valve, and 3 were in the right OT below the pulmonary valve. Classification of reentry circuit sites identified 7 as exit, 1 as central-proximal, 19 as inner loop, and 25 as outer loop sites. Catheter ablation terminated VT at 4 out of the 6 aortic sinus sites and 4 out of the 46 OT sites (p=0.0002).
Conclusions: We definitively demonstrated involvement of the ASOV in OT reentrant tachycardia using entrainment mapping, and furthermore, were able to ablate the VT successfully based on reentry circuit localization.

1253 Variant of left ventricular outflow tract tachycardia requiring ablation from multiple sites

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Introduction: Idiopathic left outflow tract (LOT) ventricular arrhythmias (VAs) can originate from several structures. The correct identification of the site of origin LOT VAs is challenging and often several procedures are required to achieve success in these patients.
Methods: 116 patients consecutive patients undergoing LOT VAs ablation have been enrolled in this study. Thirty-nine patients (34%) were referred for a redo procedure after a previously failed ablation while the remaining presented for a first procedure.
All patients had frequents PVCs or VAs originating from the LVOT. Endocardial and epicardial access were obtained in all patients. Conventional mapping was performed manually in 86 cases (74%) and with the magnetic robotic system (Stereotaxis) in the remaining cases. Tridimensional mapping was obtained in all cases with the Carto System. The aortic cusp was mapped via a retrograde aortic approach. In all cases the coronary sinus was mapped. Ablation was performed with the magnetic irrigated catheter in the stereotaxis cases and with the standard 3.5 mm open irrigated ablation catheter in the manual cases.
Results: Out of the 116 patients, 15 appear to have multiple sites of equally early activation. This was observed in 10 pts presenting for a redo procedure (26%) and in 5 patients presenting for the first procedure (6%). The sites of early activation were the interventricular vein e/o anterior coronary sinus branches, the left coronary cusp, the level of the mitro aortic continuity, the subaortic valvular region, and the the epicardial left outflow tract. The early sites of activation were shorter when compared to the rest of the patient population (-38 msec±6 vs 26±3msec P<0.005). To achieve successful suppression of the LOT VAs radiofrequency energy had to be applied at all the early sites of activation. After a mean follow up of 21±5 months, all patients with multiple early site of activation remained free from PVCs and VAs. No complications were observed.
Conclusions: We report a form of LOT VAs where multiple location with equally early activation were observed and ablation at all sites was necessary to achieve acute and long term success.

1254 STOP-VT: a multi-center trial to evaluate catheter RF ablation with magnetic navigation for ischemic ventricular tachycardia

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Background: Catheter ablation has been shown to be effective in the treatment of scar-related ventricular tachycardia (VT). It is believed that remote magnetic navigation (RMN) provides additional benefits during mapping since its flexibility allows the operator to reach difficult areas without creating excessive ectopy. This prospective, non-randomized, single-arm study evaluated RMN for mapping and ablation of ischemic VT using the Niobe Magnetic Navigation System (Stereotaxis, St. Louis, MO, USA).
Method: This was the first multi-center, global, prospective trial to evaluate magnetic navigation for the treatment of ischemic VT. Patients from five centers in the US and EU have been included in the study. The key eligibility criterion was presentation with ischemic VT indicated for treatment with an irrigated magnetic catheter. The primary endpoint was elimination of VT recurrence.. Thirtyeight patients have been enrolled into the study. The average age was 68,2 years, dominantly men (92%), with a LV EF 32,3%. Medical treatment pre-procedure included beta-blockers (89,5%) and amiodarone (73,7%).
Results: Average procedure time was 255.4 minutes (135 – 457). Total procedure fluoro time was 15.1 minutes. Average VT morphologies induced was 2.2 with a cycle length of 353 msec. Average RF time required to ablate the VT was 35.1 minutes with a power of 42.6 W. For all RF applications 30 mL/min of normal saline was used to ablate with no steam pops. Crossover to a manual catheter occurred in only 1 subject (3%); however, the target arrhythmia could not be ablated in that patient. Ability to ablate the target VT and remain non-inducible was 92.1% for the entire series of patients. Patients were discharged on beta-blockers (81.6%) and amiodarone (68.4%). Major adverse events were categorized as death, prolonged hospitalization, permanent or transient impairment in body function, or need for additional intervention or surgery. There were no major adverse events associated with the procedures.
Conclusion: Our results for RMN mapping and ablation are promising in this very difficult-to-treat arrhythmia. Additional follow-up of the remaining patients should provide a clearer understanding of the long-term effects of treating ventricular tachycardia with magnetic navigation.

1255 Impact of inducibility of ventricular tachycardia during ablation and acute success of catheter ablation on survival free from VT/VF and ICD shocks: Lessons from the VTACH Study

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Purpose: Catheter ablation of ventricular tachycardia (VT) delays time to recurrence of VT in patients with previous myocardial infarction, reduced ejection fraction and stable VT, as demonstrated by the Catheter Ablation of Stable Ventricular Tachycardia before Defibrillator Implantation in Patients with Coronary Heart Disease (VTACH) study. The current analysis of the VTACH study aimed to assess the impact of inducibility of VT during ablation and acute success of catheter ablation on the recurrence of VT/VF and first ICD shock.
Methods: A total of 45 patients (mean age 67±8, 44 male, EF 35%) at 11 European centers underwent catheter ablation and subsequent implantable cardioverter-defibrillator (ICD) implantation. Median follow-up was 22.7±7.1 months. The mapping and ablation procedure was performed with a 3-D mapping system (Carto, Biosense Webster, Inc, Diamond Bar, CA, USA or Ensite, St Jude Medical, Inc., St. Paul, Minn., USA). For patients with inducible VT, successful ablation was defined as noninducibility of any VT at the end of the procedure. For patients with noninducible VTs, the ablation endpoint was substrate modification defined as absence of all channels inside the area of interest or ablation with linear lesions based on pace mapping along the infarct scar target sites.
Results: Clinical VT was induced and targeted for ablation in 26 patients (group 1). Purely substrate-based ablation was performed in 19 patients (group 2). In group 1, 3/26 (11.5%) patients received an ICD shock versus 8/19 (42.1%) patients in group 2. Survival free from ICD shock after 12 and 24 months was 92.3% and 87.2% in group 1 and 68.4% and 62.7% in group 2, respectively (p=0.0271). There was no statistically significant difference between groups regarding survival free from first VT/VF episode after ICD implantation (p=0.2838). Successful versus unsuccessful/undetermined ablation outcome had no significant impact on survival free of VT/VF following ICD implantation (p=0.3722).
Conclusions: In patients with previous myocardial infarction, diminished ejection fraction and stable VT, catheter ablation results in fewer ICD shocks if the VT can be induced and targeted during ablation. However, acute success of ablation does not predict greater benefit and VT inducibility during ablation does not translate into longer survival free form VT/VF following ICD implantation.

1256 Long term results of ventricular tachycardia substrate ablation: identification of scar and electrophysiological predictors of recurrence in patients with previous myocardial infarction

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Background: Electrograms with isolated component/late potential (IC/LP) and conduction channels (CC) are the substrate (S) of post-MI sustained monomorphic ventricular tachycardias (SMVT). The purpose of this study was to determine the safety and long-term efficacy and identify predictors of VT recurrence after ablation of all IC/LP and CC in the scar through complete VT substrate ablation (CVTSA) during sinus rhythm.
Methods: We analyzed 59 post-MI patients (age 67±9, LVEF: 30±11%) who underwent CSVTA. Electroanatomic maps were obtained to identify the scar (≤1.5 mV), dense scar (≤0.5 mV) and the targets of CSVTA: IC/LP and CC.
Results: Scar and dense scar extension were 76±42 and 34±24 cm^2 respectively. IC/LPC were identified in 97% of the patients, voltage mapping identified ≥1 CC in 83% of these patients. All IC/LP and CC were targeted (ablated VT substrate area 14±10 cm 2), no major life-threatening complications/incessant VT occurred during or after the procedure, 66% of patients were discharged without antiarrhythmic drugs. After one year follow-up 81% and 86% of the patients were free from VT recurrences and ICD shocks and at the end of the follow-up (39±21 months) 58% and 64% of the patients were free from VT recurrences and ICD shocks respectively. Univariable analysis identified LVEF (32±11 vs. 25±8%, p: 0.01), VT cycle length (379±103 vs. 320±54, p<0,01), inferior vs. anterior infarct location (20 vs. 48%, p<0.04) and scar extension (<0.5 mV, 25±16 vs. 46±28 cm^2, p<0.0004) as predictors of VT recurrence. Cox proportional hazards model identified VT cycle length (p<0.001) and scar extension (p<0.0006) as independent predictors of VT recurrence. Patients with an above-median scar extension (0.5 mV) were at higher risk for VT than those with a below-median (62%versus 23%, log-rank P<0.0081).
Conclusion: In post-MI patients CSVTA is safe and effective. Scar extension and VT cycle length are valuable predictors of post-MI SMVT recurrence.

1257 Real-time integration of CT derived coronary anatomy and epicardial fat distribution with electroanatomical mapping: Identification of inappropriate ablation sites

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Introduction: Epicardial radiofrequency catheter ablation (CA) for ventricular arrhythmias (VA) is indicated in selected patients after endocardial ablation failure. However, the presence of coronary arteries and epicardial fat may prevent successful ablation. This study aimed to evaluate epicardial ablation failure using real-time integration and reversed registration of CT data and electroanatomical mapping (EAM).
Methods: Twenty-seven consecutive patients (21 male, 59±16 years, BMI 25±5 kg/m^2) underwent combined endo-epicardial EAM after endocardial ablation failure of VA. Cardiac CT was performed to assess coronary anatomy and to create 3D meshes of epicardial fat distribution and thickness. Prior to CA CT data were loaded into the 3D EAM system (CARTO™). Registration of CT anatomy and fat meshes was performed after endocardial EAM. CA sites were selected based on activation and/or pace-mapping and indicated on the map. Irrigated-tip CA was withheld within 5mm distance from a coronary artery confirmed by coronary angiography (CAG). All mapping data were extracted and superimposed on the CT using reversed registration matrix. Ablation sites were analyzed regarding location and fat thickness.
Results: In 27 patients (6 without structural heart disease) 43 VA were targeted (1.6±1.0 VA/pts, CL 372±104ms). Endocardial CA failed in 23 pts (38 VA). Image registration was successful and accurate in all (registration accuracy 2.8±1.3mm).The epicardial area covered with >4mm fat was 24±15%. Epicardial CA failed in 8 pts (12 VA); in 1 (2 VA) no ablation target site could be identified; in 3 (6 VA) RF delivery was withheld because of coronary artery proximity on CT and confirmed by CAG. In 4 (4 VA) RF delivery was not effective. At these sites the mean thickness of the epicardial fat layer was 15±7mm (range 8.4-24.8mm). In contrast, epicardial fat thickness at successful RF sites was 1.5±1.7mm (range 0-5mm, p<0.001).
Conclusion: Epicardial fat and the proximity of coronary arteries are important reasons for epicardial ablation failure. Real time integration of CT derived coronary anatomy and epicardial fat thickness allows for accurate identification of inappropriate ablation sites.

CONTROVERSIES IN GENDER-RELATED DIFFERENCES IN CARDIOVASCULAR DISEASE

1262 Has gender a significant impact on carotid plaque instability and inflammation? Evidence from a 457-patient clinicopathologic study

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Purpose: Severe carotid stenosis is a frequent cause of stroke in both men and women. Whereas several sex-related comparisons are available on coronary plaque features, there are few data appraising gender-specific features of carotid plaques. We thus aimed to systematically compare the pathology of carotid plaques in males versus females.
Methods: Carotid plaque specimens were collected from patients undergoing surgical thromboendoarterectomy for asymptomatic or symptomatic carotid stenosis. Standard pathologic analyses were performed, as well as sophisticated measurements for plaque hemorrhage, inflammation and foam cells.
Results: A total of 457 patients were included (132 women, 325 men). Baseline analyses showed a greater prevalence of hypercholesterolemia and hypertension in women, and higher prevalence of current smoking, despite a raised Framingham Heart score in men (all $p<0.05$). Women had a lower prevalence of thrombotic plaques, and smaller percentage area of necrotic core and hemorrhage extension (all $p<0.05$). Plaque inflammation analysis showed a lower concentration of inflammatory and foam cells in the plaque cap of females (both $p<0.05$). Even at multivariable analysis adjusting for smoking status, hypercholesterolemia, hypertension, Framingham Heart Score, plaque classification, percentage area of necrotic lipid core, hemorrhage extension, women had a significantly lower concentration of foam cells and/or lymphocytes in the cap (p=0.032).
Conclusions: Carotid plaques are significantly different in women and men. In contrast to findings observed in coronary vessels, females have a lower degree of inflammation and thrombosis, and more frequently stable plaques. Further studies are warranted to demonstrate whether such gender-related differences in carotid pathology may have implications for the clinical management and revascularization of patients with carotid artery disease.

1263 Severe endothelial dysfunction in patients with apical ballooning syndrome

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Purpose: The main characteristic of apical ballooning syndrome (ABS) is a reversible dyskinesis of the left ventricular apex in the absence of significant coronary artery stenosis in coronary angiography. A frequently associated feature is the elevation of plasma catecholamine levels, caused by emotional stress. We assumed that endothelial dysfunction is affected by catecholamines in patients with ABS. To confirm this, we examined FMD test results from patients with ABS.
Methods: We assessed endothelium function using the brachial artery flow mediated dilation test (FMD) in 4 women with ABS, 18 women with ST elevation acute myocardial infarction (STEMI), and 26 healthy female volunteers. FMD tests in all patients were performed within 24 hours of admission and again at 1–3 weeks as a follow-up.
Results: The FMD test levels on the first day were extremely low in patients with ABS (0%, 0%, -1%, and 3.3%) and were significantly lower than in patients with STEMI (0.58±1.88% vs 9.51±5.54%; $p<0.01$) and in healthy volunteers (0.58±1.88% vs 14.01±6.56%; $p<0.01$). The FMD test results in ABS patients increased greatly after the recovery of contractility disorder and after 1–3 weeks didn't differ significantly from results in the patients with STEMI (9.90±10.06% vs 10.32±3.34%) and in the healthy volunteers.

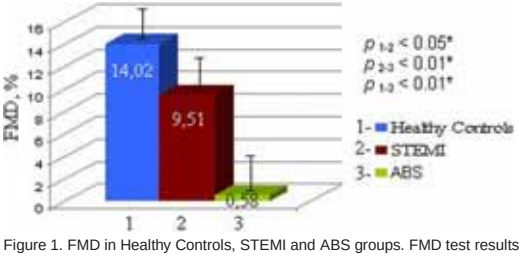

Figure 1. FMD in Healthy Controls, STEMI and ABS groups. FMD test results within the first 24 hours of patients' admission, in the groups of patients with ABS, of patients with STEMI, and of healthy volunteers. *p values according to the Mann-Whitney U-test.

Conclusions: The results obtained imply that there is a pronounced reversible endothelial dysfunction in patients with apical ballooning syndrome, which can impair myocardial perfusion.

1264 Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention

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Purpose: To compare the outcome after primary percutaneus coronary intervention (PPCI) according to sex and age in unselected real-world patients, and to compare the survival after PPCI with the survival in the general population as an indirect measure of effectiveness and safety of PPCI.
Methods: We did a population-based follow-up study in Western Denmark including 6373 patients treated with PPCI and 35885 sex-, age- and comorbidity matched general population controls. The main outcome measure was the composite endpoint of all-cause mortality, reinfarction and stroke at 30 days, 1 and 2 years. We used Cox proportional hazards regression to compute crude and adjusted hazard ratios adjusting for differences in age, comorbidity, duration of symptoms, estimated glomerular filtrations rate and levels of hemoglobin. In the comparison between PPCI patients and the general population controls we adjusted for differences in age and comorbidity.
Results: Women were older and had a more adverse baseline risk-profile than men. The cumulative risk of the composite endpoint after 30 days, 1 and 2 years were 10.4%, 17.2% and 20.6%, respectively, for women compared to 6.6%, 12.2% and 15.5% for men (adjusted hazard ratio (HR) (30 days)=1.14, 95% CI: 0.93-1.38, adjusted HR (1 year)=1.12, 95% CI: 0.96-1.30 and adjusted HR (2 years)=1.08, 95% CI: 0.94-1.24). When comparing patients treated with PPCI and general population controls, we found a substantially higher mortality among patients up to 90 days after admission. This difference was present in both men and women of all ages. However, after 90 days the mortality among the PPCI patients was comparable to the mortality in the general population.
Conclusion: Clinical outcome after PPCI was comparable in men and women after controlling for differences in baseline risk-profile. The mortality rates of PPCI treated patients beyond 90 days after the PPCI were comparable to the mortality of the general population, independent of sex and age.

1265 The impact of sex on clinical and angiographic outcomes among patients undergoing coronary revascularization with drug-eluting stents

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Purpose: To investigate sex-based differences in clinical and angiographic outcomes among patients undergoing coronary revascularization with drug-eluting stents (DES) through one year.
Methods: Individual patient data were pooled from 3 recent all-comer trials with the exclusive use of DES (SIRTAX - N=1,012, LEADERS - N=1,707, RESOLUTE - N=2,292). Out of 5,011 randomized patients, 4,923 completed one year follow up (1,172 female and 3,751 male patients) and were included in the present analysis. Angiographic follow-up was available for 1,569 lesions (353 among female and 1,216 among male patients). After stratification by sex, outcomes were compared between female and male patients. Mixed effects regression models were used to derive differences between groups. The primary endpoint was the composite of cardiac death and myocardial infarction (MI). Angiographic endpoints were in-stent late lumen loss (LL) and in-segment binary restenosis (BR).
Results: At baseline, female as compared to male patients were older, had more frequently diabetes, obesity and hypertension, less frequently smoking habits, prior MI and prior CABG, and had a smaller reference diameter of the target vessel. Through one year, female as compared to male gender was associated with a higher risk of the primary endpoint (7.3% vs 5.5%, OR=1.35, 95%CI 1.04-1.74, p=0.02). This was mainly driven by a higher risk of MI among female patients (5.5% vs 4.2%, OR=1.34, 95%CI 1.00-1.81, p=0.05), whereas the risk of cardiac death did not differ between female and male patients (2.2% vs 1.8%, OR=1.24, 95%CI 0.79-1.96, p=0.35). The risk of clinically-indicated repeat revascularization was similar for female and male patients with respect to both target-lesion (5.3% vs 5.0%, OR=1.06, 95%CI 0.79-1.43, p=0.69) and target-vessel revascularization (5.6% vs 6.4%, OR=0.87, 95%CI 0.66-1.16, p=0.34). Similarly, the risk of definite or probable stent thrombosis (Academic Research Consortium criteria) did not differ between female and male patients (2.0% vs 1.7%, OR=1.12, 95%CI 0.69-1.82, p=0.64). After adjustment for differences in baseline characteristics, the risk of the primary endpoint (OR=1.28, 95%CI 0.91-1.81, p=0.16) as well as MI (OR=1.29, 95%CI 0.87-1.92, p=0.20) were similar for female as compared to male patients. As it relates to angiographic outcomes, no differences were observed between female and male patients (in-stent LL: 0.18±0.47mm vs 0.19±0.87mm, p=0.50; in-segment BR: 8.1% vs 8.5% p=0.85).
Conclusions: The unrestricted use of DES is associated with similar clinical and angiographic outcomes among female and male patients through one year.

1266 Significance of the invasive strategy after acute myocardial infarction on prognosis and secondary preventive medication - a nationwide study of 6364 women and 11,915 men

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Purpose: To describe the long-term outcome and initiation of secondary preventive medication of patients with acute myocardial infarction (AMI), with particular emphasis on differences related to choice of invasive treatment strategy.
Method: In an observational cohort study using nationwide registries 18,279 patients (6364 (35%) women and 11915 (65%) men) admitted with AMI (median age 67, range 30–90 years) surviving for at least two months were included. By gender all patients were stratified by invasive treatment strategy: 1) Revascularised, 2) Examined with coronary angiography (CAG) but not revascularised, and 3) Not examined with CAG. Cox proportional hazard models were applied to estimate differences in men and women of long-term all-cause mortality and readmission with AMI. Initiation of secondary preventive medication was investigated.
Results: Of 18,279 patients with a first AMI who survived 2 months, 1857 (29%) women and 1756 (15%) men were not examined with CAG, 1295 (20%) women and 1563 (13%) men were examined but not revascularised and 3212 (51%) women and 8596 men (72%) were revascularised. Not being examined with CAG after AMI was associated with a threefold increase in risk of death and a 50% increase in the risk of a recurrent AMI compared with the patients who were revascularised (the analysis was adjusted for differences in age and comorbidity). This increased risk was similar in men and women. Initiation of secondary preventive medication was more prevalent in patients being examined with CAG and most prevalent in those patients being revascularised. Thus, women were in general less likely to initiate secondary preventive medication.
Conclusions: Proportionately twice as many women as men and almost a third of all women were not offered an invasive strategy after AMI. In both genders those not being examined had a highly increased risk of both recurrent AMI and death. Furthermore, initiation of secondary preventive medication was closely related to the choice of invasive strategy with more revascularised patients initiating medical therapy than those not revascularised and with those not examined having the lowest proportion of initiation.

1267 Do women benefit similarly as men from drug eluting stents? A prospective randomized comparison with bare metal stents

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Purpose: Effects of DES implantation on outcome in women versus men are controversial. Apart from differences in disease presentation and higher age the comparison of women vs. men is complicated by differences in vessel size. BASKET-PROVE was a large prospective all comers trial of patients treated for large ($\geq$3.0 mm) vessels. We performed an a priori planned gender-specific analysis of BASKET-PROVE data to test gender specific effects of DES vs. BMS.
Methods: All 2314 patients randomized 2:1 to DES vs. BMS were followed for 2 years with a primary endpoint of major adverse cardiac events (MACE: cardiac death, infarction, target-vessel revascularization). A Cox-proportional-hazard model was used to evaluate the relative risk for women and men, respectively.
Results: The 565 (25%) women were older, more frequently hypertensive, nonsmokers, and with a heart failure diagnosis, but less frequently had a history of previous coronary disease and multivessel disease on coronary angiography. Randomization was similar between women and men: BMS 31.7% vs 33.5% (p=0.42). The overall 2–year rate of MACE was the same in women (7.6%) and men (7.6%) (p=0.99). However, DES was more beneficial in women than men: MACE rates were reduced with DES, i.e., in women from 15% in BMS to 4% in DES patients ($p<0.0001$) and in men from 10% to 6% (p=0.003), respectively. Similarly, cardiac death/myocardial infarction rates were reduced by DES in women from 5.0% to 2.9% (p=0.19) and in men from 4.6% to 2.8% ($p<0.0001$) as were target-vessel revascularisation rates, i.e., in women from 10.6% to 2.3% ($p<0.0001$) and in men from 7.5% to 4.1% (p=0.003). The hazard rates for the comparisons of BMS vs. DES were higher for women (HR: 3.6, 95%CI: 2.0-6.6) than for men (HR: 1.7, 95%CI: 1.2-3.3). The gender interaction was significant (p=0.038) and present after both uni- and multitvariable adjustments. Thus, women had superior effect of DES vs. BMS.
Conclusions: BMS implantation in large coronary arteries in women resulted in a worse outcome than in men. In contrast, DES implantation reduced MACE rates more in women than men. Our data suggest that DES are more beneficial in women than men.

ARRHYTHMIAS IN THE ATHLETE

1272 Risk of arrhythmias in male cross skiers

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Background: Although physical exercise has been shown to reduce both cardiac and all cause mortality, data from small studies have suggested that extensive endurance exercise could be a risk factor for lone atrial fibrillation. Further, it has been discussed whether persons involved in extensive endurance sports may have higher risk of sudden death.
Purpose: To investigate the risk of arrhythmias in relation to race results in "Vasaloppet" – a 90 km cross skiing event in Sweden. The participants are both elite skiers and persons committed to recreational exercise.
Methods: 48.893 male participants in Vasaloppet were included in the cohort from 1989 to 1998 and followed until September 2006. 1416 with prior cardiovascular disease were excluded. We primarily examined associations of finishing time and number of run races with age-adjusted risk of all arrhythmias. Secondary outcomes were risk of atrial fibrillation/flutter, brady-arrhythmias, other supraventicular arrhythmias, and ventricular arrhythmias/cardiac arrest. We also investigated a model adjusted for educational and socio-economic status.
Results: 881 participants experienced an arrhythmia during follow upp. In age-adjusted models, we observed a lower risk of arrhythmia in those finishing at more than 240% of the winning time than in those finishing at 100%-160% of the winning time (HR 0.73 95%; CI 0.58-0.92).The result was attenuated in multivariable-adjusted models. In secondary analyses, a higher risk of ventricular arrhythmias/cardiac arrest was observed with higher number of run races (5 or more races vs. one race; HR 2.98; 95% CI 1.31-6.78) and a higher risk of bradyarrhythmias with higher number of run races (5 or more races vs. one race; HR 2.03; 95% CI 1.06-3.87) in multivariable-adjusted models.
Conclusions: Higher physical fitness, measured as lower finishing time in a strenuous 90 km cross skiing event, was associated with higher risk of arrhythmias. Further, a higher number of completed races was associated with a higher risk of bradyarrhythmias and a higher risk of ventricular arrhythmias or cardiac arrest.

1273 Left ventricular hypertrophy, late potentials and QRS dispersion in ultra endurance athletes compared to normal controls

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Background: Electrocardiographic (ECG) changes of depolarisation and repolarisation have been described in the athlete's heart. These ECG changes may occasionally be difficult to differentiate from arrhythmogenic right ventricular cardiomyopathy (ARVC) or hypertrophic cardiomyopathy. Data on prevalence of epsilon waves, QRS dispersion and late potentials in athletes are limited. We thus examined the prevalence of these findings in ironman triathletes, a good example of ultraendurance athletes (ATHL).
Methods: Signal averaged ECG (SAECG) and a regular ECG as well as a complete transthoracic echocardiographic exam were performed in 39 ATHL and compared to 23 age-and gender matched controls. All ECGs were screened for signs of ventricular late potentials (VLP): QRS duration, late amplitude signal (LAS) duration; and mean root mean square voltage (RMS voltage).
Results: Average age was 39 years in ATHL and controls. Any ECG abnormality

Abstract 1270 – Table 1. Data in athletes and controls

	HR, bpm	PR-interval, ms	QRS-dur, ms	Incomp RBBB	QRS-dur filtered, ms	RMS amplit last 40ms	LAS duration	+LP	LVH	Sokolov index, mV	QRS disp >40ms
Athletes	53±7	167±26	99±7	4 (10)	118±14	39±22	30±13	4 (11)	19 (49)	34±7	6 (15)
Controls	68±10	155±16	98±10	1 (4)	115±8	28±12	34±7	4 (17)	1 (4)	26±6	4 (17)
p-value	0.03	0.05	ns	ns	ns	0.02	ns	ns	0.0002	<0.0001	ns

HR = heart rate, bpm = beats per minute, QRS dur = QRS duration, incomp RBBB = incomplete right bundle branch block, RMS amplit = root mean square amplitude, +LP = positive late potentials. Percentages are shown in parenthesis.

was found in 30 of 39 (77%) athletes versus 4 of 24 (17%) controls ($p<0.0001$). The results are shown in the Table. The most common ECG abnormality in ultraendurance ATHL were signs of LVH. The Sokolov amplitude criteria for LVH correlated with echocardiographic LVMMI ($p<0.0001$). PR interval tended to be longer in ATHL. Filtered QRS duration was within normal limits in all ATHL. ECG criteria for late potentials were found in 4 ATHL, but also in 4 controls (p=0.45). No subject had epsilon waves or other signs of ARVC, such as negative T waves in the anterior precordial leads.
Conclusions: Apart from signs of LVH and an increased RMS voltage in the SAECG, there were no findings typical of ATHL heart. The correlation of voltage criteria with LVMMI was confirmed; pathologic ECG suggestive of ARVC were not found. Late potentials were not found to be helpful in differentiating athlete heart from a normal heart or cardiomyopathy as it can be found in all pt groups.

1274 Associations between findings on a cardiac risk assessment questionnaire and group 2 ECG abnormalities:results from the west of Ireland screening for sudden cardiac death in young people study

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Purpose: Young people who participate in sport have an increased risk of sudden cardiac death (SCD) compared to their non-sports playing counterparts. In Ireland, cardiac risk assessment in this group using a screening questionnaire has been suggested. We aimed to describe the association between findings on questionnaire and the presence of "Group 2" ECG abnormalities, proposed as a marker of possible underlying cardiac pathology.
Methods: This was a prospective cross-sectional observational study. A six-item questionnaire was developed and piloted. The population surveyed consisted of young people aged 14-34 from participating schools, colleges and sports clubs who were regularly engaged in sports of at least moderate dynamic or high static intensity. All participants had a physical examination and a 12 lead ECG. ECGs were read by a cardiologist blinded to the other results of the screening process. Presence of Group 2 abnormalities (T wave inversion, ST segment depression or pathological Q waves in 2 or more leads; right or left axis deviation; right or left bundle branch block; left atrial enlargement; right ventricular hypertrophy; prolonged or shortened QT interval; atrial or ventricular arrhythmias; delta or epsilon waves; short PR interval or Brugada pattern) were noted.
Results: Between March and June 2009, 461 participants (70.7% male, median age 19, 92% at least one high dynamic sport) completed the risk assessment process. A "yes" answer to one or more questions ("positive questionnaire") occurred in 38.6%; the majority (87.1%) of these concerned symptom related questions. Group 2 ECG abnormalities were documented in 28%. Participants with group 2 abnormalities were not more likely to have provided a positive versus a negative questionnaire (41.1%vs 59%, p=0.497). No association was seen between amount of abnormalities present and positive response to questionnaire or between these abnormalities and presence of symptoms including syncope or a family history of premature SCD. However personal history of a cardiac condition was independently associated with a group 2 ECG abnormality (OR 2.37, p=0.029).
Conclusions: High levels of group 2 ECG abnormalities were noted in this screening population. While over a third of participants returned positive questionnaires only one question relating to personal history of cardiac disease was associated with these abnormalities. This study raises potential concerns not only about the sensitivity of using a symptom incorporating questionnaire alone for sports related SCD prevention but also about the use of these ECG changes as a surrogate outcome.

1275 Self-reported atrial fibrillation in still active old cross-country skiers - the Birkebeiner aging study

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Background: Long-term strenuous endurance training seems to predispose to lone atrial fibrillation (LAF) in middle-aged athletes, but previous studies are conducted in smaller cohorts of athletes. LAF among still active old athletes has not been studied before.
Purpose: 1) To explore the prevalence of atrial fibrillation (AF) and LAF in still active old cross-country skiers with a history of strenuous endurance training through decades; 2) to compare prevalence in still active old athletes with controls from a general Norwegian population.
Methods: 483 men and women $\geq$ 65 years who completed The Birkebeiner cross-country ski race (54 kilometres) in 2009 were invited to participate. Health status, physical activity and other life-style factors were assessed using a questionnaire. Participants were asked if they had experienced AF at least once, several times or if they had permanent AF. LAF was defined as self-reported AF in absence of coronary heart disease, diabetes, antihypertensive medication and an alcohol-intake above the recommended number of units/week. Study participants and controls from The Tromso-VI health survey were matched for age and sex.
Results: 423 (87%) persons participated in the study, only 32 were female. Median age was 67 (range 65 – 89) years. The overall prevalence of AF was 14% (59/422) in the skiers and 12% (47/398) in the controls (OR[95%CI]: 1.21[0.81, 1.83], p=0.41, n.s.). The prevalence of LAF was 13% (43/334) and 6% (11/190) in skiers and controls respectively (OR[95%CI]: 2.41[1.21, 4.28], p 0.01).
Conclusion: The prevalence of self-reported LAF was significantly higher in still active old cross-country skiers compared with the general population. The overall prevalence of AF, though, did not differ significantly between still active old skiers and the general population. Our results indicates that etiology of AF in still active old athletes differ from etiology of AF in the general population and that long-term strenuous endurance training might have contributed to the higher prevalence of LAF in the still active old cross-country skiers compared with the general population.

1276 Prevalence of Wolff-Parkinson-White pattern ECG in a young southeast Asian male population: results from the SAFE study

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Purpose: Wolff-Parkinson-White (WPW) pattern electrocardiograms (ECG) are usually incidental findings in asymptomatic subjects. Almost half of the population with WPW syndrome are asymptomatic at diagnosis. An ECG based preparticipation screening programme can detect WPW pattern in subjects, and allows for timely intervention and prevention of Sudden Cardiac Death. The prevalence of WPW pattern ECG in a young South-East Asian population is unknown. We report the clinical demographics of patients with WPW pattern ECG in a young Singaporean male population.
Methods: All males who are about to enlist in the military between the ages of 16 to 30 underwent medical screening at a single medical facility from October 2008 to May 2009 were studied. Parameters including age, symptoms of palpitations, syncope or exertional giddiness and ECG features were analyzed. WPW pattern ECG was defined as presence of delta waves and/or shortened PR interval $<$120ms. These ECGs were independently verified by a cardiac electrophysiologist.
Results: Out of 18,476 (mean age 19.5, range 16 to 27) screened male subjects, 25 had WPW pattern ECGs, reporting a prevalence of 0.14%. Of these 25 patients, 84% (n=21) were asymptomatic, 12% (n=3) had atypical chest discomfort and only 4.0% (n=1) had paroxysmal palpitations. None of the subjects with WPW pattern ECGs had syncope or exertional giddiness. Based on ECG criteria, 15 had WPW Type A ECG pattern, and 10 had WPW Type B ECG pattern. The mean PR interval was 119.8$\pm$29.7ms with a mean QRS interval of 118.8$\pm$21.9ms. 15 out of 25 (60%) subjects were subsequently diagnosed to have WPW syndrome by the cardiac electrophysiologist.
Conclusion: The prevalence of WPW pattern ECG in a young Singapore male population (mean age 19.5, range 16 to 27) was 0.14% in our study, which is consistent with the previously reported prevalence of 0.1 to 0.2%. Of those with WPW pattern ECG, 60% were diagnosed to have WPW syndrome. Up to 75% of patients with WPW syndrome were asymptomatic and diagnosed only by an ECG-based screening.

1277 High prevalence of modified task force criteria for arrhythmogenic right ventricular cardiomyopathy in healthy elite male athletes

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Purpose: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is the cause of sudden death in a significant proportion of young athletes, particularly in the Mediterranean region. Modified Task Force Criteria (TFC) for diagnosis of ARVC include echocardiographic measures of right ventricular (RV) dimensions, with quoted specificity for ARVC of between 80 and 95%. Several studies have demonstrated RV enlargement as a result of systematic training. The use of transthoracic echo (TTE) to differentiate ARVC from physiological RV enlargement is an essential component of cardiovascular assessment in athletes. We investigated the prevalence of echocardiographic TFC in healthy, male elite athletes (EA). We also assessed the influence of training intensity and left ventricular (LV) dimensions on the presence of TFC in EA.
Methods: TTE was performed in 122 healthy, male EA after prior evaluation of personal and family history, and 12-lead electrocardiography (ECG). EA from 9 different sporting disciplines were included. Mean age was 21.9 years. In each case, RV outflow tract diameter was measured in parasternal long-axis and short-axis views and indexed for body surface area (BSA), as per TFC. LV end-diastolic diameter indexed for BSA (LVEDD/BSA) and hours of training per week were also recorded.
Results: RV dimensions fulfilling TFC were present in 54.9% of EA, with 8.2% meeting major criteria. Compared to EA without TFC, those exhibiting TFC had

significantly greater LV cavity dimensions, and spent more time training per week (Table 1).

Table 1. ARVC TFC in healthy male EA

	ARVC TFC +ve	ARVC TFC –ve	
n	67/122 (54.9%)	55/122 (45.1%)	
Mean LVEDD/BSA (mm/m^2)	26.9	25.6	p=0.0097
Mean sporting activity (hours/week)	22.3	18.2	p=0.0104

TFC = task force criteria; LVEDD = left ventricular end-diastolic diameter; BSA = body surface area.

Conclusions: Echocardiographic TFC for ARVC are common in healthy male EA, particularly in athletes training at the highest intensities, and in those with concomitant LV enlargement. This supports the concept of a balanced physiological enlargement of both sides of the heart as a result of training. Echocardiographic components of the TFC should be used with caution in elite athletes, and must be interpreted in the context of the history, ECG, gender, training intensity and LV dimensions.

NEW CHALLENGES FOR CARDIAC REHABILITATION

1291 Combined aerobic/ventilatory muscle training versus aerobic training in patients with chronic heart failure. The VENT-HEFT trial: A prospective randomized multi-European trial

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Purpose: A multi-center trial was designed to evaluate the potential additive benefits of inspiratory muscle training (IMT) on standard aerobic training (ATR) in patients with chronic heart failure (CHF).
Methods: Thirty-eight (n=38) patients with CHF, age 57±11 years, with left ventricular ejection fraction 29±8% and functional class according to New York Heart Association (NYHA) of 2.7±0.7 were studied. Patients were randomly assigned either to a combined ATR/IMT group (n=20), or to a combined ATR/PlaceboIMT (ATR/PIMT) group (n=18). ATR involved bike exercise for 45 minutes at 60-80% of max heart rate, 3-5/week for 12 weeks for both groups. IMT was performed for 30 min, 3/week for 12 weeks using a computer biofeedback trainer (Trainair) for both groups, although for the ATR/IMT group training intensity was set at 60% of sustained maximal inspiratory pressure (SPImax) while for the ATR/PIMT group, training intensity was set at only 10% of SPImax. Primary end-points measurements included inspiratory muscle function, exercise capacity, and quality of life (QOL). Pre- and post-training, inspiratory muscle strength (PImax) and endurance (SPImax) were measured using electronic pressure manometer and software, exercise capacity was evaluated with peak oxygen consumption (peakVO2) using cardiopulmonary exercise testing and QOL by the Minnesota Living with Heart Failure questionnaire.
Results: The ATR/IMT group improved PImax (100.7±23 vs. 81.9±22 cmH2O, $p<0.001$), SPImax (516±149 vs. 342±123 cmH2O/s/1000, $p<0.001$), peakVO2 (18.2±5 vs. 16.9±4.8 ml/kg/min, $p<0.05$) and QOL (41±25 vs. 24±15 $p<0.05$) as well as NYHA functional class (2.5±0.5 vs. 1.8±0.6 $p<0.01$). The ATR/PIMT group tended to increase peakVO2, although not significantly, (19.2±5.6 vs. 18.1±4.8 ml/kg/min, p=ns) while no significant changes were detected in the other measured parameters.
Conclusions: The present findings suggest that combined aerobic training with inspiratory muscle training resulted to increased benefits in inspiratory muscle function, exercise capacity and quality of life compared to standard aerobic training in patients with chronic heart failure. Thus, inspiratory muscle training might prove to be a new component to cardiac rehabilitation programs

1292 A cardiac rehabilitation model applied to patients with non-disabling stroke. Sustained benefits at one year in the community cardiovascular hearts in motion program

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Purpose: Evidence is abundant on the positive effects of cardiac rehabilitation in coronary artery disease (CAD). Emerging data suggests similar benefits may be seen in patients with stroke. We hypothesize that patients with non-disabling stroke, with or without diabetes (DM), will have similar outcomes in the Community Cardiovascular Hearts in Motion program (CCHIM), a polyvascular prevention and management care model.
Methods: During the 12 week CCHIM program, motivational enhancement is integrated with exercise and nutrition without changing pharmacotherapy. Patients are followed up at 6 and 12 months where the combination of program effect and pharmacotherapy is evaluated. Data collected includes lipid levels, A1c, blood pressure (BP) along with exercise capacity, weight/waist and quality of life (SF36 and HADS). Of 705 patients with complete one year data, 486 with vascular disease, CAD (n=397) or Stroke (n=89) serve as the basis for the present study. These groups were further subdivided for DM diagnosis. Analysis of variance was used to identify significant differences.
Results: Patients with stroke and DM had more pronounced outcomes in several measures compared to CAD (Figure 1); with 3.6 mmHg decrease in diastolic BP, 12% lowering in LDL-cholesterol and reduction in A1c from 7.3% to 6.9% (p=0.001). Weight loss and waist circumference were also statistically improved and sustained at one year. Exercise capacity was most improved with >18% change in all groups, most pronounced in those with Stroke+DM at 28% (1.8METS) p=0.0001

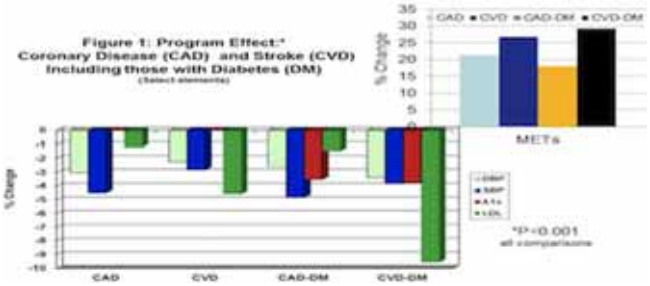

Figure 1

Conclusions: Patients suffering a non-disabling stroke gain the same if not better outcomes from being part of a multifactorial risk reduction program traditionally offered to patients with CAD. This should be a standard of care for all patients with vascular disease.

1293 Sleep disorder, exercise capacity and endothelial function in left ventricle assist device implantation (LVAD) patients after residential cardiac rehabilitation (RCR)

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Purpose: LVAD for refractory heart failure (HF) patients both as bridge to transplantation (BT) or destination therapy (DT) is increasing. We aimed to assess the presence of sleep breathing disorder, endothelial dysfunction and to measure exercise capacity in LVAD patients after residential cardiac rehabilitation (RCR).
Methods: Between October 2006 and September 2010 25 refractory HF patients (92% males, 55±9 years) due to idiopathic (52%) or ischemic (48%) dilated cardiomyopathy underwent RCR of at least 3 weeks supervised tailored exercise training program (TP) (respiratory exercises, up to 20 minutes walking and 40 minutes of cycling aerobic exercise daily session) after LVAD (64% Berlin Heart Incor, 28% Jarvik 2000, 8% Heart mate II, 68% as BT and 32% as DT). Echocardiography, flow mediated dilation (FMD) by brachial Doppler ultrasound, apnea-hypopnea index (AHI), 6-minute walking test and symptom-limited cardiopulmonary exercise test (CPET) before discharge were assessed.
Results: All patients except three (12% because of adverse events: 1 ischemic transient ischemic attack, 1 cerebral bleeding, 1 sternal infection) completed the TP. Results are reported in the Table: of note, patients had good sub-maximal exercise and peak VO2 at maximal exercise (but a VE/VCO2 still high), normal or only moderated elevation of AHI and about normal FMD before discharge.

Table 1

Ejection Fraction (%)	22±10
VTDi (ml/m^2)	112±78
TAPSE (mm)	13±4
Flow Mediated Dilation (%)	10±2
6-minutes walking test (m)	335±68
Peak VO2 (ml/kg/m^2)	13,6±1,5
VE/VCO2 slope	43±8
AHI (events/hour)	13±9
Central Sleep Apnea (%)	67

TAPSE: Tricuspid annular plane systolic excursion; VTDi: left ventricular end-diastolic volume index; VE: minute ventilation; VCO2: Carbon Dioxide output; VO2: Oxygen Uptake.

Conclusions: LVAD patients after RCR show good exercise capacity which favors a safe discharge without severe sleep breathing disorder or endothelial dysfunction

1294 Effects of functional electrical stimulation on exercise capacity and quality of life in the elderly with heart failure

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Objective: Functional electrical stimulation (FES) may have beneficial effects on functional capacity in chronic heart failure (CHF) patients. However, there is no any evidence regarding the effectiveness of this treatment modality in the elderly with CHF. This study investigates the effectiveness of FES on exercise capacity, endothelial function and quality of life in CHF patients with age >70 years.
Methods: Thirty NYHA II-III patients with stable CHF (mean age: 75±3 years; LVEF: 28±3%; Ischemic/Dilated: 20/10) randomly (1:1) underwent a 6-week FES training program or placebo treatment. Questionnaires addressing quality of life [Kansas City Cardiomyopathy Questionnaire (KCCQ), functional and overall], and emotional stress [Zung self-rating depression scale (SDS), Beck Depression Inventory (BDI)], 6-min walking distance test (6MWT) and endothelial function (Flow Mediated Dilatation, FMD) were assessed at baseline and after completion of training protocol.
Results: A significant improvement in KCCQ functional (F=68.6, $p<0.001$), KCCQ overall (F =66.9, $p<0.001$), BDI (F =66.3, $p<0.001$) and Zung SDS (F =95.1, $p<0.001$) was observed in the FES group compared to placebo. Patients in the FES group had also a significant increase in 6MWT (F =63.0, $p<0.001$) and FMD (F =59.1, $p<0.01$) compared to placebo. FES-induced percent change in FMD was significantly correlated with respective percent changes in 6-MWT (r=0.608, p=0.001) and KCCQ functional (r=0.386, p=0.039).
Conclusion: FES seems to be an effective treatment modality in the elderly with CHF by improving their exercise capacity, endothelial function and quality of life.

1295 Cardiac rehabilitation after transcatheter aortic valve implantation: a single centre experience

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Background: Transcatheter aortic valve implantation (TAVI) is assuming a major role in the routine management of aortic stenosis, and now can be considered the standard of care in patients who are not candidates for conventional surgery because of their poor conditions. Until now no data are available about the efficacy of cardiac rehabilitation (CR) in these subjects.
Patients and methods: 30 consecutive TAVI pts were studied in order to evaluate the effect of exercise-based CR. Thirty-two similar age pts who underwent traditional aortic valve surgery were used as controls. Functional capacity was assessed - when possible - by a six min walking test (6MWT) at admission and at the end of the CR programm. In a subgroup a cardiopulmonary exercise test (CPET) was also performed before discharge.
Results: The two groups were similar in terms of age (82 y vs 80 y, p=0,1), male sex (58 vs 61%, p=0,3), mean stay in CR (16 days, p=0,1). As expected, the TAVI group had more comorbidities. At the end of the CR period all pts enhanced independence and mobility and were able to walk al least with the assistance of a stick. A 6MWT could be performed in 62% of TAVI pts vs 90% of traditional surgery ones. The distance walked didn't significantly differ between the groups (290,1±108 mt vs 316,2±95, p=0.38) as well as the exercise capacity assessed by CPET (peak-VO2 11.7±3.6 vs 13.7±3.1 ml/kg/min, p=0.33).
Conclusions: At the end of CR all patients enhanced independence and mobility. A smaller percentage of TAVI pts was able to autonomously walk, in confirmation of more compromised conditions of this group. Nevertheless, in those who were able to performances reached were not different from the traditional surgery ones. Cardiac rehabilitation is feasible and effective after TAVI as after traditional surgery.

PROGRESS IN PROGNOSTIC STRATIFICATION AND TREATMENT OF CARDIOMYOPATHIES

1304 The return of the normal heart: cardiac amyloidosis disappears after bone marrow transplantation

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Purpose: Untreated amyloidosis results in a median survival of 12 months. If cardiomyopathy develops, survival drops to 5 months. High dose chemotherapy and bone marrow transplantation (BMT) have been shown to dramatically improve survival when haematologic remission is documented. Our group had noticed that some patients with cardiac amyloidosis had return to normal function as assessed by echocardiography.
Methods: Retrospective analyses of the amyloidosis database and the echocardiography database were conducted. There were 269 patients who had had high dose melphalan and BMT for amyloidosis from May 1997 to May 2010. Of these, 30 (11.2%) were identified as having cardiac amyloidosis by echocardiographic criteria (thick walls, advanced diastolic dysfunction, dilated atria and/or small pericardial effusions). Patient survival and time to normalization of cardiac structure was recorded. For each patient, interventricular and posterior wall thickness, grade of diastolic dysfunction and left atrial size was recorded before and sequentially after BMT.
Results: Of the 30 patients with cardiac amyloidosis, 13 died during the 13 years of follow-up (44.8%). Of these 13, 11 patients (84.6%) had no change in cardiac structure (non-responders), with an average survival of 49 months from BMT. There were 15 patients whose cardiac structure normalized during the time period (responders). The average time to normalization was 25 months (range 4-63 months). Of these 15, only 2 have died, with prolonged survival seen in 13 patients (83.3%). The average survival in this group is 71 months ($p<0.0001$ compared with the average survival in non-responders). Normalization of cardiac structure was highly predictive of survival (Fisher's exact test p=0.0025, relative risk 0.18).

	Pre BMT	Post BMT	p value
Interventricular septum	15.0 mm	10.7 mm	$p<0.0001$
Diastolic function grade	2	0.5	$p<0.0001$
Left Atrial Area	25.7 cm^2	20.3 cm^2	$p<0.003$

Conclusions: High dose chemotherapy and bone marrow transplantation has previously been shown to significantly improve survival for amyloid patients. Our data show that many patients with cardiac involvement have normalization of heart structure. Normalization of cardiac structure is highly predictive of survival.

1305 Prognosis of patients with isolated noncompaction cardiomyopathy - data from the German noncompaction registry (ALKK)

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Isolated Noncompaction cardiomyopathy (NCCM) is considered a genetic cardiomyopathy showing a high prevalence of heart failure, thrombembolic events and arrhythmias. But the prognosis of this disease is still controversially debated. The German NCCM registry consists of 162 pts with NCCM: 110 men, 52 women, age 18 to 87 yrs, mean 55.7 yrs with a mean follow up of 28 mths. Clinical status, LV function and clinical events were followed in 6 mths intervals. Hospitalisation, deterioration of NYHA classes, HTX, arrhythmias, cardiac and non cardiac death, thrombembolic events including cerebral ischemia or TIA were documented. The events were analysed with respect to the LV function of the pts.
Results: 15 out of the 162 pts died (9.3%): 3 sudden cardiac deaths, 2 of them prior to scheduled ICD implantation in severely reduced LV function, 6 deaths due to endstage heart failure; 6 non cardiac death occurred. 2 aborted sudden cardiac deaths occurred in 2 male pts with only mild reduced LV function. In these pts NCCM was diagnosed following these events. 4 pts received CRT therapy and 3 patients underwent HTX. In 28 pts ICD impantation was performed; 5 pts with primary preventive ICD implantation and severely reduced LV function received adequate shock therapy during follow up. Atrial fibrillation was common in NCCM even in pts with preserved LV function. Ablation therapy was performed in 3 pts with common atrial flutter or AV node reentry tachycardia. Deterioration of LV function was observed in less than 10% of the pts during follow up. In 11 pts a cerebral ischemic event occurred: 7 pts with stroke, 4 pts with TIA; 2 pts suffered from pulmonary embolism. Clinical events mainly occurred in pts with severely reduced LV function or with atrial fibrillation.
Conclusion: In pts with NCCM deaths and typical clinical events as arrhythmias, thrombembolic events and heart failure mainly occurred in cases with severely reduced LV function, but also occasionally in pts with preserved LV function. Our data suggest that pts with NCCM should be followed regularly in 6 mths intervals to identify pts at risk early. Severely reduced LV function appears a strong risk factor in pts with NCCM. Future research is needed to identify high risk pts with NCCM and preserved LV function.

1306 Contribute and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies

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Purpose: Use of left ventricular (LV) endomyocardial biopsy (EMB) for the investigation of cardiomyopathies is currently discouraged as considered more risky and less contributive than right ventricular (RV) biopsy. The aim of our study is to report our experience on advantages and disadvantages of this option.
Methods: In our center from 1983 to 2010, 2921 patients were submitted to non invasive and invasive cardiac studies including EMB because of clinically suspected myocarditis or non ischemic cardiomyopathies. In particular 1596 (55%) underwent a biventricular EMB, 853 (29%) a selective LVEMB and 472 (16%) a selective RVEMB. Rate of complications and biopsy findings were retrospectively analysed.

Results: Three to six samples from the LV and/or RV were drawn from each patient. Periprocedural major complications rate (perforation with cardiac tamponade, embolization) was 0.24% for LVEMB and 0.33% for RVEMB. Notably, pretreatment with Aspirin 800mg tid in the 24 hours before LVEMB abolished systemic thromboembolic events. Minor complication rate was 0.7% for LVEMB and 0.9% for RVEMB. In patients who received a biventricular EMB, myocarditis was diagnosed in 1099 (69%), idiopathic dilated cardiomyopathy in 244 (15%), hypertrophic cardiomyopathy in 104 (6.5%), restrictive cardiomyopathy in 50 (3.1%) (amyloidosis in 27, endomyocardial fibrosis in 9, sarcoidosis in 6, idiopathic restrictive in 4, haemochromatosis in 4), Fabry disease in 30 (1.9%), specific dilated cardiomyopathies (i.e acromegaly, dystrophinopathy, Takotsubo, GH-deficiency, anthracyclin and sclerodermic cardiomyopathy) in 43 (2.7%), ARVD in 21 (1.3%), cardiac glycogenosis in 5 (0.3%). When the functional abnormalities, assessed by echocardiography and/or cardiac MRI, affected exclusively or predominantly the LV the diagnostic yield of LVEMB was 100% compared with 71% of RVEMB. In particular, this discrepancy was evident for myocarditis (LV 100% vs 67% RV), idiopathic and specific dilated cardiomyopathies (LV 100% vs 72% RV) and for restrictive cardiomyopathies such as endomyocardial fibrosis, sarcoidosis and idiopathic restrictive cardiomyopathy (LV 100% vs 74% RV). Conversely when the cardiac dysfunction involved also the RV the diagnosis was reached in 100% of LVEMB and 98% of RVEMB. In amyloidosis, haemochromatosis, cardiac glycogenosis and Fabry disease the histologic abnormalities were always detectable in both ventricles.
Conclusions: LVEMB is as safe as RVEMB. In addition it is more contributive than RVEMB in presence of a normal of poorly compromised RV.

1307 Non-invasive identification of senile systemic amyloidosis and mutant transthyretin-related amyloidosis with exclusively cardiac phenotype by 99mTc-DPD scintigraphy

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Purpose: Diagnosis of non-mutant transthyretin (TTR)-related amyloidosis (senile systemic amyloidosis, SSA) and of hereditary TTR-amyloidosis (ATTR) with exclusively cardiac phenotype is hampered by their capability to mimic other causes of left ventricular hypertrophy (LVH), such as hypertrophic cardiomyopathy (HCM) and hypertensive heart disease (HHD). Endomyocardial biopsy (EMB) and/or DNA analysis are necessary for a definitive diagnosis, but they are not routinely available. In patients with amyloidotic cardiomyopathy (CMP), 99mTc-DPD scintigraphy accurately identifies both TTR etiologies. We assessed the diagnostic accuracy of 99mTc-DPD scintigraphy in the non-invasive identification of SSA and ATTR with isolated CMP in a clinical context of patients with echocardiographic "unexplained LVH".
Methods: We performed a retrospective analysis of all patients who underwent 99mTc-DPD and EMB in 2004-2010 due to suspected TTR-related CMP. Myocardial uptake of 99mTc-DPD (740 MBq iv) was semiquantitatively/visually assessed at 3 h (and 5 min). Patients with AL amyloidosis or with already diagnosed ATTR, were excluded from the study.
Results: A total of 57 patients entered the analysis: 25 SSA; 20 ATTR; 12 non-amyloidotic LVH (9 HCM, 3 HHD). Results are shown in the table. Sensitivity, specificity, positive and negative predictive accuracy of positive myocardial tracer uptake (ie visual score $\geq$1) for the diagnosis of TTR etiologies were 100%.

	SSA (n=25)	ATTR (n=20)	Other CMPs (n=12)	p value
Age, yrs (mean±SD)	75±7	64±10	67±6	<0.001
Mean LV wall thickness, mm (mean±SD)	18±4	17±2	17±2	0.48
LVH on ECG (Sokolow>35 mm), n (%)	3 (8)	3 (15)	1 (8)	0.72
Heart tracer retention, % (median [IQR])	8.2 [6.5-9.3]	7.5 [5.8-7.9]	1.8 [1.5-2.3]	<0.001
Heart/whole-body retention ratio (median [IQR])	11.2 [9.3-13.4]	10.5 [9.7-11.4]	3.5 [3.2-4.3]	<0.001
Visual cardiac score = 0, n (%)	0 (0)	0 (0)	12 (100)	<0.001
Visual cardiac score = 1, n (%)	0 (0)	0 (0)	0 (0)	
Visual cardiac score = 2, n (%)	7 (28)	9 (45)	0 (0)	
Visual cardiac score = 3, n (%)	18 (72)	11 (55)	0 (0)	

LV = left ventricular; LVH = LV hypertrophy.

Conclusions: In patients with unexplained LVH, 99mTc-DPD scintigraphy can provide a useful non-invasive test for identification of patients with SSA and ATTR with exclusively cardiologic phenotype.

1308 Cardiotoxicity of pegylated liposomial doxorubicin versus epirubicin in women with breast cancer: the LITE randomized study

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Purpose: Cardiomyopathy following anthracycline chemotherapy may have ominous clinical implications in cancer patients. Liposomial anthracyclines have the potential for more selective uptake by cancer cells and reduced cardiac toxicity. We thus designed an independent randomized clinical trial to compare the cardiac safety of pegylated liposomial doxorubicin vs standard epirubicin in terms of clinical and subclinical cardiotoxicity (ClinicalTrials.gov identifier: NCT00531973).
Methods: Women with non-metastatic breast cancer and indication to anthracycline chemotherapy were randomized to pegylated liposomial doxorubicin or standard epirubicin plus additional chemotherapy and radiotherapy as per standard of care at our center. Baseline, post-chemotherapy and follow-up echocardiograms included standard left ventricular systolic and diastolic parameters, as well as tissue Doppler imaging (TDI) systolic and diastolic parameters. The primary end-point were the changes from baseline to follow-up of TDI systolic function parameters, given their superior sensitivity and spatial resolution.
Results: A total of 52 patients were included, 29 randomized to pegylated liposomial doxorubicin and 23 to epirubicin, who were followed for an average of 23 months since starting chemotherapy. Repeated-measure analysis showed that chemotherapy including pegylated liposomial doxorubicin was associated with more favorable changes in left ventricular ejection fraction (p=0.025), end-diastolic diameter (p=0.003), end-systolic diameter (<0.001), TDI septal S wave (p=0.016) and TDI lateral wall Em wave (p=0.037). Even at multivariable analysis adjusting for age, diabetes mellitus, and follow-up duration, chemotherapy including pegylated liposomial doxorubicin was associated with more beneficial changes in left ventricular end-diastolic diameter (p=0.013) and end-systolic diameter (p=0.017).
Conclusions: Pegylated liposomial doxorubicin is less cardiotoxic than epirubicin in women with non-metastatic breast cancer and indication to anthracycline chemotherapy.

1309 Aliskiren protects rats from experimental cardiomyopathy

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Purpose: Doxorubicin (DXR) is a broad spectrum anthracycline antibiotic used used in neoplastic diseases.It causes causes severe adverse effects, primarily cardiomyopathy and congestive heart failure. Renin-angiotensin system (RAS) plays an important role in the development of cardiac hypertrophy, heart failure and reperfusion injury. Aliskiren is a direct inhibitor of renin and does not affect other systems involved in cardiovascular regulation. This study was designed to investigate the possible protective effects of aliskiren in DXR induced cardiomyopathy in rats.
Methods: Rats were randomly assigned to seven groups consisting of eight animals each. Group I served as normal control and received normal saline (1ml/kg, p.o.) for 42 days. Group II served as toxic control and received DXR (1.25 mg/kg, i.p.) 4 times a week for 4 weeks starting from the 2nd week of the treatment. Groups III, IV, V and VI also received DXR as Group II, along with their respective treatments with aliskiren (30 mg/kg, p.o. and 100mg/kg, p.o.), telmisartan (10 mg/kg, p.o.) and combination of aliskiren and telmisartan for 42 days. Group VII served as per se and received aliskiren alone (100 mg/kg, p.o.) for 42 days. Blood samples were withdrawn after 24 hours of the last DXR treatment for estimation of Lactate dehydrogenase (LDH) and Creatinine phosphokinase (CK-MB) in serum. Animals were sacrificed and heart tissues were collected for biochemical and histopathological evaluation. Oxidative stress biomarkers {Catalase (CAT), Superoxide dismutase (SOD), and Glutathione (GSH)} and Caspase-3 activities were estimated in heart tissues. Transmission electron microscopy (TEM) was also done to find out the structural changes due to different treatments in the cardiac tissues of rats.
Results: DXR treatment significantly ($P<0.01$) increased the serum LDH and CK-MB activities. Aliskiren (100 mg/kg) treatment prevented the animals significantly ($P<0.01$) from rise in the above indices. Aliskiren treatment also significantly ($P<0.01$) protected the animals from DXR induced increase in Caspase-3, CAT, SOD activities and MDA content. DXR induced decrease in anti oxidant defense (GSH) was also significantly prevented by aliskiren (100 mg/kg). TEM results also revealed that aliskiren treatment protected the heart tissues from DXR induced cardiotoxicity. Telmisartan, used as reference in this study also exhibited significant protection. The protective effects of aliskiren were comparable to that of telmisartan.
Conclusion: Aliskiren protects the rats from DXR induced cardiotoxicity possibly by inhibiting renin-angiotensin system.

STRUCTURAL AND FUNCTIONAL IMPLICATIONS AFTER TAVI

1314 Reverse left atrium and left ventricle remodeling after aortic valve interventions

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Introduction: Severe aortic stenosis (AS) is associated with left atrium (LA) dilatation and left ventricle (LV) hypertrophy, which are related to diastolic dysfunction and adverse clinical outcomes. Reverse LA and LV remodelling have been previously described after aortic valve replacement (AVR), however, results after transcatheter aortic valve implantation (TAVI) are scarce. This study aimed to compare reverse remodelling in patients with severe aortic stenosis referred to TAVI or to AVR at midterm follow-up.
Methods: 129 patients older than 60 years, 72 (55.8%) submitted to TAVI and 57 (44.2%) to AVR were evaluated by bidimensional (2D) and 3D transthoracic echocardiography at baseline and 6 months after the procedure. LV mass was calculated by 3D guided biplane analysis, LV and LA volumes were calculated by direct volumetric analysis.
Results: TAVI patients were older (81.9±7.6 vs. 70.6±6.6; $p<0.001$), had more frequently arterial hypertension (81.9% vs. 61.4%; p=0.016), renal insufficiency (eGFR level< 50 ml/min) (27.8% vs. 10.5% p=0.027) and chronic obstructive pulmonary disease (41.3% vs. 21.1%, p=0.032). The gender distribution was similar among the two groups, (TAVI-39 (54.2%) female; AVR- 34 (59.6%) p=0.656) as well as prevalence of diabetes and dislipidemia. At 6 months follow-up both groups presented similar significant reductions in peak (85.9±22.3 mmHg to 16.8±8.5 mmHg; $p<0.001$) and mean (54.3±14.9 mmHg to 12.5±10.7 mmHg; $p<0.001$) transvalvular gradients and an increase in aortic valve area (0.6±0.1 cm^2 to 1.7±0.6 cm^2; $p<0.001$) and left ventricle ejection fraction (59.3±13.4% to 61.5±11.1% p=0.173). LA volume was larger in TAVI patients and a significant volume decrease (46.3±14.6 ml/m^2 to 41.4±13.9 ml/m^2; p=0.029) was observed in this group. However no significant LA volume reduction was shown in AVR patients (37.8±14.8 ml/m^2 vs. 36.2±12.1 ml/m^2; p=0.574), but LV mass reduction only occurred in this group (135.7±34.1 g/m^2 vs. 115.3±30.5 g/m^2; p=0.005) vs. (130.5±39.4 g/m^2 vs. 126.1±37.9 g/m^2; p=0.495) at TAVI group.
Conclusion: LA volume reduces at midterm follow-up after TAVI but LV mass significant reduction only occurred in AVR patients. These results might be explained by differences concerning the technical procedures or by the different characteristics between the two groups, as older patients with more comorbidities might present higher levels of LV fibrosis, restricting the availability for reverse LV remodelling.

1315 Echocardiographic evolution of paravalvular leaks after transcatheter aortic valve implantation of the CoreValve prosthesis in the first year of follow up

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Purpose: The frequency of any grade of regurgitation after transcatheter aortic valve implantation (TAVI) of the CoreValve prosthesis is 70-90% in previous studies. However, little is known about the mid term echocardiographic follow-up of this patients. Our purpose was to study the evolution of the residual regurgitation in the first year after TAVI of the CoreValve prosthesis in a series of patients.
Methods: From October 2008 to December 2010, 88 consecutive patients were treated with the CoreValve prosthesis because of severe aortic stenosis. A comprehensive transthoracic echocardiographic study was performed at discharge, one month and one year after TAVI, including assessment of the type (central regurgitation versus paravalvular leak) and grade (I to IV) of the regurgitation, evaluated according to the current echocardiographic guidelines. The study group included the 35 patients with complete one-year echocardiographic follow-up.
Results: At discharge, no patients presented central regurgitation more than trivial. At that moment, paravalvular leaks were present in 26 patients (74.2%). The regurgitation was grade I in 11 patients (31.4%), grade II in 13 (37.1%) and grade III in 2 patients (5.7%). There were no cases of grade IV regurgitation. A significant reduction in the grade of the leaks was observed after one month of follow-up ($p<0.001$), with paravalvular leaks present in 21 patients (63.6%). The regurgitation was grade I in 16 patients (48.5%), grade II in 4 patients (12.1%) and grade III in one patient (3%). One year after TAVI, the severity of the leaks remained similar to one month follow-up, although a non-significant trend towards a worse outcome was observed (p=0.09). At that time, paravalvular leaks were present in 25 patients (71.4%), with grade I regurgitation in 14 patients (40%), grade II in 9 patients (25.7%) and grade III in 2 patients (5.7%).
Conclusions: In this study, a significant reduction in the severity of leaks, at least in one grade, was observed one month after TAVI of the CoreValve aortic prosthesis. No significant changes in follow up were found from one month to one year, but these outcomes should be confirmed by larger studies.

1316 New methodology for paravalvular aortic regurgitation assessment in the era of transcatheter aortic valve implantation

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Purpose: Paravalvular AR (AR) after transcatheter aortic valve implantation (TAVI) is common, but its severity evaluation by bi-dimensional transthoracic echocardiography (2D TTE) presents several constrains. In the present study, we considered the usefulness of a new methodology, using 3D transthoracic echocardiography (TTE), for better assessment of paravalvular AR after TAVI.
Methods: 2D and 3D TTE were performed in 72 patients, 5 months after TAVI, using the X5-1, PureWave micro beam forming xMATRIX probe (ie33 echocardiography system, Philips Medical Systems, Eindhoven, The Netherlands®). The position and extension of the paravalvular AR jets were described when using 2D and 3D TTE and a model was designed for paravalvular AR systematic location description. Vena contracta width was measured using 2D TTE views and the planimetry of the vena contracta was assessed after the perfect alignment plane was obtained using the multiplanar 3D reconstruction tool. The AR volume was calculated as the difference between 3D derived total left ventricular stroke volume and the transpulmonary flow.
Results: Forty-three (57.4%) patients presented AR, 10 (13.3%) had central AR and 33 (44.0%) had paravalvular AR jets. Vena contracta width was similar between patients with moderate and mild AR (2.1±0.53 cm vs. 1.9±0.16 mm, p=0.16.) but vena contracta planimetry was larger in patients with moderate AR than in those with mild AR (0.30±0.12 cm^2 vs. 0.09±0.07 cm^2, p=0.001). 3D TTE vena contracta planimetry presented a better correlation with AR volume than the vena contracta width when assessed by 2D TTE (Kendall's tau correlation: 0.82, $p<0.001$ vs. 0.66, $p<0.001$).
Conclusion: This study proposes an alternative methodology for paravalvular AR assessment after TAVI. Using 3D TTE we found a simpler and more accurate methodology for paravalvular AR jets evaluation.

1317 Early changes in left ventricular mechanics after transcatheter aortic valve implant detected using speckle tracking strain imaging

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Purpose: Successful TAVI results in acute Left Ventricular (LV) haemodynamic changes. Pulmonary oedema within 24 hours of TAVI is recognised but its aetiology is not fully understood. In some patients pulmonary oedema occurs despite good LV function as measured by ejection fraction (EF). The aim of this study was to assess the very early changes in myocardial deformation following the abrupt reduction in afterload post TAVI. Speckle tracking strain analysis, a novel and well validated method for the assessment LV myocardial deformation mechanics was utilised for the first time in this setting.
Methods: In contrast to conventional surgery TAVI was performed under local anaesthesia in the majority of patients. In those performed under general anaesthetic patients were extubated immediately. Nine patients underwent echocardiography pre TAVI. 8 of the 9 patients had an echocardiogram performed in the first 72hrs post TAVI and the remaining 1 after one week. Trans-Aortic pressure gradients and aortic valve area (AVA) were measured. A vivid 7 echocardiography system was used for 2-D and Doppler imaging. LV images (frame rates 50-80FPS) were acquired in 5 standard views. Global LS was obtained by analysing 16 segments from the apical views. Myocardial LV Radial (RS), Circumferential (CS) and longitudinal strain (LS) analysis was performed using GE Echopac speckle tracking analysis software.
Results: AVA increased from 0.51±0.11 (mean±SEM) pre-TAVI to 2.0±0.07 sqcm post procedure ($P<0.001$) with a corresponding decrease in the peak pressure drop from 77.3±5.4 to 14.5±1.3mmHg ($P<0.001$). The EF (Simpsons Biplane) improved from 48.7±1.2 (pre-op) to 63.0±3.7 to post procedure (P=0.016). Peak global LS increased in magnitude from -8.6±0.7 to -10.3±0.8 (P=0.009). Peak CS and RS did not change significantly. CS was -10.0±2.0 and -10.1±1.6 pre and post TAVI respectively (P=0.96). The corresponding RS was 18.5±1.2 and 20.5±4.8 respectively (P=0.64)
Conclusions: The correction of aortic stenosis leads to complex adaptive changes of the LV in response to the acute reduction in afterload. Although changes in strain after conventional surgery have been described, we are the first to report a significant early improvement in global LS following TAVI and, consistent with changes post conventional surgery no significant change in CS and RS. Pulmonary oedema can occur despite the improvement in EF and global LS and therefore requires cautious attention to fluid balance. This may be explained by delayed changes in RS and CS. Further study to explore mechanisms and impact of potential late changes in RS and CS are indicated.

1318 Non-coaptation index predicts perivalvular aortic regurgitation after transcatheter aortic valve implantation

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Introduction: Transcatheter aortic valve implantation (TAVI) techniques have been presenting favourable hemodynamic results. However, some degree of residual paravalvular aortic regurgitation (AR) is common. The objective of this study was to access predictors of paravalvular AR after TAVI.
Methods: The aortic annulus area was measured in 74 consecutive patients using 3 D transesophageal echocardiography previously to TAVI. The aortic prosthesis area was measured after the intervention by planimetry using 3D echocardiography images. Among these, 53 (71.6%) were evaluated after 6.5 months (3.5 to 9.8 interquartile range) by 2D and 3D transthoracic echocardiography, using the X5-1, PureWave micro beam forming xMATRIX probe (ie33 echocardiography system, Philips Medical Systems, Eindhoven, The Netherlands®). For the purpose of prosthesis coaptation analysis a non-coaptation index was considered: [(aortic annulus area- aortic prosthesis area)/ aortic annulus area].
Results: At follow-up the prevalence of AR was similar to the immediate results after TAVI. Thirty- three (62.3%) patients presented AR, 6 (11.3%) had central AR and 27 (50.9%) had paravalvular AR jets. No significant relation was found between asymmetric aortic valve calcification and AR. Conversely the annulus diameter was larger in patients with AR (21.8±2.3 mm vs. 20.5±2.0 mm, p=0.046) as well as the non-coaptation index (0.36±0.21 vs. mean 0.18±0.22; p=0.011). Patients with a non-coaptation index≥0.3 presented an increased risk of AR [7.1 IC95% (1.8-28.9)].
Conclusion: Perivalvular AR at midterm follow- up after TAVI is common and it is associated with larger annulus diameter and higher non-coaptation index. As a result TAVI patients with high non-coaptation index might be recommended for cautious follow-up.

1319 Temporal changes in left ventricular function and paravalvular aortic regurgitation after transcatheter aortic valve implantation: a cardiac magnetic resonance imaging study

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Background: Transcatheter aortic valve implantation (TAVI) has become a common procedure for high-risk patients with severe aortic stenosis. Aortic regurgitation (AR) is commonly seen after TAVI, but little is known about how it evolves over time. Similarly, the impact of TAVI on left ventricular (LV) function, LV volumes and mass is not well defined.
Methods: Patients successfully treated with transfemoral TAVI using the Medtronic CoreValve bioprosthesis without contraindications for magnetic resonance imaging (MRI) underwent cardiac MRI 20±12 days after TAVI. Fourteen patients underwent follow-up MRI 11.3±7.1 months later and represent the population of the current study.
LV volumes and function were assessed using standard cine MRI sequences. Additionally, phase-contrast imaging was conducted to quantify the degree of AR, for which the slice was positioned in the ascending aorta at the upper margin of the stent holding the CoreValve prosthesis. A calculated regurgitant fraction (RF) of 0–15% was graded as I (mild), 16–30% as II (moderate), 31–50% as III (moderate to severe) and >50% as grade IV (severe) AR.
Results: The mean age of the evaluated patients was 81±5 years and 50% were women. At baseline MRI, the median LV ejection fraction was 54.9% (range 29.0 to 67.8%), which improved significantly at follow-up to 60.8% (range 24.0 to 71.9%, p=0.0017). LV end-diastolic volume (EDV) and myocardial mass did not significantly change. This was mainly due to one outlier with severely impaired LV function at baseline with further deterioration over time. Excluding this patient, a significant reduction of LV EDV (139.7±29.5 ml vs. 121.6±22.4 ml, p=0.017) and LV mass (139.3±21.0 g vs. 124.8±23.4 g, p=0.041) was observed. This was associated with a significant reduction of NT-pro-BNP levels at follow-up (1933±779 pg/ml vs. 621±470 pg/ml, p=0.008).
Baseline MRI identified mild AR in 11 patients and moderate AR in 3 patients. Over time, aortic RF increased significantly from 8.08% (range 0.11 to 26.84%) to 11.99% (range 1.94 to 40.01%, p=0.004), resulting in 10 patients with mild, 3 patients with moderate and one patient with moderate to severe AR at follow-up MRI.
At both time points, we observed a significant negative correlation between myocardial mass and LV ejection fraction, with r = -0.66 at baseline MRI and r = -0.85 at follow-up.
Conclusion: Using cardiac MRI, mild to moderate AR is commonly seen in patients treated with TAVI. AR mildly increases over time. Nevertheless, a significant improvement of left ventricular function at follow-up MRI can be observed.

UPDATE ON CARDIORENAL SYNDROME

1332 The impact of renal function on platelet reactivity and clinical outcome in patients undergoing percuatenous coronary intervention with stenting

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Objectives: To determine the influence of an impaired renal function on the magnitude of platelet reactivity and clinical outcome.
Background: Patients with chronic kidney disease (CKD) have an increased risk of cardiovascular disease. Previous studies have suggested that patients with renal failure have less therapeutic benefit of antiplatelet therapy. There are, however, few data on the relation between renal function and platelet reactivity.
Methods: On-clopidogrel platelet reactivity was determined in 988 patients on dual antiplatelet therapy, undergoing elective coronary stent implantation, using adenosine diphosphate-induced light transmittance aggregometry (LTA) and the VerifyNow®P2Y12-assay. Patients were divided into two groups according to the presence or absence of moderate/severe CKD (glomerular filtration rate<60ml/min). Furthermore, the incidence of the composite of all-cause death, non-fatal acute myocardial infarction, stent thrombosis and ischemic stroke at one-year follow-up was evaluated.
Results: Patients with CKD (n=180) had significantly higher platelet reactivity, regardless of the platelet function test used (43.0±14.8% vs. 39.2±14.4%, p=0.002 using LTA and 226±82.2 vs. 207±73.8 PRU, p=0.004 using the VerifyNow®P2Y12-assay. Patients with CKD more frequently had high on-clopidogrel platelet reactivity (HCPR); OR = 2.00; 95%-CI: 1.43-2.83, p=0.0001 using LTA and OR = 1.64; 95%-CI: 1.16-2.30, p=0.005 using the VerifyNow®P2Y12-assay. The event-rate was the highest in patients with both HCPR and CKD (8.4%[16/87] vs. 4.8%[24/504] in those with neither HCPR nor CKD using the VerifyNow®P2Y12-assay).
Conclusion: Both the magnitude of platelet reactivity as well as the incidence of HCPR was higher in patients with CKD. CKD-patients with HCPR were at the highest risk of long-term cardiovascular events, suggesting the need for intensified antiplatelet therapy in these high-risk patients.

1333 Clinical and prognostic relevance of acute kidney injury in patients with acute coronary syndromes

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Purpose: Acute kidney injury (AKI) frequently occurs in patients admitted to the CCU for acute coronary syndromes (ACS). Several factors may contribute to its development, such as hemodynamic instability, use of contrast agents during PCI, bleeding associated with the use of potent antithrombotic agents, and drug toxicity. Regardless the causative factor(s), AKI has been associated with adverse short-term and long-term outcomes. To date, however, no standardized definition of AKI has been utilized in ACS. As a result, information on the true incidence of AKI in patients with ACS, as well as on its clinical and prognostic relevance according to severity of renal function deterioration, is still lacking. We evaluated the incidence of AKI, according to the AKIN/RIFLE definition, in a large, single-center, cohort of ACS patients, and the possible association between its severity and in-hospital morbidity and mortality.
Methods: We retrospectively considered 2166 ACS patients admitted to our CCU for at least 48 hours. For each patient, serum creatinine (sCr) was measured at hospital admission and, then, every day up to discharge. AKI was defined by the change in sCr during hospitalization compared with baseline sCr. Patients with AKI were stratified according to the maximum class reached: Stage 1 corresponds to increase in sCr>0.3 mg/dl from baseline; Stage 2 to increase in sCr>2- to 3-fold from baseline, and Stage 3 to increase in sCr>3-fold from baseline or sCr>4.0 mg/dl with an acute increase of at least 0.5 mg/dl, or need for renal replacement therapy (RRT), irrespective of the stage they are at the time of RRT.
Results: Overall, 285 (13%) patients developed AKI during hospitalization. Of them, 196 (69%) had a Stage 1, 19 (7%) a Stage 2, and 70 (24%) a Stage 3 AKI. In-hospital mortality (3% in the whole population) was higher in patients with AKI than in those without AKI (19% vs. 0.5%; P<0.001). We found a significant gradient of in-hospital mortality when patients outcome was evaluated according to the AKI severity: 0.5% (no AKI), 9% (Stage 1 AKI), 32% (Stage 2), and 41% (Stage 3) (P<0.001). A similar statistically significant trend (P<0.001) was observed for CCU length of stay (4±3, 7±5, 9±6 and 10±9 days, respectively) and for major adverse cardiac events (25%, 61%, 79% and 83%, respectively).
Conclusions: In patients with ACS, AKI represents a frequent complication (13% of cases) associated with increased in-hospital mortality. The severity of AKI, as evaluated by the AKIN/RIFLE classification is able to reflect, like in other non cardiologic settings, short-term prognosis of ACS patients.

1334 Low diastolic blood pressure is not an independent risk for cardiovascular death in revascularized coronary artery disease patients. A subanalysis CREDO-kyoto study

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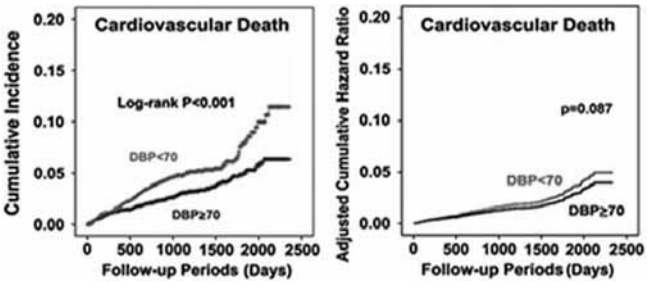
Purpose: It remains controversial whether extremely low diastolic blood pressure (DBP) is a risk for cardiovascular (CV) events in patients with coronary artery disease (CAD). Coronary revascularization therapy became prevalent in CAD patients. Accordingly, we sought to determine the impact on low DBP on the long-term CV events and to investigate the predicting factors in revascularized CAD patients.
Methods and results: This study enrolled 7,180 stable, chronic CAD patients (median follow-up period; 3.6 years) of 9,877 patients undergoing first coronary artery bypass graft or percutaneous coronary intervention in the registry of the Coronary REvascularization Demonstrating Outcome study in Kyoto (CREDO-Kyoto). Kaplan-Meier analysis revealed that unadjusted cumulative incidence of CV death was greater in patients with preprocedual DBP <70 mmHg than in those with DBP ≥70 mmHg, whereas the cumulative incidences of non-fatal myocardial infarction (MI) and stroke did not differ between the two groups. Stepwise logistic regression analysis showed that estimated glomerular filtration ratio (inversely), pulse pressure, LV ejection fraction<0.40, history of heart failure, prior cerebrovascular disease, and prior MI were independent risks for CV death in patients with DBP <70 mmHg. After adjustments by the independent risks, the cumulative hazard ratio for CV death did not differ between patients with DBP <70 mmHg and those with DBP ≥70 mmHg.



Crude and adjusted CV death incidence.

Conclusions: Renal insufficiency, more advanced vascular damage, and LV systolic dysfunction were significant factors accounting for increased CV death in revascularized CAD patients with DBP <70 mmHg. It was suggested that after adjustments by these independent risks, low DBP is not a significant risk for CV death in revascularized CAD patients.

1335 Risk of cardiovascular and bleeding events and mortality in patients with chronic kidney disease and ACS undergoing PCI: results from the APTOR-II study

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Purpose: Chronic kidney disease (CKD) is associated with poor outcomes in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). However, mid-term data are limited on the frequency of cardiovascular (CV) events, especially stent thrombosis, bleeding, and mortality in a real-world European ACS population.
Methods: ACS patients undergoing PCI from 2008-2009 were enrolled in a prospective, observational registry of 11 European countries, APTOR-II. Patients were grouped by their calculated creatinine clearance (CrCl), estimated by the Cockcroft Gault equation. 2,273 patients (75%) had no or mild renal impairment (defined as CrCl ≥60 mL/min/1.73m^2), 611 patients (20%) had moderate to severe renal impairment (<60 mL/min/1.73m^2), and 158 patients (5%) had missing information. Among patients with moderate to severe renal impairment, 90% had a CrCl ≥30-<60, 7% had a CrCl ≥15-<30 and 3% had a CrCl <15. Kaplan-Meier estimates at 12 months after PCI were calculated for the following outcomes: CV event, such as stent thrombosis, bleeding and mortality.
Results: Patients with CrCl <60 mL/min/1.73m^2 tended to be older (median age: 75 vs. 59 years) and to have a greater prevalence of hypertension (75% vs. 56%) and prior myocardial infarction (26% vs. 17%). 12 months after PCI, these patients also were at greater risk for a CV event, bleeding, and mortality compared to patients with CrCl ≥60 mL/min/1.73m^2 (table).

Kaplan-Meier (KM) estimate at 12 months

Event	CrCl ≥60 mL/min/1.73m^2 (N=1953)		CrCl <60 mL/min/1.73m^2 (N=754)	
	n at risk at 12 months	KM % (95% CI)	n at risk at 12 months	KM % (95% CI)
CV Event*	1543	14.9 (13.4, 16.3)	364	21.8 (18.4, 25.1)
Stent thrombosis	1791	1.6 (1.1, 2.1)	448	1.9 (0.8, 3.0)
Bleeding	1781	2.1 (1.5, 2.6)		435 4.7 (3.0, 6.4)
All-cause mortality	1820	1.4 (0.9, 1.9)	454	6.3 (4.4, 8.3)

*CV event includes UA, NSTEMI, STEMI, UTVR, acute heart failure, stent thrombosis, ischemic and hemorrhagic strokes, and CV death.

Conclusions: At 12 months after PCI, ACS patients with CKD tended to have greater rates of both ischemic and bleeding events and higher mortality compared to patients with no or mild renal impairment. Caution has to be exerted with CKD patients when deciding on invasive and antiplatelet treatments.

1336 Prognostic value of baseline renal function on long term outcome in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction

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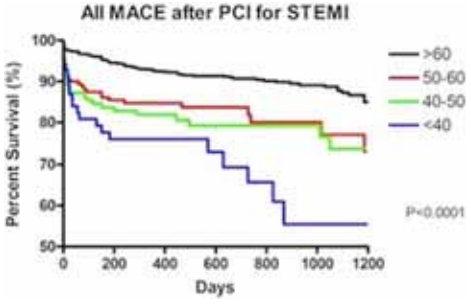
Background: Renal impairment is associated with increased cardiovascular mortality following acute coronary syndromes (ACS), however there is limited data assessing this relationship in the context of primary PCI and whether it exists with other major adverse cardiovascular events.
Methods: Clinical information was analysed from a prospective data base on 2310 STEMI patients who underwent Primary PCI between January 2004 and May 2010 at a London centre. Information was entered at the time of procedure and outcome assessed by all-cause mortality information provided by the Office of National Statistics via the BCIS/CCAD national audit. Estimated glomerular filtration rate (eGFR) was calculated using the modified diet in renal disease equation and patients were divided into groups based on eGFR (<40, 40-50, 50-60, >60 ml/minute/1.73m^2). 3 year composite of MACE (death, reinfarction, stroke and target vessel revascularisation) were compared between groups.
Results: The average eGFR in all patients was 73.40±23.37 (95% CI 72.25 – 74.56) ml/minute/1.73m^2. The prevalence of co-existing risk factors (hypertension, diabetes mellitus, hypercholesterolaemia), previous MI, previous CABG and cardiogenic shock were higher among patients with reduced eGFR. There was a progressive increase in MACE with declining eGFR (OR = 4.84, 95% CI 2.94 – 7.96, for comparison between the highest and lowest eGFR groups). After adjustment for baseline characteristics including age, diabetes and cardiogenic shock renal function based on the GFR at admission remained a strong independent predictor of outcome.



Survival post-STEMI based on eGFR

Conclusion: Baseline renal dysfunction in patients undergoing Primary PCI is associated with an increased risk for combined death, re-infarction and recurrent angina. This risk increases linearly with declining eGFR.

1337 Prognostic impact of occult renal failure on acute coronary syndromes

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Aim: Occult renal failure is frequently under diagnosed on clinical practice. Recent papers claim prognosis impact on different clinical settings. The prevalence and prognosis impact on acute coronary syndrome patients is not well established.
Our goal is to evaluate the prevalence and prognostic impact of occult renal fail-

ure, defined by creatinine clearance <60ml/min (Cockroft-Gault) and normal creatinine levels (<1,3mg/dl) in acute coronary syndrome patients.
Methods: We studied 560 patients consecutively admited to our department, average age 61±11 years, 78%males, 64% NSTEMI. Prognosis was evaluated by the combined endpoint of death or AMI on follow up (745±439 days). Demographic and clinical differences were compared between the populations with and without occult renal failure. Prognosis impact of variables was adjusted by Cox regression.
Results: Prevalence of occult renal failure was 13.3% (91patients), and was associated to older population, higher BMI, more often hypertensive, smokers and with higher prevalence of peripheral vascular disease and cerebral vascular disease. The incidence of death or AMI on follow up was 17,6% (29,6% on population with occult renal failure vs. 13.6% on the population without; adjusted HR 2.12, CI 95% 1.13-3.99; p=0.019).
Conclusions: In our population of patients with acute coronary syndrome with normal creatinine levels, occult renal failure was detected in 13.3% of cases and was an independent predictor of worse prognosis at follow up. Thus, occult renal failure should not be underestimated in clinical practice.

CARDIOPULMONARY RESUSCITATION: NEW APPROACHES TO AN OLD TREATMENT

1356 Comparison of 1-shock protocol versus 3-stacked-shock protocol for treatment of out-of-hospital ventricular fibrillation cardiac arrest

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Background: The 2005 guidelines for electrical therapies of cardiopulmonary resuscitation (CPR) led to the recommendation of single shocks plus immediate 2 minutes of CPR instead of 3-shock sequences in victims of sudden cardiac arrest (Class 2a). Emergency medical service (EMS) personnel who arrive at the patient's side may provide 2 minutes of CPR before checking the cardiac arrest rhythm and attempting defibrillation (Class 2b). It is not known whether the neurologically intact survival rate will increase if EMS personnel perform the CPR according to the new recommendations of electrical therapies.
Methods: The JCS-ReSS investigated the effect of the change in electrical therapies (2 minutes of CPR before checking the cardiac arrest rhythm, and 1 shock followed immediately by 2 minutes of CPR). Data of patients with out-of-hospital cardiac arrest from the all-Japan Utstein Registry of the Fire and Disaster Management Agency were analyzed. The primary end point was favorable neurological outcome at 30 days after out-of-hospital cardiac arrest, defined as a Glasgow-Pittsburgh cerebral-performance category (CPC category) of 1 or 2. The secondary end point was survival at 30 days after out-of-hospital cardiac arrest, defined as a CPC category of 1, 2, 3, or 4.
Results: Of the 93,540 patients with witnessed out-of-hospital cardiac arrest due to cardiac etiology, 10,596 patients with an age of 15 years and over, with no bystander CPR, and with shockable cardiac arrest rhythm on EMS arrival at patients side were included; 4,003 received defibrillation procedures according to the 2000 guidelines (the 3-shock group), 4,359 received defibrillation procedures according to the 2005 guidelines (the 1-shock group).
The 1-shock group had higher proportions of 30-day neurologically intact survival than the 3-shock group in among all patients in the study (19.4% vs. 13.1%; p<0.0001). A multiple logistic-regression analysis showed that the adjusted odds ratio for 30-day neurologically intact survival after 1-shock procedures was 1.67 (95% CI, 1. 48 to 1.89, p<0.0001).
Conclusions: The defibrillation procedures of the 2005 guidelines are superior to those of the 2000 guidelines in terms of neurological benefit.

1357 Early induction of veno-arterial extracorporeal membrane oxygenation in patients with shock before cardiac arrest

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Purpose: Veno-arterial extracorporeal membrane oxygenation (ECMO) could rapidly provide temporary circulatory assistance for patients complicated with shock or cardiac arrest. However, the optimal timing of initiation of ECMO is still unclear. The patients complicated with shock may frequently develop to cardiac arrest. We have studied the efficacy of ECMO in patients with shock in the comparison of the presence or absence of cardiac arrest. The results demonstrated that the early induction of ECMO may be useful for the patients with shock without cardiac arrest.
Methods: We conducted a retrospective study at two regional tertiary care centres. We divided the patients into two groups on the basis of more than one occurrence of cardiac arrest (CPA group) or absence of cardiac arrest (Shock group) before the initiation of ECMO. We assessed survival rate of patients with two groups by using the Kaplan-Meier method. Shock patients may become PEA (pulseless electrical activity). We compared the patients of Shock group with CPA group whose initial recorded rhythm was PEA as sub analysis.
Results: Of the 149 adult patients enrolled, 29 (19%) were assigned to the Shock group, and the remaining 120 patients to the CPA group. There was no significant difference in the baseline characteristics, age and sex. The incidence of myocarditis was significantly higher in Shock group than in the CPA group (31% vs. 3%, P<0.01). The rate of weaning from ECMO (72% vs. 42% P<0.01), 30-day survival (65% vs. 24%, P<0.01), 365-day survival (62% vs. 20%, P<0.01), and favourable neurological findings (58% vs. 19%, P<0.01) in the Shock group were significantly higher than in the CPA group. Survival analysis revealed a higher 365-day survival in the Shock group (log lank P<0.01). Stepwise Cox proportional hazard regression analysis revealed that induction of CPA (OR 1.68, 95%CI 2.42-1.25) were independent predictors of 365-day survival. Of the 89 adult patients enrolled sub analysis, 60 (68%) were assigned to the CPA-PEA group. The incidence of myocarditis was significantly higher in Shock group than in the CPA-PEA group (31% vs. 5%, P<0.01). The incidence of pulmonary embolism was lower in Shock group (3% vs. 28%, P<0.01). The similar findings were observed in the rate of weaning from ECMO, favourable neurological findings, 30-day survival, 365-day survival, survival analysis and multivariate analysis.
Conclusions: These results suggest that early circulatory support with ECMO may be useful for the treatment in patients with shock before cardiac arrest.

1358 Should we open the occluded coronary artery in patients with refractory cardiac arrest of acute coronary syndrome using extracorporeal membrane oxygenation and percutaneous coronary intervention?

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Purpose: Veno-arterial extracorporeal membrane oxygenation (ECMO) provides rapid temporary circulatory support for patients with refractory shock or cardiac arrest, enabling us to perform subsequent therapeutic interventions. We tested the hypothesis that an opened coronary artery results in improved outcomes.
Methods: We conducted a retrospective study at regional tertiary care hospitals. Patients with refractory cardiac arrest of acute coronary syndrome who failed to respond to conventional cardiopulmonary resuscitation (CPR) and who underwent ECMO were enrolled. We divided them into the percutaneous coronary intervention (PCI) group and non-PCI group (wherein no PCI was performed), and assessed tem for weaning from ECMO, 30-day survival, and favourable neurological outcomes. We plotted a 365-day Kaplan-Meier survival analysis curve. Multivariate analysis was done to assess the independent predictors of the 365-day survival.
Results: IN total, 47 and 21 patients belonged to the PCI and non-PCI group, respectively. Emergency coronary angiography and mild hypothermia was performed in 63 and 20 patients, respectively. The baseline characteristics did not differ between the 2 groups. The main reasons for not performing PCI were thrombolysis in myocardial infarction 3 flow that made PCI of the culprit lesion difficult and/or multi-vessel disease. The time interval from collapse to initiation of CPR was significantly shorter in the PCI group than in the non-PCI group (1 [IQR 0-1] min vs. 1 [0-8] min, P=0.04). Total collapsed duration was significantly shorter in PCI group than non-PCI group (56 [IQR 41-67] min vs. 32 [19-58] min, P<0.01). The rates of weaning from ECMO (62% vs. 24%, P<0.01), and favourable neurological outcomes (30% vs. 5%, P=0.03) were significantly higher in PCI group than in non-PCI group. All patients treated with PCI achieved return of spontaneous heart-beat (ROSB); thus, the rate of ROSB was significantly higher in PCI group than in non-PCI group (100% vs. 57%, P<0.01). Survival rates improved survival in PCI group as compared to those in non-PCI group (30% vs. 5%, P<0.01). Multivariate analysis showed that PCI was an independent predictor of 365-day survival (odds ratio 1.39 (95%CI 1.64-32.68), P=0.03).
Conclusions: PCI with ECMO was feasible, effective for ROSB, and may improve survival in refractory cardiac arrest.

1359 Therapeutic hypothermia, QT prolongation and ventricular tachyarrhythmias in patients after out of hospital CPR

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Purpose: It has been demonstrated that hypothermia can be associated with prolongation of the corrected QT interval (QTc), which is a known risk for ventricular tachyarrhythmias. The aim of the study was to assess the prevalence of QTc prolongation due to mild therapeutic hypothermia (MTH) and the prognostic implications on recurrent ventricular tachyarrhythmias (ventricular tachycardia/fibrilation) in patients after out of hospital CPR due to sudden cardiac arrest (SCA).
Methods: We studied 75 patients admitted to ICCU due to SCA. Forty one patients (54.7%) were treated with MTH. QT interval and serum electrolytes on admission and after 6, 12, 24 and 48 hours were measured. QTc was calculated using Bazett's formula. Logistic regression models were used to evaluate the re-

lationship between QTc prolongation and development of ventricular tachyarrythmias.
Results: The QTc at 6, 12, 24 and 48 hours in the MTH and non-MTH groups were: 512±70 and 476±49 (p=NS), 527±59 and 467±37 (p=0.001), 520±66 and 466±67 (p=0.006), 476±57 and 460±48 (p=NS), respectively. There were no statistical significant differences between the groups regarding serum electrolytes levels in the same time period. During the first 72 hours of hospitalization 4 patients (9.8%) in the MTH group and 16 (48.5%) in the non-MTH group suffered ventricular tachyarrhythmias (p=0.0001). The odd ratios for ventricular tachiarrythmia in the hypothermia group as compared with the non-hypothermia group was 0.11 (95% CI 0.03-0.39, p<0.001). After adjusting for age, gender, acute myocardial infarction, electrolytes, left ventricular systolic function and QTc at 12 and 24 hours, MTH remained strongly related to a reduced occurrence of ventricular tachyarrhythmias [OR=0.02 (95%CI 0.01-0.237; p=0.002)]. There was no difference in mortality during ICCU stay between the two groups.
Summary: Our results suggest that QTc prolongation due to mild therapeutic hypothermia is not arrythmogenic and, for out of hospital CPR due to SCA, this therapeutic strategy may protect against ventricular tachyarrhythmias.

1360 ECG changes in patients treated with mild hypothermia after cardio-pulmonary resuscitation for out-of-hospital cardiac arrest

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Background: Mild therapeutic hypothermia improves neurologic outcome in patients after resuscitation. Under hypothermia, changes in the 12-lead ECG are observed. However, the effect of mild therapeutic hypothermia on parameters of the 12-lead ECG has not yet been systematically investigated.
Methods: In consecutive patients admitted after succesful out-of-hospital cardiac arrest due to ventricular fibrillation or asystole, hypothermia (33-34°C) was induced for 24 hours via an intravenous cooling catheter. After the cooling period, controlled rewarming (0.2°C/h) was started to re-establish normothermia. On admission to hospital, during hypothermia and after rewarming a 12-lead ECG was recorded and the following parameters were determined: heart rate, PQ interval, QRS period and heart-rate-corrected QT interval.
Results: 68 patients were included (49 male, 19 female). The mean age was 65.0±12.5 years. During hypothermia, heart rate decreased significantly from 87.1±21.1/min to 72.3±20.3/min (p<0,001). PQ interval did not change significantly (167.2±23.0 ms vs. 171.4±39.2 ms during hypothermia). Compared to the time of admission to hospital, QRS duration decreased during hypothermia significantly from 128.6±31.5 ms to 119.2±26.0 ms (p=0,025) and continued to decrease during the period of rewarming (109.9±27.7 ms, p<0.01). The heart-rate-corrected QT interval showed a signficant prolongation during hypothermia from 480.3±50.4 ms to 521.2±46.9 ms (p<0,001) and a shortening after rewarming to 473.7±45.4 ms.
Conclusions: Therapeutic hypothermia leads to significant prolongation of the heart-rate-corrected QT interval. This effect must be considered in patients after cardio-pulmonary resuscitation to avoid misinterpretation of the ECG concerning the cause of cardiac arrest.

1361 Superiority of a novel index, regional brain oxygen saturation, for neurological prognostication after out of hospital cardiac arrest

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Background: There is no time to consider whether or not we should perform emergency post-cardiac-arrest interventions (PCAI) in cardiac arrest on arrival (CAOA) patients (pts). If an agile and reliable index could prognosticate neurological outcome, it would help to determine PCAI strategies as quickly as possible. Base Excess (BE) and lactate were used as conventional indexes for prognostication of out of hospital cardiac arrest (OHCA) pts, however it was reported their positive predictable values (PPV) were not 100% and it took time to obtain these results, because it was difficult to take a blood sample. So we focused on noninvasive regional brain oxygen saturation (rSO2), which efficiency of prognostication after coronary bypass surgery was reported, and compared it with conventional indexes.
Methods: Of the 153 consecutive OHCA pts, 82 non-trauma CAOA pts (mean age: 71, male: 53 pts) were prospectively included. rSO2 was measured using a near-infrared spectroscopy device (INVOS, Somanetics, USA) placed over the skin of forehead immediately after hospital arrival, simultaneously with measurements of BE and lactate. The primary endpoint was defined as good neurological outcome at hospital discharge according to the "Utstein style" guideline.
Results: Within 3 minutes after hospital arrival, we were able to measure rSO2 to all pts. Despite the best available therapy, all pts (n=51) with rSO2 ≤25% (optimal cutoff) showed poor neurological outcome at hospital discharge (PPV=100%). The area under the curve (AUC) for predicting poor neurological outcome for rSO2 was significantly larger than that for BE or for lactate (table).

Table: ROC analysis to predict poor neurological outcome.

	Optimal cutoff	AUC		P value	Sensitivity (%)	Specificity (%)	PPV (%)
rSO2 (%)	25	0.91	*	<0.0001	75.4	100	100
BE (mmol/L)	-9.9	0.73	**	0.0027	92.8	53.9	91.4
Lactate (mmol/L)	11.8	0.71		0.0054	58.0	76.9	93.0

* p=0.0461, ** p=0.0128

Abbreviations: ROC, receiver operating curve; AUC, area under the curve; PPV, positive predictive value

Conclusion: Compared with conventional indexes, rSO2 is more an agile and reliable index for neurological prognostication after OHCA, concerning specificity, PPV and AUC.

POSTER SESSION 2

ASSESSING AND INFLUENCING VASCULAR FUNCTION

P1366 Increased formation of monocyte-platelet aggregates is confined to specific monocyte subsets in heart failure

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Purpose: Monocyte-platelet aggregates (MPAs) are a marker of platelet activation and their numbers are increased in thrombotic states. Aggregation with platelets also regulates monocyte activity related to inflammation, fibrinolysis and tissue repair. Heart failure (HF) is an inflammatory process with an increased risk of thrombosis but it is unknown whether MPA formation is increased in this condition.
Methods: Patients with acute HF (AHF) were compared to stable (HF) and two controls: stable coronary disease without HF (SCD) and healthy (HC). All HF patients had an underlying ischemic etiology. Exclusion criteria included ACS and other inflammatory conditions. Monocytes are heterogenous and consist of three distinct subsets that can be discriminated by their surface marker expression: CD14+CD16-CCR2+ (Mon1), CD14+CD16+CCR2+ (Mon2) and CD14lowCD16+CCR2- (Mon3). Total MPA count and MPAs within each subset (MPA-Mon1, MPA-Mon2, MPA-Mon3) were measured by flow cytometry by the expression of platelet surface marker CD42a on monocytes.
Results: AHF patients had significantly higher total MPAs, MPA-Mon1 and MPA-Mon2 compared with SHF and controls (Table). SHF patients had significantly higher total MPAs, MPA-Mon1 and MPA-Mon2 compared with controls. There were no significant differences in MPA-Mon3 between the groups.
Conclusions: This demonstrates for the first time that HF is associated with increased numbers of MPAs and this increase is confined to monocytes from subsets Mon1 and Mon2. Patients admitted with AHF have significantly higher MPA counts than those with more stable disease. MPAs may therefore be important as a marker of the hypercoaguable state seen in HF and may also reflect a pathophysiological mechanism for the regulation of monocyte activity in HF.

Abstract P1363 – Table 1. MPAs for monocyte subsets

MPAs (per μl)	AHF (n=44)	SHF (n=38)	SCD (n=38)	HC (n=29)	p Value*
Total MPA	129.6 (93.2–159.0) a,b,c	87.5 (59.2–121.0) d,e	70.2 (45.0–97.6)	62.0 (48.2–78.5)	<0.001
MPA-Mon1	93.3 (74.8–133.7) a,b,c	69.2 (45.0–101.7) d,e	52.3 (35.1–76.0)	48.2 (34.7–69.3)	<0.001
MPA-Mon2	15.9 (8.9–25.3) a,b,c	8.6 (4.8–12.5) d,e	4.5 (2.8–8.7)	7.0 (2.6–9.5)	<0.001
MPA-Mon3	8.5 (6.1–17.4)	8.9 (6.4–12.0)	8.9 (5.8–11.1)	7.3 (4.4–9.8)	0.067

Values expressed as median (interquartile range). *Calculated by Kruskal-Wallis. Tukey post hoc analysis on log transformed data: a = AHF vs SHF p<0.05, b = AHF vs SCD p<0.001, c = AHF vs HC p<0.001, d = SHF vs SCD p<0.05, e = SHF vs HC p<0.05.

P1367 Epigenetic regulation of cell adhesion and cell communication pathways by the histone methyltransferase Ezh2 in human endothelial cells

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Purpose: Epigenetic modifications such as DNA and histone methylation have long-term effects on the expression of affected genes. Polycomb group (PcG) proteins are key regulators of the human epigenome and form so called Polycomb repressive complexes (PRC). A crucial subunit of PRC2 is the histone methyltransferase Enhancer of zeste homolog 2 (Ezh2). Ezh2 mediates (tri-)methylation of lysine 27 in histone 3 (H3K27me3) which results in long-term suppression of adjacent genes. Several previous studies identified an essential role for Ezh2 in differentiation processes of human stem cells. In contrast, little is known about Ezh2 target genes in differentiated cells. Interestingly, a recent study showed impaired "tube formation" after siRNA-mediated knock down of Ezh2 in human umbilical vein endothelial cells (HUVEC) in Matrigel assays. As this finding suggests a functional relevance of Ezh2 in differentiated endothelial cells, the aim of our recent study was to identify Ezh2 target genes in endothelial cells.
Methods and results: As a first step, we performed ChIP-on-chip experiments (i.e., chromatin immunoprecipitation using a H3K27me3 antibody followed by a whole genome promoter gene array) and identified 5585 genes whose promoters were associated with H3K27me3 in endothelial cells. Next, we transfected HUVEC with siRNA directed against Ezh2. 72 hours after transfection, Ezh2 expression was reduced by 70% on the mRNA level and virtually absent on the protein level in immunoblots. Whole genome expression arrays identified 964 genes that were regulated by more than twofold 72 hours after knock down of Ezh2. Taken together, our experiments identified 276 genes that were associated with H3K27me3 in ChIP-on-chip experiments and whose expression was upregulated by more than twofold after knock down of Ezh2. Among them, genes associated with the GO terms "cell communication" (e.g., FGF, IGF, interleukin 1-beta, TGF-alpha and Wnt5b) and "cell adhesion" (e.g., integrin 9-alpha and cadherin 13) were significantly overrepresented ($p<0.01$).
Conclusion: Combining ChIP-on-chip and mRNA expression arrays, we were able to identify 276 putative target genes of Ezh2 in endothelial cells. Bioinformatical analysis revealed a GO term pattern which suggests epigenetic regulation of cell adhesion and cell communication processes by Ezh2 in endothelial cells.

P1368 Coronary flow reserve and myocardial perfusion in type 2 diabetic patients without obstructive coronary artery disease

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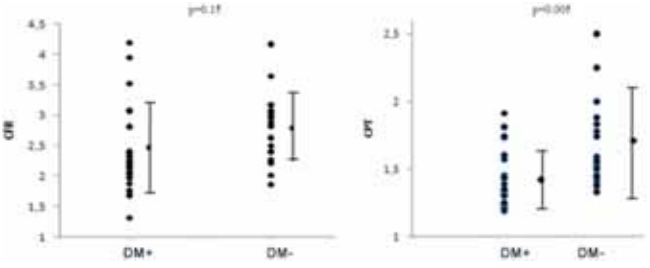
Purpose: To assess coronary microvascular function and myocardial perfusion in type 2 diabetic (DM 2) patients without Coronary Artery Disease (CAD).
Methods: 20 type 2 diabetic patients (10 men; age 62.5±10.7 years) underwent coronary angiography, single photon emission computed tomography (SPECT), transthoracic echocardiographic Coronary Flow Reserve (CFR) and Cold Pressor Test (CPT) within 1 week, and were compared to 19 age-matched non-diabetic patients (10 men; age 59.2±9.8 years) who underwent coronary angiography, CFR and CPT. CFR reflects primarily endothelium-independent vasodilation, while CPT reflects endothelium-dependent vasodilation. All patients had no angiographically significant CAD.
Results: CPT was significantly lower in patients with DM 2 compared to patients without DM 2 (1.42±0.22 vs 1.71±0.36; p=0.005); CFR was not significantly different in diabetic patients and non diabetics (2.46±0.76 vs 2.79±0.56; p=0.13). However, at SPECT only 5 diabetic patients (3 of them with impaired FR) showed mild inducible ischemia (summed difference score >3 and <7), whereas normal perfusion at rest and pharmacological stress was observed in the remaining 15 patients. Additionally, there was a significant Pearson's correlation test between CPT and fasting glycemia in the same day (r=0.345; p=0.03).



Conclusions: Type 2 diabetic patients without CAD show significantly impaired endothelial function compared to non diabetic patients without CAD, which correlates to fasting glycemia whereas no correlation was found between glycosylated hemoglobin and either CPT or CFR. However, myocardial perfusion is normal in the majority of them (15/20). These data should foster follow-up studies to evaluate the prognostic impact of impaired CFR and CPT in these patients.

P1369 Levels of soluble receptor for advanced glycation end-products are related with arterial stiffening, albuminuria and glomerular filtration rate in essential hypertensive subjects

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Purpose: Emerging evidence implicates the soluble receptor for advanced glycation end-products (sRAGE) in the development of vascular disease, while arterial stiffening, urinary albumin excretion and impaired renal function are associated with atherosclerosis progression. In the present study, we investigated the interrelationships of sRAGE with urinary albumin excretion, expressed as the albumin to creatinine ratio (ACR), estimated glomerular filtration rate (eGFR) and arterial stiffness in essential hypertensives.
Methods: Our population consisted of 320 newly diagnosed untreated non-diabetic patients with stage I to II essential hypertension [192 men, mean age=52 years, office blood pressure (BP)=145/93 mmHg]. In all participants, ACR values were determined as the mean of two non-consecutive morning spot urine samples and aortic stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV), by means of a computerized method (Complior SP). Moreover, eGFR was assessed using the Modification of Diet in Renal Disease equation and venous blood sampling was performed for estimation of sRAGE concentrations. The distribution of sRAGE was split by the median (1060.1 pg/ml) and accordingly subjects were stratified into those with high and low values.
Results: Patients with low sRAGE (n=164) compared to those with high sRAGE values (n=156) had greater body mass index (29.7±4.5 vs 27.1±2.5 kg/m^2, $p<0.05$) and 24-h systolic BP (139±8 vs 131±6 mmHg, p=0.001), while did not differ regarding metabolic profile (p=NS for all). Moreover, patients with low sRAGE compared to those with high sRAGE levels exhibited higher ACR (50.56±14.3 vs 20.75±15.5 mg/g, p=0.011) and PWV (9±1.7 vs 7.5±1.2 m/sec, $p<0.0001$), whereas had lower eGFR (65.9±7.2 vs 92.6±9.1 ml/min/1.73m^2, $p<0.05$), independently of confounders. In the total population, sRAGE was associated with body mass index (r= -0.245, p=0.006), waist to hip ratio (r= -0.462, $p<0.0001$), 24-h pulse pressure (r= -0.371, p=0.001), ACR (r= -0.274, p=0.019), eGFR (r=0.236, p=0.03) and PWV (r= -0.401, $p<0.0001$). Multiple regression analysis revealed that body mass index, 24-h systolic BP, ACR and PWV were the independent predictors of sRAGE (R2=0.57, $p<0.0001$).
Conclusions: In essential hypertension, decreased sRAGE levels are associated with increased PWV, pronounced albuminuria and impairment of renal function. Moreover, the close relation of sRAGE with arterial stiffening, ACR and eGFR, supports the potent role of sRAGE in renal and vascular atherosclerotic disease progression.

P1370 The impact of intramuscular infusion of erythropoietin and lin/sca1+ progenitor cells in limb perfusion in a murine model of hind-limb ischemia

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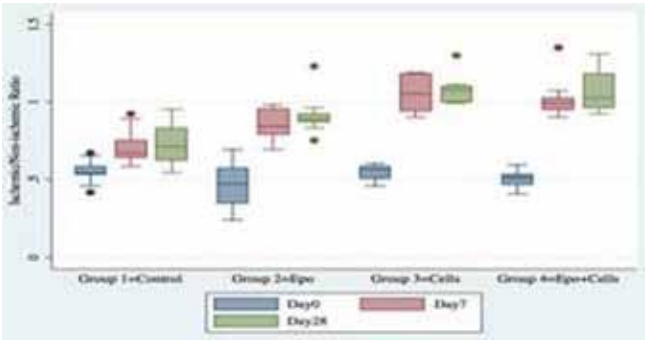
Purpose: Angiogenesis is the production of a primitivevascular network from progenitor cells. We investigated whether mobilizationof hematopoietic cells by erythropoietin (EPO) or direct intramuscular infusionof enriched hematopoietic cells, improves limb perfusion in a murine model ofhind-limb ischemia.
Methods: Wild type C57BL/6 male mice underwent unilateralhind-limb ischemia and divided in four groups to receive normal saline (0.2mlfor 5 days, IM) (control group), or EPO (400IU/kg for 5 days IM or a IMinjection of 0.5×10^5–1×10^6 cells, or both of cells andEPO. Bilateral hind-limb perfusion was estimated by laser



Doppler on days 0, 7and 28. Lin-/sca+ cells (isolated by magnetic bead separation) were analyzed byflow cytometry. Lineage positive cells were depleted by labelling with lineagespecific antibodies. Sca-1+ were selected by anti-FITC microbeads and cultured for4-7 days. Endothelial progenitors were identified by double immunostaining.
Results: Ischemic/non ischemic ratio of blood flow inday 0 was the same in all groups. Blood flow increased in the three groupscompared to the control group in day 7 and this elevation was maintained in day28 (0.67±0.03 forcontrol group, 0.82±0.07 for EPO group, 1.15±0.3 for cells group and 1.01±0.2for EPO-cells group, $p<0.05$). Blood flow increased in cells group and EPO-cells group compared to EPO group (p=0.001). However,there was no difference in blood flow between cells group and EPO-cells groupin days 7 and 28 (p=NS).
Conclusions: Directinfusion of EPO and lin/sca1+progenitor cells improves blood flow in ischemic limbs even though their combination did not show furtherimprovement. These findings reiterate the direct vasculogenic and indirectparacrine effects of both hematopoietic progenitor cells and erythropoietin onvasculature after vascular injury.

P1371 Shock waves treatment of obliterative lower limb arteriopathy

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Shock Wave (SW) therapy seems to improve endothelial function by increasing Nitric Oxide production. The aim of our study is to evaluate the effects of SW therapy in patients suffering from Peripheral Artery Disease (PAD). 22 consecutive patients were enrolled in this study, randomized to two groups: controls (10 patients, 68±12 yrs) and active SW-treatment group (12 patients, 67±9 yrs). Inclusion criteria were: age >40 years; a diagnosis of PAD; optimized medical therapy; ABI < 0.9. Exclusion criteria included: neoplasia and inflammation in the affected field; coagulation diseases and/or anticoagulant therapy; pregnancy. SW therapy was managed using the Minilith SL1 litotriptor, in association with an ultrasound guide able to detect the target area using B-mode technique and a 7.5 MHz convex probe, emitting 2000 impulses with an Energy Flux Density of 0.03 mJ/mm^2. As compared with control patients, treated patients more frequently suffered from dyslipidemia, with higher Total and LDL-cholesterol values than controls, these values being statistically significant ($p<0.014$ and $p<0.007$, respectively). Despite their history of hypertension, both groups had well controlled blood pressure. There were no significant differences between the concomitant medication regimens; optimal medical therapy was planned for each patient to reduce the incidence of risk factors and basal organic diseases on the management of our study. The variation of the degree of stenosis between the two groups before and after treatment was statistically significant ($p<0.001$). Using Fisher's Test to assess the proportion of class 3/4, an important ($p<0.001$) improvement in the Fontaine Class of PAD was observed in SW-treated patients: reduction in Pre-Post Class: SW-treated 12 (63%) vs controls 0 (0%) $p<0.001$. This result was confirmed by analyzing the "march autonomy" of the patients: Delta (difference between before/after SW therapy) pain-free walking in treated patients was 76±46 meters vs 0±0 meters in controls ($p<0.001$). Moreover, the score on the pain-free scale (present=2, reduced=1; absent=0) showed a significantly higher pain reduction in treated patients than controls ($p<0.001$). Although the POST-PRE Total ABI did not reach statistical significance (p 0.17), there was a trend toward an improvement of the Ankle-Brachial Index in SW-treated patients as compared with controls. Our study demonstrates that in patients suffering from PAD, Shock Wake Therapy has an impact on the natural clinical history of the disease, improving the quality of life and health conditions of these patients.

P1372 Direct intramuscular infusion of lin-/sca1+ progenitor cells improves perfusion and neovasculogenesis

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Purpose: It is well known that bone marrow derived progenitorcells promote postnatal neovascularization, therefore providing a potentialtherapeutic option for ischemic diseases. In this study we investigatedwhether direct intramuscular infusion of enriched hematopoietic cells, improvedlimb perfusion in a murine model of hind limb ischemia.
Methods: Wild type C57BL/6 male mice underwent unilateral hind-limb ischemia, were divided in three groups (n=12/group) and received a single intramuscular injection of 1×10^6 Lin-/sca+ cells, or granulocyte colony-stimulating factor (G-CSF) for 7 days ornormal saline. Each group Mice underwent laser Doppler perfusion imaging aftersurgery on days 0, 7and 28 for the estimation of the bilateral hindlimbperfusion. Muscle tissuesections were stained with rat anti-CD31antibody. Capillaries and arterioles inthe ischemic areas were counted with confocal microscopy at day 28.
Results: The ischemic/non ischemic ratio wassignificantly increased in ischemic limbs of cell- and G-CSF-treatedmice versus control mice at 7 days ($p<0.05$ vs control), which was maintainedat 28 days ($p<0.05$ vs control) only in the cell-treated group. There was nosignificant increase of ischemic/nonischemic ratio in the cell-treated micecompared with G-CSF at day 7 or day 28 (p=NS). Capillary density was increasedin the cell-treated group compared to G-CSF-treated group and control (2.67±0.44 vs 1.6±0.39 vs 0.71±0.59 cap/cm^2 $p<0.05$).No difference in the capillary density between the G-CSF-treated and thecontrol group was observed.
Conclusions: Direct intramuscular infusion oflin-/sca+ significantly improved blood flow and vasculogenesis compared withG-CSF and saline treatment. Direct intramuscular infusion of bone marrowderived or endothelial progenitor cells but not cell mobilization with G-CSFincreased blood flow and vasculogenesis in a murine model of limb ischemia.

P1373 Disassociation between aortic stiffness and wave reflections

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Increased wave reflection and arterial stiffness are independent determinants of cardiovascular (CV) risk, with arterial stiffness being a strong independent predictor of CV mortality in several populations. Although arterial stiffness and wave reflection levels are positively correlated, an inverse negative relationship between them is often observed, referred as "disassociation". The extent and the determinats of this disassociation are unclear. Aim of the study was to identify the extent and the physiological determinants of the disassociation between wave reflections and arterial stiffness and also to assess its possible relation with CV risk.
Methods: 415 subjects (mean age: 45.9±10.8 yrs, 191 untreated hypertensive and 224 normotensive). Wave reflections and aortic stiffness were assessed by aortic augmentation index (AIx; radial tonometry and use of transfer functions) and carotid-to-femoral pulse wave velocity (PWV), respectively. Heart Score® was aslo calculated for each subject. The population was divided according to percentiles of PWV values, providing 10 incremental levels of PWV which were assigned to each subject. Similarly, the population was classified according to AIx percentiles, which again provided 10 incremental levels. Two ordinal variables indicating each subject's PWV and AIx levels were constructed; PWV-Level and AIx-Level respectively, each ranging from 1 to 10. Then, for each subject a "Disassociation" Score ranging from -9 to +9 was calculated as the difference between PWV and AIx level per subject.
Results: Almost 15% of the population had a remarkable disassociation between AIx and PWV with a Score < -5 or >5. Multivariate regression analysis revealed that females were associated with a greater difference between levels of PWV and AIx (dissasociation score) than males, with PWV being higher than AIx level. Higher values of heart rate, timing of wave reflections, mean blood pressure and body height were independently and positively related with a greater "dissasociation" between AIx-PWV ($p<0.05$). Finally, a higher "Disassociation" Score was related with greater CV risk as assessed by the Heart Score® ($r=0.28$, $p<0.001$).
Conclusion: Almost 15% of the study population presented medium to high disassociation Scores. More importantly, a higher "disassociation" was significantly related with increased CV risk. The clinical utility of "Disassociation" between arterial stiffness and wave reflections worths further investigation in future studies or in meta-analysis of follow-up clinical data.

P1374 Autonomous Granulocyte Colony-Stimulating Factor (G-CSF) signalling promotes arteriogenesis in a murine model of hindlimb ischemia

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Impaired blood supply caused by progressive stages of the systemic inflammatory disease atherosclerosis can evoke compensatory collateral artery growth (arteriogenesis) and capillary sprouting (angiogenesis). However, both processes are usually insufficient in patients, particularly those suffering from atherosclerosis superimposed by comorbidities such as diabetes mellitus. Treatment with the recombinant cytokine granulocyte colony-stimulating factor (rhG-CSF) has been demonstrated to promote arteriogenesis and angiogenesis in animal models of ischemia. Nevertheless, the mechanisms underlying these effects are insufficiently understood. Furthermore, it is not known whether autonomously stimulated G-CSF signalling is significantly involved in arteriogenesis and angiogenesis. In the present investigation it was demonstrated by Laser Doppler Perfusion Imaging (LDPI) that deficient G-CSF signalling in G-CSF knockout (KO) mice was associated with an impairement (a delay) of blood flow recovery following surgical induction of hindlimb ischemia, not seen in wildtype (WT) mice. This delay was completely abrogated by the application of rhG-CSF suggesting that autonomously activated G-CSF signalling, although playing a significant role in arteriogenesis, does not affect the development and characteristics of preformed collateral arteries. In agreement with these findings, collateral arteries in ischemic hindlimbs of

G-CSF KO mice had smaller calibers and thinner vessel walls than those in ischemic WT hindlimbs. Elevated serum levels of endogenous G-CSF in WT mice following induction of hindlimb ischemia suggest a potential role of mobilized bone marrow-derived cells in G-CSF promoted arteriogenesis. Therefore, peripheral blood of G-CSF KO and WT mice subjected to hindlimb ischemia induction is currently being analyzed by surface marker-based FACS to determine proportions of monocytes (CD11b) and subpopulations of endothelial/hematopoietic progenitors (CD105, Sca1, Flk-1 and CD34) as these are putatively involved in arteriogenesis. Irrespective of the origin of cells facilitating arteriogensis, i.e. bone marrow-derived or resident, their proliferation, differentiation and/or paracrine activities are possibly responsible for the pro-arteriogenic effect of autonomous G-CSF signalling and are therefore currently being investigated with respect to their G-CSF dependency. In conclusion, autonomous G-CSF signalling unequivocally promotes arteriogenesis. The mechanism remains to be clarified.

P1375 Acute changes of glucose and insulin levels during oral glucose tolerance test are related to changes in arterial stiffness and wave reflection

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Hyperglycemia is linked with arterial stiffness, a factor with significant prognostic value. We investigated whether the acute changes of glucose and insulin levels during oral glucose tolerance test (OGTT) are related with acute changes in arterial stiffness.

Methods: In 40 consecutive subjects without known diabetes a standard 75-gr oral glucose tolerance test (OGTT), was performed and glucose and insulin levels were measured at 0, 30, 60, 90 and 120min after glucose loading. At the same time intervals, we measured the carotid- femoral pulse wave velocity (PWVc) using the Complior and aortic PWV (PWVa) and augmentation index (AI) using an oscillometric method (Arteriograph,TensioMed). We categorized patients in those with normal (n=14) and those with abnormal OGTT.

Results: Taking into account all measurements (n=200) during OGTT, we found that increasing glucose levels were related with increasing PWVc (r=0.28, $p<0.007$) and PWVa (r=0.42, $p<0.001$) and increasing insulin levels were related with decreasing AI (r= -0.27, p=0.003) in all patients. Patients with abnormal OGTT had higher baseline PWVc (10.4±2 vs. 9.1±1.8 m/sec, $p<0.05$),PWVa (9.4±1.9 vs. 6.9±1.8 m/sec, $p<0.05$), AI (24±9 vs. 17±11%, $p<0.05$), insulin (14±6 vs. 11±4μU/ml, $p<0.05$) and glucose (114±26 vs. 93±7 mg/dl, $p<0.05$) and similar age sex and BMI than those with normal OGTT ($p<0.05$).Compared to baseline, AI was reduced by 44% at 30 min and 17% at 60 min in patients with normal OGTT ($p<0.01$) compared to 7.8% and 11% in abnormal OGTT (p=0.7). Mean insulin levels were increased to in all patients during OGTT, though these were higher at 90 and 120 min in patients with abnormal than those with normal OGTT (76 and 55μU/ml vs. 44 and 34 μU/ml, $p<0.05$). In all patients, the % decrease in AI at 30 min was related with the corresponding %increase in insulin (r= -0.46, $p<0.05$) but not with % change in glucose. The % increase in glucose levels at 60, 90 and 120 min during abnormal OGTT was related to the % increase in PWVa (r=0.46, r=0.34, r=0.55, $p<0.05$), PWVc (r=0.40, r=0.32, r=0.33, $p<0.05$) and AI (r=0.36, r=0.34, r= -0.35, $p<0.05$).

Conclusions: Patients with normal OGTT show an acute decrease in AI related with the corresponding increase in insulin level likely because of insulin stimulation of endothelial nitric oxide synthesis. During abnormal OGTT, this beneficial effect of insulin on AI is blunted likely because of insulin resistance and the acute changes in glucose levels are linked with an increase in arterial stiffness. Thus, insulin-resistance determines the acute changes of arterial stiffness after postprandial hypeglycemia.

P1376 Models of myocardial infarction in large animal research - A comparison between LAD and LCX occlusion

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Purpose: Both, LAD as well as LCX occlusions are frequently used models of myocardial infarction in large animals. Nonetheless, there are little data about the advantages of either model. In order to provide a rational approach for future studies, we investigated differences on the course of the cardiac function between these models.

Methods: 16 female Yorkshire pigs were randomly allocated into two groups to undergo proximal occlusion of either LAD (LAD group; n=9) or LCX (LCX group; n=7) with an 1 hour balloon inflation followed by a permanent occlusion with a stainless steel coil. The positions of the balloons and coils were confirmed by angiograms. Left and right heart catheterization and echocardiography were performed at 2 days, 1 month and 3 month time points.

Results: Six out of nine (68%) animals survived in the LAD group compared to five out of seven (71%) in the LCX group. Echocardiography confirmed motion abnormalities in the anteroseptal and the inferolateral wall, repectively. In the follow-ups, dP/dt(max) was more consistantly reduced in the LAD group compared to the LCX group (Fig. 1; 1582.4±49.6mmHg/s vs. 2176.0±293.2mmHg/s at 3 months). Likewise, cardiac output, cardial index and other measures of cardiac function were lower and more stable in the LAD group.

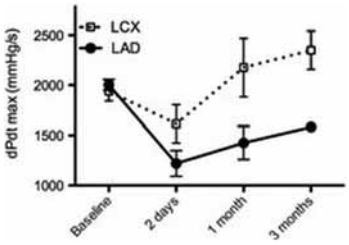

Figure 1. dP/dt(max) over time.

Conclusions: We have demonstrated feasibility and safety in both our LAD and LCX models of myocardial infarction. In efficacy trails, a highly and constantly reduced cardiac function – as was observed after LAD occlusion – can be a necessary precondition, especially in demonstrating small improvements and in achieving reliable and reproducible results.

MOLECULAR MEDIATORS OF VASCULAR FUNCTION

P1377 Micro RNA-146a represents an important mediator during vascular remodeling processes

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Background: Micro RNAs (miRNAs) are implicated to regulate mRNA levels of up to 30% of mammalian genes, comprising key regulators for cellular function including proliferation, differentiation and apoptosis. It is now obvious that abnormal miRNA expression is a common feature of human diseases, however, the miRNA expression during the development of atherosclerosis and restenosis still remains elusive. Thus, the aim of this study was to evaluate the regulation and impact of 146a for smooth muscle- and endothelial cell function during the development of neointimal lesions in vitro and in vivo.

Methods/results: For microarray based expression analysis on regulated miRNAs during the development of atherosclerosis and restenosis, aortic arches of ApoE/LDLr-/- mice 2 weeks (control), 6 and 12 months of age were isolated. The majority of all miRNAs appeared to be regulated, as well as during neointima formation in C57BL6/N mice 10 and 21 days after dilation of the femoral artery. Particularly, miR-146a appeared to be significantly upregulated during atherosclerosis as well as restenosis. Expression studies on isolated primary human vascular cell types in vitro showed that miR-146a was highly upregulated in endothelial cells (ECs) and to a lower extent in vascular smooth muscle cells (VSMCs). The upregulation of miR-146a could be attributed to inflammatory stimuli rather than mitogenic or apoptotic stimuli. VSMCs and ECs were transfected with miR-146a inhibitors for further assessment of the functional role of miR-146a resulting in a highly increased proliferation and total cell count of ECs as assessed by BrdU incorporation and Wst-1 conversion, respectively. Following miR-146a inhibition, apoptosis of ECs was significantly reduced as determined by modified TUNEL staining. In contrast, the knock down of miR-146a in VSMCs led to a significant reduction of proliferation. Subsequent in vivo experiments showed that the inhibition of miR-146a upregulation/expression in murine femoral arteries after vessel dilation significantly accelerated reendothelialization and inhibited the proliferation of neointimal VSMCs. As a consequence, neointima formation was clearly attenuated.

Conclusion: These observations reveal a pivotal role of miR-146a for vascular cell function, especially under conditions of pathological vascular remodeling processes. Thus, modulating miR-146a expression may represent a novel approach for the prevention and treatment of vascular proliferative diseases.

P1378 PI3K/p110alpha inhibition differentially regulates vascular smooth muscle and endothelial cell activation: implications for drug-eluting stent design

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Objectives: To evaluate the impact of p110α inhibition on vascular smooth muscle (VSMC) and endothelial cell (EC) activation.

Background: Impaired reendothelialization and stent thrombosis remain safety concerns associated with the use of drug-eluting stents DES, despite a reduction in restenosis rates. Phosphoinositide 3-kinase p110α (PI3K/p110α) controls crucial cellular processes including proliferation and chemotaxis, thereby repre-

senting an emerging drug target. However, its effect on vascular smooth muscle (VSMC) and endothelial cell (EC) activation remains unknown.
Methods: PI3K/p110α was inhibited by treatment with the small molecule inhibitor PIK 75 or, alternatively, a specific siRNA. Proliferation and migration of VSMC and EC were assessed by cell number and Boyden chamber, respectively. Endothelial senescence and dysfunction were evaluated by β-galactosidase assay, Western blots for expression of eNOS, TF, and PAI-1, and organ chambers for isometric tension recording.
Results: Inhibition of PI3K/p110α with PIK 75 or a specific siRNA selectively impaired proliferation and migration of VSMC while sparing EC completely. Treatment with PIK75 did not induce endothelial senescence nor inhibit eNOS expression or endothelium-dependent vascular relaxation. However, PIK 75 inhibited both basal and TNF-α induced expression of TF and PAI-1. In contrast to PIK 75, both rapamycin and paclitaxel inhibited endothelial proliferation and migration; moreover they induced expression of TF and PAI-1.
Conclusions: Inhibition of PI3K/p110α impairs proliferation and migration of VSMC, but not EC. In addition to its potent antiproliferative and antimigratory effects on VSMC, targeting p110α inhibits the expression of prothrombotic mediators on EC. Hence, PI3K/p110α inhibition may offer new options in DES design.

P1379 Factor VII-activating protease (FSAP): vascular functions and role in arteriogenesis

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To define the role of Factor VII-activating protease (FSAP) in collateral vessel growth (arteriogenesis), we investigated its impact in a mouse model of adaptive collateral artery growth. FSAP is a potent inhibitor of vascular smooth muscle cell proliferation and migration in vitro, but its role in arteriogenesis has never been examined.
C57Bl/6 mice were anaesthetized and the femoral artery was ligated. Recombinant FSAP vs. a control protease were injected intramuscularly into the upper hind limb of the mice immediately after ligation, as well as 1 day and 3 days later. Furthermore, knockout animals (FSAP-/- vs. FSAP+/+ wt) were ligated to determine the role of FSAP in vessel growth. To quantify hind limb perfusion, Laser Doppler Perfusion Imaging was performed 1, 3, 7, 14, and 21 days after ligation. Additionally, immunohistochemistry and morphometrical analysis were done to determine angiogenesis and arteriogenesis.
Perfusion index (mean pixel intensity of ligated/unligated side) dropped from 1.04±0.09 to 0.31±0.04 in FSAP+/+ and from 1.00±0.02 to 0.38±0.04 in FSAP-/- and in FSAP-injected wt animals from 1.03±0.07 to 0.28±0.03 directly after ligation.
Recovery was delayed in the FSAP injected group up to day 14 (0.75±0.04 vs. control 0.89±0.12 and mildly enhance in FSAP-/- 0.93±0.09, vs. FSAP+/+ 0.91±0.09 $p<0.05$, N=8). During the following week, FSAP-treated animals caught up to 0.90±0.03 vs. control 0.99±0.09, $p<0.05$, N=8).
Histological evaluation demonstrate more and better developed collateral arteries in the upper limb FSAP-/- (16±4.5 collaterals/quadriceps muscle vs. FSAP+/+ (6.3±2.9, $P<0.05$, N=6).
Histological workup of the upper limb showed a delayed increase in vessel diameter in comparison to control-treated wt animals one week after ligation (FSAP-treated 25.4±1.1 μm vs. wt 32.5±4 μm, $p<0.05$), supporting the finding of attenuated collateral vessel growth. However, the diameters caught up after two weeks in the FSAP-treated group up to 29.9±1.5 μm vs. wt 31±2.5 μm and to 31.7±4.4 μm vs. 32.8±2.8 μm after three weeks, respectively. Vessel diameter in the knockout group were superior to all other groups rising in vessel diameter up to 62±14μm (FSAP-/-) three weeks after ligation, (N=6, $P<0.05$).
We conclude that FSAP retards collateral growth (arteriogenesis) and the absence in knockout animals further enhance the development of collateral arteries. Further examination of the molecular mechanism of FSAPs action on arteriogenesis is warranted.

P1380 Inhibition of glycolytic activity in macrophages attenuates the development of abdominal aortic aneurysm in mice

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Purpose: Although mechanisms underlying the development of abdominal aortic aneurysm (AAA) remain largely unknown, chronic inflammation at the adventitial layer has been suggested to be involved. This study investigated whether the enhanced glucose metabolism in macrophages distributed in the adventitia contributes to the pathogenesis of AAA development.
Methods and results: Periaortic application of 0.5 mol/L calcium chloride (CaCl2) to seven-week-old C57BL/6J male mice increased the diameter of abdominal aorta by 114%, compared to the controls during the 28-day period. Protein expressions of glucose transporter (GLUT)-1, -3 and zymographic metalloproteinase (MMP)-9 activity were temporally increased in the abdominal aorta following the CaCl2 application at days 3 and 7, where the immunoreactivity for GLUT-1, -3 and MMP-9 were found in macrophages at the adventitial layer. Intraperitoneal administration of glycolysis inhibition with 2-deoxyglucose (DG) (100 mg/kg/day) for 28 days significantly ($p<0.01$) attenuated the dilatation of abdominal aorta (sham, 0.49±0.04 mm (n=10); CaCl2, 0.96±0.18 mm (n=14); CaCl2+2-DG, 0.62±0.08 mm (n=12), means ± SEM). This was accompanied by the preservation of elastin fibers in the media (sham, 0±0, CaCl2, 2.4±1.3; CaCl2+2-DG, 1.0±0.5, $p<0.01$, in which the magnitude of destruction of elastin fibers; none, score 0; mild, score 1; moderate, score 2; severe, score 3) and reduced the zymographic MMP-9 abundance (sham, 19±6; CaCl2, 63±14; CaCl2+2-DG, 26±3 optical density/mm^2, $p<0.05$). The 2-DG treatment also prevented the aneurysmal formation in 10-week-old angiotensin (Ang) II-infused apolipoprotein E knockout male mice (Ang II/saline, 2.13±0.23 mm (n=14); Ang II/2-DG, 1.43±0.15 mm (n=14), $p<0.05$).
Conclusion: This study provides the mechanistic insight into the crucial role for glycolytic activity in macrophage in the development of AAA. In addition, we propose a potential therapeutic target to inhibit the glycolytic pathway in this cell type in the disorder.

P1381 Flow cytometric assay for measurement of microparticles in cardiovascular disease

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Shedding of microparticles (MPs) into blood occurs during cellular activation and apoptosis. Although the clinical importance of MPs is unclear, the interest in circulating MPs is growing. However, studying MPs is demanding and improved standardization of the methods is necessary. Previously, we described a flow cytometry method, which measured amount of antigen expressed on MPs. We have further developed the flow cytometric method and with a more advanced flow cytometer (Beckman Gallios) been able to perform simultaneous detection of up to 5 colors. MPs are labeled with lactadherin, phalloidin, CD42a (platelet origin), CD144 (endothelial origin) and CD14 (monocyte origin).
By labeling each sample with phalloidin, a fungal toxin which binds with high affinity to intracellular f-actin on the interior surface of cell membranes, we can differentiate between membrane fragments and intact MPs. Exposure of phosphatidylserine (PS) is assessed by using lactadherin binding which is virtually calcium-independent and has a higher affinity for PS than annexin-V. MPs are thus defined as phalloidin negative, lactadherin positive events, together with a cell-specific antibody. By using this protocol we find that patients with acute coronary syndrome have more platelet-MPs, patients with antiphospholipid syndrome more endothelial-MPs and patients with Graves' disease more monocyte- and endothelial MPs. We also find that statin treatment reduces PMPs and that PMPs measured in frozen plasma samples could be a suitable method for the assessment of platelet function in large clinical studies.
The assay described above enables flow cytometry determination of MPs from three different cellular origins in previously frozen platelet poor plasma. Phalloidin could be used to detect poor sample handling and to prevent counting cell-membrane fragments as MPs. In the future, large clinical studies should be performed to investigate if MPs may be used as biomarkers of cardiovascular disease and complications.

P1382 Red blood cells - vehicles for uptake and deposition of MPO in the microcirculation

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Purpose: Myeloperoxidase (MPO) is a heme enzyme abundantly expressed in polymorphonuclear neutrophils, monocytes and macrophages. MPO conveys potent microbicidal and - upon binding to the vessel wall – vascular proinflammatory properties.
Interestingly MPO, a highly cationic protein, has been shown to not only bind to endothelial cells but also binds to the membrane of leukocytes. Given the anionic surface charge of red blood cells we investigated the affinity of MPO to the erythrocyte's membrane.
Methods and results: Immunofluorescent imaging and ELISA on native isolated human red blood cells (RBCs) revealed MPO immunoreactivity with MPO binding to RBCs in a dose dependent manner. Erythrocyte Ghosts derived from human RBCs revealed to be MPO positive as evidenced by Western Blot analysis, further underscoring the affinity of MPO to the membrane of RBC. Additionally, NO-consumption of RBC-Ghosts increased with incremental MPO-concentrations, indicating preservation of catalytic activity of MPO while binding to RBCs.
Whereas MPO -/- mice lacked a signal for MPO, immunoreactivity for MPO could be shown after incubation with MPO. To test whether membrane bound MPO is unloaded in the microvasculature, RBC from MPO -/- mice were isolated and loaded with MPO; subsequently MPO+RBC were reiinfused in MPO-/- mice and

liver sections as well as microvessels in the M. cremaster revealed positive for MPO.

Summary: MPO binds to the membrane of Red Blood Cells in vivo and in vitro. Given the abundance of RBCs in the circulation, RBCs emerge as a so far underrecognized pool for MPO, capable of redistributing MPO to the microvasculature. Given the well defined functions of MPO for regulation of vascular tone, RBCs evolve as critical modulators of vascular tone by modulating the local burden of this enzyme.

P1383 Carbamylated low-density lipoprotein induces arterial thrombus formation: role of tissue factor and plasminogen activator inhibitor type 1 expression

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Background: Cardiovascular disease is the major cause of death in patients with chronic renal failure. Carbamylation of low-density lipoproteins (cLDL) in human serum by urea-derived cyanate alters protein structure and is thought to promote vascular inflammation and dysfunction during end-stage renal disease. However, it it is not known whether cLDL exerts prothrombotic effects in vascular cells and whether cLDL affects arterial thrombus formation in vivo.
Methods and results: In human aortic vascular smooth muscle cells (AoSMC) cLDL (10-300μg/ml) induced tissue factor (TF) and plasminogen activator inhibitor type 1 (PAI-1) expression by 3.5- and 3-fold, respectively (n=4; $p<0.01$ for each mediator). cLDL also enhanced basal and TNF-α induced expression of TF and PAI-1 expression in human aortic endothelial cells (n=4; $p<0.02$ for each mediator). These effects were paralleled by an enhanced TF activity in both cell types (n=4; $p<0.01$). In contrast, native LDL (nLDL) had no effect on expression or activity of TF and PAI-1. In both cell types, cLDL induced TF and PAI-1 expression at the transcriptional level via the mitogen-activated protein kinases p38 and ERK (n=3; $p<0.05$) as well as the transcription factor NFkB (n=4, $p<0.05$). In line with these findings, intravenous administration of cLDL (2 mg/kg body weight) accelerated arterial thrombus formation in a murine photochemical carotid artery injury model as compared to treatment with nLDL (2mg/kg body weight) or vehicle (PBS) (n=8; $p<0.05$ versus nLDL and control).
Conclusions: These data demonstrate that cLDL, at physiologically relevant concentrations, exerts potent pro-thrombotic effects in human vascular cells and enhances thrombus formation in vivo. This observation may be relevant for understanding the markedly increased incidence of fatal acute thrombotic events in patients with end-stage renal disease and the development of new LDL targeting therapies in these patients.

P1384 Sildenafil exerts beneficial effects on tissue perfusion proinflammatory molecules expression in a murine model of limb ischemia and atherosclerosis

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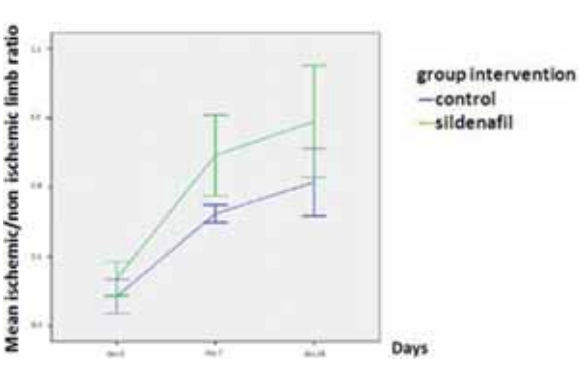
Purpose: Sildenafil, a phosphodiesterase type 5antagonist has endothelium protective and angiogenic effects. We tested thehypothesis that sildenafil might improve tissue perfusion and neovascularization and downregulate proinflammatory molecules following limb ischemia.
Methods: ApoE-KO male mice, bred with cholesterol richdiet for 6 weeks, were anesthetized and underwent sunilateral hind-limbischemia with ligation of the left femoral artery. Mice were randomized inthree groups and received sildenafil (1mg/kg for 7 days in 0.4ml solution,intraperitoneally i.p.), or normal saline (0.4ml for 7 days, i.p.). Bilateralhind-limb perfusion was estimated by laser Doppler perfusion imaging aftersurgery on days 0, 7 and 28. For capillary density assessment, the muscletissue sections were stained with rat anti-CD31 antibody and assessed underconfocal microscopy. sICAM-1, sE-Selectin and PAI-1 levels were evaluated atdays 0 and 28 with enzyme-linked immunosorbent assay.



Results: Treatment with sildenafil was associated withsignificantly increased perfusion in the ischemic limb compared to controlanimals (Figure). The increase in blood flow was maintained at day 28. Ischemiaexerted no significant effects on sICAM (from 1.91±0.15 to 0.140±0.19 ng/ml, p=NS), sE-Selectin (from 4.23±0.877 to 2.69±1.00 ng/ml, p=NS) and PAI-1 levels (from 0.219±0.055 to 0.126±0.054 ng/ml, p=NS). Sildenafil significantlydecreased sICAM-1 (from 2.1±0.15 to 1.2±0.12 ng/ml, $p<0.01$), sE-selectin (from 5.34±0.4 to2.45±0.51 ng/ml, $p<0.01$) and PAI-1 (from 0.13±0.02 to 0.07±0.012 ng/ml)levels.
Conclusions: Sildenafil exerts significant beneficial effectson tissue perfusion and neovascularisation after limb ischemia anddownregulates adhesion molecules in the atherosclerotic milieu.

P1385 ACE inhibition reduces monocyte MFG-E8 and MCP-1 expression in rats with chronic heart failure

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Purpose: Chronic Heart Failure (CHF) causes high morbidity and mortality. Immune activation and inflammation influence CHF pathogenesis. The pro-inflammatory chemokine fractalkine induces monocyte activation. Fractalkine promotes Mfg-e8 expression on macrophages. We investigated whether (a) Fractalkine serum levels are significantly enhanced in CHF, (b) high fractalkine levels influence Mfg-e8 and MCP-1 expression on peripheral blood monocytes, and (c) these proinflammatory markers can be positively modulated by a standard CHF treatment (ramipril: 1mg/kg/d).
Methods: In rats with CHF 10 weeks after coronary ligation, fractalkine levels were determined in serum and urine using ELISA. Peripheral blood monocytes were isolated via Histopaque gradient. Mfg-e8 and MCP-1 protein expression in these monocytes were assessed by Western Blotting and expressed as mean±S.E.M.
Results: Fractalkine serum and urine levels were significantly higher in CHF compared to sham-operated rats (Serum: CHF: 1509±168pg/mL; Sham: 1181±58pg/mL, $p<0.05$). Mfg-e8 and MCP-1 expression on peripheral blood monocytes were significantly enhanced in CHF animals (Mfg-e8: CHF: 1,36±0,36 abitrary units (au); Sham: 0,79±0,08au; MCP-1: CHF: 1,79±0,29au; Sham: 1,01±0,17au, $p<0.05$) and attenuated by ramipril therapy (Mfg-e8: 0,84±0,09au; MCP-1: 1,21±0,11au, $p<0.05$ vs. CHF).
Conclusions: Fractalkine serum levels and monocyte expression of its downstream target Mfg-e8 were significantly increased in experimental CHF as was the burden of MCP-1. Ramipril reversed the pro-inflammatory changes in CHF monocytes, indicating that ACE inhibition might beneficially modulate chemotactic/atherogenic signalling in CHF.

P1386 Endothelial progenitor cell mobilization is enhanced in high performance runners

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Physical exercise is recommended to prevent cardiovascular disease. Exercise stimulates the recruitment of endothelial progenitor cells (EPC) from the bone marrow, thus improving endothelial cells turnover. However, studies with high performance runners (HPR) evaluating endothelium-derived microparticles (EMP) and EPC are less reported. The aim of this study was to quantify the number of EPC and EMP in HPR and compare them with sedentary controls.
Methods: HPR (n=16), defined on basis of the time to perform a 10-km race were compared with sedentary controls (n=40), matched for gender and age. The quantification of three subpopulations of EPC was made using CD34, KDR and CD133. EMP countings were assessed by CD51 by uL of platelet-poor plasma using flow-citometry. Flow-mediated dilation (FMD%) and the intimal medial thickness of the carotid artery (c-IMT) were also evaluated.
Results: Mean time to perform a 10-km race was 31 min and 40 sec for men and 37 min and 37 sec for women in the HPR group, and they run an average of 132 km/week. HPR presented higher HDL-C ($p<0,0001$), lower body mass index ($p<0,0001$), LDL-C (p=0,0001), triglycerides, apoB ($p<0,0001$) and C-reactive protein (p=0,025). We observed a trend to higher EMP in HPR (p=0,088), and there was a greater percentage (SD) of the three subpopulations of EPCin HPR when compared with controls: CD34+/KDR+ [0.42 (0.34) versus 0.08 (0.03), p=0.05], CD34+/CD133+ [0.07 (0.02) versus 0.01 (0.01), p=0.002] e KDR+/CD133+ [0.29 (0.06) versus 0.01 (0.01), $p<0.0001$]. FMD (SD) was higher in HPR group [30 (12)% versus 16 (10)%, $p<0.0001$], without differences in c-IMT.
Conclusions: High-performance exercise is associated with increased EPC mobilization and to the vascular health.

P1387 Comparison between basal TGF-beta levels in FBN1 mutated patients versus normal controls

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Purpose: Transforming growth factor-beta 1 (TGFβ1) plays a major role in damaging aortic wall integrity in patients with Marfan Syndrome (MFS) who harbour mutations of the Fibrillin 1 (FBN1) gene. Angiotensin II blockers (ARB), widely used to treat hypertension, may block TGFβ1 activation, and thus potentially limit aortic wall damage and dilatation in MFS patients. In this study, we aimed at measuring circulating TGFβ1 levels in MFS patients harbouring FBN1 mutations versus normal controls.
Materials and methods: We analysed serum samples obtained from 212 patients, ages 1 to 55, diagnosed with MFS and carrying an FBN1 mutation, and those retrieved from 25 age- and gender-matched healthy, voluntary controls with wild-type FBN1.TGFβ1 levels were measured by the DuoSet ELISA kit (R&D System) TGFβ1 immunoassay (from DY240). In this assay, the minimal levels of detectable TGFβ1 range from 0.047 ng/ml to 24 ng/ml. The assay displays cross-reactivity with the latent TGFβ1 complex by less than 1%. The TGFβ1 total levels were measured after acid activation (with 2.5N acetic acid/10MUrea) and subsequent neutralization (with 2.7N NaOH/1M HEPES) to yield pH 7.2.The ELISA immunoassay was performed according to the manufacturer's protocol. All samples were run in duplicate.
We grouped MFS patients and controls by age (MFS series: 1-10, n = 57;11-20, n = 62;21-30, n = 31; 31-40, n= 29; 41-55, n =33), (CTRL series: 5 per age group).One-tailed Student t-test for unpaired data (alpha=0.05) with unequal variance (tested with F-test, $p<0.001$) was used to compare the MFS and normal population (STATA 10).
Results: In the control group, TGFβ1 levels increased by age and demonstrated no gender-related differences. In MFS patients,TGFβ1 levels were significantly higher than those measured in the control population (6.15 ± 7.01 versus 3.6 ± 2.4, respectively, $p<0.001$). Furthermore, we observed that the pediatric and adolescent MFS population ($\leq$16 years) had significantly increased TGFβ1 levels as compared to the adult MFS population (>16 years).
Conclusions: Circulating TGFβ1 levels are elevated in MFS patients harbouring FBN1 gene mutations, supporting the hypothesis of increased TGFβ1 in MFS and the rationale for administration of TGFβ1-lowering treatments.

P1388 Considerable difference in the reactive oxygen species-generating property among the anti-restenotic compounds commonly used in drug-eluting stents

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Background: Paclitaxel, sirolimus and everolimus are widely utilized in drug-eluting stents to prevent restenosis. The cytotoxic effect on the coronary endothelial cells hampers the therapeutic effectiveness. Many reports suggested that the cytotoxicity of paclitaxel is higher than that of sirolimus and everolimus. However, the mechanism underlying the different toxicity among those compounds still remains largely unknown. The present study thus investigated any difference in the property of generating reactive oxygen species (ROS), by using human coronary artery endothelial cells (HCAECs).
Methods: The production of ROS after 24-hour treatment with paclitaxel, sirolimus or everolimus was assessed with fluorometry using 2, 7-dichlorofluorescein diacetate (DCF). HCAECs were loaded with 10 μM DCF for 30 min in 37°C, and then subjected to fluorometry with confocal microscopy. The mRNA expression of NADPH oxidase p47phox was quantified with real-time PCR method. The protein expression of IκB was quantified with Western blotting.
Results: Paclitaxel induced ROS generation at 10 ng/ml in HCAECs (1.8-fold vs. control). However, sirolimus and everolimus induced no significant ROS generation up to 100 ng/ml, while 1000 ng/ml of sirolimus and everolimus induced a significant amount of ROS generation (sirolimus: 1.5-fold, everolimus: 1.2-fold vs. control). The expression of p47phox was up-regulated by 10 ng/ml paclitaxel (3.0-fold vs. control), but not by sirolimus or everolimus even at 1000 ng/ml. The expression of IκB was down-regulated by paclitaxel (0.7-fold vs. control). The ROS generation induced by paclitaxel was suppressed by co-treatment with 100 μM apocynin, a NADPH oxidase inhibitor, or by 20 μM SN50, a NF-κB inhibitor.
Conclusion: The present study clarified, for the first time, the clear difference in the property of generating ROS among paclitaxel, sirolimus and everolimus. The results suggested the NF-κB-mediated up-regulation of p47phox to play a major role in the ROS generation by paclitaxel. This unique property of paclitaxel appears to underlie higher cytotoxic effect of paclitaxel than sirolimus and everolimus.

ATHEROSCLEROSIS DETECTION

P1389 Lactate as an atherosclerotic plaque marker for hypoxia

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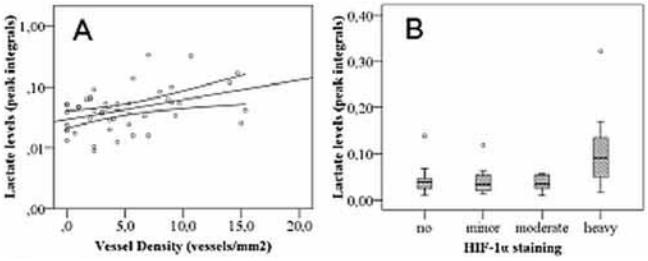
Background: It is thought that hypoxia and inflammatory cell infiltration promote neovascularization. In these hypoxic areas new vasculature is leaky and most likely the primary source of intra-plaque hemorrhage, leading to increased risk of plaque rupture. One of the metabolites associated with hypoxia is lactate. A universal technique to detect and quantify metabolites, such as lactate, is 1H-NMR spectroscopy. We hypothesize that increased levels of lactate are associated with increased plaque vessel density as well as hypoxia markers and is consequently a marker for rupture-prone plaques.
Methods and results: In femoral atherosclerotic plaques (n=50), obtained after surgery, 1H-NMR spectra analysis was performed. Frozen samples were grinded, dissolved in PBS and filtered. The filtered solution was analyzed by 1H-NMR spectroscopy at 400 MHz. Spectra were analyzed and lactate peak integrals (doublet present at 1.32ppm) used for analysis. Vessel density in the plaque was determined in histological slides stained for vascular endothelium (CD34). HIF-1α (hypoxia-inducible factor 1α) staining was graded as no, minor, moderate or heavy. We observed that vessel density increased with increasing lactate levels, the Spearman correlation plot showed a significant correlation (p=0.006) with a moderate correlation coefficient (r=0.383) (figure 1A). Additionally showed heavy HIF1α staining a significant associated with high lactate levels (p=0.015) (figure 1B).



In conclusion, high plaque lactate levels are associated with high vessel density and hypoxia in atherosclerotic plaques and could therefore serve as a marker for rupture-prone hypoxic plaques.

P1390 Hypogonadism and penile arterial disease are additively associated with increased aortic stiffness and carotid intima media thickness

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Purpose: Aortic stiffness and carotid intima media thickness (IMT) are markers of CV risk. Hypogonadism (HypG) and penile arterial insufficiency (AI) are reliable measures for predicting CV disease in erectile dysfunction (ED) patients. We examined whether there is an additive association among these parameters and early changes in arterial structure and function.
Methods: Carotid–femoral pulse wave velocity (c-f PWV), IMT and penile peak systolic velocity (PSV) were measured in 205 consecutive ED patients without manifest CV disease. PSV below 35 cm/sec was considered to indicate AI. Total testosterone (TT) levels were measured in all patients. HypG was defined when TT levels were below 3.4 ng/ml.
Results: Patients with AI (n = 79) compared to subjects without AI (n = 126) had higher age and risk factors adjusted c-f PWV and IMT (by 0.36 m/s and 0.07 mm,

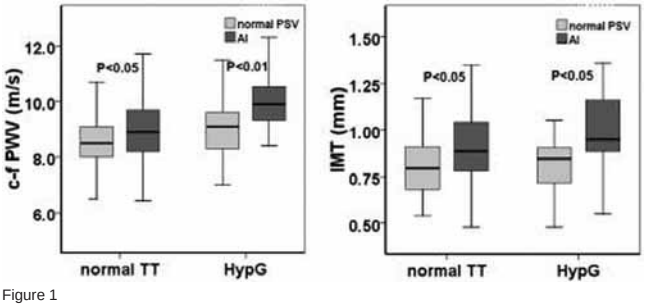

Figure 1

respectively, all P<0.01). Patients with HypG (n = 71) had increased c-f PWV and IMT compared to men with normal TT (n = 134) (by 0.95 m/s, P<0.001 and 0.05 mm, P<0.05, respectively). ED patients were categorized by PSV (normal PSV, AI) and further subdivided according to TT (normal TT and HypG) (figure). In patients with normal TT, AI (n = 88) compared with normal penile arterial function (n = 46) was accompanied by increased c-f PWV and IMT (by 0.40 m/s and 0.06 mm, respectively, all P<0.05). Similarly in men with HypG, AI (n = 29) compared with normal penile arterial function (n = 42) was related to heightened c–f PWV and IMT (by 0.82 m/s, P<0.01 and 0.10 mm, P<0.05, respectively). Patients with both HypG and AI had the highest c–f PWV and IMT compared to all the other groups.

Conclusions: Severely impaired penile vascular circulation in conjunction with low TT are additively associated with increased aortic stiffness and carotid IMT.

P1391 Effect of aging on aortic pulse wave velocity in cameroonian pygmies

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Purpose: To compare the evolution with age of aortic pulse wave velocity (PWV), a direct measure of arterial stiffness (AS), which is an independent cardiovascular (CV) risk factor, in Cameroonian traditional pygmies (TP) living in tropical forest on hunter-gather (HG) subsistence mode, in contemporary pygmies (CP) who migrated to sub-urban areas and in Bantou farmers (BF) sharing the same environment that CP.

Methods: We measured aortic PWV (ComplioR), brachial systolic (SBP) and diastolic (DBP) blood pressures (BP), and lipid profile in 78 TP, carefully matched for age and gender to 43 CP and 43BF

Results: TP were shorter than CP and BF (P=0.02) and had lower LDL cholesterol levels compared to CP and BF (P<0.01). Their brachial SBP was similar to that of CP (P=0.23), but lower compared to that of BF (P=0.01). By contrast, their DBP was higher compared to that of CP and BF (P<0.05). PWV was slower in TP (6.99±2.23 m/s, P=0.02) than in CP (7.72±2.15 m/s) and BF (8.06±2.30 m/s). In univariate analysis, PWV increased with age in TP, CP and BF (β=0.047; 0.095; and 0.127, respectively, all p<0.01). In the whole study population, multivariate analysis including CV variables of interest revealed age, MAP, LDL cholesterol and shorter stature as independent determinants of PWV (R2 = 0.48, P=0.03). By contrast, in multivariate analysis restricted to TP, height (P=0.02) and MAP (P=0.01), but not age (P=0.12) emerged as independent determinants of PWV (R2=0.56, P=0.02); suggesting a lower effect of aging on arterial stiffening in TP.

Conclusions: TP on hunter-gather subsistence mode have more distensible aortas that become less stiffer with advancing age. We therefore hypothesise that environmental factors contribute to arterial stiffening in this Cameroonian population.

P1392 Despite higher rates of coronary heart disease in British Indian Asians, coronary artery calcification levels are equivalent to those of Europeans

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Background: People of Indian Asian descent across the world have 1.5- 2 fold risk of coronary heart disease compared with people of European descent. Coronary artery calcium (CAC) is widely used as a marker of subclinical coronary atherosclerosis. However, no studies have directly compared levels of CAC in people of Indian Asian and European origins.

Methods: Cross-sectional population based UK study of men and women aged 58 -85. Participants were 592 Europeans (76% male), aged 69.7±6.3 and 408 first generation Indian Asians (84% male) age 68.5±6.0. Investigations including anthropometrics, fasting blood tests and medical history. Coronary CT was performed using a Philips 64 slice scanner to a standard protocol. Scans were read by an observer blinded to participant ethnicity and other characteristics.

Results: 9% of Europeans and 18% Indian Asians had known coronary heart disease (CHD) (p<0.001). CAC was present in 88% and 86% of European and Indian Asian men (p=0.37) and in 55% and 56% of European and Indian Asian women (p=0.64). Median (IQR) levels of CAC were respectively 151 (31, 492) and 136 (23, 518) in European and Indian Asian men (p=0.64) and 3 (0,161) and 6 (0,109) in European and Indian Asian women (p=0.96). The absence of ethnic group differences in both men and women remained following adjustment for risk factors including age, known CHD, obesity, height, smoking, glucose tolerance, lipid levels, blood pressure, lipid-lowering and antihypertensive therapies. Exclusion of those with known CHD did not alter these findings.

Conclusions: British Indian Asians, although at substantially higher high risk of CHD, have equivalent levels of coronary artery calcium irrespective of other risk factors including diabetes. This suggests that mechanisms underlying plaque formation may differ in Indian Asians and hence that coronary artery calcium levels may have different or reduced prognostic significance in Indian Asians.

P1393 Use of optical projection tomography to investigate statin effects on atherosclerotic plaque development

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Background: Statins reduce the incidence of adverse cardiovascular events through plasma lipid-lowering-dependent and -independent mechanisms. Because the reduction in the incidence of events, though significant, is relatively small, there is great interest in characterising the non-lipid-lowering actions with a view to capitalising on these in new therapies for cardiovascular disease. The apolipoprotein E (apoE) knockout mouse is a very useful model of unstable atherosclerosis in this context because statins do not produce any changes in plasma lipid levels in these animals. The best characterised anatomical site for the development of unstable lesions is the brachiocephalic artery, but this vessel is small and difficult to handle. We therefore used optical projection tomography (OPT) to assess its morphological characteristics and compared these with traditional histological methods.

Methods: Male apoE knockout mice were fed a high-fat diet for 10 weeks, with or without pravastatin (40mg/kg/day). At termination, arteries were fixed in situ at constant physiological pressure then were examined by OPT followed by standard computerised histomorphometry.

Results: There was a good correlation between atherosclerotic plaque areas measured by the two methods (r=0.59; p=0.002; Figure 1). Histomorphometry underestimated plaque area by about 15%, presumably as a result of tissue shrinkage during processing. As we have shown before by histomorphometry, pravastatin treatment caused a significant reduction in lesion size as determined by OPT (-57.4%; p<0.0001).

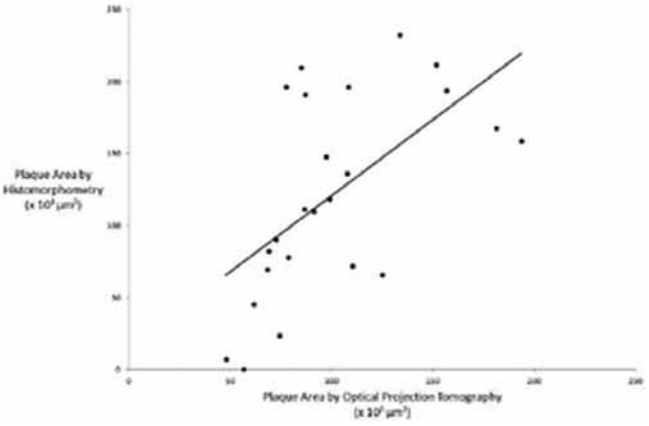

Figure 1

Conclusions: OPT is a useful modality for imaging mouse brachiocephalic artery lesions and has the advantage over standard histological methods of allowing non-destructive assessment of the entire lesion.

P1394 Carotid intima media thickness is related to HIV duration and decreased anti inflammatory status but not to antiretroviral treatment exposure. The CHIC study (ANRS EP 42)

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Purpose: HIV-infected patients are at increasing risk of cardiovascular disease. Whether HIV infection itself and/or antiretroviral agents (ARV) have impact on carotid atherosclerosis, assessed using the carotid intima media thickness (IMT), is still debated.

Methods: 100 HIV-infected patients (HIV+) (50 ARV-treated >4 years, 50 ARV-naïve but HIV-infected >2 years) and 50 HIV-negative controls were recruited in age-matched never-smoking male triads. Carotid IMT was measured using GE Vivid 7 system and 10-MHz linear array probe in a total of 12 segments in near and far walls of the common carotid, bifurcation region, and internal carotid region. Aortic stiffness (carotid-femoral pulse wave velocity) was assessed using the Complior® device. Pro- (hs-CRP, Resistin, IL-6, IL-18, Insulin, Serum Amyloid A, D-Dimer) and anti-inflammatory (total and high molecular weight adiponectin, IL-27, IL-10) markers were dichotomized into high/low scores (based on median values), creating four possible combinations of pro/anti-inflammatory profiles. Carotid IMT was compared across HIV/treatment groups, stratified by HIV-

infection duration, or inflammatory profiles using linear regression models adjusted for age, diabetes, prior hypertension.
Results: The mean age was 41.2 years (SD=6.7). In HIV+ patients, median CD4+ cell count was 499 cells/mm^3 (IQR=292) and median duration of HIV-infection was 7.9 years (IQR=7.6). After excluding 1 elite controller subject (<50 copies/mL, ARV-naïve), and adjusting for nadir CD4+ count, average carotid IMT was thicker with longer (>7.9years) HIV-infection, irrespective of ARV treatment (ARV-treated 760μm±10, ARV-naïve 757±17μm) when compared to shorter (<7.9years) HIV-duration (ARV-treated 731±16μm, ARV-naïve 731±10μm). ARV-treated subjects with >7.9 years of HIV-infection had significantly thicker carotid IMT than ARV-naïve subjects with <7.9 years of HIV-infection (P<0.05). Having a low anti-inflammatory profile was associated with thicker carotid IMT, irrespective of high- or low-proinflammatory markers (760±9μm and 768±13μm, respectively) when compared to subjects with high anti-inflammatory profiles (712±11μm and 737±12μm, for high and low pro-inflammatory profile respectively) (p<0.05). Aortic stiffness was similar in the 3 groups (8.1±1.6 ms^{-1}).
Conclusion: HIV duration, but not ARV treatment, is associated with thicker carotid IMT in these carefully selected triads. Low levels of anti-inflammatory markers highly correlate with thicker carotid IMT.

P1395 Prevalence of thoracic aortic calcification and its relationship to cardiovascular risk factors and coronary calcification in a population-based cohort: results of the Heinz Nixdorf Recall Study

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Background: Thoracic aortic calcification (TAC) and coronary artery calcium (CAC) have been proposed for risk assessment of coronary artery and cardiovascular disease events.
Objective: The aim of this article is to assess the prevalence of TAC and to determine its relationship with CAC and cardiovascular risk factors in a general unselected population.
Methods: Calcification of thoracic aorta was measured from electron beam computed tomography (EBCT) scans of 4025 participants aged 45 to 75 years (mean age 59.4±7.8 yrs, 53% female) from the Heinz Nixdorf Recall study. We quantified TAC, which ranged from the lower edge of the pulmonary artery bifurcation to the cardiac apex, by using Agatston-score. Multivariable generalized linear regression was used to evaluate relationships between TAC and cardiovascular risk factors and CAC.
Results: Overall 2538/4025 (63.1%) participants revealed TAC. Prevalence of TAC was greater in men than in women (65.2% vs. 61.7, p=0.009). TAC was most strongly associated with age, systolic blood pressure, smoking and high levels of LDL-cholesterol. Prevalence of CAC was significantly higher in participants with TAC than without (74.0% vs. 57.6%, p<0.0001) demonstrating an increased risk for development of CAC in the prevalence of TAC (PR 1.29 [95%CI: 1.22-1.35], p<0.0001, PR adjusted for risk factors 1.14 [1.09-1.20], p<0.0001).

Prevalence of CAC by TAC

Frequency (%) (%) in Row	CAC = 0	CAC > 0	Total
TAC = 0	631 (15.7) (42.4)	856 (21.2) (57.6)	1487 (36.9)
TAC > 0	659 (16.4) (26.0)	1879 (46.7) (74.0)	2538 (63.1)
Total	1290 (32.1)	2735 (67.9)	4025

Data are presented as count (%). Abbreviations: CAC = coronary artery calcium, TAC = thoracic aortic calcium.

Conclusion: Risk factors for TAC were similar to CAD risk factors in a large population-based cohort. TAC was found to be a predictor of CAC independent of CV risk factors. Further studies are needed to investigate whether presence of TAC alters the established relation between coronary events, CAC and risk factors.

P1396 Increased thermal heterogeneity in advanced atherosclerotic lesions: Experimental application of microwave radiometry

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Background: The association of inflammatory cells in atherosclerosis is considered a histological hallmark of high-risk vulnerable lesions. Intravascular thermography (IVT) is the only method currently available, which can measure heat generation from atheromatic plaques indicating local inflammation. However, the development and validation of non-invasive imaging techniques that detect inflammation in atherosclerosis still remains of major clinical interest. Microwave radiometry (MR) is a new non-invasive diagnostic method that provides accurate measurement of the temperature of tissues, reflecting local inflammation. We evaluated in an experimental model of atherosclerotic disease whether thermal heterogeneity measured by MR is correlated with IVT and histologic findings.
Methods: Microwave radiometry (RTM-01-RES system) was applied noninvasively in 60 atherosclerotic segments of rabbits aorta (5 segments, 2cm long in 6 rabbits), as well as in 60 control segments. The system measures natural electromagnetic radiation from the internal tissues at microwave frequencies that is proportional to the temperature of tissue (accuracy:±0.2°C, depth of temperature detection:1–7 cm). Thereafter, IVT was performed in the same segments. For both techniques temperature difference (ΔT) was assigned as the temperature of each segment minus the minimal temperature of the 5 segments. Aortas were excised and during histologic analysis were divided into 2 types according to the inflammatory cell content and the degree of CD3 and CD68 immunoreactivity.
Results: MR detected that ΔT of atherosclerotic aortas was significantly higher compared to controls (1.02±0.23 vs 0.21±0.09°C, p<0.001). These findings were confirmed by IVT. Segments with increased infiltration of lymphocytes (≥3) (n=27) had higher ΔT by MR compared to segments with low (n=69) (1.12±0.16 vs 0.41±0.35°C, p<0.001). Segments with increased expression of mast cells (≥3) (n=28) had higher ΔT by MR compared to segments with low (n=68) (1.10±0.23°C vs 0.41±0.34°C, p<0.001). ΔT of atherosclerotic segments assessed by both methods correlated with plaque thickness assessed by histology (MR: R=0.60, p<0.001, IVT:R =0.41, p=0.004).
Conclusion: MR may detect atherosclerotic plaque inflammation in an animal model of atherosclerosis. Increased thermal heterogeneity detected by MR reflected the presence of high-risk plaque features. This new non-invasive method may provide in vivo atherosclerotic plaque functional assessment, having thus the potential to characterize significant plaque features.

ENDOTHELIAL DYSFUNCTION

P1397 Correlation between radial artery- and peripheral arterial-tonometry derived augmentation index in patients with atrial fibrillation

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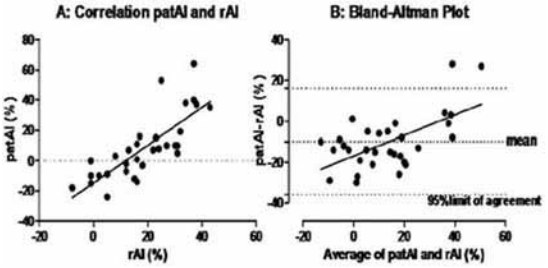
Introduction: Augmentation index (AI) is considered a surrogate marker for the stiffness of the arterial system; however its utility in atrial fibrillation is unknown. The AI is routinely recorded from the radial artery (rAI). AI can also be calculated from the fingertips by peripheral arterial tonometry (patAI). Therefore we sought to determine whether AI calculated from the fingertips (patAI) provides similar information to that of rAI in patients with atrial fibrillation.
Methods: 35 consecutive patients with paroxysmal atrial fibrillation (age 59±12) were examined during sinus rhythm. For each subject, rAI and patAI were recorded using radial applanation tonometry (SphygmoCor) and using peripheral arterial tonometry (EndoPat2000). AI is the ratio first to second peaks of the central arterial waveform) and expressed as a percentage of pulse pressure. Results are displayed as mean and SD.
Results: Overall, rAI (19±13%) was significantly (p<0.005) higher than patAI (9±21%) but both indices were highly correlated to each other. The R value was 0.79 (p<0.0001) and the R-squared value was 0.62 (Figure A). Bland–Altman plot of the difference between the two techniques (patAI-rAI values) versus their mean demonstrates that patAI under-estimates augmentation index (Figure B). The bias calculated over the range of averaged concentrations was -10%. However, the bias is not constant over this range.



Conclusion: AI can be measured by radial artery tonometry and peripheral arterial tonometry. While there is a good correlation between the AI calculated from both techniques, the lack of uniform bias between the values suggests that the two techniques are not interchangeable as estimates of arterial stiffness in patients with atrial fibrillation.

P1398 Knockout of the peroxisome proliferator coactivator 1 enhances endothelial dysfunction during chronic angiotensin II treatment by increasing mitochondrial ROS and apoptosis

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Background: Peroxisome proliferator coactivator 1 (PGC-1alpha) is an important mediator of mitochondrial biogenesis and function. We have previously shown that the AMP-activated protein kinase (AMPK) protects endothelial cells against oxidative stress by preservation of mitochondrial function in a PGC-1alpha dependent manner. Since dysfunctional mitochondria might be involved in the pathogenesis of vascular disease, we studied the effects of in vivo PGC-1alpha deletion during chronic angiotensin II (ATII) treatment in vivo.
Methods and results: Deletion of PGC-1alpha had no effect on endothelial function or mitochondrial mass under basal conditions. However, chronic angiotensin II (ATII) infusion at subpressor doses (0.1mg/kg/d) resulted in mild endothelial dysfunction, which was markedly impaired in PGC-1alpha knockout mice. In parallel, oxidative stress was increased in aortic rings from ATII-treated PGC-1alpha knockout mice while serum antioxidative capacity was decreased. We identified mitochondrial respiratory chain as the major PGC-1alpha dependent ROS source in vivo. In accordance with the role of mitochondrial ROS in the signalling events leading to apoptosis, we found positive TUNEL-staining in aortic sections from mice treated with angiotensin II, which was significantly increased in PGC-1alpha knockout mice.
Conclusion: In vivo PGC-1alpha deletion during vascular disease impairs endothelial function by augmenting oxidative stress. Mitochondrial dysfunction and associated ROS production might contribute to this process by promoting apoptosis of vascular cells.

P1399 Is poly (ADP-ribose) polymerase activity involved in eNOS activation after thrombin treatment?

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Purpose: The endothelial nitric oxide synthase (eNOS) is activated by numerous stimuli including shear stress, growth factors, vasoactive factors and hypoxia. The stimulation is mediated by complex regulatory mechanisms with phosphorylation at different sites by several protein kinases playing a vital role. We have recently reported that thrombin stimulates eNOS through phosphorylation at Ser 1177 by the AMP-actvated kinase (AMPK) but only under culture conditions that allow a fall in cellular ATP-levels. The cause of the decrease in ATP after thrombin stimulation is unknown but here we explore the possibility that it is secondary to a decrease in NAD levels caused by activation of poly(ADP-Ribose) polymerase (PARP). PARP is a nuclear enzyme that consumes NAD in response to DNA damage. Thrombin has been shown to cause an increase in reactive oxygen species in endothelial cells.
Methods: Umbilical vein endothelial cells were cultured in Morgan's medium 199 with 20% fetal calf serum. When confluent the cells were placed in either medium 199 or medium 1640 without serum. Agonist was added 10-20 minutes later and left on for 3-20 minutes. Intracellular levels of ATP and NAD were determined using a luciferase assay and an enzymatic cyclic assay respectively.
Results: Hydrogen peroxide (H2O2) caused a sharp fall in cellular NAD levels in both media prevented by the PARP inhibitor PJ34 and partly by the ADP-Ribose pyrophosphatase inhibitor LY290042. H2O2 also caused a fall in ATP levels that was totally prevented by LY290042 but only partially by PJ34. Manipulation of NAD levels by long term treatment with the NAD precursor nicotinamide or the NAD synthesis inhibitor FK866 had no effect on ATP levels or on the response to H2O2 and A23187. Thrombin as well as A23187 lowered NAD levels by 6% in both media but only lowered ATP levels in medium 199.This fall in ATP was unaffected by either PJ34 or LY290042.
Conclusions: In endothelial cells ATP levels are not tightly coupled to NAD levels regardless of whether the NAD is lowered by PARP activation or inhibition of synthesis. The fall in ATP after thrombin or ionophore stimulation are independent of PARP activity.

P1400 Partial gene deletion of endothelial nitric oxide synthase is an independent cause of coronary vascular dysfunction in mice fed with high fat diet

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Purpose: eNOS partial knockout mice (eNOS-/+) fed with a high fat diet (HFD) develop hypertension and insulin resistance (IR) similarly to eNOS knockout mice (eNOS-/-) fed with standard diet (SD) suggesting a combined effect of partial gene deletion and diet on systemic vascular function. This study aimed to investigate the interaction of eNOS gene deletion and HFD on coronary vascular function.
Methods: Wild type (WT), eNOS+/- and eNOS-/- mice were studied. WT and eNOS+/- were fed with SD or HFD for 16 wks. I.p. glucose and insulin tolerance tests (IPGTT and ITT) and measurements of arterial blood pressure (BP) were performed. Coronary function was evaluated in isolated heart. Coronary resistance (CR) was measured at baseline, and during infusions of acetylcholine (Ach) or sodium-nitroprusside (SNP) to evaluate endothelium-dependent or -independent vasodilation.
Results: Both eNOS-/- and HFD-fed eNOS+/- developed IR and hypertension, as suggested by AUC values from IPGTT and ITT as well as BP values shown in Table. HFD-fed WT developed IR but not hypertension while SD-fed eNOS+/- remained similar to WT. eNOS-/-, and eNOS+/- fed with HFD or SD, had impaired endothelium-dependent coronary function as demonstrated by significantly increased CR at baseline and after Ach as compared with other groups. Endothelium-independent vasodilation was significantly damaged only in eNOS-/- which showed no CR reduction after SNP (Table).

Metabolic and cardiovascular parameters

	WT	WT + HF	$eNOS^{+/-}$	$eNOS^{+/-}$ + HF	$eNOS^{-/-}$
AUC of IPGTT (mg/ml min)	220.1±7.8	409.4±25.5[a]	250.2±7.9	372.1±18.9[a]	198.1±6.9
AUC of ITT (ng/ml min)	1.06±0.09	2.01±0.29[b]	1.10±0.06	1.66±0.19	1.70±0.91
Non-invasive SBP (mmHg)	94.5±7.4[c]	100.1±6.3[c]	98.6±8.5[c]	114.4±11.9	128.6±7.1
Baseline CR, $mmHg \cdot g/mL^{-1}/min^{-1}$	4.4±0.83[d]	4.28±1.27[d]	5.33±1.31	5.03±1.52	5.27±1.25
CR after Ach infusion, $mmHg \cdot g/mL^{-1}/min^{-1}$	3.31±1.46[d]	3.24±1.51[d]	4.18±1.78	4.09±2.63	4.1±1.5
CR after SNP infusion, $mmHg \cdot g/mL^{-1}/min^{-1}$	3.71±1.17	3.67±1.42	4.01±1.64	3.84±2.03	4.95±3.1[e]

[a] $p<0.05$ vs WT, $eNOS^{+/-}$, and $eNOS^{-/-}$; [b] $p<0.05$ vs WT and $eNOS^{+/-}$; [c] $p<0.05$ vs $eNOS^{+/-}$ + HFD and $eNOS^{-/-}$; [d] $p<0.05$ vs $eNOS^{+/-}$ + CF, $eNOS^{+/-}$ + HFD, and $eNOS^{-/-}$; [e] $p<0.005$ vs others.

Conclusions: The present study demonstrates that eNOS gene deletions in mice have coronary functional effects independently of diet. In the case of partial gene deletion, interaction with HFD is required to cause systemic hypertension and IR.

P1401 Influence of circulating LysM positive cells on arterial hypertension

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Background: Angiotensin-II (ATII) is the most potent vasoconstrictor in arterial hypertension. It mediates infiltration of inflammatory leukocytes into the arterial wall and stimulates both vascular and inflammatory cell nicotin amideadenosine dinucleotide phosphate (NADPH) oxidases. The decisive source of ROS considering monocytes, granulocytes and vascular NADPH oxidase has not been defined yet.
Methods & results: Selective depletion of Lysozyme Mpositive (LysM+) cells was achieved by i.p. injection of low dose diphtheriatoxin in mice with LysM dependent cre inducible expression of diphtheria toxin receptor (LysMiDTR) and lead to reduced infiltration of LysM+ cells into the arterial wall following ATII infusion (1mg/kg/d for 7days), confirmed by flow cytometry and by galactosidase activity staining in LysMiDTR/LacZ mice.Depletion of LysM+ cells attenuated blood pressure increase (measured byradiotelemetry), vascular superoxide formation (measured by chemiluminescence,cytochrome c assay and oxidative fluorescence microtopography) and expression of NADPH oxidase subunits (assessed by Western blot and mRNA-RT-PCR) and ameliorated vascular endothelial and smooth muscle dysfunction (assessed byaortic ring relaxation studies). Reconstitution of depleted LysMiDTR mice with wild type monocytes, but not with monocytes lacking a functional NADPH oxidase, reestablished ATII induced vascular dysfunction, oxidative stress and arterial hypertension.
Conclusion: ATII induced vascular dysfunction seems tobe mediated, at least in part, by circulating and infiltrating LysM+ cells. The phagocytic NADPH oxidase in LysM+ cells appears to be a key component in ATII induced arterial hypertension and might represent a pharmacological target to treat arterial hypertension in the future.

P1402 Limited regulation of blood pressure by vascular endothelial nitric oxide synthase

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Disruption of eNOS in mice (eNOS-/-) causes a profound increase of blood pressure which is frequently assumed to be caused by the lack of endothelium-derived nitric oxide generation. We sought to investigate whether endothelial-specific targeting of eNOS in eNOS-/- normalises aortic reactivity and blood pressure.
Transgenic mice carrying bovine eNOS (eNOS++) were generated on C57BL/6 background using the endothelium-specific Tie-2 promoter. By breeding these mice with eNOS-/-, mice that express eNOS only in the endothelium (eNOS-/-/eNOS+) were obtained.

Western blot analysis confirmed eNOS protein expression in aorta (66.8±12.5, n=10), myocardium (49.9±5.4, n=4) and skeletal muscle (54.2±9.1, n=10) of eNOS-/-/eNOS+ as compared to C57Bl/6 (100%, n=4-10). Organ bath experiments revealed that the concentration-response-curves to acetylcholine did not differ significantly (P=0.562, n=8-11, two-way ANOVA), and the maximal relaxations were similar in eNOS-/-/eNOS+ (98.3±2.14%, n=7) and C57Bl/6 mice (92.4±3.6%, n=11) while aortic constriction was observed in eNOS-/- (137.5±12.1%, n=11, P<0.05). In addition, hypersensitivity to phenylephrine observed in eNOS-/- was blunted in eNOS-/-/eNOS+. Likewise, a significant increase in aortic sensitivity to NO-donors S-nitroso-N-acetyl-penicillamine and diethylamine/NO in eNOS-/- mice as compared to C57Bl/6 was completely abolished in eNOS-/-/eNOS+ (n=4-5, P>0.05). Endothelial-specific expression of bovine eNOS in eNOS-/- tended to result in increased phosphorylation at Ser1176/79 suggesting activation of bovine eNOS in response to shear both in thoracic aorta and in skeletal muscle. Aortic and skeletal muscle ratio of Ser239-phosphorylated and total VASP as a marker for protein kinase G activity was significantly increased by bovine eNOS (n=4-5, P<0.05). Expression of ecSOD, which is upregulated by endothelial NO, was elevated in aorta and skeletal muscle of eNOS-/-/eNOS+ when compared to eNOS-/- (n=4-9, P<0.05). Despite restoration of endothelial eNOS activity there was no effect of bovine eNOS on systolic blood pressure (sBP). While C57Bl/6 mice showed a normal sBP (118.4±3.1 mmHg, n=6), sBP in eNOS-/-/eNOS+ was strongly increased to 131.2±2.7 mmHg (n=14, P<0.05) and this was similar to that observed in eNOS-/- (131±3.0, n=14, P=0.7).
Endothelium-specific reintroduction of functionally active eNOS in eNOS-deficient mice, i.e. vascular-specific eNOS rescue, resulted in restoration of endothelial eNOS activity but not in normalisation of blood pressure. These data suggest that endothelial eNOS appears to have limited effect on systemic blood pressure.

P1403 Impairment of endothelial function, but not structural indices of vascular function, in children with juvenile idiopathic arthritis

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Purpose: Chronic inflammatory diseases (CID) have been associated with vascular dysfunction and increased incidence of cardiovascular diseases. Juvenile idiopathic arthritis (JIA) is a CID in children with very few studies so far reporting early vascular dysfunction. We aimed to assess the presence of vascular dysfunction in children with JIA compared to healthy controls and investigate the role of inherent inflammatory process of JIA in vascular health.
Methods: Thirty children with JIA were compared to 33 age- and sex-matched healthy controls (age range 7-18 years). Endothelial function was assessed by measurement of brachial artery flow-mediated dilatation (FMD). Indices of structural vascular disease such as carotid intima-media thickness (IMT), carotid-femoral pulse wave velocity (PWVcf using applanation tonometry) and large and small artery elasticity indices (LAEI and SAEI using diastolic pulse contour analysis) were also assessed. Intercellular adhesion molecule (ICAM-1) and P-Selectin were measured as indices of endothelial activation/inflammation.
Results: The two groups were well matched except for increased erythrocyte sedimentation rate (p=0.009) and ICAM-1 (p<0.001) in children with JIA compared to controls. FMD was decreased in children with JIA compared with healthy controls (7.10±2.23% versus 9.93±3.90%, p=0.001). There were no differences in IMT, PWVcf, LAEI and SAEI between groups. After adjustment for differences in inflammatory markers between groups the difference in FMD was abolished (p=0.054).
Conclusions: Children with JIA demonstrate endothelial dysfunction that is probably related to systemic inflammation. Indices of structural atherosclerotic changes did not differ between groups. Further studies are needed to confirm the clinical and prognostic significance of our findings in children with JIA.

P1404 Dynamic changes of the pro-apoptotic effect of serum on endothelial cells in ST-segment elevation myocardial infarction patients treated with primary angioplasty

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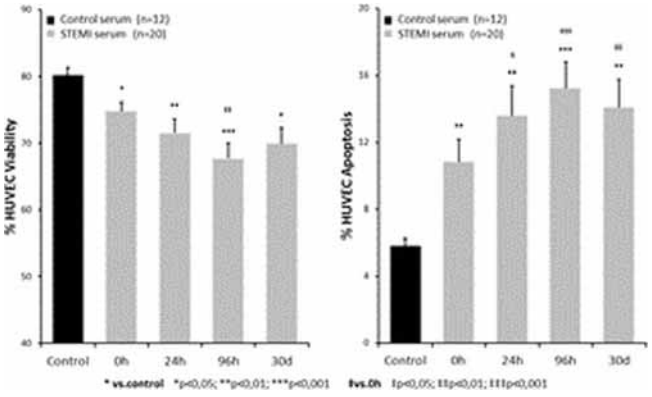
Purpose: Acute loss of endothelial cells may play a role in the ischemia-reperfusion injury process. The aim of this study was to evaluate the pro-apoptotic effect of blood serum on endothelial cells in reperfused ST-segment elevation myocardial infarction (STEMI) patients.
Methods: Human umbilical vein endothelial cells (HUVEC) were incubated with serum of 20 patients with a first STEMI treated with primary angioplasty drawn before reperfusion and 24h, 96h and 30 days afterwards. Apoptosis, necrosis and viability percentages were evaluated by flow cytometry. Cytokine levels and lymphocyte subtypes were evaluated by multiplexed immunoassay and flow cytometry respectively. Values were compared with serum of 12 age- and sex- matched control subjects with normal coronary arteries.
Results: In comparison with controls, serum of STEMI patients induced a loss of HUVEC viability mainly due to apoptosis but not necrosis. In patients, the pro-apoptotic effect of serum was maximum at 96h post-reperfusion (Figure). A pro-inflammatory response paralleled the pro-apoptotic effect of serum. In comparison with controls, at 96 hours anti-inflammatory cytokines IL-4 and IL-10 did not vary but pro-inflammatory cytokines IL-6 (p<0.001) and IL-1β (p<0.001) and pro-apoptotic cytokines TNF-α (p<0.01) and TGF-β (p<0.05) increased. Similarly a pro-inflammatory response in adaptative immune cells occurred: CD4+ cells count and Th1/Th2 ratio increased but FOXP3+ T regulatory cells count diminished (p<0.05 in all cases).



Conclusion: Serum of STEMI patients induces apoptosis on endothelial cells. This effect progressively increases in the days following reperfusion and it is acompanied by an acute pro-inflammatory deregulation of the adpatative immune system.

P1405 Hyperhomocysteinemia-induced endothelial dysfunction does not accelerate progression of atherosclerosis in hypercholesterolemic mice

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Purpose: Hyperhomocysteinemia is an independent risk factor for ischemic cardiovascular diseases but its causal role in atherothrombosis remains controversial. The objective of the current study was to analyse the effects of selective lowering of plasma cholesterol, plasma homocysteine, or both, on endothelial function and on progression of atherosclerosis in male hyperlipidemic and hyperhomocysteinemic C57BL/6 low density lipoprotein receptor (LDLr)-/- /cystathionine-β-synthase (CBS)+/- deficient mice. Second, we evaluated whether selective homocysteine lowering has anti-thrombotic effects in a model of arterial thrombosis.
Methods: A folate-depleted, methionine-enriched diet supplemented with 0.2% cholesterol (w/w) and 10% coconut oil (v/w) was started at the age of 12 weeks. Three weeks later, gene transfer was performed with E1E3E4-deleted adenoviral vectors for hepatocyte-restricted overexpression of CBS (AdCbs) or of the LDLr (AdLDLr), or with the control vector Adnull. In a fourth group, AdCbs and AdLDLr were co-administered.
Results: Three weeks after start of the diet, plasma homocysteine and plasma cholesterol levels were 82±14 μmol/L and 680±27 mg/dL, respectively. AdCbs and combined AdCbs/AdLDLr transfer resulted in a 5.6-fold (p<0.0001) and a 4.5-fold (p<0.0001) decrease of homocysteine levels, respectively, at day 14 and these effects were stable for the entire duration of the experiment. AdLDLr and AdCbs/AdLDLr transfer induced a stable 6.2-fold (p<0.0001) decrease of cholesterol levels. Six weeks after transfer, endothelium-dependent relaxation was not affected by hypercholesterolemia but was severely impaired in hyperhomocysteinemic mice compared to conditions of normal homocysteine levels. Intimal area was quantified in the aortic root and the brachiocephalic artery at 13 weeks after intervention. Intimal area in AdLDLr and AdCbs/AdLDLr mice was more than 100-fold (p<0.001) smaller than in control mice and AdCbs mice. No differences in intimal area were observed between control mice and AdCbs mice. In a model of carotid artery thrombosis, the average time to first occlusion and to stable occlusion were 1.9-fold (p<0.01) and 2.1-fold longer (p<0.01), respectively, in AdCbs treated mice than in control mice. Comparison of time to total occlusion between control mice and AdCbs mice by log-rank test yielded a highly significant difference (p<0.0001).
Conclusion: Endothelial function and homocysteine levels predict susceptibility to arterial thrombosis but do not predict atherosclerosis initiation and progression.

P1406 Endothelial function increases with age in adolescents

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Background: Endothelial dysfunction is an early indicator for developing atherosclerosis that can be found even in obese or diabetic children. The aim of this study was to characterize endothelial function in children and adolescents and to study the influence of physical activity and fitness on endothelial function.
Methods: 582 tests in 358 students in the age of 10 to 17 years (46.2% female; group 1: n=119, 11.2±0.6 years; group 2: n=191, 12.5±0.3 years; group 3: n=98, 13.5±0.3 years; group 4: n=174, 15.1±0,8 years) were analysed in this cross sectional study, that investigates the influence of one hour of physical exercise daily at school in the intervention group (IG) in comparison to two hours weekly in the control group (CG) on cardiovascular risk factors. Tests included assessment of (1) peripheral endothelial function via reactive hyperaemic index (RHI), (2) anthropometry with body mass index (BMI), (3) maximal oxygen consumption (VO2max) as a measurement for physical fitness via a maximal treadmill exercise test with spirometry, and (4) a blood sample for measurement of cholesterol, adipocytokines and hormones.
Results: With increasing age RHI increased significantly from 1.50±0.4 in group 1 to 1.80±0.6 in group 4 ($p<0.01$; r=0.33 Pearson's correlation). RHI increased in girls earlier than in boys with significant differences in group 2 (1.53±0.4 vs. 1.37±0.3, $p<0.01$) and group 3 (1.77±0.4 versus 1.59±0.6, p=0.02) between the genders. Correlation between RHI and BMI was small (r=0.2, $p<0.01$). BMI-percentiles revealed overweight and obesity in 8.2% students. We didn't found significant differences regarding the RHI in our small group of overweight/obese adolescents and the non-obese students. Endothelial function was not dependent on VO2max neither in the different age groups (52.9±8.8 ml/min/kg, 47.4±8.5 ml/min/kg, 48.7±7.7 ml/min/kg and 47.6±8.1 ml/min/kg for groups 1 to 4, $p<0.01$) nor between IG and CG. VO2max was better in the non-obese adolescents in all groups. Cholesterol levels decreased with increasing age in adolescents from 4.3±0.6 mmol/l in group 1 to 3.9±0.7 mmol/l in group 4, $p<0.01$. Measurements of adipocytokines and hormones are ongoing.
Conclusion: Endothelial function increases with increasing age in healthy children and adolescents. In preadolescents and after puberty, RHI of boys and girls is similar. Hormonal changes in puberty may cause an earlier increase of endothelial function during puberty in girls than in boys independent of maximal exercise capacity. Age-dependence of measurements has to be considered in further young study cohorts.

P1407 Critical role of endothelial MR in obesity-induced endothelial dysfunction

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Background: Aldosterone plays a crucial role in cardiovascular disease. Antagonism of its cognate receptor, the mineralocorticoid receptor (MR), decreases atherosclerosis by reducing inflammation and oxidative stress. Obesity is a chronic inflammatory disease that is characterized by increased plasma aldosterone levels. However, the role of aldosterone or MR in the context of obesity-induced vascular disease remains unknown.
Methods and results: We exposed C57BL/6 mice for 14 weeks to a high-fat diet (60% lard) or a normal chow. Obese mice showed increased plasma aldosterone levels and developed impaired endothelium-dependent relaxations to acetylcholine that was prevented by chronic administration of the MR antagonist eplerenone (200mg/kg/day). Furthermore, we observed that increased expression of inflammatory markers such as TNFα (tumor necrosis factor-α) and CD68 (macrophage glycoprotein) in the visceral adipose tissue of obese mice was restored to normal upon administration of eplerenone. Quantitative PCR analyses of freshly isolated RNA from mouse aortic endothelial cells revealed that inflammatory genes such as ICAM-1 (inter-cellular adhesion molecule 1), VCAM-1 (vascular cell adhesion protein 1) and C1-inhibitor were regulated in endothelial cells of obese mice whereas MR antagonism partially attenuates these proinflammatory events. To elucidate the role of the endothelial MR in this context, we generated mice with endothelial-specific ablation of MR expression using the Cre/loxP system and the Tie-2 promotor. We exposed these mice and the corresponding controls to a high-fat diet for 14 weeks. Endothelial dysfunction was completely prevented in obese endothelial MR knockout mice in comparison to their obese wild-type littermates.
Conclusions: Thus, obesity induces MR-mediated proinflammatory changes in the white adipose tissue and in aortic endothelial cells that result in increased oxidative stress, inflammation and endothelial dysfunction. Endothelial MR mediates obesity-induced endothelial dysfunction and therefore may play a crucial role in the initiation of vascular disease in obesity.

P1408 Glaucoma is associated with arterial dysfunction and increased inflammatory process

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Purpose: Reduced ocular blood flow, mostly caused by vascular dysregulation, plays a pivotal role in the pathogenesis of primary open-angle glaucoma (POAG). The study was designed to evaluate vascular function and inflammatory process in patients with POAG.
Methods: Forty seven POAG patients and thirty eight matched healthy subjects (Cl) were included in this case-control study. Endothelial function was evaluated by flow-mediated dilatation (FMD). Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as a measure of arterial wave reflections. Circulating levels of soluble interleukin-6 (IL-6) and soluble intercellular cells adhesion molecule (s-ICAM-1) were measured by ELISA.
Results: The POAG patients had significantly lower FMD compared to Cl (4.69±0.42% vs 6.53±0.59%, $p<0.05$) and significantly higher PWV (8.94±0.34m/s vs 7.64±0.30m/s, $p<0.05$) and AIx (27.28±1.03% vs 23.13±1.92%, $p<0.05$). Moreover, in POAG patients compared to Cl, we found a significant increase in the release of IL-6 (2.57±0.34 pgr/ml vs 1.70±0.17 pgr/ml, $p<0.05$) and s-ICAM-1 (684.20±53.60 ngr/ml vs 478.23±57.93 ngr/ml, $p<0.01$) indicating an elevated inflammatory status in POAG patients.
Conclusion: Glaucoma is associated with endothelial dysfunction, increased arterial stiffness and elevated inflammatory process, which are indicators of increased risk of cardiovascular events. These results strengthens the vascular theory considers glaucomatous optic neuropathy a consequence of insufficient ocular blood supply caused by vascular dysfunction.

P1409 Morphological and functional vascular changes induced by childhood obesity

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Childhood obesity induces severe complications: sleep apnea syndrome, dyslipidemia, insulin resistance, and hypertension, which raise the risk of cardiovascular disease in later ages by increasing the pace of the atherosclerosis process. Endothelial dysfunction is the first step in the atherosclerotic process in children.
The aim of this study was to determine whether childhood obesity is associated with early endothelial dysfunction and vascular structural alterations, and therefore constitutes the first step in the development of atherosclerotic disease in adulthood.
Methods: 93 children, aged 10.93±2.72 years, divided into two groups, normal weight subjects (controls) and overweight/obese subjects (cases), according to their Body Mass Index (BMI: 26±5 kg/m^2; median: 26 kg/m^2; interquartile range 22-28 kg/m^2) were recruited to the study.
All subjects underwent a check-up of total, HDL- and LDL-cholesterol, triglycerides, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cells count, together with ultrasound measures of flow-mediated dilatation (FMD), carotid intima-media thickness (cIMT), and anterior-posterior diameter of the abdominal aorta (APAO),as indices of cardiovascular status.
Results: We found a homogeneous gender distribution between the two groups (chi square test p=0.490) but a statistically significant difference in age (mean 11.68±2.26 years in the overweight/obese group vs. 10.07±2.97 years in the controls, p=0.004). In addition, obese children had high blood triglycerides (85±43 mg/dl versus 60±29 mg/dl in controls, p=0.002). A statistically significant difference between the two groups was found for HDL (52±11 mg/dl versus 58±12 mg/dl in controls; p=0.032) and ESR (20.7±14.6 mm/h versus 14.0±11.7 mm/h in controls; p=0.016) levels. Obese children had higher values of APAO than normal: 1.42±0.17 cm versus 1.28±0.18 cm (p=0.0001). Lower values of FMD (i.e. an impaired endothelial function) were found in overweight/obese children (7.24±2.47% versus 9.50±3.78% in controls; p=0.001).
Instead, left cIMT showed a statistically significant early impairment of vascular structures: overweight/obese cIMT: 0.53±0.06 mm versus controls cIMT: 0.50±0.05 mm (p=0.005). A similar result was found for the right cIMT values (0.53±0.08 mm vs. controls 0.50±0.06 mm, p=0.045).
Conclusions: Overweight/obese children have an initial endothelial dysfunction that represents the first stage in the development of atherosclerosis. So obesity, especially in childhood, is a primary cardiovascular risk factor that is likely to have both short and long term consequences.

P1410 Inverse association between haemoglobin A1c and flow-mediated dilation in non-diabetic women

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Purpose: Endothelial dysfunction precedes apparent atherosclerosis in humans and is associated with a number of cardiovascular risk factors, including Type 2 diabetes. To investigate the impact of long-term glucose homeostasis on endothelial function in an adult non-diabetic population, we analysed the association of serum HbA1c levels with flow-mediated dilation (FMD).
Methods: We studied cross-sectional data from 1384 subjects (696 women), aged 25 to 85, without diabetes, from the population-based Study of Health in Pomerania (SHIP-1). FMD measurement of the brachial artery was performed using standardised ultrasound techniques. Linear regression models were carried out to assess the association between serum HbA1c levels and FMD.
Results: Multivariable analyses disclosed an inverse association between serum HbA1c levels and FMD in women, but not in men. In women without current use of antihypertensive medication, increasing serum HbA1c levels were associated with decreasing FMD levels after adjustment for age, body mass index, smoking status, hypertension, low density lipoprotein cholesterol, and sex-hormone medication (β = -1.17; 95% CI -2.03; -0.30, p=0.009).

Serum HbA1c levels and FMD in women

	FMD (%)			
	Whole study population (n=696)		Study population without antihypertensive medication (n=489)	
HbA_{1c} (%)	β (95% CI)	p value	β (95% CI)	p value
Model 1	-1.61 (-2.24; -0.98)	<0.001	-1.65 (-2.45; -0.85)	<0.001
Model 2	-0.60 (-1.26; 0.05)	0.070	-0.96 (-1.78; -0.13)	0.023
Model 3	-0.74 (-1.44; -0.05)	0.035	-1.14 (-2.00; -0.27)	0.010
Model 4	-0.76 (-1.46; -0.06)	0.033	-1.17 (-2.03; -0.30)	0.009

Data are β-coefficients of linear regression (95% confidence interval). Model 1: unadjusted; Model 2: adjusted for age; Model 3: adjusted for age, body mass index, smoking, hypertension, and low-density-lipoprotein cholesterol; Model 4: Model 3 + adjusted for sex-hormone medication. FMD, flow-mediated dilatation.

Conclusions: We conclude that higher serum HbA1c levels in non-diabetic subjects are inversely associated with FMD in women without antihypertensive medication, but not in men. Our results support current considerations that subclinical disorders of glucose metabolism measured by serum HbA1c are associated with subclinical cardiovascular diseases detected by FMD, especially in women.

P1411 Coronary vasomotion one year after drug eluting stent implantation: comparison of everolimus-eluting and paclitaxel-eluting coronary stents

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Aims: First generation drug eluting stents (DES) have been associated with impaired localised coronary vasomotion, delayed endothelialisation and increased late thrombotic risk. With availability of newer generation DES, we aimed to compare coronary vasomotion after implantation of a newer generation everolimus-eluting stent (EES), with a first generation paclitaxel-eluting stent (PES).
Methods: Endothelium dependent and independent coronary vasomotion was studied in 19 patients with everolimus and 13 with paclitaxel-eluting stent (PES). Mean time from stent implantation was 11±3 and 13±8 months, respectively. Vasomotor response to right atrial pacing at increasing heart rates was measured proximally and distally to the stent and in a remote vessel (reference segment). Quantitative coronary angiography was performed offline.
Results: Stented segment showed no vasomotion in both groups. Endothelium independent vasomotion did not differ significantly between the 2 groups (p=0.65 for proximal and p=0.43 for distal segment). EES showed significant vasodilatation while PES showed vasoconstriction at both the proximal (+4.5±3.6 vs -4.2±6.9, p<0.001) and the distal (+4.6±7.9 vs -4.8±9.3, p=0.003) segments (Figure 1, panels A and B). Reference segment did not show any significant difference in vasodilatation between the 2 groups (+9.8±6.4 vs +7.2±5.2, p=0.17). Pacing induced coronary vasomotion of the distal segment correlated significantly with time from implantation in EES group (r=0.47, p=0.018).
Conclusions: Endothelium-dependent vasomotion at adjacent stent segments is preserved after EES implantation while endothelium-dependent vasoconstriction was observed long term after PES implantation. The restoration of normal endothelial function in EES group seems to be time dependent.

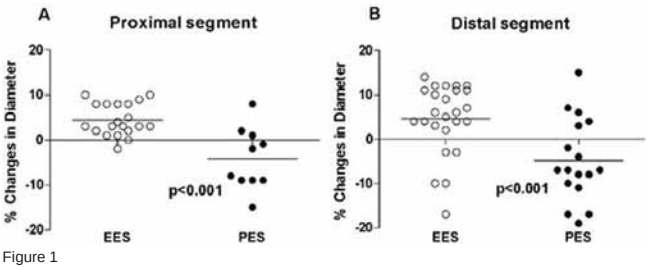

Figure 1

P1412 Carbamylated low density lipoprotein impairs nitric oxide induced vascular relaxation

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Introduction: LDL carbamylation has emerged as a potentially important cause of cardiovascular complications in smokers and patients with chronic renal failure. Hypothesis: Carbamylated LDL (cLDL) impairs nitric oxide (NO) induced relaxation in mouse aorta.
Methods: Native LDL (nLDL) was carbamylated with potassium cyanate and the degree of carbamylation measured by chromatography. TBARS assay was performed to confirm the absence of LDL oxidation. Aortic rings were suspended in organ chambers for isometric tension recording and the responses recorded in the presence or absence of 100 ug/ml nLDL or 100 ug/ml cLDL during submaximal contraction to norepinephrine (10-7 mol/L).
Results: LDL oxidation was neither detected in cLDL nor nLDL. cLDL inhibited maximal endothelium-dependent relaxations to acetylcholine as compared to vessels treated with nLDL (68.53±5.29% vs 87.04±1.68%; p=0.003; n=11) or controls (68.53±5.29% vs. 85.51±2.42%; p=0.009; n=11). Similarly, cLDL inhibited receptor-independent relaxations to the calcium ionophore A23187 (63.14±3.40% vs. 85.35±2.33%; n = 6; p=0.003 vs control). In contrast, endothelium-independent relaxations to sodium nitroprusside were not affected by cLDL (n = 11; p = n.s. vs. control). Indomethacin did not alter endothelium-dependent relaxations to acetylcholine in vessels treated with cLDL nor in controls (n = 5; p = n.s. for each group). In contrast, PEG-SOD and PEG-catalase blunted the inhibitory effect of cLDL on relaxations to acetylcholine (n = 5; p=0.005) without affecting the response of control vessels (n = 5; p = n.s.). cLDL induced the generation of superoxide anions in mouse aorta (3.02±0.55 vs. 6.00±1.06 nmol/min/mg; n = 10; p=0.02 vs control).
Conclusions: cLDL impairs endothelium-dependent relaxations by stimulating the generation of superoxide resulting in a decreased NO bioavailability. This observation may be important for understanding the high cardiovascular event rates in smokers and patients with chronic renal failure.

P1413 Impaired endothelial function and increased arterial stiffness in patients with sarcoidosis: the role of inflammatory process

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Purpose: Sarcoidosis (Sar) is a multisystemic inflammatory disease. Vascular function and structure have important impact on long term prognosis of cardiovascular patients. However, the effect of Sar on arterial performance remains unknown. In this study we assessed the hypothesis that Sar patients have impaired endothelial function and increased arterial stiffness.
Methods: A hundred fifty five (155) Sar patients and a hundred twenty five (125) matched healthy subjects (CI) were included in the study. Endothelial function was evaluated by flow-mediated dilatation (FMD). Carotid-femoral pulse wave velocity (PWV) was measured as an index of aortic stiffness and augmentation index (AIx) as a measure of arterial wave reflections. Serum levels of soluble intercellular cells adhesion molecule (sICAM-1), tumor necrosis factor alpha (TNF-α) and IL-6, were measured by ELISA.
Results: Compared to CI, Sar patients had significantly lower FMD (7.72±3.58% vs 5.44±2.82%, p<0.001) and significantly higher AIx (17.10±13.37% vs 22.73±10.72%, p<0.001) and increased PWV (7.09±1.55 m/sec vs 7.56±1.54 m/sec, p<0.01). In Sar patients PWV was correlated with serum levels of IL6 (r=0.239, p<0.05) and TNFa (r=0.201, p<0.05) and AIx was correlated with serum levels of sICAM-1 (r=0.169, p<0.05).
Conclusion: In the present study we have shown that Sarcoidosis patients have impaired endothelial function, increased arterial stiffness and increased inflammatory status. Moreover arterial stiffness in this population is associated with increased inflammatory process.

NEW ECHO MODALITIES FOR CARDIAC FUNCTION

P1414 Differences in left ventricular endocardial and epicardial strain in children: a 2-D speckle tracking imaging analysis

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Background: It has been suspected that the mechanics of left ventricular (LV) endocardium and epicardium are difference due to the myocardial fiber orientation in health children and in those with heart failure and coronary perfusion abnormalities. The advent of 2-D speckle tracking imaging (2DSTI) has made it possible to analyze endocardial and epicardial deformation in more details. In this study, we pursued the hypostheses: 1) LV endocardial and epicardial deformation can be quantitatively measured by 2-D speckle tracking imaging (2DSTI) analysis; 2) There is difference in left ventricular (LV) endocardial and epicardial deformation behavior in healthy children.
Methods: A total of 116 consecutive healthy infants and children (75 male/41 female, mean age 7.9±5.9 years) were enrolled. A Philips iE33 echocardiography system was used to obtain six views of the LV (apical 4-, 3-, and 2-chamber views, as well as parasternal short-axis basal, mid and apical views). Offline analysis was performed using dedicated software (TomTec Image Arena 4.0, TomTec, Munich, Germany). Longitudinal, circumferential and radial global peak systolic strain (PSS) of endocardium and epicardium were obtained by manual tracing and editing and semi-automated tracking of the endocardial and epicardial deformation.
Results: The image acquisition and analysis were feasible for endocardial and epicardial PSS in all patients, respectively. There is no difference in longitudinal PSS between the endocardium (25.9±4.5%) and epicardium (25.4±4.2%) (P=0.07); but the endocardial circumferential PSS (29.2±5.3%) is significantly greater than epicardial circumferential PSS (16.4±3.1%) (P<0.0001). There is no correlation between longitudinal, radial, and circumferential endocardial or epicardial PSS with age, gender, weight, height, and BSA. The normal values for these measurements were also obtained. Intra-observer variability of all the measurements range from 3.6±2.3% to 7.0±4.3%, and inter-observer variability from 4.6±3.3% to 7.6±4.4%, respectively.
Conclusions: Our study suggests measurement of LV endocardial and epicardial longitudinal, circumferential and radial PSS is feasible and reproducible in children. Circumferential deformation is significantly greater in LV endocardium than epicardium. This study established the normal ranges of LV endocardial and epicardial PSS measurements by 2DSTI. Further investigations in LV global and regional PSS in patients with coronary perfusion abnormalities and LV dysfunction are warranted to define the utility of these sensitive and quantitative techniques.

P1415 Intraventricular vorticity favors conservation of kinetic energy along the cardiac cycle: analysis in patients with dilated cardiomyopathy by post-processing color-Doppler images

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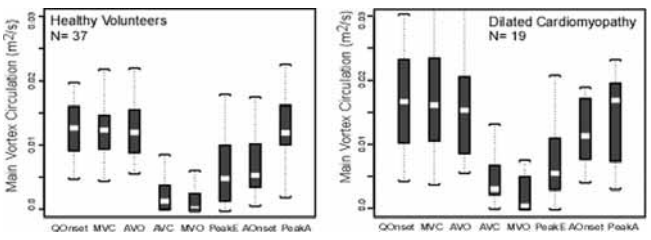
Background: Simulation studies suggest that the LV filling vortex developed during diastole may be a mechanism that improves systolic efficiency. Recently, we have developed and validated a method that derives two-dimensional maps of the LV flow from standard color-Doppler sequences. The vortices developed inside the LV along the cardiac cycle can be visualized with high temporal resolution (>100 Hz) and quantified by digital post-processing.
Purpose: To quantitatively analyze intraventricular vorticity and assess its implications on ejective efficiency in normal subjects and patients with dilated cardiomyopathy (DCM).
Methods: Nineteen patients with DCM and 37 healthy volunteers were studied. A two-dimensional map of instantaneous intraventricular flow was obtained, and circulation, energy and position of the main and secondary vortices were calculated along the cardiac cycle.



Results: A diastolic vortex is developed during rapid filling and enhanced by atrial contraction (see figure). The vortex circulation is maintained during isovolumic contraction, and abolished during the ejective period. At aortic valve opening (AVO) the vortex circulation is higher in DCM subjects than healthy volunteers (0.018±0.01 vs 0.013±0.006 m^2/s, p=0.03). However, the position of the vortex is farthest form LV outflow tract (p=0.04), and this results in lower flow velocity in LVOT at AVO (11±8 vs 18±15 cm/s, p=0.04).
Conclusion: Vortex circulation close to heart base acts as a mechanism to conserve kinetic energy developed during filling. This phenomenon is different in patients with DMC. New aspects of LV physiology can be studied by fluid dynamic quantitative analysis of conventional color-Doppler echocardiograms.

P1416 Assessment of left ventricular untwisting by speckle-tracking echocardiography in patients with aortic regurgitation

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Background: Left ventricular (LV) twist, as a result of counter-rotation of the apex and base during systole, and its subsequent untwisting during diastole represent important components of LV contractility and diastolic suction. Data regarding LV untwisting in AR patients are lacking.
Purpose: To assess LV untwisting and its determinants in patients with significant chronic AR.
Methods: We prospectively studied 35 patients with moderate and severe chronic AR and 20 normal subjects. Exclusion criteria for AR patients were LV ejection fraction (LVEF) ≤50%, significant coronary artery disease, any LV wall motion abnormality, more than mild associated valvular heart disease, non-sinus rhythm. Basal and apical LV rotation and LV torsion were quantified from two-dimensional greyscale LV parasternal short-axis images by speckle tracking echocardiography (STE). LV untwisting was assessed by measuring peak untwisting velocity as the net difference in peak diastolic apical and basal rotation rates on the torsional velocity curve. Time to peak untwisting velocity (TTPUV) was normalized to diastolic duration. Analysis of left atrium (LA) strain and strain-rate parameters was performed on the same 4-chamber view in which LA volume was measured.
Results: Age and gender of patients were similar in both groups. There was no difference in mean LVEF between groups (60±4% in AR group vs 62±3% in control group, p=0.15). Peak LV untwisting velocity was significantly reduced in the AR group compared with the control group (-117.7±35.0°/s vs -143.1±47.6°, p=0.028). Also, peak apical diastolic rotation rate was lower in the AR group (-80.8±41.0°/s vs -105.0±32.7°/s p=0.028). TTPUV was similar in both groups (p=0.189). In AR patients, peak LV untwisting velocity correlated with peak apical diastolic rotation rate (r=0.75, p<0.001) but not with peak basal diastolic rotation rate (r=0.02, p=0.934). At univariate analysis, peak LV untwisting velocity correlated significantly with age (r=0.41, p=0.014), end-systolic LV volume (r=0.35, p=0.041), LV mass index (r=0.42, p=0.013), LA volume index (r=0.45, p=0.008), and peak early-diastolic LA strain rate (ESr) (r=0.51, p=0.004). At multivariable analysis LV mass index emerged as an independent determinant of peak LV untwisting velocity (p=0.044).
Conclusions: LV untwisting is reduced in patients with significant AR and normal LVEF, and this is due to significantly decreased apical diastolic rotation rate. LV mass emerged as an independent determinant of LV untwisting velocity in these patients, suggesting that LV hypertrophy impacts on LV torsional dynamics in this setting.

P1417 New 3DE quantification of global longitudinal, circumferential, radial and area strains: reproducibility, correlations to cardiac output, and clinical applications

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Background: Two-dimensional (2D) speckle tracking echocardiographic strain analysis has demonstrated good capacities in the quantification of left ventricular (LV) contraction but it is limited by LV geometry and the assumption that speckles can be tracked from frame to frame, despite their out of plane motion.
Aims: First, to evaluate the reproducibility of 2D and tridimensional echocardiography (3DE) analysis of global longitudinal (GLS), circumferential (GCS), radial (GRS), and area (GAS) systolic strains. Second, to study values in different populations: healthy subjects, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and ischemic cardiomyopathy (ICM).
Methods and results: After exclusion of 54 patients for poor quality window or arrhythmia, GLS, GCS, GRS, and GAS were determined in 171 subjects (40 controls, 30 HCM, 34 DCM, 30 ICM, and 37 others indications) by 2D and 3DE. Mean intra-observer (novice) and inter-observer (novice vs expert) variabilities were 7% and 10% for 3D GLS, 6% and 12% for GCS, 6% and 10% for GRS, and 5% and

8% for GAS. The bests correlations with LV output were obtain for GAS (y = -0.11x+1.27, r = 0.74, p<0.001). Values obtained in controls and in the different populations of patients (HCM, ICD, DCM) are presented in the Table. Patients with HCM and normal EF had significant decrease in GLS, GCS and GAS but nor GRS (compared to controls). In ICM and DCM, all strains were significantly decreased compared to controls.

	Controls (n = 40)	HCM (n = 30)	ICM (n = 30)	DCM (n = 34)
LVEF (%)	64.2 ± 5.7	63.2 ± 10.8	42.9 ± 13.0*	37.1 ± 11.2*
GLS (%)	-19.2 ± 2.1	-16.0 ± 2.5*	-10.9 ± 3.3*	-9.6 ± 3.3*
GCS (%)	-19.5 ± 2.7	-17.5 ± 4.7*	-11.7 ± 5.1*	-9.5 ± 3.6*
GRS (%)	53.4 ± 8.9	47.1 ± 10.4	28.7 ± 12.7*	23.2 ± 9.3*
GAS (%)	-32.7 ± 3.4	-29.7 ± 5.3*	-19.7 ± 7.0*	-17.1 ± 6.1*

* p<0.05 vs controls

Conclusion: New 3DE strain analysis is robust and accurate with greater reproducibility than 2DE particularly concerning radial strain. Area strain is the greatest parameter correlated to LV output. The reference values for 3D global strains were obtained in a healthy population and are available for use in a wide clinical setting.

P1418 Left ventricular and left atrial chamber quantification by three-dimensional echocardiography: are current methodologies reliable and clinically interchangeable?

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Purpose: In an era of rapidly evolving three-dimensional echocardiographic (3DE) technology, one of the issues facing 3DE chamber quantification is that vendors use different methodologies, that may not give clinically interchangeable results. Therefore, we studied the comparability and reliability of conventional 3DE direct volumetric (3DDVE) and speckle tracking (3DSTE) methods for left ventricular (LV) and left atrial (LA) chamber quantification.
Methods: A total of 120 subjects (mean age 53±17 years, 65% men) including 88 unselected patients and 32 healthy volunteers underwent acquisitions using 3DDVE and 3DSTE methods successively. LV and LA parameters were compared between both methods. Additionally, intraobserver and interobserver reliability was assessed in 40 randomly selected patients.
Results: Measurements of LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) by 3DDVE and 3DSTE methods were comparable with excellent correlations (ICC=0.98, 0.98, and 0.87, respectively), small biases and narrow limits of agreement (-1±16mL, -1±15mL, and 0±11%). Although measurements of LA ESV and EDV by both methods correlated well (both ICC=0.96), Bland-Altman analysis revealed relatively large biases and wide limits of agreement (-2±11mL and -1±9mL, respectively). Intraobserver and interobserver reliability for LV and LA quantification were comparable between both methods (Table).

Reliability of LV and LA parameters

Parameter	Intraobserver		P value	Interobserver		P value
	3DDVE	3DSTE		3DDVE	3DSTE	
LV EDV (mL)	ICC = 0.99	ICC = 0.99	0.90	ICC = 0.99	ICC = 0.99	0.36
LV ESV (mL)	ICC = 0.99	ICC = 0.99	0.88	ICC = 0.99	ICC = 0.98	0.14
LV EF (%)	ICC = 0.96	ICC = 0.98	0.16	ICC = 0.91	ICC = 0.91	1.00
LA ESV (mL)	ICC = 0.98	ICC = 0.98	0.76	ICC = 0.98	ICC = 0.96	0.13
LA EDV (mL)	ICC = 0.98	ICC = 0.98	0.81	ICC = 0.98	ICC = 0.97	0.38

Data expressed as intraclass correlation coefficient (ICC).

Conclusions: Quantification of LV volumes and function by 3DDVE and 3DSTE methods gives comparable results with equally good reliability, making interchangeable application a viable option in daily clinical practice. However, measurements of LA volumes did not compare well between both methods, warranting further evaluation and development of dedicated software for LA chamber quantification.

P1419 Non-circular shape of right ventricular outflow tract: a real-time three-dimensional transesophageal echocardiography study

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Background: The shape of right ventricular outflow tract (RVOT) has been assumed to be circular. The aim of this study was to assess RVOT morphology and function using three-dimensional transesophageal echocardiography (3D TEE).
Methods: 90 pts who underwent 3D TEE were prospectively enrolled. 2D TEE measured maximum and minimum RVOT diameters (RVOTD max and min) during a cardiac cycle. 3D TEE assessed RVOTD max determined by larger vertical or horizontal RVOTD (Figure), RVOT area max and min, RVOT fractional area change, and RVOT shape index (Vertical RVOTD/Horizontal RVOTD). Based on RVOT shape, all patients were classified into the Group1 (RVOT shape index ≤1) or Group2 (RVOT shape index >1) (Figure).
Results: Mean RVOTD max, RVOT area max and min, and RVOT fractional area change by 3D TEE were 31.4±6.5mm, 6.7±2.1cm^2, 3.8±1.6cm^2, and 41.7±12.0%, respectively. Mean RVOT shape index were 0.85±0.20 at max (range 0.52-1.43) and 0.83±0.20 at min (range 0.50-1.48). 2D TEE, compared with 3D TEE, underestimated RVOTD max (p<0.001). As for the shape of RVOT, circular RVOT (RVOT shape index: 0.95-1.05) was found only 11 pts (12.2%) and 69 pts (76.7%) were categorized into the Group1. RV volumes, RV ejection fraction, RVOTD and RVOT fractional area change did not significantly differ between the two groups. The difference between RVOTD max by 3D TEE and those by 2D TEE was significantly greater in the Group1 than in the Group2 (p<0.01).

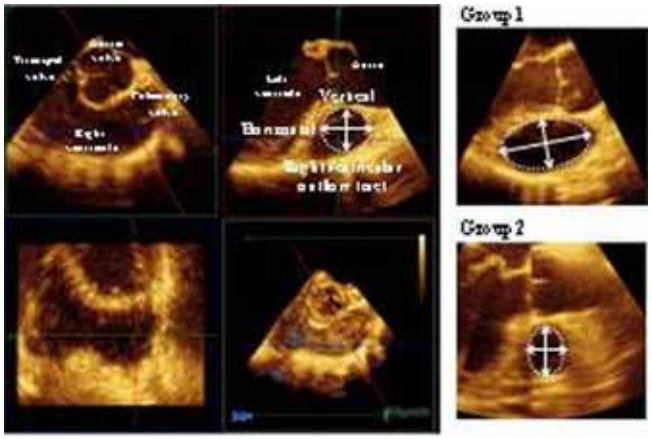

Figure 1

Conclusion: RVOT geometry was not generally circular but oval with 2 different types. 3D TEE could provide additive and unique information in RVOT assessment compared with 2D TEE.

P1420 Robustness of new 3D echocardiography quantification of left ventricular volumes and ejection fraction by novices

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Background: Tridimensional echocardiography (3DE) has previously demonstrated good capacities in the quantification of left ventricular (LV) volumes and ejection fraction (EF) but it is limited by time-consuming analysis and the need of learning curve.
Aims: First, to evaluate the robustness of a new 3DE semi-automatic analysis of LV volumes and EF, by a novice investigator. Second, to compare this new 3DE LV quantification technique against two-dimensional echocardiography (2DE), and cardiac magnetic resonance imaging (CMRI).
Methods: One hundred and ninety one subjects (151 patients hospitalized in cardiology and 40 controls) were investigated by 3DE and 2DE. Intra-observer reproducibility (novice), inter-observer reproducibility (novice vs expert), and repeatability (novice) were evaluated with linear regression and Bland-Altman analyses. Thirty patients were investigated the same day by 2DE, 3DE and CMRI.
Results: Thirty-five patients were excluded because 3 LV segments or more were not correctly visualized in 2DE and 10 for arrhythmia. Mean time analysis of the 3DE data was of 25±5 seconds. Mean intra-observer novice variability was of 5% for end-diastolic volume (EDV), 8% for end-systolic volume (ESV), and 8% for EF. Mean inter-observer variability for 3D analysis between novice and expert was of 13% for EDV, 14% for ESV, and 10% for EF. Inter-examination variability (repeatability, novice) was of 5%, 10% and 8%, respectively. Correlation between 3DE and CMRI were good (r = 0.92 for EDV, 0.96 for ESV, and 0.89 for EF) with low variability and greater agreement than between 2DE and CMRI (r = 0.78, 0.89 and 0.83, respectively).
Conclusion: This new semi-automated algorithm of LV endocardial borders detection from 3DE data is suitable for clinical use by novice investigator with greater reproducibility than 2DE. It allows rapid online, easy, accurate, and reproducible measurements of LV volumes, and EF, well correlated with CMRI.

P1421 Does 3D echocardiography improve image geometry or the assessment of left ventricle morphology and function?

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3D-echocardiography allows in principle to reconstruct ideal apical views from full volume (3DFV) data sets, promising an improved assessment of LV geometry and function. In this study, we investigated the geometric differences between standard 2D images (s2D) of the apical four, three- and two-chamber views (4CV, 3CV, 2CV) and ideal reconstructions (r2D) from 3DFV data sets and their influence on LV geometry and function assessment.
Methods: 3DFV and s2D data sets were acquired in 43 subjects with structurally normal (NH), 11 pat. with dilated (DH) and 6 pat. with hypertrophic hearts (HH). Ideal 4CV, 3CV and 2CV were reconstructed from 3DFV by aligning the LV axis with the middle of the image plane (see figure). Since the tip of the full volume sector indicates the true probe position, the deviation from the ideal image display could be described as 1) the off-set between the ideal and the true probe position on the skin and 2) the cross-plane and in-plane angle between ideal and standard image display. LV dimensions, volumes and EF were calculated from s2D and compared to the r2D.
Results: Compared to s2D, the r2D showed a minor deviation of 4.1° in-plane and 3.3° cross-plane for NH and 5.7° and 2.3° as well as 5.8° and 1.3° for DH and HH, resp. Consequently, the ideal probe position on the skin was not sign. different from the real one (7.6±4mm, 6±3.7mm and 8.5±7.2mm for NH, DH and HH, resp., all p=n.s.). In r2D, LV dimensions did not differ sign. from s2D. LV volumes and EF derived from r2D showed no sign. difference to s2D.

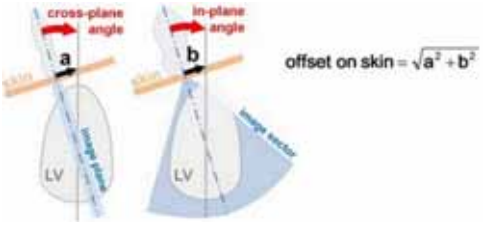

Figure 1

Conclusions: In the clinic, the geometry of ideal apical views, reconstructed from 3DFV, differs not sign. from s2D acquisitions. Likewise, LV shape and function assessment improves only little. Our data do not support the use of 3Decho for this purpose.

P1422 Interrelation of ventricular electrical activation, loading condition, and myocardial contractile status in the modulation of left ventricular mechanical coordination

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Aim: We sought to investigate Interrelation of ventricular electrical activation, loading condition, and myocardial contractility in the modulation of left ventricular mechanical coordination using pacing-induced heart failure model.
Methods: Eight normal dogs and 7 pacing-induced heart failure dogs had speckle-tracking radial strain rate images from mid-LV short axis views (Aplio 80, Toshiba Corp). Data were collected during baseline right atrial (RA) pacing and RV pacing at the heart rate of 120 beats/min. LV mechanical discoordination was assessed by averaging the frame–by-frame percent discordance between segmental and global strain rate in the 6 segments. To evaluate the effects of afterload reduction on LV mechanical discoordination, nitroprusside was administered at a dose of 2-3 μg/kg/min during RA pacing and RV pacing.
Results: Normal dogs (left ventricular ejection fraction: LVEF 50±4%) had coordinated regional strain rate in the 6 segments, however, LV mechanical coordination in dogs with heart failure (LVEF 30±8%) was significantly impaired (20±4* vs. 11±3%, *p<0.05 vs. normal dogs) during baseline RA pacing. RV pacing did not affect LV mechanical discoordination in dogs with normal LV myocardium. In contrast, large degree of LV mechanical discoordination (24±5* vs. 20±4%, *p<0.05 vs. baseline RA pacing) was observed during RV pacing in dogs with heart failure. Administration of nitroprusside improved LV mechanical coordination (17±4* vs. 20±4%, *p<0.05 vs. baseline RA pacing) in dogs with heart failure, however, RV pacing counteracted the favorable effect of afterload reduction by nitroprusside administration (24±6 vs. 24±5%, p=ns vs. baseline RV pacing). Administration of nitroprusside did not affect LV mechanical coordination in normal dogs.
Conclusion: Reduction of LV afterload may contribute to the improvement of the LV mechanical discoordination in failing myocardium; however, alteration of ventricular electrical conduction induced by RV pacing worsened LV mechanical coordination and counteracted the favorable effect of afterload reduction, which indicate that clinical attempt to correct ventricular activation is essential for maintaining LV mechanical coordination in addition to optimization of loading conditions in patients with failing myocardium and decreased LV function.

P1423 Different vendors show comparably high reproducibility of 3D strain measurements except for radial strain

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Background: Recent advances in speckle-tracking echocardiography make it possible to quantify the complex left ventricular (LV) myocardial deformation in its three-dimensional (3D) perspective. Little is known so far about the reproducibility of 3D strain parameters and almost exclusively from a single vendor's platform.
Aim: To assess and compare the reproducibility of 3D strain parameters obtained with two commercially available systems: Vivid E9 with 4V probe and EchoPac BT11 software (GE Healthcare, Horten, NO) and Artida with PST-25SX probe and 3D WMT software (Toshiba Medical Systems, Tokyo, JP).
Methods and results: Twenty patients referred for routine echocardiographic study (59±16 years, 12 men, LV ejection fraction range 30-70%) were imaged with both scanners during the same examination. 3D data sets were analyzed for inter-observer reliability by two separate observers. Intra-observer measures were performed one week apart. Peak global longitudinal, radial, circumferential and area strain were measured. Bland-Altman analysis and intra-class correlations were performed, and results for E9 are displayed in Table 1. Artida showed similar reproducibility for all strain components, except for a higher variability of radial strain in comparison to E9: bias (±LOA)=0.5%(±15.6%), ICC=0.56 for intra-observer reproducibility, and bias (±LOA)=4.8%(±22.2%), ICC=0.44 for inter-observer reproducibility (p<0.001 for both, respectively).

Table 1. Reproducibility of 3D strain

N=20	Intra-observer		Inter-observer	
	bias (±LOA)	ICC	bias (±LOA)	ICC
Longitudinal strain (%)	0.5 (±3.5)	0.94	1.0 (±3.8)	0.89
Circumferential strain (%)	0.5 (±2.2)	0.98	1.1 (±3.9)	0.91
Radial strain (%)	1.4 (±7.5)	0.97	3.6 (±8.0)	0.90
Area strain (%)	0.6 (±3.4)	0.98	1.7 (±4.1)	0.96

P<0.001 for all ICCs. LAO, limits of agreement; ICC, intraclass correlation coefficient.

Conclusions: Global longitudinal, circumferential and area strain seemed comparably and reasonably well reproducible with both systems. Conversely, the reproducibility of radial strain was different between vendors and significantly lower than of the other strain components. Different tracking algorithms and/or susceptibility to lateral versus longitudinal spatial resolution probably account for these results.

P1424 Inconsistency of 3D strain measurements between vendors

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Background: Three-dimensional (3D) speckle-tracking echocardiography provides a comprehensive analysis of left ventricular (LV) myocardial deformation, overcoming the "out-of-plane" flaw of two-dimensional (2D) method. Serious concerns have been raised about the consistency of 2D strain values between vendors. Whether discrepancies may also apply for 3D strain parameters is currently unknown.
Aim: To compare two commercially available systems and related softwares for 3D strain quantification.
Methods: In 60 consecutive patients (pts, age 58±15, 68% men, LV ejection fraction 17-65%) in sinus rhythm, two LV full-volume data sets were acquired using Vivid E9 with 4V probe (GE Healthcare, Horten, NO) and Artida with PST-25SX probe (Toshiba Medical Systems, Tokyo, JP) immediately one after another. 11 pts (15%) were excluded due to poor acoustic window or stitching artifacts. Peak global longitudinal, radial, circumferential and area strain were analyzed using the two vendor-specific softwares: 4D strain EchoPac BT 11 and 3D WMT, respectively.
Results: Average time for analysis was similar for both vendors (3:58 vs 3:44 min, p=NS). In 2 pts (3%), 4 segments/pt with inadequate tracking were rejected by GE software and global strain values were not provided. Strain results of the re-

Parameter (N=58)	GE (%, mean ± SD)	Toshiba (%, mean ± SD)	Inter-vendor correlation (R value)	Inter-vendor agreement (%, bias (LOA))
Longitudinal strain	–15.2±4.8	–14.1±4.2	0.83#	–1.1 (4.2 to –6.4)
Circumferential strain	–15.8±4.9	–22.8±8.3*	0.85#	7.0 (16.4 to –2.5)
Radial strain	39.9±20.3	17.9±8.4*	0.35$	22.0 (59.4 to –15.5)
Area strain	–27.2±7.9	–33.8±10.4*	0.88#	6.6 (16.6 to –3.4)

LOA, limits of agreement. *p<0.001 vs GE mean value, #p<0.001; $p<0.01.

maining 58 pts are shown in Table 1. Except for longitudinal strain, the two tested softwares yielded significantly different values for all parameters, most notably for radial strain. Area strain showed the closest correlation between vendors.
Conclusions: Global longitudinal 3D strain seemed reasonably comparable between the two vendors, while all the other strain components were significantly different. The largest discrepancy was found for radial strain values. Our study highlights the critical importance of using the same system to perform follow-up in longitudinal studies and, unless a uniform standard will be developed, of using vendor-specific reference values.

P1425 Comparison of speckle tracking strain measurements obtained from different echocardiography and vendor independent systems to measure global myocardial deformation

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Background: Myocardial deformation analysis, particularly measurement of strain, by speckle tracking echocardiography (STE) has been proposed to provide improved evaluation of myocardial function and is increasingly used in research protocols. However, a universally accepted industry standard is lacking and multiple vendor specific as well as third party software solutions with various algorithms exist. Whether different systems yield comparable measurements is largely unknown and must be clarified before using such measurements in clinical practice.
Methods: We performed STE in 21 healthy volunteers (15 male, age of 36,8±8,4 yrs) with a Vivid E9 system (GE Healthcare, USA) and an iE33 system (Philips Healthcare, The Netherlands). Strain was analysed by two different researchers using vendor supplied software (EchoPAC Dimension 06, GE Healthcare and QLAB, Philips). In addition, the image material obtained from both systems was analyzed with a vendor independent DICOM based analysis software (TomTec Imaging, Germany). Frame rates of GE and Philips systems were 45-63/s and 45-73/s, respectively. Measurements of longitudinal strain (LS) from apical four chamber views and measurements of circumferential strain (CS) from short axis views at the level of the papillary muscles were taken according to the manufacturers instructions and compared. Bias was calculated as the average of the differences of the measurements based on the results of Bland-Altman analyses. Results are shown as mean (±SD).
Results: Measurements of CS showed considerable variability when determined with vendor supplied software. On average Philips based analysis yielded lower values compared to GE (Bias -2,06±4,53). External analysis with independent software yielded consistently lower CS for both systems but greater differences for EchoPac, again with a wide scatter (bias, EchoPac vs TomTec -8,51±4,205; QLAB vs TomTec 4,59±5,32). LS measurements showed markedly less variability between the GE and the Philips system and independent external analysis of LS showed – incontrast to CS - good agreement with vendor specific analysis of the same images (bias, EchoPac vs TomTec 0,24±2,91; QLAB vs Tomtec 0,07±2,84).
Conclusions: Measurements of circumferential strain showed a remarkable variability when different echo systems or independent external analysis software were used. Measurement of longitudinal strain appears to be definitely more robust. Our findings stress the need for industry standards as well as standards for echo data acquisition and analysis for strain measurements.

P1426 Discordant change of longitudinal and radial strain in the hearts with progressive left ventricular systolic dysfunction: longitudinal strain as a beginning of left ventricular systolic dysfunction

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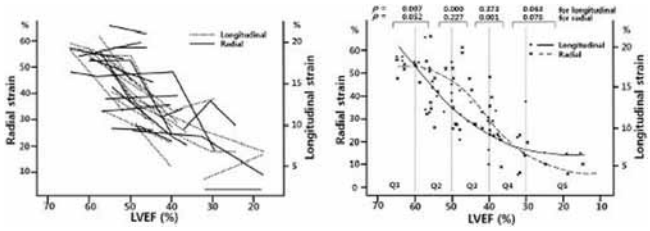
Background: The sequence of impairment of long and short axis function in the failing heart was not clearly investigated. We investigated each axis function by serially analyzing longitudinal (SL) and radial strain (SR) of LV with progressive systolic dysfunction.
Methods: Seventeen patients (M:F=8:9, mean age=53.9±16.8) with deteriorating left ventricular ejection fraction (LVEF) who underwent serial echocardiography more than twice were enrolled and forty four tests of 2DSTE available for myocardial strain analysis were analyzed. Patients with regional wall motion abnormality of LV and moderate to severe valvular dysfunction were excluded. SL from apical 4 chamber view and SR from mid-LV short axis view were taken for the study.
Result: The median follow-up duration was 172 days. In each patient, SR was decreased more slowly than SL in serial echocardiography when LVEF was more than 40% (ΔSL=25±13%, ΔSR=10±18%, p=0.005) The rate of decrease in SL and SR was not different when LVEF was <40% (ΔSL=4±35%, ΔSR=18±40%, p=0.329) (Fig. 1). When the tests of echocardiography were divided into quintiles (Q1 with LVEF ≥60%; Q2 with 50~60%; Q3 with 40~50%; Q4 with 30~40%; Q5<30%), longitudinal strain was continuously decreased from Q1 to Q3 (p=0.007, between Q1 and Q2, p=0.000 between Q2 and Q3), while radial strain was decreased only from Q3 to Q4 (p=0.001) (Fig .2).



Figures 1 & 2

Conclusions: Longitudinal strain was decreased continuously from the mild grade to the moderate grade of LV systolic dysfunction, while radial strain was preserved during the mild grade and rapidly decreased during the moderate grade. Short axis function may compensate early LV systolic dysfunction attributed by impaired long axis function and the impairment of SL may be a leading phenomenon before full-scale LV systolic dysfunction.

P1427 Can the early diastolic velocity of the mitral annulus be predicted from the mitral inflow pattern and systolic long axis displacement?

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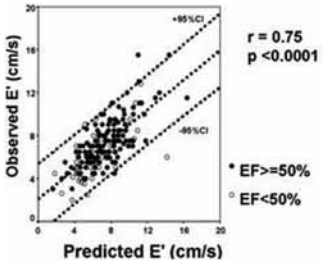
Mitral annulus (MA) early diastolic velocity (E') measured by Doppler tissue echocardiography (DTE) is widely used marker of relaxation. We assessed whether its ability to predict relaxation is its unique property, or if it can be explained by the influence of myocardial filling (a reflection of global diastolic function) and systolic long axis displacement.
Methods: We assessed 145 consecutive subjects (99 males, age 64±12 years, EF 54±12%; all in sinus rhythm, without prior mitral valve surgery or mitral stenosis) that underwent routine cardiac catheterization within 24 hours of an echocardiogram. Relaxation was assessed by time constant of isovolumic pressure decay (tau) calculated as isovolumic relaxation time divided by the difference in logarithms of LV systolic and end-diastolic pressures. To predict E', we used the equation: predicted E' = 2/Edur * E/A*(E/A+Adur/Edur)*D, where E, Edur, A, and Adur are respective velocities and durations of early and atrial waves of the mitral inflow, and D is LV long axis displacement calculated by integrating systolic wave of the mitral annulus (MA) obtained by DTE. E' was measured by averaging lateral and septal MA velocities obtained by DTE.
Results: Observed E' correlated strongly with predicted E' (r= 0.75, p<0.0001) and modestly with tau (r= -0.43, p<0.001). By multiple linear regression, predicted E' and tau were independent predictors (r=0.76, p<0.001), with observed E' being dominant (t statistics = 11.8, p<0.0001) and tau having marginal contribution (t statistics = 2.1, p=0.04).



Conclusions: E' velocity largely reflects LV long axis systolic displacement and global LV filling pattern. Direct contribution of relaxation, although present, is relatively modest.

P1428 Rapid assessment of longitudinal systolic left ventricular function with an automated tissue motion annular displacement algorithm

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Objectives: Assessment of left ventricular function (LV) is one of the most important tasks of routine echocardiography. Longitudinal LV function has been recognized to differentiate various myocardial disorders. We investigated global longitudinal LV function with tissue motion annular displacement (TMAD), a new method based on a 2-D strain tissue tracking algorithm.
Methods: 152 patients with different cardiac pathologies and 47 healthy subjects

underwent transthoracic echocardiography, tissue Doppler (TDI), strain imaging and measurement of TMAD.
Results: Regression analysis showed that 2-D EF, 3-D EF and stroke volume correlated well with TMAD (r^2=0.69, r^2=0.73 and r^2=0.41, p<0.001). An excellent correlation was found for measures of global longitudinal function such as mean peak systolic strain (SR, r^2=0.88, p<0.001) and mean peak systolic strain rate (SRR, r^2=0.78, p<0.001). It was significantly less time-consuming than strain imaging (p<0.001). The intra- and inter-observer variabilities were very low with 1.3±1% and 1.7±1.2%. TMAD was correlated with clinical parameters (NYHA, r= -0.71, p<0.001) as well as NT-proBNP (r= -0.73, p<0.001). TMAD discriminated healthy subjects with a high accuracy (AUC 0.97, p<0.001) in comparison to EF, SR, SRR and NT-proBNP. Furthermore in patients with systemic amyloidosis and preserved EF (>50%) TMAD was significantly reduced, even in those without signs of of cardiac involvement. TMAD could clearly discriminate these patients from controls (p<0.001) and was significantly better than other parameters of global longitudinal function such as SR and SRR (p<0.05).
Conclusions: TMAD correlates well with LV radial and longitudinal function in individuals with various cardiac disorders. TMAD is a new, ultra-fast, sensitive and reproducible method for the assessment of global LV longitudinal function.

P1429 Speckle tracking echocardiography analysis of left ventricular torsion dynamics in elite athletes

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Left ventricular (LV) contraction is the result of a complex three-dimensional deformation of the heart during systole. In addition to longitudinal shortening and radial thickening, LV twist motion induced by apical counterclockwise and basal clockwise rotation is a crucial element in effective LV contraction. The aim of our study was to analyze LV torsion dynamics by speckle tracking echocardiography in elite athletes and healthy sedentary volunteers as negative controls. Twenty elite athletes in kayaking, canoeing, or rowing (age: 22.4±3.3 years) and eleven healthy, regularly not exercising volunteers (age: 26.4±4.5 years) underwent cardiac MRI, as well as conventional and speckle tracking echocardiography. LV volume and mass indices and ejection fraction (LVEF) were determined by MRI. LV peak systolic rotations were measured in parasternal short-axis images by speckle tracking echocardiography at a frame rate of 60-80 frames/s. LV twist was defined as the net difference of LV rotations at the basal and apical planes, while LV torsion was defined as LV twist normalized for LV end-diastolic length. Analysis of the datasets was performed using QLAB, TMQ/A software version 8.0 (Philips). Our results indicated significantly higher LV twist and torsion in the elite athletes group compared to controls (LV twist: 7.4±0.6° vs. 6.0±0.4°; LV torsion: 0.8±0.07°/cm vs. 0.7±0.03°/cm; p<0.05). Subgroup analysis of athletes with slightly decreased LV ejection fraction (n=8, LVEF: 53.2±0.9%) did not show significant alterations in LV twist and torsion compared to controls (n=11, LVEF: 61.6±1.6%) and athletes with normal LV ejection fraction (n=12, LVEF: 60.0±1.0%) (LV twist: 8.1±0.8° vs. 6.3±0.7° vs. 6.0±0.4°; LV torsion: 0.9±0.1°/cm vs. 0.9±0.1°/cm vs. 0.7±0.03°/cm). In conclusion, speckle tracking echocardiography is a reliable method for measuring LV torsion, and adds valuable information to the assessment of LV systolic function. Higher LV twist and torsion in elite athletes might contribute to their increased functional reserve capacity.

P1430 Global area strain is a new and robust parameter to characterize left ventricular systolic function by three-dimensional speckle-tracking echocardiography

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Background: Three-dimensional (3D) speckle-tracking echocardiography enables the quantification of left ventricular (LV) myocardial deformation in all 3 directions from a single LV full-volume data set. In addition, 3D tracking has the unique advantage of computing area strain (AS) variations, corresponding to the total myocardial contraction that combines the longitudinal (LS) and circumferential strain (CS) of a particular segment.
Aim: We sought to assess the potential value of bi-directional AS in comparison to one-directional strain components to predict LV dysfunction (LVEF≤55%).
Methods and results: In 60 consecutive patients (pts, age 58±15, 68% men, LVEF range from 17% to 65%) in sinus rhythm, LV full-volume data sets were acquired using Vivid E9 with 4V probe (GE Healthcare, Horten, NO) and analyzed with 4D strain package (EchoPac BT 11). Global peak values of LS, CS, AS and radial strain (RS) and were analyzable in 58 pts. 3D LVEF was correlated with AS in overall population (r=0.87) and in pts with EF>55% (N=33, r=0.46), more closely than LS (r=0.79 and r=0.41) and comparably with CS (r=0.87 and r=0.43, respectively) (p≤0.02 for all). Conversely, RS showed weaker correlation with 3D LVEF in all pts (r=0.53, p<0.001) and no correlation with 3D LVEF in pts with preserved EF (p=0.93). Results for ROC curve analysis to assess the accuracy of various strain parameters to predict a LVEF ≤55% are displayed in Table 1. AS also showed a good intra- and inter-observer reproducibility (intra-class correlation coefficients 0.98 and 0.96; bias ± limits of agreement 0.6±3.4% and 1.7±4.1%, respectively).

Table 1. ROC curve analysis of 3D strain

Parameter	AUC	95% CI	Optimal cut-off (%)	Sensitivity (%)	Specificity (%)
LS	0.87*	0.77–0.96	–15.5	84	82
CS	0.93*	0.93–1.00	–16.5	92	89
RS	0.88*	0.79–0.88	41.0	88	82
AS	0.91*	0.91–0.99	–27.5	88	82

*p<0.001 for all AUCs; abbreviations as in text.

Conclusions: Novel AS by 3D speckle-tracking seems robust and superior than global LS to predict global LV systolic dysfunction. However, among all strain components, global CS had the best discriminative power to identify a LVEF≤55%.

P1431 Does temporal resolution affect the measurements of three-dimensional speckle tracking echocardiography?

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Purpose: To assess whether temporal resolution affects the measurement of deformation parameters in three-dimensional speckle tracking echocardiography (3SDTE).
Methods: A total of 42 healthy volunteers were studied with a mean volume per second (VPS) rate=20.6. Peak values of radial, longitudinal and circumferential strain were reported in three left ventricular levels (base, mid-ventricle, apex).
In order to assess the way that temporal resolution affects the measured strain parameters we used the volumes per cardiac cycle (VPCC) ratio, defined as: VPCC= VPS*60/heart rate. Then, three groups of studies were created depending on the VPCC. The first group consisted of 14 studies with low VPCC (mean value=13.8), the second consisted of 14 studies with average VPCC (mean value=19.6) and in the third group 14 studies with high VPCC (mean value=25.1) were included. The results of each group were compared to the results of the other two groups to assess whether VPCC affects the strain parameters significantly.
Results: The results of the three groups of studies classified by VPCC are seen in Table 1. Peak radial strain in the basal LV segments was found to be significantly different between the group with low VPCC and average VPCC (32±11% vs. 39.7±16% respectively, p value<0.05). No significant differences were found between the three groups in the rest of the strain parameters and in any of the LV levels.

Table 1. VPCC and strain parameters

	Low VPCC	Average VPCC	High VPCC
Base radial (p<0.05)	32	39.7	36.5
Mid radial	31.6	34.7	36.5
Apex radial	22.7	24.7	22.1
Base longitudinal	14.1	16	13.8
Mid longitudinal	15.8	15	16.5
Apex longitudinal	16	14.8	16.8
Base circumferential	25.2	25.5	22.9
Mid circumferential	28.6	27.5	25.8
Apex circumferential	24.9	21.6	22

Conclusion: To our knowledge this is the first study to assess the way that temporal resolution affects measurement of strain parameters in 3DSTE, suggesting that radial strain of the basal segments might be frame-rate dependent.

P1432 Left ventricular volume in patients with wall motion abnormality by volume imaging ultrasound system: a comparison between regional and global wall motion abnormalities

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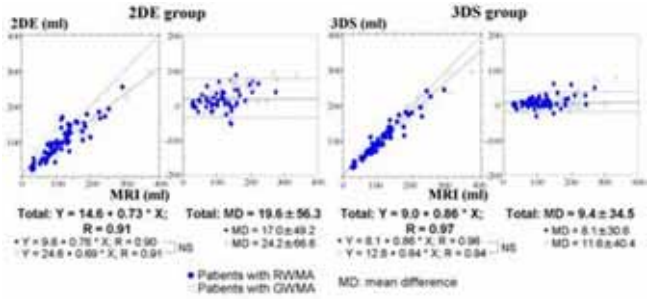
Background: Left ventricular volume (LVV) by volume imaging ultrasound system (3DS), which use a single-beat full-volume acquisition of three-dimensional echocardiography, enabled a semi-automated LVV analysis. However, in patients with wall motion abnormality the accuracy of 3DS remains unclear. Our aim was to validate accuracy of 3DS for LVV in patients with regional WMA or global WMA compared with two-dimensional echocardiography (2DE) and cardiac MRI.
Methods: We enrolled 35 patients with regional wall motion abnormality (RWMA) due to myocardial infarction and 20 patients with global wall motion abnormality (GWMA) due to cardiomyopathy or valvular heart disease, who were recorded by 2DE, 3DS acquisition of three-dimensional transthoracic echocardiography (Siemens ACUSON SC2000) and cardiac MRI (Siemens MAGNETOM Sonata 1.5T). For analysis of LVV in end-systole and end-diastole, analysis of covariance (ANCOVA) and Bland-Altman plot were used.
Results: The results were shown in the figure. The LVV by 2DE and 3DS were linearly related to the results from MRI (2DE: R=0.91, p<0.0001, 3DS: R=0.97, p<0.0001), with limits of agreement from -36.7 ml to 75.9 ml and from -25.1 ml to

43.9 ml, respectively. There were no significant differences between RWMA and GWMA in both measurements (ANCOVA: 2DE p=0.14, 3DS p=0.47).



Analysis of left ventricular volume.

Conclusion: 3DS has better correlation and closer limits of agreement to MRI than 2DE in patients regardless of the type of WMA. 3DS is a new objective solution for noninvasive semi-automated LVV analysis.

P1433 Are we following guidelines in echocardiographic assessment of left ventricular function?

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Purpose: Recent guidelines of the European Association, British Society and American Society of Echocardiography (ASE) advocate for the use of Biplane Simpson's for ejection fraction (EF) determination by echo. General acceptance in the real world is uncertain.
Methods and results: We reviewed the compliance and feasibility of Simpson's in 481 noncontrast 2D studies performed at 2 tertiary care level 3 echo labs in January 2010. All studies were re-reviewed and reanalyzed by a second reader. Studies were initially read by 7 ASE level 3 and one ASE level 2 physician. Primary indication was LV assessment in 207 (43%) and valve assessment in 111 (23%), with acceptable image quality in 434 (90%). Ejection fraction was reported as mean 54% ± SD 10%. Simpson's was used in only 63 cases (13%), with significant variation in frequency by individual MD (range 5 to 37%, Chi-square for differences 34.4, $p<0.01$)). Other methods of EF determination was not specified. On reanalysis, 391 studies (81%) were feasible for Simpson's. Agreement in EF (±5%) between original and reanalysed EF was 50% including 57% in those with abnormal systolic function and 48% with normal systolic function (Chi-square 1.85, p=0.17). Bland Altman plot (Figure 1) comparing original (EF1) and secondary (EF2) readers in 59 patients showed nonsignificant agreement, with greater spread with higher EF.

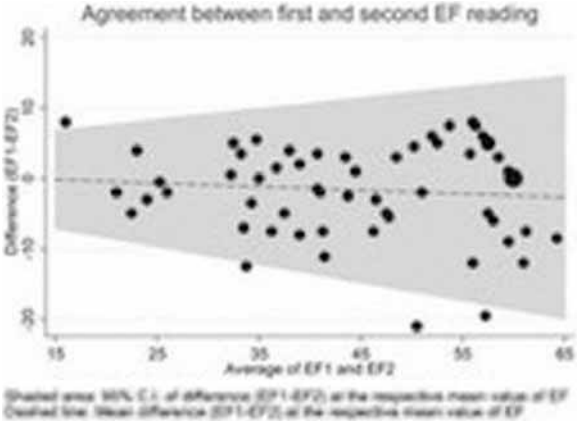

Figure 1

Conclusions: Although Simpson's methodology is recommended universally and very often feasible to perform, it is rarely used in the real world. A trend towards greater interobserver variability is seen with higher EF. Greater efforts at quality assurance and education is required to optimize quantitation.

MYOCARDIAL FUNCTION AFTER ACUTE MYOCARDIAL INFARCTION

P1434 Prediction of LV remodelling after STEMI - role of speckle tracking echocardiography

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Introduction: The frequency of postinfarction remodeling is still high. It is important to evaluate those factors that could predict LV change at early stage. The new technique: speckle tracking echocardiography (STE) allows to measure peak longitudinal (PSS) as well as radial strain of LV independently from ultrasonographic beam.
Aims: W e wanted to asses predictive value of STI for identification of patients with remodeling in 3 months follow up after STEMI.
Methods: Patients with first STEMI were enrolled. In all subjects ECG, 2D echocardiography including STI, and 3D echocardiography were performed. In three months follow up 2D and 3D studies were performed.
Results: 68 patients were enrolled. The population was divided into two groups - R– (no remodeling) which consisted of 46 (68%) patients, and R+ (with remodeling) which consisted of 22 (32%) patients. Remodeling was present in 13 patients with anterior wall MI (42%). The univariate analysis has shown that risk of remodeling is among other factors more probable in case of worse indicators of PSS. Based on ROC Curve we found cut off value (-12,5) for mean peak systolic strain (PSS) to be most accurate (80%), sensitive (69%) and specific (89%) for prediction of remodeling. Multivariate analysis has revealed that most predictive were: mean value of peak longitudinal strain and diabetes.
Conclusions: 1) In patients with STEMI frequency of remodeling after 3 months is, despite primary PCI, high – 32%, specifically in the group with anterior wall MI – 42%. Peak systolic longitudinal strain measured with STI is helpful in prediction of LV remodeling. 2) In the studied group value of peak systolic longitudinal strain measured with STI has appeared to be an independent factor predicting LV remodeling, aside other factors as Diabetes Mellitus, anterior wall MI, longer time to reperfusion, lower EF and WMSI.

P1435 Speckle-tracking derived deformation analysis for predicting long term regional contractile recovery in myocardial infarction

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Objective: To asses the accuracy of speckle-tracking analysis for predicting long term improvement of segmental kinetics in ST elevation acute myocardial infarction (STEMI).
Methods: Prospective observational study of consecutive patients (pts) with STEMI undergoing primary angioplasty. Echocardiographic study was performed during the first 72h of hospitalization. In post-processing, the longitudinal and transverse deformation were assessed by speckle tracking. We measured the systolic peak of longitudinal strain (SPLS) and strain rate (Sr) (SPLSr) and the early-diastolic peak of longitudinal Sr (DPLSr).Wall motion score (WMS) was evaluated by two independent operators with assignment of the final classification by consensus. The echocardiographic study was repeated after 12.1±2.6 months and the regional contractility was re-classified. In a per-segment analysis, regional contractile recovery was defined as a reduction in the WMS by at least one point. The accuracy of significant variables for predicting contractile recovery was assessed by the receiver operator curve analysis. For each variable, the threshold with best diagnostic performance was identified, and a new speckle-tracking derived score for prediction of myocardial recovery was computed.
Results: We studied 49 pts (male: 71%, 61±14years). Echocardiographic image quality was adequate to evaluate longitudinal and transverse deformation in 775 segments, of which 36% (N = 278) had WM abnormalities at baseline (hypokinesia, akinesia and dyskinesia in 26%, 9% and 0.4% respectively). In long term, regional contractility improved in 19% of those segments (N = 147). WMS classification in the initial study did not anticipate the long term contractile recovery. The speckle tracking derived parameters were associated with the long-term progression of regional kinetics and best thresholds for predicting contractile recovery were: SPLS $\leq$ -8% (S: 57%, E: 63%), SPLSr $\leq$ -0.8 s^{-1} (S: 67%, E: 41%) and DPLSr $\leq$ -0.8 s^{-1} (S: 67%, E: 41%). Furthermore, in regression analysis, the likelihood of long-term recovery increased with the number of criteria verified: 1: OR 1.97; 2: OR 2.19; 3: OR 3.40 (p=0.001).
Conclusion: The myocardial deformation assessment with speckle-tracking is a new tool useful for identifying myocardial stunning. The new score based on the evaluation of longitudinal deformation is able to predict long term contractile recovery after STEMI.

P1436 Longitudinal myocardial deformation can predict long term worsening of segmental kinetics in STEMI

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Aim: To determine the long-term prognostic accuracy of longitudinal and transverse myocardial deformation parameters, based on speckle tracking, in predicting worsening of segmental kinetics in ST elevation acute myocardial infarction (STEMI).
Methods: Prospective observational study of consecutive patients (pts) with STEMI undergoing primary angioplasty. Echocardiographic study was performed during the first 72h of hospitalization. The Wall Motion Score (WMS) was evaluated by two independent operators with assignment of the final classification by consensus, defining improvement in regional wall motion by a decrease in WMS at least one point. In post-processing, we measured the systolic peak of longitudinal strain (S) (SPLS), longitudinal strain rate (Sr) (SPLSr) and the protodiastolic peak of longitudinal Sr (DPLSr). The prognostic accuracy in predicting worsening of segmental long-term kinetics was determined by the area under the Receiver Operator Curve.
Results: We studied 49 patients (male: 71%, 62±14 years). The image quality was adequate to study longitudinal and transverse myocardial deformation in 775, of which 36% (N = 278) had abnormalities of segmental kinetics in the initial study (hypokinesia, akinesia and dyskinesia in 26.1%, 9, 4% and 0.4% respectively). In long term follow up, there was worsening in regional wall motion in 7.1% of segments (N = 55). The risk of worsening was higher in segments that were initially classified as hypokinetic than normokinetic (OR: 1.87 95% CI: 1.1-3.3, p=0.031). The non akinetic segments in the initial study (WMS $\leq$2) who had worsened in follow up had initial significantly less negative values of SPLS (-9.4% vs. -15.1%, P<0.001), SPLSr (-0, 84 vs. -0.97 s^{-1}, p=0.015) and lower DPLSr (0.82 vs. 1.22 s^{-1}, p<0.001). The transverse deformation parameters did not differ depending on the occurrence of subsequent worsening. The accuracy of each parameter of myocardial deformation in predicting worsening of segmental kinetics (between segments with WMS initial $\leq$2) was higher than that observed for the prediction of recovery: SPLS: AUC 0.72, 95% CI 0.66 to 0, 78, p<0.001; of SPLSr: AUC 0.61, 95% CI 0.52 to 0.70, p=0.015 and DPLSr: AUC 0.68, 95% CI 0.60 to 0.76, p<0.001.
Conclusion: Longitudinal myocardial deformation, by speckle tracking, can predict the long term worsening of segmental kinetics in STEMI. SPLS was the parameter with greater accuracy.

P1437 Association between left ventricular global longitudinal systolic strain and impaired microcirculation in patients with acute myocardial infarction

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Background: The association between left ventricular global longitudinal systolic strain (GLS) and coronary flow reserve (CFR) assessed by transthoracic echocardiography has never been investigated. We analyzed this in patients with acute myocardial infarction (AMI).
Methods and results: In consecutive first time AMI patients, who underwent successful revascularization, we performed comprehensive echocardiography. GLS was obtained from the three standard apical views. Assessment of CFR by transthoracic echocardiography was performed in a modified apical view by color Doppler guidance.
Results: The study population consisted of 183 patients (51 females with a median age of 63[54;70] years. Eighty-nine patients (49%) had a non-ST-elevation myocardial infarction and 94 patients (51%) had a ST-elevation myocardial infarction. Echocardiography was performed a median of 5[2;9] days after admission. GLS was -15.2[-19.3;-10.1] in the total population. Total wall motion score index (WMSI) in the population was 1.19 [1;1.5]. The GLS correlated with WMSI (r= -0.29, p<0.0001). Furthermore we found a strong correlation between CFR and GLS (r= -0.85, p<0.0001). This was also seen in the multivariate regression model adjusting for possible confounders including WMSI (p<0.001). By dividing the population by CFR $\leq$2 (109 patients and CFR >2 (74 patients) we found a significant difference in GLS (-11.8 [-14.9;-8.3] vs. -19.8[-21.9;-17.8], p<0.0001).
Conclusion: This study indicates that disturbances in microvascular circulation are associated with depressed left ventricular global longitudinal systolic function demonstrating an important patophysiological link between noninvasive estimation of coronary flow reserve and left ventricular function.

P1438 Echocardiographic tissue Doppler imaging can predict recovery of contraction after acute myocardial infarction

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Purpose: To assess whether echocardiographic tissue Doppler imaging can serve to evaluate myocardial viability in patients with acute coronary syndrome (ACS).
Methods: In 23 patients with ACS, we measured longitudinal tissue Doppler strain and strain rate values from left ventricular basal, mid, and apical segments (n = 414). These segments were grouped according to their acute end-systolic strain values (Ses) into those with normocontraction (Ses $\leq$ -13%), hypocontraction (Ses between -13% and -7%), and severe contraction abnormality (Ses > -7%) named "akinetic". At 8 months, we evaluated recovery of contraction: Acutely akinetic segments that improved their strain values to $\leq$-7% were defined as stunned, and those that failed to do so as non-viable. Transmurality of the infarction was assessed by magnetic resonance imaging with delayed enhancement (DE-CMR) as validation.
Results: In the acute phase, Ses, post-systolic strain, as well as systolic, early, and late diastolic strain rate values, were significantly better in the stunned segments than in the non-viable segments (Figure 1). Post-systolic strain had the best AUC 0.78, and a cut-off value of -3.8% predicted recovery from akinesia with a sensitivity of 85% and specificity of 62%. The median transmurality of the infarction by DE-CMR was 60% in the non-viable, and 19% in the stunned segments (p=0.006). Acute global Ses and systolic strain rate showed the best correlations with final global Ses and global infarction percentage after recovery.

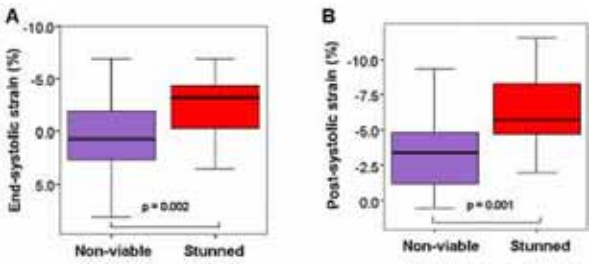

Figure 1. Acute strains in akinetic segments.

Conclusions: Strain rate imaging can serve to evaluate myocardial viability in patients with ACS, and to assess recovery of segmental as well as global left ventricular function.

P1439 Assessment of circumferential, radial and longitudinal strain in patients with left ventricular remodeling versus without left ventricular remodeling after acute myocardial infarction

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Purpose: Left ventricle (LV) remodeling is a relatively common and unfavorable event occurring after acute myocardial infarction (AMI). Development of LV remodeling after AMI is a complex process influenced by many factors and early identification of it is essential. We sought to investigate the differences of LV circumferential, radial and longitudinal strain in patients with LV remodeling and without LV remodeling after AMI.
Methods: A total of 117 patients (mean age 57.1 years ±11.2) with a first AMI were included into the study. Within 24-72 hours of the onset of AMI symptoms, 2-dimensional echocardiography with speckle-tracking imaging for evaluation of LV strain was performed. At 4 months, 38 patients (32.5%) with and 79 (69.5%) without LV remodeling were identified. LV remodeling was defined as a 15% increase from the baseline in LV end diastolic volume.
Results: The LV remodeling group had a higher troponin I level (p<0.05) and more anterior wall infarcts (p<0.01). LV ejection fraction (49.6%±7.9 vs. 54.2%±7.8, p<0.01) and LV end systolic volume (45.7 ml±15.6 vs. 38.9ml±12.7, p<0.05) at baseline were significantly different between the LV remodeling and without LV remodeling groups. Strain analysis of LV revealed no any differences in global circumferential (-13.0%±4.5 vs. -14.5%±4.5, p>0.05) and global radial strain (26.4%±11.9 vs. 28.8%±9.7, p>0.05) at the baseline. LV remodeling group had decreased global systolic longitudinal LV strain if compare to the patients without LV remodeling (-11.2%±4.1 vs. -14.2%±3.8, p<0.01). According to receiver operating characteristics analysis, peak systolic LV longitudinal strain of -10.5% (area under the curve 0.77, sensitivity 75%, specificity 78%) was found to be a significant predictor of LV remodeling.
Conclusions: Strain analysis is a novel technique in LV function assessment after myocardial infarction. LV longitudinal strain may appear a promising parameter in LV remodeling prediction after acute myocardial infarction.

P1440 Myocardial deformation indexes predict coronary artery disease severity

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Purpose: The aim of our retrospective study was to evaluate the ability of a fairly new parameters such as global longitudinal strain and strain rate (GLS, GLSR) as well as mean radial strain and strain rate (MRS, MRSR) to predict multivessel disease.
Methods: This was a single-center retrospective observational study. During a 1-year period 113 transthoracic echocardiographic findings were analysed in patients with known or suspected coronary artery disease (CAD) who were scheduled for coronary angiography. We used velocity vector imaging for the assessment of strain and strain rate. The endocardium of the left ventricle was manually traced in three standard apical views (apical two, three, and four chamber view) and short axis view at the level of the papillary muscles. From the displacement of endocardial pixels time-velocity curves were extracted which also provided strain and strain rate curves. In each apical view six curves were generated corresponding with two opposite basal, mid, and apical segments. The negative systolic peak was considered as a peak systolic strain and strain rate. In three apical views altogether 18 curves were assessed and averaged as GLS and GLSR. Similarly, in short axis view six negative systolic peaks from strain and strain rate curves of six segments were averaged and considered as MRS and MRSR. We defined 4 subgroups of patients: 1) without significant coronary stenosis, 2) single-vessel disease, 3) double-vessel disease, and 4) triple-vessel disease (3VD).
Results: As compared with patients without significant CAD, all the deformation indexes were significantly decreased in subgroups of patients with 3VD. The left ventricular ejection fraction (LVEF) and wall motion score index (WMSI) showed lower significance level as deformation parameters. Among the four deformation indexes, MRSR was the strongest predictor of multivessel disease. Based on areas under curve (AUC), MRSR had the highest diagnostic accuracy (AUC 0.84). The LVEF had poor ability to differentiate multivessel disease (AUC=0.69), and WMSI had poor to fair diagnostic accuracy (AUC=0.71). Comparing receiver-operating characteristic curves significant differences were found between MRSR versus LVEF and WMSI, i.e., MRSR had significantly higher diagnostic accuracy than LVEF and WMSI.
Conclusions: The results of our study show that global deformation indexes have a good diagnostic accuracy in differentiating multivessel disease. MRSR tended to be better in identification of 3VD than traditional indexes of global and regional left ventricular function, i.e., LVEF and WMSI.

P1441 Circumferential and radial myocardial deformation: prognostic value in predicting long term improvement of segmental kinetics in ST elevation acute myocardial infarction

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Aim: To determine the long term prognostic accuracy of radial and circumferential myocardial deformation parameters based on speckle tracking, in predicting recovery of segmental kinetics in ST elevation acute myocardial infarction (STEMI).
Methods: Prospective observational study of consecutive patients (pts) with STEMI undergoing primary angioplasty. Echocardiographic study was performed during the first 72h of hospitalization. The Wall Motion Score (WMS) was evaluated by two independent operators with assignment of the final classification by consensus, defining improvement in regional wall motion by a decrease in WMS at least one point. In post-processing, we measured the systolic peak of circumferential strain (S) (SPCS), circumferential strain rate (Sr) (SPCSr), the protodiastolic peak of circumferential Sr (DPCSr) and the systolic peak of radial strain (SPRS). The prognostic accuracy in predicting long term recovery of segmental kinetics was determined by the area under the Receiver Operator Curve.
Results: We studied 42 patients (male: 71%, 60$\pm$13 years). The image quality was adequate to study radial and circumferential deformation in 631segments, of which 36% (N = 225) had abnormalities of segmental kinetics in the initial study (hypokinesia, akinesia and dyskinesia in 25.8%, 9, 7% and 0.2% respectively). The proportion of segments with segmental kinetic abnormalities did not differ between the ventricular level, although the proportion of akinetic segments was higher in apical segments (p=0.009). In long term follow up, there was improvement in regional wall motion in at least one point in 19% of segments (N = 121). The initial WMS did not predict the likelihood of long-term recovery (p=0.27), although full recovery was less frequent among initially akinetic segments. The parameters of circumferential and radial deformation did not differ depending on the occurrence of subsequent recovering (partial or total) in segments with initial impaired contractile capacity (WMS $\geq$ 2). Therefore, these parameters were not useful in predicting improvement of segmental kinetics.
Conclusion: The analysis of myocardial deformation by circumferential and radial speckle tracking is not useful in predicting long term improvement of segmental kinetics in STEMI.

P1442 Fragmented QRS is associated with intraventricular systolic dyssynchrony in CAD patients with a narrow QRS interval

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Purpose: Fragmented QRS complexes (fQRS) on a routine 12-lead electrocardiogram, as a marker of depolarization abnormality, are associated with adverse cardiac events in patients with coronary artery disease (CAD).The purpose of this study was to investigate the relationship between fQRS and intraventricular dyssynchrony in patients with CAD.
Methods: 176 patients with CAD were recruited. The fQRS included various RSR' patterns without typical bundle branch block on a 12-lead ECG in 2 contiguous leads corresponding to a major coronary artery territory. Intra- and interventricular dyssynchrony were evaluated with Tissue Doppler imaging echocardiography. Wall motion score index (WMSI) was analyzed in all patients.
Results: fQRS was present in 55 (31%) patients (fQRS group) and absent in 121 (69%) patients (non-fQRS group). The patients in fQRS group had relative significantly larger LV systolic and diastolic dimension, lower LVEF and higher diastolic filling pressure. WMSI was significantly higher in fQRS group (1.26$\pm$0.44 vs. 1.10$\pm$0.23, P=0.002). Indices of intraventricular dyssynchrony including Ts-SD (43.7$\pm$17.7 vs. 37.8$\pm$17.4ms, P=0.04) and Ts-12 (128.8$\pm$49.6 vs. 110.6$\pm$46.3ms, P=0.019) were significantly prolonged in fQRS group compared to non-fQRS group. Seventy-five percent of the patients with fQRS had significant left ventricular dyssynchrony (Ts-SD $>$32.6ms), whereas only 58% of the patients without fQRS had significant left ventricular dyssynchrony (P=0.033). Multivariate analysis revealed that Ts-SD (Odd ratio [OR] 1.03, 95% confidence interval [CI] 1.01-1.05, P=0.009), QRS duration (OR 1.05, 95% CI 1.01-1.08, P=0.013) and LV end-systolic diameter (OR 1.14, 95% CI 1.03-1.26, P=0.009) were independent predictors for fQRS.
Conclusions: Fragmentation of QRS complexes on ECG are associated with intraventricular systolic dyssynchrony in patients with CAD, suggesting that intraventricular dyssynchrony may contribute to depolarization abnormality.

P1443 Is this CCU echocardiogram appropriate? A quality assurance audit

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Purpose: In North America, echocardiography is not considered a core element in the clinical history/physical examination of patients, but rather an additional service with financial implications. This has led to development of appropriateness guidelines to restrict use and limit costs. We sought to determine the use and appropriateness of transthoracic echocardiography (TTE) in a Canadian coronary care unit (CCU).
Method: Retrospective chart review of all CCU admissions in 2008 to a tertiary care Canadian hospital. A decision algorithm with levels of appropriateness was established. Categories were mutually exclusive with 1-4 having immediate clinical utility and 5 considered routine.
Results: There were 715 CCU admissions: 444 (62%) due to acute coronary syndrome (ACS); the remainder congestive heart failure (CHF), arrhythmia or other. The median age was 65yrs (IQR 53–76yrs) with 68% males. Table 1 summarizes TTE usage and appropriateness results. Of 165 patients with hemodynamic deterioration, same day TTE was performed in 65%. Of ACS patients, 309 (70%) had TTE despite 184 (41%) having prior left ventricular (LV) function determination during the same hospitalization. Of 85 (19%) ACS patients with ejection fraction $\leq$40%, 21 (25%) had repeat evaluation between 6 weeks and 6 months. Of 89 TTE studies performed to rule out apical thrombus, 79 (89%) were performed within 24 hours of infarction and not repeated during admission or within 3 months of discharge.

Table 1

Category	All patients [n=454] (%)	ACS [n=313] (%)	CHF [n=42] (%)
1 (Hemodynamic Deterioration)	165 (36.3)	80 (25.9)	37 (95.2)
2 (New Murmur)	12 (2.6)	8 (2.6)	0
3 (Assess Apical Thrombus)	93 (20.5)	89 (28.8)	0
4 (Presumed Significant LV Dysfunction)	93 (20.5)	64 (20.7)	1 (2.4)
5 (Routine)	91 (20)	72 (23.3)	1 (2.4)

Conclusion: This is the first study to address the use, appropriateness and timing of TTE in a Canadian CCU. TTE is appropriately performed in the majority of CCU patients. However, imaging duplication occurred often, along with investigation delay for those with hemodynamic concern, premature timing of evaluation for LV thrombus, and lack of appropriate delayed/repeat assessment for ICD candidacy. The value of echocardiography integrated with clinical care deserves further evaluation.

P1444 Temporal changes of strain parameters in the progress of chronic ischemia

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Purpose: The aim of this study was to reveal the temporal transition of strain parameters along the progression of chronic coronary ischemia.
Methods: A plastic occluder was implanted on the proximal left anterior descending coronary artery (LAD) to create a swine model of gradual chronic ischemia. A total of 14 pigs received the occluder implantation, while six pigs received a sham surgery (no occluder). Trans-thoracic echocardiographic studies were performed at baseline, 1, 2, and 3 months after the occluder implantation. Strain analysis was performed using a speckle-tracking algorithm.
Results: Eleven of the 14 pigs had total occlusion of LAD with collaterals at 1month (early occlusion) and 3 pigs showed occlusion at 3 months (delayed occlusion). Both radial strain (RS) and circumferential strain (CS) of ischemic area deteriorated at 1 month in the Early occlusion group and remained at the same level to 3 months. In contrast, RS in the control group remained at the same level, whereas CS gradually decreased. Interestingly, in the delayed occlusion group, RS gradually declined while CS declined as did the control group until 2 months. Then both deteriorated to the same level as the early occlusion group at the time of occlusion.

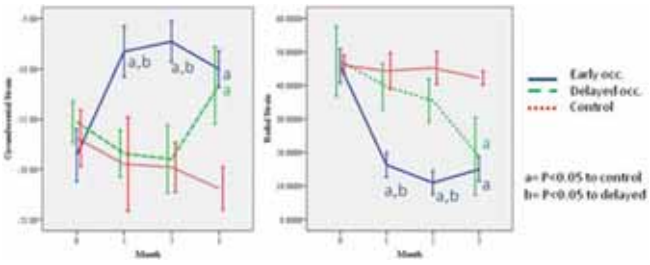

Figure 1

Conclusion: RS starts deteriorating in the early stages of the ischemia, when there is only stenosis present. Both RS and CS deteriorate by the time total occlusion is accomplished, and remain at the same level even after the occlusion in gradual chronic ischemia.

P1445 Predictive value of four-dimensional speckle-tracking longitudinal-strain for the improvement of left ventricular function after acute myocardial infarction

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Purpose: The aim of this study was to assess the predictive value of left ventricular (LV) segmental and global longitudinal strain assessed by novel four-dimensional (4D) speckle-tracking analysis for functional improvement after acute myocardial infarction (AMI).
Methods: A total of 153 patients admitted for AMI and treated with primary percutaneous coronary intervention, were evaluated with real-time three-dimensional echocardiography for the assessment of wall motion abnormalities, LV volumes and ejection fraction (LVEF), and LV segmental and global longitudinal 4D strain. Speckle-tracking 4D strain analysis was performed with novel dedicated software. At 6-month follow-up, wall motion, LV volumes and LVEF were reassessed. Improvement in segmental LV function was defined as an improvement of at least 1 grade in wall motion score. Improvement in global LV function was defined as an absolute improvement $\geq$ 5% in LVEF.
Results: Segments with functional improvement at follow-up showed a significantly higher (more negative) segmental longitudinal strain at baseline, as compared to segments without improvement (-16.4±4.0% vs -7.6±3.5%, $p<0.001$). A cutoff of -10.7% for segmental longitudinal strain had a sensitivity of 95% and a specificity of 88% to predict segmental functional improvement. In addition, 67 (44%) patients showed a global LV functional improvement at 6-month follow-up. These patients had baseline global longitudinal strain significantly higher as compared to patients without LVEF improvement (-16.7±2.1% vs -13.3±2.6%, $p<0.001$). A good correlation was found between LV global longitudinal strain and the absolute change in LVEF at follow-up ($r=0.64$, $p<0.001$). At the multivariate linear regression analysis, only global longitudinal strain ($\beta=0.610$, $p<0.001$) and peak troponin T ($\beta=-0.217$, $p=0.003$) were independent determinants of LVEF improvement. At the multivariate logistic regression analysis, global longitudinal strain provided incremental value over clinical and conventional echocardiographic variables in predicting global LV function improvement at 6-month follow-up (C-statistic improved from 0.64 to 0.71 to 0.84, $p<0.001$).
Conclusions: Longitudinal strain assessed by novel 4D speckle-tracking analysis is an important predictor for segmental and global LV function improvement after AMI.

CARDIAC FUNCTION IN NON CORONARY ARTERY DISEASE

P1446 Regional left ventricular function in patients with cardiac amyloidosis: the base to apex gradient as a typical deformation pattern shown by speckle tracking imaging

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Objective: The confirmation of cardiac involvement in patients with amyloidosis is important because of its impact on prognosis. Thus, a typical echocardiographic pattern for cardiac amyloidosis (CA) would be of clinical value during work up of these patients.
Methods: In this prospective clinical study, we assessed cardiac morphology and function in 12 patients with cardiac amyloidosis and in 15 controls. Morphology and global left ventricular systolic and diastolic function were measured by standard echocardiography. Regional myocardial deformation was assessed by tissue Doppler imaging (TDI) and by 2-dimensional speckle tracking imaging (STI). Using these two methods, both peak systolic strain rate and systolic strain were extracted from the basal, mid and apical segments of the septum and the lateral wall.
Results: Seventy-five percent of the patients with CA showed the typical sparkling texture of the myocardium and 42% patients presented a small pericardial effusion. When compared to controls, patients with cardiac amyloidosis had significantly thicker walls (end-diastolic posterior wall thickness: control = 9±1mm, CA =12±2mm; $p<0.001$), larger left atrium (control = 35±2mm, CA = 42±10mm; $p<0.05$) and higher E/E' (control = 10±3, CA = 17±8; $p<0.05$). By the use of TDI both peak systolic strain rate and systolic strain showed an intra wall gradient with lower values at the base and higher values at the apex (septal TDI strain: basal = -11±4%, apical = -14±7%). In contrast, regional deformation values were more homogenous within one wall in controls. The typical gradient for deformation within one wall in CA was confirmed by STI (septal STI strain: basal = -8±5%, middle = -11±5%, apical = -22±5%). Using a cut off value of at least 100% higher strain in the apex compared to the base by STI, typical gradient pattern was presented in 9 patients (75% of all CA patients) and in none of the controls ($p<0.0001$).
Conclusion: Beside the traditional parameters for cardiac involvement, the assessment of regional myocardial deformation provides important information on cardiac function for patients with cardiac amyloidosis. The typical pattern for regional myocardial function is a base to apex gradient within one wall which can be easily assessed by tissue Doppler imaging as well as by speckle tracking imaging.

P1447 Left ventricular systolic dysfunction in tako-tsubo cardiomyopathy: is it transmural and really regional and reversible? a two-dimensional speckle tracking echocardiographic study

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Objective: Typical tako-tsubo cardiomyopathy (TT) is characterized by a transient mid-apical left ventricular (LV) systolic dysfunction assessed by the wall motion score (WMS) and LV ejection fraction (EF). Two-dimensional strain by speckle tracking echocardiography (2DS) is a more sensitive marker of regional and global LV systolic function. Therefore, our aim was to assess systolic LV mechanics at all myocardial layers by 2DS, in patients (pts) with TT.
Methods: 2DS was performed in 15 consecutive pts with TT (78±8 years, 93% women, mean LVEF 45±10%), at the acute phase (within 24 h after symptom onset) and after recovery (one month later). Ten control (C) pts matched for age and sex (mean LVEF 71±7%), were compared to TT pts. From the apical long-axis, 4-and 2-chamber views, global longitudinal strain (LS) and strain-rate (LSR), post-systolic shortening index (PSS), and from the parasternal basal, mid and apical short-axis planes, global circumferential strain (CS), and strain-rate (CSR), and radial strain (RS), were obtained. Regional evaluation was also performed for each parameter. LV twist was defined as the net difference in degrees of apical (Ar) and basal rotation. LV torsion was defined as LV twist normalized for diastolic LV longitudinal length.
Results: At the acute phase, global LS, LSR, CS, CSR, RS, Ar, LV twist and torsion were significantly reduced, and PSS was significantly higher when compared to C (all, $p<0.01$). In pts with TT, there was an apex to base gradient of strain and strain-rate at all myocardial layers (all, $p<0.05$), and a significant correlation was found between the WMS, LVEF, and LS, LSR, CS, CSR, RS, LV twist and torsion (all, $p<0.05$), between troponine peak and LV twist, torsion, and CSR (all, $p<0.01$), and between NT-proBNP and CS, CSR, LS, LSR, RS, LV twist and torsion (all, $p<0.05$). At follow-up, there was a significant improvement of LV mechanics at all layers including LV torsion (all, $p<0.01$ vs. acute phase) with final values not significantly different from C (all, p = NS). Furthermore, in addition to a significant improvement of mid and apical LV wall mechanics at all myocardial layers, there was a significant improvement of basal CSR, LS, and LSR (all, $p<0.05$ vs. acute phase).
Conclusion: There is a transmural extent of myocardial impairment in TT, which

is correlated to LV wall stress, and is entirely reversible. In addition, LV torsion and CSR are inversely linked to myocardial injury. Furthermore, there are transient subtle abnormalities at the basal level, challenging the notion that LV systolic dysfunction in TT is wholly regional.

P1448 EuroSCORE model using longitudinal global strain in predicting outcome after cardiac surgery

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Purpose: Longitudinal strain by speckle tracking appears more sensitive than left ventricular ejection fraction (LVEF) to characterize myocardial dysfunction. We hypothesize that longitudinal global strain (GLS) may be used in alternative to LVEF to compute EuroSCORE for better predicting outcome after cardiac surgery.
Methods: The study included 196 patients (65±13 years, 75% of male) referred for cardiac surgery [valvular surgery (n=126), isolated coronary artery graft bypass (n=50) and other (n=20)]. A comprehensive echocardiography was performed before surgery to compute global strain by speckle tracking and LVEF using automated method. Two logistic Euro-Score were derived, one using LVEF and another one using longitudinal global strain as marker of left ventricular function. The two scores obtained were compared to primary endpoint defined by one month mortality and the use of inotrope support after surgery.
Results: After surgery, death was observed in 22 (11%) patients and inotropic support was required in 102 patients. This is consistent with the mean EuroSCORE value obtained using global strain (12±15%) and LVEF (11.5±14%). Despite a close correlation between the two models (r^2=0.95, p<0.0001), logistic regression steptwise showed that EuroSCORE model derived from global strain was superior to the one obtained by LVEF.
Conclusion: The use of longitudinal strain in the EuroSCORE model appears superior to LVEF to characterize post-operative risk after cardiac surgery.

P1449 Myocardial strain imaging detects early changes in global left ventricular systolic function after anthracycline chemotherapy

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Purpose: The efficacy of anthracycline chemotherapy is undermined by potentially life threatening cardiotoxicity. Cardiotoxicity is dependent upon several factors, and its timing is variable; so close monitoring of cardiac function in those treated with anthracyclines is mandatory. Currently, despite numberous limitations, left ventricular ejection fraction (LVEF) by echocardiography is used for monitoring cardiotoxicity.
Myocardial strain imaging has been shown to detect left ventricular (LV) systolic dysfunction in several diseases prior to noticeable changes in LVEF. Our aim was to determine whether strain imaging could detect early changes in LV systolic function prior to detection by LVEF in patients after receiving anthracycline chemotherapy.
Methods: 52 women with histologically confirmed breast cancer were prospectively studied. The first echocardiogram was performed immediately before anthracycline treatment and the second immediately afterwards. LVEF (by Simpson's method), global peak longitudinal, radial and circumferential systolic strain were measured before and after.
Results: Global longitudinal LV systolic strain was significantly reduced after treatment; global longitudinal strain dropped from -17.7% to -16.3% (p<0.01) with 48% of global measurements reduced by >10%. Global radial LV systolic strain after treatment was also significantly reduced; global radial strain dropped from 40.5% to 34.5% (p<0.01) with 59% of global measurements reduced by >10%. In contrast, no statistically significant reduction in global circumferential strain was observed (although strain was reduced >10% in 32% of participants after treatment). No reduction >10% in LVEF after chemotherapy was observed.

LV function before & after chemotherapy

	Before	After	% with >10% reduction
LVEF	58.6% ±2.6	56% ±2.8†	0
Longitudinal strain	-17.8±2.1	-16.3±2†	48%
Radial strain	40.5±11.4	34.5±11.4†	59%
Circumferential strain	-20.3±2.6	-20.0±3.3	32%

Values expressed as mean ± SD, †p<0.01 vs. before value.

Conclusion: We observed significantly reduced global LV systolic strain early after anthracycline treatment, prior to significant reductions in LVEF. These observations may indicate early impairment of myocardial function, and warrant longer-term surveillance to determine their clinical relevance.

P1450 The influence of segmental atrial wall synchrony on biatrial and bicaval allograft functions during the early and late follow-up after heart transplantation by speckle tracking echocardiography

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Background: In order to assess the influence of the synchronous segmental atrial wall deformation on the bicaval (BC) and the biatrial (BA) allograft functions this study was performed using speckle tracking echocardiography.
Methods: 91 heart transplanted (HTX) patients with normal allograft function underwent a speckle tracking study (EchoPac, GE Vivid 7). The early follow-up period was defined between 1-3 years after HTX and the late after 5 years for BC and after 10 years for BA. From 30 BC HTX 10 were selected for the early (EBC) and 20 for the late (LBC) follow-up. 61 BA HTX were studied: 30 during the early (EBA) and 31 during the late (LBA) follow-up. The early follow-up study was performed between the BC and BA and in comparison with 24 normal controls. Then, for each technique the early and late follow-up groups were compared. The right and left atrial (RA), (LA) strain profiles were obtained in apical 4 chamber view and the segmental peak strain values were calculated during the atrial contractile, reservoir and conduit periods, as well as the peak global strain. The left ventricular (LV) longitudinal segmental strain profiles were obtained in the apical views and the LV peak systolic global strain was compared between groups.
Results: The atrial strain profiles showed a synchronous deformation for all segments in BC patients and an asynchronous deformation in BA patients. The RA global contractile, reservoir and conduit functions were significantly higher in EBC HTX (- 14,07±2,11%; 20±5,17%; -17,5±3,1%) than in EBA HTX (-9,51±2,52%; 11,53±6,5%; -11,62±6,06%) (p<0,05) and in both groups were significantly lower than in controls (-18,37±3,74%; 34,31±10,88%; -27,32±10,85%). The LA functions showed the same variation. The LV systolic function was not different in EBC (-17,96±3,25%) than in EBA (-16,05±3,2%) HTX but in both groups was significantly lower than in controls (-20,66±2,05%) (p<0,05).The RA contractile, reservoir and conduit functions were not significantly different in LBC (-13,23±3,58%; 18,2±3,26%; -14,45±3,5%) than in EBC HTX. The LA reservoir and conduit functions were significantly lower in LBC (14,33±4%; - 12,1±2,95%) than in EBC HTX (p<0,05). The LBA RA and LA reservoir and conduit functions were significantly lower (10,49±4,5%; -9,07±3,46% and 11,4±3,83%; -8,64±2,44%) (p<0,05). The LV systolic function was not different for the LBC and the LBA.
Conclusion: Despite significant benefits with the BC technique related to a better, synchronous atrial function, the systolic ventricular function was unaffected by the surgical technique.

P1451 Predictors of one year mortality in heart transplant recipients

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Purpose: Prediction of one year mortality in heart transplant (HTx) recipients is challenging. Different clinical diagnostic tools have been introduced. Although speckle-tracking strain has been used in a growing number of clinical situations, the association between reduced left ventricular (LV) global longitudinal strain (GLS) and risk for mortality in HTx recipients is unclear. We aimed to test different clinical diagnostic tools for the ability to predict one year mortality in HTx recipients.
Methods: We included 176 consecutive adult primary single organ orthotopic HTx recipients. Creatinine and CRP, the hemodynamic parameters: mean pulmonary artery pressure, pulmonary capillary wedge pressure (PCW), cardiac output and pulmonary vascular resistance (PVR) were measured and echocardiography was performed 13±6 days post HTx. Peak systolic myocardial strain by two-dimensional speckle-tracking echocardiography was assessed in 16 LV segments, and averaged to global strain – an index of global LV function.
Results: During the first year, 16 (10%) patients died 82±72days after HTx. Recipient and donor age, CRP, all hemodynamic parameters except PCW were increased, while LVEF and LV GLS were decreased in non-survivors compared to survivors (p<0.05). However, LV GLS was the only significant (p=0.02) non-invasive and PVR was a significant (p<0.001) invasive predictor of 1 year mortality in a multivariate Cox analysis (Table 1).

Table 1. Multivariate Cox regression analyses

	Univariate	Cox Regression		Multivariate Cox Regression		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (years)	1.08	1.00–1.15	0.04	1.02	0.92–1.12	0.72
PVR (WU)	4.56	2.65–7.86	<0.001	3.88	1.84–8.17	<0.001
LV GLS (%)	1.67	1.39–2.01	<0.001	1.44	1.06–1.94	0.02
LVEF (%)	1.92	1.46–2.52	<0.001	1.29	0.74–2.25	0.36
CRP (mg/ml)	1.02	1.01–1.03	<0.001	1.00	0.97–1.02	0.86

PVR = pulmonary vascular resistance; LV = left ventricular; GLS = global longitudinal strain; LVEF = LV ejection fraction; CRP = C-reactive protein.

Conclusions: Reduced LV function by global longitudinal strain and increased pulmonary vascular resistance are related to poor prognosis in HTx recipients. Early assessment of LV GLS might be a non-invasive predictor of 1 year mortality in these patients.

P1452 Left ventricular systolic function deterioration during dobutamine stress echocardiography as an early manifestation of diabetic cardiomyopathy and reversal by optimized therapeutic approach

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Introduction: Diabetes mellitus has been associated with changes in the structure and function of the myocardium manifesting in the early stages of the disease as subtle systolic and diastolic dysfunction; the role of dobutamine stress echocardiography (DSE) in this setting remains unclear.
Aims: We sought to evaluate the prevalence of dobutamine-induced systolic dysfunction amongst diabetic patients with normal at rest left ventricular ejection fraction and no coronary artery disease and to investigate whether an optimized therapeutic approach can reverse these abnormalities.
Methods: 1363 patients with DM referred to our echocardiography laboratory for DSE between January 2008 and June 2010 were prospectively investigated. Patients with normal left ventricular ejection fraction (LVEF) at rest and significant deterioration during peak dobutamine infusion (defined as a $\geq$10% decrease) in the absence of coronary artery disease or vasospasm were enrolled. They received on top of their usual treatment 5 mg perindopril and had their glycemic control intensified. At 60 days, all of them were controlled for clinical status and underwent a control DSE.
Results: 18 patients were included, there were 9 males and 9 females, mean age was 66.1±10.2 years. All the patients had type II DM with a mean duration of 12.7±6.6 years. They all had normal at rest echocardiographic findings with no wall motion abnormalities; mean LVEF was 62±6%. At peak dobutamine, LVEF significantly deteriorated in all the patients with a mean 15±5% decrease compared to baseline. After therapeutic optimization, Glycated haemoglobin improved from 8.53±2.05% to 6.8±0.6% (δ HbA1C=1.73%, p=0.001), mean LVEF at peak dobutamine infusion evolved from 47.17±4.2% pre-optimization to 58±4.8% at control (10.83% improvement; p<0.001).
Conclusion: In patients with DM and normal at rest LVEF, Dobutamine infusion during DSE can induce a significant deterioration in LVEF in the absence of coronary artery disease or vasospasm. This specific condition could be largely reversed through an optimized therapybased on a tighter metabolic control and a more stringent renin-angiotensin-aldosterone system inhibition.

P1453 Relation between NT-proBNP levels, iron overload and early stage of myocardial dysfunction in beta-thalassemia major patients

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Background: Heart failure secondary to myocardial iron loading remains the leading cause of death in β-thalassemia major (B-tm) patients. The early diagnosis of heart failure in these patients is related to survival.
Methods: The study population included 49 B-tm patients and 48 age-matched healty controls. Doppler-echocardiographic study was performed and blood samples for NT-proBNP were drawn on the 4th day following blood transfusion. Patients were divided as group-1, without diastolic dysfunction: E/E' ratio<9 and group-2, with suspected diastolic dysfunction: E/E' ratio≥9.
Results: NT-proBNP levels and E/E′ ratio were increased in patients compared with controls (P<0.001,P<0.001) but did not correlate with each other. A strong positive correlation was detected between NT-proBNP levels and mean ferritin levels in B-tm patients (rs=0.939; P<0.001). Median (1st-3rd quartile) NT-proBNP levels were significantly higher in group-1 in comparison to controls (P<0.01). NT-proBNP levels were also increased in group-2 in comparison to group-1 but this increase was not statistically significant.

Table 1. Echocardiographic results, Doppler echocardiographic and tissue Doppler velocity data of β-thalassemia major patients and healthy controls (mean ± SD)

	β-Thalassemia patients (n=49)	Controls (n=48)	P value
EF (%)	62.2±5.8	62.3±5.1	NS
LAVI (mL/m^2)	27.6±8.6	22.8±5.7	<0.01
LVMI (g/m^2)	86.2±20.9	62.3±11.9	<0.001
E/A	1.81±0.49	1.66±0.30	NS
S' (cm/s)	7.95±1.3	8.68±0.96	<0.05
E' (cm/s)	10.7 (9.6–12.5)	13.9 (12.2–14.95)	<0.001
A' (cm/s)	6.7±1.95	7.4±1.06	NS
E/E'	9.65±2.38	6.62±1.35	<0.001

Conclusion: NT-proBNP secretion begins in the early phase of the disease before the increase in diastolic pressure becomes overt. While there was a strong correlation between the plasma NT-proBNP levels and iron overload, there was no correlation between NT-proBNP levels and diastolic dysfunction parameters in patients in the third decade of life.

P1454 Differential reduction in regional myocardial deformation occurs in cardiac amyloidosis as determined by left ventricular wall thickness

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Introduction: Extracellular infiltration in cardiac amyloidosis results in increased wall thickness. Strain measurements using velocity vector imaging (VVI) may further define differential cardiac myofibre dysfunction with varying LV wall thickness.
Methods: 46 patients with cardiac amyloidosis were compared to age matched normals. Subgroup analysis within the amyloid group was performed based on LV wall thickness (Group1:<12mm, Group2:12-14mm, Group3: ≥15 mm). LV parameters including LVEF, transmitral flow, E', E/E' were measured and extent of DD graded. Longitudinal, circumferential and radial myocardial VVI strain (S) and strain rate (SR) were determined from apical and short axis views.
Results: Increased LV wall thickness and reduced LV diastolic function was observed in the amyloid group (mean LVEF 53%). Global longitudinal (-14.0±4.1% vs -16.7±3.8%; p=0.001) and radial (27.4±13.4% vs 38.8±15.7%; p<0.001) strain were significantly lower in the amyloid group vs normals whilst circumferential strain (-21.8±5.2% vs-24.9±9.6%; p=0.062) approached significance. Similarly, significant reductions were noted in systolic and diastolic SR in the amyloid group (data not shown). Within the amyloid subgroups, differential reduction in longitudinal systolic strain and diastolic Sr were observed with increasing wall thickness, whilst circumferential and radial parameters were preserved (Table).

Subgroups based on LV wall thickness

Parameters	Group 1	Group 2	Group 3
Longitudinal S(%)	–16.1±3.3*	–14.5±3.2	–11.8±4.3
Longitudinal systolic Sr (s^{-1})	–1.1±0.2	–1.1±0.3	–0.9±0.3
Longitudinal E Sr (s^{-1})	1.1±0.3*	0.9±0.3	0.7±0.3
Longitudinal A Sr (s^{-1})	0.8±0.3*	0.6±0.3	0.5±0.2
Circumferential S (%)	–22.4±4.1	–22.8±5.6	–20.7±5.9
Circumferential systolic Sr (s^{-1})	–1.9±0.4	–1.7±0.4	–1.6±0.5
Radial S (%)	28.8±10.7	33.4±16.4	21.9±11.3
Radial systolic Sr (s^{-1})	1.9±0.7	2.1±1.2	1.4±0.7

*p<0.05 vs Group 3.

Conclusion: Reduction in longitudinal, radial and circumferential strain and strain rates occur in amyloidosis despite apparent preservation of systolic function. With increasing left ventricular wall thickness, there is differential reduction in longitudinal deformation compared to circumferential and radial functions.

P1455 Patients with growth hormone deficiency have intrinsic myocardial disease with subclinical left ventricular longitudinal dysfunction revealed by tissue Doppler

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Purpose: Growth hormone deficiency (GHD) is associated with increased cardiovascular events, however, the detailed mechanisms have not been assessed yet extensively. We set up this study in order to evaluate cardiac, arterial, and endothelial function, by conventional echo, TDI, and biomarkers (proBNP and troponin I), in GHD patients by comparison with normal individuals with similar cardiovascular risk factors profile.
Methods: 20 GHD patients (53±13 yrs, 13 male), free of any cardiovascular disease, severe hypertension or diabetes, were compared with 20 normals (N) (age and sex matched). Global LV systolic function was assessed from ejection fraction (EF), fractional shortening (FS), and indexed cardiac output (COi); global diastolic function from E/Ea and E/Vp ratios. Longitudinal LV function (mean from 12 basal and mid myocardial segments) was assessed from longitudinal systolic velocity (LS), longitudinal strain (LSS) and strain rate (LSR), mitral annular displacement (MAD), and longitudinal diastolic velocity (LE). Arterial function was assessed from intima-media thickening (IMT), local wave speed (LWS), and stiffness index (β); endothelial function from flow mediated dilation (FMD).
Results: In GHD patients all global and longitudinal systolic parameters were significantly decreased compared to N, with lower diastolic velocity (LE) and higher end-diastolic LV pressure (E/Ea, E/Vp) (table); meanwhile, proBNP levels were increased. Arterial and endothelial function parameters were similar, while troponin I was normal in all patients.
Conclusions: Patients with GHD had subclinical LV longitudinal systolic and diastolic dysfunction, best revealed by TDI; conventional systolic parameters were also lower, however, they did not exceed the normal range. Since arterial and en-

Abstract P1452 – Table 1. Comparison between GHD patients and N

	EF	FS	COi	MAD	LS	LSS	LSR	LE	E/Vp	E/Ea	proBNP
GHD	52±8.6	22.2±7	1.8±0.5	10.3±1.8	3.8±0.7	-13±1.5	-0.91±0.2	5.5±1.9	1.7±0.4	8±1	72.45±50.0
N	68±7	29.7±4	2.2±0.6	13.4±1.6	6.1±1.0	-19±2.2	-1.5±0.3	7.6±1.7	1.5±0.3	6±2	31.34±19.3
P value	<0.001	0.008	0.03	<0.001	<0.001	<0.001	<0.001	0.001	0.033	0.002	0.002

dothelial functions were not significantly affected, and troponin I was normal, our findings suggest that patients with GHD have intrinsic myocardial disease, due probably to insufficient development of the myocardial fibers.

P1456 Correlation between septal morphology and strain parameters in hypertrophic cardiomyopathy

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Fibrosis and disarray are the major structural myocardial abnormalities in hypertrophic cardiomyopathy (HCM) that predispose to ventricular arrhythmias. A recent classification based on septal morphology has described 4 septal patterns: sigmoid (maximal septal wall thickness (ST) located in the basal septum), catenoid (maximal ST in the mid-septum), neutral (uniformly thickened septum) and apical (maximal ST in the apical-septum). HCM patients with catenoid morphology were found to have clinical characteristics of advanced disease. In a previous study, the presence of reduced longitudinal strain (long S) measured with speckle tracking is correlated with myocardial fibrosis in cardiovascular magnetic resonance (CRM). To the date the correlation between subtype of septum and strain parameters has not been described.

Methods: A total of 51 consecutive patients with MCH were included. Septal morphologies were retrospectively categorized into one of four patterns of hypertrophy based on transthoracic echocardiography. We recorded images of the 4, 3 and 2-chamber apical views and short axis views. For the assessment of longitudinal (long S) and radial strain (rad S) and strain rate (SR) curves, we analyzed 16 individual segments. Diastolic function was graded using standard Doppler criteria.

Results: In order to assess the relationship between ventricular morphologic parameters and strain values, we compared catenoid septum with other subtypes, the results are shown in the table.

Conclusion: Catenoid septum is more frecuent in younger people and is associated with decreased long and radial septal S and SR. Strain 2D offers novel non-invasive indices to assess LV systolic function in patients with HCM. Our study shows the important influence of the pattern of hypertrophy on deformation parameters in HCM, which provides further insight into the pathophysiology of this disease.

P1457 Echocardiographic speckle tracking based left ventricular rotation predicts adverse events in patients with hypertrophic cardiomyopathy

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Introduction: Prognostic factors in adults with hypertrophic cardiomyopathy (HCM) are poorly defined.

Aim: We aimed to define predictive factors for major cardiovascular (CV) adverse events (MACE) - death, CV hospitalization or NYHA class deterioration in adult HCM patients over 1-year.

Methods: We studied 56 HCM patients (22 female), age 58±13, with preserved ejection fraction (EF)=58±7%. LV outflow obstruction was present in 12,5% and diastolic dysfunction (DD) in all pts (pseudonormal -20/56, restrictive – 6/56). Baseline visit included physical examination, bichemistry panel, 6-MWT and CPET test according to Bruce protocol. Echo assessment included extended diastolic function panel using TDE and speckle tracking study (longitudinal strain/strain rate and radial, circumferential strain, LV rotation). At month 12 we recorded clinical events as defined in Aim. Uni- and multivariate regression was used to identify MACE predictors.

Results: During follow-up (360±62days) 1 subject died of SCD (2%), but CV hospitalizations were frequent (19/56 pts, 18%) mainly due to arrhythmia (6/19 pts), acute coronary syndrome (5/19) or congestive heart failure (4/19). NYHA deterioration by at least 1 class was observed in 16 patients. Univariate analysis revealed a relationship between hospitalization and: concomitant ischemic heart disease (p=0,034), longitudinal strain (p=0,034) and apical LV rotation (p=0,048). Multivariate linear regression model identified apical rotation (p=0,048) as the independent predictor of hospitalization. No factors predicted NYHA class deterioration.

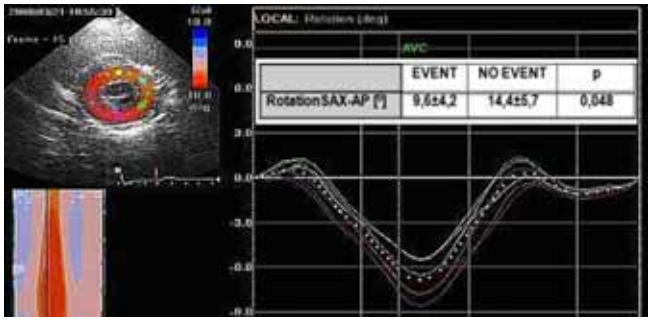

Figure 1. Rotation analysis.

Conclusions: Novel echocardiographic parameter – speckle tracking based apical LV rotation but not demographic data, biochemistry, functional tests or standard echocardiogram predicts 1-year adverse events in adults with HCM.

P1458 Latent biventricular dysfunction in autistic spectrum disorders: the case of Rett syndrome

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Purpose: Rett Syndrome (RTT) shows a 300-folds increased risk for sudden cardiac death. RTT is the second most common cause of mental retardation in the female and is caused in up to 95% of cases by mutations in the X-linked MeCP2 gene. Rhythm abnormalities and cardiac dysautonomia do not to fully account for the observed cardiac mortality risk. Conversely, heart function in RTT has not been explored to date. Recent data indicate a previously unrecognized role of MeCP2 in cardiomyocytes development. We hypothesized that a subclinical biventricular dysfunction might coexist in RTT and that Ω3-PUFAs supplementation could, at least partially, reverse cardiac function.

Methods: A total of 92 RTT girls, together with 92 healthy age-matched control girls, were evaluated. A Philips IE 33 Vision 2009 echocardiography equipment was used. Left (LV) and right (RV) ventricular systolic and diastolic functions were examined using M-mode (MAPSE, TAPSE), B-mode (Ejection fraction with Simpson's method), PW Doppler (E, A, E/A), CW Doppler (PAPs, S/D ratio) and TDI (S', E', A', E/E'). In a fraction of patients (n=25) echocardiography was re-evaluated after 12 months in order to investigate a possible progression of the myocardial dysfunction. In another subgroup of patients (n=25), the effects on myocardial function following Ω3-PUFAs (EPA+DHA) supplementation were investigated (duration: 12 months, dose: 20-40 mg/kg/day).

Results: A significant reduction of longitudinal biventricular function (TAPSE: -16.80, p<0.0001; MAPSE: -18.37, p<0.0001; S' of mitral annulus: -13.11, p=0.0008; S' of interventricular septum: -7.96, p=0.0304; S' of RV free wall: -12.78, p=0.00217) was evidenced in RTT patients as compared to controls. Diastolic function parameters were reduced (E: -10.71, p=0.002; E/A: -10.68, p=0.0315; E': -15.83, p=0.0005). S/D ratio, less preload-dependent variable, was also reduced (-0.14, p=0.0001). PAPs was decreased (-23.69, p<0.0001). No significant changes in LV ejection fraction were found (p≥0.2129). No significant changes in the echocardiographic parameters were highlighted in untreated RTT after 12 months. Following Ω3-PUFAs (EPA+DHA) supplementation, significant changes in preload dependent variables (E: p=0.0096, A: p=0.0001, E/A: p=0.0134, PAPs: p=0.0024) were observed.

Conclusions: These data indicate the presence of a previously unrecognized latent systo-diastolic biventricular myocardial dysfunction in patients with typical and atypical RTT, which is only partially reversible after Ω3-PUFAs supplementation.

Abstract P1453 – Table 1. Echo values according to subtypes of HCM

	Age	ST	LV mass	E/A	Lateral E/E'	Septal long S	Septal rad S	Long SR
Catenoid septum (n=26)	42.8±19.9	24.7±6	338±148	1.38±0.6	10.1±4.8	–9.5±3.6	14.5±8.2	–0.8 ±0.2
Other types (n=25)	56.4±17.2	21.6±3.9	285±82	1.3±1	10.7±4.7	–13±5.2	18.9±8.1	–1±0.4
p	0.013	0.029	0.123	NS	NS	0.006	0.05	0.036

ST: Septal thickness; LV: Left ventricular; long: Longitudinal; S: Strain; SR: Strain rate; NS: Non significant.

P1459 Prognostic impact of heterogeneous strain index in non-ischemic cardiomyopathy

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Background: Heterogeneous myocardial scarring contributes to an insufficient stroke volume and arrhythmic vulnerability in patients with coronary artery disease. Magnetic resonance imaging or speckle tracking echocardiography (STE) has a capability to measure regional contractile heterogeneity from myocardial strain analysis. This study was to investigate whether heterogeneous myocardial contraction assessed by STE could predict cardiac events in patients with non-ischemic cardiomyopathy (NICM).
Methods: 103 consecutive NICM patients (mean 64 years) were enrolled. Patients with ischemic etiology, predominant valvular heart disease and secondary cardiomyopathy were excluded. Echocardiographic equipment was used with GE Vivid 7 Dimension. In addition to conventional echocardiographic parameters, the STE-derived global circumferential and longitudinal strain (GCS, GLS), and the standard deviation (SD) of time to peak longitudinal strain as an index of dyssynchrony (SDt-16s) were measured. We also evaluated the heterogeneous strain index (SDes-16s), which was defined as the SD of values of end-systolic longitudinal strain in 16 myocardial segments.
Results: Mean ejection fraction, E/e', GCS, GLS, SDt-16s, SDes-16s were 37%, 16, -10%, -10%, 84ms, and 5.5%, respectively. During follow-up periods (mean 28 months), major adverse cardiac events (MACE) occurred with 20 patients (9 cardiac death, 5 lethal ventricular arrhythmia, and 6 heart failure hospitalization). Among age, gender, QRS width, EF, E/e', GLS, SDt-16s and SDes-16s, Cox proportional hazard analysis demonstrated that E/e' and SDes-16s were the independent predictors of MACE in this study population (E/e': hazard ratio [HR], 1.07; $P<0.01$, SDes-16s: HR, 1.43; $P<0.001$). According to a Kaplan-Meier plot between 2 groups devided by the median value of SDes-16s, NICM patients with higher SDes-16s$>$5.3% experienced more MACE than those with lower SDes-16s$<$5.3% (log-rank test, HR, 5.37; $P<0.001$).
Conclusions: Non-uniformity of myocardial contraction was correlated with an increased incidence of MACE among NICM patients. Heterogeneous strain index provides an incremental value in predicting the outcome in these patients.

P1460 Post-surgical changes in global longitudinal strain rate are different in different forms of left ventricular outflow obstruction: hypertrophic cardiomyopathy vs. hypertensive heart

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Background: In hypertrophic obstructive cardiomyopathy (HOCM), left ventricular outflow tract obstruction (LVOTO) is relieved by surgical myectomy (SM); but its impact on global & regional LV function is unclear. Using transthoracic echocardiography (TTE), including speckle tracking echocardiography (STE), we sought to assess the changes in global & regional LV function after SM.
Methods: 60 patients with symptomatic LVOTO (54% men, mean ejection fraction 62±5%) that underwent SM were studied. All patients had pre & postoperative TTE (>3 months after SM). Standard TTE parameters were recorded. Global longitudinal systolic & early-diastolic strain rate (SR) was measured by STE from apical 4 and 2 chamber views.
Results: Patients were divided into 2 groups, based on HOCM findings on histology (hypertrophy, disarray, coronary dysplasia & fibrosis) as follows: 48 with HCM & 12 with hypertensive disease (Table 1). Despite relief of LVOTO (mean LVOT gradient went from 105±29 to 13±14 mm Hg) & reduction in basal septum (2±0.5 to 1.4±0.3 cm, there was no change in systolic (Δ of 0.03±0.4) & diastolic (Δ of -0.08±0.05) global SR in HOCM group (both p=ns). However, systolic (Δ of -0.34±0.4, p=0.003) & diastolic (Δ of 0.22±0.2, $p<0.01$) global SR improved in non-HCM group.

Table 1. Characteristiccs of the study population

Variable	Total group	HOCM group (n=48)	Non HCM group with dynamic LVOTO (n=12)	p-value
Age (years)	52±12	52±12	51±14	0.8
Hypertension (%)	33 (55%)	21 (44%)	12 (100%)	<0.001
Maximal preoperative LVOT gradient (mm Hg)	105±29	106±32	104±17	0.3
Basal septal thickness (cm)	2.0±0.5	2.1±0.5	1.9±0.4	0.2
E/A ratio	1.1±0.7	1.26±0.8	1.20±0.5	0.4
E/E' ratio	15±7	14±7	15±7	0.8
Deceleration time (msec)	255±77	268±90	237±47	0.3
Preoperative global longitudinal systolic strain rate (1/sec)	–1.09±0.3	–1.09±0.3	–1.11±0.3	0.8
Preoperative global longitudinal early diastolic strain rate (1/sec)	1.00±0.4	1.01±0.4	0.98±0.3	0.8
Post-operative global longitudinal systolic strain rate (1/sec)	–1.13±0.3	–1.05±0.3	–1.45±0.4	<0.001
Post-operative global longitudinal early diastolic strain rate (1/sec)	0.99±0.3	0.93±0.3	1.20±0.3	0.008

Conclusion: Global SR improves in non-HCM patients; but not in HOCM patients, following SM. This is likely due to primary myopathic process in HOCM & an adaptive process in non-HCM group.

P1461 3D speckle tracking in the early detection of cardiac involvement in patients with neuromuscular disorders

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Background: Cardiac structural involvement is frequent in patients with neuromuscular diseases. Diagnosis is usually done with echocardiography once left ventricular dilatation/dysfunction is present. Speckle tracking 3D echocardiography (STE) allows evaluation of different parameters including global and regional strain that may show abnormalities before overt cardiac dysfunction develops.
Objectives: The aim of our study was to evaluate 3D speckle tracking myocardial deformation patterns compared to a control population in patients with neuromuscular diseases without evidence of cardiac involvement.
Methods: 14 patients with neuromuscular disease without cardiac involvement and 14 controls (healthy volunteers) underwent a 3D-wall motion tracking echocardiographic study with a 3D dataset acquisition. Main endocardial points in the apical views displayed are defined and the program detects the complete endocardial and epicardial borders. Global and regional deformation parameters are automatically generated. Global longitudinal, circumferential, radial strain and area strain were analyzed in all subjects as well as twist, regional twist, rotation, radial and longitudinal displacement. Segmental longitudinal strain, circumferential strain and area strain were also included for analysis in the study population.
Results: Mean age was 37.2 years, males 64%. 7 patients had myotonic dystrophy (MD) type 1, 5 mitochondrial myopathy (MM) and 2 patients other muscular dystrophies (OMD). Significant differences were noted in global radial strain between patients and controls (18, 0±6,3 vs 25,2±9,7 p=0.03). Regional radial strain differences were noted in the basal anterolateral segment (20,2±13,7 vs 37,6±21,6 p=0,025), anterior apex (10,1±6 vs 20,2±8 p=0,025) and apical septum (10,4±9.4 vs 21,9±12,8 p=0,014). In 3D myocardial strain parameters differences were noted in the basal inferorolateral segment (25±15,5 vs 44,5±20,6 p=0,009)and in anterior apex (11,9±7,1 vs 21,4±8,1 p=0,003) No significant differences were found in other analyzed parameters.
Conclusions: Patients with neuromuscular diseases tend to present lower values of 3D STE parameters evaluated. Global and segmental radial strain show significant differences and may be used as a marker of early cardiac involvement in these patients.

PRIMARY PREVENTION: IT IS ALL IN THE BLOOD

P1462 Serum 25-hydroxyvitamin D deficiency increases risk of myocardial infarction: results from the prospective MONICA/KORA Augsburg case-cohort study

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Purpose: A growing body of evidence suggests that vitamin D deficiency may adversely affect the cardiovascular system, but data from longitudinal studies are lacking. Circulating 25-hydroxyvitamin D3 (25[OH]D), the most commonly used index of vitamin D status, is converted to the active hormone 1,25-dihydroxyvitamin D3 (1,25[OH]2D), which, operating through the vitamin D receptor (VDR), inhibits in vitro cell proliferation, induces differentiation and apoptosis, and may protect against coronary heart disease (CHD). Therefore, the aim was to prospectively assess the association between serum (25[OH]D) concentrations and incident CHD.
Methods: Using a case-cohort design, serum levels of (25[OH]D) were measured in 1,783 subjects (964 men, 819 women) selected from a source population of 9,300 middle-aged participants in the population-based MONICA/KORA Augsburg studies.
Results: A total of 298 CHD cases (225 male, 73 female) were identified over an 11-year average follow-up period. Since we found a significant interaction of the effects of vitamin D with sex, we present only sex-specific analyses. After adjustment for age, survey, and season of blood sampling, the hazard ratio (HR) and 95% confidence interval (CI) comparing tertile extremes of serum levels of (25[OH]D) was 0.32 (0.16-0.65) (p-value for trend=0.001) in women, and 0.56 (0.38-0.82) (p-trend=0.005) in men. Further adjustment for standard cardiovascular risk factors (including BMI, smoking, physical activity, alcohol, systolic blood pressure, total cholesterol/HDL-cholesterol ratio, and parental history) slightly attenuated the association in women (HR: 0.39 [0.18-0.84]; p-trend=0.013, and strongly in men (HR: 0.76 [0.49-1.17]; p-trend=0.215). After additional adjustment for C-reactive protein, interleukin-6, ICAM-1, and IP-10, the effect remained signif-

icant in women (HR: 0.42 [0.19-0.93]; p-trend=0.028) while it was further reduced in men (HR: 0.84 [0.52-1.35]; p-trend=0.461).
Conclusions: Our findings suggest that higher vitamin D status is associated with decreased risk of CHD. This effect seems to be particularly pronounced in women. Further clinical and experimental studies are needed to investigate the sex differences and whether or not correction of vitamin D deficiency could contribute to the prevention of cardiovascular disease.

P1463 Small dense low-density lipoprotein is a risk for coronary artery disease in an urban Japanese cohort: the Suita study

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Background and aim: Increased plasma low-density lipoprotein (LDL) cholesterol (LDL-C) concentrations have been shown to be a significantrisk factor for coronary artery disease (CAD). Clinical evidence also indicated that small dense LDL (sd-LDL) particles are more atherogenic than large buoyant LDL particles. Because there was no easy assay to measure the amount of sd-LDL, no study has addressed the association between sd-LDL and cardiovascular disease. Therefore, we examined the association between sd-LDL cholesterol (sd-LDL-C) and CAD using a new assay kit for sd-LDL-C in an urban Japanese cohort.
Methods: The Suita study is an 11.7-year prospective study in an urban population aged 30–79 without history of myocardial infarction or stroke. Direct LDL-C and sd-LDL-C were measured in samples from 2034 participants (968 men and 1066 women) by a kit based on the precipitation method with filtration. We calculated the multivariable-adjusted hazard ratios (HRs) of sd-LDL-C and sd-LDL/LDL ratio for CAD using a proportional hazards regression model after adjusting for age, sex, hypertension, diabetes, use of lipid lowering agent, body mass index (BMI), current smoking and alcohol drinking.
Results: We divided men and women to 4 groups according to quartiles of sd-LDL-C. Levels of sd-LDL-C were positively associated with total cholesterol, triglyceride, BMI, blood pressure, and were negatively correlated with HDL-cholesterol in both genders. Levels of sd-LDL-C were positively correlated with age only in women. After adjustment by age and sex, increasing quartiles of sd-LDL-C were significantly associated with increased incidence of CAD (p=0.001). The HR of the 4th quartile was 3.35 (95% confidence intervals [95% CI]: 1.38-8.13). In multivariable adjustment, the HR of the 4th quartile was almost similar. Sex-specific analysis showed that the association between sd-LDL-C and CAD was also statistically significant in men, but not in women. We also found that sd-LDL/LDL ratio was a significant risk for CAD after age and sex- and multivariable-adjustment (p=0.001, 0.005, respectively). Furthermore, higher sd-LDL/LDL ratio was significantly associated with CAD even after LDL-C adjustment.
Conclusions: We demonstrated that sd-LDL-C and sd-LDL/LDL are significantly associated with the development of CAD in Japanese without history of myocardial infarction or stroke. Our data indicate that sd-LDL-C is an independent and new risk factor for CAD and should be incorporated for a risk assessment. However, a larger study should be done to show the role of sd-LDL on CAD in women.

P1464 On-treatment non-HDL cholesterol, apolipoprotein B, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy: the JUPITER trial

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Purpose: Guidelines focus on lowering LDL cholesterol as the primary target of therapy, yet residual risk for cardiovascular disease (CVD) among statin-treated individuals remains high and is not fully explained. Alternative lipid measures have been proposed to be related to residual risk, but their clinical utility is uncertain.
Methods: Participants in the randomized placebo-controlled JUPITER trial were adults without diabetes or CVD, and had baseline LDL cholesterol $<$3.37 mmol/L, high-sensitivity C-reactive protein $\geq$2 mg/L, and triglycerides $<$5.65 mmol/L. For this analysis, individuals allocated to rosuvastatin 20 mg daily who had baseline and on-treatment lipid measures were examined in relation to the primary endpoint of incident CVD (non-fatal myocardial infarction or stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death).
Results: Statistically significant associations of a similar magnitude with CVD were found for on-treatment LDL cholesterol, non-HDL cholesterol, apolipoprotein B, and the lipid ratios, total/HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B/A-1. The respective adjusted standardized hazard ratios (95% CIs) for each of these measures were 1.31 (1.09-1.09), 1.25 (1.04-1.50), 1.27 (1.06-1.53), 1.22 (1.03-1.44), 1.29 (1.09-1.52), and 1.27 (1.09-1.49). A threshold effect was observed whereby there was minimal residual risk for concentrations below the top tertile values for any of these lipid measures. By contrast, on-treatment triglycerides showed no association with CVD at any concentration.
Conclusions: In this large randomized primary prevention trial of non-diabetic individuals, on-treatment concentrations of non-HDL cholesterol, apolipoprotein B, and several lipid ratios were comparable with LDL cholesterol in the prediction of residual risk. A threshold effect was observed such that minimal residual risk for any lipid measure was observed for individuals with on-treatment LDL cholesterol below 1.81 mmol/L (70 mg/dL).

P1465 Candidate gene analysis of CRP change in response to rosuvastatin in the JUPITER trial

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Purpose: Statin therapy reduces C-reactive protein as well as LDL-C. However, in contrast to LDL-C reduction, data evaluating potential genetic determinants of statin induced CRP reduction is scant. To address this issue, genome-wide association and nested candidate gene analyses of change in CRP during statin therapy were performed in the JUPITER trial, where participants with baseline LDL-C $<$110 mg/dl and CRP $>$2 mg/L were randomly allocated to rosuvastatin (20 mg/day) or placebo.
Methods: The absolute and fractional change in CRP over 12 months of follow up were calculated among 5,598 JUPITER participants who had baseline CRP $<$10mg/L, were free of diabetes at baseline and through follow-up, had verified European ancestry, and whole genome genotype data derived from the Illumina Omni 1M platform. To decrease the influence of extreme outliers and reduce variance, CRP measures were transformed by inverse-quantile normalization and residualized by adjustment for sex, region, age, smoking status, BMI and population structure. Nineteen candidate genes were selected from recent genome-wide association studies for baseline CRP levels. An additional 49 candidate genes were selected for involvement in LDL-C lowering with rosuvastatin therapy. Candidate gene analysis considered SNPs within 25Kbp of the extent of transcription of each gene. A gene-wide corrected estimate of the p-value (pcor) of the most significant SNP was derived by Bonferroni correction for an effective number of alleles estimated from LD structure.
Results: No associations reached genome-wide levels of significance ($p<5\times10^{-8}$) for change in CRP among rosuvastatin allocated JUPITER participants. In candidate analysis, SNPs in HNF1A (rs2464196), CRP (rs1205), LEPR (SNP1-65842369), GRIK4 (rs12278795) and UGT2B7 (rs6600897) were identified with gene-wide significance for the percent reduction in CRP (pcor=0.0038, 0.012, 0.018, 0.046, and 0.018, respectively) with rosuvastatin allocation; and SNP12-119925217 in HNF1A and rs34096782 in CYP3A5 were associated with absolute change in CRP (pcor=0.044, and 0.039). These six candidate genes were nominally associated with absolute or fractional change in CRP, but were not significant after correction for the number of genes tested.
Conclusions: CRP lowering with rosuvastatin allocation was nominally associated with variation in HNF1A, GRIK4 and UGT2B7 on an absolute basis and with HNF1A, CRP, LEPR, and CYP3A4 on a fractional basis. No genes remained significant after correction for multiple hypothesis testing.

P1466 Evaluating benchmarking to optimize management of type 2 diabetic patients: Joint control of HbA1C, low-density lipoprotein cholesterol, and systolic blood pressure in the European OPTIMISE study

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Purpose: Diabetes complications markedly impact patient survival, quality of life and healthcare costs. Effective treatments and interventions reduce such burden and improve quality of care. Benchmarking (BM) incorporates 2-sided feedback of a physician's individual performance compared to the achievement of a peer group, as well as patient's ability to reach target levels regarding major modifiable risk indicators. This study assessed the effect of BM on quality of care in type 2 diabetes outpatients over a 12 month follow-up (FU).
Methods: OPTIMISE was a non-interventional, observational study conducted in 6 European countries (BE GR LU PT SP UK NCT00681850). Physicians were randomly assigned to either BM or control (CO). The primary endpoint was the percentage of patients achieving pre-set targets (European guidelines 2007) for 3 major modifiable variables: HbA1c ($<$7%), low-density lipoprotein cholesterol (LDL-C $<$80 mg/dL [BE], $<$100mg/dl [others]) and systolic blood pressure (SBP $<$130 mmHg).
Results: 2487 patients were randomized to BM, 1503 to CO by 368 investigators (229 BM 139 CO). Both groups were highly comparable regarding all baseline demographic, anthropometric and diabetes-related parameters. After FU, mean LDL-C, HbA1c and SBP decreased in both groups. More BM patients achieved all 3 targets (10.9% 231/2124) vs CO (5.8% 79/1363 p$<$0.001). As regards each single variable, BM significantly increased the frequency of patients achieving LDL-C and SBP targets vs CO but not that of HbA1c target attainment.

		LDL-C		HbA1c		SBP	
		BM	CO	BM	CO	BM	CO
Patients reaching target							
Baseline	%	49.0	48.3	49.2	55.0	27.3	27.1
	n/Total	1185/2417	707/1463	1226/2493	826/1503	587/2149	323/1192
FU	%	63.2*	56.8	58.9	62.7	40.0*	30.1
	n/Total	1310/2074	751/1323	1250/2124	846/1363	735/1839	325/1081
Change from baseline		-10.8±30.8	-7.2±30.6	-0.3±1.5	-0.2±1.3	-5.2±16.4	-2.6±15.5
	%	-5.93	-1.94	-3.99	-3.49	-2.44	-0.67
	95% CI	-7.8; -4.0	-4.4; 0.5	-5.0; -2.9	-4.8; -2.1	-3.3; -1.6	-1.8; 0.5

n: number of patients, CI: confidence interval, *vs CO $p<0.001$.

Conclusions: The OPTIMISE results indicate that BM may positively impact combined target attainment for three major modifiable cardiovascular variables (SBP, HbA1C and LDL-C) in European patients with type 2 diabetes.

P1467 Genetic determinants of statin induced LDL-C reduction

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Purpose: In statin trials, every 20 mg/dL reduction in cholesterol results in a 10 to 15 percent reduction in vascular event rates. However, inter-individual variation in LDL-C response to statins is wide and may partially be determined on a genetic basis. The contribution of common genetic variation to LDL-C reduction was explored by genome-wide analysis.
Methods: A genome-wide association study of LDL-C response was performed among 6,989 men and women of European ancestry who were randomly allocated to rosuvastatin 20 mg daily or placebo in the JUPITER trial. Both the absolute and fractional change in LDL-C with allocation were examined for genome-wide significant ($P<5\times10^{-8}$) association using standard additive genetic model. A nested candidate gene analysis was also performed, requiring locus-wide thresholds for significance.
Results: Single nucleotide polymorphisms (SNPs) for genome-wide significant association with LDL-C reduction on rosuvastatin were identified at ABCG2, LPA, and APOE, and a further association at PCSK9 was genome-wide significant for baseline LDL-C and locus-wide significant for LDL-C reduction. Median LDL-C reductions on rosuvastatin were 40, 48, 51, 55, 60, and 64 mg/dL respectively among those inheriting increasing numbers of LDL-lowering alleles for SNPs at these 4 loci (P-trend = 6.2×10^{-20}), such that each allele approximately doubled the odds of percent LDL-C reduction greater than the trial median (OR 1.9, 95%CI 1.8-2.1, $P=5.0\times10^{-41}$). An additional association with $P<1\times10^{-6}$ was identified for statin related LDL-C reduction at IDOL which mediates post-transcriptional regulation of the LDL receptor in response to intracellular cholesterol levels. In candidate analysis, SNPs in SLCO1B1 and LDLR were confirmed as associated with LDL-C lowering, and a significant interaction was observed between SNPs in PCSK9 and LDLR.
Conclusions: Inherited polymorphisms that predominantly relate to statin pharmacokinetics and endocytosis of LDL particles by the LDL receptor are common in the general population and influence individual patient response to statin therapy.

P1468 The CC variant of locus 9p21 increases coronary disease risk with high values of hs-CRP

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Recent genomic wide association studies have identified several loci associated with coronary artery disease (CAD) risk. Among them, SNP rs 1333049 in the locus 9p21 (variant CC) has demonstrated a solid association with CAD which has been replicated in several populations, namely ours. High sensibility C-reactive protein (hs-CRP) has also been associated with inflammatory activity and atherosclerosis. An eventual interaction among these two atherosclerotic markers is unknown. Aim: To explore the interaction between this homozygous genetic variant (CC) and hs-CRP plasmatic levels in the emergence of CAD.
Methods: Case-control study with 1561 participants, 695 consecutive coronary patients (mean age 53.9±8.9 years, 78.8% male) and 838 controls without apparent CAD (mean age 52.0±11.4 years, 71% male) selected in order not to present significant differences in sex and age. The G/C variants were studied blindly using a combined technique of PCR and TaqMan. Hardy-Weinberg distribution was analyzed.
The CAD risk was investigated by univariate analysis and the OR and 95% confidence intervals were calculated. hs-CRP values were distributed by quartiles and the highest one, considered as the risk, was evaluated. To determine the interaction between CC genotype and elevated hs-CRP values we used a 4×2 table approach, as well as synergy measurements in additive (SI) and multiplicative (SIM) models. Finally, the risk excess (RERI) and the attributable proportion (AP) due to the interaction were calculated.
Results: The CC variant was significantly associated with CAD risk in the whole population (OR=1.32; p=0.011). The presence of this genetic variant with normal hs-CRP values presented a smaller risk (OR=1.28) when compared to the association with the elevated hs-CRP values in the highest quartile (OR=1.7; p=0.007; SI=1.63; SIM=1.15; RERI=0.27).
Conclusion: The present study demonstrates that the CC variant of the 9p21 locus globally increases the risk of CAD. This risk can be further increased in the presence of elevated hs-CRP values, as shown by the addictive and multiplicative interaction. This concept allows us to foresee the possibility of genetic risk factors management through the control of associated conditions, whenever possible.

P1469 NT-proBNP plasma levels as a potential biomarker for cardiac damage after radiotherapy in left-sided breast cancer patients

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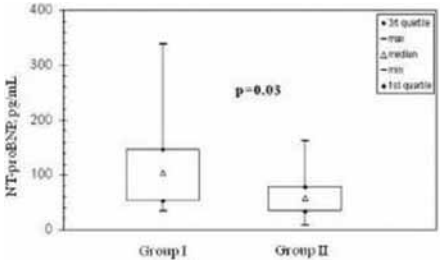
Background: Adjuvant radiotherapy (RT) after breast-conserving surgery has been associated with increased cardiovascular mortality. Cardiac biomarkers may aid in identifying patients with radiation-mediated cardiac dysfunction. We evaluated the correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and Troponin (TnI) and the dose of radiation to the heart in left-sided breast cancer patients.
Methods: NT-proBNP and TnI plasma concentrations were measured in 30 left-sided breast cancer patients (median age 55.0 years) at 5-22 months after RT (Group I) and 30 left-sided breast cancer (median age 57.0 years) before RT as control group (Group II). Dosimetric parameters of heart and ventricle were determined in all patients of Group I. All patients underwent a complete 2D echocardiography.
Results: NT-proBNP level was significantly higher (Figure) in Group I (median 90.0 pg/mL; range 16.7-333.1 pg/mL) than in Group II (median 63.2 pg/mL; range 11.0-172.5 pg/mL). nI levels remained below the cutoff threshold of 0.07 ng/mL in both groups. In patients with NT-proBNP values above the upper limit of 125 pg/ml, there were significant correlations between plasma levels and V3Gy (%) (p=0.001), the ratios D15cm^3 /Dmean (Gy)/ (p=0.01), the ratios D15cm^3/D50% (Gy) (p=0.008) for the heart and V2Gy (%) (p=0.002), the ratios D1cm^3 /Dmean (Gy)/ (p=0.03), the ratios D0.5cm^3/D50% (Gy) (p=0.05) for the ventricle.



NT-proBNP levels in the study population.

Conclusions: Patients with left-sided breast cancer show higher values of NT-pro BNP after RT when compared with non-irradiated matched patients, increasing in correlation with high doses in small volumes of heart and ventricle. Subtle forms of myocardial damage not detectable by reduction of LV function can be revealed by circulating biomarkers.

P1470 Association of IL-6 but not hsCRP with subclinical carotid atherosclerosis: a sub-analysis of the PEACE study

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Purpose: Inflammation has been recognized to play a crucial role in atherosclerosis. Icreasing evidence has shown that circulating inflammatory markers as well as carotid intima-media thickness (CIMT) are predictors of cardiovascular diseases. The objective of this study was to investigate the association between inflammatory markers and carotid atherosclerosis using the data from the PEACE study.
Methods: The PEACE study is a multicenter, prospective, randomized, open-labeled, blinded endpoints, two-arm parallel treatment group comparison study with a response-dependent dose titration scheme. Japanese patients with modest CIMT thickening (>1.1 mm) whose LDL cholesterol level was more than 100 mg/dl (303 patients, 42.6% female, mean 66.3 years) were randomized to receive either moderate (target LDL cholesterol level is 100 mg/dl) or intensive (target LDL cholesterol level is 80 mg/dl) pitavastatin treatment. The primary endpoint is the change in mean CIMT over 1 year.

Results: Multivariate analysis revealed a significant correlation of interleukin (IL)-6 at baseline with the change in mean CIMT (P=0.0460). Both hsCRP and IL-6 levels were significantly reduced by the treatment with pitavastatin. The change in neither hsCRP nor IL-6 correlated with the change in LDL cholesterol level (P=0.1054 and P=0.5921, respectively). Of note, the change in IL-6 but not hsCRP positively correlated with the change in mean CIMT (r=0.18, P=0.0418). Intensive lipid-lowering therapy did not cause greater reduction in hsCRP or IL-6 compared with the moderate therapy group. This might be partly due to the higher hsCRP and IL-6 at baseline in the moderate therapy group than those in the intensive therapy group (1.43±0.17 (mean±SE) vs 0.88±0.10, P=0.0499, and 2.78±0.31 vs 2.04±0.18, P=0.1102, respectively).
Conclusions: Our present study demonstrates that pitavastatin significantly reduces hsCRP and IL-6 in Japanese adult with evidence of subclinical atherosclerosis. IL-6 at baseline as well as the change in IL-6 is associated with the progression and/or regression of carotid atherosclerosis, suggesting that IL-6 might be a better marker for the disease state of carotid atherosclerosis than hsCRP.

P1471 Novel biomarkers as predictors of incident coronary heart disease events

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Background: We recently examined 30 novel biomarkers as predictors of incident cardiovascular disease events. Now we have determined another set of 20 additional biomarkers in the same cohort.
Aim: To examine, whether the novel biomarkers improve the assessment of coronary heart disease (CHD) risk over and above the traditional risk factors.
Subjects and methods: Levels of 20 cytokines, chemokines and growth factors were measured from plasma samples using multiplex technology. We used the population-based FINRISK 1997 cohort, where 7912 persons aged 25-74 years were examined during the spring 1997 and followed up for 11 years, until December 31st, 2008. After excluding persons with a history of major cardiovascular event at baseline investigation, 7632 individuals were included in prospective analyses. Among them, 480 incident (=first) acute CHD events were observed during the follow-up. Cox proportional hazards regression analyses were used for estimating the relative risk of a CHD event per one standard deviation increase in the biomarker concentration, adjusting for the standard Framingham risk factors.
Results: Four out of the 20 biomarkers produced significant relative risks (RR) when examined one by one: tumor necrosis factors beta (RR=1.06, 95% confidence interval (CI) 1.01-1.12, p=0.02), basic fibroblast growth factor (RR= 1.09, 95%CI 1.03-1.15, p=0.002), monocyte chemoattractant protein-1 (RR=1.05, 95% CI 1.01-1.10, p=0.03) and macrophage inflammatory protein-1 beta (RR=1.07, 95% CI 1.02-1.12, p=0.005).
Conclusions: Our study revealed at least four novel biomarkers with modest but significant independent associations with CHD risk after adjustment for traditional CHD risk factors. Further analyses are in progress to characterize in more detail their clinical significance and biological roles.

P1472 C-Reactive Protein (CRP) can predict perioperative major cardiovascular events in patients undergoing noncardiac, nonvascular surgery

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Introduction: C-reactive protein (CRP) is a biomarker of inflammation and has an important prognostic value in patients with heart failure and coronary artery disease. However, its value as a predictor of perioperative cardiovascular events in noncardiac surgery is unclear.
Methods and results: A total of 1000 patients undergoing noncardiac, nonvascular surgery were prospectively evaluated. Patients older than 18 years who underwent an elective, nonday case, open surgical procedure were enrolled. Electrocardiography and cardiac biomarkers were obtained 1 day before surgery, and on days 1, 3 and 7 after surgery. Preoperative risk factors and CRP levels were measured and evaluated for their association with the occurrence of in-hospital perioperative cardiovascular events. Plasma CRP levels were significantly higher in patients with perioperative cardiovascular events (n=97, 12.1%) in comparison to those without cardiovascular events (3.3±3.8 vs 1.9±3.7, p<0.001). Each 1-SD increase in log CRP was associated with 1.5-fold increased rate of perioperative cardiovascular events, even after adjustment for other risk predictors and traditional clinical risk factors.
Conclusions: CRP is an independent predictor of perioperative cardiovascular events in patients undergoing noncardiac, nonvascular surgery.

P1473 Subclinical vascular disease in patients with erectile dysfunction: correlation with high sensitivity C-reactive protein levels

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Background: Erectile dysfunction (ED) may be early clinical manifestation of a generalized vascular disease & carries an independent risk for cardiovascular (CVS) events. Low-grade subclinical inflammation affects endothelial function & involved in all stages atherosclerotic process.
Objectives: To test hypothesis that,erectile dysfunction in men without CVS disease or its major risk factors may be earliest sign of generalized vascular dysfunction & correlate this with high sensitivity C-reactive protein (hs-CRP) levels.
Patients & methods: The study enrolled 115 men with ED without CVS disease or its major risk factors & 40 age matched healthy men as a control group.For all participants, assessment of LV function,aortic strain (AS),distensibility (AD) & aortic wall systolic velocity (AWSV) was done using conventional echocardiography & Doppler tissue imaging. B-mode ultrasonic examination of common carotid & brachial arteries was performed for measurement of carotid intima-media thickness (CIMT),brachial artery flow-mediated (FMD) & nitroglycerine-mediated vasodilatation (NTGMD). Ultrasensitive immunoassay used to measure serum hs-CRP.
Results: CIMT& hs-CRP were significantly higher in patients than controls (0.82±0.22 mm vs. 0.53±0.31 mm & 6.72±1.5 mg/L vs. 2.1±0.78 mg/L respectively, p<0.001 for all),whereas AWSV,AS & AD were significantly lower in patients compared to control group (6.1±2.1 cm/sec vs. 9.1±1.6 cm/sec, 10.6±6% vs. 17.9±7%,& 7±3 $cm^2/dyn/10^3$ vs. 12±5 $cm^2/dyn/10^3$ respectively, p<0.001 for all). ΔFMD & FMD% that reflect endothelial function status were significantly impaired in patients compared to controls (0.67±0.33 mm vs. 2.1±0.29 mm &21% vs. 50% respectively,P<0.001 for each); while ΔNTGMD & NTGMD% did not differ significantly between two groups (2.1±0.73 mm vs. 2.3±0.59 mm & 49% vs. 51% respectively,P>0.05 for each). A strong positive correlation found between ED severity & CIMT (r=0.55), hs-CRP (r=0.6) while correlation was negative between ED & AWSV (r= -0.83), AS (r= -0.63), AD (r= -0.65), FMD (r= -0.85), p<0.001 for all.
Conclusion: Aortic, carotid & brachial artery functional parameters are all impaired in addition to elevated hs-CRP levels in patients with ED without CVS disease or its major risk factors, suggesting that, ED would represent an early clinical manifestation of a diffuse systemic subclinical vascular disease. It is, therefore, crucial to identify asymptomatic patients with ED who may be at risk of occult CVS diseases. Their early recognition may lead to treatment of risk factors & conditions associated with endothelial dysfunction, hopefully reducing the rate of major CVS events.

P1474 Gamma-glutamyl-transferase and high-sensitivity C-reactive protein independently predict coronary calcium score and echographic carotid intima-media thickness: an Italian population-based cohort-study

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Purpose: Gammaglutamyl-transferase (GGT) and high-sensitivity C-reactive protein (HS-CRP) have been recognized as predictors of cardiovascular events, related with oxidative stress and an inflammatory burden within the plaque, respectively. We aimed to evaluate their relation with coronary calcium score (CCS) at coronary computed tomography, and with echographic carotid intima-media thickness (IMT), in an unselected middle-aged Italian population, versus conventional risk factors and clinical patient background.
Methods: From January up to December 2010, out of 4000 eligible subjects, we prospectively enrolled a preliminary series of 875 (aged 45-75 years, 68±14, m±SD, males 48%, left ventricular ejection fraction was 55±2%), from the community of Montignoso, Tuscany (8000 inhabitants); all patients underwent clinical and echocardiographic investigation, laboratory assessment of GGT and HS-CRP, CCS and IMT evaluation. Age, sex, diabetes (28% of subjects), hypercholesterolemia (31%), hypertension (48%), smoking habit (41%), renal dysfunction (1.4%), atrial fibrillation (5%), previous myocardial infarction (5%) and ischemic transitory attacks (5%) were included in multivariate models for prediction of CCS and carotid IMT.
Results: Median, lower and upper quartile values of GGT and HS-CRP were respectively 19, 14-28 UI/L and 0.25, 0.12-0.62 mg/dL. Interestingly at multivariate analysis, GGT and HS-CRP were along with history of myocardial infarction the only independent predictors of CT-CCS (B=1.936; 95% CI 1.352-2.772 p<0.001 and B=1.105; 95% CI 1.001-1.220 p=0.047, using a cut-off of 400 Agatston Units); again, along with previous transitory ischemic attack only, both GGT and HS-CRP predicted carotid IMT in a linear multivariate logistic model (B = 0.558 95% CI 0.090 - 1.025, p=0.01 and B= 0.168 95% CI 0.033 -0.303, p=0.01 respectively).
Conclusions: In an unselected south-European community we showed that GGT and HS-CRP are independent predictors of atherosclerotic global burden. Thus serum GGT and HS-CRP measurement allows a better risk stratification of pa-

tients and can be used as screening parameters to direct patients towards more expensive imaging techniques.

P1475 Impact of diabetes mellitus and gender on exercise related antiangiogenic endostatin/collagen XVIII release

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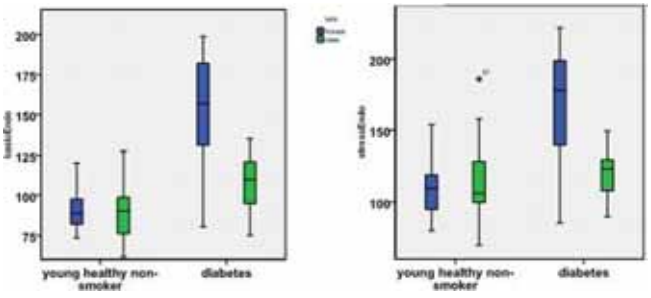
Background: Type 2 diabetes mellitus (T2DM) is one of the most important risk factors for cardiovascular diseases in men and women resulting in endothelial dysfunction and subsequent atherosclerosis. However, the cardiovascular risk is higher in diabetic women compared to diabetic men. Endostatin (Endo), a recently found potent angiostatic parameter, a fragment of collagen VXIII, might be a new way to inhibit progression of atherosclerosis. Therefore the aim of the present study was to investigate the impact of T2DM and gender on exercise related Endostatin/collagen XVIII release.
Study population and methods: A total of 64 patients, divided into diabetics (11 female; 14 male; mean age 58,5±10,1) and young healthy non-smokers (20 female; 19 male; mean age 23,1±3,9), were investigated during a graded physical stress test. Endo was measured (ng/ml) at baseline (Sample 1) and at peak workload (Sample 2). Furthermore heart rate, BMI and blood pressure were measured.



ENDO (blue=female, green=male)

Conclusion: We could show for the first time, that graded exercise is associated with a significant increase in Endo serum levels in women and men in both groups. However, female diabetics show markedly increased baseline as well as stress Endo serum levels at maximum work-load compared to young healthy females as well as diabetic men. Further studies are needed to investigate the impact of age and gender on exercise related Endo release.

PRIMARY PREVENTION: INTERVENTION AND OUTCOMES

P1476 Randomized evaluation of the effects of a structured educational program (HERZ.LEBEN) on blood pressure in essential hypertensive patients

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Purpose: Despite improved awareness and excellent therapeutic options, hypertension remains one of the greatest cardio- and cerebrovascular risk factors. Patient-related aspects like life style and adherence to medical recommendations are generally acknowledged to have a major impact on the course of chronic diseases. As a structured educational program for diabetics proved to be highly effective (DAFNE-trial), it was thought that this strategy might provide significant benefits for hypertensives as well. A previously evaluated structured curriculum was followed by doctors and hypertension nurses. Groups of 6-10 patients were instructed on blood–pressure issues including self measurement, a healthy low salt diet, active life style and pharmacologic antihypertensive therapy. This prospective multicenter randomized controlled study (NCT00453037) was designed to determine the isolated effect of participation in the educational program, neglecting the possible impact of more intense care.
Methods: Between 2007-2010, 256 patients in 13 centers (9 general practitioners' offices and 4 outpatient departments) were enrolled in the study. After initial evaluation (T0) and written informed consent, all patients were invited to two follow-up visits after 6 (T6) and 12 (T12) months. Patients at each center were randomly assigned to 2 groups (G). G-I (n=137) underwent the educational program at T0, G-II (n=119) was designated for participation after T6. The primary endpoint was an apparent difference in office and home blood pressure (BP) at T6. At this point in time, similar conditions of care for all patients could be assumed, but only G-I had undergone the educational program.
Results: Patients' characteristics and BP at baseline were comparable (office BP G-I vs G-II 158±18/88±11 and 161±18/88±14 mmHg, ns/ns). At T6 systolic office and home BP was significantly lower in G-I than in G-II (office BP 142±17/81±11 vs 150±24/84±12; $p<0.01$/ns; home BP 134±8/80±8 vs 142±16/82±9, $p<0.01$/ns). At T12 all patients had undergone the educational program; at this point in time the differences in BP observed at T6 had disappeared completely. Patient flow was as follows: At T6/T12 120/88 patients in G-I and 97/88 patients in G-II had adhered to the scheduled visits.
Conclusion: The results of this multicenter RCT provide significant evidence of a benefit when patients take part in a structured educational program, presumably because of higher levels of information and patient empowerment. Educational strategies so should be considered seriously as standard of care for hypertensive patients.

P1477 Project Raffaello: application and evaluation of the disease and care management approach in cardiovascular disease prevention

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Project Raffaello" is a Research Project to evaluate the efficacy of an innovative model of healthcare management in prevention of cardiovascular diseases, a model defined "Disease Management".
Study design was a cluster randomized trial where units of randomization are represented by Primary Care Groups (PCGs). Of 12 PCGs, 6 were randomized to implement the new model (study group), the other 6 to usual practice (control group). A total of 762 patients (35-80 years old) with at least one cardiovascular (CV) risk factor out of control (hypertension, dyslipidemia, diabetes, obesity, smoking) were enrolled and evaluated for 1 year. The intervention evaluated was the "Care Management Team" (General Practitioner, Nurse as Care Manager (CM), Patient and any Specialist needed) with the mission to define and apply patient personalized health plan based on international guidelines on CV disease prevention.
Patients of study group received (a) on-going, one-on-one health and motivational coaching sessions; (b) customized, personalized, patient focused care plans; (c) education materials, and (d) service coordination between providers.
In managing patients, the CMs used a computerised record keeping and decision support system that draws on localised care pathways and evidence-based recommendations, supporting the CM in daily activities and facilitating exchange of information between different healthcare professionals.
Primary outcome (the proportion of patients reaching the defined target in at least one of the CV risk factors present at enrolment, without worsening of any other factor) was reached in 39.1% (95% CI 34.2-44.2) of 381 patients of study group vs 25.2% (95% CI 20.9-29.9)of 381 patients of control group ($p<0.001$, intention-to-treat analysis). The defined target was mainly reached in hypertensive and diabetic patients. Furthermore, in study group 46% (95% CI 29.9-62) of high-risk patients (SCORE) became at low/medium risk vs 20% (95% CI 20.9-29.9) in control group (p=0.019), and 37.5% (95% CI 25.6-49.4)of medium-risk patients became at low risk vs 17.4% (95% CI 8.4-26.3) in control group (p=0.009).
Conclusion: The Disease and Care Management Approach, mainly represented by the participation of the patient in the definition of his health plan, by the teamwork synergy realized by "Healthcare Management Team" and by the introduction of the care manager, is effective in improving patient's cardiovascular risk profile.

P1478 Risk stratification for emergency coronary artery bypass graft following percutaneous coronary intervention

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Background: Despite a decline in need for emergency coronary artery bypass graft (ECABG) in patients undergoing percutaneous coronary intervention (PCI) in the stent era, the mortality and morbidity of ECABG remains constant and high. An increasing number of PCI procedures are also now performed at hospitals without on-site cardiac surgery. These factors create the need for more accurate risk stratification for ECABG following PCI.
Methods: Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) registry data with 109,830 cases of PCI from 2004 to 2009 was used to develop and validate a support vector machine (SVM) classification approach to predict ECABG. There were 265 cases of ECABG following PCI (0.24%). Training and testing of the SVM approach was performed using five-fold cross-validation with 72 features corresponding to patient demographics, comorbidities, laboratory

reports, medications, and procedural information recorded pre-PCI. The SVM approach was trained using L1 regularization and a linear kernel. The area under the receiver operating characteristic curve (AUROC) and the number of ECABG per decile of the SVM predicted risk scores were assessed across all testing folds.
Results: SVM classification achieved an AUROC of 0.75 for ECABG following PCI. The table presents the rate of events in patients in each decile of the SVM predicted scores. The rate of events in patients with the top 5% of the SVM predicted risk scores was 2.04% (112 of 5,491). For patients with the top 2.5% of the SVM predicted risk scores the rate of events was 3.28% (90 of 2,745). In comparison, the aggregate rate of ECABG following PCI in the lowest 90% of patients was 0.13% (134 of 98,848).

Table 1. Rate of ECABG following PCI in each decile of the SVM predicted risk scores

Decile	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100
Rate	0.12%	0.08%	0.14%	0.07%	0.12%	0.15%	0.10%	0.19%	0.25%	1.19%
Events	19	9	15	8	13	17	11	21	27	131
Patients	10,982	10,984	10,983	10,983	10,983	10,983	10,983	10,983	10,984	10,982

Conclusions: Advanced Computational models can successfully risk stratify patients who are at risk for ECABG following PCI. These models may be valuable in guiding patient selection for PCI at sites without surgical back up.

P1479 Primary results of the dal-PLAQUE study assessing the effect of dalcetrapib on structural and inflammatory atherosclerotic disease using non-invasive simultaneous multimodality imaging

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Purpose: Despite optimal therapy many patients remain at high CV risk. Raising HDL-C and improving HDL functionality may attenuate atherosclerotic progression. Dalcetrapib modulates cholesterol ester transfer protein (CETP) activity to raise HDL-C. After the failure of torcetrapib it was unknown if HDL produced by action on CETP was proatherogenic or pro-inflammatory. dal-PLAQUE is the first multicentre study to use non-invasive simultaneous multimodality imaging to assess structural and inflammatory indices of atherosclerosis as primary efficacy endpoints, and provides a rigorous safety assessment of dalcetrapib.
Methods: dal-PLAQUE is a phase IIB, double-blind trial conducted at 11 centres in patients (18-75 y) with CHD or CHD risk equivalents, treated with LDL-C lowering drugs to LDL-C <100 mg/dL (<2.6 mmol/L). Patients were randomised to dalcetrapib 600 mg or placebo daily for 24 months, with a 2-week safety follow-up. Endpoints included indices of plaque burden from the right and left carotid and abdominal aorta determined by magnetic resonance imaging (MRI) after 24 months, and plaque inflammation using 18F-fluoro-deoxyglucose uptake measured by positron emission tomography/computed tomography (PET/CT) after 6 months. Imaging data are presented as placebo-corrected change from baseline (90% CI). (ClinicalTrials.gov NCT00655473).
Results: 189 subjects were screened and 130 randomised into the trial. Based on MRI (average carotid), a significant reduction in total vessel area and a trend towards reduction in average wall area were observed with dalcetrapib vs placebo after 24 months (-4.01 mm^2 [-7.23, -0.80]; p=0.041 and -2.20 mm^2 [-4.54, 0.13]; p=0.120 respectively). Other indices of plaque burden were numerically reduced from baseline with dalcetrapib vs placebo. Based on PET/CT, mean of maximum standardised uptake value and target to background ratio were unchanged with dalcetrapib vs placebo after 6 months (-0.05 [-0.16, 0.07]; p=0.498 and 0.09 [-0.07, 0.26]; p=0.363 respectively). HDL-C increased by 31% with dalcetrapib after 24 months with no significant increases in inflammatory biomarkers. Dalcetrapib was well tolerated with a safety profile similar to placebo and was not associated with an increase in BP. Fewer adjudicated CV events occurred on dalcetrapib (2) compared with placebo (13).
Conclusions: No evidence of a pro-inflammatory effect of dalcetrapib was observed after 6 months. On MRI, significantly less progression in total vessel area was seen with dalcetrapib compared with placebo after 24 months. Dalcetrapib was well tolerated.

P1480 Cardiovascular and all-cause mortality outcomes among hypertensive patients with moderate renal dysfunction in the ASCOT-LLA, and its extended follow-up

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Purpose: To evaluate whether the use of statins among patients with moderate (or chronic) kidney dysfunction (eGFR: 30-60 ml/min/1.73 m^2: [CKD]) provides similar cardiovascular (CV) benefits, to those without CKD, and to determine, whether the effects of statins persists beyond the trial closure.
Methods: In ASCOT-LLA, 10305 high risk hypertensive patients were randomized to atorvastatin vs. placebo (follow-up: 3.2 yrs). For each of the pre-specified CV and death outcomes, a separate multivariable Cox model was developed. Interaction test was done to evaluate any heterogeneity in the statin effect. In LLA-extended, patients were followed-up for extra 2-yrs after the LLA-closure.
Results: In LLA, among those with no CKD, allocation to atorvastatin vs. placebo was associated with a significant reduction in CV-outcomes, and statistically insignificant reduction in deaths. Among those with CKD (n=2022), statin vs. placebo offered similar (albeit statistically insignificant) protection for coronary and death outcomes, but, lesser for stroke (Fig. 1). However, there was no heterogeneity in the statin effect among those with/without CKD. In LLA-extended, among those with CKD, allocation to atorvastatin vs. placebo was also associated with beneficial (but statistically insignificant) trends in coronary and death outcomes, with lesser protection afforded against stroke. Similar and statistically significant findings were observed among those with no CKD. Again, there was no significant interaction in the statin effect.

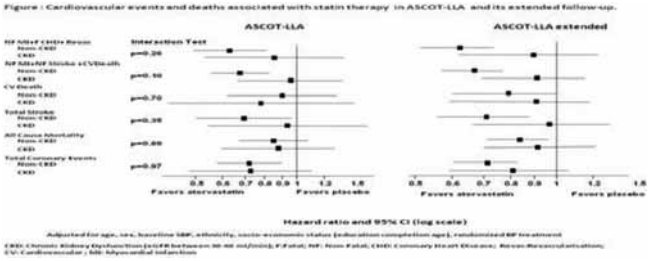

Figure 1

Conclusions: Among hypertensive patients with CKD, atorvastatin therapy was associated with a reduction in coronary, stroke and death outcomes, statistically similar to findings seen among those without renal damage. This beneficial trend remained unchanged, 2 years after LLA closure.

P1481 Automated intima-media thickness measurement: a potential screening tool for subclinical atherosclerosis

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Background and aim: Atherosclerosis starts in childhood but manifests itself in adulthood. Twenty three millions in the USA are classified as having subclinical atherosclerosis. The magnitude of such clinical threat urges stringent early identification of arterial disease and hence aggressive primary prevention. Atherosclerosis biomarkers are known for their limitations, supporting direct arterial imaging as a sensitive tool for early disease detection. Intima-media thickness is considered an appropriate screening method for that purpose but suffers from suboptimal reproducibility, being operator dependent. The objective of this study was to evaluate the reproducibility of a newly developed automated on-line carotid ultrasound system with respect to the conventionally used ones.
Methods: Fifty-six consecutive patients admitted for carotid investigation (mean age 61.5 years, range 23-84, 30% female) were examined both by the automated ultrasound system (AIDA, Panasonic Healthcare Company Ltd, Japan) followed by the Acuson Sequoia ultrasound system (Siemens Medical Solutions Inc., US). For each patient, three frozen frames of the distal 10 mm of right and left common carotid arteries (CCA) were acquired by the two systems, blinded to each other. The 3 AIDA readings were documented, again blinded to the Sequoia measurements, which were obtained from 3 points within the same 10 mm distal CCA segment, using conventional methods, and the average was calculated.
Results: The comparative coefficient of variation of the two systems for the right CCA was AIDA 6.1% and Sequoia 5.9% (p=ns) and respective values for the left CCA were 5.1% and 5.9% (p=ns). Individual absolute measurement' differences between the two operators are listed in the table

	Sonographer A	Sonographer_B
Mean	0.03935	0.03815
N	108	108
Std. Deviation	0.037047	0.034142
Std. Error of Mean	0.003565	0.003285

Conclusion: Automated measurements of IMT using AIDA system is feasible and reproducible compared with conventional manual ones. This approach may have significant implications in screening for subclinical atherosclerosis in the community, having to avoid operator dependency.

P1482 Body surface-adjusted aortic reference diameters for improved identification of patients with thoracic aortic aneurysms: results from the population-based Heinz Nixdorf Recall study

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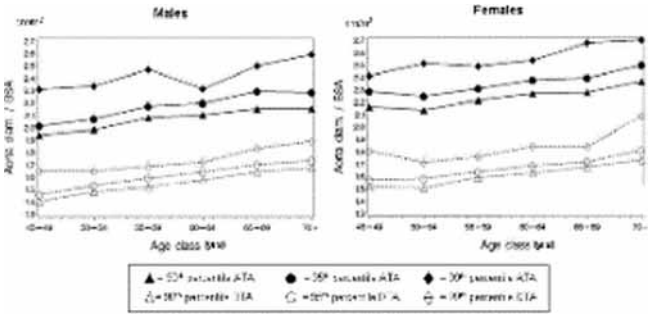
Background: Early identification of patients at risk for thoracic aortic aneurysm (TAA) has the potential of improving prognosis. So far, however, "normal" aortic dimensions are not well defined. In the present study we aimed to (1) establish age and gender-specific distribution of thoracic aortic diameters and (2) to determine the prevalence of asymptomatic TAA in a population-based European cohort.
Methods: Diameters of ascending thoracic aorta (ATA) and descending thoracic aorta (DTA) were measured from electron beam computed tomography (EBCT) scans of 4129 participants aged 45 to 75 years from the Heinz Nixdorf Recall study. Age- and gender-specific percentiles were calculated for body-surface adjusted aortic diameters. Multivariable linear regression was used to evaluate the association between aortic diameters and cardiovascular risk factors.
Results: Aortic diameters were generally greater in the ATA than in the DTA, and were greater in men than in women (ATA: 3.71±0.4 cm vs. 3.45±0.4 cm, $p<0.0001$; DTA: 2.82±0.3 cm vs. 2.54±0.3 cm, $p<0.0001$). Age, male gender, blood pressure and body surface area were independently associated with aortic diameters in both ATA and DTA. Based on our measurements age- and gender specific percentiles for indexed ATA and DTA diameters were computed. Aneurysms ≥ 5 cm were found in 12 (0.34%) out of the total of 4129 subjects.



Conclusion: Since BSA was independently associated with increasing aortic diameters, correction of aortic diameters for BSA may be more helpful in order to reliably identify patients at risk for aneurysm formation. Based on the normal distribution of body-surface adjusted thoracic aortic diameters displayed in age and gender-specific percentiles we suggest a cut-off point for aneurismal aortic diameter at the 95th percentile.

P1483 Pitavastatin evaluation of atherosclerosis regression by intensive cholesterol-lowering therapy trial (PEACE study)

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Purpose: The objective was to evaluate the effect of intensive cholesterol-lowering therapy by pitavastatin on the progression and/or regression of carotid intima-media thickness (CIMT) in patients with subclinical atherosclerosis, in comparison with moderate cholesterol-lowering therapy.
Design, setting and participants: multicenter, prospective, randomized, open-labeled, blinded endpoints, two-arm parallel treatment group comparison study with a response-dependent dose titration scheme. Japanese patients with modest CIMT thickening (>1.1 mm) whose LDL cholesterol level was more than 100 mg/dl (303 patients, 42.6% female, mean 66.3 years) were randomized to receive either moderate (target LDL cholesterol level is 100 mg/dl) or intensive (target LDL cholesterol level is 80 mg/dl) pitavastatin treatment. The data of carotid ultrasonography were all sent to a core center, and analyzed by one sonographer blinded to randomization and all clinical information. The CIMT was automatically measured at approximately 500 points by the newly developed software program, while the region of interest (20 mm) was placed on the far wall of the common carotid artery segment 5 mm proximal to the carotid bifurcation.The primary endpoint is the change in mean CIMT over 1 year, and the secondary endpoints are lipid profiles, inflammation profiles and adverse effects.
Results: At baseline, the mean (SD) LDL cholesterol level was 143.2 (28.5)mg/dl. The initial and follow-up dose of pitavastatin was 2.8 (1.1) and 3.0 (1.2) mg for intensive therapy group, and 1.8 (0.6) and 1.9 (0.8) mg for moderate therapy group, respectively ($P<0.0001$ between groups). Among patients in the intensive therapy group, LDL cholesterol level declined to 89.4 (20) mg/dl, while it declined to 95.1 (22.5) mg/dl in the moderate therapy group ($P<0.05$ between groups). The change in mean CIMT in the intensive therapy group was -0.023 (0.11) mm/year ($P=0.0376$ vs baseline). In contrast, the change in mean CIMT was -0.0078 (0.11) mm/year ($P=0.4406$ vs baseline) in the moderate therapy group. The change of mean CIMT positively correlated with the achieved LDL cholesterol level ($r=0.15$, $P=0.0222$). Both pitavastatin therapies were well tolerated with infrequent adverse effects (5.6%; moderate vs 8.8%; intensive, $P=0.30$).
Conclusions: In Japanese adults with evidence of subclinical atherosclerosis, intensive cholesterol-lowering therapy by pitavastatin resulted in the regression of carotid atherosclerotic diseases over 1 year,whereas moderate cholesterol-lowering therapy only prevents the progression of the diseases.

P1484 Evaluation of the lipid lowering effect of a combination of berberine with red rice (Armolipid plus) in monogenic and polygenic hypercholesterolemia. A comparison study with ezetimibe

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Purpose: Aims of the study were to evaluate the additive effect of a combination of berberine and red yeast rice (BBR/RR) in addition to a current therapy (statins or statin+ezetimibe) in patients with Familial Hypercholesterolemia (FH) and to compare the lipid lowering effect of BBR/RR versus Ezetimibe 10 mg (EZE) in patients with polygenic primary hypercholesterolemia (HCH).
Methods: We enrolled 15 genetically characterized FH patients and we added BBR/RR to their current therapy for three months. In parallel, we enrolled 195 patients with HCH, who were randomly assigned with a ratio 1:2 to a treatment with EZE 10 mg/die (N= 65, 57.9±12.7 years of age, BMI 23.6±2.8 kg/m^2, TC 7.69±0.53, LDL-C 5.33±0.52, HDL-C 1.58±0.33, TG 1.73±0.59 mmol/L) or to a treatment with BBR/RR 1 tb/die (N= 130, 56.8±13.2 years of age, BMI 24.0±3.0 kg/m^2, TC 7.58±0.47, LDL-C 5.34±0.44, HDL-C 1.55±0.34, TG 1.53±0.52 mmol/L). After a three months treatment the lipid lowering effects of EZE and BBR/RR were compared.
Results: In FH patients the addition of BBR/RR results in a significant additive percentage reduction of LDL-C (-55.3% with BBR/RR +current therapy versus -44.7% with current therapy alone). In HCH patients the changes induced by EZE were: TC -21.7±4.7%, LDL-C -29.3±6.9%, TG -16.6±15.7% and by BBR/RR: TC -24.1±6.1% ($p<0.002$ vs EZE), LDL-C -31.7±8.4% ($p<0.03$ vs EZE), TG -17.4±16.5% (NS vs EZE).
Conclusions: This study demonstrated that BBR/RR is a good co-adjuvant of conventional therapy for genetic FH and it's more effective than EZE 10 mg/day in reducing TC and LDL-C in HCH patients.

P1485 Increased number of obstructive segments by computed tomography angiography is associated with coronary heart disease event risk in asymptomatic familial hypercholesterolemia subjects

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Purpose: Heterozygous familial hypercholesterolemia (FH) affects 1in 500 subjects and is characterized by high LDL-C and premature coronary disease (CHD) in comparison with normolipidemic subjects. However, the onset of CHD is variable within FH subjects. In addition to coronary calcium score quantification, computed tomography coronary angiography (CTCA) allows early detection of non-calcified atherosclerotic plaques and estimates luminal stenosis degree. There are no studies evaluating the ability of CTCA to assess the risk of cardiovascular events in FH. The objective of this study was evaluating the role of CTCA on cardiovascular events prediction in asymptomatic FH subjects undergoing statin treatment.
Methods: 102 consecutive asymptomatic FH subjects (45±13 years, 36% men, LDL-C 280±54 mg /dL before treatment) underwent 64 slice CTCA. Cox regression model was used to assess the determinants of CHD events. The model was adjusted for age, classical risk factors, presence of Achilles tendon xanthomata, baseline and on treatment lipids, values of C-reactive protein, coronary calcium scores, coronary plaque type (calcified, mixed or non-calcified) and number of coronary segments with plaques and with luminal stenosis >50%.
Results: During a follow-up of 33±12 months, the rate of cardiovascular events was 6.8% (7 events, 2 acute coronary syndromes and five cases of refractory angina requiring revascularization). The total number of segments with obstruction >50% was the only independent variable associated with CHD events (HR: 3.16, 95% CI: 1.97 to 5.06, $p<0.001$).
Conclusion: Our data suggests that the number of segments with obstruction in CTCA provides predictive information of CHD event risk independently of clinical and laboratory variables, as well calcium scores in asymptomatic FH subjects undergoing statin treatment.

P1486 How many JUPITER eligible patients are there in France?

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Background: In 2008, the results of the JUPITER trial were published, showing among people without cardiovascular disease at baseline, lower rates of mortality and cardiovascular morbidity in the rosuvastatin group compared to placebo. Consequently, the marketing authorisation of rosuvastatin has been extended in Europe. The aim of the present analysis was to estimate how many French subjects could match the JUPITER inclusion criteria, in order to estimate the extra-cost related to the extension of the drug market.
Methods: We used data from a multicentre cross-sectional study on the prevalence of cardiovascular risk factors in the French general population aged 35-75. Participants were selected in 2006-07 by drawing on polling lists and a fasting blood sample was obtained. A direct standardization on age and gender was applied to means and percentages.
Results: The sample was restricted to 1527 men and women aged 50-75 and 60-75, respectively, without lipid-lowering therapy, as younger people and treated dyslipidemic patients were not included in the JUPITER trial. Among them, 6.8% (95% confidence interval: 5.5% - 8.1%, corresponding to 439 000 to 683 000 French people) fulfilled the JUPITER inclusion criteria (mainly C-reactive protein (CRP) $\geq$ 2 mg/L, LDL-c $<$ 3.4 mmol/L, triglycerides $<$ 5.6 mmol/L, no diabetes or cardiovascular disease). Jupiter eligible subjects exhibited lower mean levels of HDL-c (1.33 versus 1.45 mmol/L in people who did not fulfilled the criteria, p=0.001), LDL-c (2.88 vs 3.96 mmol/L, p$<$0.001) and higher median CRP (4.18 vs 1.40 mg/L, p$<$0.001). Smoking tended to more frequent in JUPITER eligible subjects (26.1% vs 17.5%, p=0.064), whereas no difference was observed for hypertension, family history of premature coronary heart disease, metabolic syndrome, or 10-year risk of coronary event (median Framingham risk score: 11.9% vs 12.0%, p=0.123). In the whole sample of 1527 untreated subjects aged 50-75, 20.6% had a 10-year risk of coronary event $\geq$ 20% (corresponding to 1.7 million of French people). If rosuvastatin were initiated in all subjects matching the JUPITER criteria, we would observe a 5.5 to 8.6% increase in the French annual sales revenue related to lipid-lowering drugs (89 to 138 million € if rosuvastatin 5 mg is used).
Conclusion: Among people aged 50-75, without lipid lowering therapy, 6.8% could match the JUPITER criteria leading to an expected 5.5 to 8.6% extra-expenditure if rosuvastatin were initiated in these subjects. Besides, 20.6% of these people could have a 10-year risk of coronary event $\geq$20% and thus should be treated with a statin.

P1487 Efficacy of varenicline therapy in the “board the bus and quit” smoking cessation program: six-month results

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Purpose: Tobacco control centers exist in most of European countries but in many areas they are not yet available, this is particolarly true for Italy. It would be important to set up effective smoking cessation programs, complementary to those offered by the tobacco control centers and aimed to reach smokers unable or unwilling to look for the standard treatment. Aiming to measure the efficacy of an "on the road"- based smoking cessation program, we lauched the "Board the bus and quit" smoking cessation program.
Methods: A regular city transportation bus was branded and, in the last five days of May 2010, it was placed in five different streets or squares of Genoa, Italy. Locations were selected in no traffic zones to maximize the opportunity of meeting walking-by pedestrians. On board the bus three smoking cessation well trained doctors and a nurse were available. The walking-by smokers were asked by two hostesses to exchange their empty cigarette boxes with a free cell-phone holder. Each smoker was then asked to board the bus and meet the staff to have informations about the opportunities of being supported in a quitting smoking attempt. If the bystander was interested in immediately starting a cessation program, the nurse measured the expired carbon monoxide and then gave each smoker the usual depression, anxiety and tobacco dependence scales forms. Finally one of the doctors interviewed each patient, scheduled a quitting date and prescribed the appropriate drug therapy. If not controindicated, Varenicline 1mg BID was primarely choosen. A first group follow-up visit was also scheduled just before the quitting date and weekly group follow-up visits were planned for the three-month drug therapy period. Self reported abstinence was confirmed measuring expired carbon monoxide.
Results: Among hundreds of smokers who asked for informations, 297 accepted to enter the program and received a scheduled quit date and a drug prescription. 149 actually showed up at the first scheduled visit and followed the drug treatment prescription. Six months later, 100 patients were abstinent: 80 (80%) following the entire program, 10 (10%) quitting on their own without any therapy, 10 (10%) following the Varenicline drug therapy but not the follow-up program. Among the 149 prescriptions, 90 (60%) completed the three-month Varenicline 1mg BID scheduled program and were successfully quitters at three months.
Conclusions: The "Board the bus and quit" smoking cessation program six-month results are promising and let us foresee new quit smoking intervention programs complementary to the tobacco control centers standard interventions.

P1488 Prevalence of aortic and mitral valvular calcification as a marker of atherosclerosis for improved cardiovascular risk prediction assessed by computed tomography

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Background: Valvular calcification is considered a manifestation of atherosclerosis. The impact of calcium deposits on cardiac valves on the distribution and characteristics of coronary plaque is unknown. However, calcific aortic valve disease is associated with a 50% increased risk of cardiovascular events.
Objective: The aim of this study was to asses the prevalence of atherosclerotic aortic and mitral valve calcification and to examine the association to traditional risk factors.
Methods: We examined the prevalence of aortic valve calcification (AVC) and mitral valve calcification (MVC) in a large European cohort using the population-based Heinz Nixdorf Recall study cohort. A total of 4083 consecutive asymptomatic patients (aged 45-75 years, mean 59.4$\pm$7.7 years) free of clinically overt coronary heart disease were studied by non-contrast electron-beam computed tomography for the extent of calcification on the aortic valve (AVC) and mitral valve (MVC).
Results: The prevalence of AVC and MVC was 11.2% and 2.6%, respectively. In total, AVC and MVC were more frequent in men compared to women (AVC: 15.2% vs. 7.6%, MVC: 2.8% vs. 2.3%). In different age categories, AVC as well as MVC increased with age (AVC: 45-54 yrs: 2.8%, 55-64 yrs: 9.5%, $\geq$65 yrs: 22.9%, MVC: 45-54 yrs: 0.8%, 55-64 yrs: 1.8%, $\geq$65 yrs: 5.7%). Prevalence of AVC was significantly associated with age, male gender, blood pressure and high levels of LDL-cholesterol. For MVC, the main determinants were age and diabetes.
Conclusion: Our study shows that the risk factors for valvular heart calcification correspond to those for coronary atherosclerosis. Analysis of valvular calcification in computed tomography may improve cardiovascular risk prediction.

P1489 High-risk patients and guideline implementation

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Objectives: The main objective of this study is to raise the standard of preventive cardiology through more lifestyle intervention, good control of cardiovascular risk factors and optimal use of prophylactic drug therapies in order to reduce the risk of developing cardiovascular disease in high risk individuals. One key point in the protocol is to asses the efficiency of treatment in EuroAspire III patients through optimizing the medication according to current guidelines, so that every patient receives the appropriate cardiovascular prevention treatment.
Design and metod: We conduct a prospective study of 18 months on 325 patients; 55.9+8.7 years old, 38.2% males, who took part in EuroAspire III Primary Care. They were identified by their drug treatment: antihypertensive drug therapy and/or; lipid-lowering drug therapy and/or; diabetes therapies (diet and/or oral hypoglycemic and/or insulin). The primary care physicians were trained by an interdisciplinary team (cardiologist, diabetologist, and nephrologist) to reinforce lifestyle changes (European Prevention Guideline) and to optimize medication according to each patient. So, we define the "coaching model of primary care" as 3 consecutive patient visits (every 6 months) to the primary care physician offices, consisting in lifestyle advice and medical recommendation update.
Results: The weight has decreased from 78.78$\pm$16 to 75$\pm$15.03 kg (p.0018); the body mass index has decreased from 28.64$\pm$5.3 to 27.87$\pm$4.89 (p.054); the male's waist circumference (cm) has decreased from100.2$\pm$10.9 to 98.89$\pm$11.3 (p.353) the women's waist circumference (cm) has decreased from 93.75$\pm$13.6 to 91.71$\pm$12.57 (p.119); the total cholesterol (mg/dl) has decreased from 214.39$\pm$44.17 to 203.8$\pm$42.26 (p$<$0.001) the LDL cholesterol (mg/dl) has decreased from 127.78$\pm$37.51 to 118.5$\pm$35.51 (p$<$0.001); the HDL cholesterol (mg/dl) has decreased from 56.14$\pm$15.38 to 54.20$\pm$14.48 (p.098); the triglycerides has increased from 128,5$\pm$48,5 to 140$\pm$49,5 (p.160). The number of patients who reached the target for total cholesterol has increased from 60 to 198. The number of patients who reached the target for LDL cholesterol has increased from 32 to 160.
Conclusions: Our results show the importance of lifestyle changes throw the multidisciplinary intervention on this kind of high risk patients. The empowerment in primary care practice is the key of long term patients risk reduction.

P1490 Individualized cardiac risk assessment: subclinical atherosclerosis and the 30 year Framingham risk score

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Purpose: Ten year cardiovascular (CV) risk prediction algorithms are limited by their short duration and inability to individualize cardiovascular risk assessment. A 30 year risk prediction model using the Framingham offspring cohort has been published using established CV risk factors. Carotid intima media thickness (CIMT) measurement provides incremental risk prediction to the 10 year Framingham risk score (FRS), but it is unknown if it adds incremental information to the 30 year FRS.
Methods: Subjects (n=340) undergoing CV risk evaluation from a primary care practice who underwent CIMT evaluation were used in the analysis. A 30 year FRS was calculated for the prediction of hard events (coronary death, myocardial infarction, and fatal or nonfatal stroke) and full events (hard events and coronary insufficiency, angina, transient ischemic attack, claudication, and congestive heart failure). Full and hard events were calculated with lipids or body mass index (BMI) resulting in 4 models. Subjects were stratified into low (0-11%), intermediate (12-40%), or high (>40%) risk groups. The incidence of high (plaque or CIMT >75th percentile for age, race, gender), intermediate (25th–75th percentile) and low (CIMT <25th percentile) risk CIMT result was then determined in each risk group.
Results: The mean 10 year FRS was 4.7±3.9. Men had a higher 10 year FRS than women (5.9±4.0 vs. 1.6±1.2, respectively; $p<0.0001$). In the 10 year FRS model, 1 of every 2.3 CIMT results led to risk reclassification. Mean 30 year risk scores for the population in the lipids models were 31.8±12.5% for full CV events and 19.8±9.7% for hard CV events. Mean 30 year risk scores for the population calculated with BMI were 37.0±14.0% for full events, and 24.0±11.5% for hard events. In the full and hard events model using lipids, 1 of every 1.9 and 1 of every 2.1 CIMT examinations led to risk reclassification, respectively. In both models using BMI, 1 of every 2.0 carotid ultrasounds changed individual risk. Excluding high risk scores, the percentage of individuals who were reclassified to higher risk classification with CIMT was similar between the 10 year FRS (41.4%) and the full event 30 year risk models (37.1%) and the hard event model (39.9%). A similar percentage of individuals were reclassified to lower CV risk with CIMT results in the 10 and 30 year methods (10 year FRS: 8.2% vs. Full: 14.5% vs. Hard: 11.7%).
Conclusions: In a primary care population evaluated for cardiovascular risk, CIMT reclassifies risk category in approximately 1 of every 2 individuals who are low to intermediate risk by either the 10 or 30 year FRS.

P1491 Reinforced primary care improved the adherence to lifestyle change recommendations in EuroAspire III Romania follow-up

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Purpose: To evaluate if reinforcing the primary prevention measures influenced the patient's knowledge about actual levels and targets for cardiovascular risk factors according to ESC 2007 Prevention Guidelines in asymptomatic high risk patients included in the first EuroAspire III Follow-Up.
Methods: We followed-up 325 patients (age 56±9 years, 62% women) out of 503 asymptomatic high risk patients included in EuroAspire III Romania Primary Care. These patients were evaluated every 6 months for a period of 18 months of follow-up by general practitioners (GP) that participated in a professional training performed by diabetologists and cardiologists and have been advised to reinforce lifestyle changes and to optimize drug therapy in order to reach the targets mentioned in the current guidelines.
Results: A significant improvement was observed between baseline evaluation and 18 months intervention in the percentage of asymptomatic high risk patients that respected the lifestyle change measures: eating more fruits and vegetables (86.2% versus 95.1%, $p<0.001$), reducing the sugars intake (70.8% versus 82.4%, $p<0.001$), weight loss following dietary recommendations (65.9% versus 66.9%, p=0.002), increasing physical activity by following a health professional instructor (3.4% versus10.2%, $p<0.001$) and by performing more daily physical exercise (64.6% versus 85.8%, $p<0.001$). Although recommendations about nutrition are the core of high risk management, we didn't notice significant improvement in reducing salt intake (92.6% versus 96%, p=0.09), reducing fat intake (93.2% versus 94.4%, p=0.06), reducing calorie intake (76.9% versus 81.8%, p=0.1), reducing excessive alcohol consumption (67.1% versus 67%, p=0.9). After intervention period, 1:2 patients quitted smoking (p=0.012) only due to the primary care physicians advice (no drugs or nicotine replacement were used). We also observed a reduction in the number of daily smoked cigarettes (18.23±9.20 versus 14.23±8.98, p=0.096) in patients that remained active smokers during the study.
Conclusions: Preventive intervention, conducted by general practitioners, improved the adherence to lifestyle change recommendations, even though the guidelines targets are far from being achieved. The data highlighted on one hand that it is a strong need to intensify the primary prevention measures and on the other hand that "reinforced" primary care represents a step forward from usual care and a model of changes applicable in other centers.

P1492 Optimal carotid IMT cut-off value for metabolic syndrome and coronary artery disease compared to validated Greek air force healthy subjects

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Purpose: To identify an optimal cut off value which best predicts Metabolic Syndrome (MetS) and coronary artery disease (CAD).
Methods: We evaluated intima media thickness with carotid ultrasound measurements in 141 patients (mean age: 53.5±12 years) divided into three groups, patients having metabolic syndrome (n=40) who fulfilled the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, patients with coronary heart disease (CAD) established by coronary angiography (n=52) and normal subjects (n=49) with neither metabolic syndrome, nor coronary heart disease. The latter group consisted of Greek air force pilots, who underwent annual laboratory, clinical and physical examination with treadmill test and have certification of healthy status.
Results: ROC curve analysis indentified the same optimal IMT cut off value equal to 0.80 mm with best combination of sensitivity (=100% and 95%) and specificity (=77.5% for both) for both entities (fig.1). Univariate logistic regression analysis revealed that IMT >0.80 mm was a predictor for CAD and metabolic syndrome (Odds Ratio, OR= 33.0 with 95% CI 10.9-99.0, OR=18.0 with 95% CI 6.1-52.6, respectively). IMT cut-off value remained an independent predictor for CAD after adjustment for age (Odds Ratio, OR=21.55 with 95% CI 6.64-69.95). IMT remained an independent predictor for MetS after adjustment for age (Odds Ratio, OR=18.8 with 95% CI 5.9-59.6).

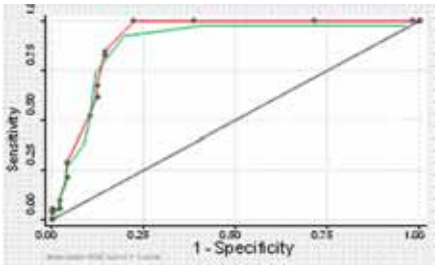

Figure 1

Conclusions: Carotid IMT value 0.80 mm which demonstrates both relatively high sensitivity (=100% and 95%) and specificity (=80% for both) for CAD and MetS, suggesting that IMT can be used as a clinically useful test for predicting the presence of both entities.

P1493 Relationship between coronary angioplasty laboratory volume and short-term outcome after hospital discharge

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Post-procedural mortality is often used as a surrogate for quality in performance evaluation of medical and surgical services. The objective of this study was to exam the relation between hospital volume and risk-adjusted short-term mortality in percutaneous coronary intervention patients. This is a retrospective analysis of the National Health Insurance Review Agency.The study data set included the patient level data as well as all the ICD-10 diagnosis and procedure codes that were recorded in the National Health Insurance Review Agency. The risk factors were adjusted with the logistic regression model. Another cardiovascular severity risk factors such as diabetes, hypertension, hyperlipidemia were used to classify patents severity. The patients mortality was evaluated among patients who underwent PCI between 2003 and 2004 at low (less 200 cases/year), medium (200~400 cases/year), and high (400 cases or more/year) PCI volume hospitals in Korea. The final risk-adjustment model consisted of nine risk factors for 7-day mortality and twelve risk factors for 30-day mortality. These factors were found to have statistically significant effects on patient mortality. The c-statistic and Hosmer-Lemeshow $\chi 2$ goodness-of-fit test showed that the model's performance was good. A total number of 60 low-volume hospitals (9,071 patients) and 27 medium-volume hospitals (15,623 patients) and 15 high-volume hospitals (19,669 patients) were identified. Crude 7-day mortality rate was 0.9% in low-volume hospitals, and 0.7% in medium-volume hospitals and 0.6% in high-volume hospitals. 30-day crude mortality rate was 1.4%, 1.1%, and 1.0% in each volume hospitals. And if, high-risk group patients had treated by PCI in high-volume hospital, may showed relatively low mortality rate compared with patients treated in low-volume hospitals at 7 and 30 days after admission (OR 2.759, p=0.0396; OR

1.953, p=0.0378). Good model performance showed that insurance review data can be used for comparing hospital mortality after adjusting for the patients' risk. So, PCI patients also showed volume-outcome relationship in Korea as shown in other country from previous studies. Compared to high-volume hospital, low-volume hospital had higher 7-day and 30-day mortality rates and this relationship more apparent in high-risk group patients.

P1494 Preventing antracyclines-induced cardiotoxicity in breast cancer patients

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Background and aim: Anthracyclines are commonly used antineoplastic drugs but their utility is tempered by a dose-dependent risk of cardiotoxicity leading to severe arrhythmias and congestive heart failure. Research has focused on early monitoring, risk stratification and prophylactic use of cardioprotective drugs.
Methods: We prospectively analysed 20 patients treated with epirubicin-containing adjuvant regimens for stage II breast cancer. Patients were evaluated and monitorised by a mixed team, oncologist and cardiologist during one year of treatment. Patients received an average number of 5.6±0.82 cycles of cyclophosphamide plus epirubicin (epirubicin 75mg/m^2, cyclophosphamide 600mg/m^2). Patients were assigned to an interventional arm (n=10) which received prophylactic low-dose ACEI (perindopril 2.5-5mg/day or trandolapril 0.5mg/day) and an observational arm (n=10) with no associated ACEI treatment. Cardiac assessment was carried out at baseline, after administration of half the total (1.000mg/m^2) anthracycline cumulative dose, at the end of chemotherapy and 1 year after chemotherapy by clinical evaluation, electrocardiography and transthoracic echocardiography.
Results: Mean left ventricular ejection fraction (LVEF) assessed by echocardiography were: interventional arm–66.90±4.88% at baseline, 63.50±4.47% after administration of half the total anthracycline cumulative dose, 60±2.21% at the end of chemotherapy and 65.60±4.06% one year after chemotherapy; observational arm–68.80±3.73% at baseline, 65,30±3,46% after administration of half the total anthracycline cumulative dose, 60.10±1,79% at the end of chemotherapy and 56.50±2.22% one year after chemotherapy. The decrease in 1-year LVEF was 1.3±2% (p=0,5258) in the interventional arm and 12.30±1.37% (p<0.0001) in the observational arm. Echocardiographic examinations at baseline and 1 year after chemotherapy revealed a significant decrease in E/A ratio from 1.17±0.2 to 0.8±0.4 in the observational arm suggesting diastolic dysfunction. Only the patients in the observational arm developed adverse cardiac events including congestive heart failure and/or arrhythmias and needed cardiac care (n=3).
Conclusions: In order to prevent cardiac events, patients undergoing anthracycline treatment need regular monitoring of LVEF prior to, during and after treatment. Currently there is no universal monitoring guideline. In our study prophylactic ACEI therapy was associated with a smaller decrease in LVEF. Our study shows that breast cancer patients undergoing antracyclines therapy are protected against adverse cardiac events if they also receive low-dose ACEI.

P1495 Bayesian analysis of rosuvastatin in the prevention of cardiovascular disease

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Purpose: Results from the JUPITER trial indicate a substantial benefit using rosuvastatin in an intermediate risk population for the prevention of cardiovascular events. However, the extent of benefit rosuvastatin in the prevention of cardiovascular disease in intermediate risk remains controversial. We sought to examine the magnitude of benefit by using Bayesian analysis.
Methods: A total of 17802 patients from the JUPITER trial were analyzed with both a null prior probability, and compared with the CORONA trial, in which patients had known systolic heart failure, but similar baseline LDL and hsCRP values. Aggregate Bayesian probabilities of benefit and magnitude of therapeutic effect were calculated.
Results: For the primary endpoint of first major cardiovascular event, there was a 99% probability of benefit, and a 70% chance of at least a 20 percent OR benefit in the Jupiter trial. The CORONA primary endpoint had a 75.7% likelihood of benefit. Posterior probabilities combining both these trials indicate a 93.9% benefit in non-fatal MI, and 94.0% probability of benefit in total MI. There was a trend towards benefit in overall mortality, with a 85.4% probability of odds ratio benefit.
Conclusions: Independent Bayesian analysis of the JUPITER trial supports the use of rosuvastatin in intermediate risk populations. Even when using the CORONA trial population with known cardiovascular disease and lower rosuvastatin dose as a prior probability, there remains a strong trend towards benefit. These results imply generalized benefit of rosuvastatin, even when tempered by higher risk populations.

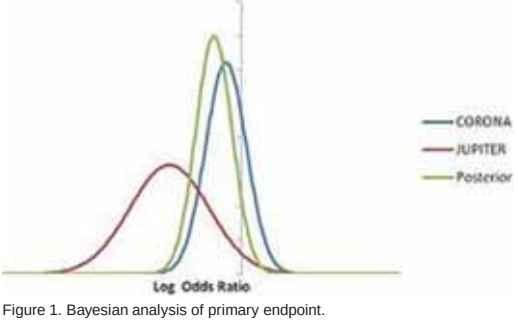

Figure 1. Bayesian analysis of primary endpoint.

P1496 What do general practitioners know about total cardiovascular risk assessment tool SCORE

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Objectives: To evaluate the knowledge of medical practitioners on total cardiovascular (CVD) risk assessment and use of the European Systematic COronary Risk Evaluation- SCORE Charts in clinical practice.
Methods: During the Workshop organized as part of the scientific activities of the Conference on Cardiovascular Diseases Prevention a survey questionnaire focused on the practical use 0f SCORE risk assessment scale. In total 60 medical practitioners from different nationalities participated in the anonymous survey with mean duration of working at the position of primary health care physician being 5.6±6.4 years.
Results: Eighty percent of the responders don't use the SCORE scale, only 10.7% were using it.66.6% don't know about the SCORE instrument. Among the SCORE components,74% of the physicians who are aware of the tool correctly reported age, gender, blood pressure and cholesterol; 63%also correctly reported smoking; 50% wrongly mentioned glucose and CVD in family history, meanwhile 44% wrongly mentioned the overweight, obesity and waist circumference. Other risk factors were wrongly reported by 17% of the doctors. Patients with diabetes mellitus, with three or more risk factors were classified as having high total CVD by 80% 0f the practitioners. Symptom-free patients with a very high level of single risk factor were classified as having high CVD risk by 20% of the participants only. Up to 54% of the responders had risk factors themselves. The interest in educational programs for doctors, focusing on SCORE use in clinical practice, was very high (90%).
Conclusion: The study demonstrated inadequate knowledge of the practitioners on the methodology of total CVD risk assessment, an important instrument of primary prevention. The doctors attending medical educational programms showed better levels of knowledge.

P1497 Coronary heart disease treatment in Bulgaria - data from EUROASPIRE III trial

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The EUROASPIRE III (European Action on Secondary and Primary Prevention by Intervention to Reduce Events III) trial was aimed to follow the doctors' keeping to the rules of ESC Guidelines for cardio-vascular prevention. For the first time Bulgaria took part in this trial participating in its 2 arms – patients with coronary heart disease (CHD) and high risk patients. The studied patients of the CHD group were patients with proved coronary artery disease treated in 3 capital hospitals and followed after the discharge by cardiologists and general practitioners. The aim of this analysis was to determine the therapeutic schemes used for studied patients on the 6-th month after hospital discharge.
Materials: The protocol of EUROASPIRE III trial comprised a standard questionnaire used by all participating into the trial countries to determine the patient's health status and to register the drug therapy during the hospital stay and after that.
Results: 711 patients (68% men and 32% women) with proved CHD (acute MI, coronary intervention or CABG) were included in the initial screening. 11% of all patients were younger than 50 years of age and 33% were older than 70 years of age. 538 out of all screened patients assisted the interview. 85% of patients were followed up by cardiologist and 77% - by GP. The interview was carried out mean 1.3 years after the hospital discharge. The mean blood pressure values were 138/83.5 mmHg. The mean values of the total cholesterol were 5.01 mmol/L, the mean values of LDL-cholesterol were 3.2 mmol/L, the mean values of HDL-cholesterol in men were 1.1 mmol/L and in women they were 1.18 mmol/L, the mean values of triglicerides were 1.56 mmol/L. 85,5% of the interviewed patients were treated with aspirin and other group of antithrombotic agents. The distribution of active drug treatment was as follows: beta blockers were used in 82.3% of patients, ACE inhibitors - in 61.8%, ARB - in 5%, calcium blockers - in 22.3%, diuretics - in 43.4%, other antihypertensive drugs were used in 3.2%. 59.1% of patients were treated with statins and with fibrates – 4.3%. Metabolism modulating drugs were used for 16.2% of patients and nitrates – for 58.3%.

Conclusions: High risk patients with CHD in Bulgaria were treated with a larger number of drugs than the other European countries. But this trend was not consistent with the ESC Guidelines for prevention of future cardio-vascular events because of the lower use rate of statins and antithrombotics at the expense of nitrates and metabolic modulators.

P1498 Rapid reductions in left ventricular mass following a community based 12-week prevention programme are partially predicted by change in fat depots

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Purpose: Adiposity and left ventricular mass (LVM) are both related with cardiovascular (CVD) risk. In this study, we aimed at jointly investigating LVM and fat depots across a novel CVD prevention programme in European and South Asian patients.
Methods: Seventeen men (8 European, 9 South Asian age 69±4 yr) with a 10 yr cardiovascular risk >20% but without prior ischemic heart disease were enrolled in a nurse-led multidisciplinary family-centred vascular prevention programme based in the community over 12 weeks [1]. LVM was assessed using 3-dimensional echocardiography before and after the programme. Total body fat, subcutaneous and visceral fat were determined using whole body magnetic resonance (MR) imaging, epicardial fat using echocardiography, while ectopic fat in liver (LF) and pancreas (PF) were determined using MR spectroscopy.
Results: LVM was significantly reduced by the programme (table, $p<0.001$). The effect was not attenuated when adjusting for blood pressure. All fat depots correlated positively with LVM ($p<0.05$ for LF and PF, $p\leq0.001$ for the rest). Adjusting for total fat or subcutaneous fat reduced the beneficial effect of the programme to –2.9gr and adjusting for visceral fat to –4.7gr, while adjusting for other fat depots did not affect the beneficial impact on LVM.

Effect of 12 week prevention programme

Measure	Baseline	Change	P value
LVM, g	117.8 (23.9)	–6.4 (–8.8, –4.0)	<0.001
LVM adjusted for BP, g	116.9 (23.1)	–6.2 (–8.5, –3.9)	<0.001
Systolic blood pressure, mmHg	134.3 (15.4)	–2.2 (–9.3, 4.9)	0.55
Total fat, L	27.5 (5.2)	–3.0 (–4.4, –1.6)	<0.001
Subcutaneous fat, L	19.4 (3.6)	–1.9 (–2.7, –1.1)	<0.001
Visceral fat, L	4.4 (1.6)	–0.6 (–1.0, –0.2)	0.003
Epicardial fat, mm	7.1 (1.3)	–1.3 (–1.5, –0.8)	<0.001
Hepatic fat, arbitrary units	2.3 (1.7, 4.6)	–1.1 (–1.4, –0.7)	<0.001

Data are means (SD) or median (IQR) or means (95% CI) for change.

Conclusions: In this bi-ethnic group, we observed marked improvements in left ventricular mass following a brief individualised programme. These improvements, which were partially related to changes in visceral and other fat depots, were more immediate and in excess of those observed in other prevention programmes.
1. Lancet. 2008 Jun 14;371(9629):1999-2012

P1499 Durability of lifestyle change and cardiovascular disease (CVD) risk factor reductions-1 year outcomes from a community based CVD prevention programme for high risk patients in Ireland

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Purpose: A common limitation of prevention programmes is the fall off in adherence to lifestyle change in the longer term. This study examines the 1 year outcomes of a community based CVD prevention programme in terms of achieving the primary end points for lifestyle, risk factor and therapeutic goals recommended by the European Society of Cardiology.
Methods: Increased CVD risk patients (Heart SCORE ≥ 5%, type 2 diabetes, peripheral artery disease) and their family members/partners were invited to attend a 16- week programme consisting of a professional multi-disciplinary (nurse, dietician, physical activity specialist) lifestyle intervention, with appropriate risk factor and therapeutic management in a community setting. Risk factors such as blood pressure, lipids, smoking, blood glucose, BMI (body mass index), waist circumference and physical activity levels were assessed at baseline and at 1 year.
Results: Data on patients and family members/partners who attended both initial assessment (IA) and at 1 year (1-yr) were analysed.
Conclusions: The preliminary data from this ongoing lifestyle intervention programme suggests that the targeted benefits observed at the 16 week follow up persist at 1 year, showing that the programme has a sustained effect. More marked reductions in CVD risk factors are recorded in the patient group than in partners. This may be related to differences in risk perception in the two groups.

P1500 Ankle brachial index predicts one year mortality and cardiovascular events after non-cardiovascular major surgery

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Objectives: Patients withcoronary (CAD), cerebrovascular or peripheral artery disease (PAD) are athigher risk of cardiovascular (CV) events. CAD and cerebrovascular disease patientsare usually easily identified. In contrast PAD patients are often asymptomatic.This study assessed the incremental prognostic value of the ABI as a screeningtool for PAD to predict long term events after a major non cardio-vascular surgery.
Methods: In 504 consecutive patients (age 69±11 yrs), we measured the ABIpreoperatively. An ABI <0.90 or >1.40 was considered abnormal. 490 were included in the one yearfollow-up. Patients were divided into 3 groups: 89 with clinical cardiovasculardisease (CVD) (including clinical PAD), 59 without clinical CVD but withabnormal ABI (asymptomatic PAD), and 342 healthy subjects (no clinical CVD,normal ABI). Troponin levels were analysed on two consecutive days aftersurgery. The outcome was composite combining death, CVD death, non fatal acutecoronary syndrome, stroke or transient ischemic attack, overt heart failure andlimb ischaemia during the year after surgery. Multivariateregression analyses, adjusted for conventional risk factors, history of renalor cardiac failure evaluated the association between abnormal ABI and outcome. Survivalswere calculated by Kaplan Meier method and compared using log rank.
Results: The outcome was recorded in 55 (11.1%) cases.Asymptomatic PAD (Odds Ratio [OR]: 2.83; 1.36-5.76; p=0.005) andclinical CVD (OR: 2.85; 1.41-5.76; p=0.003) were independent risk predictors for the outcome. Theone-year outcome-free survival rates for healthy, asymptomatic PAD and clinicalCVD patients were respectively at 97.6%, 84.1% and 83.9% ($p<0.0001$).Postoperative troponin-i elevation was also associated with an impairedsurvival, 76.3% versus 95.4% ($p<0.0001$). The worst one year survival (50%)was described in patients with asymptomatic PAOD and troponin elevation.
Conclusion: Asymptomatic PAOD detected by ABI presents aprognostic value to predict mortality and cardiovascular events during the yearafter major non-cardiovascular surgery. Asymptomatic PAD patient withpostoperative troponin elevation presented a high risk of long-termcardiovascular events.

P1501 Impact of the implementation of worksite wellness program for cardiovascular disease prevention

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Introduction: Cardiovascular diseases (CVD) are the major causes of mortality and accounts for much of the companies' medical costs and absenteeism. Experience has shown that workplace wellness programs are important strategies to prevent the major risk factors for CVD and stroke.

Abstract P1496 – Table 1. Summary of outcomes

	Patients (IA) n=53	Patients (1-yr) n=53	p-value	Partners (IA) n=28	Partners (1-yr) n=28	p-value
Mean (sd) BMI (kg/m^2)	32.2 (6.6)	31.1 (6.1)	<0.0001	28.4 (5.6)	27.7 (5.1)	0.007
Mean (sd) Waist Circumference (cm)	109.0 (14.7)	105.7 (14.4)	<0.0001	100.6 (18.1)	97.5 (17.8)	0.0002
Mean Mediterranean Score, max = 14	4	10	<0.0001	4	10.5	0.0001
% Achieving physical activity targets	16.3	59.2	0.001	24	68	0.001
% Smoking	10.6	4.3		11.1	11.1	
% Blood Pressure to target <140/90mmHg or <130/80mmHg for coronary, vascular and/or diabetes	62.5	85	0.008	84	84*	
% Lipids to target Total cholesterol<5mmol/L and LDL <3mmol/L	31.7	70.7	0.001	37.7	45.8*	
% Prescribed Cardio-protective Medication -Antiplatlet	26.4	39.6		21.4	35.7	
Statins	43.3	77.4	0.001	17.9	46.4*	
ACE inhibitors/ARBs	38.1	47.6		24	28	
Beta blockers	22.6	45.9		10.7	17.9	
Calcium channel blockers	22.6	41.5	0.037	10.7	21.4*	

*Not significant.

Objectives: To evaluate the results of two years of program implementation for CVD prevention at a company in Brazil in the following: 1) the control of diseases covered by the program, 2) the influence of the actions on the Framingham risk score (FRS), and 3) the absenteeism.
Methods: The program began in November, 2007. It was a comprehensive program which included the following: tobacco cessation and prevention, regular physical activities, stress management/reduction, early detection/screening, nutrition education and promotion, weight management, disease management, education on cardiopulmonary resuscitation and automated external defibrillator training. The employees were submitted to: 1) detection/treatment of risk factors 2) calculation of FRS. After that, they were invited to attend monthly meetings on prevention, nutrition and treatment. The rates of absenteeism were calculated based on a certificate of entry and rates of lost workdays by the International Classification of Diseases.
Results: 286 subjects were monitored, mostly men between 40 and 50 years who were sedentary, distributed as follow: 127 (44%) with dyslipidemia, 95 (33%) hypertensives, 31 (11%) with diabetes, 15 (5%) obesity without comobidities and 18 (7%) with other pathologies, such as valvular heart disease or arrhythmias. After the program implementation the percentual of hypertensive subjects with BP under control ranged from 50% to 85%. The dyslipidemic and diabetic subjects were intensively monitored. All these actions resulted in modifying the risk profile of this population, as the following: compare to the beginning of the program, the percentage of employees at low risk rose from 65% to 83%. Those with moderate and high risk decreased from 18% to 13% and 17% to 4%, respectively. In relation to absenteeism, there was a reduction of lost workdays rate due to CVD from 2.60% to 1.33% ($P<0.05$).
Conclusion: The implementation of worksite wellness program for CVD prevention promoted in two years a significant change in the risk profile of the population being monitored, typically at high risk of CV events. These data, gathered, resulted in a significant reduction of lost workdays due to cardiovascular diseases. Prevention programs at the workplace with simple identification and control of conventional risk factors adds many benefits at low costs

P1502 Have rapid socioeconomic changes influenced awareness of blood pressure in Poland?

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Purpose: The contribution of elevated blood pressure (BP) to cardiovascular risk is widely recognized. Arterial hypertension (AH) and its complications are among the most frequent reasons for medical assistance and hospitalization. It also represents one of the most important health and social problems in Poland. The unawareness of BP leads to the smaller efficacy of prevention and treatment of AH. To gain the epidemiological situation in Poland regarding AH several representative surveys were conducted.
Methods: The data presented are based on four nationwide surveys on a representative sample of adult Poles: NATPOL 1994 (2.080 respondents; limited only to a questionnaire), NATPOL 1997 (1.667 persons; a questionnaire and 3 measurements of BP on one visit), NATPOL 2002 (3.051 persons; a questionnaire and 3 BP readings – repeated on three separate occasions, if necessary) and WOBASZ 2005 (13.545 persons; a questionnaire and 3 BP readings – repeated on three separate visits, if necessary). In all studies, except for other questions, respondents were asked the same question: "Do you know your own BP?".
Results: The awareness of one's own BP decreased from 1994 to 2002 and then slightly increased in 2005. In the four surveys the BP awareness among men was 65% (1994), 60% (1997), 54% (2002) and 59% (2005); among women the corresponding numbers were: 77%, 71%, 64% and 69%. The awareness of BP differed according to the education level of respondents and place of residence. It was significantly better among higher educated compared to lower educated persons [secondary or higher educated: 75% (1994), 74% (1997), 68% (2002) and 73% (2005); primary educated: 68% (1994), 59% (1997), 51% (2002) and 56% (2005)]. We also observed significantly better BP awareness among respondents from large cities [72% (1994), 73% (1997), 67% (2002) and 70% (2005)] than from small cities or villages [73% (1994), 64% (1997), 67% (2002) and 61% (2005)].
Conclusions: The significant and rapid decrease in the awareness of own blood pressure was observed among adult Poles in the years 1994-2002 i.e. during the first decade of transition into market economy. Then, a slight increase in 2005, nearly reaching the levels from 1997, was noted. Constantly the awareness of blood pressure was much worse in men than in women, in lower educated persons and in residents of small cities and villages. These results, being most significant in people representing lower social status, emphasise the need for intensification of preventive measures.

SECONDARY PREVENTION: INTERVENTIONS AND OUTCOMES

P1503 HIV-infected status is associated with an increased recurrence of acute coronary syndrome. Final results of long term follow up in the PACS-HIV study

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Purpose: The PACS-HIV study was designed to determine the 3-year prognosis of acute coronary syndrome (ACS) in HIV-infected patients (HIV+) as compared to HIV-uninfected patients (HIV-) in a prospective observational study. We report here the long term 3-year follow-up.
Methods: We enrolled consecutively 103 HIV+ and 197 HIV- patients with a first episode of ACS matched for age (± 5 years), sex, and type of ACS. The primary endpoint was the rate of major adverse cardiac and cerebral events (MACCE), comprising cardiac death, recurrent ACS, recurrent coronary revascularization, and stroke.
Results: The mean age at enrolment was 49.0±9.4 years and 94% were men. At admission, coronary risk factors were well balanced between the 2 groups except for a higher rate of illicit drug used and hypertriglyceridemia in the HIV+ group. The GRACE risk score was low and not different (82±18 versus 85±19, P=0.18). The extent and severity of angiographic coronary artery disease did not differ between groups at the index ACS. Multivessel disease was present in 41 (41%) HIV-infected and in 76 (39%; P=0.96) HIV-uninfected patients. MACCE at 3-year are depicted in the Table. Stratified multivariable Cox model showed that the only factor associated with the recurrence of ACS was HIV status with HR 7.9 for HIV+ versus HIV- (95% CI, 1.2-50.6, P=0.03).

MACCE at 36-months follow up

	HIV-infected group (n=103)	HIV-uninfected group (n=195)	Univariate Hazard ratio [95% CI]*
Major adverse cardiac and cerebral events	17 (16.8†)	29 (15.1†)	1.4 [0.7-2.6]
Cardiovascular death	2 (3.0†)	3 (1.6†)	2.0 [0.4-9.9]
Recurrent acute coronary syndrome	12 (11.9†)	11 (5.8†)	3.4 [1.3-8.8]
Recurrent coronary revascularization	12 (11.8†)	24 (12.6†)	1.1 [0.5-2.2]
Stroke	0 (0.0†)	3 (1.0†)	–
Target lesion revascularization	8 (7.8†)	17 (9.0†)	0.9 [0.4-2.1]
Target vessel revascularization	11 (10.8†)	20 (10.5†)	1.1 [0.5-2.3]

*CI: Confidence interval. Values expressed as n (%). †Kaplan-Meier estimates.

Conclusions: At long-term follow-up, HIV-infected patients had a higher rate of ACS recurrence, despite similar coronary risk factors, clinical, and angiographic features at baseline of a first episode of ACS as compared to HIV-uninfected patients.

P1504 Exercise training vs. PCI/stenting in stable coronary artery disease: long term effects on antiatherosclerotic mediators

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Background: In patients with stable coronary artery disease (CAD) regular exercise training (ET) can improve the patient's endurance, symptoms and myocardial perfusion as compared to medical treatment. Beside this the rate of cardiovascular events can be reduced.
The antiatherosclerotic hormone adiponectin is produced by the adipose tissue and improves endothelial dysfunction. Patients with CAD exhibit an adiponectin deficiency.
Aim of this study was to investigate the long term influence of regular ET compared to PCI/stenting on antiatherosclerotic and endothelial factors in patients with stable CAD.
Method: 103 patients with CAD and proven exercise induced ischemia were randomly assigned to a training (T, n=57) and a PCI/stenting (S,n=46) group. Both groups received optimized medical treatment. At the beginning and at 6, 12 and 24 month the serum concentration of adiponectin, ICAM and VCAM was evaluated. In addition the mRNA expression of the adiponectin type I receptor in leucocytes was quantified.
Results: The event free survival after two years was 63% in the training-group vs. 40% in the group with PCI/stenting (p=0.037). After 6 month of training patients in the training group showed a significant increase (1.5 fold baseline) of adiponectin concentration as compared to the control group ($p<0.05$). The con-

centration remained increased at 12 and 24 month. Beside this an increase of the type I adiponectin receptor at 6 month in both groups with further increase at 12 and 24 month ($p<0.05$ vs. baseline, p not significant T vs. S) was detected. The VCAM concentration in the training group decreased by 10% (12 + 24 month, $p<0.05$ vs. baseline). Measuring ICAM showed neither significant differences between the two groups nor between the different time-points.
Conclusion: Regular exercise training additional to an optimized medical treatment leads to a significant increase in circulating adiponectin levels in patients with coronary artery disease as compared to PCI/stenting. This remains increased even in the long term outcome of 2 years.

P1505 Impact of diabetes on LDL-cholesterol target achievement in patients with cardiovascular disease in clinical practice in Europe and Canada: results of the dyslipidemia international study

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Background: Chronic statin treatment is well established for patients with dyslipidemia and high risk for subsequent cardiovascular events and its use is widespread. Patients with documented cardiovascular disease (CVD) and diabetes are at extraordinary risk for subsequent events. Little is known about the impact of co-existing diabetes on achievement of recommended lipid targets in CVD patients in clinical practice.
Methods: Between June 2008 and February 2009, 2,987 primary care physicians, cardiologists, endocrinologists and internists in 11 European countries and Canada enrolled 22,063 consecutive statin-treated outpatients into DYSIS (Dyslipidemia International Study) to assess the prevalence of dyslipidemia while on chronic statin treatment. ESC recommendations were used to classify patient's risk and define the LDL-C goal. We compared the level of LDL-C goal achievement of CVD patients with and without diabetes.
Results: A total of 11,520 patients had known CVD, of whom 4471 (38.8%) had diabetes mellitus. Patients with CVD + Diabetes were older, more often female, more often were obese and more often reported sedentary lifestyle. They had a higher prevalence of heart failure than patients without diabetes. Diabetics were more likely to be treated with simvastatin as with other statins. Patients with CVD and Diabetes more often reached the guideline recommended target of LDL-Chol $<$ 100 mg/dl in clinical practice. The co-morbidity of diabetes in CVD was an independent predictor of LDL-Chol goal achievement (OR 1.39, $p<0.01$).

	CVD + Diabetes n=4,471 (38.8%)	CVD w/o Diabetes n=7,039 (61.2%)	p-value
Age (years)	69	68	<0.01
Female Gender	32.7%	30.7%	<0.05
BMI $\geq$30 kg/m^2	44.9%	24.8%	<0.01
Ischemic heart disease	46.1%	34.5%	<0.01
Cerebrovascular disease	21.5%	18.6%	<0.01
Peripheral artery disease	27.1%	17.6%	<0.01
Heart Failure	23.1%	14.8%	<0.01
Sedentary Lifestyle	58.5%	47.4%	<0.01
Statin = Simvastatin	49.9%	46.7%	<0.01
Ezetimibe	12.3%	11.9%	0.56
LDL-Chol at goal ($<$100 mg/dl)	62.0%	55.8%	<0.01

Conclusion: Patients with CVD and diabetes were more likely to reach the recommended LDL-goal as compared to patients without diabetes. Within CVD, diabetes was an independent predictor with a 39% higher chance to reach LDL-C $<$ 100mg/dl in clinical practice.

P1506 Blood pressure related risk for vascular events and mortality differs according to localization of vascular disease and presence of type 2 diabetes mellitus

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Background: Recent trials and observational studies have challenged the notion that "lower is better" for blood pressure in relation to vascular events and mortality in patients with vascular disease or type 2 diabetes mellitus, while practice guidelines currently recommend to lower blood pressure to below 130/80 mmHg in these patient groups.
Purpose: To assess the effect of systolic blood pressure (SBP) level on the occurrence of cardiovascular events and mortality in patients with coronary artery disease, cerebrovascular disease, peripheral artery disease or type 2 diabetes mellitus.
Methods: 5,054 Patients with symptomatic vascular disease or type 2 diabetes mellitus enrolled in the Secondary Manifestations of ARTerial disease (SMART) study were followed-up for the occurrence of new vascular events (i.e. myocardial infarction, stroke or vascular death) and all-cause mortality.
Results: During a median of 4.8 years (interquartile range 2.4-7.7 years), 657 patients experienced a new vascular event and 652 died. There was no evidence of a U or J-shaped association between SBP level and vascular events and mortality. In patients with cerebrovascular disease each 10 mmHg increase in SBP was associated with a 22% increased risk for vascular events (95%CI 0%-50%) and a 35% increased risk for mortality (95%CI 6%-72%). In contrast, indifferent effects were observed in subjects with coronary artery disease, peripheral artery disease or type 2 diabetes mellitus.

Table 1. Hazard ratios per 10 mmHg increase in Systolic Blood Pressure (95% CI)

	Mean SBP (SD) mmHg	All vascular events # Events	All vascular events HR (95% CI)	All-cause mortality # Events	All-cause mortality HR (95% CI)
Coronary artery disease (N=2289)	140 (18)	167	0.83 (0.67–1.02)	125	0.90 (0.69–1.16)
Cerebrovascular disease (N=955)	146 (19)	167	1.22 (1.00–1.50)	161	1.35 (1.06–1.72)
Peripheral artery disease (N=1159)	146 (19)	250	1.06 (0.89–1.26)	290	0.93 (0.79–1.09)
Type 2 diabetes mellitus (N=1328)	146 (19)	181	0.91 (0.74–1.11)	172	0.81 (0.65–1.01)

SBP, Systolic blood pressure; HR, Hazard ratio. Adjusted for age and gender, history of coronary artery disease, history of cerebrovascular disease, history of peripheral artery disease, type 2 diabetes mellitus, use of blood pressure lowering medication, total cholesterol, HDL-cholesterol, current smoking status and time-dependent regression dilution effects.

Conclusions: Lower SBP is associated with lower risk for vascular events and mortality in patients with cerebrovascular disease, without evidence of a bottom threshold within the range between 110 and 200 mmHg, but not in subjects with coronary artery disease, peripheral artery disease or type 2 diabetes mellitus.

P1507 Evidence of cardiovascular therapy undertreatment in patients with rheumatoid arthritis despite established cardiovascular disease - a Danish nationwide register study

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Purpose: To examine whether RA patients receive the same cardioprotective treatment after first time myocardial infarction (MI).
Methods: We identified all patients with a first time myocardial infarction (MI) in the Danish National Patient Register from January 1st, 2002 to December 31st, 2009. Data from multiple Danish nationwide individual level registers including pharmacy records was combined in order to establish previous use of CVD medication, comorbidity and income at the time of MI. Patients with two diagnoses of RA prior to MI were considered to be RA patients. The initiation of standard care post-MI medication, i.e., statins, beta-blockers and platelet inhibitors as well as other CVD therapy were determined by identification of a redeemed prescription between the MI and 30 and 180 days post-MI, respectively. Odds ratios (OR) for RA influence were obtained by multivariate logistic regression models including gender, age, comorbidity and income. In addition, the impact of RA status on time to treatment initiation was analysed in a framework of failure analysis with competing risk (death) to examine the potential bias due to survival in redeeming prescriptions.
Results: 98,454 MI patients (39.4% women) were discharged alive from who 1,113 were identified as RA patients (62.5% women). The proportion of patients who received standard care medication within 180 days was reasonably high (statins 80%, betablockers 82%, clopidogrel 70%, aspirin 79%).
Thirty days post-MI, RA patients were associated with significantly lower degree of initiation of statins (OR 0.68 [0.57-0.82]), betablockers (OR 0.76 [0.63-0.91]) and aspirin (0.75 [0.63-0.90]), but not clopidogrel (OR 0.88 [0.75-1.04]). These estimates, including statistical significance, were virtually unchanged at day 180. Competing risk analyses supported the results from logistic regression with sub-hazard ratios for RA patients being 0.81 [0.73-0.89] for statins, 0.86 [0.78-0.95] for betablockers, 0.94 [0.86-1.03] for clopidogrel and 0.85 [0.77-0.94] for aspirin.
Conclusions: In this nationwide study of unselected patients with first time MI, we observed a reduced propensity towards initiation of standard post-MI therapy in RA patients. As post-MI treatment is more regulated than primary prevention, an undertreatment of RA patients in this setting may suggest a general lower inclination to commence cardiovascular therapy in these patients and thus contribute to the increased CVD burden in RA. Whether this is a result of patient compliance or the physicians' decision, e.g., concerns of RA drug interactions, remains to be explored.

P1508 Survival and quality of life 25 years after coronary artery bypass graft surgery

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Coronary artery bypass graft surgery (CABG) improves survival and health related quality of life (HRQOL) after myocardial infarction (MI) up to 10 years. Long term disease progression may worsen symptoms and HRQOL.
Methods: We followed 151 consecutive survivors of acute MI (aged ≤55 years), for 25 years. CABG (n=91) and medical therapy (n=60) were offered at physician's discretion. HRQOL was measured using Nottingham Health Profile (NHP) questionnaire.
Results: Age, gender and diabetic status were similar between CABG and medical therapy groups. CABG group had better survival (years, 16.0±6.0 v 13.3±6.6, p=0.04). HRQOL scores were consistently worse in CABG group p<0.05 (Table 1).

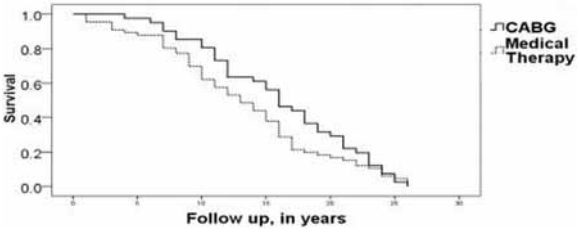

Figure 1. Kaplan Meier survival curves of patients with prior myocardial infarction, p=0.04.

Conclusion: CABG had better long-term survival but worse HRQOL compared to medical therapy. Opportunities to enhance long term HRQOL need to be explored.

P1509 Enhanced cerebrovascular protective effects of valsartan in high-risk hypertensive patients with coronary artery disease: ancillary analysis of KYOTO HEART study

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Purpose: Effects of angiotensin II receptor blocker (ARB) on clinical outcomes in hypertensive patients with coronary artery disease (CAD) have not been fully investigated. Recently the KYOTO HEART Study has demonstrated that ARB, valsartan add-on treatment prevents more cardio- cerebrovascular events than conventional non-ARB treatment in high-risk hypertensive patients (Eur Heart J 2009; 30:2461). The purpose of the present sub-analysis was therefore to examine the valsartan add-on effects on cardio-cerebrovascular morbidity and mortality in high-risk hypertensive patients with CAD.
Methods and results: In the KYOTO HEART Study, a total 3031 Japanese patients with uncontrolled hypertension (43% female, mean 66 years) were randomized to either valsartan add-on group (n=1517) or non-ARB treatment group (n=1514). The primary endpoint was a composite of defined cardio- or cerebrovascular events. Median follow-up period was 3.27 years. In the present study, accordingto the prior history of CAD at baseline, the study population was divided into two groups (with CAD; n=707 and without CAD; n=2324), in which primary endpoint events more frequently occurred in patients with CAD than patients without CAD (15.1% vs. 5.6%; HR 2.68, 95% CI 2.11-3.42). In the presence of prior CAD, the patients with valsartan add-on treatment (n=355) had significantly smaller prevalence of primary endpoints (11.3% vs. 19.0%; HR 0.59, 95% CI 0.41-0.85), new occurrence or exacerbation of angina pectoris (3.9% vs. 8.0%; HR 0.50, 95% CI 0.27-0.93), and stroke (1.4% vs. 4.3%; HR 0.33, 95% CI 0.12-0.90) than those with non-ARB treatment (n=352). In contrast, in the absence of prior CAD, although the patients with valsartan add-on treatment (n=1162) had less prevalence of primary endpoints (3.7% vs. 7.6%; HR 0.49, 95% CI 0.34-0.70) than those with non-ARB treatment (n=1162), valsartan add-on effects on angina pectoris as well as stroke were not significant. Mean blood pressure during the follow-up period did not differ significantly among the study subgroups.
Conclusions: Irrespective of prior CAD, valsartan add-on treatment prevented more cardio- cerebrovascular events than conventional non-ARB treatment in high-risk hypertensive patients. In addition, valsartan add-on treatment conferred not only anti-anginal effect but also stroke prevention only in hypertensive patients with prior CAD.

P1510 Failure to attain low density lipoprotein cholesterol goal <70 mg/dL and loss of extra clinical benefit in very high risk stable coronary patients: a three year follow-up

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Purpose: An optional target of low density lipoprotein cholesterol (LDLc) <70 mg/dL (1.8 mmol/L) has been proposed in very high risk patients with coronary heart disease (CHD). The aim of this study was to investigate the proportion of these patients who achieve the optional LDLc goal, the factors that influence the success rate and the impact on their prognosis.
Methods: We enrolled 1337 consecutive patients with stable CHD. Fasting lipids were determined and all cardiovascular events were recorded during a median follow-up of 33 months.
Results: The majority (86.5%) of patients were taking lipid-lowering medication, mainly statins, but only 50.6% had LDLc levels <100 mg/dL (2.6 mmol/L). Very high risk patients were considered 941 (70.4%) patients and only 15.1% of them had LDLc levels <70 mg/dL (1.8 mmol/L). In multivariate analysis, the use of intensive lipid-lowering medication (decrease of LDLc levels >50%) was associated with 12-fold (95% confidence interval [CI]: 6.98-20.76, p<0.001) higher possibility in achieving the LDLc target of <70 mg/dL (1.8 mmol/L). Multivariate Cox regression analysis showed that among 562 very high risk patients, LDLc levels <70 mg/dL (1.8 mmol/L) were independent predictors of all cardiovascular events (hazard ratio: 0.35, 95% CI: 0.13-0.96, p=0.041). The figure shows the event free cardiovascular event rate during the follow-up period according to the LDLc goal of <70 mg/dL (1.8 mmol/L) among very high risk patients with stable CHD.

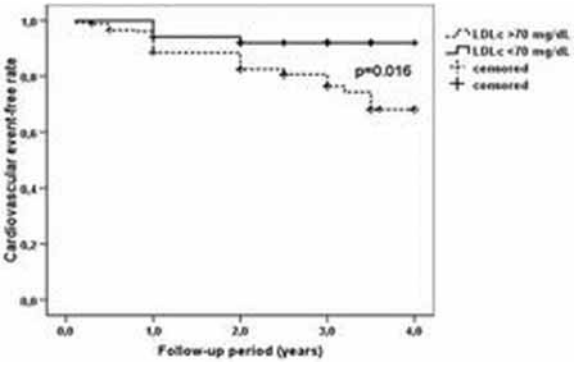

Figure1

Conclusions: The vast majority of very high risk patients does not achieve the optional goal of LDLc <70 mg/dL (1.8 mmol/L) and this is translated into loss of clinical benefit. Therefore, it is imperative for the physicians to titrate carefully statins' dose until the target is achieved.

P1511 A new metabolic risk score to predict short-term outcome after an acute coronary syndrome

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Background: Fatal and non-fatal events are common after an acute coronary syndrome (ACS). Several scores have been developed to better predict

Abstract P1505 – Table 1. Median NHP scores

	Energy		Pain		Emotional reaction		Sleep		Social isolation		Physical mobility	
Years	Med Rx	CABG	Med Rx	CABG	Med Rx	CABG	Med Rx	CABG	Med Rx	CABG	Med Rx	CABG
6	9.78*	19.06*	4.55	4.33	4.18	6.32	11.67	14.14	2.77	3.55	6.20	9.79
9	12.48	19.20	4.25	3.00	4.49	6.54	9.94	15.75	3.67	4.15	5.90	7.66
12	16.39	20.90	4.93	3.89	3.70*	9.86*	11.85*	25.52*	2.23	6.33	5.84	10.66
15	9.37	15.20	5.94	7.17	4.08*	10.20*	10.06*	15.81*	2.19	4.19	8.10	11.20
20	6.75*	18.35*	5.22	12.07	1.71*	8.13*	12.57	21.70	1.83	4.23	11.95	10.93
25	6.26	13.71	4.12	5.83	3.35	8.13	10.59	15.02	1.69	4.89	21.77	11.00

HRQOL was measured using Nottingham Health Profile (NHP) questionnaire. Scores range from 0 (best HRQOL) to 100 (worst HRQOL) for each domain. MedRx: medical therapy. *P<0.05.

post-ACS outcome; however, these scores are usually complex and difficult to apply to a broad unselected ACS population.
Aim: To determine the ability of a new metabolic risk score to predict in-hospital outcomes in ACS patients.
Population and methods: We studied 2124 consecutive patients admitted to our coronary care unit with ACS. A new metabolic risk score (RS) was derived by dividing in 5 percentiles admission C-reactive protein, Creatinine clearance, Age, glycemia (Sugar), and Hemoglobin (C2ASH). The higher the risk carried by the variable, the higher the percentile value. The sum of the 5 variables percentiles yielded a 5 to 25 RS.
Results: Mean age was 67.53±12.42 years (67.2% males). Clinical follow-up was available for all patients, with a mean duration of 36 months. Median C2ASH value was 12.5. Patients were divided in two groups, according to the fact of being alive (Group A – n=2041) or death (B – n=83) at hospital discharge.
Group B patients were older, had more prior heart failure, higher admission and peak killip class, lower blood pressure, higher TIMI risk score (p=0.046), they required more often Levosimendan and were less often in sinus rhythm at admission. They received less often beta-blockers, ACE-inhibitors and statins in the first 24h, but were more often early treated with diuretics. There were no differences between groups regarding coronary anatomy, but group B patients were less often completely revascularized; ST-elevation myocardial infarction was more common in these patients, unlike unstable angina. They also had a lower left ventricular ejection fraction. The best cut-off value for identifying high risk patients for in-hospital death was 12.5 (69% sensitivity, 67% specificity). The area under yelded by the C2ASH score for in-hospital mortality was 0.722, higher than that for the GRACE (0.689) and TIMI (0.678) risk scores for our population.
Conclusion: The 5-variable simple to calculate C2ASH demonstrated a better predictive accuracy for in-hospital mortality in ACS patients than GRACE and TIMI, thus enabling the better identification of high-risk patients for worse early outcome.

P1512 Effectiveness in primary care of low-dose acetylsalicylic acid, clopidogrel and dual antiplatelet therapy for the secondary prevention of coronary outcomes

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Purpose: Low-dose acetylsalicylic acid (ASA) is recommended for prevention of secondary cardiovascular events, with the addition of clopidogrel (dual antiplatelet therapy [DAT]) in patients with acute coronary syndromes (ACS) or coronary stents. However, there are limited data available on the long-term effectiveness of these therapies in primary care. This study aimed to evaluate the risk of myocardial infarction (MI) and coronary death in primary care patients treated with ASA monotherapy, clopidogrel monotherapy or DAT following hospitalization for a coronary event (MI, unstable angina or coronary percutaneous revascularization).
Methods: Two UK primary care databases (the General Practice Research Database and The Health Improvement Network) were used to identify all individuals aged 50–84 years who had documented evidence of a hospitalization for a coronary event, and who were alive 1 month after this event (N = 42 542). The cohort was followed for a mean of 3.5 years. Individuals with a new diagnosis of non-fatal MI (n = 1888) or a record of coronary death (n = 658) were identified and all patient records were manually reviewed. Controls with no MI/coronary death were sampled from the same study cohort (n = 10 000) and frequency-matched to the cases by age, sex and calendar year. Nested case–control analysis was performed to estimate the association between the different antiplatelet treatments and the risk of MI/CHD death using unconditional logistic regression.
Results: The overall incidence of MI/coronary death was 17.3 per 1000 person-years (95% confidence interval [CI]: 16.6–17.99); the incidence of non-fatal MI was 12.8 per 1000 person-years (95% CI: 12.2–13.4) and the incidence of coronary death was 4.5 per 1000 person-years (95% CI: 4.1–4.8). The risk of MI/coronary death was significantly lower among current users of low-dose ASA monotherapy (relative risk [RR]: 0.62; 95% CI: 0.52–0.74), clopidogrel monotherapy (RR: 0.58; 95% CI: 0.42–0.82) or DAT (RR: 0.63; 95% CI: 0.49–0.82) compared with patients not treated with antiplatelet drugs.
Conclusion: Patients discharged from hospital after a coronary event who received treatment with ASA, clopidogrel or DAT in primary care have a lower risk of MI/coronary death than patients not treated with antiplatelet drugs. Observed treatment effects were similar with the different agents.

P1513 RESICARD prevention trial: a randomized multicentre study comparing standard care with supervised nurse-led therapeutic education. Results of a French network of cardiac risk-factor correction

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Purpose: Conflicting results have been reported from home-based, nurse-led cardiac prevention programmes, particularly in patients at low or intermediate risk, compared with usual care or centre-based programmes. We sought to compare the impact on modifiable cardiac risk factors (RFs) of a supervised nurse-led therapeutic education programme involving planned visits to a "House of Education" vs standard care in patients discharged after an acute coronary syndrome (ACS).
Methods: The RESICARD-prevention trial is a multicentre parallel group randomized controlled trial of 502 patients discharged after an ACS with at least one of the following cardiovascular RFs: active and current smoking, sedentary lifestyle, obesity or overweight. Patients were randomized in the RESICARD-prevention program a supervised nurse-based therapeutic education program (n= 245) or in the usual care group (n=247) based on standard unplanned but regular visits to GPs and/or ambulatory cardiologists. Blinding was not feasible in this trial. The primary endpoint was composite endpoint defined as correction of at least one of the above-mentioned CRF at one year follow-up. All analyses were done according to the intention-to treat principle.
Results: Of the 492 patients enrolled (mean age 56.9±10.9, 84% male), 250 (50.8%) had 1 RF, 189 (38.4%) had 2, and 53 had 3 (10.8%). There were no statistically significant differences between groups in the primary composite endpoint (adjusted OR 1.27, 95% CI 0.83–1.95); and in the secondary endpoints: smoking cessation (adjusted OR 0.97, 95% CI 0.59–1.58); weight reduction (adjusted OR 1.14, 95% CI 0.73–1.79); physical activity (adjusted OR 1.28, 95% CI 0.78–2.08). The groups did not differ at one year in terms of health-related quality of life (QoL) score; in mental QoL score; or the questionnaire on disease knowledge score.
Conclusion: The RESICARD-prevention programme did not achieve any significant reduction in modifiable cardiovascular RF levels despite a reinforced and structured follow-up through planned visits to a dedicated House of Education, compared with standard ambulatory care.

P1514 Apolipoprotein A-I induction therapy is associated with reduction in inflammatory biomarkers: potential implications for functionality of high-density lipoproteins

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Background: High-density lipoproteins (HDL) have been proposed to possess anti-inflammatory properties. The effect of apolipoprotein (apo) A-I induction therapy on inflammatory biomarkers has not been investigated.
Methods: In a phase 2 study increasing doses of an apoA-I inducer (RVX-208 100-300 mg daily) and placebo were administered for 12 weeks in statin-treated patients with stable coronary artery disease to evaluate effects on lipid efficacy. Factors associated with changes in CRP levels with RVX-208 were characterized.
Results: Administration of RVX-208 was associated with dose-dependent increases in levels of apoA-I by 0.1-5.6%, HDL cholesterol by 3.2-8.3% and large HDL particles by 11.1-21.1%. A non-significant dose-dependent reduction in CRP by 13.0-22.0% was observed. A significant inverse relationship was observed between changes in HDL cholesterol and CRP in RVX-208 treated patients (r= -0.19, p=0.004). When RVX treated patients were stratified according to tertiles of percent change in CRP, those with the greatest reduction in levels demonstrated the greatest elevation in apoA-I (+5.6 vs +0.1%, p=0.004), HDL cholesterol (+7.7 vs +2.8%, p=0.02), and concentration of large HDL particles (+27.5 vs +3.9%, p=0.003).
Conclusion: Administration of an inducer of apoA-I synthesis was associated with reductions in inflammatory biomarkers in patients with greater increases in HDL related parameters. This may reflect the generation of functional HDL particles with this therapy. The impact on extent and vulnerability of atherosclerotic plaque remains to be determined.

P1515 A randomized controlled trial to test an intervention to reduce pre-hospital delay time in patients diagnosed with acute coronary syndrome (ACS)

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Introduction: Patient delay in seeking treatment for acute cardiac symptoms is

the major factor that limits timely use of definitive therapies for acute coronary syndrome (ACS). The purpose of this multi-site Irish study was to determine whether ACS patients randomised to intervention vs. control would have lower pre-hospital delays if they subsequently had another ACS event.
Methods: A total of 1,947 patients (mean age 63.9±11.6 years; 72% male) with confirmed ACS were recruited and randomised. Baseline pre-hospital delay time was measured for all patients. Those randomised to the intervention group were given a 30-minute individualised education session that focused on: motivating behavioural change through education, addressing misconceptions about heart disease and the development of an individualised action plan related to pre-hospital delay for future use. The education was reinforced one month later when those in the intervention group were telephoned. When patients from either group were re-admitted to an emergency department with ACS symptoms, their pre-hospital delay times were again measured. Data were analysed using using repeated measures ANOVA on log transformed delay-time.
Results: Baseline comparisons between groups revealed no significant differences in pre-hospital delay time. Of the sample, 162 (16.6%) in the intervention group and 126 (13.0%) in the control group were readmitted to an emergency department with a further ACS event. Those in the intervention group demonstrated a significant decrease in delay time compared to both their own baseline and to that of the control group (p=0.02; Figure 1).

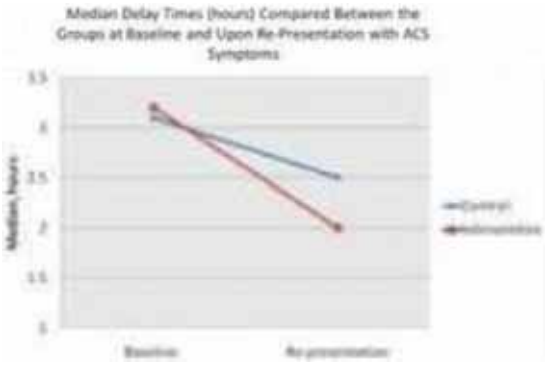

Figure 1. Median delay times.

Conclusion: A simple, practical education programme for patients diagnosed with ACS can reduce pre-hospital delay time in the event of further symptom presentation.

P1516 Beta blocker therapy is associated with depressive symptoms 12 months post percutaneous coronary intervention

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Background: Beta blocker therapy may induce depressive symptoms, although current evidence is conflicting. We examined the association between beta blocker therapy and depressive symptoms in percutaneous coronary intervention (PCI) patients and the extent to which there is a dose-response relationship between beta blocker dose and depressive symptoms.
Methods: Patients treated with PCI (N=685) completed the depression scale of the Hospital Anxiety and Depression Scale 1- and 12 months post PCI. Information about type and dose of beta blocker use was extracted from medical records.
Results: Of all patients, 68% (466/685) were on beta blocker therapy at baseline. In adjusted analysis, beta blocker use at 1 month post PCI (OR:0.82; 95%CI:0.53-1.26) was not significantly associated with depressive symptoms. At 12 months post PCI, there was a significant relationship between beta blocker use and depressive symptoms (OR:0.51; 95%CI:0.32-0.84), with beta blocker therapy associated with a 49% risk reduction in depressive symptoms. There was a dose-response relationship between beta blocker dose and depressive symptoms 12 months post PCI, with the risk reduction in depressive symptoms in relation to a low dose being 36% (OR: 0.64; 95% CI: 0.37-1.10) and 58% (OR: 0.42; 95% CI: 0.24-0.76) in relation to a high dose.

Beta blockers		% depressive symptoms	Mean (SD) depressive symptoms	Depression (Univariable) OR [95% CI]	Depression (Multivariable) OR [95% CI]
Baseline (n= 685)	BBL +	15.9	4.32 (3.7)	0.85 [0.55-1.29]	0.82 [0.53-1.26]
	BBL -	18.3	4.59 (3.9)		
12 months (n= 685)	BBL+	9.7	3.71 (3.2)	0.53 [0.33-0.84]	0.51 [0.32-0.84]
	BBL -	16.9	4.62 (3.6)		

BBL=Beta Blocker; OR=Odds ratio; CI=Confidence interval

Conclusions: Patients treated with beta blocker therapy were less likely to experience depressive symptoms 12 months post PCI, with there being a dose-response relationship with a higher dose providing a more pronounced protective effect.

P1518 Symptoms of anxiety and depression after percutaneous coronary intervention are associated with decreased heart rate variability, impaired endothelial function and inreased inflammation

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Background: Depression and anxiety are prevalent risk factors for cardiac events in patients with coronary artery disease. However, little is known about the pathophysiological mechanisms responsible for this association.
Methods: Four weeks after successful revascularization by percutaneous coronary intervention for angina pectoris or an acute coronary syndrome 94 patients completed the Hospital Anxiety and Depression Scale (HADS), underwent ultrasound based measurement of endothelial function, assessment of heart rate variability by 24-hour Holter registration and measurement of plasma levels of C-reactive protein (CRP).
Results: Twenty-three patients showed a HADS-anxiety (HADS-A) score ≥8 and 19 patients had a HADS-depression (HADS-D) score ≥5. Those patients had significant lower means of heart rate variability measures reflecting parasympathetic activity (root mean square of differences between successive NN intervals (rMSSD) and the percentage of differences between adjacent NN intervals that are >50 msec (pNN50), impaired endothelial function (flow mediated dilation (FMD)) and higher plasma levels of CRP compared to patients with normal HADS scores (Table 1). Seven patients with a HADS-A score ≥8 had a cardiovascular event, while there were six events in the group with normal HADS-A scores during 30±10 months follow-up (p=0.017).

Table 1

	Normal HADS score	HADS-A score ≥8	HADS-D score ≥5
rMSSD (ms)	40±19	23±14***	20±9***
pNN50%	11±10	3±4***	3±2***
FMD (%)	9±5	5±5**	4±4**
CRP	2.1±1.9	3.8±2.9*	3.8±2.9*

*p<0.05, **p<0.01, ***p<0.001.

Conclusions: Depressive and anxiety symptoms after revascularization for coronary artery disease are prevalent and are associated with decreased parasympathetic mediated heart rate variability, impaired endothelial function and increased inflammation, potentially contributing to explain the association between anxiety and depression and the increased risk for cardiac events in this patient population.

P1519 Automated outreach for cholesterol-lowering medication refill reminders

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Purpose: Considerable evidence indicates that control of risk factors in patients with cardiovascular disease can have a great impact on reducing risk of subsequent cardiovascular morbidity and mortality. Many patients with cardiovascular disease, however, have suboptimal adherence to prescribed medications. This study was conducted to test the effectiveness of an automated telephone reminder intervention to improve adherence to medications to lower cholesterol among adults with cardiovascular disease in a large, diverse integrated healthcare system.
Methods: All participants were 18 years of age and older identified from a cardiovascular disease case-identification database. Participants had a prescription for a cholesterol-lowering agent overdue for refill between 2 weeks and 6 weeks. Participants were randomly assigned to either an automated telephone outreach or a control group (usual care). The outreach consisted of an automated telephone call that instructed the member to order a refill for their overdue prescription by calling the number on their medication bottle or by using an online refill system. The primary outcome was refill rate at 2 weeks among the two groups. We further examined refill rates at 2 weeks according to duration of being overdue (2 weeks to 4 weeks and 4 weeks to 6 weeks).
Results: The number randomized over 3 months was 15,254 in the control group and 15,356 in the outreach group. The refill rate at 2 weeks was 21.5% (n=3,309) in the control group and 27.8% (n=4,318) in the outreach group (absolute difference 6.3%; p<0.001). Refill rates at 2 weeks were higher in participants who were 4 to 6 weeks overdue (absolute difference between outreach and control group 7.0%; p<0.0001) versus those who were 2 to 4 weeks overdue (absolute difference between outreach and control group 5.8%; p<0.001).
Conclusions: This low-cost outreach intervention of automated prescription refill reminders resulted in a significant increase in refill rates. Further analyses will

examine the relationship between demographic and clinical factors and refill rates as well as mean cholesterol levels and medication adherence and persistence in this population.

P1520 Risk factors control, treatment of atherothrombosis and habits of life in the secondary preventions of cardiovascular disease

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Purpose: The aim was to determine the annual rate of cardiovascular events in an outpatient population with established cardiovascular disease or multiple atherothrombotic risk factors and their relationship to sociodemogrphic and clinical variables
Methods: The PREVENT-A is a prospective epidemiological study to determine the occurrence of cardiovascular events in 1032 patients with symptomatic cardiovascular disease (94,5%) or multiple risk factors (5,5%) in a region of southern Spain. The primary endpoint was the occurrence of cardiovascular death (CVD), nonfatal myocardial infarction (NFMI) or stroke and combined endpoint (MACE), one year follow-up.
Results: Since January 2008, results were obtained in 1032 patients (72.4% men) with a mean age of 67.2 years (SD: 9.4) years. The annual rate of CVD, NFMI and stroke was 1.7%, 31.6% and 30.7% respectively and 35% for combined endpoint (MACE). The events rates increased with the number of symptomatic arterial disease locations, ranking from 22,0% for patients with multiple risk factors to 32,3%, 32,9% an 43,8% for patients with 1, 2 and 3 o more sumptomatic arterial disease location (p: 0,03).
Patients were generaly adecuate treatment with antihypertensive drugs (97%), antipletelet agents (95%) and statins (88,9%). Hypertension, diabetes and hypercholesterolemia was controlled in 25,1%, 56,1% and 50,9%, respectively according to the current recomendation for secondary prevention. Statistically significant differences were observed in the control of diabetes and the presence of combined endpoint (55.9 vs 66.7% vs, P $<$0.05) but not in the control of blood pressure, dyslipidemia and abdominal obesity.
The MACE rate was significantly more frequent in smokers (36.5% vs 27.1%, p=0.002). Moderate alcohol consumption and physical exercise regularly were significantly more frequent in patients without events (14.6% vs 8.8%, p=0.008) and (51.0% vs 38.2%, p=0.0002). There were no differences in educational attainment and field of residence between patients with and without events
Conclusions: In this study in southern Spain in most patients with atherosclerotic coronary disease, there was a high annual rate of ischemic events: these rates increase in close association with polyvascular disease, smoking and poorly controled diabetes and decrease with exercise and moderate alcohol drinking. Despite the use of risk reduction interventions, ideal secondary prevention od ischemic events has not been achieved Thus, additional efforts to modify the habits of life in this population should be achieved

P1521 The factors that influence pre hospital delay time in acute coronary syndrome patients

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Introduction: The recent literature indicates that the time taken from symptom onset to presentation to hospital with acute coronary syndrome (ACS) symptoms varies greatly and ranges from 1.5-16 hours. Pre-hospital delay time has changed little over time and there are many factors that influence it. The purpose of the study was to ascertain the main factors that continue to influence pre-hospital delay time.
Methods: This cross-sectional Irish study was a component part of a multi-site RCT examining the impact of an intervention on pre-hospital delay time. Data were collected using questionnaires and patient interview, which were confirmed against patients' notes. Data were analysed using PASW version 18. Multiple regression was used to determine predictors of delay time (transformed) from among sociodemographic (i.e., age, gender, marital status, education level, employment status, medical insurance), clinical (i.e., history of AMI, bypass surgery, angioplasty, diabetes, hypercholesterolemia, hypertension, family history of heart disease), symptom (i.e., symptoms experienced during their ACS event), and cognitive (i.e., knowledge, attitudes and beliefs about heart disease, symptoms and how to respond to symptoms) predictors.
Results: 1,947 patients who had a recent ACS event were enrolled in the study. Of these 28.1% had an STEMI; 36.3% NSTEMI; and 35.5% had unstable angina. The mean age was 63.9$\pm$11.6 years, BMI was 27.5$\pm$4.7 kg/m^2 and 72% were male. Median delay time was 4.2 hours (25th percentile, 1.67 and 75th percentile, 18.9 hours). No sociodemographic factor predicted delay time. History of bypass surgery (p=0.04) and hypercholesterolemia (p=0.04) predicted longer delay times. While patients' whose ACS event was a STEMI (p$<$0.001) had shorter delays than those with non-STEMI or unstable angina. Patients with more accurate or better attitudes had shorter delays (p$<$0.001). Presence of the following symptoms during the patient's ACS event predicted shorter delays: chest pain or pressure (p$<$0.01), shortness of breath (p=0.022), dizziness (p$<$0.001), dread (p$<$0.001), sweating (p=0.03) and fatigue (p$<$0.001). Patients who had a headache during their ACS event experienced longer delays (p=0.026).
Conclusion: The identification of the factors, particularly the modifiable factors that influence pre-hospital delay is important so that strategies can be developed to address these deficits and further reduce pre hospital delay time.

P1522 Do cardiovascular patients with multivascular disease constitute an important clinical subgroup?

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Purpose: NICE recognises patients with multivascular disease (MVD) as distinct from patients with atherosclerotic disease in a single vascular bed. This distinction is not reflected in cardiovascular drugs trials or clinical practice. We report the data analyses underpinning NICE's ground-breaking guidance on the use of clopidogrel.
Methods: As part of a multiple technology appraisal, we asked the manufacturer of clopidogrel to reclassify CAPRIE trial patients (n=19,185) into those with disease in a single vascular bed (myocardial infarction [MI] only, ischaemic stroke [IS] only or peripheral arterial disease [PAD] only) or those with disease in more than one vascular bed (MVD).
Results: Distinguishing between patients (single disease versus MVD) changes the risk of future IS or MI for different patient groups (Table 1). Future IS risk for IS only patients remains stable, but is reduced for patients with MI or PAD; future MI risk for MI only patients remains stable, for patients with IS or PAD the risk is reduced. The risk of IS or MI for MVD patients is much greater than for the MI, IS or PAD groups.

Table 1 Changing risk of IS and MI

CAPRIE patient group	Original published IS rate %		New* IS rate % using data from manufacturer		
Qualifying event	Clopidogrel	Aspirin	New classification	Clopidogrel	Aspirin
Ischaemic stroke (IS)	9.74	10.57	IS only	9.03	9.54
Myocardial infarction(MI)	1.34	1.33	MI only	0.98	1.00
PAD	2.51	2.54	PAD only	2.20	1.62
			MVD	6.14	7.13
			New* MI rate % using data from manufacturer		
Ischaemic stroke (IS)	1.36	1.59	IS only	1.01	0.84
Myocardial infarction (MI)	5.19	5.51	MI only	4.53	5.18
PAD	2.11	3.34	PAD only	1.18	1.78
			MVD	3.96	5.27

PAD = peripheral arterial disease; MVD = multivascular disease. *After creation of MVD population.

Conclusions: MVD patients are at increased risk of future vascular events; reanalysis of other trials is likely to deliver similar results. How the MVD group is defined is important. The clinical community should discuss how definition(s) of MVD can be agreed and how patients with MVD can be appropriately assessed in trials.

P1523 One-year cardiovascular ischemic event rates in high risk outpatients in southern Spain: The PREVENT-A registry

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Purpose: The aim was to determine the annual rate of cardiovascular events in an outpatient population with established cardiovascular disease or multiple atherothrombotic risk factors and their relationship to sociodemogrphic and clinical variables
Methods: The PREVENT-A is a prospective epidemiological study to determine the occurrence of cardiovascular events in 1032 patients with symptomatic cardiovascular disease (94,5%) or multiple risk factors (5,5%) in a region of southern Spain. The primary endpoint was the occurrence of cardiovascular death (CVD), nonfatal myocardial infarction (NFMI) or stroke and combined endpoint (MACE), one year follow-up.
Results: Since January 2008, results were obtained in 1032 patients (72.4% men) with a mean age of 67.2 years (SD: 9.4) years. The annual rate of CVD, NFMI and stroke was 1.7%, 31.6% and 30.7% respectively and 35% for combined endpoint (MACE).

Of the baseline variables analyzed, BMI and waist circumference were significantly higher in patients with MACE (29.8 vs. 29.3, p=0.04) and (105.4 vs 101.2; p: 0.02): Vascular interventions were more frequent among patients with MACE both at baseline and during follow-up (47.2% vs 36, 0%, p=0.0006). Statistically significant differences were observed in the control of diabetes and the presence of combined endpoint (55.9 vs 66.7% vs, P<0.05) but not in the control of blood pressure, dyslipidemia and abdominal obesity.
The MACE rate was significantly more frequent in smokers (36.5% vs 27.1%, p=0.002). Moderate alcohol consumption and physical exercise regularly were significantly more frequent in patients without events (14.6% vs 8.8%, p=0.008) and (51.0% vs 38.2%, p=0.0002). There were no differences in educational attainment and field of residence between patients with and without events
Age >68 years was associated with an increased risk of CVD, OR: 0.108 (95% CI 0.025 to 0.474, p=0.003) and MACE, OR: 0.887 (95% CI: 0.832 to 0.946, p=0.0003). Between smokers/ex-smokers had a higher risk of NFMI and stroke. OR: 1.80 (95% CI: 1.31 to 2.47, p=0.001 and OR: 1.88 (95% CI: 1.369 to 2.581, p=0.0005) Patients are not consumers of alcohol had almost twice the risk of NFMI and stroke. OR: 1.880 (95% CI: 1.190 to 2.996, p=0.007) and OR: 1.947 (95% CI: 1.220 to 3.106, p=0.005).
Conclusions: In this study in southern Spain in most patients with atherosclerotic coronary disease, there was a high annual rate of ischemic events in relation to age, smoking, prior vascular interventions and inadequate control of diabetes. We observed a protective effect of moderate alcohol consumption.

P1524 Prognostic role of pVO2 in 2011 in an unselected Italian population with cardiac disease

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Purpose: Variables derived by cardiopulmonary exercise test, as peak oxygen consumption (pVO2) and the slope of the relation between ventilation and carbon dioxide production (VE/VCO2 slope), have been used to evaluate exercise tolerance in different heart disease patients groups. Both have been used as prognostic indicators along the last twenty years, despite updates of disease management. We aimed to confirm the role of pVO2 and VE/VCO2 slope as prognostic indicators, at one year follow-up in an heterogeneous heart disease population up-to-date treated; moreover we assessed the relation with possible confounding factors like left ventricular ejection fraction (LVEF), age and co-morbidities affecting exercise capacity.
Methods: We enrolled from January to June 2008, 466 consecutive patients, who underwent maximal (goal RER >1.05) cardiopulmonary stress test in eight different italian exercise laboratories; we aimed to assess the prognostic power of pVO2 and VE/VCO2 slope at one-year follow-up, with a composite end-point of all-cause mortality and hospitalizations. All patients underwent a careful clinical and echocardiographic evaluation.
Results: Our population was composed by an heterogeneous group of cardiac diseases: idiopathic dilatative cardiomyopathy (34%), ischaemic (45%), hypertensive (7%), congenital (10%) and valvular (2%) heart disease, hypertrophic cardiomyopathy (2%). Mean age was 60±17 years (range 9-91), males were 76%, mean LVEF was 39±12% (range 11-74), mean peakVO2 14.1±5 ml/kg/min (range 4-41) and mean VE/VCO2 slope was 32±8 (range 19-66). At 360 days follow-up we observed 65 events (54 hospitalizations and 11 deaths respectively). At Kaplan Meier analysis pVO2 and VE/VCO2 slope (median values) predicted the combinate end-point (p<0.01 at log Rank for both). At univariate analysis LVEF, peakVO2, VE/VCO2 slope, age and different co-morbidities affecting exercise capacity (renal failure, anaemia, diabetes, chronic obstructive pulmonary disease) were all predictors of events. At multivariate analysis pVO2, when adjusted for age and co-morbidities, continued to hold an independent predictive value, together with LVEF. (HR 0.932, 95%CI 0.874-0.994, p=0.031 and HR 0.958, 95%CI 0.938-0.979, p<0.001 respectively). Conversely, VE/VCO2 slope did not predict events at multivariate analysis.
Conclusion: In 2010 pVO2 but VE/VCO2 slope, still has an independent prognostic value in an heterogeneous population with cardiac disease, even when adjusted for age, LVEF and co-morbidities affecting exercise capacity.

P1525 The quality of cardiovascular care delivery in primary care in Canada

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Background: Extensive evidence exists illustrating the important role that family practice plays in the prevention and management of cardiovascular disease. Despite this significant role, many primary care physicians struggle to implement evidence based cardiovascular treatment guidelines, resulting in patient care that is suboptimal. The objective of this study is to provide a current snapshot of the quality of cardiovascular care in the Canadian province of Ontario by examining primary care practice adherence to evidence-based cardiovascular treatment guidelines.
Methodology: This study was conducted in 84 primary care practices that are participating in the Improved Delivery of Cardiovascular Care (IDOCC) program, a quality improvement initiative in Ontario, Canada. We conducted a baseline cross-sectional review of 4896 randomly selected medical charts of patients either with or at high risk for developing cardiovascular disease. The review evaluated primary care practice adherence to the Champlain Primary Care Cardiovascular Disease Prevention and Management guidelines: an integrated evidence based care guideline.
Results: Amongst this group of patients, 46% have diabetes, 30% have coronary artery disease (CAD), 13% have cerebrovascular disease, 18% have chronic kidney disease and 6% have peripheral vascular disease. Data on cardiovascular disease risk factors show that 77% of patients have hypertension, 83% have dyslipidemia and 21% are smokers. Overall, 88% of CAD patients are receiving appropriate drug therapy; 64% of diabetics are receiving the recommended HbA1c tests; 77% of high risk patients had a lipid profile done while 55% of patients were recommended aspirin; 80% of hypertensive patients had their blood pressure monitored at least twice in the last year while 94% received appropriate drug therapy; 83% of those with dyslipidemia had a lipid profile done while 91% were recommended or prescribed a lipid lowering drug; 52% of smokers received cessation counseling; and only 10% of patients had a waist circumference measurement during the evaluation year.
Conclusions: Although adherence to guidelines for patients with hypertension dyslipidemia and CAD were relatively high, results indicate significant care gaps for diabetes management, waist circumference management and smoking cessation management. Results of this study indicate that there is room for improvement in the quality of primary care delivered to those patients with or at high risk for developing cardiovascular disease.

LONG TERM FOLLOW UP AFTER PERCUTANEOUS CORONARY INTERVENTION

P1526 Impact of bivalirudin therapy on mortality in patients with high risk features undergoing PCI: a patient-level pooled analysis from the REPLACE-2, ACUITY and HORIZONS-AMI trials

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Purpose: Compared to Heparin + GP IIb/IIIa inhibitors (GPI), bivalirudin has been shown to decrease bleeding complications in several clinical presentations including: percutaneous coronary intervention (PCI) in stable ischemic syndromes, unstable angina, NSTEMI and STEMI (REPLACE-2, ACUITY and HORIZONS trials). A survival benefit was observed in STEMI patients, but not in other scenarios. We investigated the impact of bivalirudin on survival in pts enrolled in these trials according to high risk clinical features (reduced LVEF, advanced age, diabetes mellitus (DM), anemia, chronic kidney disease (CKD), clinical presentation, and prior MI).
Methods: We examined patient-based pooled data of 3 randomized trials, identified 14,258 pts who received dual anti-platelet therapy undergoing PCI, and constructed a risk adjusted mortality model using the following variables: age >65, presence of DM, hypertension, CrCl <60mg/mL, LVEF <35%, NSTEMI, STEMI, previous MI and hematocrit <36%. Cox regression methods were used for statistical analysis.
Results: The relative risks of 1-year mortality favored bivalirudin over heparin + GPI and were concordant in the presence of each individual high risk feature

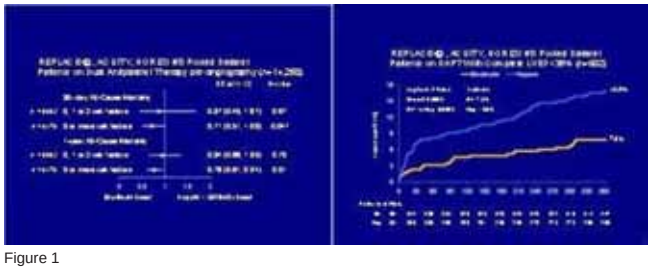

Figure 1

examined; the lowest relative risk was associated with LVEF <35% (0.47, 0.30-0.72, p=0.0004) (Figure 1, right). The presence of 3 or more risk factors (n=6176; 43.3% of all pts) was also associated with lower 1-month and 1-year mortality with bivalirudin therapy compared to GPI (Figure 1, left). All above results were consistent in all three trials.
Conclusions: Treatment with bivalirudin may improve survival in patients with high risk features and ACS and/or undergoing PCI. The largest benefit was present in patients with moderate/severe LV dysfunction. Further studies are required to confirm these results.

P1527 Sudden death in bare metal and drug-eluting stents: gain in restenosis in drug-eluting stent is lost due to late stent thrombosis

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Purpose: Recent clinical trials have shown that the incidence of late sent thrombosis (LST) is similar between bare metal (BMS) and drug-eluting stents (DES) based on the Academic Research Consortium (ARC) definition of "definite" or "probable" thrombosis. Sudden death from unknown cause occurring at least 30 days after stenting is clinically identified as "possible" thrombosis; however, precise cause of death in the sudden death population remains unclear because of the lack of autopsy data. We sought to evaluate the cause of death in patients with BMS and DES who died suddenly.
Methods: Histopathologic evaluation was performed in consecutive 164 sudden death cases with coronary stents implanted for >30 days (72 BMS, 92 DES [46 sirolimus- (SES), and 46 paclitaxel-eluting stents (PES)]) obtained between 1998 and 2010. Sudden death was defined as that occurring ≤6 hours of the symptom onset or ≤24 hours of the time that the victim was last seen alive in normal state. Death from coronary cause was defined as a luminal narrowing of >75% or a presence of acute thrombus.
Results: Age, sex, and risk factors were similar between BMS and DES. The median duration of implant was shorter in DES than BMS (13 vs. 25 months, p<0.001). Causes of death in BMS and DES are shown in Table. Restenosis-related death was more frequent in BMS; however, the majority of restenosis were accompanied by diffuse coronary artery disease (CAD), and isolated restenosis was an infrequent cause of death. LST was more frequent in DES than BMS. There were no differences seen between SES and PES with regard to the cause of death.

Causes of sudden death in BMS and DES

Causes of sudden death	BMS (n=72)	DES (n=92)	P value
Restenosis related death	26 (36%)	10 (11%)	<0.001
– with diffuse CAD	24 (33%)	9 (10%)	<0.001
– without diffuse CAD	2 (3%)	1 (1%)	0.423
Diffuse CAD without restenosis	14 (19%)	27 (29%)	0.146
Acute myocardial infarction in non-stented artery	13 (18%)	9 (10%)	0.123
Late stent thrombosis	4 (6%)	22 (24%)	0.001
Non-coronary death	15 (21%)	24 (26%)	0.433

Conclusions: Causes of sudden death are different between BMS and 1st-generation DES. Restenosis with diffuse CAD is a frequent cause in BMS, whereas LST is more frequent in DES as compared to BMS.

P1528 Predictors and implications of infarct artery patency at initial angiography in patients with acute myocardial infarction: lessons from the CADILLAC and HORIZONS-AMI trials

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Aims: We sought to identify the predictors and implications of spontaneous reperfusion before primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI).
Methods and results: We combined databases from the CADILLAC and HORIZONS-AMI trials, and analyzed the predictors of core laboratory-determined baseline TIMI 3 flow and 1-year outcomes according to baseline TIMI flow.
Baseline TIMI 3 flow was present in 932 (17.5%) of 5,332 patients. The independent predictors of baseline TIMI 3 flow were diabetes, longer delay to PCI, smoking, and more extensive coronary disease. Patients with, compared to without, baseline TIMI 3 flow had significantly higher rates of post-PCI TIMI 3 flow (99.1% vs. 91.4%, P<0.0001) and lower 1-year all-cause mortality (2.7% vs. 4.3%, P=0.03). By multivariable analysis, both baseline TIMI 3 flow (hazard ratio [95%CI] = 1.65 [1.01, 2.71], P=0.046) and final TIMI 3 flow (3.67 [2.45, 5.48], P<0.001) were significant independent predictors of 1-year survival.
Conclusions: TIMI 3 flow is present in ~1 in every 6 patients prior to PCI, and paradoxically is more common in patients with selected high risk characteristics. TIMI 3 flow prior to, as well as after PCI, is an independent predictor of greater 1-year survival. These results should inform future strategies to increase pre-PCI TIMI 3 flow rates to further improve outcomes in STEMI.

P1529 The impact of long-term dual antiplatelet therapy in patients with stent fracture after sirolimus-eluting stent implantation

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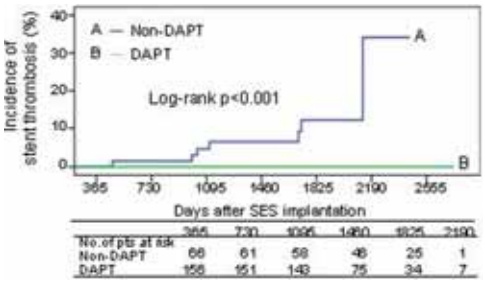
Purpose: The optimal duration of dual antiplatelet therapy (DAPT: aspirin and thienopyridine) after drug-eluting stent implantation remains unclear, especially in high risk patients. As stent fracture (SF) could be related to stent thrombosis, we evaluate the impact of DAPT duration on stent thrombosis in patients with stent fracture after sirolimus-eluting stent (SES) implantation.
Methods and results: A total of 2494 patients with 4885 lesions were treated with SES from November 2002 to December 2007 in our hospital, of whom SF occurred in 227 patients with 234 lesions excluding hybrid stenting during the follow-up period (1529±431 days). Among them, 67 patients had DAPT discontinuation after stent implantation (duration 535±458 days), of whom 11 had stent thrombosis: 2 with early stent thrombosis (within 30 days), 2 with late (from 31 days to 1 year), and 7 with very late (more than 1 year). The duration from discontinuation of DAPT to stent thrombosis was 560±500 (12 to 1460) days. The cumulative incidence of stent thrombosis on non-DAPT or DAPT in the 1-year landmark analysis was evaluated by the Kaplan-Meier method (non-DAPT vs. DAPT; Log-rank p<0.001). Results are shown in the figure.



Landmark analysis in non-DAPT and DAPT

Conclusion: Long-term DAPT could be recommended in patients with SES fracture.

P1530 Statin reduces TLR rate as well as mortality after sirolimus-eluting stent implantation: from j-cypher registry

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Background: Numerous studies have demonstrated the importance of statins in prevention of cardiovascular events among patients with coronary artery disease. However, whether statins reduce target lesion revascularization (TLR) after drug-

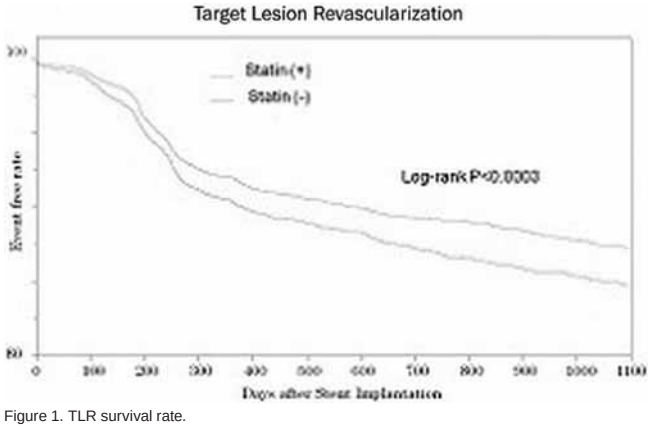

Figure 1. TLR survival rate.

eluting stent (DES) implantation was not addressed. This study aimed to evaluate the influence of statin therapy on the incidence of TLR after DES implantation.
Methods: A total of 12,706 patients undergoing sirolimus-eluting stent (SES) implantation were identified from the J-Cypher registry. Patients were divided into 2 groups according to the use of statins at hospital discharge (Statin group; 6208 patients, No-statin group; 6,498 patients). Three year clinical outcomes were compared between the 2 groups.
Results: Patients with statin had lower all-cause (5.2% vs 10.6%; $p<0.0001$) and cardiovascular (2.4% vs 4.3%; $p<0.0001$) mortality as compared with those without statin. TLR rate was significantly lower in patients with statin (11.1% vs 13.0%; $p<0.0008$). After multivariate analysis with 25 co-variables, statin therapy remained as independent predictors of reduced all-cause mortality (relative risk ratio (RR) 0.63, 95% confidence interval (CI) 0.56-0.73, $p<0.0001$) and TLR (RR 0.84, 95% CI 0.76-0.94, p=0.0017).
Conclusions: Statin therapy reduces both mortality and TLR rate after SES implantation

P1531 One-year degree of neointimal coverage of different drug eluting stents. A comparative study with optical coherence tomography

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Purposes: Late stent thrombosis is a major concern in patients treated with drug eluting stents. Lack of endothelization or late strut malapposition might be involved in this complication. The aim of this study was to compare the degree of strut endothelization and apposition of three different drug eluting stents (sirolimus, paclitaxel and everolimus) as evaluated more than one year after stent implantation.
Methods: We studied 40 patients, 64±10 years old, with coronary heart disease who presented late success after treatment with sirolimus, paclitaxel or everolimus eluting stents and and were angiographically reevaluated, at least, one year after the initial procedure (39±21 months). The reasons for the second angiographic study were clinical recurrence due to restenosis of another treated segment, progression of arteriosclerotic disease, or chest pain without significant coronary stenoses. The target segment was analysed by optical coherence tomography (frequency domain imaging) after a high rate infusion of 10 ml of contrast medium.
Results: A total of 66 stents with 35202 struts were analysed: 11841 from sirolimus, 11638 from paclitaxel and 11723 from everolimus eluting stents. Most of the struts (87%) were covered by a tiny neointimal tissue of 87±35μm. The thickness of the neointimal coverage was different among the three studied stents: sirolimus 72±27μm, paclitaxel 84±26μm and everolimus 109±40μm ($p<0.001$). Everolimus eluting stents showed a lower rate of uncovered struts ($p<0.001$), malapposed struts ($p<0.001$) or the combination of both ($p<0.001$) as compared with sirolimus or paclitaxel eluting stents (table). On the contrary, the paclitaxel eluting stent showed a higher rate of malapposed struts than sirolimus ($p<0.001$) or everolimus eluting stents ($p<0.001$) (table).

Table 1

	Sirolimus (n=11841)	Paclitaxel (n=11638)	Everolimus (n=11723)
Uncovered	1683 (14%)	1296 (11%)	637 (5%)
Non-apposition	191 (2%)	753 (6%)	19 (0.2%)
Both	1874 (16%)	2049 (17%)	656 (6%)

Sirolimus vs Paclitaxel ($p<0.001$); Sirolimus vs Everolimus ($p<0.001$); Paclitaxel vs Everolimus ($p<0.001$).

Conclusions: Different late stent healing patterns were observed among three widely used drug eluting stents. The everolimus eluting stent showed the lowest rate of uncovered and malapposed struts after one year follow up.

P1532 Impact of contrast nephropathy on long term outcomes after acute MI: three year results from HORIZONS-AMI study

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Purpose: Contrast induced acute kidney injury (CI-AKI) is an important cause of in-hospital renal failure and has been associated with worse thirty day and one year clinical outcomes. However, the impact on late outcomes (>one year) after acute myocardial infarction is not known. We therefore sought to investigate the impact of CI-AKI on long-term cardiovascular outcomes three years after primary PCI in the HORIZONS-AMI trial.
Methods: Patients were stratified by the occurrence of CI-AKI, defined as an increase in serum creatinine of ≥0.5 mg/dL or ≥25% within 48 hours of PCI. Outcomes were compared at designated follow-up intervals of thirty days, one year, and three years, using the log rank test. The primary outcomes were major adverse clinical events (MACE: death, reinfarction, ischemic TVR, stroke), major bleeding not related to CABG, and net adverse clinical events (NACE: MACE or major bleeding).
Results: CI-AKI occurred in 483/3344 pts (14.4%), the implications of which are shown in Table 1.

Table 1

	CI-AKI(n=483)	No CI-AKI (n=2861)	RR (CI)	P Value
30 days				
NACE	22.2% (107)	9.5% (270)	2.47 (1.97, 3.09)	<0.0001
MACE	11.8% (57)	4.5% (128)	2.71 (1.98, 3.70)	<0.0001
Death	7.9% (38)	1.7% (48)	4.80 (3.14,7.35)	<0.0001
Major bleeding	14.7% (70)	6.0% (170)	2.54 (1.92, 3.35)	<0.0001
Ischemic TVR	4.0% (19)	2.1% (59)	1.94 (1.15, 3.25)	0.01
Stent thrombosis	3.6% (15)	2.3% (58)	1.57 (0.89, 2.76)	0.12
3 years				
NACE	40.4% (192)	24.4% (675)	1.90 (1.61, 2.23)	<0.0001
MACE	34.2% (161)	20.0% (548)	1.90 (1.59, 2.26)	<0.0001
Death	16.3% (77)	5.1% (141)	3.42 (2.59, 4.52)	<0.0001
Major bleeding	17.3% (81)	7.3% (205)	2.48 (1.92, 3.21)	<0.0001
Ischemic TVR	18.1% (78)	12.5% (335)	1.50 (1.17, 1.91)	0.001
Stent thrombosis	7.6% (30)	4.6% (113)	1.65 (1.11, 2.48)	0.01

Conclusions: CI-AKI after primary PCI is associated with worse short and long-term outcomes related to ischemia, bleeding, and death. These data support close surveillance of patients with risk factors for CKD for the development of CI-AKI in STEMI.

P1533 Prognosis after percutaneous coronary intervention in patients with psoriasis: a cohort study using Danish nationwide registries

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Background: Psoriasis is a prevalent inflammatory disease associated with increased risk of coronary artery disease and need for coronary revascularization. However, the potential impact of psoriasis on the prognosis following percutaneous coronary intervention (PCI) is unknown.
Methods: The study comprised the entire Danish population undergoing a first-time PCI in the period 2002-09. Cox regression models, controlling for age, gender,socioeconomic status, pharmacological treatment, and comorbidity were used to assess the risk of 1) a composite endpoint of myocardial infarction or reintervention (PCI and coronary bypass surgery) and 2) all-cause mortality.
Results: A total of 53,141 patients, including 1074 with mild psoriasis and 315 with severe psoriasis, with first-time PCI in the study period were identified. Patients with severe psoriasis were younger, there were a higher percentage of women, and they received more pharmacotherapies (antihypertensive, cholesterol-lowering, anti-diabetic,and antidepressive agents) compared to patients without psoriasis. Patients with severe psoriasis had increased risk of endpoints, including death, compared to patients without psoriasis. For the composite endpoint incidence rates were 45.9 (95% confidence interval [CI] 44.8-46.9), 49.0 (CI 41.9-57.4), and 64.8 (CI 49.1-85.5) per 1000 patient-years for patients without psoriasis, mild psoriasis, and severe psoriasis, respectively. Hazard ratios were 1.03 (CI 0.88-1.21) for mild psoriasis and 1.39 (CI 1.05-1.84) for severe psoriasis. The corresponding HRs for all-cause mortality were 1.09 (CI 0.90-1.33) and 1.67 (CI 1.24-2.26). Sensitivity analyses accounting for post-PCI treatment confirmed the results and subanalyses of patients undergoing primary PCI suggested an additional risk increase for all patients with psoriasis.
Conclusion: This nationwide study of recurrent ischemic events and mortality following PCI demonstrated an increased risk in patients with severe psoriasis compared to patients without psoriasis. Increased systemic inflammation may contribute to this novel finding.

P1534 Association of symptom onset-to-door time and door-to-balloon time with one-year mortality after primary percutaneous coronary intervention: result from the KAMIR

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Purpose: In patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI), early reperfusion is believed to improve left ventricular systolic function and reduce mortality. However, long-term (>1 year) data are sparse. The purpose of this study was to eval-

uate the association of symptom onset-to-door time (SDT) and door-to-balloon time (DBT) with one-year mortality.
Methods: A cohort of 4,564 consecutive patients (median age 63 years, 73% male) with STEMI treated with primary PCI enrolled in the Korea Acute Myocardial Infarction Registry were stratified according to SDT and DBT and analyzed for death and composite of major adverse cardiac events (MACE, death or myocardial infarction or revascularization) during hospitalization and at one-year.
Results: Primary PCI was performed at median SDT of 160 minutes (range, 16 - 720) and median DBT of 82 minutes (range, 16 - 360) after presentation. Among the quintiles of SDT (<90 min, 90-180 min, 180-270 min, 270-360 min, and 360-720 min), there was significant difference in in-hospital death and composite of MACE (4.7%, 4.4%, 5.4%, 5.2%, and 7.1%, p=0.036; 5.2%, 5.0%, 6.1%, 6.4%, and 7.5%, p=0.035, respectively) and one-year death and composite of MACE (6.4%, 6.5%, 7.3%, 9.6%, and 12.0%, p<0.001; 14.0%, 13.9%, 15.0%, 16.7%, and 18.2%, p=0.012, respectively). Among the quintiles of DBT (<60 min, 60-90 min, 90-120 min, 120-180 min, and 180-360 min), there was significant difference only in one-year death (6.4%, 7.9%, 9.6%, 8.6%, and 9.2%, p=0.024). In multivariable modeling, SDT was identified as an independent predictor of one-year mortality (OR 1.185, 95% CI 1.061-1.324, p=0.0027) and DBT was marginally significant as a predictor of one-year mortality (OR 1.113, 95% CI 0.987-1.256, p=0.0814).
Conclusions: In a real-world cohort of STEMI, this study showed that both SDT and DBT were associated with increased one-year mortality after primary PCI for STEMI. These results suggest that physicians and health care systems as well as the community should work together to minimize both SDT and DBT.

P1535 Impact of vascular access on in-hospital and one-year mortality in patients with acute myocardial infarction undergoing percutaneous coronary intervention: result from the KAMIR

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Purpose: Bleeding has recently emerged as a predictor of early and late mortality after percutaneous coronary intervention (PCI). The need for full anticoagulation and multiple anti-platelet therapies including glycoprotein IIb/IIIa inhibitors contributes to the risk of bleeding complications after PCI in acute myocardial infarction (AMI). Transradial access (TRA) reduces bleeding after PCI compared with transfemoral access (TFA), although its association with mortality is controversial. This study was designed to determine the association of vascular access with mortality in patients with AMI.
Methods: A cohort of 13,865 patients (mean age 66.6 year, female 28.5%) treated with PCI were selected from a prospective cohort study, the Korea Acute Myocardial Infarction Registry, and stratified according to TFA or TRA and analyzed, including a multivariable modeling, for death and composite of major adverse cardiac events (MACE, death or myocardial infarction or revascularization) during hospitalization and at one-year.
Results: PCIs were undergone using TFA in 11,427 (82.4%) patients and TRA in 2,438 (17.6%). Transradial cohort was younger, more male and had lower frequency of higher Killip class and medical illness. Median length of hospitalization was shorter in transradial cohort (6.0 days vs. 5.0 days, p<0.0001). Major bleeding was not different (0.4% vs. 0.3%). Death and composite of MACE were higher in TFA group during hospitalization (4.9% vs. 1.4%, p<0.0001; 7.0% vs. 2.6%, p<0.0001, respectively). These differences were sustained at one-year (7.7% vs. 2.5%, p=0.0001; 15.1% vs. 8.3%, p<0.0001, respectively). In multivariable analysis, major bleeding and TRA were independent predictors of in-hospital mortality (OR 7.80, 95% CI 3.137-19.4, p<0.0001; OR 0.29, 95% CI 0.142-0.583, p=0.0005, respectively) and one-year mortality (OR 5.52, 95% CI 2.403-12.678, p<0.0001; OR 0.45, 95% CI 0.303-0.672, p<0.0001, respectively). In analysis adjusted with propensity score matching, TRA was remained as predictor of in-hospital and one-year mortality.
Conclusions: In the analysis of a large contemporary multicenter AMI registry, PCI using TRA is associated with significantly better clinical outcomes and mortality during hospitalization and at one year compared with PCI using TFA. These results, in the context of prior clinical trials, suggest that wider adoption of TRA for PCI in clinical practice improves clinical outcomes in patients with AMI.

P1537 Impact of sirolimus-eluting stent fracture on 5-year clinical outcomes

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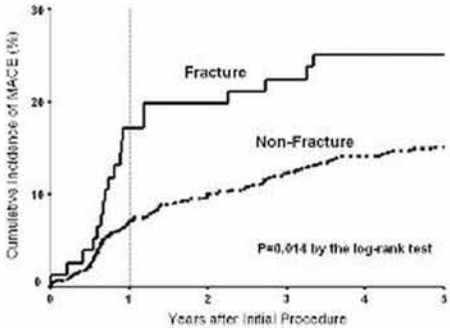
Purpose: Although stent fracture (SF) has been recognized as one of the predisposing factors of in-stent restenosis, it remains uncertain whether SF can increase the risk of major adverse cardiac events (MACE), especially beyond 1 year after sirolimus-eluting stent (SES) implantation. The purpose of this study was to assess the impact of SF relative to non-SF on 5-year clinical outcomes after treatment with SES of comparable unselected lesions.
Methods: A total of 923 lesions in 840 patients undergoing SES implantation and subsequent coronary angiography 6 to 9 months after index procedure were analyzed.
Results: At 6- to 9-month angiographic follow-up, SF was identified in 77 of 923 lesions (8.3%), and 76 of 840 patients (9.0%). In-stent late loss was significantly higher in SF lesions vs. non-SF lesions (0.45±0.58 mm vs. 0.14±0.50 mm, P<0.001), resulting in a significantly higher in-stent restenosis rate (20.8% vs. 4.3%, P<0.001). At 5 years, SF vs. non-SF was associated with a significantly higher MACE rate (25.0% vs. 14.8%, P=0.020), mainly driven by significantly higher target-lesion revascularization (21.1% vs. 11.8%, P=0.020) rate. Adverse effects of SF on clinical outcomes occurred mostly within the first year (17.1% vs. 7.1%, P=0.002), with similar MACE rate between 1 and 5 years (7.9% vs. 7.7%, P=0.957). No significant differences between SF vs. non-SF patients were observed in frequency of stent thrombosis (2.6% vs. 1.6%, P=0.366), death (0% vs. 2.6%, P=0.147) or myocardial infarction (5.3% vs. 3.0%, P=0.222).



Kaplan-Meier cumulative survival curve.

Conclusions: SF of SES was associated with higher MACE rate up to 1 year, mainly driven by higher target-lesion revascularization. Between 1 and 5 years, however, an increase in MACE rate was low and equally acceptable in SF and non-SF patients.

P1538 Incidence and outcome of surgical procedures after coronary stent implantation

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Background: There still remain lingering safety concerns on surgical procedures after coronary drug-eluting stents (DES) implantation.
Methods and results: During 3-year follow-up of 12207 patients (DES: 6802 patients, bare-metal stent [BMS] only: 5405 patients) who underwent stent implantation in the CREDO-Kyoto registry cohort-2, surgical procedures were performed in 2398 patients (3-year incidence: 22%). Surgical procedures, early surgery in particular, were more frequently performed in the BMS group than in the DES group. Cumulative incidences of death/myocardial infarction (MI)/stent thrombosis (ST) and bleeding at 30 days after surgical procedures were low (3.2%, and 2.6%, respectively). The adjusted risk for death/MI/ST and bleeding was similar between BMS and DES (hazard ratio (HR) 1.28 [95% confidence interval (CI): 0.96-1.70], p=0.09, and HR 0.83 [95%CI: 0.64-1.07], p=0.08, respectively). The adjusted risk for death/MI/ST and bleeding was significantly higher in surgical procedures within 42 days than in those beyond 42 days after stent implantation (HR 1.68 [95%CI: 1.23-2.27], p=0.001, and HR 1.53[95%CI: 1.13-2.06], p=0.007, respectively). The adjusted risk of perioperative single relative to dual antiplatelet therapy (APT) for death/MI/ST was marginally significant favoring single APT (HR 0.63 [95%CI: 0.36-1.01], p=0.053).
Conclusions: Surgical procedures were commonly performed after stent implantation, and incidences of ischemic and bleeding complications after surgical procedures were acceptably low with no differences between BMS and DES. Early as compared with late surgical procedures carried significantly higher risk for both ischemic and bleeding complications. Patients receiving perioperative dual APT tended to have higher risk for ischemic events.

P1539 Comparison of 4 years clinical outcome of drug-eluting stent implantation in high-angled bifurcation and lower-angled bifurcation lesion of unprotected left main coronary arteries

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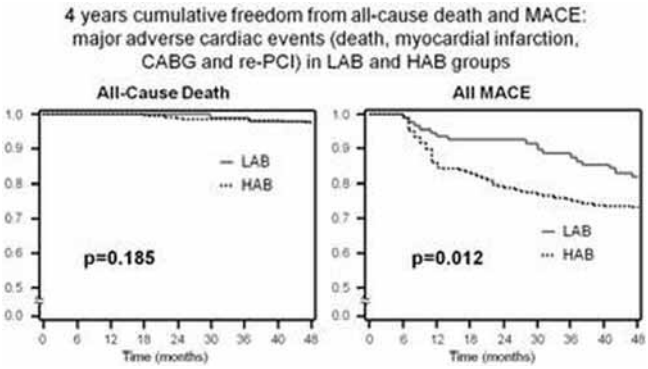
Aim: The aim of study is to compare the 4 years clinical outcome of drug-eluting stent implantation in high-angled (≥70°) bifurcation (HAB) and lower-angled (≤70°) bifurcation (LAB) lesion of unprotected left main coronary arteries.
Methods: A prospective analysis of 488 patients with LMT stenosis (374 HAB and 114 LAB) in five high volume Asian centers after successful stenting in LMT was performed. LMT was treated with 5 strategies (single 195, mini-crush 116, culotte 89, T 47 cases, crush 32 cases, kissing 9).
Results: At 4 years overall cardiac events of LAB (18.4%) were significantly lower than HAB (27.0%) (p=0.012).



Conclusion: Drug-eluting stent implantation in low-angled LMT bifurcation lesion showed lesser incidence of cardiac events (death, myocardial infarction, CABG and PCI) compared with high-angled LMT bifurcation lesion of unprotected left main coronary arteries at 4 years clinical follow-up.

P1540 Comparison of 4 years clinical outcome of stent implantation in renal failure patients with dialysis: comparison with bare metal stents, first and second generation drug-eluting stents

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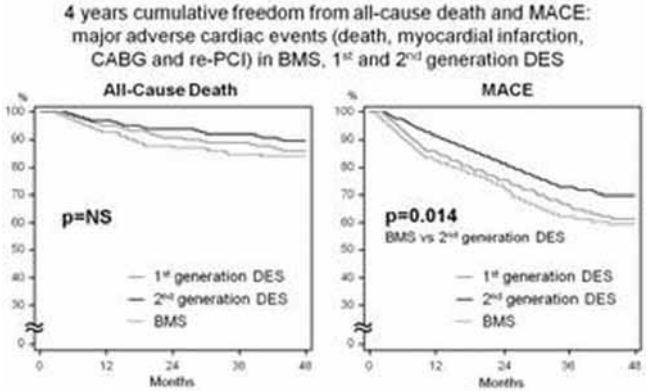
Aim: The aim of study is to compare the 4 years clinical outcome of stent implantation with bare metal stent (BMS), first generation (sirolimus-eluting and paclitaxel eluting stent: 1st DES) and second generation (Xience V and Nobori: 2nd DES) drug-eluting stent implantation in chronic renal failure with dialysis (CRF-HD).
Methods: A prospective analysis of 898 CRF-HD patients with CAD (288 BMS, 311 1st DES and 299 2nd DES) in five high volume Asian centers after successful stenting was performed. The study endpoints were all cause of death and major adverse cardiac events (MACE: death, MI, CABG, CV event and re-PCI) at 4 years.
Results: The baseline clinical characteristics between 3 groups were similar. See figures for clinical results.
Conclusion: The use of 2nd generation drug-eluting stents in patient with CRF-HD was significantly lesser incidence of MACE than that of BMS at 4 years.



P1542 Health care system delay and heart failure in patients with ST-elevation myocardial infarction

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Context: In patients with ST-Elevation Myocardial Infarction (STEMI), delay from contact to the health care system to initiation of reperfusion therapy (system delay) is associated with mortality, but there is no data regarding the association between system delay and long-term risk of heart failure (CHF).
Objective: To evaluate the association between system delay and the risk of readmissions or outpatient contacts with CHF, following Primary Percutaneous Coronary Intervention (PPCI) in patients with STEMI.
Design, Patients: Historical follow-up study using population-based medical registries. The study population comprised patients with STEMI, transported by the emergency medical service from 1999 to 2010, and treated with PPCI within 12 hours of symptom onset, and with a system delay of ≤6 hours (n=7952). The median follow-up time was 3.1 years.
Results: Cumulative incidence of readmissions or outpatient contacts with CHF was determined using competing risk regression analysis, with death as the competing risk. Crude and adjusted cause specific sub-hazard ratios (SHR) for readmissions or outpatient contacts with CHF were determined for system delay and other covariates.
Results: A system delay of ≤60 (n=451), 61-120 (n=3,457), 121-180 (n=2,655) and 181-360 (n=1,389) minutes corresponded with long-term risk of readmissions or outpatient contacts with CHF of 10.1%, 10.6%, 12.3% and 14.1%, P<0.001 (Figure). In multivariable analysis, system delay was an independent predictor of readmissions or outpatient contacts with CHF (adjusted SHR per hour increase in delay=1.10, 95% Confidence intervals 1.02-1.18, P=0.010).

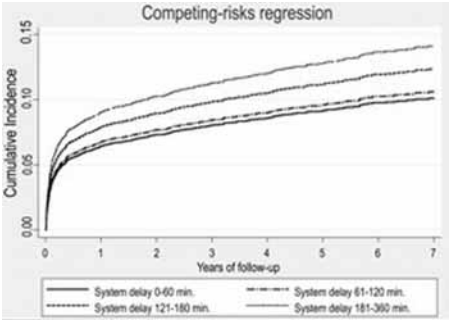

Figure 1

Conclusion: In patients with STEMI, optimal health care system performance is associated not only with reduced mortality, but also reduced risk of CHF among survivors.

P1543 Outcome after PPCI for STEMI is predicted by SYNTAX tercile

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Purpose: Patient specific factors that are known to affect prognosis after primary percutaneous coronary intervention (PPCI) for ST-elevation myocardial infarction (STEMI) include age, the presence of diabetes mellitus and left ventricular function. Although debate continues over optimal revascularisation strategy (immediate, staged or culprit-only), little is known about the impact of extensive coronary artery disease at presentation on prognosis after PPCI. The SYNTAX score is an angiographic tool that quantifies the burden of coronary disease in an individual. It has been validated in stratifying outcomes in multivessel PCI and left main stem intervention, but to date no studies have assessed its utility in PPCI.
Methods: Consecutive patients attending a single UK centre undergoing PPCI for STEMI between September 2008 and June 2010 (n=695) were included. SYN-

TAX scoring was performed on angiographic images obtained before coronary intervention by a single trained operator blinded to patient details and outcome. Scoring was validated by analysis of 3 separate cohorts by 2 other experienced trained operators. Patients were split into 3 subgroups as in the SYNTAX trial (score $\leq$22 (low, L), 22.5-32 (intermediate, IM) and $\geq$ 32.5 (high, H)), and patient data and outcome measures obtained by interrogation of local and national databases.
Results: 674 of 695 patients (mean age 64.1±12.5, 78.4% male) were included in the analysis with 21 being excluded owing to inability to score (previous CABG, images unavailable). The ability to allocate a SYNTAX tercile was reproducible between observers (K = 0.75). The median SYNTAX score was 19, with scores of L 14 (n=437), IM 26 (n=170), H 36 (n=67) in each tercile. There were linear relationships between SYNTAX tercile and age (p=0.0002), blood glucose (p<0.0001) and serum creatinine (p<0.0001). An established diagnosis of diabetes mellitus (p=0.04) and a history of previous myocardial infarction (p=0.004) were also associated with progressively higher SYNTAX tercile. Overall 1-year mortality was 7.9%, while 1-year absolute survival for SYNTAX tercile was: L 94.9%, IM 90.5%, H 85.7% (p=0.002). 1-year freedom from a composite of mortality and unplanned revascularisation was: L 92.2%, IM 86.9%, H 79.4% (p=<0.001).
Conclusions: The SYNTAX score, when applied to an unselected population of patients undergoing PPCI for STEMI, provides useful prognostic information regarding 1-year survival from death and revascularisation. These findings may provide supporting evidence towards routine complete revascularisation of non-culprit coronary artery disease after PPCI.

P1544 Prognostic value of the corrected TIMI frame count in the era of direct PCI and GP IIb/IIIa antagonists for patients with acute myocardial infarction

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Background: Data from studies of the "thrombolytic era" suggest that the quality of epicardial reperfusion measured by the CTFC significantly correlates with the prognosis. Higher values of the CTFC were related with an increased risk of adverse outcome. But several studies of the "post-thrombolytic era" disproved this prognostic significance. To resolve this controversy about the benefit of determining the CTFC, this question needs to be reanswered in a modern population of patients in AMI.
Methods: In a large unicenter, clinical study we included 2309 consecutive patients who underwent direct PCI for AMI in an university hospital setting from 2000 to 2006. In a subgroup of 821 patients, for whom TIMI parameters were assessed, survival analyses were performed to evaluate the prognostic value of the CTFC.
Results: After direct PCI, 8.8% of the patients showed a CTFC of < 14 frames, 46.6% a CTFC of 14 – 27 frames, 25.8% a CTFC of 28 – 40 frames and 18.8% a CTFC of >40 frames. Univariate Cox Proportional Hazards Regression and Kaplan Meier analyses revealed that the CTFC was not a significant predictor for survival on the basis of a significance level of p≤0.050 (Figure 1). Whereas treatment with GP IIb/IIIa antagonists was associated with a significant reduction in risk for these patients (HR: 0.636; CI 95%: 0.430 – 0.940; p=0.023). Stratifying treatment with GP IIb/IIIa antagonists by the different categories of CTFC, this significance in risk reduction disappeared.

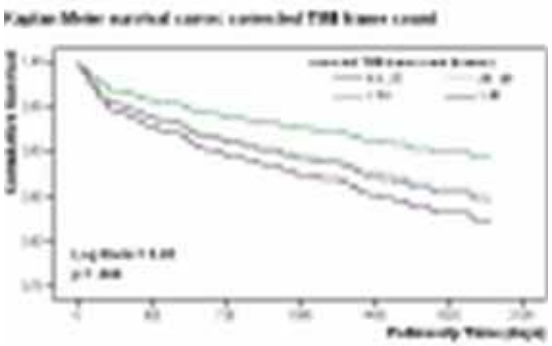

Figure 1

Conclusion: In contrast to studies of the "thrombolytic era", demonstrating the association of immediate CTFC and mortality, the present data suggest that, after "state-of-the-art" treated MI, there is no significant difference in long-term mortality between patients categorized by this parameter of epicardial reperfusion.

P1545 Clinical characteristics of the patients who developed cardiac events after deferral of percutaneous intervention according to intracoronary pressure measurement

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Purpose: Percutaneous coronary intervention (PCI) is usually deferred in patients with functionally nonsignificant intermediate coronary lesions. The aim of this study was to examine the characteristics of the patients who developed cardiac events after their PCI was deferred according to intracoronary pressure measurement.
Methods and results: The study included 107 consecutive patients (mean age 63±10 years; 77% men) whose revascularization was deferred based on a FFR value ≥0.75. Indications for coronary angiography were angina pectoris (53%), positive or inconclusive stress testing (26%) and acute coronary events (21%). Cardiac events were defined as death, MI, revascularization and CCS II-IV angina. A total of 124 lesions were evaluated, mean FFR value was 0.86±0.06 and mean lesion percent diameter stenosis was 60±7%. At 30±17 months of follow-up, cardiac events occurred in 44 patients (42%, 4 deaths, 10 acute coronary events, 11 revascularizations, 19 CCS II-IV angina). Age, cardiovascular risk factors, history of previous cardiac events, number of stenotic coronary arteries, mean FFR and lesion diameter stenosis, drug usage after the procedure, glucose, LDL and non-HDL level during follow-up were similar in the two groups. Patients with cardiac events were more frequently men (94% vs. 71%), had lower HDL cholesterol (39 mg/dl vs. 46 mg/dl), lower ejection fraction (0.51 vs. 0.62) and more frequently documented ischemia (79% vs. 8%) after the procedure compared to those without events. In Cox regression analysis, persistence of ischemia after the deferral was the only important determinant of the cardiac events (RR 8.5, 95%CI 2-39; p=0.006).
Conclusion: Although deferring PCI in patients without critical reduction in FFR is a safe option during long-term follow-up, persistant ischemia despite optimal medical management is an independent predictor of adverse outcome.

CHALLENGING PERCUTANEOUS CORONARY INTERVENTION ON THE LONG TERM

P1546 Five-year clinical outcomes of dialysis patients after sirolimus-eluting stent implantation compared with bare metal stent

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Purpose: Several studies demonstrated that sirolimus-eluting stent (SES) improves short term clinical outcomes in dialysis patients. However, there is little information of long-term outcomes after SES implantation in a subset of dialysis patients. Our aim was to investigate whether SES improves long term clinical outcomes of dialysis patients compared with bare metal stent (BMS).
Methods: The study population consisted of 123 consecutive patients on dialysis. A total of 56 dialysis patients were treated with SES between August 2004 and November 2006 (SES group). As a control group, we selected 67 consecutive dialysis patients who were treated with BMS from January 2000 to July 2004 before the approval of SES (BMS group). Clinical follow-up was obtained by clinical records or telephone contact. Major adverse cardiac events (MACE) included all cause death, myocardial infarction (MI) and target lesion revascularization (TLR).
Results: The baseline patients' characteristics of the 2 groups were well matched. The prevalence of diabetes mellitus was approximately 50% in the both groups. Clinical follow-up was obtained in all patients. The 1-year MACE was significantly lower in the SES group (26.8%) than in the BMS group (43.3%; p=0.02). However, 5-year MACE was not significant different between the 2 groups (SES: 67.8% vs. BMS: 73.1%, p=0.29), mainly due to high mortality in the both groups (SES: 55.4% vs. BMS: 49.3%, p=0.63). The incident of TLR was not significant different at 5 years (SES: 30.4% vs. BMS: 28.4%, p=0.98).
Conclusions: Approximately 70% of patients on dialysis have MACE during 5 years regardless of stent type, mainly due to high mortality. SES did not improve 5-year clinical outcomes compared with BMS in dialysis patients.

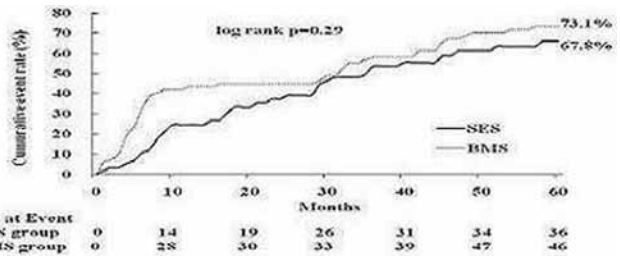

Figure 1. MACE after procedure.

P1547 Association between P2Y12 platelet receptor(C34T and G52T) polymorphisms and risk of cardiovascular events in coronary heart disease with clopidogrel in Chinese

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Background: Recent datas have implicated a haplotype of P2Y12 platelet receptor, as potential risk determinant for atherothrombosis. We wanted to investigate whether the platelet P2Y12 receptor polymorphims affected long-term prognosis of Chinese patients who were treated with clopidogrel after percutaneous coronary intervention (PCI).
Methods: Between November 1,2008 and November 31,2009,268 Patients who received PCI and were exposed to clopidogrel treatment for almost 12 months, were enrolled in Hospital and underwent P2Y12 (G52T and C34T) determination. Follow-up was 12 months. The primary endpoint was a composite of death, myocardial infarction, urgent coronary revascularisation and stent thrombosis occurring during exposure to clopidogrel.
Results: The patients were grouped H1/H1 (n=195) and H2 carriers (H1/H2 and H2/H2, n=73) by P2Y12 G52T genetype. Baseline characteristics were balanced between the two groups, except the proportion of H1/H1 is higher than H2 carriers in two vessel lesions ($P<0.05$). The combined end points also occurred more frequently in H2 carriers than in H1/H1 (10 vs 9, $P<0.05$). There were no significant difference between two groups with myocardial infarction, stent thrombosis, Urgent coronary revascularization and death ($P>0.05$). During the following time, cumulative survival of H2 carriers was lower than H1 (HR=2.543,95%CI:1.033-6.259, P=0.042). The patients were also grouped CC genetype (n=174) and T carriers (CT and TT,n=94) by P2Y12 C34T genetype. Baseline characteristics were balanced between the two groups. There were no significant difference between two groups with the combined end points and cumulative survival (HR=1.081,95%CI: 0.426-2.746,P=0.870).
Conclusion: P2Y12 platelet receptor H2 haplotype (G52T) is a major determinant of prognosis in chinese patients with cardiac heart disease (CHD) who are receiving clopidogrel treatment after PCI. But there is not a strong association between C34T and an increased risk of cardiovascular events in patients with CHD receiving clopidogrel.

P1548 Association between cytochrome P450 2C19 681G>A polymorphisms and risk of cardiovascular events in coronary heart disease with clopidogrel in Chinese

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Background: The frequent genetic functional variant 681 G>A (*2) of cytochrome P450 2C19 (CYP2C19) is an important contributor to the wide variability between individuals of the antiplatelet effect of clopidogrel. We wanted to investigate whether the CYP2C19*2 polymorphisms affected long-term prognosis of Chinese patients who were treated with clopidogrel after percutaneous coronary intervention (PCI).
Methods: Between November 1,2008 and September 31,2009, 267 Patients who received PCI and were exposed to clopidogrel treatment for almost 12 months, were enrolled in Hospital and underwent CYP2C19*2 determination. Follow-up was 12 months. The primary endpoint was a composite of death, myocardial infarction, urgent coronary revascularisation and stent thrombosis occurring during exposure to clopidogrel.
Results: The patients were grouped CYP2C19*1/*1 (n=130), CYP2C19*1/*2 (n=111) and CYP2C19*2/*2 (n=26) by genetype, and baseline characteristics were balanced among the three groups. Urgent coronary revascularization occurred more frequently in CYP2C19*2/*2 and CYP2C19*1/*2 than in CYP2C19*1/*1 (3 vs 7 vs 2, $P<0.05$). There were no significant difference among three groups with myocardial infarction, stent thrombosis and death ($P>0.05$). The combined end points also occurred more frequently in CYP2C19*2/*2 and CYP2C19*1/*2 than in CYP2C19*1/*1 (4 vs 7 vs 3, $P<0.05$). During the following time, cumulative survival of CYP2C19*2/*2 was lower than CYP2C19*1/*1 (HR=5.65[95%CI:1.63-19.49],P=0.006). Comparing Cumulative survival of CYP2C19*1/*2 with CYP2C19*1/*1, there were no significant difference (HR=1.69[95%CI:0.53-5.36],P=0.376).
Conclusion: CYP2C19*2 genetic variant is a major determinant of prognosis in chinese patients with cardiac heart disease (CHD) who are receiving clopidogrel treatment after PCI. CYP2C19*2/*2 (homozygous) brings a worse influence than CYP2C19*1/*2 (heterozygous).

P1549 Reduced positive affect (anhedonia) is associated with long-term mortality in patients treated with percutaneous coronary interventions: results from the RESEARCH Registry

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Purpose: Negative mood states, like anxiety and depression, have been associated with increased cardiovascular morbidity and mortality in coronary artery disease (CAD). Despite studies showing that negative and positive emotions are not merely opposites on the same continuum, little is known about the impact of positive emotions on these outcomes. We examined whether anhedonia (i.e., the lack of positive affect) was associated with long-term mortality in patients treated with percutaneous coronary interventions (PCI).
Methods: Consecutive PCI patients (N=1236; 72.0% men; mean age 62.0±11.1 years) from the Rapamycin- Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry (Erasmus Medical Center, Rotterdam, the Netherlands) completed the Hospital Anxiety and Depression Scale (HADS) to assess anhedonia at 6 months post-PCI. Anhedonia was defined as a score $\leq$7 (i.e., one SD below the mean) on the Positive Affect scale of the HADS. Endpoints were defined as all-cause mortality and a composite of death and non-fatal myocardial infarction (MI). Information on survival status was obtained from patients' medical records and the Municipal Civil Registries.
Results: The prevalence of anhedonia was 23.6% (292/1236). After a mean follow-up of 6.5±1.6 years, 188 deaths from any cause and 263 events for the composite endpoint were recorded. The incidence of all-cause death at follow-up in anhedonic patients was 22.3% (65/292) versus 13.0% (123/944) in non-anhedonic patients. Cumulative hazard functions were significantly different for anhedonic versus non-anhedonic patients (log-rank χ^2=16.58, p=<0.001 for all-cause mortality and log-rank χ^2=20.26, p=<0.001 for death/non-fatal MI, respectively). In univariable analysis, anhedonia was associated with all-cause mortality (HR=1.63, 95%CI[1.17-2.29], p=0.04) and death/non-fatal MI (HR=1.68, 95%CI[1.27-2.23], p=<0.001). In multivariable analysis, anhedonia remained independently associated with both all-cause mortality (HR=1.50, 95%CI[1.02-2.22], p=0.04) and death/non-fatal MI (HR=1.58, 95%CI[1.14-2.19], p=0.006), after adjusting for socio-demographic and clinical characteristics.
Conclusions: Anhedonia was independently associated with a 1.5-fold increased risk for all-cause mortality and the composite of death and non-fatal MI in patients treated with PCI. Enhancing positive emotions, in addition to reducing negative emotions, may form a target for future psychological intervention trials in patients with CAD.

P1550 Long-term (>5 years) outcomes after percutaneous coronary intervention with bare-metal stents for unprotected left main coronary artery disease

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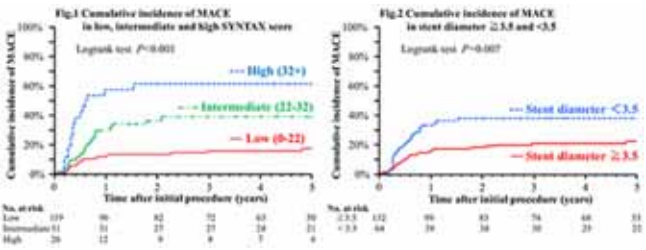
Purpose: Long-term outcomes and potential predictors after percutaneous coronary intervention (PCI) with bare-metal stents (BMS) for unprotected left main coronary artery disease (ULMCAD) were still unknown.
Methods: From March 1991 to December 2004, consecutive 196 patients who underwent PCI with BMS for ULMCAD were evaluated in this retrospective cohort study. Baseline clinical characteristics, plaque distribution in the left main coronary artery, stent profile, and the SYNTAX score were also evaluated. The endpoints of this study were cardiac death (CD), non-fatal myocardial infarction (MI), target lesion revascularization (TLR), and major adverse cardiac events (MACE) including CD, non-fatal MI, and TLR.
Results: Median follow-up duration was 5.2 years (interquartile range, 2.3 to 8.2 years). The mean age was 70.1 years (range from 18 to 90), 139 patients (70.9%) were male. Median SYNTAX score was 19 (interquartile range, 13 to 28). Stents with more than 3.5 mm in diameter were deployed in 132 patients (67.3%). At 5 years, the rate of CD, non-fatal MI, TLR and MACE were 5.3±1.8%, 2.0±1.2%, 22.8±3.2%, and 29.3±3.7%, respectively. In Cox proportional hazard regression model, although any variables were not significantly associated with CD or non-fatal MI, both the SYNTAX score and stent diameter implanted in ULMCAD were significantly associated with TLR (adjusted hazard ratio (HR) [95% confidence interval (CI)], 1.05 [1.01 to 1.08], P=0.008; 0.27 [0.094 to 0.72], P=0.008) and MACE (1.06 [1.03 to 1.09], $P<0.001$; 0.35 [0.14 to 0.83], P=0.017), respectively.



Kaplan-Meier curves for MACE

Conclusions: Lower SYNTAX score and larger stent diameter were significantly associated with long-term (>5 years) TLR and MACE. BMS implantation for ULMCAD with low SYNTAX score and larger vessel size was feasible for as long as 5 years.

P1551 Involvement of rho-kinase activation in the pathogenesis of coronary hyperconstricting responses by drug-eluting stents in patients with coronary artery disease

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Purpose: Drug-eluting stents (DES)-induced impairment of coronary vasomotion has recently received much attention in addition to late stent thrombosis with DES. Enhanced coronary vasoconstriction in response to acetylcholine (ACh) or exercise was demonstrated in the coronary segments adjacent to DES. We have previously demonstrated that activation of Rho-kinase, the effector of the small GTP-binding protein Rho, plays a central role in the pathogenesis of DES-induced coronary hyperconstricting responses in pigs in vivo. We examined whether Rho-kinase activation is also involved in the DES-induced coronary hyperconstricting responses in patients with coronary artery disease (CAD). We also examined structural changes of the coronary segments with DES-induced hyperconstricting responses using optical coherence tomography (OCT).
Methods: In 25 patients with CAD who underwent coronary intervention with either DES (n=16, M/F 10/6, 69±11 [SD] years) or bare-metal stents (BMS, n=9, M/F 7/2, 70±8 years), we examined coronary vasomotor responses to intracoronary ACh before and after intracoronary pre-treatment with a Rho-kinase inhibitor, fasudil (300 μg/min for 15 min). We evaluated coronary vasomotor responses by quantitative coronary angiography (QCA) and coronary vascular structure by OCT.
Results: QCA showed that the coronary vasoconstricting responses to ACh were significantly enhanced in the DES group compared with the BMS group both at the proximal and the distal segments adjacent to the stents (proximal: BMS -13.0±10.7% vs. DES -24.7±14.2%, P=0.043; distal: BMS -24.4±12.2% vs. DES -42.8±14.8%, P=0.004). Importantly, fasudil markedly attenuated the enhanced vasoconstricting responses to ACh in the DES group (proximal -10.2±11.3%, distal -14.2±10.2% vs. before fasudil, both P<0.01). Coronary vasodilating responses to isosorbide dinitrate from the baseline diameter at the proximal and the distal segements adjacent to the stents were comparable between the 2 groups (proximal: BMS 16.2±12.5% vs. DES 12.9±10.8%, P=0.855; distal: BMS 22.4±9.8% vs. DES 17.8±10.8%, P=0.378) with no significant difference in diameter changes in the reference segments (BMS 18.0±11.5% vs. DES 12.5±10.2%, P=0.392). In the OCT imaging analysis, there was no significant correlation between intimal thickness and coronary vasoconstriction to ACh.
Conclusions: These results indicate that Rho-kinase activation is also involved in the pathogenesis of the DES-induced coronary hyperconstricting responses in patients with CAD, suggesting the therapeutic importance of the Rho-kinase pathway.

P1552 High-density lipoprotein cholesterol can predict clinical outcomes in patients who achieving target low-density lipoprotein cholesterol with statin treatment after percutaneous coronary intervention

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Objectives: We investigate the significance of high-density lipoprotein cholesterol (HDL-C) after statin therapy on cardiovascular events in patients with coronary artery disease (CAD) after drug eluting stents (DES) implantation.
Background: A low level of HDL-C is strongly associated with cardiovascular events. However, the significance of HDL-C after stain therapy on the outcomes of patients who underwent percutaneous coronary intervention (PCI) with DES is unclear.
Methods: Patients who underwent PCI with DES from January 2004 to December 2009 were prospectively enrolled. We analyzed follow up (f/u) lipid panel of 2,693 patients (median lab f/u duration 225 days) who had kept on using statin after PCI and who attained low density lipoprotein cholesterol (LDL-C) < 100 mg/dL, and we compared major adverse cardiac events (MACE) including all-cause death, nonfatal myocardial infarction, and target vessel revascularization according to f/u HDL-C level (40 mg/dL for men or 50 mg/dL for women) with the use of propensity scores matching.
Results: Median f/u duration was 832 days. 1,585 (58.9%) patients had low f/u HDL-C level and the other 1,108 patients had high f/u HDL-C level. Low f/u HDL-C group had significantly higher rates of composite of MACE. Low f/u HDL-C was a significant independent predictor of MACE (adjusted hazard ratio 1.404, 95% confidence interval 1.111 to 1.774, p=0.004). In further analysis with propensity scores matching, overall findings were consistent.
Conclusions: Raising HDL-C level with statin treatment may be a subsequent target after achieving the goal of LDL-C level in patients with DES implantation.

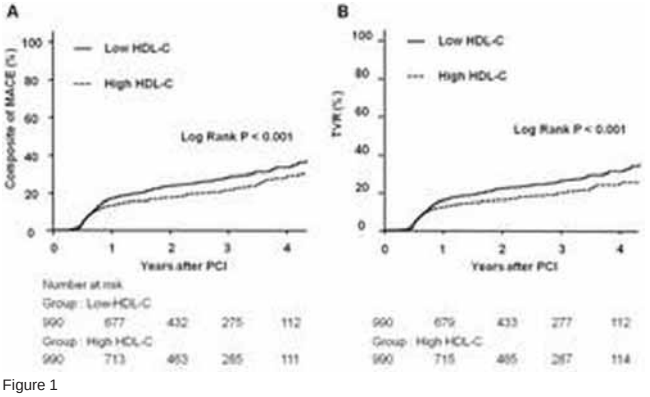

Figure 1

P1553 The impact of (a)symptomatic noncoronary artery disease on prognosis in patients undergoing percutaneous coronary intervention

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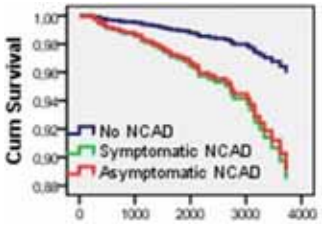
Purpose: Patients undergoing percutaneous coronary intervention (PCI) with symptomatic concomitant noncoronary artery disease (NCAD) are at risk for future cardiovascular events. It is unknown whether patients with asymptomatic NCAD diagnosed by standardized vascular screening have a similar prognosis.
Methods: A standardized vascular screening program was applied to 1650 daily practice PCI patients. Asymptomatic NCAD was defined by the presence of a carotid stenosis >50%, aortic aneurysm >50 mm or an ankle brachial index < 0.9 in patients without any clinical manifestation of NCAD. Patients with a clinical manifestation of NCAD were classified as symptomatic. Outcomes of interest were: vascular death; non-fatal and fatal myocardial infarction; coronary re-intervention or combined cardiovascular events. Survival free hazard ratios (HRs) were calculated separately for patients with asymptomatic or symptomatic NCAD and were compared to patients without NCAD (reference group). HRs were adjusted for baseline characteristics such as age, sex, extent of coronary disease and cardiovascular risk factors.
Results: A total of 257 patients (15.6%) had NCAD, of whom 139 asymptomatic (54.1%) and 118 symptomatic (45.9%). The presence of asymptomatic or symptomatic NCAD predicted vascular death similarly (asymptomatic: HR 2.8 (CI 1.36-5.81) and symptomatic: HR 3.0; (CI 1.42-6.22)). This was also the case for the combined vascular endpoint (asymptomatic: HR 2.4 (CI 1.50-3.77) and symptomatic: HR 2.2 (CI 1.34-3.72)).



Vascular death, follow up in days.

Conclusion: In patients undergoing PCI, both asymptomatic and symptomatic concomitant noncoronary artery disease determine a worse long-term prognosis. Vascular screening should be recommended in all PCI patients to identify those at risk for future events.

P1555 Combined influence of PPIs, CCBs and CYP2C19*2 on on-treatment platelet reactivitiy and on the occurrence of atherothrombotic events in patients undergoing coronary stent implantation

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Background: Carriage of CYP2C19*2 and the use of proton pump inhibitors (PPIs) and calcium channel blockers (CCBs) has been associated with diminished efficacy of clopidogrel. However, previous studies only assessed the isolated impact of these risk factors for clopidogrel poor-response.
Aim: To investigate the impact of combined presence of three pharmacokinetic risk factors for clopidogrel poor-response, i.e. the use of CCBs, PPIs and carriage of CYP2C19*2, on on-treatment platelet reactivity and the occurrence of

atherothrombotic events in 725 patients on dual antiplatelet therapy undergoing elective coronary stenting.
Methods: In a prospective follow up study, on-treatment platelet reactivity was quantified using ADP-induced light transmittance aggregometry and the VerifyNow P2Y12 assay. The clinical study endpoint was the composite of all-cause mortality, myocardial infarction, stent thrombosis and stroke at one year after stenting.
Results: Patients with either one or more than one risk factor exhibited increased platelet reactivity (mean relative increase one risk factor: 11% and >1 risk factor: 28%, respectively). Sixty-four events occurred during follow-up (8.8% of the study population). Patients with one risk factor for clopidogrel poor-response did not have an increased risk of the composite endpoint. However, patients using both CCBs and PPIs and carriers of CYP2C19*2 who used CCBs had a statistically significant increased risk of the composite endpoint (HRadj 2.1 95% CI, 1.0-4.4, p=0.037 and HRadj 3.3 95% CI, 1.1-9.5, p=0.029, respectively).
Conclusions: The presence of more than one of the three investigated pharmacokinetic risk factors for clopidogrel poor-response is associated with an increased risk of adverse cardiovascular events within one year after elective coronary stenting.

P1556 Application of a prior contrast induced acute kidney injury score to patients with STEMI undergoing primary PCI: the HORIZONS-AMI trial

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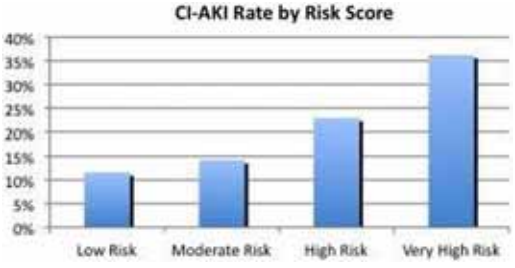
Purpose: We sought to apply a previously validated contrast induced acute kidney injury (CI-AKI) risk score to patients with STEMI undergoing primary PCI in the HORIZONS-AMI trial to ascertain its predictive value in this population.
Methods: We previously developed a CI-AKI risk score from a large prospective database of over 8,000 pts undergoing PCI, from which pts with STEMI were excluded. CI-AKI was defined as an increase in serum creatinine ≥0.5 mg/dL or ≥25% within 48 hours after PCI. The model identified and assigned scores for the risk factors: hypotension (5 points), use of intra-aortic balloon pump (5), congestive heart failure (5), age >75 years (4), anemia (3), diabetes mellitus (3), contrast volume (1 for each 100 cc3), serum creatinine >1.5 (4), and chronic kidney disease (2 for creatinine clearance 40-60 mL/min, 4 for 20-40 mL/min, and 6 for <20 mL/min). Patients were stratified into low (≤5), moderate (6-10), high (11-15), and very high risk (>15) groups. Increasing risk score was strongly associated with higher rates of CI-AKI. We applied this risk score to patients with STEMI undergoing primary PCI in the HORIZONS-AMI trial.
Results: CI-AKI developed in 483/3344 (14.4%) of patients. Increasing risk score was strongly associated with CI-AKI: low risk (11.6% [132/1134]), moderate risk (14.3% [164/1151]), high risk (22.9% [89/388]), and very high risk (36.27% [37/102]) (p<0.0001).



Conclusions: A CI-AKI risk score previously developed for patients undergoing PCI without STEMI is also useful for stratifying the risk of CI-AKI in pts with STEMI undergoing primary PCI.

P1557 Incidence and outcomes of sirolimus-eluting stent thrombosis 8 years after implantation in unrestricted clinical practice

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Purpose: Little is known about the very long-term (>5 years) incidence of Academic Research Consortium (ARC) defined stent thrombosis (ST) and the related clinical outcomes after sirolimus-eluting stent (SES) implantation.
Methods: All consecutive patients with significant coronary artery stenosis treated with implantation of at least one SES between December 2001 and February 2003 were analyzed in order to assess the incidence (estimated by the Kaplan-Meier method) of ST and the consequences related to this event. According with guidelines at the time of implantation, dual antiplatelet therapy (DAT) was prescribed for at least 3-6 months after the index procedure.
Results: 447 consecutive patients (954 lesions) treated with SES were evaluated. Mean age was 61.9±10.4 years, 99 patients (22.1%) had diabetes mellitus and 356 (79.6%) had multi-vessel disease. The mean number of stents implanted per patient was 2.03±1.4. Median DAT duration was 253 (IQR 162-1197) days. Two-hundred and sixteen patients (48.3%) were on DAT at 1 year, 151 (33.8%) at 2 years and 101 (22.6%) at last clinical contact. No intra-procedural neither acute ST occurred while the 8-year cumulative incidence of any ST was 7.4% (9 definite, 3 probable, and 17 possible). Definite/probable ST occurred in 12 patients (cumulative incidence: 3.1%): 2 subacute (1 definite and 1 probable), 1 late (definite) and 9 very late (7 definite and 2 probable). The annual incidence of definite/probable very late ST was between 0.2 and 0.5% up to 8-year follow-up. At the time of ST, 2 patients were still on DAT while the others only on aspirin. Only 1 thrombotic event (that occurred 18 days after the index procedure) was clearly related to a premature DAT discontinuation because of emergent general surgery 7 days before the event. All the cases of definite/probable ST presented as an acute myocardial infarction, which was successfully managed with PCI in 9/12 while 3/12 patients not survived the event. Of the patients, which survived definite/probable ST, 8 were alive at last clinical contact while 1 died for non-cardiac cause.
Conclusions: SES implantation in unselected patients resulted associated with a relatively low incidence of definite/probable ST at very long-term follow-up. However very late ST was still encountered with no evidence of diminution up to 8 years follow-up.

P1558 Impact of initial treatment strategy and timing of intervention on one-year clinical outcomes in non-ST-segment elevation myocardial infarction: result from the KAMIR

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Purpose: Trials comparing early invasive strategy with conservative strategy in patients with non-ST-segment elevation myocardial infarction (NSTEMI) have produced conflicting results that have delayed the current general consensus of up to 48 to 72 hr regarding the benefit of early invasive strategy. A recent study, however, reported that delaying revascularization with percutaneous coronary intervention (PCI) >24 hr in patients with NSTEMI was an independent predictor of mortality and adverse ischemic outcomes. Aim of this study was to determine the impact of initial treatment strategies and timing of PCI on one-year clinical outcomes in patients with NSTEMI.
Methods: A cohort of 4,929 patients with NSTEMI enrolled in the Korea Acute Myocardial Infarction Registry were stratified according to initial treatment strategies and timing of PCI and analyzed for death and composite of major adverse cardiac outcomes (MACE, death or myocardial infarction or revascularization) at one-year.
Results: PCI was performed in 3,584 (73%) patients at median of 26.1 hr (≤12 hr [n=936], 12 to 24 hr [n=643], 24 to 48 hr [n=671], 48 to 72 hr [n=431], and 72 hr to 30 days [n=724]). Composite of MACE at one-year was significantly better in PCI group than in non-PCI group (11.1% vs. 28.3%, p<0.0001). Among patients treated with invasive strategy, timing of PCI was significantly associated with one-year composite of MACE (12.9%, 10.6%, 12.4%, 7.2%, and 10.5%, respectively; p=0.041). In multivariable analysis, timing of PCI was an independent predictor of one-year composite of MACE after adjusting significant factors; age, pulmonary edema or cardiogenic shock, and TIMI risk score. Adjusted ORs for one-year composite of MACE in ≤12 hr, 12 to 24 hr, 24 to 48 hr, and 48 to 72 hr groups of timing of PCI, compared with that in 72 hr to 30 days group, were 1.57 (p=0.005), 1.29 (p=0.16), 1.52 (p=0.017), and 0.78 (p=0.27), respectively.
Conclusions: In a real-world cohort of NSTEMI, this study showed that invasive strategy have benefit in reducing clinical outcomes at one-year and delaying revascularization with PCI >24 hr was not an independent predictor of one-year composite of MACE. These results suggest that, in most patients with NSTEMI, urgent PCI is not mandatory and timing of PCI can be flexible and determined on an individual basis, depending on the patient's risk and clinical course

P1559 Does the obesity paradox exist for survival after a percutaneous intervention?

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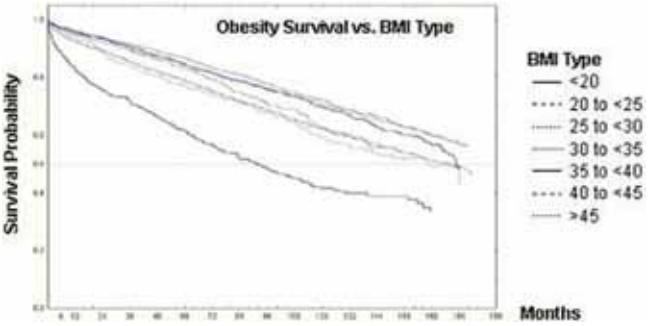
Background: Conflicting literature exists regarding the "Obesity paradox" in patients with coronary artery disease. We sought to examine whether this phenomenon exists in a large cohort of patients who had undergone a percutaneous intervention (PCI)
Methods: We identified 25,815 PCI patients from 01/01/1994 to 12/31/2009. Patient data was obtained from our PCI database, electronic medical records and

social security death index. Patients were classified according to their Body mass index (BMI) into 6 groups (Class 0 - BMI <20, Class 1-BMI 20 to <25, Class 2 - BMI 25 to<30, Class 3 - BMI 30 to<35, Class 4 - BMI 35 to<40, Class 5 - BMI 40 to <45 and Class 6- BMI>45). Kaplan-Meyer survival curves were used in analysis and Bonferroni corrections were applied to the post-hoc pairwise comparisons. A Cox proportional hazard model was constructed to assess the correlations between mortality and race, age, gender, hypertension, diabetes, heart failure, hyperlipidemia and current smoking.
Results: BMI of<25 and BMI>40 had the poorest survival curves while BMI of 25 to 40 had the best survival of all BMI groups (p<0.0001). The final reduced model identified significant correlations between mortality and age (OR 1.06, p<0.0001), mortality and diabetes (OR 1.6, p<0.0001), mortality and heart failure (OR 2.3, p<0.0001,) and mortality and current smoking (OR 1.3, p=0.003)



Conclusion: Obesity paradox does exist with BMI of 25 to 40 conferring a survival advantage over extremes of BMI and normal BMI. Age, current smoking and history of diabetes and heart failure are associated with decreased survival

P1560 Everolimus-eluting stents show no stent thrombosis with similar one year outcomes compared with 1st and 2nd generation drug-eluting stents for the treatment of ST-segment elevation myocardial infarction

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Background: There were no published data regarding the clinical efficacy and safety of second generation drug-eluting stent (everolimus-eluting stent, EES) following primary percutaneous coronary intervention (PCI) in ST-elevation myocardial infarction (STEMI). We evaluated the one-year outcome of everolimus-eluting stent versus to 1st generation (sirolimus-eluting stent, SES and paclitaxel-eluting stent, PES) and 2nd generation (zotarolimus-eluting stent) drug-eluting stents (DES) for the treatment of STEMI.
Methods: A prospective, open-labeled, multi-center cohort has been performed at 4 centers in Korea. All patients will be clinically followed-up for two years. The primary endpoint was major adverse cardiac event (MACE): the composite of cardiac death (CD), recurrent MI and ischemia-driven target vessel revascularization (TVR) at 1 year. Stent thromboses (ST) by ARC definition were analyzed.
Results: Total 797 patients (EES=197, ZES=203, SES=203, PES=194) who were completed more than one year were analyzed. One-year MACE were 2.0%, 5.9%, 3.4% and 5.7% in EES-, ZES-, SES- and PES-group, respectively (p=ns). Cardiac death was 1.0%, 2.5%, 1.5% and 1.0% in EES-, ZES-, SES- and PES-group, respectively (p=ns). ST was 0%, 2.0%, 2.0% and 2.0% in EES-, ZES-, SES- and PES- group, respectively (p=ns).

Table 1. Clinical outcomes and stent thrombosis at 12 months

	EES (n=197)	ZES (n=203)	SES (n=203)	PES (n=194)	p value
MACE	6 (3.1%)	12 (5.9)	7 (3.4)	11 (5.7)	0.322
Cardiac death	2 (1.0%)	5 (2.5)	3 (1.5)	2 (1.0)	0.646
Recurrent MI	1 (0.5%)	2 (1.0)	4 (2.0)	6 (3.1)	0.781
Ischemia-driven TLR	3 (1.5%)	5 (2.5)	0 (0%)	3 (1.5)	0.190
Stent thrombosis	0 (0%)	4 (2.0)	4 (2.0)	4 (2.0)	0.719

EES: everolimus-eluting stent; ZES: zotalimus-eluting stent; SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; MACE: major adverse cardiac event; MI: myocardial infarctin; TLR: target lesion revascularization.

Conclusions: Campared to 1st and 2nd generation DES (SES and PES, ZES), EES showed similar one-year clinical outcomes in terms of MACE in patients with STEMI following primary PCI and no stent thrombosis.

P1561 Does the target vessel impact on results of percutaneous coronary intervention for bifurcation lesions?

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Purpose: Coronary bifurcations remain a challenging lesion subset for percutaneous coronary intervention (PCI). However, it is unclear whether a bifurcation on the left anterior descending (LAD) has the same early and long-term prognosis of a bifurcation on the left circumflex (LCX) or on the right coronary artery (RCA), which have typically a smaller amount of myocardium at stake. We thus appraised the early and long-term outlook of bifurcation PCI stratifying for target vessel.
Methods: Consecutive patients undergoing bifurcation PCI between January 2002 and December 2006 in 22 Italian centers were retrospectively enrolled. Subjects undergoing bifurcation PCI on the LAD were compared to those undergoing bifurcation PCI on the LCX and on the RCA. The primary end-point was the long-term rate of major adverse cardiac events (MACE, i.e. death, myocardial infarction or target lesion revascularization [TLR]).
Results: A total of 3985 patients were included, 2811 (70.5%) treated on the LAD or its branches, 898 (22.5%) on the LCX or its branches, and 276 (6.9%) treated on the RCA or its branches. Early (30-day) MACE were significantly higher in the LAD group (2.4%) and RCA group (2.2%) in comparison to the LCX group (0.9%, p=0.022). However, cumulative long-term (average 24 months) outcomes were similar in the three groups, with MACE in 15.0%, 16.3% and 16.8% (p=0.400), death in 4.6%, 5.1%, and 4.7% (p=0.934), myocardial infarction in 3.8%, 3.6%, and 3.0% (p=0.226), TLR in 10.9%, 11.2%, and 13.3% (p=0.152), and definite stent thrombosis in 1.5%, 1.4%, and 1.2% (p=0.873).
Conclusions: Despite a theoretically smaller amount of myocardium at risk, coronary bifurcation lesions treated with PCI and localized in the LCX and RCA are associated with event rates similar to those localized on the LAD. Thus, care should be taken to skilfully perform PCI and maximize post-PCI medical therapy wherever the bifurcation lesion is located.

P1562 Impact of smoking cessation on the long-term outcome after percutaneous coronary revascularization. Another smoker's paradox?

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Background: Smoking has been shown to be one of the major avoidable causes of cardiovascular diseases. However, the effect of smoke cessation on the clinical outcome of percutaneous coronary revascularization (PCI) is still controversy.
Aim: To describe the impact of quitting smoking on mortality and revascularization after PCI.
Method: A cohort of 9866 consecutive smokers who had undergone successful PCI between 2004 and 2009 were followed in a prospective, observational study. Extensive data, including self-reported smoking habits, were obtained at baseline and during follow-up. Cox proportional hazards regressions were used to assess the hazard ratios (HRs) for death and revascularization associated with smoking categories.
Result: The pre-PCI quitters were older, more likely to be male and had a higher prevalence of diabetes and hypertension than post-PCI and persistent smokers and had more unfavorable clinical and angiographic characteristics. The multivariable-adjusted HRs for mortality were 0.18 (95% confidence interval [CI]: 0.05 to 0.69) for pre-PCI quitters, 0.36 (95% CI: 0.14 to 0.90) for post-PCI quitters, compared with persistent smokers. However, the quitters were more likely than the persistent smokers to undergo additional PCI (1.65 [95% CI:1.35 to 2.07] for pre-PCI quitters and 1.50 [95% CI:1.28 to 1.76]).
Conclusion: The cessation of smoking either before or after percutaneous revascularization was beneficial in all-cause mortality, but not in revascularization, which caused us further study.

P1563 Superior long term outcome associated with native vessel versus graft vessel PCI following secondary PCI in patients with prior CABG

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Background: Secondary percutaneous coronary intervention (PCI) in patients with prior coronary artery bypass graft surgery (CABG) is increasingly common. However, graft vessel (GV) PCI has an inferior outcome with high rates of restenosis, occlusion and re-interventions compared with native coronary vessel PCI. We investigated the outcome of patients who underwent secondary PCI of either a graft vessel (GV) or a native coronary vessel (NV).
Methods: We studied 220 patients (84% male) who underwent PCI to either GV (n=89), NV (n=103) or both VG and NV [NG group] (n=28) between December 2004 and December 2010. Average age was 73.9, 72.9 and 76.1 years for the GV,

NV and NG groups respectively. The prevalence of diabetes mellitus (DM);32.2%, hypertension;90%, hypercholesterolaemia;88%, chronic renal failure (CRF);26%, PVD;9%, CVA/TIA;8%. The p value was not significant between the groups.
Results: The study population underwent 378 procedures (1.7 procedures per patient), GV group; n=126, NV group; n=164 and NG group; n=88. 15.8% [n=20] of the index procedures in the GV, 3.6% [n=6] in the NV group and 17% [n=15] in the NG group were due to in-stent restenosis [ISR]. All other procedures treated de novo lesions. Acute coronary syndrome (ACS) was the clinical presentation in 43% of cases. Drug eluting stent use was 83%, bare metal stent use 17%, average stent per case 1.2, average size of stent 3×20mm, with no significant difference between groups. The median follow up was for 29 months [range 2-69 months]. Target vessel revascularisation (predominantly due to ISR) occurred in 16% of the GV group, and 4% in the NV group [p=0.0004]. The overall mortality for our study population was 15% [n=34] with 17 deaths in the GV group (19.1%), 14 in the NV group (13.5%) [p=0.2 for GV vs NV]. 3 patients died in the NG group (10.7%). Using the Gehan-Breslow-Wilcoxon test there was no difference in the survival rate between GV and NV groups over the six years follow up [p=0.2]. Using univariate analysis the overall risk of death was higher in patients with CRF [RR 2.2, 95% CI 1.2-4.1, p=0.009] and in patients presenting with ACS [RR 2.1, 95% CI 1.1-4, p=0.01]. No difference was seen between groups. Hypertension, hypercholesterolemia, DM, PVD, and CVA/TIA were not associated with increased risk of death.
Conclusion: This registry study demonstrates worse long term outcome of patients undergoing secondary PCI of GV versus NV with higher rates of TVR and mortality. CRF and ACS are independent predictors of death in all patient groups. A strategy of NV rather than GV target PCI should be considered in patients with prior CABG.

P1564 Timing of coronary stent thrombosis in patients treated for bifurcation lesions by 2-stent strategy in the drug-eluting stent era: The comparison between culotte and T-stent techniques

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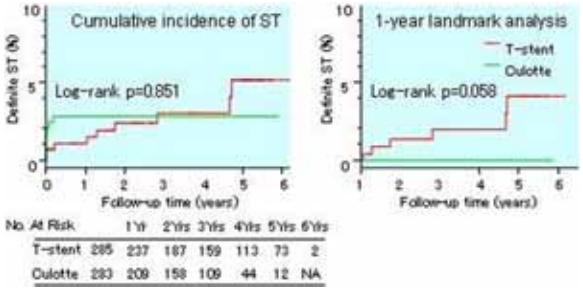
Purpose: Several studies have shown persistent risk of blood clot formation inside drug-eluting stent (DES) over a longer time period after implantation than observed with bare-metal stent. In addition, bifurcation lesions (BLs) and bifurcation stenting have been reported to be risk factors of stent thrombosis (ST). However, the impact of the stenting strategy for BL on ST remains unclear, especially that of 2-stent strategy, in the DES era. We investigated the incidence of ST after DES implantation for BL with culotte and T-stent techniques.
Method and results: Of the 568 patients treated for BLs by 2-stent strategy with DES from October 2000 to February 2006 in our hospital, culotte stent technique was used for 283 and T-stent technique for 285. A total of 17 patients with definite ST were confirmed angiographically during the follow-up period (2.80±1.71 years). In the T-stent group (follow-up period: 3.30±1.79 years), 9 patients had ST: 2 with early ST (within 30 days), 1 with late (from 31 days to 1 year), and 6 with very late (more than 1 year). On the other hand, in the culotte group (follow-up period: 2.44±1.46 years), all 8 ST events had occurred within 78 days after DES implantation: 6 patients with early ST and 2 with late ST. The cumulative incidence of ST which might relate to culotte or T-stent technique was evaluated by the Kaplan-Meier method (culotte vs. T-stent technique; Log-rank p=0.851) and a 1-year landmark analysis (culotte vs. T-stent technique; Log-rank p=0.058). Results are shown in the figure.



Definite ST Landmark Analysis.

Conclusion: Culotte stent technique should be adopted for bifurcation treatment by 2-stent strategy in the DES era.

P1565 Long-term clinical outcome after percutaneous coronary intervention in grafts versus native vessels in patients with previous coronary artery bypass grafts

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Background: The long-term clinical outcome of patients with previous Coronary Artery Bypass Grafting (CABG), undergoing percutaneous coronary intervention (PCI) is not clear.
Methods: This was an observational retrospective study design. Our database was queried for patients with previous CABG, who underwent PCI of either graft or native coronary artery.
Results: Between Feb 2004 and Dec 2008, out of 4741 consecutive patients subjected to PCI, 221 (4.7%), had a history of CABG. Patients were excluded from further analysis if PCI was performed in both native vessel and graft (N=16), if PCI had procedural complications (N=12) or due to lack of clinical follow-up data (N=15). The remaining 178 patients had a mean age of 66.5±9.6 years and there was no difference in baseline charecteristics between patients who underwent PCI in graft (N=83, group G) compared to native vessel (N=95, group N). Patients in group G, compared to group N, had more occluded native vessels (2.1±0.8 vs 1.5±0.8, p<0.001), less occluded grafts (0.52±0.6 vs 0.73±0.8, p=0.05), less frequently presence of at least 1 patent arterial graft (54.2% vs 71.6%, p=0.02), more frequently periprocedural administration of a IIb/IIIa inhibitor (30.1% vs. 14.7%, p=0.02), were treated less frequently with drug-eluting stent (22.9% vs 444.2%, p=0.004) and received larger diameter stents (3.33±0.5 vs 2.96±0.4, p<0.001). During follow up (median duration of 26 months), the incidence of MACEs, cardiac death and repeat revascularization was higher in group G compared to group N (41% vs 17.9% log rank p<0.001, 15.7% vs 5.3% log rank p=0.009 and 25.3% vs 12.6%, log-rank p=0.008). PCI in graft was independently associated with higher risk for MACEs (HR=3.77 1.85-7.65 95%CI, p<0.001), cardiac death (HR=4.89 1.39-17.19 95%CI, p=0.01) and need for revascularization procedure (HR=3.14 1.31-7.51 95%CI, p=0.01).
Conclusions: Our study demonstrates that post-CABG patients, undergoing PCI of graft compared to native coronary artery, have worse long-term clinical outcome. Prospective studies are needed to elucidate the optimal revascularization strategy for such patients.

PERCUTANEOUS CORONARY INTERVENTION: EFFICACITY OF PROOF ON THE LONG RUN

P1566 Long-term follow-up of the patients with multiple drug eluting stent implantation: single vs. multivessel stenting with or without left main coronary stenting

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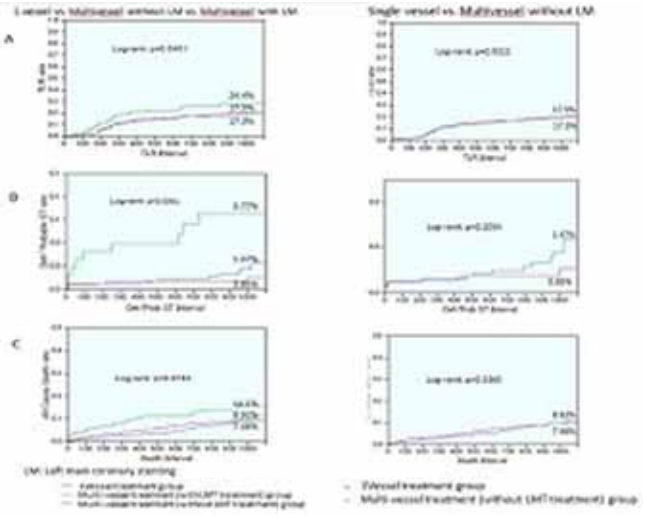
Purpose: The purpose of this study was to evaluate 3-year clinical outcomes (TLR, definite/probable stent thrombosis and all cause death) of extensiveness of treated vessels in very long stent implantation group.



Method: Three-year clinical follow-up data was completed in 10,773 pts (14651 lesions) underwent successful implantation of SES. All patients were divided into four groups based in quartiles. The longest quartile (total stent length per patient 56mm-293mm, n=2,184) were further divided into three groups according to the treated vessel disease; 1) Single vessel treatment group (SVT, n=942), 2) Multivessel treatment without left main coronary stenting (MVT-LM, n=1086), 3) MVT with Leftomain stenting (MVT+LM, n= 156).
Results: Compared with SVT and MVT-LM groups, the proportion of high age, two stent implantation at bifurcation, history of heart failure, and insulin treated diabetes was high in MVT+LM groups. TLR rates through three years were 17.3% in SVT, 17.5% in MVT-LM and 24.4% in MVT+LM (p=0.0451). The incidences of definite/probable stent thrombosis (def/prob ST) were 0.85% in SVT, 1.47% in MVT-LM and 5.75% in MVT+LM ($p<0.0001$). the incidences of all cause death were 7.46% in SVT, 8.97% in MVT-LM and 14.1% in MVT+LM (p=0.0184). There was no difference in the inicdences of TLR, def/prob ST and all cause death between SVT and MVT-LM.
Conclusion: In the very long coronary stenting cohorts, multivessel with left main coronary stenting groups was significantly high risk of three-year clinical events compared with single and multivessel without leftmain coronary stenting.

P1567 Long term outcome of percutaneous coronary intervention in octogenarians 2007-2009

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Purpose: To determine the clinical risks and procedural outcomes for elderly (age >80 years) patients undergoing Percutaneous Coronary Intervention (PCI) and compare results with previous analysis in a similar population.
Method: A retrospective analysis on all patients greater than 80 years, undergoing PCI at a single tertiary referral centre, between 2007 and 2009. Patient demographics, procedural details and in-hospital complications were obtained from patient notes. 30-day, 6 month and 1 year mortality were obtained from analysis of the death registry. Results were compared with a similar study performed previously from 2003-2005 at the same centre.
Results: A total of 118 procedures were carried out in 106 patients over the two year study period, 2007-2009. This compares with 55 procedures performed over a similar time period 2003-2005. Mean age was 82.5 years, with 35% female cases. Mean TIMI risk score for acute coronary syndromes was 5, overall mean logistic Euroscore was 16.75% (additive score 8.8) and BCPCI (British Colombia Percutaneous Coronary Intervention 30 day mortality) mean score was 7.44%. Actual 30-day, 6 month and 1 year mortality was 2.75%, 7.3% and 10.1% respectively. Cardiac related mortality (as per cause of death on death registry) was 2.75% at 30 days, 4.6% at 6 months and 4.6% at one year. Equal numbers of deaths were secondary to cancer as to a primary cardiac cause (n=7). This compares with 21.2% (18.2% cardiovascular) 1 year mortality in the 2003-2005 cohort. The use of radial access for procedure increased from 9.8% in 2007 to 37% in 2008.
Conclusions: The number of elderly patients undergoing PCI is increasing at our centre. The patient group is high risk as per TIMI, Euroscore and BCPCI risk calculators. Despite this, overall outcomes appear better than expected and superior to the previous 2003-2005 cohort.

P1568 Deteriorating quality of life in the elderly three years after percutaneous coronary intervention

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Purpose: It has been previously suggested that elderly patients experience substantial improvements in health-related quality of life (HRQOL) 1 year after percutaneous coronary intervention (PCI). However, a long-term impact of PCI on HRQOL in the elderly is unknown. As PCI is increasingly being performed in older patients, information on the long-term HRQOL after PCI in such older patients is clearly needed. The objectives of this study were, therefore, twofold: 1) To compare the HRQOL of elderly PCI patients ($\geq$70 years of age) with that of younger patients ($<$70 years) at 1, 12, and 36 months post-procedure, and 2) to see if predictors of impaired HRQOL at 36 months post-PCI differed for older versus younger patients.
Methods: A prospective single-centered registry was performed on 651 PCI patients (26.3%$\geq$70 years, 72.4% male) who completed the SF-36 at 1, 12, and 36 months post-PCI. The SF-36 assesses eight self-reported aspects of HRQOL, including: physical functioning, role limitations due to physical health functioning, bodily pain, general health, vitality, social functioning, role limitations due to emotional functioning, and mental health.
Results: Older patients experienced a poorer physical HRQOL at all time points and worse mental HRQOL with respect to vitality and role emotional functioning (all ps$<$0.05). By 36 months, the HRQOL for the older patients worsened in five of the eight sub-domains (all ps$<$0.05). Younger patients did not experience enduring changes in HRQOL, with exception of role physical functioning (increase of +6.29 points; p=0.01). Predictors of impaired HRQOL were generally different for the elderly (diabetes, previous PCI and poor1-month HRQOL) and younger cohorts (smoking, previous bypass surgery, ACE inhibitors and poor 1-month HRQOL).
Conclusions: Elderly PCI patients experience a deteriorating and poorer HRQOL than younger patients across a period of 3 years. This information on the long-term HRQOL of older patients can help care providers counsel them effectively following a PCI; elderly patients with diabetes and a prior PCI, for example, should be given extra medical attention to prevent deterioration of their HRQOL.

P1569 Does the choice of contrast media impact outcomes after primary PCI? Results from HORIZONS-AMI

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Purpose: Previous studies have shown conflicting results on the choice of contrast media for preservation of renal function and prevention of contrast induced acute kidney injury (CI-AKI) and clinical outcomes. We sought to investigate the impact of contrast media type on rates of CI-AKI and clinical outcomes during early and late follow-up from pts with STEMI enrolled in the HORIZONS-AMI trial.
Methods: Pts were stratified according to the type of contrast received (low osmolar or iso-osmolar contrast media). CI-AKI was defined as an increase in serum creatinine of $\geq$0.5 mg/dL or $\geq$25% within 48 hours of PCI. The primary outcomes were major adverse clinical events (MACE: death, reinfarction, ischemic TVR, stroke), major bleeding not related to CABG, and net adverse clinical events (NACE: MACE or major bleeding).
Results: There were no significant differences between rates of CI-AKI with low osmolar vs. iso-osmolar (15.3% vs. 14.3%, RR 1.07 (0.82-1.38), p=0.62). Rates of clinical events at thirty days and one year are shown (Table).

	Low Osmolar (n=1693)	Iso-Osmolar (n=563)	RR (CI)	P Value
30 days				
NACE	10.4% (176)	13.7% (77)	0.74 (0.57, 0.97)	0.03
MACE	4.6% (78)	6.6% (37)	0.69 (0.47, 1.02)	0.06
Death	2.2% (38)	2.9% (16)	0.79 (0.44, 1.41)	0.42
Major bleeding	7.2% (121)	9.0% (50)	0.80 (0.57, 1.11)	0.17
Ischemic TVR	1.7% (29)	3.2% (18)	0.53 (0.29, 0.95)	0.03
3 years				
NACE	27.0% (442)	30.4% (166)	0.85 (0.71, 1.02)	0.08
MACE	22.3% (362)	24.3% (131)	0.90 (0.73, 1.10)	0.29
Death	6.5% (106)	8.5% (46)	0.76 (0.53, 1.07)	0.11
Major bleeding	8.6% (142)	11.1% (61)	0.76 (0.56, 1.03)	0.07
Ischemic TVR	13.6% (213)	14.0% (73)	0.95 (0.73, 1.24)	0.70

Conclusions: In patients undergoing primary PCI for STEMI, the type of contrast media did not affect the rates of CI-AKI. Low-osmolar contrast media was associated with lower rates of NACE and ischemic TVR at 30 days, although these differences were no longer statistically significant at 3 years.

P1570 Angio-guided versus fractional flow reserve-guided percutaneous coronary intervention in patients with small coronary vessel lesions

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Purpose: True small vessels are supplying small myocardial territories therefore functional significance of correspondent lesions is questionable. Moreover, percutaneous coronary intervention (PCI) of not-functional small vessel lesions might be associated with worse clinical outcome. The aim of this study was to assess the clinical impact of Fractional Flow Reserve (FFR) versus Angiography for guiding PCI in the treatment of small coronary vessel lesions.
Methods: From January 2004 to December 2008, all patients treated with PCI for stable or unstable angina in a native small coronary vessel (defined by a reference vessel diameter $<$ 3mm) were enrolled. Patients were divided into two groups according to type of strategy used: Angio vs. FFR-guided PCI.
Results: A total of 717 patients were enrolled (495 Angio-guided PCI, 222 FFR-guided PCI). Clinical follow up was obtained in 97.5% (median follow-up 3.3$\pm$1.3 years). The proportion of patients treated with drug-eluting stent was similar in both groups. At five years, patients treated with FFR-guided PCI showed significantly lower death or non-fatal myocardial infarction (MI) (HR 0.41, 95%CI 0.23-0.75, p=0,004), target vessel revascularization (TVR) (HR 0.52, 95%CI 0.32-0.83, p=0.006) and major adverse cardiac events (MACE) (HR 0.46, 95%CI 0.31-0.68, $p<0.001$). No significant differences were observed between the two groups as to

death and myocardial infarction. Costs of procedures were also reduced in FFR guided strategy ($p<0.0001$).
Conclusions: FFR-guided PCI is more effective than Angio-guided PCI in reducing death or non-fatal MI, TVR and MACE and in patients with small vessel disease.

P1571 Gene mutations or polymorphisms in association with platelet response to aspirin and/or clopidogrel and long-term clinical outcome following coronary stenting

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In pts with aspirin (ASA) and clopidogrel (CL) medication after PCI, low reponse (LR) to ASA and/or CL have been correlated with the risk of stent thrombosis (ST). Moreover, the relationship among some gene mutations or polymorphisms and LR to ASA/CL and risk of ST remained controversial.
In this non-randomized and single-center prospective study (134 pts, age 56±9.9),we assessed several gene mutations or polymorphisms in relation to LR to ASA and/or CL and definite ST (dST),stroke and bleeding after primary,urgent or elective BMS or DES placement.Factor V Leiden, factor V H1299R (R2), protrombin G20210A, factor XIII V34L, β fibrinojen -455 G-A, MTHFR C677T, MTHFR A1298C mutations, and human platelet antijen-1 (HPA-1) (GPIIIa L33P), Apo-E, PAI and ACE gene polymorphisms were investigated.Multiplate analyser was used to assess platelet aggregation (PA) response to ASA and CL.All pts received a prePCI CL loading dose of 600 mg.The duration of CL treatment was 9 to 12 months (m) for BMS, and >12 m for DES.The daily dose of CL was 150 mg for first week, and 75 mg thereafter,and daily ASA dose was 100 to 300 mg.Mean FU period was 660±230 days, and visits including ECG, laboratory and PA assessment were performed within first 7 and 30 days, 3, 6, 9 and 12 mos after PCI. Definite (d)ST were noted in 2 (%1.6) pts,and occurred within the first 22 days.TIMI major and minor bleeding events were noted in 2 (1.6%) and 4 (3.2%)pts, respectively.None experienced a documented ischemic stroke. Baseline median PA (AU.min) response to ADP (ADP-PA) and collagen (Col-PA) were 293±247 and 231±211, respectively.Meaures of PA showed no difference compared with baseline values along the FU period (p=NS).The ADP-PA and Col-PA range were subdivided into quintiles, and 495 and 358 AU.min, the borders of upper quintiles were defined as cut-off values for CLLR and ASALR, respectively.The % of dual LR was 8.6.The CLLR related to platelet count ($p<0.001$) but not with other clinical,laboratory and procedural characteristics (p=NS).Factor V Leiden, factor V H1299R (R2), protrombin G20210A,factor XIII V34L,β fibrinojen-455 G-A,MTHFR C677T and MTHFRA1298C mutations were not associated with CLLR,ASALR or clinical outcome (p=NS). Moreover, none of the variants of ACE gene, Apo-E and HPA-1 related to CLLR, ASALR as well as dST,stroke or bleeding (p=NS).
Conclusions: Factor V Leiden,factor V H1299R (R2), protrombin G20210A,factor XIII V34L,β fibrinojen -455 G-A,MTHFR C677T and MTHFR A1298C mutations,and HPA-1,Apo-E, PAI and ACE gene polymorphisms were not associated with LR to ASA and/or CL and long-term clinical outcome after BMS or DES placement.

P1572 The duration of dual antiplatelet treatment (DAPT), after coronary stent implantation. Doubt the DAPT?

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Purpose: The currently modified recommendations state that the patients with previously implanted coronary stent [Bare-Metal-Stent (BMS) or Drug-Eluting-Stent (DES)] should be treated with dual antiplatelet therapy (aspirin 100 mg plus clopidogrel 75 mg daily) for at least 12 months (Class I, LoE B), followed by aspirin for lifetime. Our purpose was to evaluate the therapeutic effectiveness of this strategy.
Methods: In this observational, one-center study, we enrolled every patient who proceeded for hospitalization in our department and had undergone coronary stent implantation.
Results: From January 2008 until January 2011, 582 patients (men 503 (86.4%), age 65.9±11.3 years) were identified with history of prior coronary stent intervention. 333 (57.2%) of them had been treated with BMS, 152 (26.1%) with DES and 97 (16.7%) with both types. The median time from the angioplasty to the interview was 6.2 years [IQR 1-13 years]. 270 patients (46.4%) had received long-term DAPT for a median time of 3.6 years and only 45 (7.7%) had been treated according to these recommendations. 12 cases (2%) of premature discontinuation were reported. We divided the DAP-treated patients into 4 sub-groups regarding to the duration of the treatment [1 year, >1 year - ≤2 years, >2 years - ≤5 years and >5 years] and we reported the combined [TVR(target-vessel-revascularization) + non-TVR/bleeding] complication rate. In the first sub-group (45 pts) we reported 30 cases of acute coronary syndromes (ACS) (TVR/non-TVR: 37.7%) and 6 bleedings (13.3%). In the second sub-group (70 pts) 34 ACS (TVR/non-TVR: 28.6%) and 19 bleedings (27.1%) were reported. In the third sub-group (126 pts) 81 ACS (TVR/non-TVR: 31.7%) and 43 bleedings (34.1%) were reported. In the last sub-group 74 pts) we reported 54 ACS (TVR/non-TVR: 44.6%) and 31 (41.8%) bleeding events.
Conclusions: In this study, the long-term (more than 12 months) dual antiplatelet treatment was associated with a 2.6-fold increase of the bleeding risk (13.3% vs 34.4%, $p<0,01$). No significant difference in the occurrence of the repeat revascularization was reported (37.7% vs 34.5%, $p>0.5$). These data highlight the need identify not only the minimum but also the optimum duration of dual antiplatelet therapy, taking under option the not-well recognized, bleeding cost.

P1573 Safety of short-term dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting balloons

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Purpose: Clinical studies demonstrated the safety and effectiveness of drug-eluting balloons (DEB) in various clinical scenarios and support the use of paclitaxel-eluting balloons for the treatment of in-stent restenosis (ISR), of small coronary arteries and bifurcations lesions. We analyzed the safety, focused on the rates of late thrombosis (LT), of short-term DAPT for 4 weeks after DEB.
Methods: We analyzed the rates of LT and the duration of DAPT in 8 DEB studies including 1195 patients.
Results: The rates of LT in the DEB trials and the use of DAPT are shown in Table 1. Summarizing the follow-up of 6 to 12 months LT was reported after plain old balloon angioplasty in none of 54 patients (0%), after BMS in none of 37 patients (0%), after DEB alone in 2 of 258 patients (0.8%), after DEB plus BMS in 8 of 284 patients (2.8%) and after DES in 2 of 423 patients (0.5%). Although clopidogrel was administered for 4 weeks only after DEB alone in some trials, no differences regarding thrombotic complications between DEB and DES were reported. The rate of LT after DEB alone was 0% (none of 165 patients) in studies with DAPT for 4 weeks and 2.2% (2 of 93 patients) when DAPT was given for 3 months. After DEB plus BMS all studies used the DAPT for at least 3 months and the rate of LT was 2.1% (8 of 384 patients).
Conclusions: The present analysis shows comparable rates of late thrombosis after DEB with DAPT for 1 month in comparison to DES with long-term DAPT. Beside the proven efficacy of DEB the possible reduction in the duration of DAPT to 1 month may represent an additional advantage regarding safety, patient compliance and costs.

Abstract P1570 – Table 1. LT and DAPT in DEB studies

Trial	Devices used	Treated Lesion	Duration of dual antiplatelet therapy	Late thrombosis at follow-up
PACCOCATH ISR I	Paccocath vs. uncoated balloon	In-stent restenosis	1 month	At 12 months: Paccocath 0%, uncoated balloon 0%
PACCOCATH ISR II	Paccocath vs. uncoated balloon	In-stent restenosis	1 month	At 12 months: Paccocath 0%, uncoated balloon 0%
PEPCAD I SVD	SeQuent™ Please	De novo, small vessels	DEB: 1 month, DEB + BMS: 3 months	At 12 months: DEB 0%, DEB + BMS: 6.3%
PEPCAD II ISR	SeQuent™ Please vs. Taxus™ Liberté™	In-stent restenosis	DEB: 3 months, DES: 6 months	At 12 months: DEB 0%, DES: 0%
PEPCAD III	Coroflex™ DEBlue vs. Cypher™	Complex de novo lesions	6 months	At 9 months: DEB+BMS: Definite 1.3%, probable 0.6%, DES: Definite 0.3%, probable 0%
PEPCAD V	SeQuent™ Please + Coroflex™	Bifurcation	3 months	At 9 months: Definite 3.6%, probable 3.6%
PICCOLETO	Dior™ II vs. Taxus™ Liberté™	De novo, small vessels	1 month in cases of stable angina and lone DEB use, 3 months after DEB and provisional stenting	At 9 months: DEB 0%, DES: 0%
DEBUIT	Liberté™ + Dior™ vs. Liberté™ + plain old balloon angioplasty vs. Taxus™ Liberté™ + plain old balloon angioplasty	Bifurcation	DEB: 3 months, DEB + BMS: 3 months, DES: 12 months	At 6 months: DEB: 0%, DEB + BMS: 0%, DES: 2.5%

LT: late thrombosis; DAPT: dual antiplatelet therapy; DEB: drug-eluting balloon; BMS: bare-metal stent; DES: drug-eluting stent.

P1574 Clopidogrel 150 mg/day versus 75 mg/day in real clinical practice of percutaneous coronary interventions

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Purpose: After presentation data of CURRENT-OASIS 7 we want to estimate impact of double increase in daily oral maintenance dose of clopidogrel in percutaneous coronary intervention (PCI) outcomes. Because improve clinical outcomes in patients undergoing percutaneous coronary intervention after double increase of daily dose of clopidogrel is still debated. This prospective registry evaluated the relative effect of a 150- versus 75-mg daily maintenance dosage of clopidogrel on clinical end-points in patients undergoing PCI at real practice.
Methods: We collected data from October 2009 and included a total of 1247 patients. 614 pts had got clopidogrel, 150 mg/day, during a week after PCI and 633 pts had got clopidogrel, 75 mg/day, at the same time - during a week after PCI, both groups continued clopidogrel support in usually dose, 75 mg/day, till 12 months.
Results: Clopidogrel, 150 mg/day, was associated with significant reductions in major adverse cardiac and/or cerebrovascular events (odds ratio [OR] 0.74; 95% confidence interval [CI]: 0.41 to 0.97), myocardial infarction (OR 0.79; 95% CI: 0.56 to 0.93), target vessel revascularization (OR 0.44; 95% CI: 0.19 to 0.74), and stent thrombosis (OR 0.71; 95% CI: 0.51 to 0.86). However, the 150-mg daily maintenance dosage significantly increased the risk of minor bleeding (OR 1.29; 95% CI: 1.04 to 1.53), as compared with 75 mg/day.
Conclusions: As compared with the currently recommended 75-mg/day maintenance dosage of clopidogrel, the 150-mg/day dosage can reduce major adverse cardiac and/or cerebrovascular events but may increase the risk of minor bleeding.

P1575 Impact of stent type on survival in left main stem PCI

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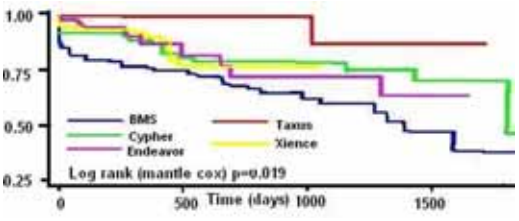
Introduction: There are conflicting data on survival after LMS PCI by stent type.
Methods: We tracked all-cause mortality of 268 consecutive patients after LMS PCI at a single centre from 09/08/11 - 19/04/10.
Results: Mean (SD) age: 70.2 (12.8) years, 194 (72.4%) males. Diabetes: 18.6%; previous PCI: 15.3%; protected LMS: 20.4%. STEMI: 9.7%, NSTEMI: 56.0%, CSA: 34.3%. Mean (SD) SYNTAX score: 36.7 (14.5), median EuroSCORE: 9.1. DES: 65.7% of cases. 74 deaths over 602 patient years (maximum 5.1, median 1.8). Mortality at 5.1 years: 27.6%. There were survival differences when data were stratified by BMS versus DES type (Figure 1). Table 1 shows the 95% HR for the cohort.

Survival (95% HR) stratified by DES use

	Censored at 30 days	Censored at 1 year	Full survival: 5.6 years
Unadjusted	0.28 to 1.56	0.10 to 0.35	0.33 to 0.82
Model 1	0.31 to 2.07	0.13 to 0.50	0.36 to 0.91
Model 2	0.31 to 1.84	0.10 to 0.36	0.38 to 0.96
Model 3	0.31 to 2.08	0.11 to 0.46	0.40 to 1.03
Model 4	0.22 to 1.10	0.09 to 0.35	0.36 to 0.90
Model 5	0.35 to 2.26	0.10 to 0.44	0.42 to 1.06

Model 1: Clinical presentation: STEMI, NSTEMI, CSA. Model 2: EuroSCORE. Model 3: Model 1 + model 2. Model 4: SYNTAX score. Model 5: Model 3 + model 4.



Conclusions: Survival following LMS PCI, both unadjusted and adjusted for clinical characteristics, was greater when patients received a DES than a BMS at 1 year. No significant difference was seen at 30 days or at long-term follow-up.

P1576 Late and very late stent occlusion: IVUS analysis of a series of consecutive patients

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Purpose: To analize the clinical presentation and imaging data obtained with the intra vascular ultra sound (IVUS) performed in patients (pts) referred to our centre for urgent catheterization with the clinical hypothesis of a late or very late stent occlusion.
Methods: Between 2007 and 2010, 29 consecutive pts with late or very late total/subtotal stent occlusion were observed. Each patient underwent IVUS analysis in the diagnostic phase of the angiographic procedure.
Results: Twenty-two pts had a late/very late DES-occlusion (10 Chyper, 4 Taxus, 6 Xience and 2 Endeavor R), and 7 of a BMS. Mean time to repeated angiography was longer for DES than for BMS (28.2±20.37 vs 8.43±4.08 months; p=<0.001). In DES pts STEMI presentation was significantly higher than in BMS pts (50% vs 14.3%; p=0.001). Anti-platelet regimen at the time of the event in the DES group was still dual in 27.3% of pts, single in 50% and discontinued in 22.7%. Sixty percent of DES occluded within 6 months of the interruption of the dual anti-platelet regimen. In the BMS group, anti-platelet therapy was still dual in 43% and single in 57% of cases; no patient had completely discontinued the anti-platelet regimen. QCA parameters after the index stenting procedure comparing DES and BMS pts were not statistically different in terms of post-procedural stenosis,MLD and lesion length. IVUS analysis performed at the time of the late stent failure showed a higher incidence of incomplete stent apposition (ISA) in the DES group compared to the BMS group (57.1% vs 14.3%; p=0.05). In DES group, ISA was found more frequently in pts still under anti-platelet therapy (80 vs 20%). The in-stent IVUS analysis showed similar DES and BMS results regarding EEM CSA: 20.9±4.8 vs 21.6±6.7mm^2, p=0.8; and stent CSA: 7.45±2.3 vs 8.62±2.6 mm^2, p=0.4; but a larger neo-intimal area in the BMS group: 6.5±1.2 vs 3.5±2.2 mm^2, p=0.04. According to the "AVIO" and "MUSIC" criteria, optimal stent expansion was achieved in 31% of DES and 50% of BMS and in 43% of DES vs 85.7% of BMS. Good stent apposition was higher in the BMS group (85 vs 43%, p=0.05).
Conclusions: 1) late DES failure often causes STEMI; 2) BMS-related late events do not correlate with the interruption of anti-platelet therapy while DES-related late events do; 3) in our series, QCA variables do not predict these late stent failures; 4) IVUS observation obtained during the acute presentation show less neo-intimal growth and more ISA in DES, and this is particularly frequent in pts with late DES failure despite ongoing dual anti-platelet therapy, although we cannot determine whether ISA is acquired or acute.

P1577 Comparison of long-term outcomes after PCI in STEMI and NSTE-ACS

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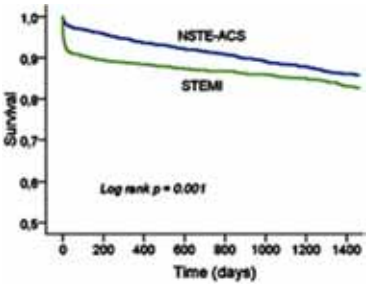
Purpose: Little is known about the comparative long-term outcomes after percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS). We therefore compared the 4-year event rates of NSTE-ACS and STEMI patients treated in consecutive real world cohorts with either bare-metal stents (BMS) or drug-eluting stents (DES).
Methods: A total of 1749 STEMI and 1921 NSTE-ACS patients were treated with a BMS or DES. Median follow-up was 3.7 years. Cox proportianal-hazards regression analyses were used to adjust for potential confounders.
Results: At 4 years, all-cause mortality was significantly lower in NSTE-ACS patients compared to STEMI patients (13.0% vs. 15.5%; Adj. HR 0.67, 95% CI 0.54-0.83). However, a 30-day landmark analysis showed a trend towards higher long-term mortality rates in NSTE-ACS patients (10.9% vs. 7.6%; Log Rank p=0.018; Adj. HR 0.89, 95% CI 0.68-1.17). The observed late catch-up phenomenon (figure) is probably caused by the higher clinical and angiographic risk profile in NSTE-ACS patients. NSTE-ACS and STEMI patients had comparable 4-year incidences of MACE, myocardial infarction and TVR.



Conclusions: STEMI patients had a higher 4-year mortality compared to NSTE-ACS after PCI, mostly due to higher 30-day mortality rates. However, NSTE-ACS

patients seem to have a less favourable long-term prognosis, probably due to their higher risk profile.

P1578 Comparison of multiplate, VerifyNow and PFA-100 in the assessment of on-treatment platelet reactivity in patients treated with aspirin and clopidogrel following coronary stenting

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In pts treated with aspirin (ASA) and clopidogrel (CL) following percutaneous coronary intervention (PCI), the needs for definition of high and low on-treatment platelet reactivity (HOTPR, LOTPR) remained unmet. Although VerifyNow (VN), PFA-100 and multiplate (MPL) have been proposed as novel methods to assess PR, measures of these methods are not interchangable.
In this study we investigated the response to ASA and CL in 614 pts (58.9±10.2 yrs) assessed by MPL.Mean FU period was 752 +253 days, and visits including MPL were performed within first 7 and 30 days,3,6,9 and 12 mo after PCI. Moreover, 107 and 100 of 614 pts were also asssessed by VN and PFA-100, respectively. A good correlation (r=0.63, $p<0.01$) was found between ASA and CL response on MPL. The distribution of MPL were subdivided into quintiles; and borders between 4th and 5th, and between first and second quintiles were regarded as cut-off values for HOTPR and LOTPR, respectively. The interquintile borders were 44,121, 218, 373 and for ADP-PA, and 34, 83, 161, 301 for ASPI-PA, respectively. MPL-ADP showed a weak correlation with VN-PRU (r=0.20, p:0.04) whereas MPL-ASPI and VN-ARU were not correlated (r=0.04, p=NS). Moreover no correlation was found between MPL-ADP and PFA-100-ColADP (r=0.07, p=NS), and between MPL-ASPI and PFA-100-ColEPI (r=0.05, p=NS). Similarly, measures of VN and PFA-100 were not correlated (r=0.05, p=NS). Neither VN,nor PFA-100 measures were different among quintiles of corresponding ADP and ASPI measures on MPL (p=NS). HOTPR for CL and ASA defined by MPL related to a 20 times (4% vs 0.2%, p=0.001) and a 4 times (2.4% vs 0.6%, p=0.001) higher risk of dST; respectively. Moreover dST was noted in 5% of dual HOTPR subset but in none with dual response defined by MPL criteria ($p<0.05$).However, neither cathegorically defined HOTPR or LOTPR, nor stepwise increment in PA with ADP and ASPI on MPL was the independent predictor for ischemic end-points, and bleeding (p=NS). The measures of VN and PFA-100 were not associated with event rate during FU.
Conlusions: The measures of MPL,VN and PFA-100 were not correlated. The measures of VN and PFA-100 showed no relation to clinical events whereas HOTPR on MPL seemed to predict only early risk of dST, but not mid and long-term outcome following the BMS or DES implantation, irrespective of the clinical, metabolic and procedural characteristics.

P1579 An international collaborative meta-analysis of predictors of coronary stent thrombosis including 30 studies, 225,536 patients, and 4,203 thromboses

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Purpose: Stent thrombosis remains among the most feared complications of percutaneous coronary intervention (PCI) with stenting. However, data on its predictors are sparse and conflicting. We thus aimed to perform an international collaborative systematic review focusing on predictors of stent thrombosis.
Methods: PubMed was systematically searched for eligible studies from the drug-eluting stent (DES) era (1/2002-7/2010). Studies were selected if including≥2,000 patients undergoing stenting or reporting on≥25 thromboses. Study features, patient characteristics, and predictors of stent thrombosis were abstracted and pooled, when appropriate.
Results: A total of 30 studies were identified (225,536 patients, 4,203 thromboses), with DES used in 87%. From a total of 47 candidate variable, the most reliable predictors of definite/probable stent thrombosis were diabetes (62% of studies), acute coronary syndrome at admission (57% of studies), and total stent number/length (57% of studies). Age, bifurcation treatment, extent of coronary disease, renal failure and smoking also appeared as significant predictors of thrombosis, but less consistently. Premature discontinuation of dual antiplatelet therapy was also a powerful predictor of stent thrombosis (risk estimate 36.5, $p<0.05$).
Conclusions: Despite numerous possible risk factors, the strongest predictors of stent thrombosis are diabetes, acute coronary syndromes, stent length/number, and premature discontinuation of dual antiplatelet therapy.

P1580 Significant narrowing of circumflex artery leads to worse early and long-term outcome than right coronary artery narrowing in patients with ACS treated with PCI of left descending artery

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Purpose: Significant narrowing of circumflex artery (Cx) often doesn't give an ischemic signs in the ECG, even if it is occluded. It can lead to wrong qualification to delayed angiography during ACS. Thus narrowing of this artery treated inadequately can lead to worse outcome. The aim of this analysis was to establish if the narrowing of Cx is related to diverse outcome in comparison to the narrowing of the right coronary artery (RCA) in patients with ACS treated with PCI of left descending artery (LAD).
Methods: Inclusion criteria were: acute coronary syndrome treated with PCI of LAD and separate significant (≥70%) narrowing of Cx or of the RCA- two vessel disease. Inclusion criteria met 90 consecutive patients with ACS: 71% (N=64) with STEMI and 29% (N=26) with NSTE-ACS. Mean follow-up was 639 (±224) days. Total mortality was estimated during hospitalization and at follow-up. Composite endpoint (MACE) of death, stroke, myocardial infarction and revascularization was established during the longterm observation.
Results: Study population was composed in 30% (N=26) of patients with Cx narrowing and in 70% (N=64) with RCA narrowing. Compared groups were not different according to baseline clinical data. Hospital and longterm mortality were 4% and 17%, respectively. MACE appeared in 39% of patients. Patients with narrowing of Cx had worse hospital and long term outcome according to mortality (hospital: 11% vs 2%, $p<0,05$; longterm: 30% vs 11%, $p<0,05$, respectively) and MACE (59% vs 30%, $p<0,01$, respectively). Multiple regression analysis showed that independent risk factors for death during the follow-up were: age, ejection fraction and the narrowing of Cx (R=0.5317; F(5.84)=6.6239; $p<0.00003$ for the model).
Conclusions: Significant narrowing of Cx leads to worse outcome than narrowing of RCA in patients with ACS treated with PCI of LAD. Thus patients with Cx narrowing should be treated more cautiously and demand a special attention after ACS treated with PCI of LAD.

P1582 Long-term clinical outcomes of overlapping heterogenous drug-eluting stents compared with homogenous drug-eluting stents

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Purpose: The safety and efficacy of overlapping heterogenous DES remains unknown. Furthermore, outcomes of overlap with second generation DES remain to be established. We aimed to compared long-term clinical outcomes of overlapping heterogenous drug-eluting stents compared with homogenous drug-eluting stents.
Methods: The study involved patients with one vessel disease treated with two overlapping DES in one lesion between January 2005 and December 2009. The study end point was the occurrence of major adverse cardiac events (MACE), defined as cardiac death, myocardial infarction (MI), or target lesion revascularization (TLR).
Results: Overlapping homogenous DES were used in 940 (87.0%) patients and overlapping heterogenous DES were used in 140 (13.0%) patients. The two patient groups were similar in terms of baseline clinical and angiographic characteristics. The MACE, cardiac death, MI and TRL rates were not significantly different between the homogenous and heterogenous DES group (9.9% vs. 11.4%, P=0.574; 2.7% vs. 3.6%, P=0.578; 1.5% vs. 1.4%, P=1.000; 5.7% vs. 6.4%, P=0.747, respectively). In addition, we found that overlap with second generation DES might be safe and effective, and the sirolimus-eluting stent (SES)+SES group had higher rate of MACE-free survival than paclitaxel-eluting stent (PES)+PES group (P=0.014).
Conclusion: Overlapping heterogenous DES showed similar long-term safety and efficacy outcomes as overlapping homogenous DES.

P1583 Successful recanalisation of Chronic Total Occlusions (CTO) is associated with increased long term survival

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Introduction: Chronic total occlusions (CTO) remains a challenging lesion subset with many CTO patients not offered PCI as physicians perceive procedural success lower, and the anatomy stable. The aim of this study was to investigate the impact of procedural success on mortality following CTO-PCI in the drug eluting stent era.
Methods: 6,122 consecutive patients underwent elective PCI at a single centre

(Oct 2003 - May 2010), 836 (13.7%) for CTO. In hospital MACE (myocardial infarction, urgent revascularisation, stroke or death) was documented at discharge. All cause mortality data was obtained from the Office of National Statistics via the BCIS/CCAD national audit out to 4 years (mean 2.9±1.6).

Results: 572 (68.4%) CTO procedures were successful. Coronary stents were implanted in 96.9% (mean 2.3±0.1 stents, 70% DES). Previous CABG (16.5% vs 7.4%, p<0.0001) and PCI (36% vs 21.2%, p<0.0001) were more frequent among patients with unsuccessful PCI than successful. Baseline characteristics were otherwise similar. Intra-procedural complications (coronary dissection, perforation, access site complication) were more frequent in unsuccessful cases (19% vs. 4.1% (p=<0.0001), but did not have an impact on in hospital MACE (2% vs. 1.8%, p=0.6). All cause mortality was 10% in the unsuccessful group and 2% in the successful group out to 4 years, (figure 1). Mortality following successful CTO-PCI was similar to that of the non-CTO elective PCI group (5.1%, p=NS). With regard to revascularisation 20% of failed CTOs went on to undergo CABG. In the successful group 2% underwent CABG and 6% repeat PCI in the subsequent 4 years.

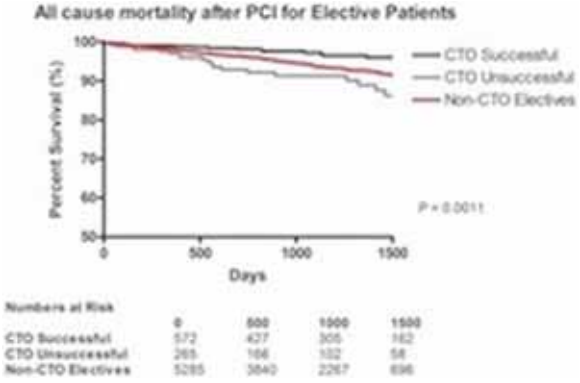

Figure 1. Mortality outcome following CTO PCI.

Conclusion: A successful angiographic outcome following CTO-PCI is associated with a survival advantage out to 4 years, suggesting that improving procedural success may improve prognosis.

P1584 Four-year clinical outcomes of drug-eluting stent implantation for patients with unprotected left main coronary artery lesions

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Aims: Limited data are available on the long-term outcome of drug-eluting stent (DES) implantation for patients with unprotected left main coronary artery (LMCA) lesions. The purpose of this study was to evaluate the risk factors associated with the long-term adverse outcomes following DES implantation for unprotected LMCA lesions.

Methods and results: We identified consecutive 125 patients with unprotected LMCA lesions who had received DES implantation between March 2003 and December 2007, and investigated 4-year clinical outcomes (median 1559 days) including all-cause death, cardiac death, target vessel revascularization (TVR), and definite or probable stent thrombosis defined by the ARC. The exclusion criteria included previous PCI or CABG and acute myocardial infarction. The mean age was 69.6±10.4 years (range 41-90), with 75.2% male gender. Among all patients, 35.2% had diabetes mellitus, 11.2% cerebral vascular disease, 8.8% peripheral artery disease, and 10.4% acute coronary syndrome. The mean additive EuroSCORE, SYNTAX score, and left ventricular ejection fraction were 4.4±2.6 (range 0-12), 26.7±9.4 (range 11-53), and 57.6±9.9 (range 25-76). Sirolimus-eluting stent was used in 82.4% of all LMCA lesions. Among all lesions, 75.2% had distal LMCA lesions and 41.5% of those were treated with 2-stent technique. At 4-year clinical follow-up, all-cause death occurred in 18.4% of the patients, cardiac death 7.2%, TVR 24.8%, and definite or probable stent thrombosis 1.6%. In multivariate analysis, severe renal insufficiency (estimated glomerular filtration rate <30 ml/min/1.73m^2 or hemodialysis) (HR 5.19, 95% CI 2.16-12.48, p<0.001), left ventricular ejection fraction≦40% (HR 4.48, 95% CI 1.54-13.00, p=0.006), and EuroSCORE≧6 (HR 2.90, 95% CI 1.22-6.91, p=0.016) were independent predictors of all-cause death. Severe renal insufficiency (HR 4.82, 95% CI 1.38-16.80, p=0.014) was an independent predictor of cardiac death. Furthermore, severe renal insufficiency (HR 3.86, 95% CI 1.50-9.94, p=0.005) and SYNTAX score≧33 (HR 2.95, 95% CI 1.36-6.39, p=0.006) were independent predictors of TVR.

Conclusions: At 4-year clinical follow-up, in this single-center experience, overall clinical outcomes after DES implantations in unprotected LMCA lesions were favorable. Not SYNTAX score but rather clinical factors were closely related to mortality. Severe renal insufficiency was a strong independent predictor of death and TVR.

P1585 The Syntax Score more accurately predicts future cardiovascular death after percutaneous coronary intervention by adding the inferiority of systemic status

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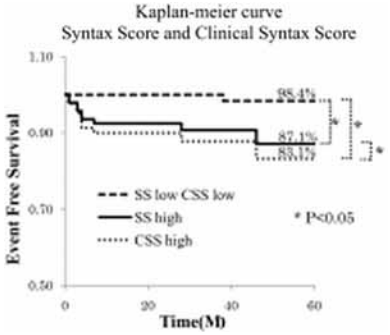
Background: The Syntax Score (SS) expresses the complexity of coronary artery disease (CAD) and is known to predict clinical outcome after percutaneous coronary intervention (PCI). We aimed to determine whether the newly-defined Composite Syntax Score (CSS) modified from SS can be more accurate predictor.

Methods: We analyzed the complexity of CAD, conventional risk factors, and follow-up data in 301 consecutive patients who received elective denovo PCI. SS was caliculated by reviewing coronary arteriogram. Since age ≧ 75, decreased LVEF (< 40%) or chronic kidney disease (CKD) was found to be the independent predictor of cardiovascular death, CSS was defined as the sum of the number of these predictors (0 ~3) and SS multiplied by 0.1.

Results: Averaged score of SS was 18.8±9.5 and that of CS was 2.6±1.4. The total of 12 patients died due to cardiovascular disease during the follow-up period (31.9±17.5 month). The patients with high SS (≧ 24) had significantly lower survival rate from cardiovascular death (p=0.0017), as well as those with high CSS (≧ 3.5, p<0.0001). Multivariate analysis showed that CSS was more sensitive than SS (Hazard Ratio: 9.748 vs. 1.7874).

Table 1

	Hazard ratio	95% Confidential Interval	P Value
Syntax Score ≥ 24	1.7824	0.3933–8.0781	0.4535
Clinical Syntax Score ≥ 3.5	9.7480	1.6845–56.4101	0.0110



Conclusion: The Syntax Score more accurately predicts the long-term outcome after PCI by adding the inferiority of cardio-renal system and the influence of aging.

P1586 Low incidence of stent thrombosis in Asian races: multicenter registry in Asia 6 years follow-up result

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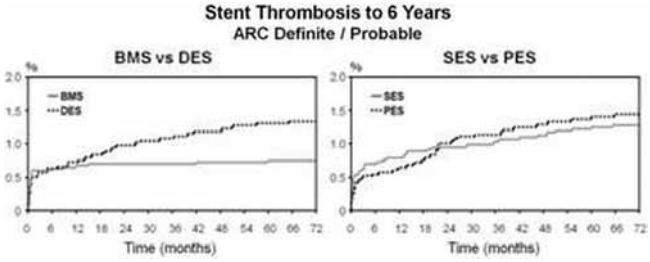
Background: The aim of this study was to evaluate the frequency, predictors and the clinical outcome of stent thrombosis after DES implantation and bare metal stent (BMS) implantation in Asian races.

Method: A total of 14,577 consecutive patients who underwent successful DES implantation (8,809 patients, 62% of the lesion with Sirolimus-eluting stent: SES, 38% of the lesion with Paclitaxel-eluting stent: PES) and BMS implantation (5,768 patients) were included in this study. We evaluate the frequency, predictor of stent thrombosis.

Results: At a mean follow-up of 78.5±29.9 months in DES and 81.8±26.4



months in BMS. The cumulative incidence of stent thrombosis were subacute stent thrombosis (SAT): 0.5% with DES and 0.6% with BMS, late stent thrombosis (LAST): 0.18% with DES and 0.1% with BMS, very late stent thrombosis (VLAST): 0.18% per year with DES and no BMS. Independent predictors of stent thrombosis are bifurcation lesion (OR=1.90, 95% CI: 1.83 to 24.24, p=0.01) and ejection fraction (OR=0.90, 95% CI: 0.86 to 0.94, p=0.03). Only 0.2% of the patients were died because of the myocardial infarction after stent thrombosis in both groups.
Conclusions: The incidence of stent thrombosis in Asian races is relatively low (0.5% with DES and 0.6% with BMS of SAT, 0.18% increase per year with DES of late stent thrombosis) at mean follow-up to 6 years. Particular attention will need to be directed to this complication when the patients have bifurcation lesions or low ejection fraction.

P1587 Angioplasty in patients with multivessel coronary artery disease and left ventricular systolic dysfunction

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Introduction: Coronary artery disease is the main etiology of left ventricular dysfunction in the developed countries. Modalities and timing of revascularization in the presence of multivessel coronary disease is often a topic of discussion.
Object: To determine predictors of improved ventricular function and factors influencing long-term survival.
Methods: Among 1142 patients with multi vessel coronary artery disease hospitalized between 2007 and 2008 in Henri Mondor Hospital, we identified patients with left ventricular systolic dysfunction (EF $\leq$40%) excluding patients with an history of coronary syndromes with ST elevation in 3 months before hospitalization or a significant valvular disease.
Results: One hundred twenty-four patients were included. The mean age was 70.6$\pm$23 years with a male predominance (85.5%). Diabetes and a history of myocardial infarction ($>$3 months) were present in 41.9% and 41.1% respectively. Silent ischemia (44.4%) and coronary syndrome (42.7%) were the main clinical presentation.
The left ventricular fraction average was 34.47% $\pm$ 6.69%. Patients had three vessel diseases in 53.2%. 79% of patients had a syntax score $<$23%. The mean Euroscore was 12.75$\pm$10.62%. Coronary angioplasty was performed with drug eluting stents in 48.4% of cases and has led to a complete revascularization in 79%. Intra-hospital MACE were marked by two deaths, one ventricular failure, one acute intrastent thrombosis and one ischemic stroke.
After a mean follow up of 23.4$\pm$10.1 months, overall survival was 86.3%. The new admissions were mainly due to heart failure (20.2%) and intra-stent restenosis (10.5%).
Sixty-one patients received an echocardiogram showing a significant improvement in left ventricular function 33.4$\pm$6.7% to 37.3$\pm$9.5% (p=0.007).
After multivariate analysis, complete revascularization has been identified as an independent predictor of left ventricular function improvement of more than 5% (p=0.002). On the analysis of survival curves, Kaplan-Meier survival was significantly impaired in patients with ventricular dysfunction $\leq$30% (p=0.01) and a trend toward an improvement of survival among patients with complete revascularization (p=0.06) was found.
Conclusion: Angioplasty in patients with multivessel coronary artery disease and left ventricular systolic dysfunction resulted in a significant improvement in ventricular function. Complete revascularization is an independent predictor of more than 5% of ventricular function. The long-term survival was related to the severity of ventricular dysfunction and to a lesser degree to the completeness of revascularization complete.

P1588 Short and long-term outcomes in octogenarians undergoing percutaneous coronary intervention with stenting

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Purpose: To investigate the incidence of cardiac events in octogenarians who underwent percutaneous coronary intervention (PCI) with stenting, as well as to evaluate the efficacy and safety of drug eluting stents (DES) in this population.
Methods: The study included 6,129 consecutive patients who underwent PCI with stenting from 2000 to 2005 in our center, of whom 291 (4.7%) were octogenarians. Patients were divided in two age groups according to their age: $<$80 years and $\geq$80 years (octogenarians). The primary endpoint was all-cause mortality, which was evaluated at 30 days, 1 year and 4 years after the procedure. Secondary endpoints were nonfatal myocardial infarction (MI), target vessel revascularization (TVR), major adverse clinical endpoints (MACE, defined as the composite of all-cause death, nonfatal MI or TVR), target lesion revascularization (TLR) and stent thrombosis at 1-year and 4-year follow-up.
Results: After adjusting for multiple confounders, age equal to or higher than 80 years appeared a significant predictor of high mortality at 30 days (3.3 vs. 8.5%, adjusted hazard ratio [aHR]1.92, 95% CI 1.23-3.01), and 4 years (34.9 vs. 115.2 per 1,000 peson-years, aHR 2.25, 95%CI 1.77-2.85). No differences were seen with respect to incident MI, but target lesion (63.2 vs. 32.6 per 1,000 person-years at 1 year and 27.9 vs. 16.6 per 1,000 person-years at 4 years) and vessel (83.1 vs. 52.9 per 1,000 person-years at 1 year and 37.7 vs. 25.0 per 1,000 person-years at 4 years) revascularization rates were lower in octogenarians. When comparing DES with bare-metal stents (BMS) in octogenarians, mortality and MI rates were comparable, but there was a significantly lower incidence of TLR at one (9.5 vs. 0.6 per 1,000 person-years, aHR 0.07, 95% CI 0.01-0.57) and 4-year (3.4 vs. 0.7 per 1,000 person-years, aHR 0.16, 95% CI 0.04-0.59) follow-up in patients who received a DES.
Conclusions: Octogenarians undergoing PCI with stenting have an increased mortality risk, whereas the rates of repeat revascularization on octogenarians are lower. The benefit of DES in reducing revascularization rates is extended to elderly patients.

P1589 The ACEF (Age, Creatinine, Ejection Fraction) score is an accurate clinical risk prediction tool for percutaneous coronary intervention of bifurcation lesions

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Purpose: Coronary bifurcations are among the most challenging lesions for percutaneous coronary intervention (PCI). There is no simple and effective tool to identify patients with a good prognosis despite such complex coronary disease. We aimed to appraise the predictive accuracy of a novel and user-friendly risk score, the ACEF (age, creatinine, ejection fraction), in patients undergoing PCI for coronary bifurcations.
Methods: A multicenter, retrospective study was conducted enrolling consecutive patients undergoing bifurcation PCI between January 2002 and December 2006 in 22 Italian centers. Patients with complete data to enable computation of the ACEF score were divided in 3 groups according to tertiles of ACEF score,. The primary end-point was the long-term rate of all cause mortality. The discrimination of the ACEF score as a continuous variable was also appraised with area under the curve (AUC) of the receiver-operating characteristic.
Results: A total of 3,535 patients were included: 1119 in the lowest quartile of ACEF score, 1190 in the 2nd quartile, and 1153 in the highest quartile. Increased ACEF score was associated with significantly different rates of early all cause death (0.1% in the 1st quartile vs 0.5% in the 2nd quartile and 3.0% in the 3rd quartile, p$<$0.001), with similar differences in myocardial infarction (0.3% vs 0.7% and 1.8%, p$<$0.001) and major adverse cardiac events (MACE, 0.5% vs 1.2% and 4.3%, p$<$0.001). After an average follow-up of 24.4$\pm$15.1 months, increased ACEF score was still associated with a higher rate of all cause death (1.3% vs 2.4% and 11.0%, p$<$0.001), cardiac death (0.9% vs 1.4% and 7.2%, p$<$0.001), myocardial infarction (3.4% vs 2.7% and 5.7%, p$<$0.001), MACE (13.6% vs 15.9% and 22.3%, p$<$0.001), and stent thrombosis (2.3% vs 1.8% and 5.0%, p$<$0.001). Discrimination of ACEF score was good for early all cause death (AUC=0.82 [0.77-0.87]), early MACE (AUC=0.73 [0.67-0.78]), long-term all cause death (AUC=0.76 [0.72-0.79]) long-term cardiac death (AUC=0.76 [0.72-0.81]), and modest for long-term major adverse cardiac events (AUC=0.58 [0.55-0.60]).
Conclusions: The simple and user-friendly ACEF score can accurately identify patients undergoing PCI for coronary bifurcation lesions at high risk of early fatal or non-fatal complications, as well as long-term fatality.

THROMBOSIS IN CARDIOVASCULAR DISORDERS: INSIGHTS INTO MECHANISMS

P1590 Prognostic significance of mean platelet volume on admission in unselected cohort of patients with non ST-segment elevation acute coronary syndrome

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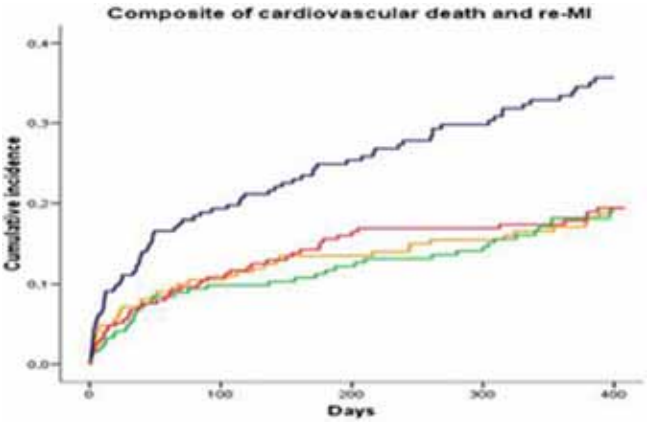
Purpose: We sought to investigate the prognostic significance of mean platelet volume (MPV) in patients with non-ST Elevation acute coronary syndrome (NSTE-ACS).
Methods: We included 1041 consecutive patients with NSTE-ACS. Patients were divided in quartiles according to the MPV value on admission (fl) i.e. Q1$<$7.5; Q2=7.5-8.0; Q3=8.1-8.8; Q4$\geq$8.9. The primary study endpoint was the composite of cardiovascular death and re-myocardial infarction (MI) at 1 year. Secondary study endpoints were individual cardiovascular death and re-MI.
Results: Patients in Q4 were older, had a higher prevalence of previous MI, peripheral artery disease and advanced Killip class compared to patients in Q1-Q3.

Elevated MPV levels (Q4) was independently associated with gender, smoking status, platelet count and creatinine level. Overall, 210 patients (20.2%) reached the primary endpoint, 124 (12.1%) died from cardiovascular causes and 125 (12.0%) suffered from re-MI. On multivariable analysis patients in Q4 were at higher risk of primary endpoint (HR=1.42; 95%CI 1.06-1.90; P=0.019) (Figure) whilst the association with cardiovascular death and re-MI was attenuated. MPV as continuous variable was independently associated with both primary endpoint (HR=1.19;95%CI 1.06-1.33; p=0.003) and cardiovascular death (HR=1.23;95%CI 1.06-1.42, p=0.005). The incorporation of MPV into a comprehensive model of risk significantly increased the likelihood ratio chi-square for prediction of both the composite endpoint (p=0.004) and cardiovascular death (p=0.008).



Kaplan Meyer estimates.

Conclusion: Increased value of MPV on admission is an independent predictor of serious adverse cardiovascular events and could be useful to improve risk stratification in NSTE-ACS

P1591 High on-treatment platelet reactivity by various platelet function tests: is the currently reported VASP PRI cutoff too low?

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Background: High on-treatment platelet reactivity (HPR) to ADP measured by multiple methods has been linked to adverse post-PCI clinical event occurrence, but the correlation between these methods is still a matter of debate.
Methods: Platelet function (PF) [5 μM ADP-induced light transmission aggregation (LTA5uMADP); P2Y12 reaction units by VerifyNow (PRU), and platelet reactivity index by VASP assay (PRI)] was measured (n=1022 samples) in stable CAD patients on dual antiplatelet therapy. Correlations between assays were determined by Pearson and Kappa statistics, and ROC curve analysis was used to compare HPR defined by different assays.
Results: LTA5uMADP showed a significant correlation with PRU and PRI (Figure). Risk stratification (HPR vs. non-HPR) based on Consensus PRU criteria (>235) correlated well with LTA5uMADP criteria (>46%), whereas Consensus PRI criteria (>50%) overestimated the risk of HPR. Using the cutpoint of LTA5uMADP, comparative values of PRU and PRI were 234 (AUC 0.932, p<0.001, sensitivity 86% and specificity 88%) and 55.5% (AUC 0.881, p<0.001, sensitivity 85% and specificity 79%). New PRI criteria for HPR (>55.5%) correlated well with LTA5uMADP criteria (>46%).

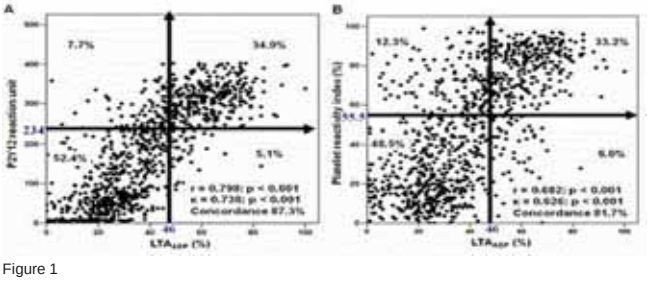

Figure 1

Conclusion: The cutoff of Consensus-defined HPR by PRU correlated well with the Consensus-defined HPR cutoff by LTA5uMADP. We propose a new cutoff of PRI = 55.5% for risk stratification by VASP in future trials.

P1592 First comparison of platelet inhibition by cilostazol versus clopidogrel in patients with cytochrome 2c19 mutant allele: results of the Accel-Switch study

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Background: Cilostazol not only inhibits platelet aggregation, but also has beneficial pleiotropic effects on various cardiovascular systems. In addition, antiplatelet effect of cilostazol is mainly determined according to the activity of the CYP3A4 pathway.
Methods: Twenty-four CYP2C19 variant carriers undergoing coronary stenting (20 heterozygotes) were enrolled. After long-term dual antiplatelet therapy with 100mg aspirin and 75mg clopidogrel daily (11±2 month), clopidogrel was switched with cilostazol 100mg twice daily. Platelet reactivity was measured before switch and at 2-3 weeks post-switch using conventional aggregometry and VerifyNow assay. Primary endpoint measure was maximal platelet aggregation (Aggmax).
Results: Clopidogrel versus cilostazol treatment showed similar Aggmax values after the addition of 5 and 20 μmol/l ADP (44.1±15.8% vs. 44.8±17.3%, p=0.842, and 57.6±14.4% versus 59.8±17.5%, p=0.561, respectively). Late platelet aggregation did not differ between two regimens. Likewise, P2Y12 reaction unit and % inhibition were not different after clopidogrel versus cilostazol treatment (254.4±62.8 vs. 259.1±79.8, p=0.729, and 22.7±12.7% versus 21.3±18.9%, p=0.699, respectively). Furthermore, cilostazol could decrease significantly 6μg/ml collagen- and 1.6mM arachidonic acid-induced platelet aggregation compared to clopidogrel (46.9±16.5% vs. 58.2±16.3%, p=0.005, and 7.1±7.3% versus 11.1±9.9%, p=0.016, respectively).
Conclusions: In carriers of CYP2C19 mutant allele on aspirin, cilostazol treatment can not only achieve comparable inhibition of ADP-induced platelet aggregation to clopidogrel, but also control sufficiently other agonists-induced platelet aggregation. These findings may suggest the fundamental rationale of a long-term treatment with cilostazol for these patients.

P1593 High on-treatment platelet reactivity after prasugrel loading dose and cardiovascular events after percutaneous coronary interventions in acute coronary syndromes

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Objectives: Post-treatment platelet reactivity (PR) has been shown to be critical in the occurrence of major adverse cardiovascular events (MACE) following percutaneous coronary intervention (PCI). We aimed to investigate the relationship between PR following prasugrel loading dose (LD) and thrombotic events.
Method: A prospective multicentre study included all patients that had successful PCI for an acute coronary syndrome (ACS) and received prasugrel therapy. The Vasodilator-Stimulated Phosphoprotein index (VASP index) was measured after prasugrel LD. High on-Treatment PR (HTPR) was defined as a VASP index ≥50%. MACE included cardiovascular death, myocardial infarction and definite stent thrombosis at one month.
Results: Three hundreds and one patients were enrolled. The mean VASP index after 60mg LD of prasugrel was 34.3±23.1%. Patients experiencing a thrombotic event following PCI had a significantly higher VASP index compared to those free of event (64.4±14.4 vs 33.4±22.7%; p=0.001). ROC curve analysis found a cut-off value of 53.5 of the VASP index to predict thrombotic events at one month (r=0.86; p<0.001). HTPR was observed in 76 patients (25.2%). Kaplan-Meier analysis comparing good responders and patients with HTPR demonstrated a significantly higher rate of MACE in patients with a sub-optimal PR inhibition (p<0.001). Patients with a minor or major non-CABG related TIMI bleeding and those without had similar VASP index (30±17.8 vs 34.3±23.1%; p=0.7).
Conclusion: Despite the use of prasugrel a significant number of acute coronary syndromes patients undergoing PCI do not achieve an optimal PR inhibition. Such patients have a higher risk of MACE following PCI.

P1594 Polymorphisms of alpha2a adrenergic receptor gene modulates platelet reactivity in response to epinephrine in stable angina patients despite dual antiplatelet therapy and irrespective of CYP2C19

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Platelet α2A-adrenergic receptors (α2A-ARs) mediate platelet aggregation in response to sympathetic stimulation. The 6.3 kb variant of α2A-AR gene has been associated with increased epinephrine induced platelet aggregation in healthy volunteers. We aimed at assessing the influence of 6.3 kb variant of α2A-AR gene on residual platelet aggregation in stable angina patients (pts) taking dual anti-platelet therapy.
Methods: 141 consecutive stable angina pts were screened for 6.3/6.7kb α2A-AR

polymorphism. Pts were also screened for CYP2C19*2 polymorphism to account for possible interaction with epinephrine-mediated platelet aggregation. All pts were loaded with 600mg clopidogrel and 500mg aspirin at least 12 hours prior to platelet function testing. Whole blood aggregation was assessed using increasing concentrations of epinephrine (0.156, 0.313, 0.625, 2.5 and 10 μmol/L) using the Multiplate Platelet Function Analyzer. P2Y12 Reactivity Units (PRU) were assayed using the Verify Now Assay.
Results: Genotype frequency was 38% for 6.3kb carriers (1 homozygote 6.3kb) and 62% for 6.7kb homozygote. Factors known to influence platelet reactivity such as age, gender, body mass index, diabetes mellitus, hypertension, hyperlipidaemia and smoking were equally distributed among the 2 groups. Platelet aggregation in response to epinephrine was significantly higher in 6.3kb carriers (n=52) compared to 6.7kb homozygotes (n=89) in response to each concentration of epinephrine (0.156μmol/L - 13±9U vs. 10±6U, p=0.023; 0.313μmol/L - 15±9U vs. 11±7U, p=0.014; 0.625μmol/L - 18±11U vs. 14±8U, p=0.03; 2.5μmol/L - 26±15U vs. 19±12U p=0.0099) apart from 10μmol/L epinephrine (28±17U vs. 22±13U, p=0.077). There was no association between CYP2C19*2 polymorphism with 6.3 kb variant of α2A-AR gene (p=0.27), and no interaction with platelet aggregation in response to any concentration of epinephrine, ($p>0.2$ for all). There was a significant correlation between the CYP2C19*2 polymorphism and PRU (p=0.012) and a significant negative correlation with % inhibition (p=0.005). In contrast, there was no association between the 6.3 kb variant of the α2A-AR gene and PRU (p=0.13) and only a weak correlation with % inhibition (p=0.048).
Conclusion: Genetic polymorphisms of the α2A-AR may influence platelet reactivity in response to epinephrine in pts with stable angina despite loading with 600mg clopidogrel and 500mg aspirin, irrespective of the presence of the CYP2C19*2 polymorphism. Carriers of the α2A-AR polymorphism may be at higher risk of cardiovascular events.

P1595 Insights on the mechanism of platelet inhibition by omega-3 polyunsaturated fatty acids; results of the LEAP trial

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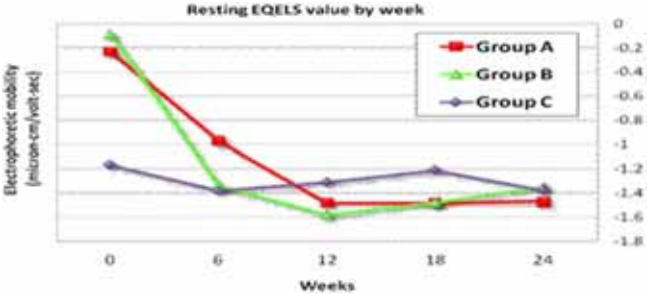
Purpose: Omega-3 polyunsaturated fatty acid (PUFA) supplements may inhibit platelet function, but the mechanism is poorly defined. We evaluated the effect of escalating doses of omega-3-PUFA using electrophoretic quasi-elastic light scattering (EQELS), a novel method that measures electrophoretic mobility of platelets by virtue of the surface charge density.
Methods: LEAP was a prospective non-randomized pilot study. A total of 30 subjects received escalating doses of omega-3-PUFA (from 2 to 8 g daily). Ten subjects were on no background antiplatelet therapy (Group A), 10 subjects on aspirin alone (group B), and 10 subjects on aspirin and clopidogrel (group C). Blood samples were collected at baseline and at 6, 12, 18 and 24 weeks. Platelet function was assessed by bleeding time and EQELS.
Results: EQELS showed a significant stepwise increase in the magnitude of negative surface charge density compared to baseline with increasing doses of omega-3-PUFA up to 4g/day. The median electrophoretic mobility for all patients was -0.72 mobility units at baseline, -1.33 mobility units at 6 weeks, and -1.47 mobility units at 12 weeks ($p<0.001$). This effect was marked in patients that were not on background clopidogrel therapy. Standard bleeding time increased among patients not taking background antiplatelet therapy (median 150 sec at baseline vs. 240 sec at week 12 in Group A, $p<0.05$).



Conclusions: This pilot study suggests that the mechanism for platelet inhibition by omega-3-PUFA is by increasing the magnitude of negative platelet surface charge density and, therefore, attenuating platelet activation. Measuring omega-3-PUFA platelet inhibition may have important implications in cardiovascular disease management.

P1596 Clopidogrel degradation by esterases is a major contributor to the attenuated response to clopidogrel observed in subjects who are low responders

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Purpose: Although absorbed clopidogrel is extensively degraded to an inactive acid metabolite by human carboxylesterase (HCE1) activity, most research on clopidogrel response variability has focussed on the metabolic pathway (mostly cytochrome P450 2C19, more recently PON-1). The aim of this study was to evaluate the incremental effect of clopidogrel 150 mg/day maintenance therapy vs clopidogrel 75 mg/day on the pharmacodynamics (PD) and pharmacokinetics (PK) of clopidogrel in subjects with different levels of clopidogrel response.
Methods: Healthy males were screened in an open-label run-in phase comprising 7 days' treatment with clopidogrel 75 mg/day. At the end of this period, subjects were assigned to one of three clopidogrel-response groups, designated "average" (40–71% inhibition of platelet aggregation [IPA] to 5 μM ADP vs baseline; n = 11), "high" (>80%; n = 6) and "low" (≤ 30%; n = 5) responders. After a 14-day washout period, clopidogrel 75 mg/day was administered for 8 days, followed by clopidogrel 150 mg/day for 8 days. Blood samples were taken at baseline and 4 hours after each clopidogrel dose on Day (D) 4 and D8 (on 75 mg) and on D11 and D15. The primary PD parameters P2Y12 receptor occupancy and Bmax were correlated to PK parameters (plasma levels of unchanged clopidogrel, inactive acid metabolite, and active metabolite). Other PD endpoints included light transmittance aggregometry using ADP, and VASP index. Surrogate endpoints of efficacy and safety were inhibition of thrombosis in an ex-vivo human model of thrombosis and quantitative bleeding time/blood-loss volume, respectively.
Results: During standard-dose clopidogrel, high responders were characterized by the highest IPA, P2Y12 occupancy, inhibition of thrombus formation, bleeding-time prolongation, and the lowest level of plasma inactive acid metabolite. The low-responder group was characterized by the highest level of inactive metabolite, while average responders had intermediate levels. Double-dose clopidogrel produced the highest increase in plasma levels of inactive acid metabolite in low responders. The relative effect of switching from clopidogrel 75 mg/day to 150 mg/day on all PD efficacy and safety parameters was much higher for the high- and average-responders than for low responders.
Conclusions: These data support the hypothesis that clopidogrel degradation by esterases is a major contributor to the attenuated response to clopidogrel observed in subjects who are low responders, and the lack of effect of high-dose clopidogrel in low responders, as judged by PD efficacy and safety parameters.

P1597 The influence of genetic polymorphism and drug-drug interaction on antiplatelet effect in patients treated with long-term dual antiplatelet therapy

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Background: Genetic polymorphisms can influence clopidogrel pharmacodynamics and clinical outcomes. The PLATO genetic subanalysis and racial disparity make long-term impact of genetic polymorphism on antiplatelet effect questionable.
Methods: We prospectively enrolled 200 PCI-treated patients on long-term therapy with 100mg aspirin and 75mg clopidogrel daily (≥ 6 mo). Platelet reactivity was assessed with conventional aggregometry and VerifyNow. CYP3A5*3, CYP2C19*2/*3/*17 and ABCB1C3435T genotypes were performed. HPR was defined as the highest quartile of 5μM ADP-induced maximal PR (≥ 56%). We assessed the influence of genetic polymorphism and drug-drug interaction on platelet reactivity and the risk of HPR.
Results: Although CYP3A5 and ABCB1 genotypes did not affect PR, axial PR increased proportionally according to the number of CYP2C19 LOF allele (40.9±19.4% vs. 43.8±15.4% vs. 47.0±16.4%, p=0.026). Compared with normal responders, HPR patients were more frequently female (44.0% vs. 28.0%, p=0.036) and on calcium channel blocker (CCB) (48.0% vs. 31.3%, p=0.033), and smoked less (8.0% vs. 20.7%, p=0.041). In multivariate analysis to assess predictors of HPR, CCB use was the only independent predictor of HPR (OR 2.427, 95% CI 1.080-5.464, p=0.032). When we classified CCBs into P-glycoprotein (Pgp) inhibiting (n = 23) and non-Pgp-inhibiting CCBs (amlodipine, n = 48), amlodipine use only increased significantly the risk of HPR (OR 3.165, 95% CI 1.333-7.519, p=0.009). Increased PRs by CCB usage were consistent irrespective of CYP2C19 phenotype and comparable to those in CYP2C19 poor metabolizers.

Predictors of HPR in multianalysis

Variables	OR	95% CI	P
Calcium channel blocker	2.427	1.080–5.464	0.032
Female	1.727	0.804–3.717	0.161
Smoking	2.688	0.804–8.988	0.108
CYP2C19 poor metabolizer	1.815	0.789–4.184	0.160

Conclusions: During long-term clopidogrel treatment, CYP2C19 polymorphisms seems to have moderate effect on PR and the risk of HPR. CCBs, especially

non-Pgp-inhibiting, can interact with clopidogrel significantly, and its clinical implications need to be validated in large clinical studies.

P1598 Serotonin increases residual platelet reactivity in patients treated with aspirin and clopidogrel after coronary stent placement

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Purpose: Residual platelet reactivity remains a major burden in cardiovascular disease (CVD) patients who received a coronary stent. Stent thrombosis endangers many patients despite dual anti-platelet therapy with acetylsalicylic acid (ASA) and clopidogrel. We examined whether the endogenous platelet helper-agonist serotonin affects platelet aggregation in patients with dual anti-platelet therapy.
Methods: Multiple electrode aggregometry was performed with arachidonic acid (AA, 0.5mM) and adenosine diphosphate (ADP, 6.5μM) in addition to different concentrations of serotonin (1-100μM) in whole blood from 40 CVD patients after coronary stent placement and a control cohort of 9 healthy subjects. Light transmission aggregometry in platelet-rich plasma was used as a gold standard in 13 of the included CVD patients and 9 control subjects to verify the results. Patients with a residual aggregation response upon stimulation with AA or ADP of more than 50% of maximal thrombin receptor stimulation were defined as ASA or clopidogrel low responders, respectively.
Results: Serotonin increased aggregation dose-dependently in CVD patients who responded to ASA and clopidogrel treatment. With ADP, the mean area under the multiple electrode aggregation curve increased from 33.7±1.3% of maximal aggregation to 40.9±2.0% with 50μM serotonin ($p<0.05$) and to 48.2±2.0% with 100μM serotonin ($p<0.001$). This increase was not observed in control subjects or ASA or clopidogrel low-responders. The platelet serotonin receptor antagonist ketanserin decreased ADP-induced aggregation significantly in control subjects (from 74.1±4.2% to 58.6±5.0%, $p<0.05$) and clopidogrel low-responders (from 59.9±3.1% to 37.4±7.9, $p<0.01$).
Conclusions: Serotonin increases residual platelet reactivity in patients who respond to ASA and clopidogrel after coronary stent placement. In clopidogrel low-responders, serotonin receptor antagonism improves platelet inhibition, almost reaching responder levels. This may justify further investigation of triple antiplatelet therapy with anti-serotonergic agents.

P1599 Does oral contraceptive therapy induce platelet nitric oxide resistance?

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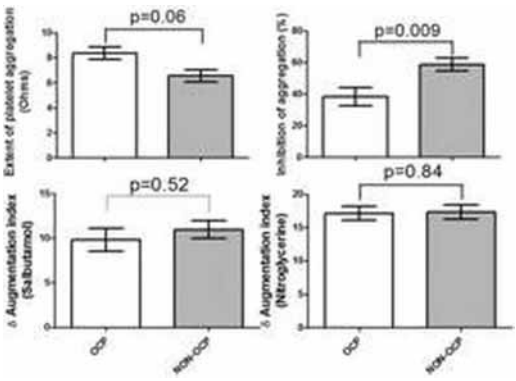
Introduction: Utilization of oestrogen-progesterone combination oral contraceptive pills (OCPs) has been associated with elevated incidence of venous and arterial thrombosis, of uncertain cause. We have previously demonstrated that impaired platelet responsiveness to nitric oxide (NO) represents an independent risk factor for thrombotic events in patients with ischemic heart disease. We have therefore evaluated, in a randomly selected population of women aged 20-40 years, the potential impact of OCP therapy on platelet and vascular function.
Methods: Among a cohort of 52 women of age (30.1±0.7 SEM) years, 14 were receiving OCPs. Investigations performed included whole blood platelet aggregation by adenosine diphosphate (ADP; 2.5μM) and its inhibition by the NO donor sodium nitroprusside (SNP; 10μM). Vascular endothelial function (salbutamol) and vascular NO responsiveness (nitroglycerine) were determined by applanation tonometry. Biochemical parameters including hs-CRP and hormonal profile were measured in fasting blood samples.
Results: While neither vascular NO responsiveness nor endothelial function varied between groups, subjects receiving OCPs had borderline increases in ADP-induced platelet aggregation ($p=0.06$) and substantially impaired platelet NO responsiveness ($p=0.009$) (see Figure). Furthermore OCP users had higher hs-CRP levels (1.8±0.3 vs 1.3±0.5, $p=0.004$) and lower oestrogen levels (304.5±36.5 vs 53±8.8, $p<0.0001$). Backward multiple linear regression showed that OCP use was the only independent correlate of impaired platelet NO responsiveness ($p=0.023$).
Conclusion: Induction of platelet NO resistance by OCPs represents a potential modulator of the increased thrombotic risk occurring with this medication.



P1600 First comparison of thrombelastography versus light transmittance aggregometry to define high platelet reactivity

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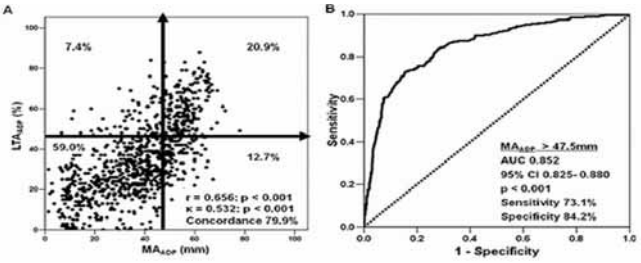
Background: Thrombelastography (TEG) is a promising method to personalize antiplatelet therapy since high ADP-and thrombin-induced platelet-fibrin clot strengths (>47mm MAADP, and >69mm MATH, respectively) are risk factors for post-PCI ischemic events. However, the correlation of TEG indices to high on-treatment platelet reactivity measured by light transmittance aggregometry (HPRADP) as defined in a recent J Am Coll Cardiol White Paper, is not known.
Methods: MAADP, MATH and platelet aggregation (LTA5uMADP) (n=955 samples) were assessed in CAD patients on dual antiplatelet therapy. Correlation between assays was determined by Pearson and Kappa statistics, and ROC curve analysis was used to identify the optimal matched points of TEG.
Results: No correlation was observed between MATH and LTAADP ($r=0.031$, $p=0.335$). A significant correlation was observed between LTA5uMADP and MAADP (Figure A). MAADP >47.5mm was well matched with the recent J Am Coll Cardiol White Paper cutpoint of LTAADP >46% (Figure B).



Conclusion: MAADP >47.5mm is a new proposed high platelet reactivity cut-point for future investigations of personalized antiplatelet treatment.

P1601 The role of dual antiplatelet therapy in late and very late thrombotic events in the era of new generation DES

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Purpose: New generation drug-eluting stents (DES) have significantly decreased the restenosis and thrombosis rate. However, stent thrombosis (ST) is still a concern due to its catastrophic clinical consequences. Therefore, the long-term dual antiplatelet therapy (DAT) is a mandatory treatment to prevent ST. Premature DAT discontinuation is common in clinical practice due to medical and non-compliance reasons. We thus aimed to appraise the safety of the new generation DES implantation after premature discontinuation in patients with an isolated lesion in the proximal segment of the left anterior descending artery.
Methods: We evaluated 600 consecutive patients. Of these, 531 patients received DAT for at least 12 months, and 69 interrupted the therapy prior to 12 months mainly due to severe medical complications. All patients received either everolimus- or zotarolimus-eluting stents. Primary outcome of interest was evaluation of the ST, defined according to the Academic Research Consortium definition, whereas secondary end points were the major adverse cardiac events (MACE) defined as: Death, non-fatal myocardial infarction (MI) and target lesion revascularization (TLR).
Results: Subacute thrombosis rate was similar between the 2 groups (0.0% for patients with DAT discontinuation vs 0.56% patients without discontinuation, $p=0.99$). Late thrombosis was 4.34% for the group with premature cessation of the DAT vs 0.18% for the control group ($p=0.005$). Very late thrombotic events did not occur. The definite thrombosis rate was significantly increased in patients with discontinuation of the DAT [4.34% in patients with discontinuation of the DAT vs 0.75% in patients with non-DAT cessation ($p=0.03$)]. The overall MACE was statistically significantly higher in patients with the discontinuation of the DAT as compared with the control group [15.94% vs 5.08%, respectively ($p=0.002$)] during the 20.70±7.61 months mean follow-up period. This unfavourable result was mainly due to increased rate of non-fatal MI in patients with premature cessation of the DAT [(5.79% vs 0.56%, respectively ($p=0.004$)] and the increased rate

of death also in patients with premature discontinuation of the DAT [(4.34% vs 0.75%, respectively p=0.03)]. Finally, the TLR rate was 5.79% in patients with the interruption of the DAT vs 3.76% in patients without cessation of the DAT (p=0.50).
Conclusion: The long term DAT after new generation DES implantation is a mandatory treatment approach as the late ST was increased after the premature cessation of the DAT. However, the role of DAT for the prevention of very late ST is debatable.

P1602 Farnesyl pyrophosphate is an endogenous antagonist to ADP-stimulated P2Y12 receptor-mediated platelet aggregation

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Background: Farnesyl pyrophosphate (FPP) is an intermediate in the mevalonate synthetic pathway, but it has also been reported to activate platelet LPA (lysophosphatidic acid) receptors. The aim of this study was to investigate the role of extracellular FPP in platelet aggregation.
Methods and results: Human platelets were studied with light transmission aggregometry, flow cytometry and [35S]GTPγS binding assays. As shown previously, FPP could potentiate LPA-stimulated shape change. Surprisingly, FPP also acted as a selective non-competitive antagonist to ADP-induced platelet aggregation. The results revealed a clear, dose dependent inhibition of aggregation (**P<0.01, n=15). However, the inhibitory effect was specific for ADP-mediated aggregation, as both TRAP (15 μM), (n.s, n=7) and epinephrine (1uM), (n.s, n=10) stimulated aggregation were unaffected by 30 μM FPP. In the next experiment, we tested the other intermediates of the mevalonate pathway, related in chemical structure to FPP, for their ability to inhibit ADP-stimulated aggregation, and we found that FPP is the sole member with this activity (**P=0.01, n=6). The FPP mediated inhibition of aggregation was dose-dependent resulting in 40% (±5) inhibition at 10 uM (**P=0.01, n=15) (Fig. 3B). FPP inhibited ADP-induced expression of P-selectin and the activated GpIIb/IIIa receptor. FPP blocked ADP-induced cAMP inhibition and [35S]GTPγS binding in platelets. In CHO cells expressing the P2Y12 receptor, FPP caused a rightward shift of the [35S]GTPγS binding curve. Docking of FPP in a P2Y12 receptor model revealed molecular similarities with ADP and a good fit into the binding pocket for ADP.
Conclusions: FPP is a noncompetitive antagonist of ADP-induced platelet aggregation mediated by the P2Y12 receptor. It could be an endogenous antithrombotic factor modulating the strong platelet aggregatory effects of ADP in a manner similar to the use of Clopidogrel, Prasugrel or Ticagrelor in the treatment of ischemic heart disease. The effects of statins on the mevalonate synthetic pathway and thereby on FPP synthesis remain to be evaluated.

P1603 Increased rate of stentthrombosis due to clopidogrel resistance in patients in therapeutic hypothermia after sudden cardiac death

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Purpose: Patients treated with therapeutic hypothermia (32-34°C) for 24 h after sudden cardiac death (SCD) often suffer from acute coronary syndrome (ACS), which is treated by percutaneuos coronary intervention (PCI) with implantation of a coronary stent. Thereafter inhibition of platelet aggregation routinely with ASS and Clopidogrel (CL) is recommended to prevent thrombotic complications like stent thrombosis. Variable response to CL has been observed. It was hypothesized that therapeutic hypothermia may modulate CL responsiveness.
Method: 57 patients presented with ACS and underwent PCI. 27 patients were treated with therapeutic hypothermia, 30 patients were evaluated as normothermic-control. All patients received a loading dose (LD) of 600mg CL. The VASP index was measured 24 h after the LD, VASP index above 50% was defined as CL nonresponder.
Result: VASP Index in the hypothermia group was significantly higher compared to normothermia group (69,1±16,8 vs. 30,3±23,0, p<0,01). There were significant more CL nonresponder in the hypothermia group compared to normothermic control (81% vs 16%).
In-hospital mortality was significantly higher in the hypothermia group (44% vs 7%, p<0,01), with significant elevated rates of early stentthrombosis in the hypothermia group (14,8% vs 0%, p<0,05). Early stentthrombosis was associated with a 50% mortality rate. No strokes were observed. TIMI bleedings did not differ significantly between the two groups.
Conclusion: Patients in therapeutic hypothermia after cardiac arrest show high rates of Clopidogrel nonresponders with increased thrombotic complications.
We hyothesize that the metabolic conversion of CL to its active metabolite may be partially impaired in the hypothermic liver resulting in decreased platelet inhibition. Thienopyridines without the need of metabolic conversion to its active metabolite may be indicated in these critically ill patients under hypothermia. Further studies using new thienopyridines will have to address this hypothesis.

P1604 Megakaryocyte proteomics following aspirin and salicylate exposure

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Purpose: Aspirin has been shown to reduce the risk of myocardial infarction and stroke in susceptible patients by approximately 25%. However, some patients, despite aspirin therapy, experience further vascular events suggesting that they are perhaps aspirin "resistant". Clinical aspirin resistance refers to patients who, despite compliance with a therapeutic dose (≥75 mg), continue to experience recurrent thrombotic events; biochemical aspirin resistance uses laboratory methods to indicate the failure of aspirin to inhibit platelet activity.Proteomics (the study of proteins) offers a real capacity to investigate changes in the platelet proteome associated with aspirin resistance. In this study we employed the human megakaryoblastic cell line (MEG-01) as a model, which exhibits both phenotypic and biochemical properties observed in pro-platelet megakaryopoiesis. We exposed Meg-01 cells to clinically relevant concentrations of aspirin and salicylate (to which aspirin is rapidly converted in the blood) to observe the resultant global and sub-proteomes.
Method: A total of 2×10^8 Meg-01 cells were exposed to therapeutic concentrations of aspirin and salicylate (0.5mM and 1.0mM/day). After 5 days of treatment cells were harvested and protein extracted or stimulated by incubation with thrombin (0.5 Unit/mL) at 37°C and then extracted. Changes in proteomes were observed by two-dimensional gel electrophoresis. Protein spot intensities were quantified and analysed using ProgenesisTM SameSpots v4.0. Spots of interest were excised and identified by MALDI-TOF-MS.
Results: Drug treatment effected changes in the global Meg-01 proteome. Gels from each treatment group (at least n=5) were compared generating a list of spots. Spots were statistically ordered, ranked by their p-value from one way ANOVA analysis, revealing statistically significant up- and down-regulation in the expression of particular spots. A total of 37 proteins from the Meg-01 cells were identified as having significantly altered expression following drug incubation and with drug incubation with agonist exposure.
Conclusions: This study has shown that the expression of important proteins in the well characterised megakaryocyte cell line, Meg-01, are modified following exposure to both aspirin and salicylate.This data suggests that the collective and cumulative effects of many proteins with altered expression affect processes and pathways, which may be associated with a different ability to respond to aspirin.

P1605 Effects of prasugrel, ticagrelor and high dose clopidogrel compared to placebo evaluated by three different statistical approaches for indirect treatment comparisons

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Purpose: Since novel ADP antagonist treatments are tested against standard clopidogrel, no RCTs of these new agents exist for comparison against placebo or each other. To evaluate their performance against placebo, we performed indirect treatment comparisons (ITC) using 3 different statistical approaches.
Methods: Electronic databases were searched systematically to identify RCTs examining standard dose clopidogrel, high dose clopidogrel, prasugrel and ticagrelor in patients with acute coronary syndromes (ACS) and/or undergoing percutaneous coronary intervention (PCI). Trials had to report efficacy and bleeding outcomes to be included. ITC were performed with Bayesian methods for mixed treatment comparisons (MTC) using Winbugs, general linear mixed models (GLIMMIX) using SAS, and adjusted indirect comparison according to Bucher. Subgroup analysis was performed for long-term trials.
Results: Seven trials met the inclusion criteria. As all new treatments had been directly compared to clopidogrel, and clopidogrel to placebo, the Bucher approach could be applied,which showed results almost identical to MTC. The use of GLIMMIX was limited by the small number of trials. All 3 tested treatments significantly reduced the composite of CV death, MI, stroke and increased total bleeding rate. Only ticagrelor showed a significant reduction in all cause mortality,whereas prasugrel reduced stent thrombosis most. (see table). The results were similar in patients undergoing PCI and when only long-term trials were included.

ITC: ADP antagonists versus placebo

Outcome (OR (95% CI))	Prasugrel	Ticagrelor	High dose clopidogrel
All cause mortality	0.89 (0.72, 1.09)	0.73 (0.62, 0.85)	0.90 (0.75, 1.07)
Composite CV death, MI, stroke	0.70 (0.62, 0.80)	0.74 (0.66, 0.82)	0.82 (0.72, 0.94)
Myocardial Infarction	0.60 (0.52, 0.71)	0.68 (0.59, 0.78)	0.69 (0.57, 0.84)
Stent thrombosis	0.42 (0.22, 0.82)	0.58 (0.30, 1.11)	0.63 (0.34, 1.20)
Total major bleeding	1.51 (1.11, 2.04)	1.05 (0.85, 1.31)	1.30 (0.99, 1.71)
Non CABG related major bleeding	2.00 (1.40, 2.85)	1.89 (1.38, 2.61)	2.06 (1.48, 2.88)
Minor bleeding	1.56 (1.20, 2.03)	1.45 (1.20, 2.03)	1.59 (1.38, 1.83)
Major or minor bleeding	1.69 (1.39, 2.05)	1.35 (1.19, 1.53)	1.55 (1.36, 1.77)

Conclusion: ITC can be used to synthesize the available evidence in the absence of head-to-head clinical trials. However, such comparisons are subject to greater bias and results must be interpreted cautiously.

P1606 Indices of platelet adhesiveness and size in patients with acute coronary syndrome

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Background: In pts with ACS it has been shown that platelet adhesiveness is increased; it is not known if platelet size is also increased. The current study assessed the impact of shear stress on indices of platelet activation.
Methods: We studied 233 pts admitted with symptoms of ACS before thienopyridine treatment. A platelet adhesion assay (PADA) was performed that uses the activation of platelets via 5-minute shear stress by treating a citrated whole-blood sample in a shake incubator. Platelet counts from a sample to which special polymer particles were added and a control sample (without polymer particles) were used to calculate the adhesion index (AI). From the control sample, we determined the platelet size before and after shear stress: mean platelet volume (MPV), platelet large cell ratio (PLCR), i.e., the number of platelets >12 fl by the number of platelets ≤12 fl, and platelet deviation width (PDW), i.e., the width of platelet volume distribution at 20% of the maximum.
Results: Of the 233 pts, 89 pts (38%) had an ACS and 144 had no ACS (NACS). AI was increased in ACS pts (57.5% vs. 43.0% in NACS pts, P=0.003). Concordant measures of increased platelet activation after shear stress were obtained for MPV (ACS 9.7±1.0 fl vs. NACS 9.3±1.0 fl, P=0.004), PLCR (ACS 25.1±7.2% vs. NACS 21.5±7.0%, P=0.0006), and PDW (ACS 12.7±2.3 fl vs. NACS 11.9±2.0 fl, P=0.015). The relative increase in PLCR induced by shear stress was significantly higher in ACS pts (Figure).

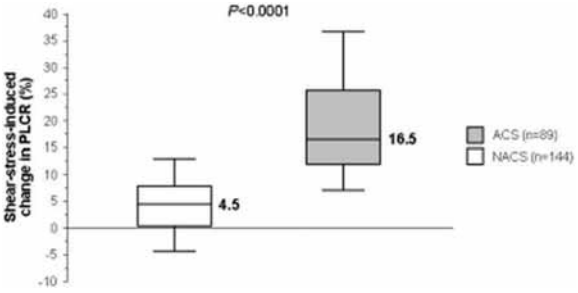

Figure 1

Conclusions: Shear stress increases adhesiveness and platelet size in ACS pts to a larger extent than in NACS pts, indicative of augmented platelet activation in the former. Studies assessing the impact of thienopyridine treatment on these parameters in ACS pts are warranted.

P1607 Is increased arterial stiffness related to aspirin responsiveness in patients with coronary artery disease: a possible mechanism for increased cardiovascular events in aspirin non-responders?

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Purpose: Various interactions between the vascular endothelium and platelets are well-recognised. Given the relationship between arterial stiffness and cardiovascular events, we tested the hypothesis that responsiveness of platelets to aspirin may be associated with abnormal arterial stiffness in patients with coronary artery disease (CAD).
Methods: 113 patients (mean age 66±9.4 years, 83% male) with proven stable CAD, on long term aspirin therapy (75mg daily) were recruited. We excluded patients receiving clopidogrel and those with recent (<6 months) acute coronary syndromes. Compliance with medications was assessed by interview. Optical aggregometry of platelet rich plasma stimulated with 0.5mg/ml arachidonic acid (AA) was used to define responsiveness to aspirin (aggregation >20% was used as a cut off level). Arterial stiffness was determined by quantification of carotid-radial (predominantly muscle-type arteries) and carotid-femoral (predominantly elastic-type arteries) pulse wave velocity (PWV) and aortic augmentation index (AI) (Sphygmocor, Australia).

Study parameters

	Responders (n=83)	Non-responders (n=30)	p-value
Age	64.5±9.5	68.9±8.5	0.028
Gender, % males	84.3	80.0	0.795
Diabetes, %	26.5	33.3	0.635
Platelets	238.0 (196.0–270.0)	220.0 (176.0–270.8)	0.398
AI	21.7±11.0	26.5±10.4	0.044
PVW carotid-radial	7.8±1.1	7.6±1.0	0.288
PVW carotid-femoral	9.3±2.4	11.4±2.7	0.001

Results: 30 patients were defined as "aspirin non-responders" (Table). Aspirin non-responders were older and had significantly higher AI and carotid-femoral PWV, but not carotid-radial PWV. On regression analyses, AI [odds ratio 0.92 (95% confidence intervals0.86-0.97)] was predictive of status of aspirin non-responsiveness (p=0.048).
Conclusion: Aspirin non-responders have features of increased stiffness of elastic-type (but not muscle-type) arteries. Increased arterial stiffness may relate to aspirin responsiveness in patients with CAD, and provide a possible mechanism for increased cardiovascular events in aspirin non-responders

P1608 Proteomic profiling of platelets from aspirin-resistant and aspirin-sensitive patients

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Purpose: Aspirin has been proven to be therapeutically beneficial reducing the risk of myocardial infarction and stroke in susceptible patients by approximately 25%. Some patients, despite aspirin therapy, experience further vascular events suggesting aspirin "resistance". The term 'aspirin resistance' is used to cover the inability of aspirin at therapeutic doses (≥75 mg), to protect patients against recurrent ischaemic vascular events (clinical aspirin resistance), biochemical aspirin resistance uses laboratory methods to indicate the failure of aspirin to inhibit platelet activity. As platelets are anucleate, proteomic techniques can investigate changes in protein expression associated with aspirin resistance. This study examined protein expression changes in response to therapeutic doses of aspirin in the global and sub-proteomes of platelets isolated from a healthy volunteer population classified as ASA-sensitive or ASA-resistant based on the PFA-100 platelet functionality test.
Method: Platelet samples were collected as part of a repeated measures crossover trial. All participants attended for baseline screening and testing and were followed up at visits 2, 3, 4 and 5. Aspirin resistance was defined by the PFA-100® System, a closure time <193 seconds was used to define aspirin resistance. A total of 2×10^8 platelets were harvested and protein extracted or stimulated by incubation with thrombin (0.5 Unit/mL) at 37°C and then extracted. Changes in proteomes were observed by two-dimensional gel electrophoresis. Protein spot intensities were quantified and analysed using ProgenesisTM SameSpots v4.0. Spots of interest were excised and identified by MALDI-TOF-MS.
Results: Protein expression in the global and sub-proteomes of ASA-resistant and ASA-sensitive platelets differ. Gel replicates (at least n=5) were compared generating a list of spots. Spots were statistically ordered, ranked by their p-value from one way ANOVA analysis, revealing statistically significant up- and down-regulation in their expression. A total of 38 proteins were identified as having significantly modified expression between platelets isolated from ASA-resistant and ASA-sensitive healthy individuals.
Conclusions: This study has shown the proteomes of platelets isolated from ASA-resistant and ASA-sensitive individuals differs in terms of the expression of proteins. This suggests at the platelet level there are differences in platelet activity due to the cumulative effects of modified protein expression identified in this study, which are linked to and endow platelets with an ability to form thrombi despite aspirin treatment.

P1609 The impact of high HDL-C on platelet reactivity in patients undergoing percutaneous coronary intervention

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Background: Low high-density lipoprotein cholesterol (HDL-C) is an established risk factor for coronary disease, but its effect upon high on-treatment platelet reactivity in patients following percutaneous coronary intervention (PCI) is not well understood.
Methods: The platelet reactivity of 241 patients who were subjected to PCI was tested with VerifyNowP2Y12 (VN) at 6 to 24 hours after PCI and correlated with the patients' HDL-C levels. All patients were loaded with 600mg of clopidogrel. High on-treatment platelet reactivity (HOPR) was defined as maximum platelet reactivity units ≥230 for VN. High HDL-C was defined as >40mg/dL for males and >50mg/dL for women. Univariable association between Low HDL-C and HOPR was evaluated with the chi-square test, and multivariable association was evaluated with logistic regression.
Results: 43.2% of patients had high HDL-C upon admission for PCI with 22.3% of patients with high HDL-C having HOPR, compared to 35.3% of patients with low HDL-C (p=0.033). Patients with high HDL-C were less likely to be current smokers (23.1% vs. 35.8%, p=0.034) and more often male (80.8% vs. 68.6%, p=0.033). The overall rate of diabetes mellitus was 33.8% with no difference noted between high and low HDL-C. Following multivariable adjustment for age, current smoking, history of renal insufficiency and diabetes, high HDL-C demonstrated a trend toward an association with HOPR (OR 0.57, 95% CI 0.31, 1.04, p=0.067).
Conclusions: Poor outcomes in patients with low HDL-C may be attributed to

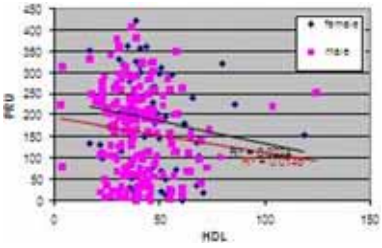

Figure 1

HOPR. More potent antiplatelet therapy should be considered in this patient population.

P1610 ADAMTS13 antigen levels are associated with increasing atherosclerotic burden in patients with stable coronary artery disease

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Purpose: ADAMTS13 is a metalloproteinase which regulates the thrombogenic potential of von Willebrand factor (VWF). While lower levels of ADAMTS13 have been associated with increased cardiovascular risk, the relationship between ADAMTS13 levels and atherosclerotic burden has not been explored. The aim of this study was to assess the relationship between ADAMTS13 and atherosclerotic burden in patients with stable coronary artery disease.
Methods: ADAMTS13 antigen levels (ADAMTS13:Ag) were determined in 188 consecutive stable angina patients undergoing cardiac catheterization by immunosorbent assay using pooled normal human plasma (n=20) as a reference set to 100% corresponding to 1μg/mL. VWF antigen levels (VWF:Ag) and VWF activity (VWF:RiCo) were also assayed. To assess atherosclerotic burden the number of diseased vessels and the Bogaty coronary atheroma score was recorded in each case. Demographic information was recorded in all cases.
Results: A total of 564 coronary arteries were assessed. ADAMTS13:Ag levels were significantly higher in patients with 2 or 3 vessel disease (n=91) compared to 0 or 1 vessel disease (n=97) (82.7±19.2 vs. 74.2±20.3%, p=0.004). In addition, the mean ADAMTS13:Ag levels were significantly higher in the highest tertile compared to the lowest tertile of extent of atherosclerotic disease as assessed by the Bogaty score (74.4±19.6 v. 82.6±19.2%, p=0.025). There was no association between either VWF:Ag levels or VWF:RiCO and extent of disease. After adjustment for age, BMI, gender and risk factors using multivariate analysis, the association between ADAMTS13 antigen levels and extent of atherosclerotic disease as assessed by the Bogaty score remained significant (Beta=0.187, p 0.017).
Conclusion: Increasing levels of ADAMTS13 are associated with increasing atherosclerotic burden in patients with stable coronary artery disease.

P1611 Relationship between abdominal obesity and platelet indices in patients with metabolic syndrome

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There is evidence that patients with the metabolic syndrome (MS) have altered platelet (PLT) indices including higher mean platelet volume (MPV). According to the 2009 IDF criteria of MS diagnosis, elevated waist circumference (≥94 cm in M, ≥80 cm in F), as a determinant of abdominal obesity (AO), is not an obligatory component of MS. Little is known about the relation of abdominal obesity to platelet indices in pts with MS.
Purpose: The aim of this study was to evaluate the relationship between platelet indices and abdominal obesity in patients with MS.
Methods: 253 consecutive pts were enrolled based on MS diagnosis. The pts were divided into two groups depending on waist circumference: group A – 218 pts with AO (132 M, mean age 65.3±10.9 yrs), and group B – 35 pts without AO (28 M, mean age 63.3±11.2 yrs).
Results: No significant differences were found between the groups with respect to PLT count (226.3±78.1 vs. 224.5±57.1×10^9/L, p=0.745) and MPV (10.70±1.01 vs. 10.64±1.03 fL, p=0.448). However, in the group A, a significant association between waist circumference and MPV (r=0.15, p=0.045) was found. Furthermore, in pts with AO, MPV was significantly correlated with PLT count (r= -0.36, p<0.001), total cholesterol serum level (r= -0.22, p=0.004), triglycerides (r= -0.18, p=0.017), LDL-cholesterol (r= -0.20, p=0.009), and the occurrence of left ventricle diastolic dysfunction (r= -0.21, p=0.005). In group B, MPV was correlated significantly only with PLT count (r= -0.45, p=0.009).
Conclusion: 1. There are no significant differences in PLT count and MPV between MS patients with abdominal obesity and those without abdominal obesity. 2. In individuals with abdominal obesity there is a significant positive correlation between waist circumference and MPV.

P1612 Platelet CD147 expression is upregulated within the coronary circulation in patients with stable coronary disease

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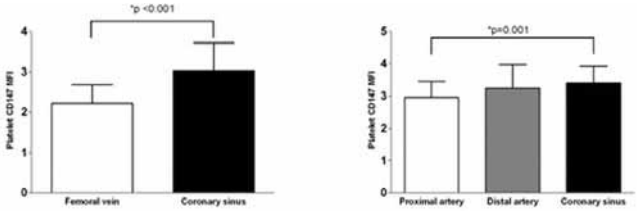
Purpose: Matrix metalloproteinases (MMP) are implicated in atherosclerosis progression, lesion destabilisation and plaque rupture. CD147 (extracellular MMP inducer), is present in atherosclerotic plaques, and on circulating platelets and leukocytes in patients with coronary disease. We investigated whether platelet CD147 is upregulated within the cardiac circulation in patients with coronary disease.
Methods: Consecutive patients had blood sampled prior to undergoing elective coronary intervention of a target lesion in the left coronary system. To assess the difference between peripheral and cardiac circulation, blood from the femoral vein (FV) and coronary sinus (CS) were compared in 15 patients. To investigate CD147 upregulation within the coronary circulation, blood from the coronary artery proximal (PA) and distal (DA) to the target lesion, and in the CS were compared in 15 patients. Blood samples were analysed for platelet and leukocyte CD147 expression by flow cytometry, and soluble CD147 by enzyme linked immunosorbent assays.
Results: Platelet CD147 was higher in the CS compared to FV (mean fluorescence intensity [MFI]: 3.0±0.7 vs. 2.2±0.5, P=0.01). There was a significant increase in platelet CD147 expression from the PA to the DA, and subsequently to the CS (P=0.001) (see figure). Platelet CD147 expression was higher in the CS compared to the PA (MFI: 3.6±0.7 vs. 3.0±0.6, P=0.01). There were no differences between the various sites for soluble CD147, monocyte CD147 or granulocyte CD147 expression. Trans-lesion gradient of platelet CD147 correlated with trans-lesion gradient of soluble CD147 (r=0.73, P=0.002).



Conclusions: These data show, for the first time, evidence of platelet membrane-bound CD147 upregulation within the coronary circulation of patients with stable coronary disease.

P1613 An attenuated fibrinolytic profile is associated with risk of a first time myocardial infarction as measured by a global assay of haemostasis

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Purpose: To assess whether an abnormality of haemostasis measured using a global assay developed by He and coworkers in 2007 is associated with risk of developing a first myocardial infarction (MI).
Methods: Using the global assay, Coagulation profile (Cp) and Fibrinolysis profile (Fp) were measured in platelet-poor plasma from 800 MI cases and 1123 controls included in the Stockholm Heart Epidemiology Program (SHEEP). Added to the plasma were tissue factor (together with purified phospholipids) and tissue plasminogen activator (tPA) in order to trigger fibrin formation and the subsequent degradation respectively. Odds ratios (OR) of MI with 95% confidence intervals (CI) were calculated using unconditional logistic regression.
Results: A Fp value below the 10th percentile from the distribution of Fp in controls was significantly associated with risk of developing MI, crude OR 1.93 (95% CI 1.35-2.76) in men and 1.94 (95% CI 1.21-3.09) in women; after multivariate adjustments for conventional cardiovascular risk factors, the ORs were 1.69 (95% CI 1.15-2.50) and 1.74 (95% CI 1.01-2.99) respectively. Adjustments for PAI-1 levels lowered the ORs in both men (1.28, 95% CI 0.85-1.93) and women (1.28, 95% CI 0.73-2.25). This indicates that though Fp would stem from the combined effects of plasminogen activation, fibrinogen concentration, fibrin network porosity, etc, increases of PAI-1 levels seem to be a key contributor to attenuation of Fp in MI. A high Cp value was not significantly associated with risk of MI in either men or women, probably due to insufficient sensitivity of this method to mirror thrombin generation in platelet-poor plasma samples.

Conclusion: This global assay may identify an attenuation of overall fibrinolysis that associates with increased risk of a first MI.

P1614 Reduced thrombin formation, altered fibrin clot properties and decreased oxidative stress induced by polyunsaturated omega-3 fatty acids on top of dual antiplatelet therapy in patients undergoing PCI

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Objective: To investigate whether omega-3 polyunsaturated fatty acids (n-3 PUFA) are able to alter plasma fibrin clot properties and reduce thrombin formation in stable coronary artery disease patients undergoing percutaneous coronary intervention (PCI)
Methods and results: In an investigator-initiated, prospective, double-blind, placebo-controlled, randomized study patients undergoing PCI who received standard pharmacotherapy were randomly assigned to the treatment with 1 g/day n-3 PUFA ethyl esters (n = 30) or placebo (n = 24) for 1 month. Plasma fibrin clot permeability (Ks), lysis time (t50%), prothrombin fragment 1.2 (F1.2, a thrombin generation marker), 8-isoprostaglandin F2α (8-iso-PGF2α, an oxidative stress marker) and C-reactive protein (CRP) were determined at baseline, 3-5 days and 30 days after randomization.
At baseline both treatment groups did not differ significantly. A 1-month treatment with n-3 PUFA compared with placebo was associated with 15.3% higher Ks indicating larger pores in the fibrin network (p=0.002), 14.3% shorter t50% indicating increased susceptibility to fibrinolysis ($p<0.001$), 33.8% lower F1.2 ($p<0.001$) and 13.1% lower 8-iso-PGF2α (p=0.041). Treatment with n-3 PUFA had no effect on fibrinogen and CRP. After 1 month of treatment, fibrinogen (r= -0.41, $p<0.001$), 8-iso-PGF2α (r= -0.27, p=0.009), treatment assignment (r=0.24, p=0.016) and F1.2 (r= -0.20, p=0.047) were independently associated with clot permeability ($p<0.0001$, R2=0.61).
Conclusions: Adding omega-3 PUFA to standard therapy in stable patients undergoing PCI significantly decreases thrombin formation, oxidative stress and favorably alters fibrin clot properties. These findings indicate novel antithrombotic effects induced by n-3 PUFA in humans.

P1615 Reticulated platelets and platelet activity in patients with atrial fibrillation

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Purpose: The percentage of reticulated platelets (RP%) in the peripheral blood reflects platelet turnover. The relationship between platelet turnover and subsequent activation in patients with atrial fibrillation (AF) remains unclear.
Methods: Fifty-nine AF patients and eighteen healthy controls were consecutively recruited. The RP% and expression of P-selectin, COX-1, and COX-2 were determined by flow cytometry. Platelet aggregation was measured by turbidimetry.
Results: AF patients were older and had a higher incidence of hypertension and lower platelet count; moreover, most of the patients were males. The RP% in AF patients was significantly higher than those in the controls (12.8±0.9% vs. 7.8±1.4%, p=0.006). After logistic multivariate analysis, RP% was still independently associated with AF. In AF patients, RP% was inversely correlated with platelet count and left ventricular ejection fraction. RP% did not differ between paroxysmal and non-paroxysmal AF patients. AF patients were divided into high and low RP% groups on the basis of a mean value of 11.5%. Compared to the low RP% group, the high RP% group had higher levels of COX-1 and COX-2 expression, as well as higher platelet aggregation, P-selectin expression, and incidence of residual platelet function after exposure to aspirin (Figure). An increase in aspirin concentration caused a dose-dependent decrease in platelet aggregation.

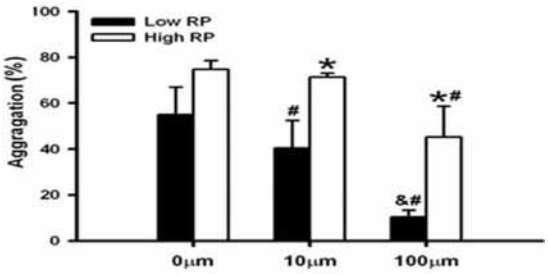

Figure 1

Conclusions: In AF, increased RP% was associated with the activation of platelets and COX expression and may increase the risk of thrombogenesis.

P1616 The effect of clopidogrel on the generation of thromboxane B2 in patients taking regular, low dose aspirin therapy

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Purpose: No consensus exists regarding the optimal method of measuring aspirin response, and all currently available aggregation or point-of-care assays are invalidated by the addition of clopidogrel. Thromboxane B2 (TxB2) measurements are not dependent on platelet aggregation and might be a more reliable method of assessing aspirin response in patients taking dual antiplatelet therapy. We investigated the effects clopidogrel on the residual ability of platelets to generate TxB2 in patients with cardiovascular disease taking regular low dose aspirin.
Methods: 73 patients attending for percutaneous coronary intervention (PCI) taking 75mg/day of aspirin were tested before and after the introduction of clopidogrel therapy. Venous blood was collected into vaccutainer tubes containing thrombin to maximally stimulate platelets. A separate citrated tube was collected to measure VASP phosphorylation.
Results: There was a wide variation in the level of serum TxB2 (mean 2.7ng/ml, SE 0.7ng/ml). Following the introduction in of clopidogrel there was a trend towards a lower level of TxB2 in serum (mean 2.1ng/ml, SE 0.63ng/ml) although this difference did not reach statistical significance, p=0.19. There was a good correlation between level of TxB2 before and after the introduction of clopidogrel (r2= 0.65, Figure 1) Measurements of VASP phosphorylation confirmed a wide range of clopidogrel response but there was no evidence that response to clopidogrel influenced levels of TxB2 generation ($p<0.0001$).

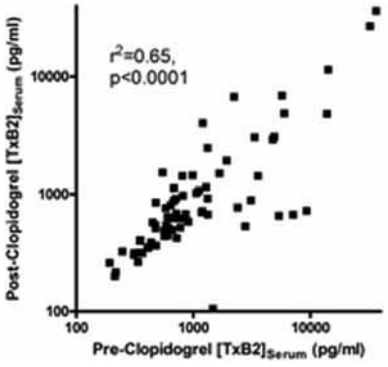

Figure 1

Conclusion: This study demonstrates that TxB2 generation continues in patients taking regular low dose aspirin. Critically, it also demonstrates that this measurement may be valid in the presence of additional P2Y12 inhibition and is not influenced by the extent of this inhibition.

ROLE OF INFLAMMATION AND MICROCIRCULATION IN ISCHAEMIC HEART DISEASE

P1617 Rho-kinase activity in circulating neutrophils of patients with vasospastic angina - non-invasive method for diagnosis and disease activity assessment-

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Purpose: We have previously demonstrated that activated Rho-kinase pathway plays a central role in the molecular mechanism of coronary spasm in animal models and patients with vasospastic angina (VSA). Recently, it has been reported that Rho-kinase activity in circulating leukocytes is associated with various diseases, such as pulmonary hypertension, metabolic syndrome, coronary artery disease and hypertension. In the present study, we thus examined whether Rho-kinase activity is systemically enhanced in VSA patients and if so, whether it could be useful as a non-invasive diagnostic tool for VSA.
Methods: Consecutive 53 patients with chest pain (M/F 32/21, 58±13 [SD] years) who underwent acetylcholine provocation test for coronary spasm were enrolled and divided into the 2 groups, depending on the response to the test; VSA (n=33) and non-VSA group (n=20). Venous blood samples were collected to measure Rho-kinase activity in circulating neutrophils, as determined by the extent of phosphorylation of myosin binding subunit (MBS), a substrate of Rho-kinase.
Results: Although high sensitivity C-reactive protein levels and the accumulated number of coronary risk factors were comparable between the 2 groups, the Rho-

kinase activity was significantly higher in the VSA group than in the non-VSA group (phosphorylated MBS/total MBS ratio, 1.33±0.37 vs. 0.95±0.22, P<0.001). In the VSA group, no correlation was noted between Rho-kinase activity and accumulated number of coronary risk factors. Interestingly, Rho-kinase activity was higher in the patients with unstable or severe angina than in the patients with stable angina (phosphorylated MBS/total MBS ratio, 1.47±0.42 vs. 1.21±0.28, P=0.05). After 3-months medical treatment, Rho-kinase activity in the VSA group was significantly decreased to 1.08±0.31 (P<0.001), and %change in Rho-kinase activity was significantly correlated with the degree of symptomatic improvement (P<0.05). With receiver-operating characteristic curve analysis, phosphorylation ratio of 1.18 was identified as the best cut-off level to predict the diagnosis of VSA (AUC 0.85) with 82% sensitivity and 90% specificity.
Conclusions: These results indicate that Rho-kinase activity in circulating neutrophils is enhanced in VSA patients and may be useful for diagnosis and disease activity assessment of the vasospastic disorder.

P1618 Association of local macrophage inflammation in epicardial adipose tissue with left ventricular function in patients undergoing coronary artery bypass surgery

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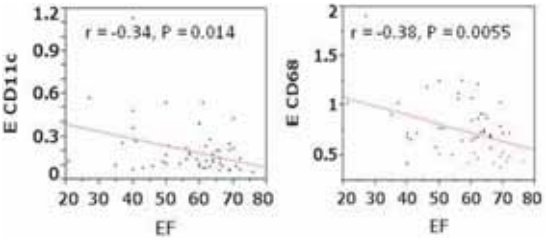
Background: Inflammation is associated with risk factors for heart failure and also directly affects left ventricular function. Local inflammation in adipose tissue is associated with progression of coronary atherosclerosis. However, the association of local tissue inflammation with left ventricular function remained uncertain in patients with severe coronary artery disease. We hypothesized that the inflammation in epicardial adipose tissue (EAT), which is the most adjacent adipose tissue to heart, correlates to cardiac function.
Methods: EAT, pericardial and subcutaneous adipose tissues (PAT and SAT) were obtained from 52 patients with CAD undergoing elective coronary artery bypass surgery (Mean age; 66.6 years old, Male; 84.6%, BMI; 23.6kg/m^2). The expression of inflammatory cytokines and CD68 (macrophage surface marker), CD11c (inflammatory macrophage) and CD206 (anti-inflammatory macrophage) in each adipose tissue was compared using real-time qPCR. We evaluated the correlation between the preoperative left ventricular (LV) function and the expression of inflammation associated genes in 3 adipose tissues.
Results: CD68 and CD206 expression was significantly higher in EAT than in other adipose tissues whereas inflammatory cytokines did not highly express in EAT. The expression of CD 68 and CD11c significantly inverse correlated to ejection fraction (Figure). CD68 and CD11c gene expression in EAT was higher in low cardiac function than that in normal function whereas there was no correlation between CD206 gene expression and cardiac function.



Correlation between LVEF and mRNA in EAT

Conclusion: CD68 gene and CD11c expression in EAT was inversely correlated to ejection fraction of the patients with CAD. Accumulation of macrophage and depolarization to inflammatory macrophage in EAT could be associated with LV function

P1619 Long term endothelial receptor antagonism attenuates coronary plaque progression in patients with early atherosclerosis

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Purpose: The endothelium-derived peptide endothelin-1 constricts coronary vessels predominantly via smooth muscle endothelin-A (ETA) receptor activation and contributes to endothelial dysfunction, an early stage of atherosclerosis. This study was designed to test the hypothesis that long-term treatment with ETA receptor antagonist can slow down progression of coronary atherosclerotic plaque in patients with coronary endothelial dysfunction.
Methods and results: Thirty-five patients with non-obstructive coronary disease and coronary endothelial dysfunction were randomized in a double blind manner to treatment with placebo or Atrasentan (10 mg, ETA receptor antagonist) for six months. Coronary endothelial function was evaluated by intracoronary infusion of acetylcholine at increasing concentrations (10-6 to 10-4 mol/L) into the LAD. Normalized mean total atheroma volume (TAVMEAN), percent atheroma volume (PAV) and changes of atheroma volume were assessed by intravascular ultrasound (IVUS) at baseline and 6-month follow-up. In the segments with coronary endothelial dysfunction in placebo group, TAVMEAN and PAV were significantly increased at follow up compared to baseline median (IQR), 63.0 (31.8, 79.5) vs. 54.0 (30.0, 73.4), p=0.009; 28.48 (21.05, 30.22) vs. 21.79 (20.54, 29.72), p=0.018. In segments with coronary endothelial dysfunction, changes of TAVMEAN and PAV were significantly higher at six months from baseline in placebo compared to Atrasentan group: 9.11, (1.23, 14.05) vs. -2.00, (-7.28, 2.53), p=0.0024; 3.85, (-0.39, 14.59) vs. -0.955, (-3.43, 1.70), p=0.010. There were no differences in changes PAV in segments with normal endothelial function between the groups (p=0.3).
Conclusions: This study demonstrates that 6-month treatment with Atrasentan prevents progression of coronary plaque in segments with endothelial dysfunction, and suggests a potential therapeutic role for long-term ETA receptor antagonism for patients with coronary endothelial dysfunction and non-obstructive coronary artery disease to prevent plaque progression.

P1620 Plasma biopterins as a novel inflammatory marker in cardiovascular disease: discordance between plasma biopterins and endothelial function in response to acute inflammation

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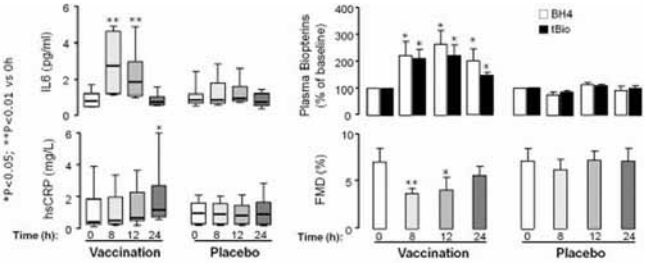
Background: Tetrahydrobiopterin (BH4) is a co-factor of endothelial nitric oxide synthase (eNOS), essential for the maintenance of its enzymatic coupling. Although vascular BH4 is positively associated with NO bioavailability, the value of circulating BH4 as a biomarker is unknown, since GTPCH, the rate limiting enzyme for its biosynthesis, is upregulated by inflammation. We examined relationships between circulating BH4 and endothelial function after induction of acute inflammation.
Methods: Twenty healthy young adults were randomised to receive either Salmonella Typhii vaccine or placebo, in a double-blind placebo controlled study. Endothelial function was evaluated in the brachial artery (by flow mediated dilation-FMD) at baseline and 8h, 12h and 24h after the intervention. Blood samples were also obtained at all time-points, to determine circulating c-reactive protein (hsCRP) and interleukin 6 (IL-6) by ELISA, and plasma BH4 and total biopterins (tBio, that include BH4 and its products of oxidation) by HPLC.
Results: Vaccination induced a significant elevation of IL-6 at 8h and 12h, then returned to baseline at 24h (A); hsCRP was increased at 24h (B). Importantly, plasma BH4 and tBio (C) were increased at 8h and 12h following the same pattern as IL-6, while FMD was reduced at the same time points (D).



Conclusions: Acute inflammation induced by S. Typhii vaccine, rapidly increased circulating biopterins, following the same pattern as circulating IL-6. However, endothelial function was reduced in parallel to the increase of plasma biopterins. This discordance between circulating BH4 and endothelial function under conditions of acute inflammation, suggests that circulating biopterins should be considered as a marker of inflammation, and are not directly related to endothelial function.

P1621 Interleukin-1b is a major determinant of LV remodelling following STEMI treated by primary PCI

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Purpose: Increased levels of interleukin (IL)-1-related molecules are seen during myocardial infarction (MI), but data on their relation to infarct size and left ventricular (LV) remodeling are lacking.
Methods: Forty-two patients with first time ST segment elevation MI (STEMI)

with a single occluded vessel, successfully treated by percutaneous coronary intervention (PCI), were recruited. Cardiac magnetic resonance (CMR) was used for assessment of infarct size and LV remodeling at 2 days, 1 week, 2 months and 1 year. Plasma levels of IL-1β, IL-1 receptor antagonist, IL-18 and caspase-1 were analyzed until 2 months after PCI.
Results: Univariate analysis showed that IL-1-related mediators were strongly (IL-1β), moderately (caspase-1), slightly (IL-1Ra), associated with impaired myocardial function and non-infarct mass, but not infarct size, one year after STEMI (Table - demonstrates only IL-1β relationships). In multivariate analyses, troponin T predicted ($p<0.001$) LV ejection fraction (LVEF), infarct size, LV end-diastolic and end-systolic volume indexes (LVEDVi, LVESVi). However, significant additional variance was explained by IL-1β, IL-18 and caspase-1. IL-1β levels at 2 months ($p<0.05$), IL-18 at 2 days ($p<0.01$) and pre-PCI caspase-1 ($p<0.05$) were predictors of LVEF. Caspase-1 ($p<0.01$) and in particular IL-1β at 2 days ($p<0.01$) were the only predictors of non-infarct mass. IL-1β ($p<0.01$) at 2 days and IL-18 ($p<0.01$) at 2 days were predictors of LVEDVi, while pre-PCI levels of IL-1β ($p<0.01$)contributed to prediction of LVESVi. In contrast, pro-B-type natriuretic peptide and C-reactive protein had no significant association with these CMR parameters.

IL-1β and CMR findings at 1 year

	Infarct mass	Non-infarcted mass	LVEDVi	LVESVi	LVEF
IL-1β					
Pre PCI	0.05	0.24	0.36*	0.39*	-0.33
2 days	0.19	0.40*	0.41**	0.35*	-0.36*
1 week	0.13	0.35*	0.41**	0.34*	-0.23
2 months	0.05	0.09	0.33*	0.36*	-0.39*

*$p<0.05$, **$p<0.01$.

Conclusions: IL-1β levels after STEMI were strongly associated with impaired myocardial function and non-infarct LV mass after 1 year. This finding suggests a role for IL-1β in maladaptive myocardial remodeling following MI.

P1622 Lymphocyte activation and apoptotic process in acute coronary syndromes

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Purpose: Stimulation of inflammatory mechanisms in acute coronary syndrome (ACS) is not limited to the microenviroment of the plaque and it involves circulating cell populations. In the present study we evaluated the lymphocyte activation and apoptosis during the acute and sub-acute phase of ST elevation myocardial infarction (STEMI).
Methods: The study population consisted of 41 patients with STEMI (AMI group), 25 patients with unstable angina (UA group) and 19 healthy age-matched volunteers (H group). Blood samples were collected from AMI and UA groups on admission 0 h and at 24, 48 and 72 h thereafter. Group H was sampled once and the results served as the normal control values. Samples were stained for flow cytometry (FCM). To measure membrane changes associated with apoptosis, peripheral lymphocytes were labeled with Annexin V-FITC and PI. The combination of conjugated Annexin V and PI allowed for the discrimination between early apoptotic (Annexin+/PI-), late apoptotic (Annexin V+/PI+), necrotic (PI+) and viable cells (Annexin-/PI-). Expression of cell surface markers CD11a and CD11b were also determined by flow cytometry. Fluorescence of the measured adhesion molecules was expressed as mean fluorescence intensity (MFI).
Results: Total lymphocyte percent was significantly decreased on admission in the AMI group as compared to the UA and H groups (p=0.027 and p=0.002, respectively). In the AMI group, the percentage of Annexin V+/PI- lymphocytes demonstrated a significant decline at 24 h as compared to 0 h (p=0.006) followed by a non significant increase afterwards. No significant alterations in Annexin V+/PI- lymphocytes were observed in the UA group during the first 72 h after admission. In the AMI group the CD11a expression intensity on lymphocytes was significantly elevated on admission 0 h as compared to the UA and H group (p=0.031 and p=0.043, respectively). Anterior infarcts presented with elevated late apoptotic lymphocytes (Annexin+/PI+) at 0 and 24 hours (p=0.018 and p=0.047, respectively), and elevated (Annexin+/PI-) lymphocytes at 24 hours (p=0.021). In the AMI group, Annexin+/PI- and Annexin+/PI+ lymphocytes were correlated with left anterior descending artery (LAD) stenosis at 0 hours (r=0.558 p=0.002 and r=0.526 p=0.004, respectively).
Conclusion: Our data showed that during the acute phase of myocardial ischemia peripheral lymphocyte life span and function are modified. Although peripheral lymphocyte population is reduced, cells become primarily activated and resistant to apoptosis during the first 24 h after AMI.

P1623 TTR (pre-albumin) forms are decreased with increased cardiovascular risk. Analysis of serum and HDL TTR forms

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Purpose: Cardiovascular disease progression and its clinical manifestations are usually linked to inflammatory processes. Acute phase inflammatory proteins have been associated with short-term mortality following acute myocardial infarction (AMI). By applying a proteomic expression profiling approach we have identified transthyretin (TTR) in serum of AMI-patients. Our objective has been to characterized TTR and its distribution pattern in serum and high density lipoprotein (HDL) in AMI patients and in patients with high cardiovascular risk (heterozygous familiar hypercholesterolemia, FH).
Methods: Characterization of serum and HDL TTR was performed by 2D-electrophoresis (2DE) followed by mass-spectrometry (MALDI-ToF) and Western blot analysis (WB). Serum TTR levels in AMI-patients (n=39), FH-patients (n=61) and in a control population (n=60) were determined by ELISA.
Results: TTR was identified by 2-DE in serum of AMI-patients as a single spot (pI=5.6, Mw=42 kDa) that revealed a 10-fold decrease in its intensity in association with diabetic dyslipemia ($P<0.05$ vs. TTR levels in AMI-patients without dm and dl). By ELISA, serum TTR levels were significantly lower in AMI- and FH-patients than in controls (Median [IQR] μg/mL; AMI: 170 [148-189] and FH: 198 [173-213] vs. Control: 223 [203-250]; $P<0.0001$; Mann-Whitney). TTR levels in AMI-patients reached their lowest value at 72-96 hours after admission ($P<0.001$ vs. t=0), time point where no TTR spot was detected by 2-DE (in 88% of AMI-patients), and higher CRP levels were detected ($P<0.05$). Differing from serum, western Blot and 2-DE of HDL samples depicted only a monomeric 14 kDa TTR form. Moreover, TTR was present in HDL3, but not in HDL2 fraction.
Conclusions: Our results demonstrate alterations in TTR proteomic profile, along with an important decrease in its serum levels after an acute myocardial infarction. The association between changes in the TTR trimer and the presence of cardiovascular risk factors might highlight an implication of TTR in patients' outcome after an AMI. The significant changes in TTR between serum and HDL underscore the importance of TTR-forms transported in the circulation and deserve further investigation to understand their function.
Supported: SAF2006/10091, CIBERobn CB06/03, Redinscor R006/003/0015 and R006/003/0000, "Fundación Lilly" and CNIC-08/2008.

P1624 Monocyte subsets differently express CD59, correlate with cardiovascular risk factors and are affected by statin treatment

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Purpose: Monocytes play a key role in modulating inflammation in coronary artery disease (CAD). Different monocyte subsets can be distinguished via expression of CD14 and CD16. CD59 attenuates atherosclerosis through inhibition of the formation of the membrane attack complex. The aim of this study was to analyze the distribution of monocyte subsets and their expression of CD59 in a cohort of patients with stable CAD. Furthermore the influence of CAD severity and known risk factors for CAD such as inflammation and diabetes should be examined, together with the impact of therapeutic intervention such as statin treatment.
Methods: 94 patients suffering from angiographically proven stable CAD were enrolled. Monocytes were classified as CD14++/CD16low ("classical monocytes", CM), CD14low /CD16+ ("non-classical monocytes", NCM), CD14++/CD16+ ("intermediate monocytes", IM) and CD14low/CD16low ("so far undefined monocytes", SFUM, a subset that has not been described yet) and expression of CD59 on each subtype was measured. We further measured their correlation with CRP levels, HbA1c and the impact of CAD severity on the monocyte distribution. Current statin medication was noted.
Results: SFUM expressed significantly higher levels of the protective CD59 ($p<0.0001$) than all other subtypes, NCM showed the lowest levels of CD59 ($p<0.0001$). Levels of CRP correlated inversely with levels of SFUM (ρ= -0,424, $p<0.001$), while levels of HbA1c correlated positively with NCM (ρ=0,336, $p<0.05$)
Patients suffering from severe CAD, defined as 3VD, showed higher levels of NCM than all other subtypes ($p<0.05$) and lower levels of CM than all other subtypes ($p<0.05$).
Patients treated with atorvastatin showed less NCM than patients treated with simvastatin ($p<0.05$) and higher levels of CM ($p<0.05$). However, patients treated with 40mg simvastatin had higher levels of CM than patients treated with 20mg ($p<0.05$).
Conclusions: The fact that "non-classical" monocytes expressed lower levels of CD59 than all the other subtypes supports the notion that this subset acts "pro-atherogenic". The very high levels of CD59 on a subset that has not yet been described, the SFUM, together with inverse correlation with levels of CRP, could suggest that this subset acts protective. The positive correlation of HbA1c

and NCM contributes to the observation that diabetics are especially prone to atherosclerosis. The different effects of statins on monocyte subset distribution, with atorvastatin leading to a more "anti-inflammatory" distribution, might add another piece to the puzzle in understanding the anti-inflammatory effects of statins.

P1625 The role of asymmetrical dimethylarginine in inflammation-related endothelial dysfunction in coronary artery disease and rheumatoid arthritis

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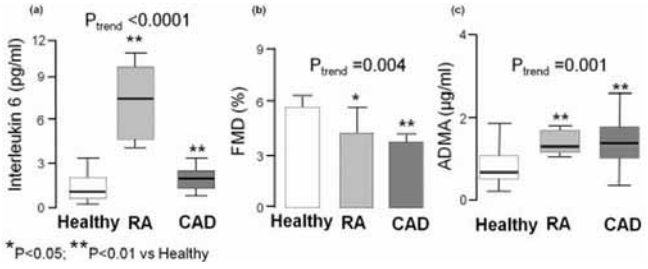
Background: Experimental evidence suggests that asymmetrical dimethylarginine (ADMA) synthesis is regulated by proinflammatory stimuli, but it is unclear whether ADMA is a link between inflammation and endothelial dysfunction in humans. We examined the interrelationships between ADMA and background inflammation and their impact on endothelial function in different inflammatory states, such as coronary artery disease (CAD) and rheumatoid arthritis (RA).
Methods: In study 1 (cross-sectional) we recruited a population of 351 patients with CAD and 87 healthy individuals of similar age. In study 2 (case-control) we recruited 69 CAD patients, 69 matched healthy controls and 10 patients with RA without CAD. Endothelial function was determined by flow mediated dilation (FMD) in the brachial artery, while serum IL-6 and ADMA were determined by ELISA.
Results: In Study 1, ADMA was inversely correlated with FMD in healthy individuals (r= -0.433, $P<0.0001$) and CAD patients (r= -0.321, $P<0.0001$). IL-6 was strongly inversely correlated with FMD in healthy individuals (r= -0.373, $P<0.001$) but weakly in CAD (r= -0.121, $P<0.01$). The positive correlation between ADMA and IL-6 was stronger in healthy (r=0.515, $p<0.0001$) than CAD (r=0.289, p=0.0001). In Study 2 (case-control), FMD was similarly reduced and ADMA similarly increased in patients with CAD or RA (Figure).



Conclusions: ADMA levels are increased in the presence of low (CAD) or high (RA) grade inflammation, and endothelial function is similarly impaired. ADMA appears to be a key regulator of endothelial function in inflammatory states, independently of the presence of advanced atherosclerosis.

P1626 The long term impact of glycemic and inflammatory status in non-diabetics with acute coronary syndromes

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Purpose: Serum levels of glucose and inflammatory biomarkers upon presentation seem to confer incremental predictive value for no-diabetics (and diabetics) with acute coronary syndromes. We sought to investigate the possible interrelation of serum levels of glucose and inflammatory biomarkers upon presentation as well as the interaction of all these biomarkers in the prediction of 1-year death in this setting.
Methods: 848 STEMI and 666 NSTE-ACS consecutive pts, without history of diabetes, who presented in the first 12 and 24 h of index pain respectively, were studied. Serum glucose levels upon presentation and during hospitalization was ≤11 mmol/L in all pts. Each cohort was divided into 3 groups according to the serum glucose levels upon presentation: Group A with <6.1 mmol/L, Group B with 6.1-7 mmol/L and Group C with 7-11 mmol/L. Serum levels of inflammatory biomarkers including hs-CRP, interleukin-6 (IL-6) and fibrinogen (FIB), were measured upon presentation.
Results: There was a significant gradual increase of serum levels of all inflammatory biomarkers from Group A to Group C in pts with STEMI and NSTE-ACS. Particularly, serum levels of hs-CRP ($p<0.001$ and $p<0.001$), IL-6 ($p<0.001$ and $p<0.001$) and FIB (p=0.02 και p=0.01) were gradually and significantly increased from Group A to Group C in pts with STEMI and NSTE-ACS. The incidence of 1-year mortality in A, B, and C Groups was 11.2%, 16.2%, 20.4% and 8%, 12.6%, 19.1% for STEMI (p=0.02) and NSTE-ACS (p=0.002) pts respectively. Inflammatory biomarkers were significantly related to the incidence of 1-year mortality in pts with STEMI and NSTE-ACS. Particularly, hs-CRP ($p<0.001$ and $p<0.001$), IL-6 (p=0.004 and p=0.008) and FIB (p=0.03 και p=0.02) were significantly related to 1-year death in STEMI and NSTE-ACS pts respectively. By multivariate Cox analysis (in which inflammatory biomarkers were not included), glucose levels upon presentation was an independent predictor of 1-year death (p=0.007 and $p<0.001$, for STEMI and NSTE-ACS pts respectively). However, by multivariate Cox analysis (in which inflammatory biomarkers were included), glucose levels upon presentation was not an independent predictor of 1-year death (p=0.5 and p=0.6, for STEMI and NSTE-ACS pts respectively).
Conclusions: According to the present results serum glucose levels upon presentation are strongly associated with the degree of inflammatory response in non-diabetics with acute coronary syndromes. This may at least partially explain the association of serum glucose levels upon presentation and adverse outcome in non-diabetics with acute coronary syndromes.

P1627 Pioglitazone reduces coronary microvascular damage after percutaneous coronary intervention for the patients with stable angina pectoris

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Backgrounds: The status of coronary microcirculation has long-term prognostic significance. Minor cardiac marker elevation after percutaneous coronary intervention (PCI) indicates microvascular damage resulting from PCI, possibly due to plaque embolization or inflammation. It has been reported that pre-treatment with statin reduced myocardial damage after PCI because of anti-inflammatory and plaque stabilizing effects. Pioglitazone may have similar effects, and potentially reduce the incidence of myocardial damage after PCI. We examined the effect of pioglitazone using a coronary pressure wire-derived Index of Microcirculatory Resistance (IMR).
Methods: Forty patients with stable angina pectoris were randomized to receive either pioglitazone (15 mg/day, n=20) or control (n=20). All patients were previously received statin at randomization. There was no difference in terms of other medicines, such as aspirin, beta-blockers and calcium channel blockers. We performed 75g-oral-glucose-tolerance-test one day before PCI, and underwent PCI with intravascular ultrasound (IVUS), fractional flow reserve (FFR), and IMR. Patients with significant side branch occlusion, slow flow, and usage of nicorandil during PCI were excluded.
Results: Percentage of abnormal glucose tolerance, fasting insulin (IRI), and HOMA-R were identical between the pioglitazone group and the control group (85 vs. 93%, 6.7±3.5 vs. 6.4±2.9μu/ml, 1.86±1.21 vs. 1.77±0.9, ns for all), however 2hr-IRI was significantly lower in the pioglitazone group than that in the control group (57.1±57.6 vs. 96.1±53.9μu/ml, $p<0.001$). Other clinical characteristics and procedural results including coronary risk factors, all volumetric IVUS parameters, number of stents, and total stent lengths were similar between the two groups. Despite similar post-FFR, ΔFFR and Δpercent plaque volume (post-FFR: 0.91±0.09 vs. 0.92±0.05, ΔFFR: 0.16±0.2 vs. 0.13±0.13, Δpercent plaque volume: 18.7±7.9 vs. 17.6±7.6%, ns for all). The pioglitazone group showed significantly lower post-PCI IMR and ΔIMR than the control group (post-PCI IMR: 17.5±11.5 vs. 21±19.1units, and ΔIMR: 0.48±13.2 vs. 6.6±17.9units, $p<0.01$ for all).
Conclusions: Administration of pioglitazone appears to reduce microvascular damage after PCI, possibly associated with IRI fluctuation. These results suggest that pioglitazone may have not only effect of improving IRI resistance but also pleiotropic benefits.

P1628 Complicated dental root canal treatment and risk of prehospital sudden cardiac death

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Purpose: Previous studies have suggested an association among coronary heart disease (CHD), myocardial infarction (MI), and microbial infections. As dental procedures cause bacteremia, we studied whether root canal treatment (RCT), a common and complication-prone dental procedure, would associate with the risk of sudden cardiac death (SCD).
Methods: We performed panoramic dental tomography in Helsinki Sudden Death Study (n=300) comprising prehospital SCDs among 33-69 year-old males during one year (1991-2). Specific primers/probes for typical periapical absess bacteria, periodontal pathogens and Chlamydia pneumoniae and broad-range bacterial 16S rDNA PCR were used to detect bacterial DNAs in thrombosed coronary plaques from recent autopsies and in thrombus aspirates from patients with ST-elevation MI undergoing percutaneus coronary intervention.
Results: In multivariate analysis adjusted for age, BMI, hypertension, smoking, diabetes, education and number of teeth, previous RCT complicated by dental periapical abscess was linked with the risk of SCD due to CHD (OR 3.2; 95% CI 1.3 – 8.0, p=0.011), acute MI (OR 3.1; 1.2 – 8.0, p=0.021) and especially to

coronary thrombosis (OR 7.9; 2.2 – 28.6, p=0.002). Uncomplicated RCT or periapical abscesses without RCT showed no associations. Men who had RCT with periapical abscess also often had concomitant chronic periodontitis. Several oral bacterial species typical for periapical abscesses, mostly of viridans streptococci, were detected in 85.7% of coronary plaques and in 72.7% of thrombus aspirates. Periodontal pathogens were found in 28.6% and 36.4% of cases, respectively. Chlamydia pneumoniae was not detected despite the use of specific primers.
Conclusions: Complicated dental root canal treatment may be an unrecognized risk factor of SCD, contributing to the inflammation of coronary plaques. Periapical abscesses are difficult to eradicate because antibiotics do not enter root canals or abscesses. Surgical interventions in case of periapical lesions refractory to endodontic therapy and also the alternative use of dental implants should be more often planned. Our results suggests that regular and careful dental care offered for middle-age men might be one option to reduce the risk of unexpected cardiac death

P1629 Natural killer cell apoptosis in coronary artery disease: is it reflected by soluble markers of apoptosis?

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Purpose: Patients with coronary artery disease (CAD) exhibit a perturbed immune homeostasis in peripheral blood. We have previously shown a reduced number of natural killer (NK) cells in vivo and an increased susceptibility to NK cell apoptosis ex vivo in CAD patients. The aim of the present study was 1) to follow changes in NK cells over time in CAD patients and 2) investigate whether soluble markers of apoptosis reflect NK cell apoptosis.
Methods: For in vivo studies, blood was collected from 37 patients with acute coronary syndrome (ACS) and 35 patients with stable angina (SA), all referred for coronary angiography, and 30 healthy controls. In patients, blood sampling was repeated at 3 and 12 months. NK cells were assessed by flow cytometry using anti-CD3, anti-CD8, anti-CD56 and Annexin V. For ex vivo studies, NK cells were isolated from 16 individually matched pairs of SA patients and controls. After 18 h of incubation, NK cell apoptosis was determined. Four soluble markers of apoptosis, Tumor Necrosis Factor Receptor (TNFR) I, sTNFR II, sFas and sFas ligand (FasL), were measured by ELISA in plasma from all participants.
Results: At admission, the percentages of NK cells were significantly reduced in ACS, 12 (5)%, and SA, 15 (8)%, compared to controls, 19 (9)%. At follow-up, the fractions of NK cells showed increases in both ACS and SA groups, being most prominent among ACS patients ($p<0.01$). ACS patients also exhibited increases in apoptotic NK cells (from 1.6 to 4.3%, $p<0.001$). Among markers of apoptosis, the levels of sTNFR II and sFasL increased significantly in both ACS and SA patients, most prominently in ACS. Both of these markers correlated with NK cell apoptosis ex vivo but not with apoptotic NK cells in the circulation. Instead, sFasL correlated with the percentages of peripheral NK cells in both ACS and SA at 3 and 12 months ($p<0.01$). There was no correlation between sFasL and other lymphocyte subsets.
Conclusion: In CAD patients, particularly those with ACS, peripheral NK cells showed dynamic changes during rehabilitation possibly reflecting an increased cell turnover. Although soluble markers of apoptosis did not reflect the number of apoptotic NK cells in blood, our data indicate that sFasL may be a potential surrogate marker of NK cell changes in CAD patients.

P1630 The effect of the duration of clopidogrel use on hsCRP levels after stenting the target vessel in patients with acute coronary syndrome

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Aim: The aim of the study is to investigate the relation between the duration of the clopidogrel use and the inflammation process after acute coronary syndrome in patients who received bare metal stent (BMS) or drug eluting stent (DES).
Method: Sixty patients with acute coronary syndrome, who received a stent in our clinic were included in the study. The patients were divided into three groups, 20 patients with BMS, receiving clopidogrel for one month (BMS1 group), 20 patients with BMS receiving clopidogrel for 6 months (BMS6 group) and 20 patients with DES, receiving clopidogrel for 6 months (DES group). High sensitive C-reactive protein (hsCRP, mg/L) was measured in all study patients at baseline, first month and sixth month.
Results: The hsCRP levels were high and similar in three groups at baseline. There was a statistically significant decrease in the hsCRP levels in all patients at first month comparing to the baseline values (7.1±1.9 to 3.8±2.3 in BMS1 group, 6.5±2.8 to 4.3±2.5 in BMS6 group and 7.7±2 mg/L to 3.6±2.4 mg/L in DES group, respectively)
In the BMS1 group, after the quiting the clopidogrel treatment at first month, there was a significant increase in the hsCRP levels at third and sixth month comparing to the first month. In the BMS6 and DES groups, the decrease in hsCRP levels were continued at the third month and also continued until the sixth month.

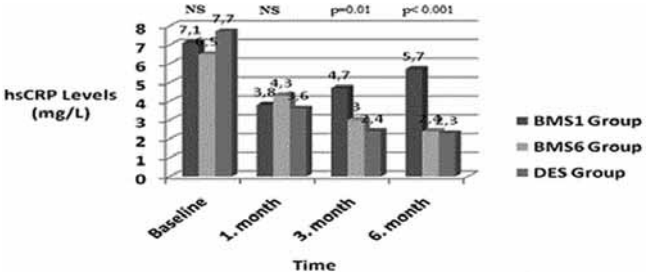

Figure 1. The change of hsCRP levels.

Conclusion: It was determined that clopidogrel achieves a decrease in hsCRP levels in patients with acute coronary syndrome. The duration of the clopidogrel therapy should be kept longer in these patients because of its anti-inflammatory effects.

P1631 The relationship between admission C - reactive protein levels and microvascular dysfunction in patients with non-ST elevation acute coronary syndrome undergoing stenting

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Purpose: The impact of admission C-reactive protein (CRP) levels on changes in microvascular resistance after percutaneous coronary intervention (PCI) in patients with non-ST elevation acute coronary syndrome (NSTEACS) is not known.
Methods: This study consisted of 38 patients with NSTEACS undergoing PCI. Microvascular resistance (MR) was measured at maximal hyperemia by using dual sensor (pressure and Doppler velocity) guidewire before and after PCI as follows: Pa (1/APV) [(Pd-Pw)/(Pa-Pw)], where Pa represents aortic pressure, APV is average peak velocity measured distal to stenosis, Pd is distal coronary pressure and Pw is coronary wedge pressure. Post-PCI MR was calculated at maximal hyperemia as Pd/APV. Percent and absolute changes in MR from pre to post-PCI were calculated. CRP values, white blood cell (WBC) and neutrophil counts were collected at admission.
Results: MR increased from 1.75±0.8 to 2.05±0.7 after stenting (p=0.014). Mean of admission CRP was 8.9±9.1 mg/L. Admission CRP values were significantly correlated with post-PCI MR (R=0.34, P=0.043), percent change in MR (R=0.462, p=0.005) and absolute change in MR (R= 0.532, p=0.001). There were no correlations between WBC and neutrophil count at admission and absolute and percent changes in MR after PCI. In multivariable model, CRP is the only independent predictor of impaired microvascular perfusion (increased ΔMR) after PCI ($p<0.01$).
Conclusion: These findings suggest that admission CRP values strongly predict post-PCI microvascular damage in patients with NSTEACS undergoing PCI.

P1632 Multiple complex coronary lesions and periodontal disease

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Context: Periodontal disease, in which bone loss is the main symptom, increases the risk of atherosclerosis and is thought to be involved in plaque destabilization by inflammation. Multiple complex coronary lesions (MCL), defined by stenosis exceeding 50%, and at least two of the following criteria, chronic occlusion, impaired flow, thrombus, irregularity, and ulceration of the lesion, are associated with multifocal destabilization of atherosclerotic plaque in the coronary system. We investigated whether significant bone loss could predict the presence of MCL.
Materials and methods: This prospective study included 150 consecutive patients who initiated outpatient cardiac rehabilitation between 2007 and 2010 for myocardial infarction <1 month and who underwent coronary angiography. Patients without coronary lesions or simple complex coronary lesions (SCL group) were compared to patients with MCL. A panoramic dental x-ray was made at the beginning of rehabilitation, with several criteria including bone loss >50% to evaluate the state of dental health.
Results: Over 20% of patients had MCL (32/150). Patients in the SCL and MCL groups had similar cardiovascular risk factors. However, patients with MCL were less likely to be women and more likely to have multivessel disease than were patients in the SCL group (21% vs. 6%, p=0.051, and 88% vs. 46%, $p<0.001$). Bone loss >50% tended to be more frequent in patients with MCL than in those with SCL (50% vs. 32%, p=0.063). In addition, patients with MCL had a higher

CRP level (CRP >10 mg/L: 15% vs. 42% p=0.001). In multivariate analysis, multivessel disease (OR (95% CI): 6.63 (2.09-21.03), and CRP >10 mg/L (OR (95% CI): 3.98 (1.48-10.69)) were associated with the presence of MCL. Female sex (OR (95% CI): 0.23 (0.04-1.22) tended to be associated with SCL. In addition, bone loss >50% significantly increased the risk of MCL (OR 2.63 (1.03- 6.71) p=0.043)) even after adjustment for other predictors of MCL.
Conclusion: Bone loss, a simple parameter of periodontal evaluation, correlated with complex and multiple coronary lesions, independently of other known factors associated with MCL, including systemic inflammation.

P1633 Modified electronegative LDL and coronary atherosclerosis

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Backgruond: Low density lipoprotein (LDL) are involved in atherosclerotic plaque formation. However, the proatherogenic power of specific LDL fractions is not well known. In particular, a minor fraction of the total LDL has an electronegative charge and is represented by electronegative LDL (LDL-), with high potential to induce endothelial injury. We aimed at assessing the association between serum LDL- levels and coronary atherosclerosis, as assessed by angiography.
Methods and results: Consecutive anginal patients with angiographic evidence of coronary artery disease (CAD) [stable angina (SA) or non-ST-elevation acute coronary syndrome (NSTE-ACS)], or with angiographically normal coronary arteries (NCA) were enrolled between May 2010 and November 2010. Patients with and without angiographic CAD were matched for age and sex and had similar total LDL serum levels. Among CAD patients those with history of hypercholesterolemia were on statin treatment that produced LDL levels similar to the overall population. Baseline LDL- serum levels were measured in all patients. Isolation of LDL- from total LDL was accomplished through preparative anion exchange chromatography in an AKTA-FPLC system using a MonoQ 5/50 GL column and a multistep gradient from 0 to 0.3 M NaCl. Fractions corresponding to native LDL and to LDL- were pooled, and salts removed by overnight dialysis against Chelex-treated argon-purged PBS. Of 47 patients (age 65±12 years, male sex 61%), 17 (age 65±11 years, male sex 63%) had stable angina, 15 (age 62±12 years, male sex 59%) had NSTE-ACS and 15 (age 64±12 years, male sex 62%) had NCA. Total LDL serum levels were similar among the three groups (p for all 0.78). LDL- levels were significantly higher in SA [25.7 (18.3-30.2) p=0.0001] and NSTE-ACS [27.1 (18.9-30.2, p=0.0001] as compared to NCA [6.7 (4.3-9.7)], without significant difference between SA and NSTE-ACS (p=0.92).
Conclusions: Our study demonstrates that LDL- serum levels are associated with angiographic CAD while total LDL do not. This exploratory analysis should prime further larger studies in order to assess the proatherogenic role of LDL- as compared to total and other subfractions of LDL.

P1634 Role of free radicals in myocardial reperfusion injury in patients undergoing percutaneous coronary interventions

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Purpose: Data about oxidative stress in percutaneous coronary interventions (PCI) are still controversial. We assessed the oxidative stress and enzymatic antioxidants activities in Acute Coronary Syndrome (ACS) patients going for PCI, whether complicated or uncomplicated. Evaluations for role of various clinical variables and oxidative stress markers on TIMI flow before and after PCI were also studied.
Methods: A total of 108 patients were taken. Out of which, 11 were controls, 76 patients from uncomplicated PCI (TIMI 3 flow) and 32 patients were from complicated PCI (TIMI 0, 1, 2 flows). Mechanical cause for reduced flow e.g. dissection, spasm, visible thrombus distal to lesion were excluded. Collection of blood sample (5ml) prior to PCI and within 30 minutes of balloon inflation was done through guiding catheter in related coronary artery and collected in heparinised tubes. Estimation of free radical markers e.g.MDA and antioxidants assays were done at biochemistry lab.
Results: The mean level of all antioxidants was comparatively low while the level of MDA was comparatively high in both PCI groups than the respective control before going for interventions. After PCI, the level of all antioxidant enzymes in both groups of patients decreased further while the level of MDA increased as compared to respective pre PCI levels ($p<0.01$). A total occlusion showed highest and significant ($r= -0.61$, $p<0.01$) inverse relation with the TIMI flow, followed by LV dysfunction diabetes, thrombus and least by smoker. Pre PCI level of all antioxidants and free radical marker did not show any association ($p>0.05$) with post PCI TIMI flow. Pre PCI TIMI flows are much dependent on clinical characteristics rather than antioxidants and free radical levels. LV dysfunction, total occlusion, diabetes and thrombus are significant ($p<0.05$ or $p<0.01$) predictors of TIMI flows and among these, total occlusion showed maximum influence ($\beta= -0.71$, $t=5.03$; $p<0.01$) on TIMI flow. Decrease in antioxidants after PCI minimally effects response of TIMI flow (odds ratio=0.00, 95% CI: 0.00 - 0.22) but increase in MDA induced 116.4 times more risk on TIMI flow (odds ratio=116.41, 95% CI: 3.19 – 4251.87).
Conclusion: Although oxidative stress is induced following PCI as shown by increase level of free radicals markers but post PCI TIMI flows are much dependent on various clinical parameters rather than these markers. The role of clinical parameters like LV dysfunction, total occlusion, diabetes and thrombus play important role in outcome of any PCI than free radicals estimation.

P1635 The investigation of serum vaspin levels in atherosclerotic coronary artery disease

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Aim: Atherosclerosis, the most common reason for coronary artery disease (CAD), is the leading cause of mortality and morbidity in all over the world. It was speculated that fatty tissue originated adipocytokines may play role in pathogenesis of atherosclerosis. These adipocytokines may alter vascular homeostasis by effecting endothelial cells, arterial smooth muscle cells and macrophages. Vaspin is newly described member of adipocytokines family. We aimed to investigate the role of plasma vaspin levels in coronary artery disease.
Method: Fourty patients who have any ≥70% stenosis at least one coronary vessel that demostrated angiographically and 40 healthy subject were included into the study. Exclusion criteria consisted; acute myocardial infarction, history of diabetes mellitus, morbid obesity, coronary artery disease, heart failure and cardiomyopathy.Serum vaspin levels were measured by ELISA method that was obtained by centrifigation of venous blood samples. The length, weight and body mass index of patients were measured. Biochemical parameters including total cholesterol, LDL-C, HDL-C, urea, creatinine and hs-CRP levels were measured in all study patients.
Results: The baseline charecteristics of subjects in two groups were similar ($p>0.5$).The level of biochemical markers were also similar in two groups. Serum vaspin levels were significantly lower in CAD patients than control group (256±219,7 pg/ml vs. 472,5±564,2 pg/ml, respectively, $p<0,001$). The serum vaspin levels were significant negatively correlated with systolic blood pressure in the control group (r:-0,349, p=0,027).
Conclusion: Serum vaspin level was found significantly lower in patients with coronary artery disease than control group. Vaspin may be used as a predictive factor in coronary artery disease.

P1636 The high-density lipoprotein levels influence the systemic inflammatory activity and the process of coronary artery calcification in the very elderly - GEROS STUDY

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Purpose: To verify the existence of association between plasma high-density lipoprotein (hdl) levels, inflammatory mediators, calcification mediators and coronayartery calcification (cac) in individuals aged of 80 or more years old.
Methods: Healthy individuals aged between 80-102 years old (n=178) underwent evaluation of lipid profile, plasma high-sensitivity c-reactive protein (hs-crp), serum tumor necrosis factor-alfa (tnf-alfa), serum interleukin 10 (il-10), serum osteopontin (opn) levels, plasma and cac by cardiac computed tomography. After have been grouped in quartiles of HDL,the means of hs-crp, tnf-alfa, il-10, opn and cac were compared between groups.
Results: The groups with the highest levels of hdl had the lowest levels of plasma hs-crp (p=0,004), serum opn (p=0,049) and cac (p=0,043). There were no statistical significant difference between the groups' means of tnf-alfa and il-10.

Characteristics according HDL quartiles

	1°	2°	3°	4°	p
HDL, mg/dL	39±5	50±3	59±3	73±9	≤0,001
PCR, mg/dL	6,7±11,2	3,5±5,8	2,5±2,6	2,5±2,5	0,004
TNF-alpha, ng/mL	0,14±0,8	0,49±1,89	0,56±1,67	0,41±1,84	0,561
IL-10, ng/mL	1,84±2,11	2,32±2,61	2,85±3,41	1,91±2,26	0,221
OPN, ng/mL	0,97±0,50	0,83±0,48	0,96±0,52	0,73±0,48	0,049
CAC, Agatstone units	385±462	307±373	304±368	150±214	0,043

Conclusions: In very old individuals, hdl was inversely associated with opn and cac, and positively associated with innate inflammatoryresponse. There was no such association between hdl-c and adaptive immune responseTh1 or Th2.

P1637 Effect of atherosclerotic risk factors on microvascular resistance: a further obesity paradox?

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Normal 0 0 1 283 1617 13 3 1985 11.1287 0 0 0

Purpose: Elevated BMI has been shown to be associated with improved prognosis in patients with coronary artery disease and following PCI – the so called "obesity paradox". There is little data on the impact of obesity and other established atherosclerotic risk factors on measured microvascular resistance. We aimed to assess the relationship between atherosclerotic risk factors and microvascular resistance.

Methods: Microvascular resistance was measured utilizing the index of microcirculatory resistance (IMR) in 24 patients undergoing elective PCI for stable angina. A coronary PressureWire was used to measure IMR prior to PCI using the equation PaTmn (Pd-Pw/Pa-Pw), where Pa and Pd refer to hyperemic aortic and distal coronary pressure respectively, Tmn the mean transit time of 3mls of saline injected into the culprit artery and Pw the coronary wedge pressure. Hyperemia was achieved using intravenous adenosine administered via a right femoral vein. Body mass index, age, fasting LDL, HDL and blood sugar, blood pressure and smoking status (pack years) were recorded in each patient prior to PCI. Associations were assessed using Pearson's correlation coefficients. Linear regression analysis was used to assess correlates of IMR.

Results: Mean IMR was 14.3±7.9. There were positive correlations between IMR and age (r=0.55, p=0.006), fasting blood sugar (r=0.35, p=0.08). There were also negative correlation between LDL (r= -0.52, p=0.01) and BMI (r= -0.53, p=0.007). There was no correlation between IMR and HDL, smoking status or blood pressure. Multivariate regression analysis showed that reduced BMI was the only independent predictor of higher microvascular resistance in our model (B= -0.684, p=0.033).

Conclusions: Microvascular resistance is correlated with risk factors for atherosclerosis however a lower BMI appears to be a primary determinant and possibly a further aspect of the obesity paradox. Further research in this area is warranted.

P1638 Platelet endothelial cell adhesion molecule levels are increased in men with erectile dysfunction. Identifying a common molecular mechanism for erectile dysfunction and cardiovascular disease

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Purpose: Erectile dysfunction (ED) and coronary artery disease (CAD) share common pathophysiologic mechanisms including endothelial cell activation and systemic inflammation. Platelet endothelial cell adhesion molecule (PECAM-1) is considered a critical mediator of atherosclerosis, however the association of circulating PECAM-1 levels with ED and CAD is unknown.

Methods: 51 consecutive asymptomatic men with ultrasonographically documented ED, were prospectively evaluated for CAD. Coronary angiography revealed significant stenosis in 13 patients with a positive stress test. 31 age-matched non-ED subjects without CAD (control group) with a similar risk factor profile were also entered the study. PECAM-1, C-reactive protein (CRP) and fibrinogen levels were measured in all subjects.

Results: PECAM-1 levels were comparable among men with CAD and ED patients without CAD and significantly higher than those measured in control group (P<0.01, figure). PECAM-1 levels correlated with penile peak systolic velocity (PSV) (figure). The inverse correlation between PSV and PECAM-1 remained significant in linear regression analysis after controlling for age, mean pressure, metabolic profile and levels of CRP and fibrinogen (b= -0.33, P=0.032, adjusted R2=0.27). Figure also shows a positive association between PECAM-1 concentration and ED duration. Interestingly, PECAM-1 was significantly correlated with the extent of coronary atherosclerosis as assessed by modified Gensini's score (figure).

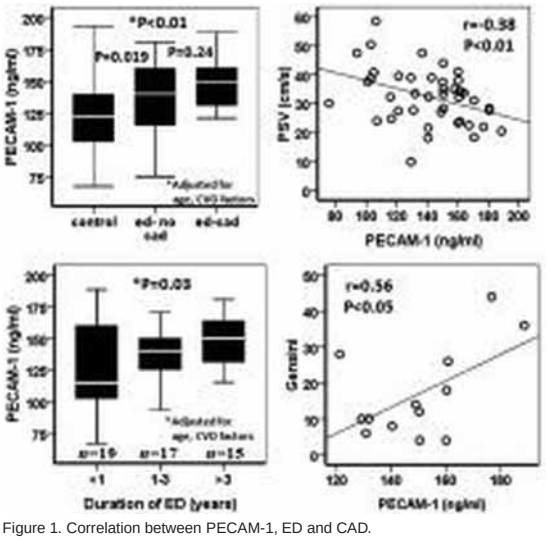

Figure 1. Correlation between PECAM-1, ED and CAD.

Conclusions: PECAM-1 levels are increased in ED patients and correlate with increasing severity and duration of penile vascular disease. This finding points out the important role of PECAM-1 as a marker of arterial damage in the penis and provides mechanistic links for the association between ED and CAD.

P1639 Radiotherapy provokes carotid arteries inflammation with increased uptake of F-18 fluorodeoxyglucose detected by positron emission tomography/computed tomography scans in head and neck cancer patients

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Purpose: Although radiotherapy has been shown to increase risks of carotid artery stenosis and stroke in head and neck cancer patients, the mechanism remains elusive. We sought to investigate whether there was increased F-18 fluorodeoxyglucose (FDG) uptake, a surrogate marker of vascular inflammation and atherosclerosis, in bilateral carotid arteries during radiotherapy for head and neck cancer patients by positron emission tomography and computed tomography (PET/CT) hybrid imaging before and after radiotherapy.

Methods: A total of 17 head and neck cancer patients (14 men, 3 women; aged, 48±11 years) who received 30–40Gy radiotherapy to the affected regions were enrolled in the study. All subjects received PET/CT scans before and 1 month after radiotherapy. The F-18 FDG uptake of the representative local arteries (carotid arteries) near the radiation site and the remote arteries (iliac arteries) away from radiation were measured.

Results: The F-18 FDG uptakes 1 month after radiotherapy were significantly increased in the right (p=0.007) and the left carotid arteries (p=0.048) as compared to those before radiotherapy in each artery. On the contrary, there was no significant change of the F-18 FDG uptake in the right (p=0.177) and the left iliac arteries (p=0.103) before and 1 month after radiotherapy (Table).

F-18 FDG Uptakes in the Carotid and Iliac Arteries Before and 1 Month After Radiotherapy

	Before Radiotherapy	After Radiotherapy	P-value
Right carotid artery (SUV)	1.42±0.25	1.56±0.27	0.007
Left carotid artery (SUV)	1.48±0.29	1.60±0.27	0.048
Right iliac artery (SUV)	1.50±0.24	1.61±0.34	0.177
Left iliac artery (SUV)	1.58±0.28	1.69±0.36	0.103

SUV = standardized uptake value.

Conclusions: Radiotherapy in patients with head and neck cancer may result in increased uptake of F-18 FDG in bilateral carotid arteries detected by PET/CT hybrid imaging. Our findings suggest that localized vascular inflammation and subsequent atherosclerotic changes might be provoked by radiotherapy.

P1640 Comparison of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced nephropathy in patients with renal insufficiency undergoing elective cardiac catheterization

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Background: Contrast-induced nephropathy (CIN) is a recognized complication after contrast agent administration especially in patients with renal dysfunction that has been associated with longer hospitalization and adverse clinical outcome. The objective of the study was to investigate whether the use of 2 antioxidants, N-acetylcysteine (NAC) or ascorbic acid, reduce the incidence of CIN in adequately prehydrated patients with preexisting renal insufficiency.

Methods: In this randomized, double-blind, prospective, placebo-controlled, single-center study, 520 consecutive patients with stable renal insufficiency (creatinine clearance < 60 mL/min) undergoing elective coronary angiography with or without intervention were randomly assigned using a computer-generated list of 3 blocks on a 2:1:2 basis to NAC, ascorbic acid or placebo on the day before and the day of angiography. Only iopromide, a nonionic, low-osmolality contrast agent, was used. Primary endpoint was the incidence of CIN defined as an absolute increase in serum creatinine concentration of ≥ 0.5 mg/dL (≥ 44 μmol/L) within 72 hours after contrast agent exposure.

Results: In 520 patients recruited, demographic and baseline characteristics, contrast volume and incidence of diabetes mellitus (51.7%) were comparable in the 3 groups. The primary endpoint of CIN occurred in 27.6% (53 of 192 patients) receiving NAC, 24.5% (24 of 98 patients) receiving ascorbid acid and 32.1% (62 of 193 patients) receiving placebo. The rate of CIN was not different between the 3 groups (placebo vs NAC p=0.37, placebo vs ascorbic acid p=0.22, NAC vs ascorbic acid p=0.67). The failure of a preventive effect of NAC and ascor-

bic acid was consistent among various patient subgroups. There were no major treatment-related adverse events.
Conclusion: There remains a high incidence of CIN despite prehydration in patients with preexisting renal dysfunction undergoing coronary angiography and/or percutaneous intervention. The prophylactic administration of the antioxidants NAC or ascorbic acid, along with prehydration, was not associated with a significantly reduced risk of CIN compared with placebo in patients with chronic renal insufficiency.

P1641 Nuclear factor kappa beta activation in monocyte subsets in patients with ST-elevation myocardial infarction

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Background: Nuclear factor kappa B (NFkB) pathway is a major signal transduction pathway of monocyte inflammatory activation.
Methods: We assessed NFkB activity in different monocyte subsets in patients admitted with acute coronary syndromes (on Day 1 of admission). We recruited 44 patients with ST elevation myocardial infarction (STEMI), who were compared to 20 non-STEMI, 48 stable coronary artery disease (SCD) and 36 healthy controls. Peripheral blood monocyte subsets were enumerated by flow cytometry within 1 hour of sample collection. Activation of NFkB was assessed by mean fluorescent intensity (MFI) of intracellular staining of inhibitor of nuclear factor kappa-B kinase beta (IKKbeta; increased levels of IKKbeta indicate activation of NFkB pathway), and expressed as Mean Fluorescent Units (MFU). The MFIs for 3 monocyte subsets, defined as CD14+CD16- (M1), CD14+CD16+CCR2+ (M2) and CD14lowCD16+CCR2- (M3) cells, were calculated.
Results: All 3 monocyte subsets had higher IKKbeta in the STEMI group compared to SCD (post-hoc Tukey's test; p=0.005, p=0.001 and p<0.001 for M1, M2 and M3, respectively), healthy controls (p=0.002, p=0.001 and p<0.001, for M1, M2 and M3 respectively) but not the non-STEMI group (Table). MFI of IKKbeta were broadly similar in the non-STEMI, SCD and healthy control groups.

Table 1. Differences between groups were evaluated by ANOVA and post-hoc Tukey's test

Monocytes (MFU)	STEMI	Non-STEMI	SCD	Healthy	p ANOVA
M1	79.5±18.0	70.9±19.9	67.9±15.8	65.7±12.7	0.001
M2	90.9±21.9	79.5±24.7	74.4±18.4	73.3±15.3	<0.001
M3	76.1±14.1	68.5±19.5	63.7±13.4	63.0±10.5	<0.001

MFU, mean fluorescent units.

Conclusion: Transcriptional factor NFkB is activated in patients admitted with STEMI but not with non-STEMI. This could have implications for the pathophysiology of myocardial damage and repair post-STEMI.

P1642 Decreased number of circulating endothelial progenitor cell is a risk factor for acute myocardial infarction due to coronary artery spasm

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Purpose: Occlusive coronary artery spasm can induce acute myocardial infarction (AMI). Circulating endothelial progenitor cells (EPCs) are known to be involved in vasculogenesis and endothelial dysfunction. We investigated the relation between the circulating endothelial progenitor cell (EPC) and the development of AMI in patients with coronary vasospasm.
Methods: We enrolled 60 patients (57.4±10.7 years, male 60.0%) with documented coronary vasospasm by ergonovine provocation test. The number of EPC and the levels of serum vascular endothelial growth factor (VEGF), macrophage chemoattractant protein (MCP-1), and interleukin-10 (IL-10) were measured in the peripheral blood before PCI. The patients were divided into two groups: acute myocardial infarction (group I: n=24) and angina pectoris (group II: n=36).
Results: The levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), peak creatine kinase-MB (CK-MB), peak troponin I (TnI), and homocysteine were significantly higher in the group I than those in the group II (p=0.020, p=0.005, p<0.001, p=0.003, respectively). Also, the levels of total cholesterol and low density lipoprotein cholesterol were significantly higher in the group I compared with those of the group II (p=0.013, p<0.001, respectively). The level of MCP-1 was significantly higher in the group I than that in the group II (52.2±19.0 vs. 32.7±16.4 pg/mL, p=0.002). The levels of VEGF and IL-10 were no significant differences. CD34+VEGFR2+ cells and CD45lowCD34+VEGFR2+ cells were significantly lower in the group I than those in the group II (401.9±341.5 vs. 683.8±347.1/106 leukocyte, p=0.045; 91.6±123.1 vs. 326.8±221.4/106 leukocyte, p=0.004, respectively). CD45lowCD34+VEGFR2+ cells correlated positively with apolipoprotein A1 level (r=0.443, p<0.001) and negatively with the levels of fibrinogen, high-sensitivity C-reactive protein, lipoprotein (a) (r= -0.233, p=0.044; r= -0.433, p<0.001; r= -0.255, p=0.028, respectively). In multivariate analysis, the decreased CD45lowCD34+VEGFR2+ cell and the increased MCP-1 level were independent determinants for the AMI due to occlusive vasospasm (OR, 3.33, 95% CI 1.34-9.80, p<0.001; OR, 5.00, 95% CI 1.28-19.53, p=0.021, respectively).
Conclusion: Decreased number of endothelial progenitor cell and elevated level of MCP-1 were associated with AMI due to occlusive coronary spasm, suggesting that they may play important roles in the genesis of thrombotic coronary occlusion subsequent to coronary spasm.

P1643 Cyclosporine prevents factor seven activating protease (FSAP) expression in monocytes/macrophages during acute cardiac allograft rejection

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Introduction and hypothesis: Factor Seven Activating Protease (FSAP) is a circulating serine protease strongly expressed in monocytes/macrophages of unstable plaques and may serve as a marker of plaque destabilization. Based on its properties with respect to the regulation of haemostasis, inflammation, and remodeling processes it is likely to play an important role in the pathogenesis of acute cardiac allograft rejection. The present study was performed (i) to characterize FSAP expression in acute cardiac allograft and (ii) to investigate whether cyclosporine attenuates acute cardiac graft rejection by suppression of FSAP expression.
Methods: Lewis rats were challenged with Wistar-Furth cardiac allografts and transplant recipients were randomized to a control group (n=10) and a cyclosporine-treated group (n=12; 2.5 mg or 5 mg/kg body weight, respectively cyclosporine SC per day). Grafts were harvested on days 1, 3, and 6 after transplantation and laser-assisted microdissection/real-time polymerase chain reaction as well as immunohistochemistry analyses were performed.
Results: Acute rejection occurred within 7 days after engraftment and graft intimal cells, isolate by laser-assisted cell picking, showed a marked upregulation of FSAP gene transcription on day 3, which was prevented by cyclosporine (p<0.01). Cyclosporine significantly (p<0.05) suppressed the expression of FSAP in the treated grafts at days 3 and 6 after transplantation, independent of the applied dose. As demonstrated by immunohistochemistry and quantitative analyses of FSAP mRNA levels by real-time polymerase chain reaction, cyclosporine treatment resulted in a significant reduction of FSAP protein and mRNA expression (p<0.001).
Conclusion: Thus, cyclosporine may be protective against acute rejection after cardiac transplantation through suppressing the expression of FSAP in monocytes/macrophages.

P1644 Non-invasive assessment of coronary flow reserve and endothelial dysfunction in systemic sclerosis

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Purpose: The association between autoimmune diseases and atherosclerosis is well described in many connective tissue diseases and lead to increased cardiovascular (CV) morbidity and mortality. Systemic sclerosis (SSc) is characterized by multi-system organ inflammation, endothelial wall damage and vasculopathy, all of which can increase the risk for atherosclerosis and CV disease (CVD). The increase in carotid intima-media thickness (cIMT) in SSc patients (pts) was demonstrated to be a useful marker of systemic subclinical atherosclerosis. At the same time, early coronary dysfunction can be studied by coronary flow reserve (CFR) assessed with trans-thoracic echocardiography (TTE). Finally, asymmetric dimethylarginine (ADMA), the major endogenous inhibitor of nitric oxide synthase, has been well recognized as a new marker of endothelial dysfunction.
Aim of the study was to find out an early CV involvement in SSc pts.
Methods: 18 pts with SSc (2 male, 16 female, aged 52±15 years) without signs or symptoms of CVD and 18 controls matched for age and sex. All of them underwent a dypiridamole echocardiographic stress test with CFR evaluation, cIMT measurement and plasma ADMA levels determination.
Results: Despite normal standard echocardiographic examinations, SSc pts showed lower CFR (2.81±0.48 vs 3.19±0.20; P<0.05) and increased plasma ADMA levels (0.83±0.08 vs 0.60±0.02; P<0.01) compared to controls in absence of stastical differences of cIMT (0.70±0.09 vs 0.69±0.08; NS). We found a significant negative correlation between CFR and ADMA (r= -0.39; P=0.0002). No other correlations were detected.
Conclusions: In our study, SSc pts without clinical evidence of CVD showed a subclinical impairment of coronary microcirculation in association with endothelial dysfunction, while cIMT was still in normal range. This suggest that CFR and ADMA could be considered preclinical markers of CVD in SSc, able to detect an earlier stage of atherosclerosis before anatomic change in cIMT.

P1645 Systemic inflammation and impaired coronary flow in subjects with coronary artery ectasia

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Aim: Coronary artery ectasia (CAE) is an uncommon presentation of coronary atherosclerosis. Typical diffuse coronary atherosclerosis detectable in CAE, often involving even coronary micro-circulation, is usually featured by increased circulating levels of inflammatory markers (V-CAM, I-CAM, metallo-proteinases, interleukin (IL)-6,TNF). We therefore aimed to investigate possible correlations between severity of CAE, inflammatory activation and coronary flow.
Methods: 35 consecutive patients (9 with evidence of CAE on right coronary artery, 14 with non-ectasic significant (>70%) coronary stenosis (CS) and 12 controls (C) with normal findings at coronary angiography) were enrolled in the study: circulating levels of IL-1b, IL-8, IL-10 and TNF-α were ascertained. Severity of coronary CAE was expressed as number of coronary segment involved by CAE. Coronary flow was evaluated with TIMI frame count (TFC).
Results: TNF-α (14.4±2.8 pg/ml), IL-10 (5±0 pg/ml) levels were increased in subjects with CAE subjects when compared with CS subjects (10.8±3.7 pg/ml, p 0.05; 2.1±2.6 pg/ml, $p<0.05$ respectively) and controls (2.5±2.6 pg/ml, $p<0.05$, IL-10). TFC in right coronary artery was proportionally increased in C, CS and CAE subjects (11.3±2.7, 14.4±5.8, 17.9±9.1, $p<0.05$). In CAE subjects, number of coronary segment involved by CAE was significantly related to TFC (r 0.87, $p<0.05$) and circulating levels of IL-1b (r 0.91, $p<0.05$) and IL-8 (r 0.82, $p<0.05$).
Conclusions: An activated systemic inflammation and an impaired coronary flow, proportional to CAE severity, are detectable in subjects with CAE.

P1646 Impact on fibrinogen and soluble CD40L of a single nucleotide polymorphism on interleukin 6 gene promoter in patients with stable coronary artery disease

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Purpose: The role of inflammation and thrombosis in the pathogenesis of atherosclerosis is well established. However, it is still unclear, whether the genetic variability on IL-6 gene could affect both inflammatory and thombotic biomarkers. In the present study we examined the impact of the G174C genetic polymorphism on serum levels of fibrinogen, soluble CD40Ligand (sCD40L) and interleukin 6 (IL-6) in patients with stable angina.
Methods: The study population consisted of 272 patients angiographically documented for coronary artery disease (CAD) and 115 healthy controls. The G174C polymorphism was determined by PCR and the SFA NI restriction enzyme. Serum levels of fibrinogen were measured by the von Clauss method, while IL-6 and sCD40L levels were assessed by enzyme-linked immunosorbent assay (ELISA).
Results: The genotype distribution in CAD patients was GG: 47%, GC: 30.5% and CC: 22.5%, and GG: 47.8%, GC: 43.8% and CC: 8.4% in the control group. There was a significant difference in IL-6 levels (pg/ml) between the G carriers and CC homozygotes both in the CAD group (3.88±2.81 vs 6.07±3.75, $p<0.001$) and the control group (3.15±2.35 vs 5.85±2.81, $p<0.01$). However, there was not significant difference in fibrinogen levels (mg/dl) between the G allele carriers and CC homozygotes, not only in the CAD group (443.91±124.04 vs 451.59±154.63, p=NS), but also in the control group (384.43±100.76 vs 322.96±82.743, p=NS). Similar results were observed for sCD40L (ng/ml) levels both in CAD (2.445±1.764 vs 2.248±1.014, p=NS) and controls (2.058±1.740 vs 1.311±1.048, p=NS) for CC homozygosity vs G allele carriers.
Conclusions: The G174C polymorphism on interleukin 6 gene affects significantly interleukin 6 levels. Moreover this polymorphism does not affect the expression of fibrinogen and soluble CD40Ligand.

P1647 Circulating platelet - CD34+ cell coaggregates are increased in patients with acute coronary syndromes

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Aims: Progenitorcells play a vital role in tissue andmyocardial regeneration after myocardial infarction. The existence ofheterotypic coaggregates between platelets and progenitor cells has not beendescribed in literature so far. The aim of the present study was to evaluatethe number of coaggregates between platelets and CD34+ or CD34+/CD133+cells in patients with stable coronary artery disease (SAP) compared to healthyelderly controls, as wells as in patients with acute coronary syndromes (ACS).
Methods and results: Platelet binding on the surface of circulating CD34+ and CD34+/CD133+progenitor cells forms heterotypic coaggregates which are increased in patientswith ACS compared to patients with SAP, as shown by flow cytometry. Platelet-CD34+and platelet-CD34+/CD133+ coaggregates correlate with theextent of myocardial necrosis (troponin I) in patients with ACS. Platelet-CD34+and platelet-CD34+/CD133+ coaggregates are associatedwith inflammation (C-reactive protein). Formation of platelet-CD34+coaggregates correlates with platelet activation in patients with coronary arterydisease as defined by expression of platelet-bound P-selectin and SDF-1.
Conclusion: Thesefindings imply that circulating platelet-CD34+ cell coaggregates areincreased in patients with ACS, which may play an important role in domiciliationof progenitor cells to vascular wall and subsequent tissue regeneration.

P1648 Selective plaque progression in coronary artery segments with endothelial dysfunction: serial volumetric evaluation by intravascular ultrasound

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Purpose: Coronary endothelial dysfunction is regarded as an early stage of atherosclerosis and is associated with plaque vulnerability. Using intravascular ultrasound (IVUS), the present study was designed to test the hypothesis that within the same coronary artery, segments with endothelial dysfunction show accelerated progression of atherosclerosis compared to segments with normal endothelial function.
Methods and results: Seventeen patients with non-obstructive coronary disease underwent coronary angiography and testing of coronary endothelial function by intracoronary infusion of acetylcholine (Ach) at increasing concentrations (10-6 to 10-4 mol/L) into the LAD. Mean total atheroma volume (TAVMEAN) and percent atheroma volume (PAV) were assessed by IVUS at baseline and 6-month follow-up. Follow-up TAVMEAN and PAV were significantly increased in the segments with coronary endothelial dysfunction compared to baseline [median (IQR): 2.70 mm^3 (1.50 to 3.67) to 3.15 mm^3 (1.59 to 3.98), p=0.009; 21.8% (20.5 to 29.7) to 28.5% (21.1 to 30.2), p=0.018]. There were no significant changes in follow-up TAVMEAN and PAV in segments with normal coronary endothelial function at six months compared to baseline: 3.35 mm^3 (1.78 to 4.89) vs. 3.27 mm^3 (1.97 to 5.0), p=0.568; 21.5% (8 to 30.0) vs. 25.1% (19.6 to 28.7), p=0.102 (Table 1).

Table 1. Comparison of the Intra-individual IVUS results between the segment with endothelial dysfunction and segment with normal endothelial function by paired t test

	Segments with endothelial dysfunction (n=17) mean±SE	Segments with normal endothelial function (n=17) mean±SE	p value
Baseline normalized TAV, mm^3	55.86±6.09	70.01±8.12	0.063
median (IQR)	54.00 (30.00, 73.40)	67.00 (35.60, 98.07)	
Follow-up normalized TAV, mm^3	61.15±6.54	70.96±7.96	0.162
median (IQR)	63.00 (31.80, 79.55)	65.40 (36.50, 100.07)	
Change of the normalized TAV, mm^3	5.29±1.77	0.95±0.96	0.047
median (IQR)	2.60 (0.40, 9.45)	1.00 (–1.67, 4.30)	0.047
Baseline PAV, %	25.04±1.58	25.34±1.47	0.875
median (IQR)	21.790 (20.535, 29.720)	24.50 (19.82, 29.990)	
Follow-up PAV, %	27.06±1.54	25.38±1.57	0.255
median (IQR)	28.48 (21.045, 30.220)	25.140 (19.640, 28.670)	
Change of the PAV, %	2.02±0.77	0.12±0.44	0.027
median (IQR)	0.780 (–0.085, 3.590)	0.49 (–1.275, 1.53)	

Conclusions: Coronary segments with endothelial dysfunction show greater progression of atherosclerosis compared to those with normal endothelial function. The study supports the role of endothelial dysfunction as an early stage of coronary atherosclerosis in humans.

P1649 Diminished toll-like receptor 2 and 4 response in patients with inducible cardiac ischemia

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Background: Toll-Like Receptor (TLR) activation, by either pathogens or endogenous molecules, induces an inflammatory response. We previously showed that TLR dependent leukocyte responsiveness is acutely attenuated following percutaneous coronary intervention (PCI) or vascular surgery. Furthermore, cytokine release following whole blood TLR-2 and -4 stimulation is negatively correlated with fractional flow reserve, suggesting that chronic ischemia can elicit an enhanced inflammatory response. In the current study we assessed the association between pre-existent and inducible ischemia on TLR-2 and -4 responsiveness in patients undergoing single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI).
Methods: TLR2, TLR4 and CD11b expression on monocytes were measured in blood samples that were obtained from 100 patients with suspected coronary artery disease, before and after myocardial stress testing for SPECT MPI. IL-8 levels were determined after whole blood stimulation with Pam3Cys (TLR2)

and lipopolysaccharide (LPS; TLR4). Patients were categorized in three groups: reversible defect, irreversible defect or no defect.
Results: IL-8 production before myocardial stress induction was not associated with SPECT MPI results. After stress, IL-8 production following TLR stimulation was significantly decreased (4605±473 vs. 3122±461 for Pam3Cys 500 ng/ml; p<0.001). A comparable decrease was also observed for TLR4 and CD11b expression (TLR 4 [MFI]: 1.70±0.2 vs. 1.61±0.16, p=0.001; CD11b [MFI]: 82±1.9 vs. 72.4±1.8, p<0.001). Interestingly, the percentage decrease in TLR response was higher in patients with a reversible defect (TLR4 induced IL-8: reversible defect 31.6% decrease vs. irreversible defect 15.24% decrease vs. no defect 15.39% decrease; p=0.035).
Conclusion: Inducible ischemia is associated with a decrease in TLR-2 and -4 response. These results point to a regulating role of TLR responsiveness in order to prevent excessive inflammatory events known to occur during acute ischemia.

P1650 Plasma myeloperoxidase level and prognosis in patients with ST segment elevation myocardial infarction

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Objectives: We sought to investigate the prognostic importance of plasma myeloperoxidase (MPO) levels in patients with STEMI at long term follow-up period and to analyse the correlations of plasma MPO levels with other biochemical parameters.
Methods: We evaluated plasma MPO levels in 73 consecutive patients (56 men, mean age; 56±11 years) diagnosed with acute ST elevation myocardial infarction and 46 age- and sex- matched healthy control subjects. The median plasma MPO levels of the patients were 68 ng/ml. Patients were classified into 2 groups according to the median MPO value (Group 1: plasma MPO ≤68 ng/ml and Group 2: plasma MPO >68 ng/ml). Patients were monitored for the occurrence of major adverse cardiovascular events (MACE). Major adverse cardiovascular events were defined as cardiac death, reinfarction, new hospital admission for angina, heart failure and revascularization procedures.
Results: Mean follow-up period was 25±16 months. Plasma MPO levels were higher in STEMI patients than the subjects in control group (82±34 ng/ml vs 20±12 ng/ml p=0.001). Patients with high MPO levels were more likely to have anterior wall myocardial infarction, low LVEF and multi-vessel coronary artery disease than those with low plasma MPO levels. Composite MACE occurred in twelve of the patients with high MPO levels (33%) and four of the patients with low MPO levels (11%) (p=0.020). The incidences of nonfatal recurrent myocardial infarction and verified cardiac death were higher in the high MPO levels group. At multivariate analysis, high plasma MPO levels were independent predictors of MACE [odds ratio (OR) 3.843, <95% confidence interval 1.625–6.563; p=0.003] together with CRP (OR 2.863, 95% confidence interval 1.337–6.452; p=0.012) and LVEF <40% (OR 3.225, 95% confidence interval 1.434–6.554; p=0.001). Plasma MPO levels were also correlated with CRP levels (r=0.451, p=0.004), troponin T (r=0.390, p=0.004), and NT pro BNP levels (r=0.445, p=0.002) but not with WBC count (r=0.166, p=0.189) in the STEMI patients.
Conclusions: High plasma myeloperoxidase levels identify patients with a worse prognosis after acute ST elevation myocardial infarction at two-year follow up period. Evaluation of plasma MPO levels may be useful in determining patients at high risk of death and MACE, who might benefit from a further aggressive treatment and closer follow-up.

P1651 The effect of p22-phox (CYBA) polymorphisms on premature coronary artery disease (below 40 years of age)

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Aims: Acute myocardialinfarction at a young age is associated with high morbidity and long-term mortality. The NADPH oxidase system as a main source of reactive oxygen species in vascular cells has been implicated in development and progression of coronary artery disease. In our study, we investigated the effect of polymorphisms in the p22-PHOX (CYBA) gene on coronary artery disease in young patients (≤40 years).
Methods and results: We prospectively recruited 302 subjects into our multicenter case control study, including 102 young myocardial infarction patients (≤40 years) from two high volume cardiac catheterization hospitals and frequency-matched them on age, gender, and center to 200 hospital controls in an approximate 2:1 ratio per case patient. Both groups fulfilled the Hardy Weinberg equilibrium criteria for all investigated polymorphisms. The homozygote c.-930A>G promoter polymorphism was significantly more prevalent in the controls than in the infarction patients. In the adjusted logistic regression analysis, we detected a protective effect of the c.-930A>G promoter polymorphism against premature myocardial infarction. Using a log-additive/per-allele model, we detected an unadjusted OR of 0.63 (95% CI 0.45-0.9, p-value 0.011). In the adjusted model the association was more pronounced with an odds ratio of 0.5 (95% CI 0.3–0.81, p-value 0.005). The C242T polymorphism and the 640A>G polymorphism did not differ significantly between the study groups. Furthermore we could not detect a significant effect for these polymorphisms in the logistic regression analysis.
Conclusion: The present study suggests a protective association between the c.-930A>G promoter polymorphism in the p22-PHOX (CYBA) gene and the development of myocardial infarction in young individuals (≤40 years), which could be mediated by slightly increased ROS production. Additionally, we confirmed the absence of a significant effect of the p22-PHOX (CYBA) C242T polymorphism for the occurrence of CAD in Caucasians.

P1652 Influence of CYP2C19 polymorphisms in on-treatment platelet reactivity and prognosis in an unselected population of non ST elevation acute coronary syndrome

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Residual on-clopidogrel platelet reactivity is associated with the risk of adverse clinical events. Some studies have suggested that polymorphisms affecting CYP system may be responsible, at least in part, of interindividual variability in the response to clopidogrel. Certain alleles such as CYP2C19*2 and CYP2C19*17 appear to reduce and increase, respectively, clopidogrel metabolism and thus on-treatment platelet reactivity. The aims of the present study were: (1) To assess the phenotype-genotype relationship of CYP2C19*2 and *17 allele carriage and (2) to explore the clinical impact of those polymorphisms at 6-months-follow-up of an acute event in an unselected population of non-ST elevation acute coronary syndrome.
Methods: Forty steady ischaemic patients under dual antiplatelet therapy, 12 months after coronary stent placement, and an unselected population of 493 consecutive patients with non-ST elevation acute coronary syndrome were recruited for first and second objectives, respectively. Blood samples were collected in 3.2% citrated tubes. Platelet reactivity was assessed by optical aggregometry in unadjusted platelet rich plasma induced by 5 and 10μM ADP and 25μM TRAP. Also, levels of phosphorylated VASP were measured in whole blood using flow cytometry to asses the effect of clopidogrel on P2Y12 receptor. Genotypes were determined with a TaqMan assay. We defined "adverse endpoints" as cardiovascular death, and recurrent ACS (new episode of ACS requiring hospital admission).
Results: VASP phosphorylation measurement, but not ADP-induced platelet aggregation detected significant differences in residual platelet response to clopidogrel among wild-type subjects and CYP2C19*2 (p=0.020), and *17 allele carriers (p=0.048). Complete 6-months follow-up data were available in 471 (95.5%) patients entering the study, of whom 111 (23.6%) had adverse events. No significant influence was found between CYP2C19*2 ([HR (95% CI): 1.17 (0.78-1.75)], p=0.285) or *17 ([HR (95% CI): 0.98 (0.66-1.46)], p=0.930) allele carriage and the occurrence of cardiovascular ischaemic events or death at 6-months-follow-up. TIMI risk score ([HR (95% CI): 1.39 (1.22-1.58)], p<0.001) and female gender ([HR (95% CI): 1.58 (1.09-2.29)], p=0.017) were significant predictors of adverse events.
Conclusion: Despite CYP2C19 genotype affecting clopidogrel metabolism is associated with variable on-treatment platelet reactivity, it has no significant influence on cardiovascular outcomes in clinical practice. This fact strengthens that prognosis of complex diseases, such as acute coronary syndromes, is influenced for a myriad of variables.

P1653 Increased risk of bleeding during combination therapy with warfarin and ibuprofen in a large population with atrial fibrillation

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Purpose: Important pharmacodynamic interactions between ibuprofen and warfarin are well described
We examined whether combination therapy with warfarin and ibuprofen increased risk of bleeding or death compared with warfarin monotherapy in a large population of patients with atrial fibrillation.
Methods: All patients hospitalised with atrial fibrillation in Denmark in the period 1997 to2009 were identified by individual-level-linkage of nationwide registers. Prescriptions of warfarin and ibuprofen claimed after discharge were identified using nationwide registries of drug dispensing from pharmacies. Risk of hospitalisation for bleeding, thromboembolism or death was assessed by multivariable time dependent Cox proportional hazards analyses adjusted for age, sex, concomitant pharmacotherapy and comorbidities. Patients on warfarin monotherapy were used as reference group.
Results: In all, 168,796 patients were discharged after a first time hospitalisation with atrial fibrillation in the study period. Of these, 10,723 patients received combination therapy with warfarin and ibuprofen and 80,025 patients received warfarin monotherapy (reference group). Patients on combination therapy were

slightly younger (mean±standard deviation; 69.0±10.0 vs. 70.9±10.7 years) and more frequently male (65.1% (n=6,977) vs. 59.5% (n=47,604)).
After 1 year of follow up the risk of bleeding (n=8,219) was significantly increased whereas risk of death (n=29,837) and thromboembolism (n=11,955) remained unchanged (Table 1).

Table 1. Multivariable time-dependent Cox proportional hazards analysis of risk of bleeding, death and thromboembolism in patients receiving combination therapy with ibuprofen and warfarin with warfarin monotherapy as reference

	Risk of bleeding	Risk of death	Risk of thromboembolism
Ibuprofen + Warfarin, Hazard Ratio (95% CI)	1.48 (1.11–1.97)	1.08 (0.77–1.51)	1.27 (0.93–1.74)

CI: Confidence interval.

Conclusions: In an unselected population of patients with atrial fibrillation, combination therapy with ibuprofen and warfarin is associated with an increased risk of bleeding.

HYPERTENSION AND THE HEART

P1654 Association between left ventricle function, blood pressure, renal function and cytokiens in patients treated with angioplasty for renal artery stenosis

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The benefit of renal angioplasty (PTA) in patients with atherosclerotic renal artery stenosis (RAS) is still the matter of debate.
The study aimed to search for associations between echocardiographic left ventricle mass (LVM) and diastolic function (DF), cytokines level in relation to systolic and diastolic blood pressure (SBP, DBP) and renal function improvement.
Methods: 24-hour ambulatory blood pressure monitoring, echocardiographic LVM and DF (E wave/ Tissue Doppler E' wave velocity, E/E' ratio), levels of serum creatinine (CR), aldosterone, transforming growth factor (TGF-β) and BNP were assessed in 95 (45 men) patients, age 64±10 years, prior to PTA, then 3 and 12 months afterwards.
Results: PTA was technically successful in all patients, however 5 (5.2%) died before 1-year F-U. In a group of 90 patients, a significant reduction in mean SBP (>10mmHg) and DBP (>5mmHg) was observed in 39 (43.3%) and 34 (37%) patients at 12 months ($p<0.001$), respectively. Worsening of SBP (increase >10mmHg) and DBP (>5mmHg) was seen in 6 (6.6%) and 7 (7.7%) patients, respectively. CR level decreased by at least 10% in 46 (51.1%) and increased by >10% in 18 (20%) patients ($p<0.001$). The mean LVM reduction was 30.6±34g, and significant LVM decrease (by at least 15g) was observed in 60 (66.7%), deterioration (increase >15g) in 6 (6.6%) patients at 12 months ($p<0.001$). DF impairment (E/E' ratio>15) was observed in 43 (47.7%) patients before PTA, improvement was observed in 9 (10%), normalization in 4 (4.4%) patients at 12 month (p=0.17). The mean levels of TGF-β, BNP and aldosterone, before PTA vs. at 12 months, changed from 18.2±35.4ng/mL to 10±9.2ng/mL (p=0.04), 44.7±50.2pg/mL to 59.4±52.7pg/mL (p=0.026), and from 20.2±22.6ng/mL to 17.9±12.8ng/mL (p=0.452). LVM reduction vs. LVM enlargement was observed in patients with a significant CR level decrease (ΔCR: -17.3±33 vs. +17.5±46 μmol/l, p=0.024) at 3 month, DBP improvement (p=0.077) at 3 month, with higher baseline levels of BNP (43.4±50pg/mL vs. 140±185 pg/mL, p=0.003) and aldosterone (19.3±16.38ng/mL vs 49.3±76.38ng/mL; p=0.033). The independent predictors of LVM reduction were: BNP (RR 1.27, CI 1.04-1.54, p=0.019) and aldosterone (RR 1.24, CI 1.02-1.51, p=0.032) levels prior to PTA. A baseline BNP (RR 1.28, CI 1.05-1.55, p=0.016) was also an independent predictor of renal function improvement after renal PTA.
Conclusions: PTA induces regression of LVM in 67% of patients with RAS. A significant LVM reduction is associated with decrease in CR level and DBP. However, the only identified independent predictors of LVM reduction were BNP and aldosterone levels prior to PTA.

P1655 Relationship between brachial blood pressure obtained by cuff method and central blood pressure measured with invasive method

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Objective: Aortic systolic blood pressure (aSBP) is an important determinant of cardiovascular risk. Generally, the brachial SBP (bSBP) is higher than aSBP when they are compared with invasive method, but difference between aSBP by invasive method and bSBP by non-invasive method has not been fully evaluated. We measured aSBP and bSBP by invasive method and compared with bSBP measured by cuff method.
Methods: The study subjects consisted of 20 patients (68.9±8.1 years, 65% males) undergoing coronary angiography. aSBP was measured by pressure guide wire (RADI MEDICAL) via right radial artery. After measuring aSBP at ascending aorta, invasive bSBP was measured when the wire was pulled back to the radial artery. The bSBP was also measured by cuff-oscillometoric method on the left arm (HEM-9000AI).
Result: bSBP by cuff method and aSBP by invasive method were 133.5±18.6, 138.1±18.5 mmHg (mean±SD) respectively, and invasive aSBP was 4.7mmHg higher than cuff bSBP (Figure, top). bSBP by invasive method and cuff method were 141.8±19.2, 133.5±18.6 mmHg respectively, and cuff bSBP was 8.3 mmHg lower than invasive bSBP (Figure, bottom).

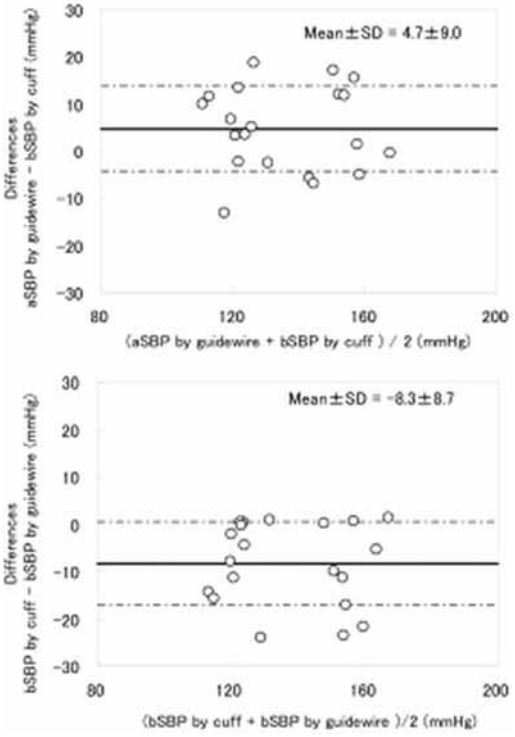

Figure 1

Conclusions: Invasive aortic SBP showed 4.7 mmHg higher when it was compared with cuff-oscillometric brachial SBP. This was due to cuff-oscillometric brachial SBP shows 8.3 mmHg lower than invasive brachial SBP.

P1656 Left ventricle remodelling in patients with volume-dependent hypertension

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Objectives: The aim of our study was to evaluate the influence of increased intravascular volume on the heart anatomy and function in patients with salt – sensitive types of hypertension, represented by primary aldosteronism (PA) and low–renin essential hypertension (LREH).
Methods: A total of 82 patients with PA, 65 patients with LREH and 73 patients with normal-renin essential hypertension (NREH) involved in our study underwent echocardiography examination. The patients were carefully matched for demographic characteristics, blood pressure, duration of hypertension and antihypertensive treatment.
Results: In comparison with NREH patients, patients with PA and LREH showed greater end-diastolic left ventricle (LV) diameter (53.1±5.6; 51.4±4.7 resp. vs. 49.2±5.2 mm; $p<0.0001$; $p<0.05$) resulting in lower relative wall thickness (0.39±0.06; 0.38±0.07 resp. vs. 0.43±0.08; $p<0.01$; $p<0.01$). Among all groups,

Echocardiography findings

Parameter	PA (n=82)	LREH (n=65)	NREH (n=73)
LVED (mm)	53.1±5.6***	51.4±4.7*	49.2±5.2
LVEDI (mm/m^2)	26.6±2.2**	25.8±2.5	25.2±3.1
LVES (mm)	35.0±5.7***	33.8±4.6*	31.5±4.3
IVS (mm)	10.7±1.7	10.5±1.9	11.0±2.0
PWT (mm)	10.1±1.6	9.9±1.8	10.4±2.0
RWT	0.39±0.06**	0.38±0.07**	0.43±0.08
LV mass index (g/m^2)	107±28	98±25	102±30

PA = Primary aldosteronism; LREH = Low-renin essential hypertension; NREH = Normal-renin essential hypertension; LVED, LVES = Left ventricle enddiastolic and endsystolic diameter; LVEDI = LVED index; IVS = Inerventricular septum thickness, PWT = Posterior wall thickness; RWT = Relative wall thickness.Variables are shown as means ± SD. *P<0.05; **P<0.01; ***P<0.001 vs. NREH.

there were no significant differences neither in LV wall thicknesses (10.1±1.6; 9.9±1.8 resp. vs. 10.4±2.0mm, p=0.16) nor LV mass index (107±28; 98±25 resp. vs. 102±30 g/m^2; p=0.12); although, higher percentage of patients with PA met the criteria of the eccentric type of LV hypertrophy (24% vs. 10% in NREH, p=0.03). The groups did not differ in parameters of diastolic dysfunction of the LV (E/A and E/E')

Conclusions: Expansion of the plasmatic volume affects the myocardial remodelling and it is expressed in increased LV internal diameters in patients with volume-dependent types of arterial hypertension.

P1658 Endothelial function and pulse-wave analysis in patients with arterial hypertension and heart failure with preserved left ventricular ejection fraction

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Purpose: To evaluate changes in pulse-wave shape and endothelial function (EF) in patients with essential arterial hypertension (AH) and heart failure with preserved left ventricular ejection fraction (HF-PEF) treated with calcium-channel blockers- (CCB) or ACEi-based regimens.

Methods: Sixty one patients (mean age 59±10 years) with AH and HF-PEF were consequently enrolled in the study and than randomized to CCB-based regimen or ACEi-based therapy. Also, in most of patients, thiazide or loop diuretics was added to achieve blood pressure (BP) goals. EF (in reactive hyperemia test) and pulse-wave characteristics were measured both before and after 5 weeks of treatment using finger photoplethysmographic device and traditional ultrasonographic method. Stiffness index (SI), reflection index (RI), augmentation index (AIx), systolic BP in aorta (SPa), digital pulse amplitude augmentation (PAA, by photoplethysmography), and flow-mediated dilation (FMD, by ultrasound) were accessed.

Results: In most of patients before the treatment normal SI, and elevated RI, AIx, Spa, and significantly impaired EF were shown. BP goals (< 130 and 90 mmHg) were achieved in all patients validating further analysis. Decrease in SI, RI and SPa were revealed in both treatment arms, whereas trends towards AIx decrease and EF improvement were demonstrated only in ACEi-treated patients (Table 1). Also, substantial correlation (r=0.4, p<0.05) between finger photoplethysmographic and traditional ultrasonographic EF assessment was found.

Table 1. Assested parameters

Parameter	ΔSI, m/s	ΔRI, %	ΔAIx, %	ΔSPa, mmHg	ΔFMD, %	ΔPAA, folds
ACE group	–0.98	–8.11	–2.06	–20.68	1.15	0.19
CCB group	–0.97	–7.39	–0.09	–26.94	0.02	0.08
p-level (betweengroups)	0.202	0.350	0.086	0.469	>0.05	>0.05

Conclusions: Pulse-wave analysis in patients with AH and HF-PEF demonstrated pattern of increased vascular stiffness and peripheral vasoconstriction, accompanying by impaired EF. Both ACEi and CCB treatment resulted in central BP, RI and SI decrease, whereas only ACEi use was associated with trends in EF and AIx improvement in short-term follow-up. Fair accuracy of photoplethysmographycally assessed digital pulse amplitude augmentation (compared with ultrasonographicaly measured FMD) allow to use this more simple and convenient method in clinical practice.

P1659 Peculiarities of renal perfusion and intrarenal circulatory dynamics in patients with essential hypertension in early hypertensive nephropathy

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Purpose: To study peculiarities of renal perfusion and intrarenal circulatory dynamics in patients with essential hypertension with microalbuminuria using renal scintiangiography.

Methods: 36 men at the age of 48.7±4.5 years were studied. The examination was carried out at the background of antihypertensive therapy discontinuation within not less than 3 days. The patients with primary renal pathology, coronary artery disease and a reduced left ventricular ejection fraction (LVEF) were not included into the study. Microalbuminuria presence was detected by a semiquantitative method with reagent test strips. All the patients included into the study were divided into two groups. In the first group there were 14 patients with microalbuminuria, the second group consisting of 22 patients without any signs of renal pathology. There were no reliable differences in the age, serum creatinine levels and estimated glomerular filtration rate (e-GFR) in these groups. Renal scintiangiography with 99mTc - diethylenetriaminepentaacetate was carried out according to a standard procedure on a double-head gamma camera (E.Cam "Siemens"). Time-activity curves (angiograms) for the kidneys and abdominal aorta were generated. For both kidneys the following indices were estimated: time to peak angiogram (Tmax), angiogram peak amplitude (Amax), angiogram amplitude on the 5th second and a relative perfusion index.

Results: Amax (p<0.05) decreasing and Tmax (p<0.05) increasing were observed in all the patients with essential hypertension as compared to standard values. However, in the absence of microalbuminuria the Tmax value was higher (p<0.05) than that for the patients with microalbuminuria. There was inverse correlation as regards to the Amax value. In the presence of microalbuminuria the Amax value exceeded the similar one (p<0.05) for the patients without nephropathy. An activity level on the 5th second as well as the relative perfusion index did not differ reliably.

Conclusions: Amax decrease and Tmax increase in an angiogram of patients with essential hypertension characterize relative renal hypoperfusion. With microalbuminuria the alterations of these values indicate development of intraglomerular hypertension and hyperperfusion that leads to further impairment of the glomerules with formation of nephroangiosclerosis and chronic renal insufficiency.

P1660 Impact of left ventricular mass and function on left atrial volume in hypertensive patients

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Background: Left ventricular mass index (LVMI) is the most important variable associated with left atrial volume (LAV) in mild to moderate essential hypertensive patients. Strain imaging has been suggested as a useful tool for the evaluation of myocardial function.

The aim of this study was to examine the impact of left ventricular mass and function on LAV.

Methods: 65 hypertensive patients, with preserved ejection fraction, were divided in two groups according the LVMI (I group-LVMI<95g/m^{2}women, 115g/m^{2}men, n=36; II group-LVMI>95g/m^{2}women, 115g/m^{2}men, n=29). Left atrial volume was measured at three time points (maximal LAV, pre-atrial contraction volume and minimal LAV) and the following left atrial (LA) emptying volumes were then derived: LA passive emptying volume (LAPEV), LA conduit volume (LACV), LA active emptying volume (LAAEV) and LA total emptying volume (LATEV). All LA volumes were corrected for maximal LAV, which was indexed to body surface area (LAVI).

We measured coresponding velocities from tissue Doppler at the level of the septal mitral annulus (e,a,s), including global function index[GFI=(E/e)/s]. Longitudinal, circumferential and radial two-dimensional strain was derived from speckle-tracking.

Results: There was significant correlation between of GFI and LAVI (r=0.547, p=0.003), LAPEV (r= -0.385, p=0.001), LACV (r= -0.363, p=0.003) and LATEV (r= -0.342, p=0.005). LAAEV significantly correlated with longitudinal strain from basal (r= -0.394, p=0.001) and mid segmental levels of septum (r= -0.344, p=0.005). Significant diference of LAVI (16.5 vs 20.7, p=0.0001) and LACV (4.48 vs 3.70; p=0.01) was found between two groups, with significantly lower longitudinal strain from basal and mid segmental levels of septum in second group of patients (Table 1).

Table 1

	Group I mean±SD	Group II mean±SD	
Long. strain (%) basSep	–18.1±3.07	–15.6±4.07	p=0.007
Long. strain (%) midSep	–16.1±4.46	–12.9±4.97	p=0.005

Conclusion: In hypertensive patients left atrial volume was morphophysiologic expression of left ventricular global dysfunction and hypertrophy. Structural and functional left ventricular changes couse LAVI augmentation and resulting in lower atrial emptying volumes.

P1661 Cardioprotective effects of red palm oil diet in spontaneously hypertensive rats

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Purpose: Spontaneously hypertensive rats (SHR) that mimic human essential hypertension have been previously shown benefit from omega-3 unsaturated fatty acids supplementation that is salutary in clinic as well. Recently, cardio-protective effect of red palm oil (RPO) containing 50% saturated fatty acids, carotenoids, tocoferol and tocotrienols has been reported. The purpose of this study was to examine whether SHR may benefit from RPO supplementation.

Methods: SHR and healthy WKY rats fed a standard rat chow plus RPO (200microL/day) for 5 weeks were compared with untreated controls. Systolic blood

pressure (SBP), plasma cholesterol (CH), triglycerides (TG) and blood glucose (BG) were registered at the end of experiment. Nitric oxide synthase (NOS) activity was determined in the heart left ventricle and aorta. Expression of myocardial cell-to-cell coupling protein connexin-43 (Cx43) was determined by western blots. Isolated perfused heart was used to test its susceptibility to post-ischemic reperfusion-induced arrhythmias and electrically inducible ventricular fibrillation (VF).
Results: RPO significantly reduced BP (160+ 13 vs 184+20 mmHg) in SHR and BG in both SHR and WKY (4.48+0.2 vs 5.61+1.1 and 5.5+0.4 vs 6.38+0.8 mmol/L). While there were no significant differences in plasma CH and TG among the groups. Body and heart weights were not affected by RPO as well. Compared to WKY rats the activity of NOS was higher in SHR heart and aorta (4.67+0.3 and 3.18+0.5 vs 3.02+0.3 and 1.54+0.1 pmol/mg/min). RPO reduced NOS activity in the heart of both SHR and WKY rats but increased in the aorta. Expression of total and phosphorylated forms of Cx43 was reduced in SHR compared to WKY, whereas increased in RPO-treated rat hearts. Duration of reperfusion-related bradykardia was markedly shorter in SHR vs. WKY and prolonged due to RPO, which also significantly suppressed reperfusion-induced arrhythmias and incidence of electrically-induced VF in both strains.
Conclusions: Results suggest anti-hypertensive and antiarrhythmic effects of RPO supplementation in hypertensive rats and challenge to elucidate possible mechanisms more in details.
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P1662 Reflected waves are associated with left ventricular filling pressures and diastolic function in patients with stable coronary artery disease

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Purpose: Non-invasive markers of arterial stiffening are indicative of increased myocardial afterload and have been associated with LV diastolic function as assessed by tissue Doppler echocardiography in healthy and hypertensive individuals without cardiovascular disease. The aim of this study was to examine this relationship in patients with established coronary artery disease.
Methods: Ninety-nine patients with angiographically confirmed stable CAD were consecutively recruited. Aortic augmentation Index (cAI), aortic augmentation pressure (cAP) and aortic blood pressures assessed by pulse wave analysis (PWA) were measured as indices of systemic arterial wave reflection. Carotid–femoral pulse wave velocity (PWVCF) was measured as an index of aortic stiffening. Laser Doppler fluximetry was used to assess microvascualr skin function. Diastolic mitral inflow velocities (E and A waves) and diastolic mitral annulus velocities (E' and A' waves) were measured by pulsed Doppler and tissue Doppler echocardiography. E/E' ratio was calculated as a surrogate of left ventricular filling pressures.
Results: E/E' ratio positively correlated with cAI (r=0.247, p=0.027), central DBP (r= -0.226, p=0.043) and time to recovery of post-ischemic flow (r=0.561, $p<0.001$), a marker of microvascular dysfunction. By multivariate regression analysis cAI, cDBP and the presence of atrial fibrillation were independent determinants of E/E' ratio (r square=0.266, $p<0.001$) while the presence of CAD and LV ejection fraction did not significantly alter these results. In patients with at least grade 2 diastolic dysfunction, by criteria of pulsed and tissue Doppler indices and left atrium area, cAP was significantly higher as compared to those without high grade diastolic dysfucntion (19.1±9.5 versus 11.9±7.8 mmHg, respectively, p=0.002).
Conclusions: Increased reflected waves correlate with high LV filling pressures and advanced diastolic dysfunction in patients with stable CAD. These findings suggest a role of reflected waves in vascular-ventricular coupling in CAD. Further research is needed to investigate possible clinical utilities of reflected wave assessment in this population.

P1663 Differences in day time physiological pulse pressure variability between the brachial artery and the aorta

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Background: Brachial blood pressure variability is, both, a source of inaccuracy and a risk factor, regarding the assessment of cardiovascular (CV) risk. Independently of time, pulse pressure (PP) varies substantially between the brachial artery and the aorta, generating major clinical implications regarding CV risk reduction and treatment strategies. There is no data indicating whether: (i) the brachial and aortic PP variability during the day are similar and (ii) the aortic-to-brachial (AtB) disparity (gradient) exhibits significant variation during the day. Purpose of the study was to investigate: (i) the potential differences of within-subject PP day variability between the brachial artery and the aorta and (ii) the presence of substantial day time variation in the spatial disparity of PP between the brachial artry and the aorta.
Methods: In 13 healthy volunteers hourly (8:00 to 19:00) assessment of brachial and aortic PP (radial tonometry and transfer functions) was performed, under controlled conditions at home.
Results: Aortic PP day variability was consistently and significantly lower than the brachial one (assessed by: standard deviation (SD) and variance, $p<0.05$, figure). The AtB difference in PP (mmHg) varied substantially during day time within all the 13 subjects; a significant day variation in the AtB amplification (brachial/aortic PP) ($p<0.001$) was also found.

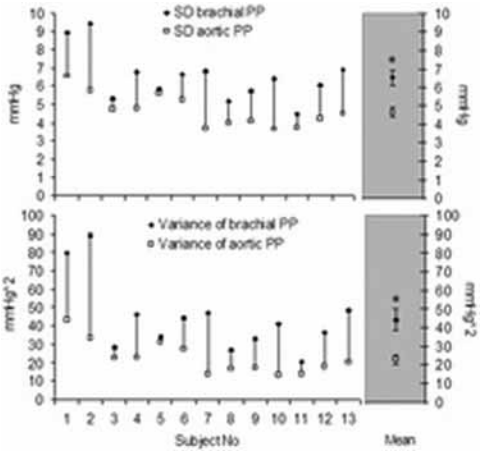

Figure 1

Conclusion: This is the first study that evaluated the within subject PP variability taking into account two factors: time and arterial space. The physiological differences that were found in PP day variability between the peripheral and central arteries may have major clinical implications which remain to be confirmed by 24-hr non-invasive monitoring of central BP.

P1665 Relation of central and brachial blood pressure to left ventricular hypertrophy. The Czech Post-MONICA study

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Objective: Central blood pressure was shown to be a better predictor of target organ damage, cardiovascular events and mortality than brachial blood pressure. Whether central blood pressure is a better predictor of left ventricular hypertrophy determined by electrocardiographic criteria (ECG LVH) is not know.
Methods: Radial applanation tonometry and ECG were performed in 728 individuals from the Czech post-MONICA study (a randomly selected 1% representative population sample). ECG LVH was determined using Sokolow-Lyon index and Cornell product; central pressure was derived from radial pulse.
Results: Of 700 subjects included in the analysis 17 (9.4%) below 45 years and 52 (10%) over 45 had ECG LVH. In younger individuals ECG LVH was only associated with male sex and low BMI, while no difference in central or brachial blood pressure was found. In older individuals LVH was associated with higher central and brachial blood pressure. In separate binary logistic regression analyses the odds ratio for central systolic (1.08, 95% CI 1.06-1.11) and pulse pressure (1.09, 95% CI 1.06-1.12) was higher than for brachial systolic (1.03, 95% CI 1.01-1.05) and pulse pressure (1.03, 95% CI 1.01-1.05). Similarly in the ROC analysis central pressure had higher diagnostic value LVH prediction.
Conclusion: Noninvasively determined central pressure in subjects over 45 years is more strongly related to ECG LVH than brachial pressure. This is a further support of closer association of central pressure with target organ damage. Voltage criteria of LVH are not independently associated with central or brachial blood pressure in younger individuals.

P1666 Separate measurement of intima and media thickness as the novel approach to the evaluation of vessels remodeling type in patients with arterial hypertension

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Background: Arteries remodeling is the inevitable arterial hypertension (AH)

consequence classically carried out through the media hypertrophy. High determinant ability of modern ultrasonic devices makes it possible to measure sequentially and separately layer-by-layer intima and media thickness of arterial wall.
Aim of the work was to measure the thickness of intima-media complex (IMT) in patients with AH, including layer-by-layer evaluation of intima and media for individualization of cardiovascular risk level.
Materials and methods: 20 female (to avoid sex difference) patients with AH I – II degree without any additional risk factors (disease duration 2 – 15 yrs) with the average age 44,9±4,5 yrs have been examined. 20 apparently healthy women (the average age 38,4±7,2 yrs) have formed the control group. The the carotid IMT has been measured by LOGIC P5 PRO, GE (B-regime) using ZOOM function (at the level 1 sm aside from the bifurcation area following the standard procedure); simultaneously the intima thickness (as hyperechogenic stripe and according to its echogenicity which corresponds to surrounding tissues of the vessel) and the media thickness (as hypoechogenic stripe which is located under intima and its echogenicity corresponds to the vessel lumen) have been measured separately.
Results: The IMT of the female patients with AH was 0,059±0,008 mm, in the control group 0, 049±0,006 mm ($p<0,0007$). The IMT was equal in both groups - 0,023±0,003 mm. The media layer thickness was 0,036±0,008 mm in the patients group and 0,026±0,006 mm in the control group. It is easy to mention that reliably higher IMT in the patients group in comparison with the control group was exclusively due to the media layer thickness ($p<0$, 0004). Statistically significant difference of the intima layer thickness between the groups was absent ($p>0,92$).
Conclusions: The carotid artery IMT difference observed at middle aged women with AH without additional risk factors in comparison with control group is exclusively due to the media layer. Ultrasonic method is simple noninvasive and suitable for the usage while diagnosing differential layer-by-layer evaluation of the arterial wall and further cardiovascular risk level individualization in patients with AH.

P1667 Use of scintigraphy with metaiodobenzylguanidine to prognose early abnormalities of perfusion and kinetics of miocardium in patients with essential hypertension

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Purpose: To study correlation between a functional state of the sympathetic nervous endings, perfusion indices and kinetics of the left ventricle based on data obtained by means of scintigraphy of the heart in patients with essential hypertension.
Methods: 27 men at the age of 47.5±4.2 years were examined. The patients with myocardial ischemia, marked hemodynamic heart rhythm and conduction defects, cardiomyopathies and the patients with a reduced left ventricular ejection fraction were not included in the study. The exercise stress-test on exercise bicycle was negative in all the cases examined. Functional state of the sympathetic nervous endings and myocardial perfusion were studied using single photon emission computed tomography of the heart with a double-head gamma-camera "E.Cam" (Siemens). Therefore, 123I - metaiodobenzylguanidine (MIBG) and 99mTc - methoxyisobutyl isonitrile (MIBI) were used.
Results: The reliable defects of MIBI accumulation in a myocardium were not revealed in any patient included in the study. Moreover, there was a positive correlation between the MIBG and MIBI accumulation indices both at rest ($r = 0.82$; $p<0.05$), and on exercise ($r = 0.79$; $p<0.05$). The correlation between the MIBG accumulation and the size of left ventricle wall thickening in a systole was negative ($r= -0.54$; $p<0.05$). The range of the left ventricular wall motion in a systole and vice versa had positive correlation with the local MIBG accumulation ($r = 0.51$; $p<0.05$).
Conclusions: Thus, to reveal regions of a myocardium with abnormal sympathetic innervations and perfusion preserved is considered to be risk zones in terms of ischemic abnormalities formation. The accumulation index of MIBG in the heart of the patients with essential hypertension can be a predictor of early regional perfusion and kinetics abnormalities of a myocardium.

P1668 Counterregulation in skeletal muscle vascular bed of primary hypertension patients during effective treatment with verapamil

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Objective: Calcium channel blocker Verapamil posseses both vasodilating and cardiodepressive action. However, there is no general agreement concerning the haemodynamic response pattern providing the hypotensive effect of Verapamil. The aim of this investigation was to ascertain central and peripheral haemodynamic changes in primary hypertensives during treatment with verapamil type calcium channel antagonist.
Design and methods: The central haemodynamic parameters - blood pressure, heart rate, cardiac output (CO), systemic vascular resistance (SVR), and peripheral haemodynamic parameters - forearm blood flow, resting vascular resistance (Rrest), minimal vascular resistance (Rmin) and distensibility (D) of large arteries, were investigated in 30 essential hypertension patients (WHO II) after 1-week and 2-month treatment with long acting verapamil (Flamon-240 SR). CO and SVR were derived from echocardiographic findings. D was calculated as a ratio between volume pulse amplitude and pulse pressure. Rrest and Rmin of the forearm were calculated from data on mean arterial pressure and forearm blood flow measured by venous occlusion plethysmography.
Results: It was found that a significant reduction in systolic (-18,8±1,9 mm Hg), diastolic (-8,7±1,2 mm Hg), mean (-13,7±1,6 mm Hg) and pulse pressure (-12,5±1,5 mm Hg) was ensured by two different haemodynamic patterns: by a decrease in CO (n=17) or by a decrease in SVR (n=13). A simultaneous decrease of CO and SVR was observed only in two patients. The hypotensive effect was almost always accompanied by counterregulation from the opposite main determinant of blood pressure which tended to restore the previous elevated blood pressure. Investigation of the forearm vascular bed showed that D of forearm large arteries always increased, average by 53±4% ($p<0.01$), whereas skeletal muscle precapillary vessels were found to be involved in the counterregulation. In the case when hypotensive effect was caused by a decrease in CO, Rrest and Rmin did not change, but in the case when hypotensive effect was ensured by a decrease in SVR, Rmin during treatment increases from 2,7±0,15 to 3,8±0,3 units ($p<0,05$) and an inverse relationship was observed between changes in SVR and Rrest ($r = -0,6$; $p<0,05$).
Conclusion: During effective treatment with Verapamil skeletal muscle precapillary vessels of primary hypertension patients were found to be involved in counterregulation and vasoconstrictor action of this mechanism prevented the manifestation of vasodilator action of Verapamil on these vessels.

P1669 The association between resistant hypertension and aortic stiffness

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Objectives: Resistant hypertension (RH) and aortic stiffness (AS) share the same associated conditions such as older age, isolated systolic hypertension, obesity, chronic kidney disease etc...Until now there is no study investigating the role of AS in RH. In our study we aimed to determine whether there is an association between AS and RH.
Methods: Among 87 patients enrolled in this study, 30 were resistant hypertensives (based on the definition of AHA 2008 statement) (group 1), 29 were controlled hypertensives (group 2) and 28 were normotensives (group3). AS was assessed both by applanation tonometry and by echocardiography. Augmentation index (AIx) and carotid to radial pulse wave velocity (PWV) were measured by Sphygmocor Applanation tonometry. Aortic strain and distensibility were calculated according to diameter change of ascendan aorta in systole and diastole by M-mode echocardiography in parasternal long axis view. Diastolic function parameters were also assessed.
Results: In group 1 AIx and carotid-radial PWV were significanly higher than group 2 and group 3.($p=0,03$ and $p<0,01$) Aortic strain and aortic distensibility were significantly lower in group 1.($p<0,01$ and $p<0,01$) All the AS parameters were similiar among group 2 and group 3. Among diastolic function parameters, left atrial volume index and left ventricular mass index significantly differ between groups. These two parameters were significanly higher in groups 1 and 2 ($p<0,01$ and $p=0,02$) Systolic and diastolic blood pressure levels were significantly different between groups as expected (Table).

Table 1

	Resistant hypertension (n=30)	Hypertension (n=29)	Control (n=28)	P value
Aortic strain (%)	3.67±1.43	4.44±1.55*	5.01±1.77*	0.001
Aortic distensibility ($cm^2\ dyn^{-1}\ 10^{-3}$)	1.89±0.92	2.50±1.03*	2.76±0.85*	0.008
Augmentation index (%)	27.69±16.18	19.07±13.18*	17.75±13.58*	0.03
Pulse wave velocity (m/sn)	5.81±0.97	4.42±0.29*	4.41±0.44*	0.00
Systolic blood pressure (mmHg)	134.47±18.16	122.69±9.07	110.29±13.14	0.02
Diastolic blood pressure (mmHg)	83.23±6.53	80.62±7.56	74.50±7.74	0.01
Left atrium volume index (ml/m^2)	29.60±7.28*	28.75±6.53*	20.89±4.13	0.001
Left ventricular mass index (g/m^2)	112±32.23*	111.96±25.04*	82.00±20.54	0.02

*Nonsignificant ($p>0,05$ between the two groups).

Conclusion: AS was found to be associated with RH. The inconsistency of association in controlled hypertensives suggest a possible role of AS in RH pathogenesis.

P1671 Effects of insulin resistance on resting heart rate and blood pressure levels, and on hemodynamic response to orthostatic stress

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Purpose: The mechanisms by which insulin resistance (IR) contributes to hypertension and cardiovascular disease need to be better understood. In particular, the effects of IR on the hemodynamic responses to postural changes need to be

better characterized. Aim of our study was to assess whether IR affects resting heart rate (HR) and blood pressure (BP) levels, and hemodynamic response to orthostatic stress.
Methods: In the frame of the Medellin's Heart Study (Colombia), a random sample (n=800) from the general population was recruited. Individuals were classified into quartiles of IR (HOMA-index: (glycemia (mg/dL)/18) x insulinemia (uU/mL)/22.5). Beat-to-beat stroke volume (cardioimpedance) and ECG were recorded during 5 min while resting supine, and BP levels repeatedly measured. Individuals were prompted to stand up, and recording continued during 1 min. Hemodynamic indices were computed and averaged: HR was derived from RRI, and changes in HR, SBP and DBP between supine and standing were calculated.
Results: Multiple regression analysis adjusting for age, sex, BMI, smoking and diabetes showed significant differences among IR quartiles for all parameters but one. See table. Both, while resting supine and during standing, IR was associated with significantly higher HR, SBP, and DBP; but also with significant greater increases in HR and DBP in response to the shift from supine to standing.

Hemodynamic variables by quartiles of IR

Variable*	Q1 (≤0.89) (n=201)	Q2 (0.9–1.41) (n=194)	Q3 (1.42–2.25) (n=192)	Q4 (≥2.26) (n=196)	P value ANOVA	Adjusted p (ANCOVA)**
SBP supine (mmHg)	127±1.5	128±1.4	129±1.4	139±1.5	<0.001	0.009
SBP standing (mmHg)	121±1.5	123±1.4	125±1.4	132±1.6	<0.001	0.003
SBP change (mmHg)	–6.2±0.8	–5.0±0.7	–3.6±0.7	–6.5±0.8	0.03	0.05
DBP supine (mmHg)	77.0±0.9	77.7±0.8	78.1±0.8	82.0±0.9	<0.001	0.02
DBP standing (mmHg)	79.7±0.9	80.9±0.8	81.8±0.8	86.0±0.9	<0.001	<0.001
DBP change (mmHg)	1.5±0.6	3.1±0.5	3.7±0.5	4.5±0.6	0.02	0.007
HR supine (bpm)	64.1±0.7	65.8±0.6	67.6±0.7	71.3±0.7	<0.001	<0.001
HR standing (bpm)	73.5±0.8	76.0±0.8	78.8±0.8	82.4±0.9	<0.001	<0.001
HR change (bpm)	9.3±0.5	10.1±0.4	11.1±0.4	11.2 0.5	0.04	0.03

*Values are expressed as least square means ± standard error; **P values after adjustment for age, sex, BMI, smoking and diabetes (ANCOVA).

Conclusions: Our results not only show that IR affects resting HR and BP levels, but also the hemodynamic response to the orthostatic stimulus.

P1672 Effect of aliskiren on QT dispersion in diabetic and non diabetic hypertensive patients

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Purpose: Aim of this study was to compare the effect of aliskiren on QT dispersion in hypertensive patients with or without diabetes.
Methods: After a 2 week placebo period 98 mild hypertensive patients with well controlled type 2 diabetes (HbA1c < 7%) and 102 mild hypertensive patients without diabetes were treated with aliskiren 300 mg for 12 weeks. At the end of the placebo period and of treatment period BP was evaluated and an ECG was recorded using a paper speed of 50 mm/s. The QT intervals were measured manually in all the 12 leads in blinded fashion and 3 consecutive QT intervals were measured and averaged for each lead. The QT dispersion was corrected for the heart rate (QTc).
Results: The treatment induced a significant and similar SBP/DBP reduction in both groups of patients ($p<0.001$ vs baseline). In hypertensive patients with type 2 diabetes aliskiren induced a significant reduction in QTc dispersion (-10.6±22.6 ms, p=0.03) and in QTmax (-12.1±22.1 ms, p=0.02); the QTc dispersion change did not correlate with BP change. In hypertensive patients without diabetes aliskiren induced a smaller and non significant reduction in QTc dispersion (-4.8±19.6 ms, p=0.09) and in QTmax (-3.9±19.6 ms, p=0.11).
Conclusions: Aliskiren reduces QT dispersion in hypertensive diabetic patients and this effect is not related to the BP lowering. It suggests that aliskiren has the potential to reduce severe arrhytmic complications in this type of patients.

P1673 Long-term effects of proBNP cardiac gene delivery in experimental hypertensive heart disease

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Purpose: In the current study, we tested the effects of sustained cardiac proBNP gene delivery on blood pressure (BP), cardiac function and remodeling in spontaneously hypertensive rats (SHR). In normotensive Wistar rats, we further tested whether the cardiac effects of BNP gene overexpression were independent of BP reduction.
Methods: We used the myocardium-tropic adeno-associated virus serotype 9 (AAV9) vector to achieve continuously enhanced cardiac rat proBNP expression. *P<0.05 vs treated rats.
Results: In SHR, a single systemic administration of AAV9 vector allowed longterm, cardiac BNP overexpression, resulting in reductions in systolic (121±11 vs 184±13* mm Hg) and diastolic (103±5 vs 148±24* mm Hg) BP for nine months after injection as compared to untreated SHR. Left ventricular (LV) thickness (1.87±0.1 vs 2.16±0.3* mm), LV end-systolic dimensions (3.96±0.3 vs 4.66±0.6* mm) and LV mass (0.4±0.01 vs 0.49±0.01* gr) were reduced, while ejection fraction was increased (83±2 vs 74±4* %) in BNP-treated compared to untreated SHR. Circumferential systolic strain (-5.04±0.4 vs -3.74±0.4* %) and strain rate of the early phase of diastole (-4.57±2.1 vs -2.41±1.3 1/s) were improved in BNP-treated compared to controls. Non-cardiac overexpression of BNP via AAV2 vector was not associated with changes in BP and plasma BNP in SHR. Furthermore, normotensive Wistar rats injected with AAV9 proBNP vector showed significantly reduced heart/body weights (0.31±0.1 vs 3.9±0.1* %) four weeks after injection without BP reduction compared to untreated rats.
Conclusions: AAV9 vector facilitates sustained cardiac proBNP overexpression improves LV function in hypertensive heart disease. Long-term proBNP delivery improved both systolic and diastolic function. The effects on cardiac structure and function occurred independently of BP lowering effects in normal Wistar rats.

P1674 Central and peripheral hemodynamics in healthy Germans during the finals of the soccer world cup 2010

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Although emotional stress has been assumed as a potential risk factor for cardiovascular events the underlying pathophysiology remains unclear. Emotional stress during World Cup Soccer is associated with an increase of the risk of an acute cardiovascular event. To evaluate whether and to which extent emotional stress effects peripheral and central hemodynamics thirteen healthy soccer fans were studied during the live TV coverage of the finals with German national team participation (GP). The respective finals without German participation were used as control (noGP).
Methods: Thirteen healthy German soccer fans (mean age 37.6 years, range 24-56 years, mean height 176.5 cm, range 164-192 cm, mean weight 71.9 kg, range 56-97 kg, mean body mass index 23, range 19.3-26.9) were studied during the 2010 Championships eightsfinal, quarterfinal and semifinal games for effects of match-induced emotional stress on peripheral and central hemodynamics. The following parameters were measured every 15 minutes by the Mobil-O-graph®: Peripheral systolic, mean, and diastolic blood pressure, heartrate, central systolic and diastolic blood pressure, augmentation pressure, augmentation index corrected for heart rate (Aix@75), cardiac output, and peripheral resistance.
Results: In the 1st hour before the match all parameters were not significantly different between the groups. However, during the matches peripheral systolic pressure, mean blood pressure, diastolic blood pressure, heart rate, cardiac output, and peripheral resistance were increased up to 6.8% ($p<0.001$), 7.3% ($p<0.001$), 8.1% (p=0.004), 18.2% ($p<0.001$), 8.9% (p=0.002), and 6.1% (p=0.05), respectively in the GP group. All these parameters recovered directly after the match. In clear contrast, the systolic central aortic pressure remained elevated (6.0%, p=0.03) during the second hour after the match, whereas the central diastolic blood pressure had already recovered to baseline. Thus, pulse pressure was elevated for at least two hours after stress (GP: 38.5±2.7 mmHg versus noGP: 31.3±1.3 mmHg, $p<0.05$). AIx@75 was significantly elevated during the 1st hour of the matches (+48.3%, p=0.03).
Conclusions: We observed profound and persistant changes in overall hemodynamics during emotional stress. Despite normalization of peripheral values directly after the end of the finals, we observed prolonged elevation of central systolic blood pressure and pulse pressure. These finding may explain the increased risk of cardiovascular events during and after emotional stress.

P1675 Central blood pressure predicts development of hypertension on top of ambulatory blood pressure

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Objective: Central blood pressure (BP) has been found to be associated with target organ damage in adult and elderly hypertensive patients. The clinical significance of central BP in young to middle age hypertensive subjects is less known. The aim of the present study was to evaluate the association of central BP with target organ damage and the risk of future hypertension in a cohort of subjects from the HARVEST study. Design and Methods. We studied 305 subjects screened for stage I hypertension (mean age, 38±10 years), to determine which subjects developed hypertension needing therapy according to current guidelines. Central BP was obtained from radial artery tonometry. Target organ damage was defined as the presence of left ventricular hypertrophy and/or microalbuminria. Central mean BP and central pulse pressure were tested in the multiple regression models.
Results: Baseline peripheral BP was 138±12/86±7 mmHg, 24 hour BP was 130±11/80±8 mmg and central BP was 125±13/86±8 mmHg. In a multiple logistic regression including ambulatory BP, central mean BP was associated with degree of target organ involvement (p=0.01). During 9 years of follow-up, 155 subjects developed hypertension needing treatment. In logistic regression analy-

ses including sex, age, smoking, alcohol and coffee use, physical activity, parental hypertension, body mass index, and heart rate, central mean BP was an independent predictor of future hypertension (p=0.004), whereas central pulse pressure was not associated with outcome. Also ambulatory systolic (p=0.002) and diastolic (p=0.02) BPs were independendent predictors of future hypertension. When all pressures were included in the same logistic model, central mean BP remained a predictor of future hypertension (p=0.004) on top of ambulatory BP. In the subjects divided according to whether their central mean BP was above or below the median (98.7 mmHg), sustained hypertension was developed by 38.8% of the subjects with low central mean BP and by 64.5% of the subjects with high central mean BP ($p<0.001$). Subjects with high central BP had a 2.5 (95%CI, 1.4-4.2) increased adjusted risk of hypertension compared to those with low central BP.
Conclusion: These data show that in young to middle age subjects in the early stage of hypertension, high central BP is a significant predictor of adverse outcome on top of 24 hour BP.

P1676 The effect of nighttime sleep duration on blood pressure levels in hypertensive patients with obstructive sleep apnea

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Objectives: Short sleep duration has been associated with increased blood pressure (BP) and incident hypertension. However, the same applies for obstructive sleep apnea (OSA) which is characterized by sleep fragmentation. We investigated the association of sleep time with BP levels in hypertensive patients with OSA.
Methods: We studied 65 patients (aged 56 years, 77% males) with essential hypertension and obstructive sleep apnea diagnosed with polysomnography (apnea-hypopnea-index-AHI>5) at least 6 months prior to the study. Total sleep time at night (TST) was assessed by self report. Depending on sleep duration patients were divided into short-sleepers (TST≤6hours, N=30) and long-sleepers (TST>6hours, N=35). Subjects were further divided into 2 groups depending on whether they applied continuous positive airway pressure therapy (CPAP-on, N=24) or had refused treatment (CPAP-off, N=41).
Results: Short sleepers compared to non-sleepers did not differ regarding AHI, number of antihypertensive drugs or CPAP-on subjects (p=NS for both). However, short sleepers exhibited higher systolic and diastolic BP compared to long sleepers (138±14 vs. 131±9 and 89±9 vs. 84±7, respectively, p=0.02 for both). In CPAP-on patients, both systolic and diastolic BP were correlated to TST (r=0.41 and 0.39 respectively, p=0.05 for both). In CPAP-off patients, only systolic BP was significantly correlated to TST (r= -0.33, p=0.03). In models of multiple linear regression analysis with age, gender, BMI, logAHI, CPAP application and number of antihypertensive drugs as covariates, sleep time duration independently predicted both systolic and diastolic BP (b=0.37 and b=0.36, p=0.004).
Conclusions: In treated hypertensive patients with OSA, a longer sleep time is associated with lower BP levels independently of OSA severity and number of antihypertensive drugs. Our findings suggest that OSA-induced sleep disruption does not ameliorate the benefits of sufficient sleep in terms of BP control.

P1677 A wave to mitral flow propagation ratio. A new index to characterize asymptomatic patients with essential hypertension

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Purpose: Changes of peak flow velocity during atrial contraction (A wave) by using pulse Doppler are known to be related with diastolic abnormalities in left ventricular hypertrophy (LVH). Mitral flow propagation velocity (Vp) is a diastolic function parameter, relatively independent of preload variations, that represents a useful non-invasive index for assessing LV relaxation. Whether the A/Vp ratio could be useful to characterize asymptomatic patients with essential hypertension (HT) remains unknown.
Methods: We have studied 260 patients without arrhythmia or heart failure, age 60±13, diagnosed with HT. A HT questionnaire and echo-Doppler study were performed on these patients. All plasma samples were centrally analyzed and NT-proBNP (pg/ml) was determined. Vp (cm/s) and A wave (cm/s) were calculated. We also measured systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), E/A, left atrial size (LAS, mm), deceleration time (DT, ms), IVRT (ms), ejection fraction (EF), body mass index (BMI) and left ventricular mass index (LVMI).
Results: For the whole population NT-proBNP levels were 147±266, A/Vp 1.8±0.85, SBP 148±20, DBP 87±11, PP 61±18, A wave 78±21, E/A 0.9±0.25, Vp 48±11, LAS 33.7±0.42, DT 200±38, IVRT 95±7, E/Vp 1.5±0.55, EF 59±5 and LVMI 52.4±17. Interobserver variability (IV) for A/Vp was 6.2±6%. When we correlated A/Vp with LVMI and with NT-proBNP, we found for both r=0.6, $p<0.0001$. When we correlated A/Vp with E/A, DT, IVRT, LAS and E/Vp we found $p<0.0001$. When we divided A/Vp in quartiles (1.0±0.14, 1.4±0.12, 1.9±0.15, 2.9±0.86) and we compared with the correspondent LVMI values (42±8, 47±14, 54±14, 66±19), we found $p<0.0001$. The ROC curve of A/Vp for detection of LV hypertrophy (LVH) yielded an AUC of 0.80±0.03 ($p<0.0001$). From the ROC of A/Vp, the optimal cut-off value (1.71) had a specificity and sensitivity of 83% and 61% for detection of LVH higher than any other diastolic function parameter. Furthermore, multivariate linear regression was performed using LVMI as dependent variable. When the multivariate model was applied (age, gender, SBP, DBP, PP, heart rate, BMI, LAS, diabetes, EF, IVRT, DT, NT-proBNP, known hypertension duration, medication and A/Vp), BMI ($p<0.0001$), NT-proBNP ($p<0.0001$), A/Vp ($p<0.0001$), age ($p<0.05$) and known hypertension duration ($p<0.05$) were independent predictors of LVMI ($r^2=0.72$, $p<0.0001$).
Conclusions: In conclusion, A/Vp is significantly correlated with left ventricular mass index and all diastolic parameters in HT. A/Vp is the best echo-Doppler diagnostic and predictor factor of LVH in asymptomatic patients with HT.

HEREDITARY CARDIOMYOPATHIES

P1678 Quantitative expression profiles of the mutated Lamin A/C gene in patients with dilated cardiolaminopathies

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Purpose: Dilated cardiolaminopathy is an age-dependent entity characterized by a dilated cardiomyopathic (DCM) phenotype with conduction disease and increased risk of arrhythmias. The diagnosis is confirmed by sequencing of the Lamin A/C (LMNA) gene. Little is known about the myocardial expression of the Lamin A/C protein, as well as the quantitative expression of the mutated LMNA gene in the myocardium and peripheral blood.
Methods: We performed immunohistochemistry on myocardial samples, including endomyocardial biopsies (EMB) and hearts removed at transplantation, from 25 DCM patients with mutated LMNA gene (DCM-LMNA-Mut), as well as on EMB from 20 normal donor hearts, with anti-Lamin A/C antibodies. We investigated mutated LMNA mRNA levels in 20 myocardial and 67 blood samples from DCM-LMNA-Mut patients. We further examined wild-type LMNA mRNA levels in 20 myocardial and 96 blood samples from DCM patients with wild type LMNA gene (DCM-LMNA-WT), and in 115 blood samples from normal control individuals (CTRL).
Results: Myocardial samples from DCM-LMNA-Mut patients revealed variable, irregular loss of protein expression at the level of the nuclear membrane of cardiac myocytes. In contrast, DCM-LMNA-WT and CTRL samples demonstrated normal immunostaining. The LMNA gene was significantly under-expressed in myocardial samples from DCM-LMNA-Mut patients as compared to DCM-LMNA-WT individuals. In mRNA from peripheral blood, the LMNA gene was also significantly under-expressed in DCM-LMNA-Mut patients as compared to DCM-LMNA-WT and CTRL individuals, with the highest degree of under-expression found in splice site as well as out-of-frame and premature termination codon mutations, followed by missense and in-frame insertion/deletion mutations.
Conclusions: DCM patients harboring LMNA gene mutations reveal loss of protein expression at the level of myocyte nuclei and demonstrate decreased gene expression in myocardial and peripheral blood mRNA. Immunohistochemistry and gene expression are important aspects of the diagnostic work-up for cardiolaminopathies, as well as promising tools for investigating mechanisms of myocardial damage.

P1679 Mutations in the human gene encoding melusin in patients with dilated cardiomyopathy

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Background: Melusin, a cysteine-rich cytoplasmic protein expressed exclusively in skeletal and cardiac muscle, binds to the cytoplasmatic domain of integrin β1. Under pressure overload mice lacking the melusin gene (itgb1bp2) develop dilation of the left ventricle with a reduced contractility. The aim of this study was to investigate whether mutations in the human melusin gene are also associated with dilated cardiomyopathy (DCM).
Methods: Within the scope of the German Heart Failure Network (KNHI) we screened the itgb1bp2 gene for mutations in patients with dilated cardiomyopathy. Briefly, blood samples from patients with clinically diagnosed DCM (n=257) and healthy blood donors (n=300) were collected and DNA was extracted from peripheral lymphocytes. Most of the DCM patients were previously genetically screened for mutations in the following DCM responsible genes: lmna, des, myh7, mybpc3, tnnt2, mypn, ankrd1. Coding regions from the itgb1bp2 gene were amplified by

PCR and analyzed by dideoxy fingerprinting (ddF) and/or denaturing gradient gel electrophoresis (DGGE), followed by direct sequencing of samples with different banding patterns. Sequence variations were checked by restriction fragment length polymorphism (RFLP).
Results: In one DCM patient presenting with heart failure we identified a hemizygous missense mutation in the coding sequence of the X-chromosomal itgb1bp2 gene (c.938C>G). The mutation resulted in the substitution of glycine for alanine in codon 312 (A312G). A heterozygous variant of this mutation could be detected in a female family member whereas in four family members as well as in the cohort of healthy blood donors the mutation was absent.
Summary and conclusion: In our DCM study group we identified a single missense mutation in the gene encoding melusin, while there was no detectable mutation the healthy control group. The point mutation resulted in an amino-acid exchange in the highly conserved carboxy-terminal fragment of melusin, which may have functional relevance for the pathogenesis of the disease. Our study demonstrates that the human melusin gene may be a new candidate gene for the pathogenesis of DCM. Further analysis of additional family members as well as functional studies of the mutation are in progress.

P1680 Genetics of dilated cardiomyopathy: novel mutations in the RNA-binding motif protein 20 gene (RBM20)

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Introduction: Dilated cardiomyopathy (DCM) can have an acquired or genetic etiology. It is well known that the genetic form of the disease is heterogenous. More than 20 different genes have been shown to cause familial DCM. Affected are different cellular compartments of the cardiomyocyte like the sarcolemma and the membrane of the nucleus as well as the sarcomere and the cytoskeleton. RBM20, encoding the RNA-binding motif protein 20, is a key regulator of gene splicing highly expressed in the heart. Recently, it has been established as a novel disease gene with a mutational hotspot in exon 9.
Methods: To further evaluate the role of RBM20 in DCM pathogenesis, we retrospectively evaluated a cohort of 120 unrelated patients with idiopathic DCM. The DNA of the patients was systematically analyzed in exon 9 of RBM20 using PCR and direct sequencing (ABI Dye Terminator chemistry).
Results: In total, we detected three different heterozygous missense mutations (Ser635Ala, Arg636Ser, Ala818Ser) in three unrelated patients. These genetic variants were excluded in 260 control alleles from individuals without cardiomyopathy. While the mutation Arg636Ser is known, the mutations Ser635Ala and Ala818Ser are novel ones. The exchanged aminoacids show different physiochemical properties (non-conservative exchange). The aminoacids of codons 635 and 636 are highly conserved in different orthologs (from mouse to zebrafish). They are located in the arginine/serine (RS)-rich domain which is predicted to be involved in interaction with other spliceosome proteins. All three patients suffered from a severe DCM with arrhythmias. Two patients had an ICD implanted. This phenotype is in concordance with the clinical data published recently.
Conclusions: We have confirmed the mutational hotspot in the RS-rich domain of RBM20 and an interestingly homogenous phenotype of the mutation carriers. We could expand the RBM20 mutation spectrum in DCM by detection of two novel mutations (one outsite the RS-rich domain). Our results further emphasize the role of RBM20 in the etiology of dilated cardiomyopathy.

P1681 Increased oxidative stress contributes to cardiomyocyte dysfunction in Fabry disease cardiomyopathy

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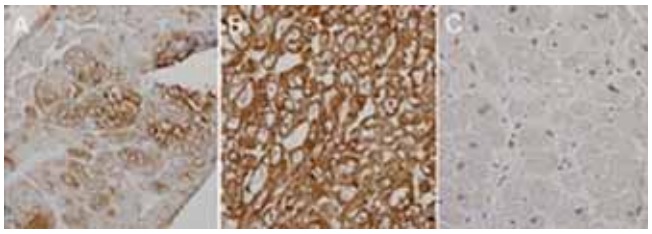
Purpose: Cardiac dysfunction in Fabry disease (FD), an X-linked lysosomal deficiency of alpha-galactosidase A, is associated with myofilament proteins degradation and dysfunction. Aim of the study is to determine whether an imbalance of myocardial nitric oxide (NO) production with increase in oxidative stress contributes to cardiomyocyte dysfunction in FD cardiomyopathy.
Methods: Myocardial tissue from 20 patients with FD (14 M, 44.8±13.4 years) and 20 sex and age matched controls was investigated for the expression of iNOS, eNOS, and nitrotyrosine by immunohistochemistry. Intensity of immunostaining was semiquantitatively evaluated as absent (grade 0), mild (grade 1), moderate (grade 2) and strong (grade 3). Oxidative damage to DNA was investigated by immunostaining for 8-hydroxydeoxyguanosine (8-OHdG). Western blot analysis for iNOS and nitrotyrosine was performed on frozen samples.
Results: iNOS and nitrotyrosine expression was increased in patients with FD compared with controls (2.5±0.7 vs 0.2±0.4 for iNOS and 2.0±0.4 vs 0.1±0.1 for nitrotyrosine), while eNOS was similarly expressed. Eight-OHdG expression was increased in cardiomyocyte nuclei of FD patients. Western blot analysis showed



Immunostaining for iNOS in FD and controls.

an increase in cardiomyocyte protein nitration. In female patients a patchy distribution of positive immunostaining was observed (panel A, iNOS immunostaining) while in male patients the cardiomyocytes stained homogeneously (panel B) compared with negative immunostaining of controls (panel C).
Conclusions: FD cardiomyopathy is characterized by cardiomyocyte NO overproduction with oxidative stress, protein nitration and DNA damage, resulting in cell dysfunction. Therapeutic options with selective NOS inhibitors and antioxidants might improve cell function.

P1682 Protein studies of desmoplakin mutations in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and the Carvajal syndrome

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Purpose: Several desmoplakin (DSP) mutations have been identified in ARVC and Carvajal syndrome patients. The impact of DSP mutations on disease development is largely unknown not least due to difficulties in obtaining cardiac tissue for protein investigations. DSP protein is abundantly expressed in both heart and skin tissue. Therefore, we aimed to investigate the expression of wildtype DSP (wtDSP) and mutated DSP (mtDSP) protein variants in skin tissue from individuals with DSP mutations.
Methods: DSP protein expression in keratinocytes cultured from skin samples was investigated by immunoblotting and mass spectrometry. Immunohistochemical DSP protein staining was made on myocardial and epidermal biopsy material.
Results: ARVC patients having additional desmosomal gene variants expressed higher levels of mtDSP protein in comparison to healthy relatives carrying a single DSP mutation only (table). A Carvajal patient carrying a homozygous mutation expressed high levels of truncated DSP protein in contrast to healthy heterozygous relatives, who expressed very low levels of mtDSP. No differences in DSP protein localisation in myocardial and epidermal biopsies were observed by immunohistochemistry.

Investigated desmoplakin mutations

Phenotype	DSP genotype	Additional desmosomal gene variants	Total DSP protein * expression*	mtDSP vs. wtDSP protein
Healthy	V30M / wt	–	Normal	32% / 68%
ARVC	V30M / wt	DSG2: R46Q / wt	Normal	47% / 53%
Healthy	K323_E324del / wt	–	Reduced	0% / 100%
ARVC	K323_E324del / wt	PKP2: T526M / wt	Reduced	19% / 81%
Healthy	S2594fsX8 / wt	–	Reduced	5% / 95%
Carvajal	S2594fsX8 / S2594fsX8	–	Normal	100% / 0%

Abbreviations: DSP, desmoplakin; DSG2, desmoglein-2; PKP2; plakophilin-2; wt, wildtype. *Compared with DSP expression in wt controls.

Conclusion: Patients with ARVC or Carvajal syndrome carrying DSP mutations incorporate mtDSP protein into desmosomes. MtDSP protein was higher expressed in individuals having additional gene variants compared with single mutation carriers, who remain healthy despite low levels of wtDSP protein expression. This suggests a modifying role for co-existing sequence variants and indicate that isolated DSP haploinsufficiency is tolerated. In conclusion, we speculate that mtDSP protein destabilises desmosomal function and contributes to pathogenesis in ARVC and the Carvajal syndrome.

P1683 SCN5A mutations and echocardiographic findings

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Background: Mutations in the human cardiac sodium channel alpha-subunit gene (SCN5A) are involved in the pathophysiology of cardiac arrhythmias (Brugada syndrome (BS), Long QT syndrome (LQTS), cardiac conduction defects and idiopathic ventricular fibrillation), cardiomyopathies (dilated cardiomyopathy (DCM) and left ventricular non-compaction (LVNC) and other cardiac structural abnormalities. We aim to evaluate echocardiographic findings in carriers of SCN5A variants.
Methods: Sequencing of SCN5A gene was performed in 103 patients diagnosed with BS (93,89%), LQTS (8, 8%) and cardiac arrest or ventricular arrhythmias in (3, 3%). SCN5A mutations/variants (3 families G1743R and 1 family each R27H, S524Y, R620H, V728I, E901K, E1032K, E1151stop and N1443S) were identified in 11 unrelated probands after excluding known polymorphisms. Echocardiographic findings from both probands and relatives from these 11 families were analysed. Echocardiograms from carriers (34, 65%) and non-carriers (18, 35%) were compared.
Results: 52 individuals (ind.) from 11 different families (mean 4.7 ind. per family) comprised the study population. Reason for SCN5A study was BS in 9 families (39 ind.), cardiac arrest in 1 (5 ind.) and ventricular arrhythmias in 1 (8 ind.). 12 (23%) ind. had echocardiographic abnormalities. 3 ind. had DCM (all from the same family, all carriers), 3 had left ventricular hypertrophy (from 3 different families, all carriers of SCN5A mutations, 2 with G1743R, 1 with E901K), 2 had left ventricular hypertrabeculation (both from same family and carriers of the same mutation S524Y), 1 had right ventricular dilatation (carrier of G1743R), 4 had significant valvular disease (3 aortic regurgitation and 1 tricuspid regurgitation, 3 of them carriers). 2 out of the 3 patients with aortic regurgitation had significant aortic and left ventricular dilatation (both carriers of R620H). 1 non-carrier had subaortic membrane and another non-carrier had anterior scar from an old myocardial infarction. 10 (26%) of carriers had echocardiographic abnormalities versus 2 (11%) non-carriers (p=0.1).
Conclusion: Structural abnormalities seems to be particularly frequent in SCN5A carriers. Chamber dilatation, left venticular hypertrophy, left ventricular non-compaction and valvular disease have been demonstrated in our series. Larger and multicentre registries are needed to appropriately address this observation.

P1684 A novel mutation in alpha-actinin-2 responsible for hypertrophic cardiomyopathy identified by massively parallel next generation sequencing

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Objectives: Aim of the present study was to evaluate the capacity of sequence enrichment and next generation sequencing (NGS) to successfully identify mutations in a large family with an atypical variant of hypertrophic cardiomyopathy (HCM) which proved negative to standard Sanger sequencing of the eight principal sarcomeric genes.
Background: Sequence capture target enrichment and massively parallel NGS might be particularly advantageous in testing for genetically heterogeneous hereditary conditions, such as HCM. Current diagnostic evaluation proceeds by sequencing a large number of genes, based mainly on the relative frequency of the mutations. In more than 35% of patients, the pathogenic mutation is unknown even after very extensive and expensive molecular testing.
Methods and results: We designed a custom in-solution SureSelect enrichment system covering 36 genes. The genes were chosen based on reports of identified mutations in at least one patient. We tested the proband, an 82 year-old man with a mild, asymmetric LV hypertrophy localized to the apex, marked biatrial dilatation, restrictive LV filling patter and juvenile onset of atrial fibrillation. After the run on GAIIx and bioinformatics analysis, three variants were identified: TTNchr2:17918115C>T; p.Arg13823Gln ACTN2 chr1:234961223T>C; p.Met228Thr and MYH3 chr11:47313204C>G; p.Ala1198Thr. Of these, only ACTN2 chr1:234961223T>C; p.Met228Thr co-segregated with the disease manifestations (mostly juvenile onset of atrial arrhythmias and atrial dilatation in the proband's pedigree (figure down). This novel variant was absent in 300 healthy controls and produced a change in a highly conserved residue among species and isoforms.
Conclusions: This is the first study that showed the feasibility of using genomic enrichment by sequence capture followed by NGS to investigate genetic causes of HCM. Such strategy allows simultaneous, efficient and low-cost sequencing of all genes implicated in a particular genetic disorder, with potential implications for other monogenic cardiovascular disorders.

P1685 Characterization of gene mutations in hypertrophic cardiomyopathy with evidence of "end-stage" progression: a multicentric study of 161 patients

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Purpose: A minority of patients with hypertrophic cardiomyopathy (HCM) exhibit rapid progression of left ventricular dysfunction and symptoms over the years, reaching a condition generally known as "end-stage" (about 5-10% of tertiary referral center cohorts). Such condition carries an ominous prognosis due to heart failure and sudden arrhythmic death. Little is known regarding the prevalence and type of genetic mutations in HCM patients with end-stage disease. Therefore, aim of the present study was to assess the genotype of a large cohort of patients with end-stage HCM undergoing comprehensive mutational screening (11 genes) in Italian referral centers.
Methods: One-hundred and sixty HCM patients, since 1980, consecutively found to have an left ventricular ejection fraction <50% (end-stage) underwent complete sequencing of 8 sarcomere protein genes (MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC) and 3 metabolic genes (GLA, PRKAG2, and LAMP2) implicated in idiopathic cardiac hypertrophy.
Results: 136 mutations (26 novel - 19%) were identified in 107 patients (67%); mutations occurred predominantly (>65%) in MYH7 and MYBPC3. Eighty-three patients (52%) had single mutations (39 MYBPC3, 26 MYH7, 10 TNNI3, 3 TNNT2, 2 TPM1, 2 MYL2, and 1 MYL3). Twenty-four patients (15%) had complex genotypes characterized by had double-gene mutation heterozigosity (n=8; 5%), compound heterozigosity (n=11;7%), and triple mutations (5;3%). LAMP gene mutations were only identified in 2 patients who also had sarcomeric mutations (in MYL3 and TNTT2, respectively): both were novel. No significant differences with regard to clinical and echocardiographic variables at baseline were found between patients with or without identified mutations. However, a higher prevalence of positive mutation was found in patients with family history of HCM compared to patients with sporadic HCM (68% vs 51%, p=0.04). Among patients with sporadic HCM, prevalence of HCM-related death was more frequent in genotype positive individuals compared to negative (51% vs 27%, p=0.05).
Conclusions: Sarcomeric mutations were highly prevalent in patients with end-stage HCM, although not qualitatively dissimilar from those found in unselected HCM populations. Complex genotypes characterized by double or triple mutations were frequent in this cohort, suggesting that, genetic screening may play a role in the identification of HCM patients at risk of disease progression.

P1687 Mutations in left ventricular non compaction

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Background and objective: Left ventricular non compaction (LVNC) has recently been classified as a primary cardiomyopathy with a genetic origin. LVNC is morphologically characterized by a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses. This study sought to evaluate the hypothesis that there is a shared molecular etiology of LVNC and other cardiomyopathies
Methods: Cohort-based study including 46 families with LVNC and 101 affected patients (37 families in which the index case had been diagnosis of LVNC and another 9 families in which the proband had another diagnosis but LVNC was present in a relative). Mutation screening was performed with genomic DNA samples from 39 families in 15 genes (MYH7, MYBPC3, TNNT2, TPM1, ACTC, MYH6, MYL2, MYL3, MYLK2, MYO6, PRKAG2, TCAP, TNNC1, TNNI3 and TTN).
Results: Mean age at diagnosis was 36.5±18 years old, with a wide range (5-73). 42% were women. 60% of cases presented as a familial disease. 20 families (71.4%) presented mixed phenotypes (relatives with either hypertrophic or dilated cardiomypathy). We identified a definitive or very probable disease causing mutation in 40% of the patients (87% of them in cases that LVNC presented as a familiar disease and only 13% of them in cases that LVNC presented as a sporadic disease), with 11 different mutations in four genes, six different mutations in MYH7 (G181R, G716R, G771-L773delGLL, A1128T, E1752del, M1840I), 3 in MYBPC3 (R273C, A833T, P873L), 1 in ACTC (E101K) and 1 in LMNA (R190W).
Conclusion: LVNC is predominantly a familiar condition and shows high intrafamilial phenotypic variability. LVNC is within the diverse spectrum of myocardial diseases caused by sarcomere protein gene defects. The profitability of a genetic study in patients with familiar LVNC is high.

P1688 Exercise capacity predicts prognosis in anderson fabry disease

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Purpose: To determine the clinical and prognostic significance of exercise limitation in patients with Anderson Fabry disease (AFD).
Methods: 193 patients (age 43±14.5 years, 50% male) underwent cardiopulmonary exercise testing, ECG and echocardiography. Disease severity was assessed using the Mainz Severity Score Index (MSSI). Exercise limitation was defined as peak oxygen consumption (VO2) <70% predicted for age, gender and height. Patients were followed for 4.8±2.8 years (Range 0 to 14.7 years).
Results: Peak VO2 was 23.3±7.2 ml/min/kg (range 9.2 to 46.5); 74 patients (38.1%) had a peak VO2 <70% of predicted. Those with impaired exercise capacity were male, had higher MSSI scores, larger left atria and LV mass (Figure 1). 11 patients died during follow-up. Peak VO2 <70% was associated with higher all cause mortality (Figure 2, p=0.034).

Table showing differences between those with normal (peak VO2 ≥70% of predicted) and impaired (peak VO2 <70% of predicted) exercise capacity

	Impaired exercise capacity N=74, Mean ± SD	Normal exercise capacity N=119, Mean ± SD	Significance
MSSI	25±13	19±10	p<0.05
Age (years)	44±16	42±14	NS
Left atrial diameter (mm)	39±8	37±6	p<0.05
Ejection fraction (%)	61±10	63±7	NS
Left ventricular mass index	124±56	107±39	p<0.05
Male	N=45 (61%)	N=51 (43%)	P<0.05

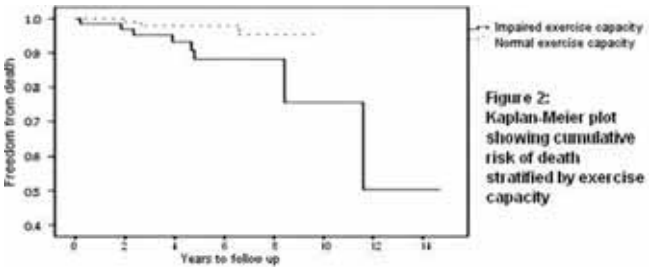

Figure 2: Kaplan-Meier plot showing cumulative risk of death stratified by exercise capacity

Figure 2. Kaplan-Meier Survival graph.

Conclusion: Exercise limitation is common in AFD and is a predictor of long-term survival.

P1689 The prevalence and characterization of left ventricular crypts in asymptomatic hypertrophic cardiomyopathy mutation carriers

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Purpose: In a small group of asymptomatic mutation carriers of hypertrophic cardiomyopathy (HCM), we previously described morphological abnormalities before the development of left ventricular (LV) hypertrophy. Using cardiovascular magnetic resonance imaging (CMR), we demonstrated sharp-edged, abrupt invaginations of the inferoseptal LV wall ("crypts"), while none were found in age and gender matched controls. The aim of this study was to determine the prevalence and localization of LV crypts in a large group of asymptomatic HCM mutation carriers with the use of a tailored CMR imaging protocol.
Methods: A total of 56 genotyped asymptomatic relatives of HCM index patients underwent CMR imaging at a 1.5-Tesla (Magnetom Avanto or Sonata, Siemens, Erlangen, Germany). The majority of carriers harboured a founder mutation in the MYBPC3 gene (50/56, 89%). The remainder carried a TPM1 mutation. Standard long- and short axis cine images (with typical image resolution of 1.3*1.6mm) were acquired with complementary modified two-chamber cines to visualize inferoseptal LV crypts. Based on predefined criteria, crypts were characterized according to their location and prevalence.
Results: The majority of carriers (39/56, 70%) displayed crypts, located at the basal and mid inferoseptum. Crypt-positive carriers often showed multiple crypts (32/39, 82%). Notably, four or more crypts were detected in 13/39 (33%) of patients. Intra- and interobserver analyses showed an excellent reproducibility in scoring the presence of crypts on the CMR images, with κ-values of 0,95 and 0,92 respectively.
Conclusions: Left ventricular crypts are frequently seen in a large group of asymptomatic HCM carriers with various sarcomeric mutations. Crypts in HCM mutation carriers occur at the inferoseptum and typically appear clustered. It is important to further study the role of the crypts in the clinical course of HCM.

P1690 Cardiac microvascular dysfunction in anderson-fabry disease: a dipyridamole PET-based study in a cohort of male and female patients

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Anderson Fabry disease (AFD) is an X-linked lisosomal disease, caused by deficiency of the enzyme α-galactosidase A. It is a multisystem disorder and cardiac involvement is frequent, with left ventricular hypertrophy (LVH),hypertrophic cardiomyopathy (HCM), heart failure, sudden death. Cardiac microvascular dysfunction (CMD) was described in a small cohort of male AFD patients with LVH, by myocardial Pet after adenosine infusion. However no data exist in females and in patients without LVH.
Purpose: CMD evaluation is based on measurement of myocardial blood flow during dipyridamole induced hyperemia (Dip-MBF) by myocardial PET. We evaluated CMD and its relationship with clinical and genetic data in a cohort of males and females with AFD.
Methods: The study cohort comprised 23 patients (11M, 12F; mean age 53±14 years) who underwent ECG, echocardiography and PET. LVH and HCM were defined by maximal LV wall thickness on Echo ≥13 mm and ≥15mm, respectively. CMD was defined by Dip-MBF <3 ml/g/min and severe CMD by DipMBF <1,1ml/g/min.
Results: ECG signs of LHV were present in 12 (52%) patients. By Echo, LVH was detected in 2 (9%) and HCM in 15 (65%) patients. Mean maximal LV wall thickness was 17±6 mm (range 8-29 mm). TDI septal e' values were normal in 7 (30%) patients, including 3 with HCM. Dip-MBF was reduced in all patients (mean Dip-MBF=1,7 ml/g/min; range 0,86-2,75) and there was no difference between males and females (1,5 vs 1,9; p ns). Dip-MBF was also reduced in 6 (26%) patients without ECG or Echo signs of LVH. Severe CMD was detected in 4 (17%) patients, 3 males with HCM and 1 female with LVH. A significant inverse relationship between Dip-MBF and LV maximal wall thickness (R2=0,64; p<0,01) and between Dip-MBF and age (R2=0,4; p<0,05) was found only in males. The Ans215Ser mutation was identified in 9 (40%) patients, who showed more severe CMD compared to those with other mutations (1,3 vs 1,9ml/g/min; p<0,01).
Conclusions: CMD is present and is the earliest sign of cardiac involvement in all patients with AFD, including females and those without ECG or Echo signs of LVH or HCM. In males the severity of CMD is directly correlated with age and maximal LV wall thickness. CMD is more severe in patients with Ans215Ser mutation. Further studies are necessary to determine the impact of CMD on patients outcome and whether medical treatment, including ERT, may improve CMD.

P1691 Variability of clinical expression in Danon's cardiomyopathy

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Purpose: Danon disease (DD) usually mimics severe hypertrophic cardiomyopathy (HCM). Natural history and phenotypic expression of this disease is incompletely resolved. The aim of the study was to determine the prevalence, clinical outcome, and phenotypic expression of DD among HCM patients (pts).
Methods: We evaluated 600 HCM pts trying to identify DD pts among them. A detailed clinical evaluation, histochemical analysis of the peripheral muscles and molecular genetic analysis was performed in 28 pts with the clinical suspicion of DD, like severe LVH in early age, ECG (pre excitation sign, premature conduction disease), peripheral muscle or liver function abnormalities, learning or speaking difficulties and suitable mode of inheritance.
Results: Three pts (A, B and C) among the 600 HCM pts fulfilled the clinical, histochemical and genetic criteria for DD (0.5%). Phenotypic expression, clinical course and outcome were prospectively assessed in those 3 young male pts with defined LAMP2 mutations, from the time of diagnosis (age 1, 9 and 7 years old for each patient, respectively) to October 2010. The mean (SD) follow-up was 12 (5.5) years (range 6-17years). During adolescence, two of the studied pts (A and B, brothers) developed left ventricular systolic dysfunction (ejection fraction 20% and 25% respectively), cavity enlargement, as well as particularly adverse clinical consequences, including arrhythmias and progressive refractory heart failure which led to death for patient A and successful transplantation for patient B (he is still alive and well 6 years after transplatation). Severe left ventricular hypertrophy (LVH) was identified from their childhood (maximum thickness, 35mm and 25mm, respectively). Their mother died suddenly at 28yrs old due to "HCM". It is of inter-

est that the third patient (C) at 7 years old revealed specific ECG abnormalities, peripheral myopathy and mild learning and speaking problems, but no structural expression of heart disease. At the age of 10yrs, mild LVH was expressed. Since then, he remains stable (15yrs old). There is no family history of sudden cardiac death or HCM. In all 3 pts, a ventricular pre-excitation pattern at study entry was associated with markedly increased voltages of R-wave or S-wave and deeply inverted T-waves. The two more severely affected pts (A and B) had a novel LAMP2 point deletion lying in exon 5. The LAMP2 mutation carried by patient C is an already reported mutation (c.928G>A).
Conclusions: The phenotypic variability of our cases prevent from determining a clear-cut genotype-phenotype correlation regarding Danon disease.

P1692 Expanding the cardiac phenotypes of laminopathies: novel LMNA mutations in two patients with left ventricular noncompaction before ventricular systolic dysfunction

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Background: Mutations in lamin A/C (LMNA) gene are responsible for dilated cardiomyopathy (DCM) with or without conduction system disease and a high risk of cardiac dysrhythmia and sudden death.
However, recent clinical and experimental evidence suggest that more heterogeneous cardiac phenotypes may be associated to LMNA mutations.
Aim: To investigate the prevalence of LMNA gene defects in patients presenting heritable cardiomyopathy with different cardiac phenotypes.
Methods: The study comprised 23 unrelated patients with familial DCM (n=16), left ventricular noncompaction (LVNC) (n=3) and conduction system disease (n=4). All patients were screened for mutations by direct sequencing of all coding regions and intron-exon boundaries of the LMNA gene (CEQ 8800 Beckman Coulter, Germany).
Results: The frequency of mutations in familial DCM was 2/16 (12.5%), with two new missense mutations identified (D461Y and R189W) both associated with conduction system disease. Two novel missense mutations in exon 1 of LMNA gene were identified in 2/3 (66.7%) of patients with LVNC: the K117R mutation was present in a proband with LVNC who underwent to ICD implantation for conduction system disease, while the R110S was present in a subject with LVNC and mild ventricular systolic dysfunction. Moreover, a known disease-causing variant (R190W) was identified in a patient with conduction system disease in absence of a significant dilatation of left ventricle. All new mutations were absent in 100 control subjects.
Conclusions: Our data showed that lamin A/C gene mutations may occur in isolated left ventricular noncompaction and in patients without DCM or before the development of severe left ventricular dysfunction.

P1693 Myocardial structural alteration and segmental dysfunction in hypertrophic cardiomyopathy mutation carriers without phenotype expression

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Introduction: Familial screening of hypertrophic cardiomyopathy (HCM) patients may identify asymptomatic mutation carriers without HCM phenotype, i.e. apparently normal echocardiogram and normal electrocardiography. The aim of the present study was to evaluate whether myocardial structural alterations and subtle myocardial dysfunction could be detected in this group of patients.
A total of 16 HCM families with an identified pathogenic mutation were studied and 43 patients (52±16 yrs, 74% male) with phenotype expression (Mut+/Phen+) and 44 (37±14yrs, 46% male) patients without phenotype expression (Mut+/Phen-) were observed. In addition, 25 normal control subjects, matched for age and gender with the Mut+/Phen- group were recruited for comparison. All subjects under went transthoracic echocardiogram for the evaluation of conventional parameters,myocardial structural alteration by calibrated integrated backscatter (cIBS) and global and segmental longitudinal strain by speckle tracking analysis.
Results: Majority of patients (70%) had one of the Dutch founder mutations in the Myosin binding protein C gene. All 3 groups had similar LV dimensions and ejection fraction (EF). The anteroseptal cIBS of Mut+/Phen+ was higher than Mut+/Phen- patients (-14.2±4.8 vs. -16.9±2.9 dB, $p<0.01$), suggesting a greater myocardial structural alteration in the segment most frequently involved by LV hypertrophy. Moreover, Mut+/Phen- group anteroseptal cIBS was significantly higher than controls (-22.6±2.9 dB, $p<0.01$).
Global (-16.6±4.3%, $p<0.01$) and segmental anteroseptal strains (-9.1±4.5%, $p<0.01$) were most impaired in Mut+/Phen+ patients as compared to the other two groups. Although the global strain was similar betweenMut+/Phen- group and controls (-21.2±2.4 vs. -21.3±1.3%, p=ns), anteroseptal strain value was more impaired in the Mut+/Phen- group (-14.5±4.1%, $p<0.01$) as compared to controls (-19.9±2.9%, $p<0.01$). A combination of > -19.0 dB anteroseptal calibrated IBS and > -18.0% anteroseptal strain had asensitivity of 100%, a specificity of 74%, a positive predictive value of 100% and a negative predictive value of 66% in differentiating Mut+/Phen- group from controls.
Conclusion: Despite normal LV dimensions and EF and normal wall thickness, patients with HCM+/Phen- exhibited a significantly higher myocardial structural alteration and impaired segmental strain in the anteroseptal region as compared to controls. Moreover, the use of cIBS and segmental strain can accurately differentiate Mut+/Phen- patients from controls.

P1695 High prevalence of myocardial structural abnormalities by cardiac magnetic resonance in asymptomatic patients with lamin A/C mutations

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Purpose: Early detection of myocardial disease is warranted in subjects with lamin A/C mutations (LMNAm). Sudden death may be the first clinical manifestation, independently of dilated cardiomyopathy (DCM). Our aim was to assess myocardial structural involvement in asymptomatic LMNAm carriers using contrast-enhanced cardiac magnetic resonance (CMR).
Methods: Fifteen LMNAm carriers (4 probands, 6 males, age 43±17 years, all NYHA class I) underwent a complete clinical, echocardiographic, biohumoral evaluation and contrast-enhanced CMR. Thus were compared to 15 healthy controls (11 males, age 43±12 years). Late gadolinium enhancement (LGE) CMR was used to detect replacement myocardial fibrosis whereas pre- and post-contrast T1 mapping was used to quantified the T1 values myocardium and blood pool. At steady-state gadolinium partition coefficient (GPC) was calculated and used as an estimate of interstitial myocardial remodelling.
Results: At cine CMR LV end-diastolic volume was larger in LMNAm patients than controls (86±16 vs 75±12 ml/m^2, p=0.03) whereas LV ejection fraction was similar between the two groups (62±8% vs 68±5%, p=NS). Three LMNAm patients (20%) showed mild LV systolic dysfunction (age 65±10 years, LV ejection fraction <55%, mean 50±2%), as well as increased NT-proBNP plasma levels (333, 42-943 ng/L, median, range), ventricular tachyarrhythmias (Lown class 4) and myocardial LGE (1 patchy and 2 midwall pattern, involving 16±2% of LV mass). Among the 12 LMNAm carriers with normal systolic function (age 43±17 years, LV ejection fraction 65±6%, NT-proBNP plasma levels 57, 26-94 ng/L), 3 patients (20%) still presented myocardial LGE (2 patchy, 1 midwall) involving 10±4% of LV mass. Overall, GPC was higher in LMNAm patients as compared to controls (0.51±0.07 vs 0.47±0.04, $p<0.001$). Even after excluding LMNAm patients with LGE (n= 6), GPC remained consistently higher in LMNAm patients than controls (0.51±0.07 vs 0.47±0.04, p=0.001). Receiver-operating characteristic analysis yielded a GPC cut-off = 0.48 for LMNAm (area-under-the curve: 0.769, 95% CI 0.583 to 0.954, p=0.012), with 87% sensitivity and 73% specificity.
Conclusions: In asymptomatic LMNAm carriers, replacement and interstitial myocardial fibrosis may represent the early cardiac phenotypic expression, possibly favouring life-threatening arrhythmias.

P1696 Yield of genetic testing in patients with familial vs. non-familial idiopathic dilated cardiomyopathy

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Purpose: It has been estimated that 20% to 50% of idiopathic DCM cases are of familial/genetic origin, generally with autosomal dominant inheritance, but information about the efficiency of mutation screening is scarce.
Methods: We report the results of the ongoing genetic and familial study of 125 index cases with idiopathic DCM (mean age at diagnosis 44±20 years, 74% males) followed-up in a single reference unit. DCM was considered "familial" when there was at least one relative with DCM, according to previously established criteria. The genetic study has included the screening by a Sequenom platform of 600 previously described mutations and the sequencing of LMNA in all the patients. Direct sequencing of 9 sarcomeric genes was performed in a minority of patients.
Results: Familial DCM was present in 29 cases (23%). Till now we identified a potentially pathogenic mutation in 21 cases (13%): 9 of 29 cases with familial DCM (31%), and 12 of 96 cases (13%) with non-familial DCM (p=0.024). The majority of them were identified in MYH7 (45%), MyBPC3 (25%), and LMNA (20%). Thirteen mutations had been previously described in association with either DCM (LMNA: R190W, S573L; MYH7: I201T; TNNT2: R131W), HCM (MYH7: G716R; MyBPC3: IVS23+1G>A, A833T, V771M and A627V) or both (MYH7: I736T, R787H, T1019N and MYH6: A1004S). Five mutations had not been previously described (LMNA:S22X, R349L; MyBPC3: P873L, E838Q and MYH7: A1128T). We found two double and one compound heterozygote. Additionally, in two families with sporadic presentation of the disease in whom a known pathogenic mutation was found, excessive alcohol consumption appeared to be a predisposing factor to develop a more severe phenotype.

Conclusion: The probability to identify a causal mutation was significantly higher in patients with familial vs. non-familial idiopathic DCM, thus a complete familial evaluation would be the first step and one of the conditions that could help to improve the mutation screening efficiency in DCM.

P1697 Cardiac dysfunction in the course of nucleopathies

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Background: Nucleopathy is a rarely occurring genetic disease with mutations in nuclear proteins: lamin A/C and emerin. Phenotypic presentation is cardiomiopathy with concominant musculoskeletal abnormalities with a high risk of sudden cardiac death. The aim of the study was an analysis of clinical presentation, left ventricular function and the risk of sudden cardiac death.
Methods: We prospectively observed 34 patients with genetically confirmed nucleopathy (24pts with an X-linked inheritance [defect in the STA gene, emerinopathy] and 10pts with an autosomal dominant form [defect in LMNA, laminopathy] for mean time of 6,1 years. Echocardiography, ECG, tissue doppler, and natriuretic peptides levels were measured in all patients as well as in 25 healthy volunteers matched in terms of age, sex, and body mass.
Results: The mean age of first disease presentation was 27,1±11,6. 76% presented mostly benign peripheral muscle involvement. The mean LV ejection fraction (EF) was 54,0±10,3% and 65,5±2,6 for nucleopathic pts and for controls respectively ($p<0,001$). Significantly higher E/E' (9,4±5,4 vs. 6,0±0,8; p=0,01) in comparison to the controls were documented. NT-proBNP levels were significantly higher in this group in comparison to the controls (159±227 vs. 41,1±31,5; p=0,002). During observation 26% of pts presented HF symptoms, 15% had ventricular arrhythmias, 44% atrial fibrillation/flutter. 62% had a pacemaker (6% ICD) implanted because of advanced AV conduction defects, 15% suffered stroke and 9% sudden cardiac death.
Conclusions: Conduction defects requiring pacemaker implantation and supraventricular arrhythmias are frequently present in nucleopathic pts and usually precede the occurrence of systolic dysfunction. Left ventricular systolic dysfunction (24%) as well as diastolic dysfunction (41%) are common in nucleopathic pts and may be responsible for a high risk of sudden death.

P1698 High exercise-induced platelet reactivity in patients with Anderson-Fabry disease

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Purpose: Cerebrovascular events represent a major causeof disability in young patients with Anderson-Fabry disease (AFD). However the pathogenesis of cerebrovascular accidents in these patients is not fully understood and prevention, besides enzyme replacement therapy (ERT), is empirically based on antiplatelet drugs. We evaluated platelet function in patients with AFD without evidence of coronary or carotid atherosclerosis.
Methods: Fifteen patients with genetically confirmed AFD (mean age 42, 6 F) underwent treadmill exercise stress test (EST). Platelet reactivity was assessed by flow cytometry at baseline and at peak EST, with and without ADP stimulation, by measuring monocyte–platelet aggregate (MPA) formation (expressed as percentage of monocyte binding platelets) and CD41 platelet expression (assessed as mean fluorescence intensity). All patients underwent carotid ultrasound and coronary angiography to rule out carotid or coronary artery disease. Patients on ERT were submitted to EST the day before drug infusion. Thirty healthy sex- and age-matched subjects were studied as controls.
Results: Coronary angiography and carotid ultrasoundshowed no evidence of atherosclerosis in all AFD patients; EST showed signs of ischemia in 3 patients with AFD cardiomyopathy. Thirteen patients were on ERT at the time of the study. Compared to resting values, MPA and CD41 expression,with and without ADP stimulation, significantly increased after exercise in the AFD group but not in controls. Exercise-induced values of MPA (20.1 vs 18.7, p=0.001 – with ADP:25.2 vs 22.0, $p<0.0001$) and CD41 expression (20.3 vs 19.4 p=0.006 – with ADP:26.1 vs 21.9, $p<0.0001$) were higher in AFD patients than in controls, while resting values did not significantly differ.
Conclusions: High exercise-induced platelet reactivity has been reported in patients at high risk for thrombotic events, like those with coronary or peripheral atherosclerosis. In this study we found high exercise-induced platelet reactivity in patients with AFD, suggesting that enhanced platelet reactivity may contribute to the pathogenesis of cerebrovascular events in these patients. Our data support the inclusion of antiplatelet drugs in conventional therapy for AFD. The effect of ERT on platelet function remains to be clarified.

P1699 Arrhythmogenic right ventricular cardiomyopathy caused by mutations in the lamin A/C gene

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Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart muscle disease caused by mutations in desmosomal protein genes. Lamin A/C gene (LMNA) mutations are associated with dilated cardiomyopathy, conduction abnormalities and high incidence of sudden cardiac death. In this study we report for the first time a phenotype resembling ARVC caused by mutations in LMNA.
Methods and results: Forty-seven consecutive patients with borderline or definite diagnosis of ARVC without desmosomal gene mutations were tested for LMNA mutations. Four patients were found to carry a Lamin A/C gene variant. Three patients had severe RV involvement, two died suddenly and one from congestive heart failure; all three had conduction abnormalities on resting ECG. Myocardial tissue from two patients showed myocyte loss and fibro-fatty replacement (Figure 1a). In one of these, immunohistochemical staining with antibody to plakoglobin was performed and showed reduced/absent staining of the intercalated discs in the myocardium (Figure 1b).

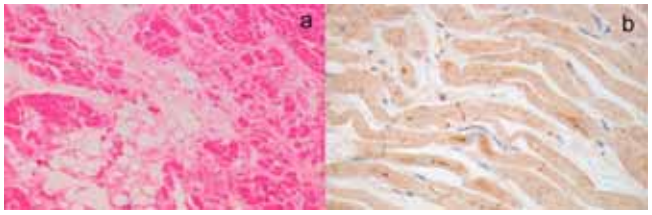

Figure 1

Conclusions: Mutations in the LMNA gene can cause ARVC. The poor outcome in three of the four LMNA mutation carriers suggests that this form of ARVC should be managed with early consideration of ICDs and aggressive anti-failure medication.

P1700 Comprehensive assessment of long term enzyme replacement therapy on fabry disease - the 5 year data

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Background: Fabry disease, an X-chromosomal lysosomal storage disease, mainly involves the heart, kidney and the neurological system. Since 2001 a specific therapy, enzyme replacement therapy (ERT), is available. However, long term ERT effects on all these main organs remain unknown.
Methods: We followed 20 ERT-treated Fabry patients over 5 years at yearly intervals. Comprehensive clinical, cardiac, renal and neurological assessment was performed. Cardiac evaluation included standard echocardiography with strain-rate-imaging and magnetic-resonance-tomography guided late-enhancement-imaging (for replacement fibrosis). Renal function was determined by DTPA-clearance [glomerular filtration rate (GFR)] and measurement of proteinuria. Moreover, major neurological events of the central and symptoms of the peripheral nervous system were assessed.
Results: Left ventricular wall thickness was reduced over 5 years compared to baseline (13.3±1.7mm vs. 11.4±2.2mm; $p<0.0001$). However, the development of fibrosis could not be prevented by ERT in 5 patients with initial left-ventricular hypertrophy and without myocardial fibrosis. Major kidney involvement at baseline, e.g. proteinuria>1g/day and GFR< 60ml/min, were independent risk factors for progression of kidney dysfunction, while 5 out of 6 patients with no proteinuria at baseline showed a non significant improvement of GFR (80±21 ml/min vs. 86±18 ml/min, p=0.15). New neurological major events were seen in 3 patients showing severe cardiac involvement, one event being thromboembolic. In contrast, there was a trend for a reduction of neuropathic pain during 5 years follow-up especially in midly effected Fabry patients.
Conclusions: These 5 year data suggest that ERT can stabilize and improve organ function in Fabry patients in early disease stages. However, the long term outcome of Fabry patients already severely affected at therapy initiation seems to be not altered by ERT.

CARDIOMYOPATHIES, OTHER

P1701 Impact of the new 2010 task force criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomayopathy

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Introduction: The International Task Force for diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD) has recently modified the diagnostic criteria formerly established in 1994 (TFC 1994) by a new ones (TF 2010), aimed to obtain a better sensitivity in the diagnosis, especially in incipient phases of the disease and in first-degree relatives.
Methods: We have analyzed the new TFC 2010 in 47 patients (66% male, 55±15 years) and comparing them with the previous TFC 1994. Both TFC included imaging techniques (mainly echocardiography and RV angiography), histology, ECG, presence and type of ventricular arrhythmias and family history. In the new TFC we included also magnetic resonance. In the TFC 2010, diagnosis is divided in: 1) Definite (2 major or 1 major plus 2 minor criteria or 4 minor criteria); 2) Borderline (1 major and 1 minor or 3 minor criteria); 3) Possible (1 major or 2 minor criteria).
Results: In the imaging techniques, 15 patients (32%) fulfilled major criteria and 32 (68%) minor criteria in both TFC. In ECG, with the TFC 1994, 47% of the patients had major criteria and 47% minor criteria. With the TFC 2010, 60% had major criteria and 97% minor criteria ($p<0.05$). In ventricular arrhythmias, with the TFC 1994, 96% of the patients had minor criteria and with the TF 2010, 98% of them had major criteria. In family history, there were no differences between TFC (both of them consider it as a major criteria) and was present in 15% of the patients. With the TFC 1994, 31 patients (66%) had a definite diagnosis for the disease and 16% (34%) were considered borderline. With the TFC 2010, 40 patients (85%) had a definite diagnosis and 7 (15%) were considered borderline ($p<0.05$). Of the 31 patients with a definite diagnosis with the TFC 1994, all except one were considered again definite with the TFC 2010, but of the 16 patients considered borderline with the TFC 1994, 6 of them remained borderline and 10 were diagnosed as definite carriers of the disease.
Conclusions: The new TF 2010 confers a greater sensitivity in the diagnosis of ARVD, without lack of specificity, especially when ECG and ventricular arrhythmias criteria are considered. There are no significant differences in imaging techniques and family history. Those new criteria will have a significant impact in the diagnosis of the disease, especially in minor or incipient forms of ARVD

P1702 Clinical significance of giant negative T-waves in patients with tako-tsubo cardiomyopathy

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Purpose: Tako-tsubo cardiomyopathy (TTC) mimics acute myocardial infarction. Electrocardiographic changes include ST-segment elevation during the acute phase and widespread T-wave inversion during follow-up. Some patients develop giant negative T waves ≥ 1 mV resembling those in apical hypertrophic cardiomyopathy (AHCM). This study assessed the requency and clinical significance of giant negative T waves in patients with TTC.
Methods: Over a 9-year period, we observed 76 TTC patients (69 f, 7m; 70±12 years). By angiography, 45 patients (59%) had apical ballooning (AB) and 31 (41%) mid-ventricular ballooning (MB) of the left ventricle. ECG on admission, at the time of maximal T-wave inversion, before discharge and the daily QTc-interval were compared.
Results: Giant negative T waves ≥1 mV were seen in 16/76 patients (21%). All were documented in the precordial leads V2 (n=3), V3 (n=9), V4 (n=10), V5 (n=4) and V6 (n=1). Patient with giant negative T waves were older (75±11 vs 69±12 years, p=0.05) and they had significantly more frequent the apical ballooning variant (88% vs 12%, $p<0.01$). Time interval from symptom onset to first ECG (7.8±7.7 vs 8.6±8.9 hours, p=ns), heart rate on admission (96±25 vs 87±21/min, p=ns) and the number of leads with ST-segment elevation on the admission ECG (4.3±1.6 vs 3.8±2.4 leads, p=ns) were not different in patients with and without development of giant negative T waves. Cardiac markers CK and troponin, left ventricular ejection fraction and left ventricular end-diastolic pressure were comparable in both groups, and complications during the acute stage occurred with similar frequency (69% vs 43%, p=ns).
The maximal QTc interval was significantly longer in patients with giant negative T waves during follow-up (606±70 vs 559±71 msec, $p<0.02$), however, the occurrence of ventricular arrhythmias and atrial fibrillation was not different. Time to ECG normalization was similar (59±21 vs 68±82 days, p=ns).
As assessed by echocardiography, 15/16 patients with giant negative T waves developed wall thickening in the apical area within 2 weeks of presentation with a ratio of apical to posterobasal wall >1.5:1 which is typical for AHCM. Cardiac MRI performed in 4 of these 15 patients disclosed myocardial oedema in the apical area. Time to complete normalisation of LV function was significantly longer in patients with giant negative T waves (32±24 vs 20±15 days, $p<0.02$).
Conclusion: Giant negative T waves ≥1 mV in the precordial leads resembling those in AHCM develop in 21% of patients with TTC and are associated with apical wall thickening due to myocardial oedema.

P1703 Prolonged mobilization of endothelial progenitor cells post takotsubo cardiomyopathy

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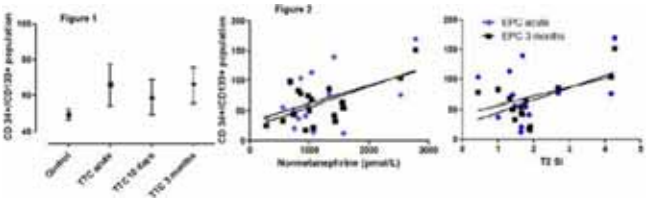
Tako-Tsubo cardiomyopathy (TTC) is characterized by the presence of transient segmental, usually peri-apical, systolic left ventricular dysfunction. It has been suggested that hypersecretion of catecholamines plays in the initiation of TTC and it is associated with a marked release of BNP/NT-proBNP. Both of these factors could precipitate release of circulating endothelial progenitor cells (EPC). Therefore, the objectives of the study were:
(1) To test the hypothesis that the EPC count is normal acutely and during recovery post TTC.
(2) To evaluate the relationship between possible precipitators and the mobilization of EPC.
Methods: EPC counts were performed utilizing flow cytometric analysis in 20 TTC patients [age 68±9 (SD)] at diagnosis, after 10 days and 3 months, and in 55 age-matched female controls (age 68±6). Correlations with extent of hypokinesis [measured by wall motion score index (WMSI) on cardiovascular magnetic resonance], catecholamine release, NT-proBNP release, high sensitive C-reactive protein and myocardial oedema utilizing T2-weighted signal (T2 SI)] on CMR were examined.
Results: At baseline, EPC counts were elevated approximately 35% above control values (mean 65±41 vs. 50±23; p=0.04) and remained significantly elevated after 3 months (67±38; p=0.02 vs. control) (Figure 1). While there was no correlations between EPC counts and either hs CRP or WMSI, there were direct correlations with initial plasma normetanephrine, extent of oedema (r = 0.63, p=0.003; r = 0.61, p=0.01, respectively) (Figure 2) and peak NT-proBNP levels (r = 0.46, p=0.04).



Conclusion: TTC is associated with prolonged and extensive EPC mobilization. In particular, EPC mobilization reflects severity of initial catecholamine release and induction of intramyocardial inflammation.

P1704 RNA interference targeting the matricellular protein CTGF (CCN2) modulate multiple interrelated pro-inflammatory and pro-fibrotic pathways in cardiofibroblasts

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Background: Pathogenic fibrotic processes are important components of multiple diseases including cardiomyopathies. Current drug-based antifibrotic strategies show low efficacy. We therefore investigated an alternative, RNA interference (RNAi)-based approach to silence the gene CTGF which plays a crucial role in the development of cardiac fibrosis.
Methods and results: Prescreening of short hairpin RNA (shRNA) sequences targeting CTGF, using cotransfection experiments in 293 cells, identified two efficient sequences w/o recognizable toxic or off-target effects. One sequence was cloned into an adenoviral vector AdV-shCTGF for in vitro work in primary cardiac fibroblasts (PCBFs). Treatment of resting and mechanically stressed PCFBs with AdV-shCTGF resulted in silencing of the CTGF gene to 42% (resting conditions) and 17% (mechanical stress), respectively, of baseline.
Mechanical stress induced several genes in PCFBs: matrix metalloproteinase 2 (MMP2) 22.3-fold, connexi43 (Cx43) 6-fold, collagen3α1 (Col3a1) 2.9-fold, CCL2

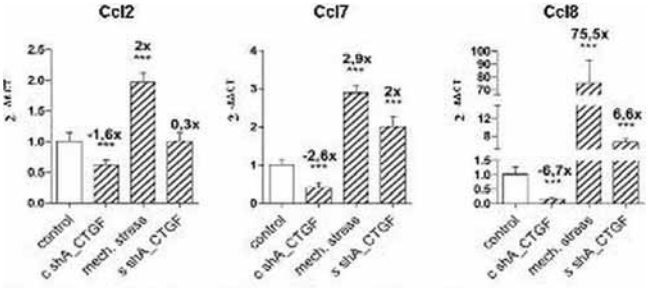

Fig. 1: Expression level changes of inflammation-associated genes during mechanical stress (induction) and AdV-shCTGF treatment (reduction).

(MCP1) 2-fold, CCL7 (MCP3) 2.9-fold and CCL8 (MCP2) 75.5-fold. AdV-shCTGF treatment led to significant reduction of these genes (Fig. 1) in both resting and stressed PCBFs, most markedly for chemokines.
Conclusion: RNAi achieves efficient silencing of CTGF and several pro-inflammatory and pro-fibrotic genes in stressed PCBFs and offers a new therapeutic approach to attenuating cardiac inflammatory and fibrotic processes by changes in the PCBF gene expression pattern.

P1705 Diverse morphologic spectrum of stress-induced cardiomyopathy and its clinical presentation

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Background: Stress-induced cardiomyopathy (SCMP) is regarded as an acute reversible cardiomyopathy that mimic acute coronary syndrome. Traditionally, it is characterized by transient regional wall motion abnormalities of the left ventricular (LV) mid and apical segment demonstrating apical ballooning feature. Recently, several case reports suggested that SCMP reveal various morphologic features of LV, which differ from previous reports. Therefore, the purpose of this study was to investigate the morphologic features of LV in SCMP patients, and differentiate their clinical presentations.
Methods: This was a multi-center, retrospective study. We enrolled 228 patients diagnosed as SCMP according to "Proposed Mayo Clinic criteria". Morphologic features of LV was determined by echocardiography and categorized as 1) apical ballooning type, 2) mid LV ballooning type, 3) reverse type, 4) apical tip sparing type, 5) global hypokinesia type, and 6) regional wall motional abnormality (RWMA) type.
Results: Among the 228 patients, apical ballooning type showed preponderance (58.7%) of SCMP followed by mid LV ballooning (30.7%), apical tip sparing type (4.4%), reverse (2.6%), global (1.8%) and RWMA (1.8%), respectively. SCMP patients with apical ballooning type were older (p=0.022) and hypertensive (p=0.023). There was a trend that initial CK was highest at apical ballooning type (890±6259 mg/dl) and RV involvement was frequent at mid LV ballooning type (Table 1).

Table 1. Comparison of clinical characteristics and presentations among SCMP patients with diverse LV morphologic features

	Apical ballooning (n=134)	Mid LV ballooning (n=70)	Reverse (n=6)	Apical tip sparing (n=10)	Global (n=4)	RWMA (n=4)	p-value
Age (yrs)	68±13	61±14	63±5	65±14	62±19	66±17	0.022
Gender (M:F)	1:2.4	1:2.5	1:1	1:4	1:1	0:4	0.525
Diabetes	31%	21%	17%	20%	0%	50%	0.400
Hypertension	61%	39%	33%	40%	25%	75%	0.023
Initial CK (mg/dl)	890±6259	187±202	437±398	126±61	143±129	82±50	0.969
Initial LVEF	41±12%	43±13%	33±9%	35±12%	31±18%	53±8%	0.019
RV involvement	1.7%	13.6%	0%	25%	0%	0%	0.105

Conclusions: Diverse morphologic spectrum of LV was observed in SCMP patients. Therefore, it is necessary that we should pay more attention when undergoing differential diagnosis of patients with acute coronary syndrome.

P1706 Stress-induced cardiomyopathy (tako-tsubo syndrome) in Austria: a retrospective analysis

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Background: Tako-Tsubo Syndrome (TS) is a still infrequently diagnosed clinical syndrome characterized by transient cardiac dysfunction with (usually) reversible wall motion abnormalities (WMA).
Aim: To investigate the type of TS, the causative triggers, underlying risk factors, as well as clinical complications in the short and long-term follow-up of TS patients (pts), we performed a multicenter retrospective analysis.
Methods: Type of TS, causative triggers, clinical characteristics as well as outcome of 179 consecutive pts with proven diagnosis of TS were analysed retrospectively.
Results: Of the 179 pts, 168 (94%) were women and 11 (6%) were men. Mean age was 69.2±11.5 years (range 35 to 88 years). Cardinal symptoms of TS were acute chest pain (82%) and dyspnea (32%). All pts demonstrated typical WMA, of which 3 different types could be defined: 1) the more common apical form of TS (n = 71; 40%); 2) a combined apical and mid-ventricular form of TS (n = 30; 17%) and 3) a less frequent pattern of an isolated midventricular TS (n = 8; 5%), respectively. In retrospect, only in 101 pts (57%) a causative trigger for onset of symptoms could be identified: physical stress was present in 52 pts (51%), emotional stress in 41 pts (41%) and a combined emotional/physical trigger in 8 pts (8%). During hospital stay cardiovascular complications were found in 22 pts (12%): These consisted of cardiac arrhythmias in 10 pts (46%), cardiogenic shock in 6 pts (27%) and cardiac decompensation in 8 pts (36%), respectively. Control of left ventricular function was available in 124 pts (69.3%), whereby 46 pts (25.7%) underwent a control echocardiography prior to discharge, within 7.2±4.8 days and 78 pts (43.6%) had an examination of regional WMA at a later occasion, after 186.4±316.7 days. Control echocardiography showed complete recovery of WMA in 75 pts (60.5%) and persistent WMA in 49 pts (39.5%). Recurrences of TS events were only seen in 4 pts.
Conclusions: This study represents to date one of the largest series of pts suffering from TS. As confirmed by our study the prevalence of TS in women was significantly higher than in men and the apical type of TS was detected most frequently. The clinical presentation was similar to the clinical picture of acute myocardial infarction (AMI) and TS could only be differentiated from AMI by coronary angiography demonstrating no or non-significant plaque formations in epicardial coronary arteries. Emotional and physical triggers were involved in about half the pts each. In contrast to international reports, only 60% of TS pts showed a complete recovery of the initial WMA.

P1707 Interleukin-1 receptor antagonist ameliorates radiation-induced cardiomyopathy in the mouse

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Purpose: Mediastinal irradiations in cancer treatment are associated with development of cardiomyopathy. Radiation induced enhancement of interleukin-1 (IL-1) activity in the heart and lungs has been reported. We proposed a mouse model of thoracic irradiation to study radiation-induced cardiomyopathy progression and the role of IL-1 in its development.
Methods: C57BL/6J mice (N=10) received a dose (20 Gray) of thoracic irradiation equivalent to a therapeutic cycle for breast cancer treatment. Sham irradiated mice were used as controls. Left ventricular (LV) ejection fraction (EF) and fractional shortening (FS) were evaluated by echocardiography at days 3, 5, and 14 and at 1, 4 and 6 months. The beta-adrenergic receptor agonist isoproterenol (10 ng/mouse) was used to measure the contractile reserve (LVEF change) at 3 days, 4 and 6 months. Histochemistry was performed to evaluate myocardial fibrosis. Caspase-1/IL-1-converting-enzyme activation and IL-1beta (IL-1b) mRNA levels were assessed by western blot and real time PCR, respectively. Both sham and irradiated mice (10/group), treated with recombinant human IL-1 receptor antagonist (anakinra, 10 mg/kg), were analyzed at day 3 to assess changes in contractile reserve and to evaluate IL-1 activity.
Results: Between 4 and 6 months, 50% of all the irradiated mice died (vs 0% non-irradiated, P=0.02) while the LVFS was reduced significantly (28±1%; $p<0.01$ vs baseline [36±1%] and vs sham [34±1%]). Analysis of fibrosis revealed a doubling of interstitial collagen deposition (0.8% controls vs 1.62% irradiated; $p<0.05$). Irradiated mice had decreased contractile reserve 3 days after radiation (+9±3% LVEF increase vs +37±4% sham; $P<0.05$) and increased activation of caspase-1 (p=0.03). Anakinra treatment prevented the decline in contractile reserve (+37±4% increase, p=0.01 vs saline-irradiated mice), and reduces IL-1b mRNA levels.
Conclusions: Radiation-induce cardiomyopathy in the mouse is associated with reduced LVFS after 6 months, decreased contractile reserve and activation of caspase-1. Anakinra treatment preserves contractile reserve and reduces IL-1beta production after radiation injury.

P1708 Heart T2* for prediction of cardiac complications in well-treated thalassemia major patients

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Purpose: T2* Magnetic Resonance Imaging (MRI) technique allows noninvasive quantification of organ-specific iron burden, playing a key role in the management of thalassemia major (TM) patients. There are few data on the incidence of heart failure and arrhythmias in TM patients according to baseline T2* values. So, the aim of this study was to establish prospectively the risk of cardiac complications in a large cohort of well-treated TM patients.
Methods: We considered 527 TM patients (252 males, mean age 30±9) for who clinical data relative to a period of 5 years after the first MRI were collected in a central data base. At time of the first scan mean ferritin levels were1653±1559

ng/l, global heart was 27±13 ms, and excellent/good level of compliance were present in the 96% of the study population.
Results: At 5 years of follow-up, we recorded 24 cardiac events: 4 episodes of cardiac failure, 15 of arrhythmia, 1 of pulmonary hypertension and 4 of other cardiac complications. The majority of these events (21/24) happened within the first 24 months subsequent to the MRI, so we considered this follow-up period.
At the first MRI scan, in patients with cardiac complications the global heart T2* was 22.5±12.4 ms. In comparison with global heart T2* values ≥20 ms, there was not a significantly increased risk of cardiac complications associated with global heart T2* values <20 ms (HR= 2.028 P=0.09).
In the heart failure patients the global heart T2* was 19±12 ms. In comparison with global heart T2* values ≥20 ms, there was not a significantly increased risk of heart failure associated with global heart T2* values <20 ms (HR=1.9 P=0.524) or <10 ms (HR=2.6 P=0.443).
In the arrhythmic patients the global heart T2* was 25±13 ms. In comparison with global heart T2* values ≥20 ms, there was not a significantly increased risk of arrhythmia associated with global heart T2* values <20 ms (HR=2.1 P=0.179) or <10 ms (HR=0.8 P=0.824). During the follow up changes in the chelation therapy (type and/or dose-frequencies) were found in >25% of the study population.
Conclusion: We detected very few cardiac events, almost all concentrated in the first 24 months. In a large cohort of well-treated TM patients heart T2* lost its power in predicting cardiac events probably due to a patient-specific adjustment of the chelation therapy MRI-guided.

P1709 A new animal model of takotsubo cardiomyopathy by pilocarpine-induced epilepsy in rodents

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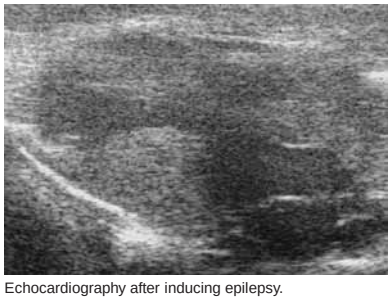
Background: Takotsubo cardiomyopathy is a relatively novel syndrome in cardiology, which was first reported in 1990. It occurs predominantly in the post menopausal women soon after exposure to the emotional or physical stress. Although twenty years have passed from the first case report, little is known about its pathogenesis. The aim of this study was to develop a new animal model that mimics the clinical manifestation.
Methods and results: 1) Epilepsy is reported to be one of the risk factors of Takotsubo cardiomyopathy. We induced epilepsy in Wistar rats by injecting pilocalpine, an agonist of muscarinic receptors. 2) After inducing epilepsy, we examined the rat heart by electrocardiogram and echocardiography (Vevo770, Visual sonics, Canada). Interestingly, electrocardiogram revealed typical ST elevation in the limb leads. EKV mode-echocardiography (Probe: RMV716) clearly demonstrated that wall motion of the left ventricular apical segment was akinetic or dyskinetic. These changes occurred in 10% (n=10) after 30 minutes, in 30% (n=10) after one hour and in 67% (n=12) after two hours from epilepsy induction. 3) The day after epilepsy, however, the wall motion of the left ventricular apical segment was completely recovered. 4) These changes were observed also in mice after inducing epilepsy. 5) Coronary angiography revealed that there was no significant stenosis in the coronary artery of Wister rats after inducing epilepsy. 6) Furthermore, the serum levels of adrenaline, noradrenaline and dopamine were about three times higher two hours after epilepsy induction.



Echocardiography after inducing epilepsy.

Conclusions: We developed a new animal model of Takotsubo cardiomyopathy that mimics the clinical manifestations in humans. This animal model might be a powerful tool to investigate the mechanisms of this disease.

P1710 Cardiac involvement in systemic sclerosis: the added value of magnetic resonance imaging

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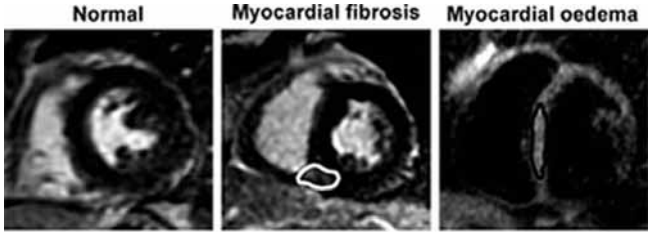
Purpose: Cardiac involvement in systemic sclerosis (SSc) has high prognostic relevance. The pathological hallmark is myocardial fibrosis that has been reported in >50% of cases in necropsy. Echocardiography is the routine imaging tool to detect cardiac involvement, but it is not accurate for myocardial fibrosis. Cardiovascular magnetic resonance (CMR) might be proposed to assess myocardial fibrosis (by delayed gadolinium enhancement, DE_CMR) and myocardial oedema (by T2-weighted images, T2_CMR). Our aim was to evaluate the added value of CMR to echocardiography in SSc patients.
Methods: After a thorough clinical characterization, 53 SSc pts (age=52±14, 95% females, 34% diffuse form) underwent on the same day a comprehensive ecocolorDoppler, including tissue Doppler imaging (TDI), and CMR.
Results: Echocardiography showed normal systolic function (ejection fraction=64±6%) and wall motion score index (=1) in 100% pts, whereas DE_CMR showed a pattern of non-ischaemic myocardial fibrosis in 12/53 (23%) pts. In 2/53 (4%) pts, T2_CMR showed myocardial oedema, that resolved after steroid therapy. Among clinical (age, duration of disease, skin and activity scores), echocardiographic (indexed left atrium and left ventricular volumes, right atrium and ventricular dimensions, 2D and TDI parameters of left and right ventricular function, and pulmonary arterial systolic pressure) and CMR parameters, only TDI mitral annulus E/E' was an independent predictor of myocardial fibrosis at multivariate analysis (HR 1.8; 95% C.I. 1.1-3.1).



Conclusions: Subclinical cardiac involvement is relatively frequent in SSc. CMR can detect different patterns of reversible (by T2-weighted images) and irreversible (by DE) cardiac involvement. Elevated E/E' at echocardiography may raise the suspicion of myocardial fibrosis.

P1711 Takotsubo cardiomyopathy with critical coronary stenosis: clinical characteristics and comparison with typical takotsubo without coronary stenosis

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Aim: Diagnostic criteria for takotsubo cardiomyopathy (TTC) include typical reversible wall motion abnormalities (WMA) in the absence of critical (>50%) coronary disease (CAD) or previous myocardial infarction (MI); however, reversible apical (A) or midventricular (MV) WMA typical of TTC can be observed in pts with acute ischemic syndrome and critical CAD. The aim of the study was to assess the prevalence, clinical characteristics and short-term prognosis of pts with TTC-like syndrome associated with critical CAD and to compare these pts with those with typical TTC with no CAD.
Method and results: We studied 101 pts (aged 68±11 yrs, 97% women) admitted with an acute coronary syndrome who showed a reversible pattern of TTC (68% with an apical (A) and 32% with a midventricular (MV) ballooning); 12/101 pts (11.8%) had >50% stenosis of ≥ 1 coronary vessel or a previous MI; 10/12 (83%) had A TTC and 2 (17%) MV TTC. Comparison of pts with critical CAD with those with no CAD showed no significant difference in age, sex, prevalence of hypertension (66% vs 57%), family history of CAD (17 vs 35%), dyslipidemia (58 vs 39%), presence of a trigger event (58% vs 52%), peak troponin I (3.1±3.7 vs 2.2±3.1 ng/ml), prevalence of ST-elevation (66% vs 47%) or negative T waves (34 vs 54%) at admission and acute ejection fraction (46±19 vs 54±9%).During the acute phase LV failure or shock occurred in 2/12 (17%) pts with CAD vs 8/89 (9%) in those without CAD; 1/12 (8.3%) pts with CAD died in the acute phase vs 3/89 (3.3%) pts without CAD. Of the 12 pts with TTC and critical CAD, 9 had 1 vessel CAD, 1 two vessel CAD, 1 a previous inferior MI and 1 a previous PTCA with no residual stenosis. In 10/12 pts (83%) there was no relation between the site of critical CAD and that of reversible WMA.
Conclusions: 1) A sizable minority of pts with TTC shows critical CAD; 2) In most of these pts the site of reversible WMA is unrelated to that of critical CAD, suggesting that the stenosis is an innocent bystander; 3)Pts with TTC with critical CAD have a higher incidence of LV failure and a higher acute mortality; 4) Pts with TTC and with critical CAD may represent an extreme of the large spectrum of TTC.

P1712 Altered cytoskeletal protein localization in cardiomyocytes of cardiomyopathy patients

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Introduction: Some forms of idiopathic cardiomyopathy (CMP) are associated with mutations in genes encoding cytoskeletal proteins affecting their expression and leading to impairment of the cardiomyocyte function. Desmin is a component of the sarcomeres and intercalated disks. Vinculin localizes to sarcolemma, costameres and intercalated disks, and participate in signal transduction during myocardium contraction. Changes in the desmin and vinculin expression and localization may be linked to some forms of CMP. The goal of this work was to study localization of vinculin and desmin in cardiomyocytes from patients with various forms of cardiomyopathy, and from patients at different time after heart transplantation.
Methods: Tissue samples were obtained from 34 patients with dilated CMP -24 patients, ischaemic CMP -10 patients. We examined 29 diagnostic endomyocardial biopsies from patients from 6 days to 11 years after allotransplantation. Cryostat sections were prepared for immunofluorescent analysis. We used antibodies to cytoskeletal proteins: anti-vinculin, anti-desmin and secondary antibodies against mouse immunoglobulins.
Results: Examination of endomyocardial biopsies even from patients with acute rejection revealed normal cytoskeletal protein localization. In dilated CMP patients, a dramatic decrease was found in desmin expression in intercalated disks: in 22 out of 24 patients desmin reactivity was totally missing, whereas in two cases desmin was detected only in a few intercalated disks. Desmin expression in contractile disks remained unchanged. Vinculin expression in this group of patients was also altered: in 20 out of 24 cases, we found enlarged costameres and their expansion into the sarcoplasm, which may compromise the contractility of the cardiomyocytes. In two of ten ischaemic CMP patients, we found a decreased desmin expression in contractile disks, whereas in one case, an elevated vinculin imunoreactivity was observed in hypertrophied costameres.
Conclusions: The cytoskeletal protein localization in cardiomyocytes of the allotransplants is preserved even during acute rejection. Desmin appears to be a rather unsteady cytoskeletal protein in the myocardium, as it is missing from intercalated disks of the dilated CMP patients. Such changes may reflect mutations of the desmin gene and/or genes that specify its subcellular localization. The deficit of one of the cytoskeletal proteins involved in intercellular communications may lead to functional insufficiency of the myocardium. The data obtained might be used for generating a novel approach for diagnosing the dilated CMP.

P1713 Clinical characteristics and outcome of patients with left ventricular aneurysms and diverticula presenting with arrhythmic manifestations: experience of a tertiary care center

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Introduction: Congenital left ventricular aneurysms and diverticula (LVA/D) are rare cardiac malformations, which can be detected during childhood or later using echocardiography or other imaging techniques. Some of these patients present with ventricular arrhythmias. This study investigates the clinical characteristics and outcome of patients with LVA/D presenting with arrhythmic manifestations.
Methods and results: Since 1990, 244 patients were diagnosed to have a congenital LVA/D. The diagnosis was made using echocardiography after exclusion of coronary artery disease, local cardiac inflammatory process, traumatic causes or cardiomyopathies. 30 patients (44±21 years, 20 male) had arrhythmic manifestations at initial presentation. In five patients more than one LVA/D was found. Two simultaneous lesions were present in four patients and three in one patient. There was posterobasal, apical, anteroseptal and anterolateral involvement in 12, 11, 4 and 4 patients, respectively. The most common complaints were syncope in 14 patients and palpitations in 12 patients. One patient presented with survived sudden cardiac death. During cardiac investigations, ventricular tachycardia (VT) or ventricular fibrillation (VF) could be documented in 14 patients (of them 3 non-sustained VT). Nine patients were treated with an ICD and three patients underwent ablation for VT. Three patients died 10, 41 and 89 months after initial presentation.
Conclusion: Patients with congenital left ventricular aneurysms and diverticula may rarely present with arrhythmic manifestations. In these patients, posterobasal or apical involvement is most commonly observed. These patients commonly have documented VT/VF during cardiac screening and one third of the overall cohort had hemodynamically significant VT/VF requiring ICD therapy.

P1714 Prospective assessment of incidence of tako-tsubo cardiomyopathy

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Background: Tako-Tsubo cardiomyopathy (TTC) has been recently described. Most of studies are retrospective and incidence of TTC in a global population is still uncertain. The aim of this study was to prospectively assess TTC incidence.
Methods: We performed a multicentric prospective study. All consecutive patients referred for coronary angiography were included in three catheterization laboratories. The institutional review board approved the study protocol, and each patient provided written informed consent. Patients were classified as having (or not) coronary artery stenosis defined as a lesion of at least 50% diameter narrowing. In all patients without significant coronary artery stenosis, a right and left anterior oblique left ventricular angiogram was systematically performed. All these left ventricular angiograms were anonymously randomized and were systematically reviewed by three experts. Finally, we used the CARDIO-ARIF (Agence Régionale d'Hospitalisation d'Ile-de-France) registry, for the assessment of TTC incidence in Ile-de-France.
Results: Among 2973 patients including 888 acute coronary syndromes, 20 patients presented with TTC (19 women, mean age: 63 years [55-73]). Incidence of TTC was 2.3% of acute coronary syndrome (7.4% in women versus 0.2% in men, $p<0.0001$). In the CARDIO-ARHIF registry, 51,403 coronary angiographies were performed. Each year, in this region, the number of TTC is estimated at 344 cases (95% confidence interval = 216-514). The annual incidence of TTC is estimated at 29.7 per 1,000,000 inhabitants (95% confidence interval = 18.7-44.4), at 54.9 per 1,000,000 inhabitants (95% confidence interval = 30.4-79.1) among women and at 215.5 per 1,000,000 inhabitants (95% confidence interval = 104-327.4) among women $\geq$ 60 years.
Conclusion: Incidence of TTC is at 29.7 per 1,000,000 inhabitants in a large urban agglomeration and increased to 215.7 per 1,000,000 inhabitants in women $\geq$ 60 years. This recent cardiomyopathy could be until now underestimated and affects particularly women $\geq$ 60 years, representing a growing patient population.

P1715 Beta2-adrenoceptor coupling to Gi protein: a key role in cardiac contractility impairment at early stage of doxorubicin-induced cardiomyopathy

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Purpose: Doxorubicin (Dox) is an antitumor agent but its clinical use is limited by its cardiotoxicity leading to a dilated cardiomyopathy (DCM). At end stages of DCM, β-adrenergic system is altered but there is only few data about Dox-induced cardiomyopathy (Dox-CM). Our aim was to evaluate the expression and function of each cardiac β-adrenoceptor (β-AR) subtypes, β1, β2 and β3, during Dox-CM.
Methods: Dox-CM rats were induced by Dox injections (total dose: 15 mg/kg) and validated by echocardiography. β-AR protein expression in left ventricle (LV) was evaluated by western blot and the ex vivo cardiac contractility (dP/dtmax, dP/dtmin) was evaluated on isolated perfused heart in response to isoproterenol or to specific β-AR stimulation.
Results: Dox-CM hearts were characterized by mild LV dilation, mild systolic dysfunction and diastolic dysfunction (Table), suggesting an early stage of Dox-CM. In Dox-CM rat, both β-AR expression and function were altered (all results are expressed as Dox-CM versus Control): LV β1-AR protein expression was decreased (-68±6%, p=0.003), β2 increased (+58±22%, p=0.039) and β3 unchanged. Isolated Dox-CM hearts presented a decrease of positive inotropic (-13±6%, p=0.009), but not lusitropic, response to isoproterenol, which can be due, in part, to a mild negative inotropic effect of β3-AR stimulation (-11±5%, $p<0.001$). Surprisingly, the β2-AR stimulation lead to an increase of inotropism and lusitropism (+28±6%, $p<0.001$ and +44±8%, $p<0.001$) which were abolished in the presence of PTX, a specific Gi protein inhibitor.

	Control (n=9-25)	Dox-CM (n=8-22)
Heart rate (bpm)	354±6	343±5
LV end-diastolic diameter (mm/g of LV mass)	12.0±0.3	14.3±0.5 *
LV ejection fraction(%)	85.0±1.0	80.4±1.4 *
LV isovolumic relaxation time (ms)	20.8±1.3	31.1±0.9 *

In vivo parameters obtained by echocardiography. Results are expressed by mean ± sem. LV: left ventricle. *: $p<0.05$ versus Control.

Conclusion: At early stage of Dox-CM, the myocardial function began to be impaired and β-AR expressions and functions were already altered. LV β2-AR protein expression was increased and correlated with an increased β2-AR-induced contractility by activation of Gi protein pathway. These results suggest that β2-AR/Gi pathway could be considered as a new therapeutic target at early stage of Dox-CM.

P1716 Novel speckle tracking motion-based endocardial tracking algorithm provides accurate left ventricular volumes: validation with quantitative cardiac magnetic resonance

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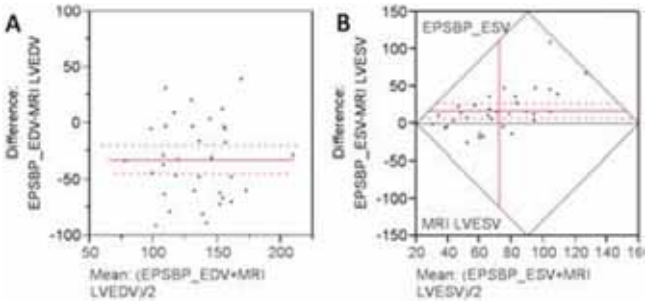
Intro: Estimation of left ventricular (LV) volumes by echocardiography (echo) is fraught with difficulty due to inaccurate tracking of the endocardial border. We used a novel, speckle-based algorithm that uses myocardial motion to track the endocardial border in patients with hypertrophic cardiomyopathy who underwent echocardiography and cardiac magnetic resonance (CMR)
Methods and results: LV volumes were calculated in 34 patients, mean age 47±16 years. CMR volume analysis was performed by a cardiologist with 3 years experience using Qmass version 7.2 software. Echo was performed within 12 hours of CMR. A novel speckle-based semi-automated algorithm (Echo Insight) was implemented on standard B mode echo images to derive volumes. Linear regression showed close correlation between CMR and Echo Insight for end-diastolic volume (r=0.84; p=0.015) and end-systolic volume (r=0.65; p=0.0019). Mean difference for volumes was 32±4 ml.
End-diastolic volume by Echo Insight was 120±42 ml and end systolic volume was 81±34 ml. There was good intra and inter-observer reliability for all measurements.



Conclusions: A novel, speckle-based algorithm for endocardial border accurately tracks LV end-systolic and end-diastolic volumes when compared to CMR. This novel approach may allow rapid and reliable measurement of LV volumes by echocardiography obviating the current practice of manually outlining the endocardial border, which is both subjective and unreliable.
Figure a: Bland-Altman Figure for LVEDV-echo vs LVEDV MRI. Figure B. Bland-Altman Figure for LVESV-echo vs LVESV MRI

P1717 Left ventricular hypertrabeculation in afro-caribbean individuals: an inherited cardiomyopathy or a physiological response to increased cardiac preload

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Introduction: Studies in heart failure patients of Afro-Caribbean (black) origin reveal a high prevalence (up to 30%) of myocardial trabeculations and raise the potential diagnosis of isolated left ventricular non-compaction (ILVNC). It is unclear whether the myocardial morphology is representative of ILVNC or if it represents an ethnicity related epiphenomenon to increased cardiac preload. Pregnancy is associated with an increase in physiological preload. This study sought to investigate the impact of increased cardiac preload on LV morphology in previously healthy black and Caucasian pregnant women.
Method: Between 2008 and 2010, 106 normotensive and previously healthy pregnant females (90% Caucasian) underwent cardiac echocardiography in the third trimester. Echocardiograms were analysed for trabeculations defined as localised protrusions of the ventricular wall ≥3mm in thickness associated with intertrabecuar recesses filled with blood from the LV cavity as assessed by colour Doppler. The results were compared with 80 healthy non-pregnant females (51% Caucasian) of similar age.
Results: There was no difference in mean age (29±6 years v 32±6 years; p=0.278) or blood pressure (111±16mmHg v 114±15mmHg; p: 0.664) between pregnant black and Caucasian females. Pregnant black females demonstrated a higher prevalence of LV hypertrabeculation compared with pregnant Caucasian females (n=5; 45.5% vs n=12; 12.6%; p=0.014). Pregnant black females were three times more likely to have LV hypertrabeculation compared with pregnant Caucasian females. In contrast none of the non-pregnant females of either ethnicity exhibited any hypertrabeculaton. None of the black or Caucasian pregnant females with LV hypertrabeculation showed objective features of left ventricular systolic or diastolic dysfunction. The mean EF by Simpsons was 56.8±12% v 58±9.8%; p=0.792. The E/A ratio was 1.47±0.33 v 1.30±0.44; p=0.218 and isovolumic relaxation time was 81.2±1.89ms v 80.6±15.46ms; p=0.6.
Conclusion: Black pregnant females exhibited a significantly higher frequency of LV hypertrabeculation compared with pregnant Caucasian females with similar BP in the absence objective markers of abnormal systolic/diastolic function. Based on the results of this study, it is highly likely that increased cardiac preload in heart failure is associated with an ethnically mediated myocardial response comprising of an increased number of myocardial trabeculations in black individuals and should be regarded as an epiphenomenon rather than ILVNCC outside the context of familial heart failure. The hypothesis requires prosposective longitudinal evaluation.

P1718 Reduced thickness of compacted myocardial layer: a sensitive and specific echocardiographic criterion for left ventricular non-compaction

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Introduction: Left ventricular non-compaction (LVNC) is characterized by a thickened myocardium with a non-compacted inner and a compacted outer layer. A ratio of endsystolic thickness of non-compacted to compacted layer >2 is an important diagnostic criterion. However, recent studies suggest that this criterion alone may be too sensitive. This study evaluates whether the absolute thickness of the compacted layer could serve as an additional criterion improving diagnostic accuracy.
Methods: Echocardiography was performed in 41 patients with definite diagnosis of LVNC and in 41 age-matched controls without cardiac disease. Absolute septal thickness (M-mode of parasternal long axis) as well as absolute thickness of non-compacted and compacted layers of affected ventricular segments (parasternal short axis) were measured. Mann-Whitney-test was used for statistical analysis (SPSS 19). Results are indicated as mean±SD.
Results: In patients with LVNC, maximal endsystolic thickness of the non-compacted layer was 1.80±0.41 cm compared to 0.19±0.05 cm in controls (p<0.0001), while maximal endsystolic thickness of the compacted layer was significantly lower than in controls (0.53±0.12 cm vs 1.13±0.22 cm; p<0.0001). The endsystolic ratio of non-compacted to compacted layer was 3.54±0.96 in patients with LVNC compared to 0.18±0.06 in controls (p<0.0001). Endsystolic thickness of the compacted layer was <8 mm in 40 cases and =8 mm in 1 case with LVNC; conversely, endsystolic thickness of the compacted layer was >8 mm in 40 controls and =8 mm in 1 control. The indexed ratio of septal wall thickness (M-mode) to compacted layer thickness was >0.64 (range = 0.64-1.85) in all patients with LVNC as opposed to <0.63 (range = 0.27-0.63) in all controls. To differentiate LVNC from normal hearts, an endsystolic thickness of the compacted layer <8 mm has a sensitivity of 98% and a specifity of 100%, and an indexed ratio of septal wall thickness to compacted layer thickness >0.64 has a specificity of 100% and a sensitivity of 100%.
Conclusion: Endsystolic thickness of the compacted layer <8 mm and indexed ratio of septal wall thickness to compacted layer thickness >0.64 have a very high sensitivity and specificity for the differentiation of LVNC from normal hearts. These critieria should be considered as additional parameters for the diagnosis of LVNC.

P1719 Prospective study about relation between tako-tsubo cardiomyopathy and major anxiety trouble

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Background: Tako-tsubo cardiomyopathies (TTC) are usually associated with emotional or physics stress as aetiological factors. Nonetheless, exposition to stress does not unconditionally lead to TTC development. We hypothesize that TTC may occur in a predisposed population.
Purpose: The aim of our prospective study was to define the prevalence of major anxiety troubles in a population of patients with TTC compared with a population of sex and age matched patients with acute coronary syndrome with troponinST elevation (ACS STE).
Method: Between December 2009 and December 2010, 23 patients with TTC confirmed by coronary angiography, cardiac MRI and clinical evolution were prospectively underwent to the psychiatric MINI test to research new or past major depressive episode (MDE), generalized anxiety trouble (GAT), post-traumatic stress state (PTSS) or dysthymia (DT). The same test was realized in a population of 23 matched patients with ACS STE.
Results: Mean age was 77±7 years in the TTC group and 71±15 in the ACS STE group (p=0.,06) with 15% men in each group. There was no difference between TTC group and ACS STE group regarding cardiovascular risk factors. Among the 23 patients with TTC, 14 (60.8%), 9 (39%), 6 (26%), 3 (13%) and 1 (4%) patients had new MDE, past MDE, GAT, PTSS and DT respectively. Among the 23 patients with ACS STE 3 (13%; p<0.005), 3 (13%; p<0.05), 1 (4%; p<0.05), 1 (4%; p=0.3) and 1 (4%; p=0.9) patient had new MED, past MED, TAG, PTSS and DT respectively. Major anxiety troubles were found in 16 (69%) patients in the TTC group versus 4 (17%) patients in the ACS group (p<0.005).
Conclusion: TTC are more frequently associated with major anxiety troubles and particularly new MDE or GAT. This association is not present for PTSS or DT. These findings suggest that TTC and depression may share common pathophysiological pathway.

P1720 Different patterns of myocardial iron overload by multislice T2* cardiovascular MR as markers of risk for cardiac dysfunction in thalassemia major

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Purpose: Multislice multiecho T2* Cardiovascular Magnetic Resonance (CMR) allows to detect different patterns of myocardial iron overload (MIO). Our aim was to verify the risk of biventricular dysfunction related to different patterns of MIO in a large cohort of thalassemia major (TM) patients.
Methods: 1135 TM patients (538 M, 30±19 yrs) underwent CMR. For the assessment of MIO, a multislice approach was used. The T2* value on each segment was calculated as well as the global value. Biventricular function parameters were evaluated by cine images.
Results: Four groups of patients were identified: homogeneous MIO (all segments with T2*<20 ms) (N=173), heterogeneous MIO (some segments with T2*≥20 ms and others with T2*<20 ms) and global heart T2*<20 ms (N=160), heterogeneous MIO and global heart T2*≥20 ms (N=337) and no MIO (all segments with T2*≥20 ms) (N=465). The left ventricular (LV) ejection fraction (EF) was significant different among the groups (P<0.0001; fig. 1 left). Odds Ratio for LV dysfunction (LVEF<57%) was 4.8 (3.1-7.3 95%CI; P<0.0001) for patients with homogeneous MIO vs patients with no MIO and 1.9 (1.2-3.2 95%CI; P=0.007) for patients with heterogeneous MIO and global heart T2*<20 vs patients with no MIO. The right ventricular (RV) EF was significant different among the groups (P<0.0001; fig.1 right). Odds Ratio for RV dysfunction (RVEF<55%) was 2.1 (1.4-3.2 95%CI; P=0.001) for patients with homogeneous MIO vs patients with no MIO.

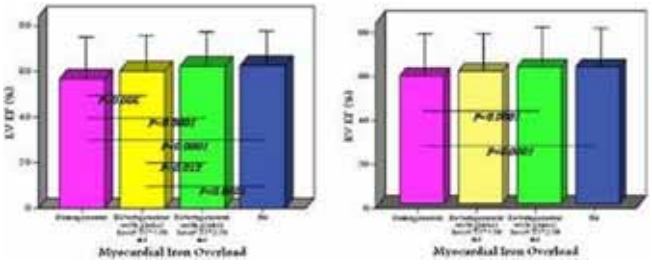

Figure 1

Conclusions: Biventricular dysfunction is correlated with MIO distribution decreasing from the patients with homogeneous MIO to the patients with no MIO. Homogeneous MIO and heterogeneous MIO with a global heart T2*<20 predicts a significantly higher risk to develop cardiac dysfunction suggesting an intensive chelation therapy in this group of patients.

P1721 Different patterns of myocardial iron overload by T2* cardiovascular magnetic resonance as markers of risk for cardiac complication in thalassemia major

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Purpose: Cardiac complications mainly related to myocardial iron overload (MIO) remain the main cause of morbidity and mortality in thalassemia major (TM). Thalassemia cardiomyopathy is treatable and partly reversible if appropriate chelation therapy is instituted in time. The validated multislice multiecho T2* Cardiovascular Magnetic Resonance (CMR) technique has permitted to quantify segmental and global myocardial iron burden detecting different patterns of iron overload. Aim of our study was to verify the risk of cardiac complications related to different patterns of MIO in a large cohort of TM patients.
Methods: We considered 812 TM patients for who CMR and cardiac data were collected in the Myocardial Iron Overload in Thalassemia (MIOT) data base. Three short-axis views (basal, medium, apical) of the left ventricle were acquired using a multislice multiecho T2* sequence. Using a previously validated software the 16 segmental T2* values and the mean global heart T2* value were provided. A conservative cut off of 20 ms was considered the limit of normal for the segmental and global T2* values.
Results: We identified 4 groups of patients: group I (17%) with homogeneous MIO (all segments with T2*<20 ms), group II (12%) with heterogeneous MIO (some segments with T2*<20 ms and others with T2*≥20 ms) and global heart T2*<20 ms; group III (29%) with heterogeneous MIO and global heart T2*≥20 ms; group IV (42%) with no MIO (all segments with T2*≥20 ms).
The percentage of patients with cardiac complications was significantly different in the 4 groups (group I 24.6% vs group II 20.6% vs group III 8.4% vs group IV 16.4%; P<0.0001). In particular, the percentage of patients with heart failure was significantly different among the groups (group I 17.4% vs group II 16.5% vs group III 4.2% vs group IV 8.3%; P<0.0001). No significant differences were found among groups in the percentage of arrhythmias and pulmonary hypertension. Odds Ratio for cardiac complications was 1.7 (1.0-2.7 OR 95% CI; P=0.041) for patients with homogeneous MIO vs patients with no MIO. Odds Ratio for heart failure was 2.3 (1.3-4.2 OR 95% CI; P=0.004) for patients with homogeneous MIO versus patients with no MIO and 2.2 (1.1-4.2 OR 95% CI; P=0.020) for patients with heterogeneous MIO and global heart T2*<20 ms versus patients with no MIO.
Conclusions: Homogeneous MIO predicts a significantly higher risk to develop cardiac complications, especially heart failure, suggesting an intensive chelation therapy in this group of patients.

P1722 Three-dimensional echocardiographic characterization of patients with left ventricular non-compaction

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Purpose: Despite several efforts have been performed by 2D-echocardiography (2DE) and cardiac magnetic resonance in the diagnosis of left ventricular non-compaction (LVNC), there are no universally accepted diagnostic criteria. The aim of our study was to describe the extent of non-compacted myocardium by a new 3D echocardiography-derived parameter.
Methods: 17 patients with an established diagnosis of LVNC based on 2DE and clinical criteria, 26 elite rowing athletes and 49 healthy volunteers underwent 3D echocardiography. By off-line analysis we calculated left ventricular volumes, mass, ejection fraction and sphericity index. Trabecular Volume (TV) was calculated as the difference between left ventricular end-diastolic volume obtained including and after excluding the trabeculae in the cavity contour. TV was also normalized by left-ventricular end-diastolic volume (TV%)
Results: As shown in figure both the TV and TV% were significantly higher in LVNC (33.7±10.9ml and 24±7%) as opposed to controls (7.1±2.2ml, p<0.001; 6±2%, p<0.001) and athletes (8.0±3.0 ml, p<0.001; 5±2%, p<0.001). In detail, a TV >15.8ml and a TV% >12.8% yielded a sensitivity of 100% and a specificity of 100% in the identification of LVNC (AUC=1.00). A mild positive correlation of TV and TV% was found with sphericity index (respectively r=0.294, p=0.004 and r=0.301, p=0.004) and negative correlation was found with ejection fraction (r= -0.454, p<0.001 and r= -0.217, p=0.038).

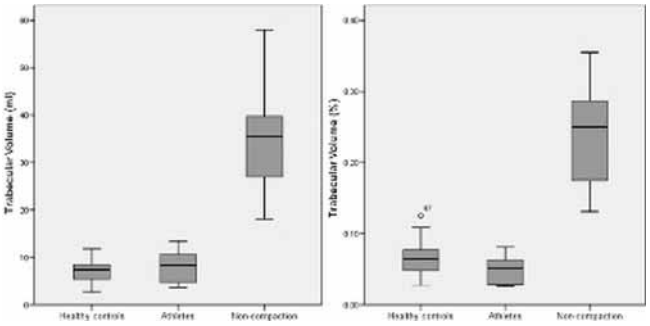

Figure 1. Trabecular Volume.

Conclusions: Due to high spatial resolution and accuracy in volumetric quantification, 3D echocardiography allows accurate measurement of the extent of non-compacted myocardium and identification of LVNC patients.

P1723 Angiographic evidence of coronary microvascular dysfunction in tako-tsubo syndrome

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Purpose: Using myocardial contrast echocardiography, we have previously demonstrated that myocardial dysfunction in Tako-Tsubo syndrome (TTS) is sustained by transient and spontaneously reversible coronary microvascular dysfunction. In the present study we aimed at the angiographical assessment of myocardial perfusion within left ventricular (LV) dysfunctional area in patients with TTS.
Methods: We retrospectively analyzed all coronary angiographies of TTS pa-

tients with typical LV apex dysfunction enrolled in our Department in the period 2007-2011. In all cases coronary angiography was performed within 48 hours after symptoms onset. As controls, we selected a group of age and gender-matched patients showing normal coronary arteries at coronary angiography in the same period. Angiographic analysis was performed on angiographic runs lasting more than 90 frames. All coronary angiograms were recorded at 15 frames per second. TIMI frame count (TFC), the presence of TIMI flow <3 on left anterior descendent coronary artery and both qualitative and quantitative myocardial blush grade in LV apex were assessed. Specifically,myocardial perfusion was quantitatively evaluated using Quantitative Blush Evaluator (QuBE), an open source software previously validated in the setting of ST-elevation myocardial infarction.
Results: Angiographic analysis was feasible in 23 out of 31 (74%) TTS patients (all female, 66±14 years). Control group did not differ for sex (all female), age (67±12 years, p=0.87) and common CV risk factors. TFC was significantly higher (31±16 vs 20±7, p=0.006) and TIMI 3 flow < 3 more frequent (30 vs 4%, p=0.02) in TTS than in controls. With regard to myocardial perfusion, MBG was significantly lower in TTS than in controls (2.3±0.8 vs 2.9±0.2, p<0.001, respectively). Notably, computer-assisted myocardial blush quantification revealed a significantly lower QuBE score in TTS than in controls (7.3±3.1 vs 14.1±5.1, p<0.001).
Conclusions: Our data indicate that myocardial perfusion within LV apex region is significantly reduced in the acute phase in TTS patients. These results provide a further confirmation that myocardial dysfunction in TTS is sustained by a condition of acute coronary microvascular dysfunction.

P1724 Mechanical dyssynchrony in non-compaction cardiomyopathy: underlying mechanism for improved response to cardiac resynchronization therapy

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The aim of our study is to assess the presence of ventricular mechanical dyssynchrony in isolated left ventricular non-compaction (IVNC) and the potential usefulness of cardiac resynchronization therapy (CRT) in those patients.
Methods: We studied 25 patients consecutively diagnosed with IVNC and a control group of 25 patients with dilated cardiomyopathy (MCD) of different etiologies but normal QRS width. Mechanical dyssynchrony was assessed using the presence of septal flash, the time from peak septal to posterior wall displacement (Pitzalis method) and the time from septal to lateral wall peak systolic velocity (Bax method-SL delay). Besides assessing the presence of an echocardiographic marker of dyssynchrony we analysed the relation to QRS duration. QRS width was classified as wide QRS (>120ms) or narrow QRS (<120ms). In the subgroup of patients with IVNC, 9 received CRT and they had follow-up at 6 and 12 months. Response to CRT was defined as a reduction >15% of LV end-systolic volume.
Results: Overall, dyssynchrony parameters were significantly more frequent in IVNC, regardless of QRS duration (Figure 1). All of the 9 patients with IVNC treated with CRT showed a septal flash and favourable response was observed in 8/9 (89%) at follow-up regardless of QRS width (narrow QRS: response 3/3 and wide QRS response 5/6, Figure 1).

	All IVNC N=25	IVNC & QRS<120 ms N=15	IVNC & QRS>120 ms N=10	Control grup (MCD & QRS <120 ms) N=25
SF (n patients(%)	17 (68%)*	8 (53.4%) *	10 (100%)*	2 (8%)
Pitzalis (ms)	223±114*	200±117*	257±106*	86±39
SL delay (ms)	115±66*	96±49	137±79*	68±32

*p<0.05 Vs Control Group

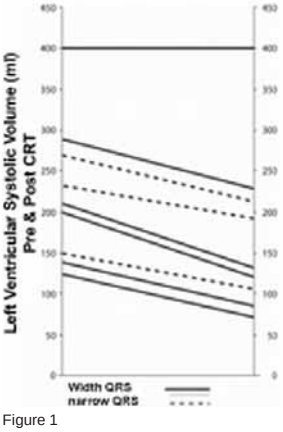

Figure 1

Conclusions: The presence of mechanical dyssynchrony, amenable to be corrected with CRT, is common in the group of patients with IVNC, independently of the QRS width. This could be the justification for the high response rate to CRT observed in these patients, regardless of QRS duration.

P1725 Frequency of silent left ventricular systolic dysfunction in patients with malignant hemopathies treated with autologous peripheral blood stem cell transplantation

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Purpose: The current treatment of some hematological malignancies may require autologous peripheral blood stem cell transplantation (PBSCT) preceded by high-dose chemotherapeutic combinations (conditioning regimen). Many of these treatments could induce asymptomatic left ventricular systolic dysfunction (LVSD) that can hamper the prognosis and long-term quality of life of these patients. The purpose of this study was to evaluate the frequency of asymptomatic LVSD after PBSCT.
Methods: Patients who underwent an autologous PBSCT in our institution during the period 2008-2010 were included in the study. All patients had received chemotherapy for the specific hematological malignancy before the PBSCT was indicated. The conditioning regimen consisted on BEAM (BCNU, etoposide, cytarabine, and melphalan) combination in 32 patients (9 with Hodkgin's and 23 with non-Hodgkin's lymphomas), and high dose melfalan in 22 pts with multiple myeloma. An echocardiography study was performed on admission for the PBSCT and 6 months after the procedure.
Results: 54 pts (33 male/22 female) with a median age of 49 (22-69) years entered the study. All of them had normal LV ejection fraction (EF) at baseline (mean: 62±6%). Six months after the procedure, 8 pts (15%) had a ≥10% absolute decrease in LVEF, and 17 pts (32%) a ≥5% absolute decrease in LVEF. In addition, one patient had congestive heart failure.
Conclusions: Among pts with malignant hemopathies undergoing autologous PBSCT, one-third of pts suffer mild to moderate asymptomatic LVSD. Preventive measures and early detection of LVSD are warranted in these patients to implement specific treatment and improve their long-term outcome.

P1726 Myocardial interstitial remodelling in paucisymptomatic patients with initial dilated cardiomyopathy

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Purpose: Aim of the study was to investigate the occurrence of myocardial interstitial remodelling by contrast-enhanced T1-mapping cardiovascular magnetic resonance (CMR) in paucisymptomatic patients with nonischaemic dilated cardiomyopathy (DCM) and initial left ventricular (LV) dysfunction.
Methods: Nineteen consecutive DCM patients (13 males, age 55±16 years, mean±SD) with mild LV systolic dysfunction (ejection-fraction 40-55%) and/or dilation (end-diastolic volume >100 ml/m^2), with no (n=17, 89%) or mild symptoms (NYHA II, n=2, 11%), were prospectively studied by contrast-enhanced CMR and compared with 16 healthy controls (12 males, age 43±11 years). Replacement myocardial fibrosis was detected by late gadolinium enhancement (LGE) CMR, whereas interstitial remodelling was estimated by pre- and post-contrast (5, 10 and 15 minutes after gadolinium administration) myocardial T1 mapping with gadolinium partition coefficient (GPC) calculation.
Results: DCM patients presented larger LV end-diastolic volume (103±19 vs 76±12 ml/m^2) and worse LV ejection fraction (50±10% vs 68±6%) than controls (both p<0.001), but preserved right ventricular (RV) end-diastolic volume (80±18 vs 73±9 ml/m^2), RV systolic function (63±9% vs 69±5%, p=NS), and only mildly increased NT-proBNP plasma levels (median [quartiles], 115 [58-236] ng/l, vr <157).
Six (32%) DCM patients presented LGE, representing 9±4% of LV mass (1 patchy, 4 midwall, 1 subendocardial pattern). In DCM patients, GPC was higher than controls (0.52±0.06 vs 0.46±0.06, p<0.001), even after exclusion of LV segments with LGE (0.52±0.06 vs 0.46±0.06, p<0.001).
Myocardial interstitial remodelling (GPC) resulted moderately related to LV dilation (R=0.52, p=0.02), RV dilation (R=0.48, p=0.04), and longer QT duration (R=0.60, p=0.01).
Conclusions: Myocardial interstitial remodelling can be detected in DCM from the early stages of the disease. Further studies will investigate whether it holds a prognostic role and it represents a potential therapeutic target.

P1727 Spironolactone attenuates fibrosis via inhibiting TGF-beta-1 Smad signaling in dilated cardiomyopathy

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Purpose: Fibrosis formation plays an important role in dilated cardiomyopathy (DCM). TGFβ1 stimulates fibroblast to synthesize collagen. To evaluate the effect

of spironolactone, a mineralocorticoid receptor antagonist (MRA), on attenuating fibrosis of DCM is by inhibiting TGFβ1-Smad signaling.
Methods and results: DCM model was established by coxsackievirus B3 (CVB3) infection of Balb/c mice (DCM group). Infected mice were administered spironolactone (Spi) daily until they were sacrificed 9 months post-infection (DCM+Spi group). Echocardiographic analysis demonstrated that cardiacfunction of CVB3-infected mice were significantly improved in the presence of Spi. The collagen in the hearts was analyzed by picrosirius red staining and H&E staining in comparison with the DCM group. Decrease in collagen volume fraction was observed in the DCM+Spi group. The mRNA expressions of collagen I and Procollagen C-proteinase enhancer (PECP) were decreased in the DCM+Spi group. These indicated that Spi inhibited fibrosis formation in CVB3-infected hearts. The Western blot for TGF-β1 and its downstream components showed decreased expression levels of TGF-β1, Smad2/3, Smad4, and increased Smad7 in the DCM+Spi group compared with the DCM group.
Conclusion: Spi can improve CVB3-induced DCM by inhibiting fibrosis formation, which is related to inhibition of TGFβ1-Smad signaling in cardiomyocyte. The experimental data indicate that MRA can prevent cardiac remodeling in DCM and appropriate dose of MRA combine with ACE inhibitor may be better than ACE inhibitor alone for attenuating remodeling in DCM patient.
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P1728 Comprehensive assessment of endomyocardial biopsy specimens in patients with recent-onset dilated cardiomyopathy

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Recent studies suggested beneficial effects of immunosupressive treatment in individuals with virus-negative inflammatory cardiomyopathy (ICMP). We aimed to assess prevalence of ICMP and cardiotropic agents in myocardium in individuals with recent-onset dilated cardiomyopathy (DCM). Our ultimate goal was identification of patiens suitable for targeted treatment of ICMP
Methods: We performed endomyocardial biopsy (EMB) in 39 patients (pts) with recent-onset DCM with a history of symptoms shorted than 6 months (age 45±8 years, NYHA class 2.6±0.9, left ventricular (LV) end-diastolic diameter 68±7 mm, left ventricular ejection fraction 24±9%). The diagnosis of inflammatory cardiomyopathy was based on positive immunohistochemical analysis of EMB samples showing more than 7 CD3 and/or CD68 lymphocytes per mm^2. Using a quantitative polymerase chain reaction (PCR), we analysed presence of borreliae, parvovirus B19, cytomegalovirus, Ebstein-Barr virus, human herpes virus 6, adenoviruses and enteroviruses in EMB samples.
Results: ICMP was diagnosed in 19 pts (49%). The following agents were detected in EMB samples: parvovirus B19 in 25 pts (64%), borrelia burgdorferi sensu lato u 10 pts (26%), cytomegalovirus in 3 pts (8%), enterovirus in 1pt (3%). Simultaneous positivity of two agents was present in 10 pts (26%). Median of parvovirus B19 quantity in EMB was 398 copies per mikrog of DNA. No cardiotropic agent in EMB samples was found in 8 pts (20%). Just three individuals (8%) of this subgroup had positive immunohistochemical analysis showing inflamation. Two of them showed improvement of LV systolic function on conventional therapy, and the remaining patient was diagnosed to have polymyositis and recieved combined immunosuppression. Nine of ten patients with borrelia positive EMB were treated with intravenous ceftriaxone. Three of these individuals had improvement of LV ejection fraction above 40% at 12 months of follow-up.
Conclusion: Prevalence of inflammatory cardiomyopathy without persistence of cardiotropic agents in EMB was low (8%). Further studies are needed to define clinically relevant quantity of infectious agents in EMB samples.
Research grant IGA NS-9697/2008.

P1729 Early detection of epirubicin-induced cardiac dysfunction in patients with breast cancer by assessment of myocardial systolic rotation and deformation

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Epirubicin is an effective drug widely used in breast cancer, but its application is limited by the cumulative dose-dependent cardiotoxicity. Assessment of LV ejection fraction (EF) and fractional shortening (FS) are recommended to diagnose cardiac dysfunction, however, their normal values can mask subclinical LV impairment. Therefore, we tested whether myocardial systolic rotation and deformation might represent better markers of early dysfunction, and can predict further LV function changes.
Methods: 52 women with breast cancer (54±6 years), without known cardiac disease, EF>60%, scheduled to be treated with epirubicin, were assessed at baseline, and after 1st and 6th cycles of epirubicin (cumulative dose of 287±15 g/m^2). Conventional echo was used to assess LV geometry, EF, and FS;speckle tracking to measure LV systolic rotation parameters – peak apical rotation (RotA), peak basal rotation (RotB), LV twist (LVT), and twist rate (LVTR), and also LV systolic deformation - radial and longitudinal strain (rS, LS) and strain rate (rSR, LSR).
Results: No changes in LV dimensions, EF or FS were observed after 1st cycle of epirubicin, although there was a decrease in EF after the 6th cycle (66±4 vs 60±5%, $p<0.01$). However, rotational (RotA, LVT, and LVTR) and deformational (radial and longitudinal) parameters decreased after the 1st cycle of epirubicin, and persisted after the 6th cycle (table). Univariate analysis showed that reduction of LS and LVT correlated with epirubicin cumulative dose after 6 months of treatment (r=0.59 and r=0.79; $p<0.01$). Multiple regression analysis showed that LS represents the main predictor for an EF reduction after the 6th cycle of epirubicin ($r^2=0.52$, $p<0.01$).

LV systolic rotation and deformation

Epirubicin	RotA (°)	RotB (°)	LVT (°)	LVTR (°/s)	rS (%)	rSR (1/s)	LS (%)	LSR (1/s)
Baseline	8.1±1.5	-4.8±1.2	13.8±1.9	91±28	47.5±6.8	1.8±0.2	-24.3±2.7	-1.42±0.2
1st cycle	5.7±0.3	-4.6±1.8	10.2±1.4	72±34	38.4±5.6	1.4±0.8	-17.05±2.5	-1.21±0.6
6th cycle	5.2±0.6	-4.2±1.8	9.5±1.7	64±31	35.4±6.6	1.2±0.6	-20.5±2.5	-1.11±0.6
P (1st cycle vs baseline)	0.001	0.89	0.01	0.01	0.01	0.001	0.001	0.01
P (6th cycle vs baseline)	0.001	0.67	0.01	0.005	0.001	0.001	0.01	0.01

Conclusion: Assessment of myocardial rotation and deformation parameters by speckle tracking can detect subclinical LV dysfunction, and can predict further changes in EF; therefore, they should be recommended to monitor epirubicin-induced cardiac dysfunction.

P1730 Value of serial measurements of troponin I and BNP to detect left ventricular systolic dysfunction in patients with malignant hemopathies treated with intensive chemotherapy

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Purpose: To determine if serial plasma levels of troponin (TnI) and of brain natriuretic peptide (BNP) could be of value for the early detection of systolic left ventricular (LV) dysfunction among patients (pts) with hematological malignancies who are submitted to intensive chemotherapy (CHEM) or to autologous peripheral blood stem cell transplantation (PBSCT).
Methods: 84 pts were prospectively studied: 30 pts with a new diagnosis of acute leukemia (myeloblastic in 23, lymphoblastic in 7), and 54 with other hemopathies undergoing autologous PBSCT (9 with relapsed or refractory Hodgkin's lymphoma, 23 with non-Hodgkin's lymphoma, and 4 with multiple myeloma). Plasma TnI was measured daily during CHEM, and BNP levels were determined before and 12 hours after each cycle of CHEM, and following infusion of harvested PBSCT. Echocardiography was performed before and 6-9 months after initial treatment.
Results: There were 48 men and 36 women with a median age of 48 (18-70) years. 11 pts (18%) had TnI elevation over the 99th percentile (0.04 ng/ml), 8 of them (10%) above>0.10. Thirty pts (36%) had BNP >100 pg/ml, and 8 (10%) >200 pg/ml. In pts with TnI>0.04, no significant changes at the end of study were observed from baseline in LV ejection fraction (EF) or LV diameters. However, those pts with TnI elevation >0.10 had a significant increase in LVEDD (47±4 mm to 50±2 mm, $p<0.01$), and in LVESD (28±3 mm to 31±4 mm, p=0.05). On the contrary, LVEF and LV diameters were not different in patients with elevated BNP at both cut-off levels. Only one patient with a BNP >1000 pg/ml showed a marked decrease in LVEF (60% to 45%) and signs of congestive heart failure.
Conclusions: Monitoring of TnI during intensive chemotherapy may be useful to early detect myocardial toxicity and potential further LV dysfunction. On the contrary, moderate elevations of BNP do not seem to be useful to predict LV dysfunction in this setting.

P1731 Diabetes mellitus is an independent determinant of impaired left ventricular diastolic reserve: a potential marker of subclinical diabetic cardiomyopathy

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Background: Diastolic dysfunction is an important prognostic marker of cardiovascular death and hospitalisation and is an early sign of diabetic cardiomyopathy. Examining diastolic reserve may allow earlier detection of subclinical abnormalities. We evaluated exercise E/e' as a measure of diastolic reserve and the determinants of raised exercise E/e'.
Methods: 54 patients (37 male, aged 47±14 years, 10 diabetics, mean LVEF 65%, range 39-78%) underwent rest and Bruce protocol exercise echocardiography. Global mean peak systolic longitudinal strain (ε) and strain rate (SR) were measured in the 3 apical views at rest and septal e' was measured at rest and post-exercise.

Results: The mean exercise duration was 11±5 minutes. No patient had inducible ischaemia on exercise echo. Diabetics and patients presenting with dyspnoea had a shorter exercise time (7 vs. 12 minutes, p=0.004 and 8 vs. 12 minutes, p=0.002, respectively). Exercise duration was correlated with exercise E/e' (ρ = -0.34, p=0.01), age (r= -0.46, p=0.001) and resting e' (r=0.30, p=0.045) but not with resting ε or SR. Diabetics had significantly higher E/e' (16.8 vs. 8.8 p=0.0003). Exercise E/e' was correlated with age (ρ=0.35, p=0.01), resting SR (ρ=0.32, p=0.03), resting ε (ρ=0.29, p=0.045) and resting e' (ρ= -0.52, p<0.001). Multivariate linear regression identified resting e' (p=0.002) and diabetes (p=0.019) as the only independent determinants of exercise E/e', adjusted R^2 = 0.38, p<0.001). Resting systolic ε and SR, and hypertension were not significant determinants.
Conclusions: 1) Resting diastolic function measured as resting e', and diabetes were the only independent determinants of diastolic reserve; 2) Diabetic patients had abnormal exercise E/e' indicating impaired diastolic reserve; 3) Examining diastolic reserve may allow earlier detection of diabetic cardiomyopathy.

P1732 Impaired myocardial perfusion is an independent predictor of chronic diastolic dysfunction in obstructive sleep apnoea

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Purpose: Moderate to severe obstructive sleep apnoea (OSA) is associated with local and generalized endothelial dysfunction. It has previously been shown that impaired myocardial perfusion is present in OSA and effective continuous positive airway pressure (CPAP) therapy improves myocardial perfusion. In this study, we tested the hypothesis that abnormal coronary flow reserve (CFR) in OSA causes subendocardial ischaemia and thus may lead to chronic diastolic dysfunction.
Methods: We recruited 40 subjects with moderate-severe OSA. A comprehensive tissue Doppler, 2D and 3D echocardiography was performed. Left ventricular ejection fraction (LVEF), mitral valve inflow indices, mitral annular velocity and LA volume index (LAVI, a marker of chronic diastolic function) were calculated. Real-time rest-stress myocardial contrast echocardiography (MCE) was performed to calculate coronary flow reserve (myocardial blood flow following vasodilator stress/myocardial blood flow at rest). MCE and LAVI measurements were repeated after 26 weeks of CPAP therapy (n=37).
Results: Using multivariate analysis only systolic blood pressure (p=0.02), CFR (p=0.006) and E/A (p=0.0003) emerged as independent predictors of 3D echocardiographically assessed LAVI, (all p<0.05) (Table). CFR and LAVI were modestly correlated (rs=0.31; P<0.05). Following CPAP therapy, an improvement in CFR (1.7 to 3.1; p<0.001) and reduction in LAVI (26±8 to 22±7 ml/m^2; p<0.001) was noted.

Variables and P Value

	Variables in study population [Mean (SD)]	Independent predictors of 3D LAVI using multivariate analysis P Value
Age (years)	50 (10)	0.06
Body Mass Index (kg/m^2)	34 (8)	0.14
Systolic Blood Pressure (mm/Hg)	142 (1)	0.02
Diastolic Blood Pressure (mm/Hg)	83 (11)	0.23
IVRT (ms)	0.01±0.02	0.51
E/A	1.01±0.35	0.0003
E/E' sep	9.5±3.93	0.56
CFR	1.7	0.006
3D LVEF	66±8	0.12

IVRT: Intraventricular relaxation time; E/A: Early and late mitral diastolic inflow velocity; E': Early mitral annular diastolic velocity.

Conclusion: Impaired myocardial perfusion is an independent predictor of LAVI and thus chronic diastolic dysfunction in OSA patients.

P1733 Effects of granulocyte-colony stimulating factor on diabetic cardiomyopathy in sucrose fed Otsuka Long-Evans Tokushima fatty rat

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Purpose: There are no established treatments in diabetic cardiomyopathy (DCMP). Conventional therapeutic practices including strict blood glucose level are often effective, but do not fully prevent cardiac complications. In the present study, we investigated effects of G-CSF on DCMP in sucrose fed Otsuka Long-Evans Tokushima Fatty (OLETF) rats.
Methods: Seven-week old 20 male OLETF rats and 10 male Long-Evans Tokushima Otsuka (LETO) rats were used as the experimental and control subjects. All of the LETO and 8 randomly selected OLETF rats were free access to tap water and other 12 OLETF rats were free access to sucrose contained water. After 10 weeks, Each group was divided randomly into two groups and saline or recombinant human G-CSF (100μg/kg/day) was injected intraperitoneally for 5 days; Blood glucose, cholesterol and triglyceride were measured and Doppler echocardiography was done at the end of 17 weeks just before treated with saline or G-CSF and at the time of sacrifice (the end of 22weeks). Histopathology of light microscopy and electromicroscopy (EM), immunohistochemistry for transforming growth factor-β (TGF-β) of myocardium were examined.
Results: There was no significant difference between OLETF treated with G-CSF (OG) and OLETF treated with saline (ON) in body weight, fasting blood glucose, cholesterol, and triglyceride levels. But in the Doppler echocardiography data, diastolic dysfunction was slow progression in the OG group. In the Masson Trichrome stain and computed quantitative analysis of fibrosis, the progression of perivascular and/or interstitial fibrosis was significantly decreased in OG group. In the immunohistochemical findings, the extent of TGF-β immunoreactivity in the interstitial and perivascular tissue was significantly decreased in OG group. In the EM findings, heterogenous structural alterations of myocardial tissue were more apparent in ON group. The ultrastructure of ON group myocardium displayed intracellular edema, deposition of collagen fibers in pericapillary region, swelling and/or disrupted cristae of mitochondria, damaged myofilaments and intracellular junctions, as well as increased accumulation of lipid droplets and lysosomes in cardiac cells. In contrast, OG group revealed absence of collagen deposition and relatively decreased number of abnormal mitochondria. Moreover the disruption of cristae network of the enlarged mitochondria, damaged myofilaments and intracellular junctions were less frequently observed in OG group.
Conclusions: The present study provides evidence of the functional and histological beneficial effects of G-CSF on DCMP in OLETF rats.

HEART FAILURE – LEFT VENTRICULAR DYSFUNCTION

P1734 Severe low-cardiac output heart failure patients bridged to beta-blockade by enoximone: prolonged survival without heart transplantation

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Background: Patients suffering from acute (or acute on chronic) low-cardiac output heart failure have a very high mortality risk. In order to improve prognosis, therapeutic measures require the early use of inotropic support and mechanical devices, and the optimal timing of blockade of deleterious neurohormonal effects. Beta-blocker therapy would improve prognosis in the long term, but introduction of this medication is often hampered by hypotension and worsening of heart failure.
Purpose and methods: In patients who could not be weaned from inotropic support elsewhere and who were referred for heart transplantation we therefore sought for characteristics associated with successful weaning from inotropic support and introduction of beta-blocker therapy. Records of consecutive patients were analysed.
Results: Of 75 consecutive patients with severe heart failure (cardiac index 2.0±0.4 L/min/m^2, left ventriculair ejection fraction 17.4% ± 4%), 33 patients (44%) could not be weaned from inotropic support and had a left ventricle assist device (LVAD) implanted, underwent heart transplantation or died after a median of 25 days (range 1-117 days). Characteristics associated with the inability to wean from inotropic support were an ischemic etiology of heart failure (Hazard Ratio [HR] 2.3; 95% Confidence Interval [95%CI] 1.3-4.2), the need for short-term mechanical devices (IABP or ECMO) (HR 2.9; 95%CI 1.6-5.1), and the use of vasopressor agents (HR 4.1; 95%CI 2.3-7.5). However, the 42 remaining patients (56%) were successfully weaned from inotropic support, and in this group transplantation-free cumulative survival was 83% at 1-year, and 64% after a median follow-up of 780 days (range 94-2310 days). After achieving an euvolaemic state, weaning was successful in 30 (71%) of the patients by introducing beta-blockade during intravenous enoximone with an overlapping duration of 13±6 days. Patients weaned of enoximone had a significantly shorter delay until a beta-blocker could be successfully started and had a lower heart rate at discharge as compared to the remaining of 12 patients which were weaned of dobutamine [25±15 vs 48±26 days (p=0.02), 70±9 vs 80±7 bpm (p=0.005), respectively].
Conclusion: In a considerable number of severe low-cardiac output heart failure patients, especially those without a need of vasopressors and with a non-ischemic etiology, introduction of beta-blockade is well tolerated after achieving euvolaemia and during concomitant administration of intravenous enoximone. This enables postponement of transplantation or even withdrawal from the waiting list.

P1735 Predictors of outcome in patients with chronic heart failure over a 5 year follow-up period

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Introduction: Chronic heart failure (CHF) is associated with a significant morbidity and a mortality rate worse than many cancers. Contemporary observational studies have demonstrated an improvement in expected survival but nonetheless survival remains limited. Currently used prognostic models, though helpful, are largely derived from pharmaceutical randomised controlled trials where comorbidities (e.g. renal failure, cancer or dementia) were screened-out to a greater extent. These models are not widely used as some of these models require fairly complex calculations and others have not been validated recently in the era of modern drugs and device therapies. We aimed to identify factors influencing out-

come in ambulatory heart failure patients and to devise a simple scoring system to identify patients approaching end stage CHF and, hence, suitable for palliative care approach.
Methods: Demographic, clinical and social data were extracted from Lothian heart failure database for ambulatory CHF patients enrolled from 2004 to 2010. Hospital records were reviewed to obtain missing data. Multiple regression and Cox proportional-hazards model was used to identify factors predicting outcome.
Results: The overall study cohort included 1326 ambulatory CHF patients managed in physician or nurse led out-patient clinics. The mean age for patients was 76 years and 63% were males. 54% patients had ischemic heart failure and 76% patients had moderate to severe left ventricular systolic dysfunction on echocardiogram. Every patient was considered for evidence-based therapy, but only 54% patients could tolerate beta-blockers and 74% received ACE inhibitors throughout study period. Independent predictors of mortality included: higher NYHA class, low systolic BP, lack of exercise, anaemia, low body weight, renal impairment, lack of beta-blocker therapy, diabetes mellitus and number of hospital admissions. Hospital admissions were predicted by higher NYHA class, lack of ACE inhibitor and beta-blocker therapy, high white cell count, old age, living with carer, lack of exercise and mitral regurgitation on echocardiogram.
Conclusion: Our study provides a contemporary real-world overview of factors affecting outcomes in ambulatory CHF patients. We have proposed a simple scoring system to identify end stage CHF patients appropriate for consideration of palliative care. A formal prospective study to evaluate this scoring system is warranted.

P1736 Post traumatic stress disorder is associated with increased mortality in stable outpatients with elevated B-type natriuretic peptide

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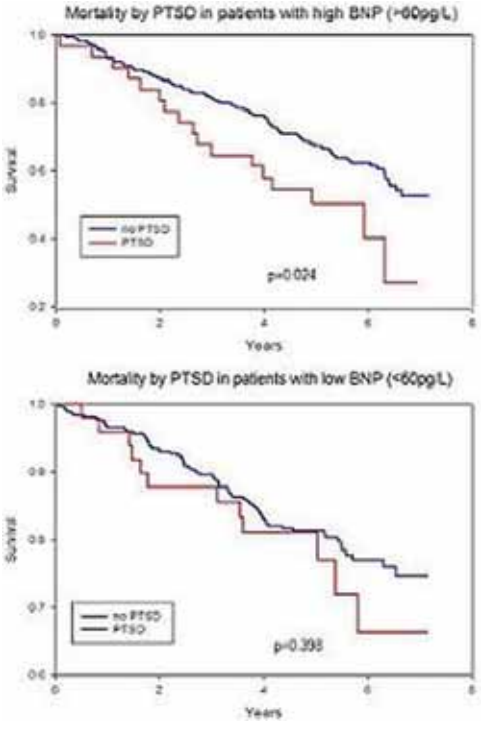
Introduction: Post traumatic stress disorder (PTSD) is gaining increasing recognition as a risk factor for morbidity and mortality. PTSD is associated with hyperarousal resulting in heightened sympathetic activation. This study aims to examine the impact of PTSD and elevated cardiovascular biomarkers on mortality among stable outpatients referred for routine echocardiography.
Methods: 891 outpatients referrred for echocardiography were enrolled in this study, with 91 having prior PTSD. Baseline cardiac risk factors, echocardiography, and biomarker concentrations were obtained. Patients were followed for up to 7.5 years for the endpoint of all cause mortality.
Results: Patients with PTSD were younger and thinner with fewer cardiac risk factors, lower blood urea nitrogen, lower B-type natriuretic peptide (BNP), lower N-terminal proBNP (NT-proBNP), lower creatinine, and higher ejection fraction. However, patients with PTSD had a trend towards worse survival on Kaplan Meier curve (p=0.057). Furthermore, amongst patients with elevated BNP (>60pg/L), PTSD patients had significantly increased mortality (p=0.024). (Figure) Among patients with PTSD, mid-region proadrenomedullin (MR-proADM), creatinine, and C-terminal proendothelin (CT-proET) were significant predictors of mortality (p=0.006, p=0.024, and p=0.003, respectively). In a multivariate model, PTSD, BNP, and MR-proADM were significant predictors of mortality while C-terminal pre-pro-vasopressin, creatinine, and CT-proET were not.



Conclusion: This study confirmed that PTSD was related to increased mortality. In patients with BNP >60pg/L, PTSD was associated with significantly increased mortality. In addition, among patients with PTSD, biomarkers of endothelial dysfunction, MR-proADM and CT-proET, were significant predictors of mortality.

P1737 The prognostic value of a new tissue Doppler parameter in patients with heart failure

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It has been shown that a cut-off value of 1.6 for a new tissue Doppler index, E/(E'×S'), including the ratio between early diastolic transmitral velocity (E) and early mitral annulus diastolic velocity (E'), and the systolic mitral annulus velocity (S'), is useful to predict high left ventricular (LV) end-diastolic pressure.
Objectives: To evaluate the prognostic value of E/(E'×S') in patients with heart failure (HF).
Methods: Echocardiography was performed in 113 consecutive hospitalized patients with HF. Patients were divided into 2 groups: group I with E/(E'×S')≤1.6 and group II with E/(E'×S')>1.6. The primary end-point consisted of cardiac death or readmission due to HF worsening.
Results: During the follow-up period (35.7±11.2 months) cardiac events occurred in 70 patients (62%): 18 cardiac deaths (16%) and 52 readmissions for HF (46%). Worsening of HF [39 (65%) versus 13 (24%), p<0.001] and cardiac death [16 (27%) vs. 2 (4%), p<0.001] were significantly higher in group II than in group I. On multivariate Cox regression analysis including all the variables that predicted cardiac events on univariate analysis [E, E', S', E/E', E/(E'×S'), early/late diastolic transmitral velocity (E/A), E-deceleration time, LV ejection fraction (LVEF), indexed left atrial volume, pulmonary artery systolic pressure, N-terminal pro-brain natriuretic peptide, age, sex], E/(E'×S') was the best independent prognostic predictor (hazard ratio=3.2, 95% confidence interval =1.70-5.8, p<0.001). The addition of E/(E'×S') index resulted in significant incremental improvement in the predictive value of the clasical echocardiografic parameters (E/A ratio, LVEF, E/E' and S' wave) (Figure 1).

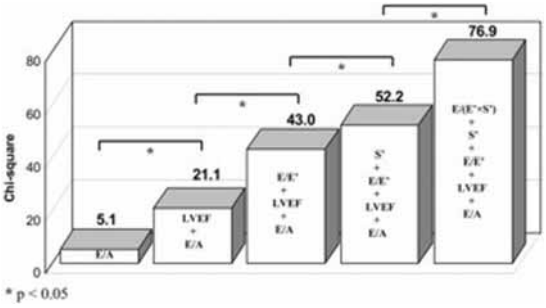

Figure 1

Conclusions: The new E/(E'×S') index is a powerful predictor of the clinical outcome in patients with HF in sinus rhythm.

P1738 Outcome of patients with right ventricular systolic dysfunction and left ventricular systolic dysfunction and/or heart failure. A meta-analysis

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Purpose: Right ventricular systolic dysfunction (RVSD) has been related to prognosis in patients with heart failure and/or left ventricular systolic dysfunction. However, most of the studies addressing this issue are not large enough, have different inclusion criteria, and use different methods to evaluate right ventricular function to draw definite conclusions. We sought to investigate the association between right ventricular systolic dysfunction (RVSD) and outcomes in patients with left ventricular dysfunction.
Methods: We conducted a systematic review of the published studies, searching the MEDLINE and SCOPUS databases and the references of the retrieved documents. A fixed effects model or random effects model was applied depending on the heterogeneity analysis.
Results: Eleven studies out of 40 (27.5%), with 4732 patients, were included in the meta-analysis. RVSD was present in 2234 patients (47.2%). Four of the studies had admission for HF as an end point. We found a significant association between RVSD and overall mortality: OR=2.98 (2.02-4.39); p<0.001, with significant between-studies heterogeneity (chi-2=41.96; p<0.001) and presence of publication bias (funnel plot). A significant association was found between RVSD and admission for HF: OR=1.51 (1.27-1.79); p<0.001 (fixed effects model).
Conclusions: RVSD is associated with overall mortality and admission for HF

during follow-up. Significant between-studies heterogeneity and publication bias must be taken into account while interpreting this information.

P1739 Right ventricular dysfunction predicts clinical outcomes for patients following the implantation of cardiac resynchronisation therapy

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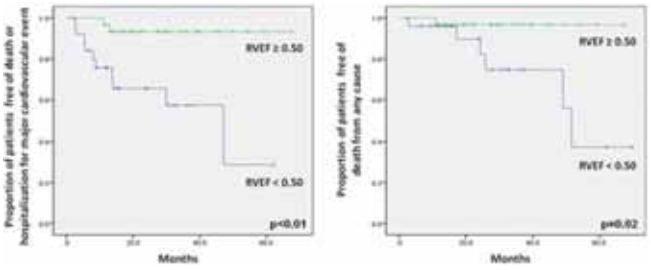
Background: Cardiac Resynchronisation Therapy (CRT) is an established treatment for symptomatic heart failure. (HF) A large number of patients however do not gain the anticipated clinical benefit following CRT. RV dysfunction has a predictive capacity in HF cohorts, but the significance of RV dysfunction in CRT patients remains unclear. We assessed the prognostic significance of RV function assessed by cardiac magnetic resonance (CMR) for predicting outcomes following CRT.
Methods & results: A series of 56 consecutive patients was evaluated with CMR prior to the implantation of CRT. The primary end point was a composite of death from any cause or unplanned hospitalisation for a major cardiovascular event. Clinical, biochemical, ECG and imaging data were collected. Biventricular function and myocardial scar were assessed by CMR including gadolinium enhancement. The mean age of the study population was 64.9±12.6 years. Heart failure was ischaemic in 44.6% of patients. Atrial Fibrillation was found in 25% of patients. The mean QRS duration was 156±22ms. Twelve patients (21%) met the primary end point over a median follow up period of 27 months. On time-to-event analysis only atrial fibrillation (HR 3.5, p=0.03) and RV dysfunction, either by reduced RVEF (HR 0.96, p=0.006) or TAPSE (HR 0.80, p=0.002) were independent predictors of the primary end point.



RVEF and effect on ACM and CVS event.

Conclusion: RV dysfunction predicts a poor outcome following CRT. Routine evaluation of RV function should be considered in the patient being assessed for CRT.

P1740 Soluble ST2 predicts outcome in heart failure of ischemic aetiology

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Purpose: Soluble ST2 (sST2) is a decoy receptor for interleukin (IL)-33 and thus modifies inflammation. Serum levels of sST2 are elevated in patients with chronic heart failure (HF) compared with healthy controls.
We examined the prognostic value of sST2 in a sub-study involving approximately 30% of participants in the CORONA study (Controlled Rosuvastatin Multinational Trial in HF).
Methods: The prognostic value of sST2 was investigated in 1449 patients ≥ 60 years with ischemic, systolic HF, who were in NYHA class II-IV on optimal pharmacological therapy. They were randomly assigned to 10 mg rosuvastatin or placebo. The primary composite end point of the CORONA study was cardiovascular death, nonfatal myocardial infarction or stroke. By Cox proportional hazard analyses, adjusting for clinical and biochemical variables, we explored the association between baseline levels of sST2 and the primary end point as well as the following end points: Death from any cause, death from cardiovascular causes, sudden death, death from worsening of HF, death from other causes, any coronary event, all-cause hospitalization, hospitalization for cardiovascular causes and hospitalization for worsening of HF. sST2 and NT-proBNP levels were log-transformed prior to statistical analyses.
Results: Patients were on average 72 years old, 73% were male, 12% were smokers and 26% were diabetics, most were in NYHA class 2 or 3, and mean left ventricular ejection fraction was 0.32±0.07. The median follow-up time was 2.6 (IQR 2.2 – 3.0) years. Median baseline sST2 was 21 (IQR: 13 - 25) ng/ml. 408 of 1449 patients met the primary end point. In multi-variable analyses, adjusting for 8 clinical and 2 biochemical variables, higher sST2-levels were associated with a higher risk of all the specified end points, including the primary end-point [HR 1.65 (1.38-1.98), p<0.001]. When N-terminal pro-B-type natriuretic peptide (NT-proBNP) was added to the model, the association between sST2 and the primary end point was attenuated and no longer significant. However, sST2 levels remained associated with all cause hospitalization, hospitalization for worsening of HF [HR 1.32 (1.06 – 1.64)] and death from HF [HR 1.68 (1.13 – 2.50)] even after adjusting for NT-proBNP. No treatment interaction was observed.
Conclusions: sST2 is associated with outcome in patients with chronic HF. sST2 is an independent predictor of worsening of HF as well as death from HF, indicating that the IL-33 pathway is a potential target for intervention in HF.

P1741 A novel risk model for patients admitted for acute decompensated heart failure incorporating N-terminal pro-B-type natriuretic peptide levels: EFFECT-HF score

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Introduction: Models to stratify risk for patients admitted for acute decompensated heart failure (HF) do not include natriuretic peptides like N-terminal pro-B-type Natriuretic Peptide (NT-proBNP). We pooled individual patient data from several studies to develop a prognostication score for acute decompensated HF including NT-proBNP.
Methods: We gathered original patient data from seven prospective cohorts of patients admitted for acute decompensated HF where admission and discharge NT-proBNP was measured. The endpoints studied were time till death of any cause and time till the first readmission for cardiovascular reason within 180 days after discharge. We generated a prognostication risk score using Cox regression models by assigning weights to individual risk factors proportional to regression coefficients.
Results: The present study consists of 1301 patients. The median age of the study population was 74 years and 49% of the patients were known to have an ischemic aetiology. The cumulative 180-day mortality rate was 15% and the composite event (death and readmission) rate was 43%. Event rate increased in a stepwise manner in accordance with the strata of NT-proBNP levels at discharge as well as for the percentage reduction. The model incorporating NT-proBNP yielded the best c-statistic (AUC 0.77, 95% CI 0.73-0.81) and the addition of this biomarker to a reference model significantly improved prediction for mortality as shown by the net reclassification improvement (0.54, P<0.0001). The simple risk score (EFFECT-HF) we designed, incorporating NT-proBNP, identified a very-high-risk subgroup with a significant higher mortality when compared with high-, intermediate- or low-risk subgroup (Table 1).

Table 1. EFFECT-HF score

	180-day event rate (%)	
Risk groups	Observed	Expected
Low ≤2	4.7	4.6
Intermediate 3–4	12.9	11.4
High 5–6	24.4	22.4
Very high >6	44.4	31.6

Conclusion: Our data shows that combination of NT-proBNP measurements and selected risk factors generates a relatively simple risk score that importantly improves the prediction of adverse events in patients admitted for acutely decompensated HF.

P1742 Serum albumin level reflects nutritional and inflammatory status in patients with acute decompensated heart failure

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Background: Hypoalbuminemia is associated with poor outcomes in patients with acute decompensated heart failure (ADHF). However its pathophysiological mechanisms have not been well established.
Methods: The present study enrolled 329 patients who were hospitalized for ADHF in our university hospital. Patient characteristics and 6-month mortal-

ity were examined according to serum albumin tertile on admission; Tertile-1 (≦3.2g/dL), Tertile-2 (3.3-3.6g/dL), and Tertile-3 (≧3.7g/dL).
Results: Lower albumin tertile was associated with several factors including malnutrition (lower hemoglobin and total cholesterol level), inflammation (higher CRP level), fluid overload/congestion (peripheral edema and increased BNP level), and hemodilution (lower sodium and hemoglobin level). Multiple regression analysis identified peripheral edema, lower hemoglobin, and higher log CRP and log BNP levels as independent predictors of lower albumin level. In particular, CRP level had the strongest association with hypoalbuminemia. Cardiac mortality rates in Tertile-1, Tertile-2, and Tertile-3 were 14.1%, 5.3%, and 0.7%, respectively ($p<0.01$). After adjustment for covariate, the lowest albumin tertile was independently associated with 5-fold increased risk of mortality (HR 4.975, 95% CI 1.770-13.889, p=0.002).
Conclusions: Serum albumin level on admission predicts 6-month mortality in patients hospitalized for ADHF. In addition to malnutrition, acute inflammatory response plays a key role in the development of hypoalbuminemia that may result in fluid retention and HF exacerbation in patients with ADHF.

P1743 Exercise-induced reduction of lymphocyte G-protein coupled receptor kinase-2 (GRK2) strongly predicts improved survival in patients with heart failure

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Purposes: Increased cardiac G-protein coupled receptor kinase-2 (GRK2) expression/activity are pivotal events in the pathogenesis of heart failure (HF)-related β-adrenergic receptor (βAR) dysfunction. Importantly, in human HF, abnormalities of βAR signaling in the heart can be mirrored in circulating lymphocytes and are correlated with HF severity. Thus, in the present study we evaluated whether lymphocyte GRK2 and its changes after an exercise training program can predict long-term survival in HF patients.
Methods and results: At this aim, we prospectively studied 221 patients with advanced post-ischemic HF who underwent 3 months of exercise training. Lymphocyte GRK2 protein and mRNA levels, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) and norepinephrine were measured at baseline and after training along with clinical and functional parameters (left ventricular ejection fraction, NYHA class, and peak-VO2). Cardiac-related mortality was evaluated during a mean follow up period of 37±12 months.
Although basal lymphocyte GRK2 protein expression was not superior to the traditional prognostic markers in predicting cardiac mortality, exercise-induced reduction of this kinase in peripheral lymphocytes was the most powerful predictor of improved survival. Interestingly, the lack of any significant effect of exercise to reduce lymphocyte GRK2 protein levels identified those HF patients with the poorest outcome.

Multivariable Cox Proportional Hazard Survival analysis for exercise-induced changes (delta) of blood and functional parameters

Variable	Wald	P value
Delta lymphocyte GRK2 protein	45.27	<0.0001
Delta lymphocyte GRK2 mRNA	31,90	<0.0001
Delta Heart Rate	17.04	<0.0001
Delta Norepinephrine	15.91	<0.0001
Delta peak VO_2	4.10	0.043
Delta LVEF	3.80	0.051
Delta NT-proBNP	0.34	0.56

Conclusions: Our data offer the first demonstration that exercise-induced changes of lymphocyte GRK2 can strongly predict outcome in patients with advanced HF.

P1744 Risk factors for fatal and non-fatal cardiovascular events in 9306 subjects in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial

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We identified independent predictors of the composite of CV death, MI or stroke in 9306 pts with impaired glucose tolerance (IGT) using Cox multivariable proportional hazards regression modeling. 639 (6.9%) experienced the composite outcome; median follow-up was 6.4 yrs. Male sex, older age, black race, CV disease, abnormal ECG, smoking, and LDL predicted CV events. AF/flutter, DVT/pulmonary embolism, and COPD were also predictors. eGFR and urinary alb/Cr ratio gave additional predictive information. HbA1c, fasting and 2-hour post-load glucose levels were not predictive of CV events, but the range of these was narrow (due to inclusion/exclusion criteria) and follow-up was ~6 yrs.

Baseline characteristic	HR	Wald χ^2	P Value
Age (per 10 yr)	1.32	21	<0.001
Male vs female	1.89	41	<0.001
Black vs white	1.75	6	<0.02
Smoker	1.64	20	<0.001
Latin America vs North America	1.48	9	<0.01
Known coronary heart disease	2.10	69	<0.001
Cerebrovascular disease	1.56	16	<0.001
COPD	1.44	7	<0.01
AF/flutter	1.34	4	<0.05
DVT/pulmonary embolism	2.12	11	0.001
PAD	1.65	12	<0.01
Pulse pressure (per mmHg)	1.01	8	<0.01
Waist circum (per 10 cm)	1.08	5	<0.02
Hemoglobin (per g/dL)	1.09	6	<0.02
LDL (per mmol/L)	1.19	16	<0.001
Sodium (per mmol/L up to 140)	1.11	6	<0.02
Urinary alb/Cr ration (per log unit)	1.10	9	<0.01
eGFR per 10 mL/min/1.73m^2 (up to 60)	1.31	13	<0.001
Abnormal vs normal ECG	1.59	18	<0.001

In addition to traditional CV risk factors/existing CV disease, renal markers, pulmonary disease and history of venous thromboembolism may identify additional subjects with IGT who may benefit from CV preventive treatment.

P1745 Sitagliptin reduces myocardial fibrosis and hypertrophy and enhances PPAR-delta activation in experimental Type-2 Diabetes

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Background: Major characteristics of myocardium in DM2 are fibrosis and hypertrophy, and their related-molecular mechanisms need to be investigated. The anti-diabetic Sitagliptin (a dipeptidyl peptidase-4 inhibitor) improves insulin secretion in DM2 patients, but its cardiac effects have not been unveiled.
Methods: Goto-Kakizaki DM2 rats received Sitagliptin (100 mg/kg/day) for 10 weeks (n=10) or vehicle. Wistar rats were used as controls. Echo-Doppler was performed and plasma and left ventricles were collected for analysis. H9c2 cardiomyocyte cell line was used for in vitro assays.
Results: DM2 rats presented increased plasma levels of glucose, triglycerides, HDL, non-HDL and total cholesterol that were reduced by Sitagliptin. Blood pressure was normal in all rats. By Echo-Doppler, DM2 rats showed an increase of posterior wall (2.42±0.83 vs 1.89±0.75 mm; p=0.037) and septum thickness (2.15±0.4 vs 1.71±0.58 mm; p=0.021) with a prolonged deceleration time, suggesting diastolic dysfunction. Under histological examination, myocardium showed interstitial fibrosis and hypertrophy. By Western Blot and Q-PCR, there was increased expression of pro-fibrotic [Transforming growth factor-β (TGFβ; 4.0-fold vs control), Connective Tissue Growth Factor (CTGF; 4.8-fold), fibronectin (FN; 3.2-fold) and metalloprotease inhibitor (TIM-1; 3.43-fold)] and pro-hypertrophic [Atrial natriuretic peptide (ANP; 2.3-fold) and Cardiotrophin-1 (CT-1; 5.8-fold)] factors (all $p<0.05$). By EMSA, Peroxisome proliferator activating receptor-delta (PPARd) activation was diminished (0.38-fold; $p<0.05$). Sitagliptin reduced septum thickness (1.85±0.22 mm; p=0.019 vs DM2 rats), fibrosis and hypertrophy, and restored FN, TIM-1, ANP, CT-1 and PPARd levels. In cultured cardiomyocytes, co-stimulation with high concentration of glucose and palmitate diminished PPARd and induced pro-fibrotic (TGFβ, CTGF and FN) factors.
Conclusions: In experimental DM2 there is an increase of fibrosis and hypertrophy along with an enhanced expression of TGFβ/CTGF/FN and CT-1, and a reduced PPARd activity. Sitagliptin reverses these changes and could be useful to prevent DM2-induced myocardial damage.

P1746 The polymorphism G5665T on endothelin-1 gene affects endothelin-1 levels in patients with heart failure

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Purpose: Endothelin-1 is strongly implicated into the pathophysiology of heart failure, while its circulating levels are associated with the degree of heart failure. Although genetic polymorphisms have been identified in endothelin-1 gene, their effects on the expression of endothelin 1 and its circulating levels are unclear.

We examined the effect of G5665T polymorphism on endothelin-1 gene on left ventricular function and endothelin-1 levels in patients with ischaemic heart failure (IHF).
Methods: The study population consisted of 366 individuals: 204 patients with IHF and 162 healthy controls. Left ventricular ejection fraction was estimated by echocardiography. Plasma levels of ET-1 were measured by ELISA, while the presence of G5665T polymorphism on endothelin-1 gene was determined by PCR.
Results: Genotype distribution was GG: 53.2%, GT: 40% and TT: 6.8% for IHF and GG: 61.1%, GT: 32.1% and TT: 6.8% for the controls. There was no difference in the risk for IHF between the 5965G carriers and 5965T homozygotes (OR=0.90, 95%CI: 0.39-2.09, p=NS). Homozygosity for the T allele was associated with significantly higher levels of ET-1 (pg/ml) compared to the carriers of the G allele (2.44±1.9 vs 1.75±1.55, $p<0.05$) overall. The difference was not significant in the controls group (1.51±1.42 vs 1.10±0.73, p=NS). However, we observed a significant difference in the IHF group (2.44±1.9 vs 1.75±1.55, $p<0.05$). No effect was observed in the ejection fraction in all groups for TT vs GG+TG (59.5±1.6 vs 59.1±1.9 and 30.3±11.3 vs 28.4±6.6, p=NS for controls and IHF respectively)
Conclusions: The presence of 5665TT genotype of endothelin-1 gene is associated with significantly higher levels of endothelin-1. These findings suggest that G5665T polymorphism on endothelin-1 gene may have a significant impact in the pathophysiology of heart failure, by regulating the levels of endothelin-1.

P1747 Improvement in left ventricular ejection fraction during clinical follow up in the Canadian heart failure network

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Background: In heart failure (HF) patients, left ventricular (LV) function has been shown to improve with treatment in some randomized clinical trials. In a cohort of HF patients referred to, and followed clinically in, the HF outpatient clinics of the Canadian HF Network, we wished to identify the change in LV function in clinical practice.
Changes in LV ejection fraction (EF) at one and two years were compared to the first recorded LVEF measurement at a CHFN visit. 21 clinics contributed data from both academic and community centers between 1999 and 2010. Each clinic used Canadian and other national guidelines to direct appropriate HF therapies in their patients. The decision to perform an ECHO and its timing was made locally in each clinic.
Results: 599 patients had ECHO's with measurements of LVEF at time of their first CHFN clinic visit (±30 days) and a repeat measure at 1 yr (±3 months). 74% were male, mean age was 63.4±14.7 sd, and 43.4% were ischemic in aetiology. Mean LVEF at first visit was 31.8±14% (sd), at 1 yr was 38.4±14.5%, and at 2 yrs was 37.9±14.4%. Differences between baseline and 1 and 2 yrs were both statistically significant ($p<0.001$) as was the difference between yr1 and 2 (p=0.01). For categorized changes from baseline, 12.0% had an absolute increase in LVEF >20%, 14.7% had a 10-20% increase, 11.9% had a 5-10% increase, 54.9% had no change (within 5%), and 6.5% had a decrease in absolute LVEF >5%. Patients with age ≥70yrs or history of type II diabetes not on insulin, were significantly less likely to have an absolute LVEF change >5% while ischemic aetiology were more likely to improve LVEF >5% (both $p<0.05$). In those with an absolute increase of LVEF >5%, utilization of beta-blocker and ACEi increased from baseline (63.2, 52.4% respectively) to 1 year (85.3%, 68.8%) but similar increases in utilization occurred in those with no change or decrease in LVEF.
Conclusion: In an outpatient setting of specialized multidisciplinary HF clinics, clinically relevant improvements in LVEF were observed and may be associated with increases in evidence based therapies and follow up in specialized HF clinics.

P1748 Left sympathetic surgical blockade in systolic heart failure patients with optimised medical therapy

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Purpose: Sympathetic nervous system modulation is the cornerstone treatment for systolic heart failure (SHF). We sought to evaluate the feasibility, safety and potential beneficial effects of additional surgical sympathetic blockade in SHF patients.
Methods: In this prospective randomised controlled trial, inclusion criteria were: NYHA functional class II or III, left ventricular ejection fraction (LVEF) ≤40%, sinus rhythm and resting heart rate >65 bpm, despite optimal medical therapy (MT). Fifteen patients were randomly assigned in a 1:2 basis either to MT alone or MT plus surgical treatment (ST). ST consisted of left lower 1/3 stellar ganglion and T3-T4 thoracic interspinal space videothoracoscopic clipping. Primary endpoints were feasibility and safety. Secondary endpoints were changes in clinical status, exercise capacity, quality of life, LVEF and remodeling by echocardiography and heart rate before and after 6 months of randomisation.
Results: 10 patients underwent ST and there were no adverse events attributable to surgery. ST improved: LVEF (25±6.6 vs 33±5.2, p=0.03); 6-min walking distance in meters (167±35 vs 198±47), p=0.02); 24h-Holter mean HR (77±5 vs 72±4, p=0.0003; MLHFQ score (48±10 vs 40±14, p=0.01. 123I-MIBG radionuclide scan heart/mediastinum ratio, LV end diastolic diameter, sympathetic peripheral nerve activity, peak VO2, LVEF by Gated, serum BNP levels and 24h Holter NN standard deviation were unchanged. Two patients died at each group. Clinical status improvement was only observed at ST.
Conclusions: ST was feasible and safe in SHF patients. Its beneficial effects warrant the development of a larger randomized trial.

P1749 Disparity between matrix metalloproteinase-9 and tissue inhibitors of matrix metalloproteinase-1 correlated with the severity and adverse prognosis in patients with heart failure and systolic dysfunction

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Background: Serum matrix metalloproteinase (MMP) activity are upregulated in the failing human heart and influenced ventricular remodeling. We investigated whether circulating MMP species are related to the prognosis risk of heart failure (HF) and the correlations between circulating MMP-9, tissue inhibitors of MMP-1 (TIMP-1) levels and other biomarkers in patients with heart failure and systolic dysfunction.
Methods: We enrolled 173 HF patients with reduced left ventricular ejection fraction<50% and New York Heart Association (NYHA) class I-IV. Circulating levels of MMP-9, TIMP-1 and other biomarkers was determined by ELISA. Major adverse cardiovascular event (MACE) and cardiac death were assessed during the follow-up period. All patients were treated with ordinary regimen.
Results: Values of MMP-9/TIMP-1 increased with the severity of NYHA functional class (r=0.23, $P<0.05$). Values of MMP-9/TIMP-1 had significant positive correlations with levels of interleukin-6, noradrenaline and tumor necrosis factor-alpha. Patients who had MACE had high values of MMP-9/TIMP-1 ($P<0.05$). Non-ischemic heart failure patients (n=101) had higher values of MMP-9/TIMP-1 ratio compared with ischemic ones (n=72) ($P<0.05$). During the follow-up period (average of 88±49 months), 44 patients had MACE, including 25 cardiac deaths. We divided our follow-up population into two groups based on the median values of MMP-9/TIMP-1. Kaplan-Meier analysis demonstrated a higher probability of MACE and cardiac death in the high values of MMP-9/TIMP-1 group ($P<0.05$). According to stepwise multivariate analysis, only high values of MMP-9/TIMP-1, not B-type natriuretic peptides, remained significantly predictive of MACE throughout the follow-up period.
Conclusions: Values of MMP-9/TIMP-1 correlate the severity and inflammatory cytokine in HF patients. The high value of MMP-9/TIMP-1 is a significant predictor of clinical outcomes and a strong predictor of MACE in heart failure. MMP-9 and TIMP-1 levels allow further risk stratification, suggesting the disparity between MMP-9 and TIMP-1 contribute to the occurrence of MACE in patients with HF and systolic dysfunction.

P1750 HCN channel inhibition with ivabradine prevents sudden arrhythmic death in a mouse model of dilated cardiomyopathy

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Purpose: Pharmacological interventions for preventing sudden arrhythmic death in patients with chronic heart failure still remain limited. Growing evidence in humans and animals demonstrates that the hyperpolarization-activated cyclic nucleotide gated channels (HCN channels) is over expressed in failing hearts and potentially involved in the increased arrhythmogenicity. The ability of HCN channels inhibition to prevent lethal arrhythmia associated with heart failure, independent of heart rate reduction, has never been tested, however.
Method: Transgenic mice expressing a dominant-negative mutant of neuron-restrictive silencer factor in a cardiac–specific manner (dnNRSF-Tg) exhibit dilated cardiomyopathy, high susceptibility to arrhythmia and sudden death. We showed that the HCN channels are over-expressed in this model, and are potentially responsible for the observed arrhythmic death. We therefore examined the effects of ivabradine (Iva, 7 mg/kg/d in drinking water from 8 weeks of age), a specific HCN channel inhibitor on survival and arrhythmogenicity in dnNRSF-Tg.
Results: The dose of Iva used did not significantly reduce the heart rate in dnNRSF-Tg (after 12 weeks treatment, Tg/vehicle; 575±21 bpm,and Tg/iva; 547±20 bpm; p=0.48). Iva significantly improved the survival among dnNRSF-Tg mice (%survival at 32 weeks of age; 75.3% with Iva (n=28), 36.1% without

Iva (n=54); $p<0.05$). Though echocardiographic, hemodynamic, and histological analyses showed no significant difference between dnNRSF-Tg mice with and without Iva, ECG telemetric monitoring showed the reduction of arrhythmias in dnNRSF-Tg mice treated with Iva compared to those without Iva (VT; 19/h with Iva (n=7), 92/h without Iva (n=7), $p<0.05$), suggesting that Iva improved the survival by preventing lethal arrhythmias.
Conclusion: Iva significantly reduced lethal arrhythmias in the mouse model of dilated cardiomyopathy and sudden death independently of heart rate reduction. Our findings suggest HCN channel inhibition with Iva is a useful approach to preventing lethal arrhythmias in some pathological conditions of hearts.

P1751 Transthoracic echocardiography with Doppler tissue imaging for predict weaning failure from mechanical ventilation

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Objective: New onset of heart failure during spontaneous breathing trial (SBT) is a frequent cause of weaning failure from mechanical ventilation. We evaluate the ability of transthoracic echocardiography with E/Ea mitral ratio measurement, to predict weaning failure from mechanical ventilation in intensive care unit.
Method: The sample included patients on mechanical ventilation for over 48 hours who underwent a first SBT. A complete echocardiography was performed just before the SBT and 10 minutes after starting the SBT. Value of E/Ea mitral ratio was compare between baseline and 10 minutes after starting the SBT in all patients.
Results: 38 patients were included,12 failed the weaning process and were assessed in the failure group, The others 26 patients were assessed in the success group. Before the SBT E/EA ratio was higher in the failure group than in the success group (13,2 vs 8,35 p=0,01), E/Ea measured during SBT was also higher in the failure group (18 vs 10,4 p=0,0002) Cutt off values using ROC curve analyses to predict weaning failure was 12, 3 for E/EA ratio at baselinep=0,01. SBT was accompanied by a significant increase in E/Ea mitral ratio in failure group (13,2 vs 18 p=0,004) while no variation was observed in the success group (8,35 Vs 10,4, p=0,62). LVEF did not differ between the 2 groups (60 vs 55%, p=0,9) whereas Ea velocity was lower in the failure group (6,5 vs 8 cm/sec, p=0,03)

Baseline characteristics of patients

	Success of weaning (N=26)	Weaning failure (N=12)	P
LVEF	60 (50–60)	55 (45–65)	0.9
E wave	71,2 (66–75,6)	74,7 (59–91,2)	0.55
Ea	8 (7–9,5)	6,5 (5,9–7,9)	0.03
E/Ea	8,35 (7,5–10,35)	13,2 (8,5–16,6)	0.01
Relaxation abnormalities prevalence n(%)	8 (30.7%)	10 (83.3%)	0.004
Systolic dysfunction n	7 (27%)	4 (33%)	0.7

Data are presented as the percentage of patients or median with interquartile. LVEF: left ventricular ejection fraction; Ea: protodiastolic mitral annulus velocity.

Conclusion: E/Ea ratio measured with TTE and DTI used detect LVFP rising during SBT and could predict weaning failure.Diastolic dysfunction with relaxation impairment is closely associated with the weaning failure whereas systolic function seems to not influence the weaning outcome.

P1752 A mechanism of sudden cardiac death in patients with congestive heart failure and Cheyne-Stokes respiration

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Introduction: Previous studies confirmed Cheyne-Stokes respiration (CSR) an independent risk factor for malignant arrhythmic events and sudden cardiac death in patients (pts) with congestive heart failure (CHF). However, mechanisms involved remain unclear. This study aimed to clarify the role of nocturnal hypoxaemia and respiratory instability as underlying mechanisms.
Methods: 215 pts with CHF (persistent LVEF $<$ 40%, functional NYHA-class $\geq$ 2) and implanted cardioverter-defibrillator device (133 pts with concomitant CSR (apnoea-hypopnea index (AHI) $>$5/h, and 82 pts with obstructive sleep apnoea (OSA, AHI $>$5/h) as a control-group) were included. At baseline, all pts underwent cardiorespiratory polygraphy, capillary blood gas analysis, echocardiography, cardiopulmonary exercise testing (CPX), and rebreathing test. We defined lowest oxygen saturation, longest apnoea, longest hypopnoea and AHI during polygraphy as measures of hypoxaemia, and increased hyperoxic, hypercapnic, ventilatory response (HCVR), higher VE/VCO-slope during CPX, and daytime hypocapnia as measures of respiratory instability. Patients were followed up for a median period of 15months (range 3 to 51 months), and end point was defined as aborted sudden cardiac death (ventricular tachyarrhythmia treated by cardioverter-defibrillator).
Results: Among the CSR group 49 pts (36.8%) suffered from appropriate defibrillator therapies, among the control group 27 pts (32.9%). Forward stepwise logistic regression analysis, adjusted for sex, age, functional NYHA-class, BMI, and LVEF revealed lower daytime pCO2 (p=0.01) and higher VE/VCO2-slope during CPX (p=0.03) independent predictors for appropriate cardiverter-defibrillator therapies. In addition, increased HCVR (p=0.07) tended to be an independent predictor. Lowest oxygen saturation, longest apnoea duration, longest hypopnoea duration and AHI did not show an association. In the control-group only lowest oxygen saturation (p=0.07) tended to be a predictor.
Conclusion: This study suggests that among CHF pts with CSR daytime hypocapnia and increased VE/VCO2-slope during CPX, eliciting neurohormonal derangement and respiratory instability, but not measures of nocturnal hypoxaemia predict malignant ventricular arrhythmias. Treatemt of CSR therefore should not only focus on suppressing apnoeas and hypopnoeas but even more important on stabilizing respiratory instability.

P1753 Impact of high risk pregnancy on left ventricular function during peripartum period: from the Toyota peripartum cardiomyopathy study

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Background: Peripartum cardiomyopathy (PPCM) is a rare (1 in 3000 to 4000 live births) but serious form of cardiac failure affecting women in the last months of pregnancy or early puerperium. However, it remains uncertain whether mildly impaired left ventricular (LV) function without typical symptom, which could not achieve the criteria of PPCM, can occur in a significant proportion of patients. The goal of the present study was to evaluate LV systolic and diastolic function during perinatal or puerperal period in high-risk pregnant women
Methods: A consecutive series of 112 high-risk pregnant women without history of cardiac disease underwent ultrasound cardiography within 10 days before and/or after delivery. High risk pregnancy was defined as gestational hypertension, twin pregnancy, tocolytic therapy, or $\geq$35 years of age.
Results: PPCM occurred in 3 cases (2.7%) during postpartum period. There were no significant differences in LV ejection fraction, the ratio of the mitral E velocity to E' (E/E'), B-type natriuretic peptide or troponin-I levels between pre- and post-delivery. LV diastolic function was deteriorated (E/E' $\geq$15) in 15 cases (15.0%) at pre- or post delivery, whereas only 3 patients (2.7%) showed an impaired LV systolic function (LV ejection fraction $<$45%). Pregnant women with E/E' $\geq$15 were more likely to have gestational hypertension (73% vs. 39%, P=0.013) and undergo caesarian delivery (79% vs. 46%, P=0.023). Multivariate analysis identified the presence of gestational hypertension (odds ratio, 4.09; 95%CI, 1.18-14.19; P=0.026) as independently associated with an impaired LV diastolic function (E/E' $\geq$15) during peripartum period.
Conclusions: In women with high risk pregnancy, frequency of PPCM after delivery was higher than rates reported previously. Our results also suggested that an impaired diastolic function was found to be relatively common during peripartum period, which might be associated with gestational hypertension in this particular population.

P1754 Evidence of subtle left ventricular systolic dysfunction and worse prognosis in asymptomatic hemodialysis patients with preserved left ventricular ejection fraction and elevated cardiac troponin T

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Purpose: Among stable end-stage renal disease (ESRD) patients, the increased level of cardiac troponin T (cTnT) is an independent predictor of poor prognosis. However, accurately assessing cardiac function of asymptomatic ESRD patients with raised cTnT concentration and preserved left ventricular ejection fraction (LVEF) remains a challenge. We conducted a cohort study to examine the LV systolic function and prognosis between asymptomatic hemodialysis patients with different level of cTnT.
Methods: One hundred and nine asymptomatic ESRD patients undergoing maintenance hemodialysis ($\geq$3 months), without LVEF $<$50%, severe valvular heart disease, atrial fibrillation, pulmonary edema, or acute coronary syndrome, received echocardiography with tissue Doppler imaging analysis, and 2-dimensional speckle-tracking echocardiography with strain analysis (2D strain analysis). Serum cTnT, high sensitivity C-reactive protein (hsCRP), and albumin were measured. Patients were stratified by level of cTnT $\geq$0.05 ng/ml (age 70.1$\pm$13.3 years, male 46%) and cTnT $<$0.05 ng/ml (age 66.5$\pm$10.3 years, male 50%).
Results: These patients were studied over a 2-year period. Between these 2 groups, there was no significant difference of gender, age, LVEF, systolic myocardial velocity, and the level of hsCRP. Patients, with high level of cTnT ($\geq$0.05 ng/ml), presented with lower serum albumin level (3.13$\pm$0.33 g/dL vs. 3.38$\pm$0.41 g/dL, p=0.008) than those in the other group. By strain analysis, among patients with high cTnT level, reduced global LV peak systolic longitudinal strain (GSl;

high level cTnT vs. low level cTnT group:-16.8±3.3% vs. -19.0±3.6%, p=0.02), and circumferential strain rate (high level cTnT group vs. low level cTnT group:-1.72±0.40 vs. -2.02±0.60, p=0.02) developed. There was a correlation between GSI and level of cTnT (r=0.36, p<0.001). In a multivariate regression analysis, deteriorated GSI was an independent correlate of cTnT level in asymptomatic hemodialysis patients (p=0.03, 95% C.I. 0.531-0.974). Importantly, 2-year mortality rate was higher in the high cTnT group (high level cTnT group vs. low level cTnT group: 40% v.s. 9.8%, p=0.003)
Conclusions: Among stable hemodialysis patients, LV systolic function deteriorated along with the increasing level of cTnT. Those hemodialysis patients with increased level of cTnT (≥0.05 ng/ml) presented with worse LV systolic function and higher mortality rate than others with cTnT <0.05 ng/ml.

P1755 High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction

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Purpose: For a long time, enteroviruses have been considered to be the most common cause of acute viral myocarditis (MC), with possible transition from MC to dilated cardiomyopathy (DCM). Recent investigations have shown, however, that other viruses are also frequently encountered in MC patients, suggesting that persistence of various virus species may play a pathogenic role in the transition from MC to DCM. The purpose of this study was to screen endomyocardial biopsies (EMBs) from patients with "idiopathic" DCM for the presence of viral genomes by using polymerase chain reaction (PCR) to assess the frequency of cardiac viral infections that may be involved in the pathogenesis of the disease.
Methods: EMBs were obtained for PCR analysis from 90 consecutive patients (median left ventricular ejection fraction, 35.0%; range, 9% to 59%). PCR was performed to detect the genomic sequences of enterovirus (EV), adenovirus (ADV), human cytomegalovirus (HCMV), herpes simplex virus, Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), parvovirus B19 (PVB19), and influenza A and B viruses. Myocardial inflammation was assessed by histological and immunohistological analyses.
Results: Viral genomes could be amplified from EMBs of 75 (83.3%) of the 90 DCM patients: EV=25 (33%), ADV=5 (6.6%), PVB19=5 (6.6%), HHV-6=4 (5.3%), EBV=5 (6.6%), HCMV=6 (8%), including n= 35 cases (46.6%) with multiple infections. Active or borderline myocarditis according to the Dallas classification did not exist in any case. Lymphocyte and macrophage infiltrates were not significantly different in virus-positive versus virus-negative patients.
Conclusions: Viral genomes were frequently detected in EMBs of patients with systolic left ventricular dysfunction. Our data suggest that myocardial persistence of various viruses, often presenting as multiple infections, may play a role in the pathogenesis of DCM far more frequently than suspected so far.

P1756 Anaemia versus iron deficiency in heart failure

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Background: Anaemia is known to impact adversely on outcome in heart failure. This study investigated in a cohort with chronic heart failure (CHF) the prevalence of anaemia and various factors involved in haematopoesis. The aim was to elucidate their individual importance and possible causative role for anaemia development.
Methods: The study population consisted of 427 patients attending follow-up six months after hospitalization for decompensated systolic HF. Besides clinical assessment, blood chemistry including Hb, markers of iron metabolism and renal function, hsCRP and BNP were analyzed. Anaemia was defined according to WHO-criteria ((Hb <13/12g/dL in men/women), renal dysfunction as glomerular filtration rate <60mL/min/1.73m^2 and iron deficiency as ferritin <100μg/L or ferritin 100-300 μg/L plus transferrin saturation <20%. Patients with mild and advanced HF were compared.
Results: At follow-up 158 patients were in NYHA III/IV. NYHA I/II patients were younger (64±13 vs. 69±11 years, p<0.001). There were no significant differences regarding sex (77% vs. 73%, p=0.41), left ventricular ejection fraction (LVEF; 32±8 vs. 31±8%, p=0.26), and CHF aetiology. Results on anaemia, renal dysfunction, markers of iron metabolism and inflammation are shown in the table. Iron deficiency was more common and serum erythropoietin higher in this group.
Conclusion: While anaemia is common in CHF, iron deficiency is even more prevalent. Besides renal dysfunction and systemic inflammation, iron deficiency might thus play the most crucial role in CHF-related anaemia.

Heart Failure Symptoms	NYHA I / II	NYHA III / IV	p
Number of Patients, N	269	158	
Anaemia (%)	15.7	26.5	<0.01
GFR <60mL/min/1.73m^2 (%)	29.4	57.7	<0.001
BNP [pg/mL]	134,3 [54,4; 291,6]	274,4 [156,2; 661,6]	<0.001
High sensitive CRP [mg/L]	2,2 [1,1; 6,4]	4.0 [1,5; 10,9]	0.01
Iron deficiency (%)	36.4	47.1	<0.01
Ferritin [μg/L]	175 [96; 300]	143 [88; 291]	0.157
Transferrin [mg/dL]	276 [246; 309]	279 [246; 317]	0.102
Transferrin saturation [%]	24,9 [20,0; 31,7]	21,0 [14,7; 28,3]	<0.01
Erythropoietin [mIU/mL]	12,0 [7,9; 18,9]	16,5 [10,0; 29,0]	<0.01

P1758 Accurate design of randomized placebo-controlled clinical trials for assessment of stem cell effects on cardiac regeneration

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Background: Currently performed randomized trials on stem cells (SC) in congestive heart failure (CHF) have been focused on such end-points as left ventricular (LV) volumes, ejection fraction (EF), infarct size, life quality and not aimed to assess more subtle processes of SC actions.
Purpose of our randomized prospective placebo-controlled trial was to evaluate paracrine effects of autologous bone-marrow CD133+ progenitors in CHF patients.
Methods: Fifty CHF patients (24 with ischemic dilated cardiomyopathy [ICMP] and 26- idiopathic dilated cardiomyopathy [IDCMP]) were randomized to CD133+/placebo delivery: selectively percutaneously intracoronary or transendocardially. Apart from standard methods, we assessed 11 plasma biological markers (VEGF165, FGFb, PlGF, Angiogenin, Angiopoetin-1/2, Endostatin, MMP-9, TNF-a, SDF-1α, NTpro-BNP).
Results: Single isolated transendocardial CD133+ delivery resulted in LVEF increase in 3-6 months in ICMP patients and perfusion defects reduction in CD133+ "treated" viable segments compared to placebo. Paracrine effects exerted transiently in ischemic scarred viable myocardium and did not exert in non-ischemic dilated myocardium (Figure 1).

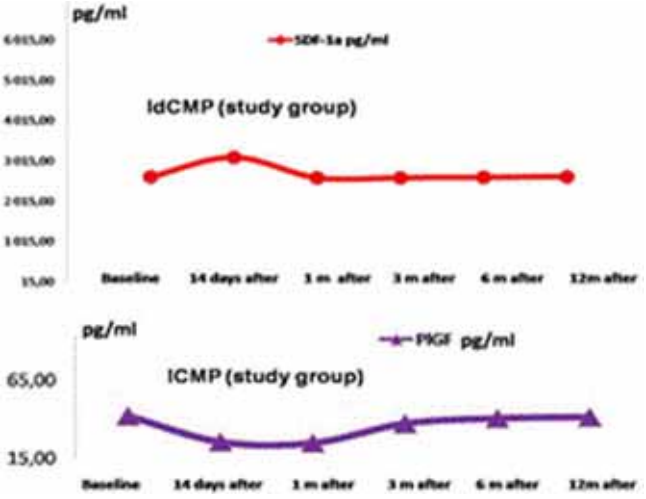

Figure 1. SDF-1a/PlGF dynamics.

Conclusions: CD133+ had transient paracrine effects in ICMP patients and were inefficient in IDCMP patients. This phenomenon is due to significant up-regulation of SDF-1α and other SC homing factors in scarred myocardium. Similarly designed studies can enlighten future potential for successful restoration of degenerated myocardium.

P1759 Does malnutrition determined by the Mini Nutritional Assessment (MNA) test retain its influence on long-term mortality in hospitalized patients with heart failure?

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In the study of heart failure (HF), a great number of prognostic factors have been identified. Previously, our working group has established that malnutrition determined by the Mini Nutritional Assessment (MNA) test is an independent predictor of medium-term mortality in hospitalized patients with HF. The MNA test has been designed and validated to provide a single, rapid assessment of nutritional status. The sum of the MNA score distinguishes between patients with: adequate nutritional status, MNA ≥24; undernutrition, MNA <17; at risk for malnutrition, MNA between 17 and 23.5. The aims of this study were to evaluate if malnutrition determined by MNA score retains its influence on long-term mortality in patients with HF. For this purpose, 208 consecutively discharged patients after a HF

hospitalization from January 2007 to March 2008 were prospectively analysed. Previous to discharge, a global evaluation by the MNA test were performed (anthropometric measurements, global assessment, dietary questionnaire and subjective assessment). In addition to this, usual demographic, clinical, functional and treatment variables were studied. The mean age was 73±10 years, 46% were female and the most frequent etiology was ischemic heart disease (41,8%). Overall mortality was 37,2% (the median of follow-up was 25 months, interquartile range 12-32 months). 13% of the patients were classified as undernutrition (group A) and 59,5% were classified as at risk of malnutrition (group B). The remaining 27,5% were classified by the MNA as adequate nutritional status (group C). All 3 groups were homogenous in the etiology of heart failure (ischemic etiology: 40%, 39% and 45%, respectively, p=0,11). However, patients of groups A and B were older than patients of group C (78.6±7.9, 72-6±9.6 and 70-8±10.9 years, respectively, p=0,005). Moreover, groups A and B presented a higher percentage of female (80%, 47,8% and 22,6%, respectively, p<0,001), lower serum hemoglobyn (11.16±2, 12.02±1,9 and 12.9±2 g/dl, respectively, p=0,001) and lower creatinine clearance (40,2±20,5, 55,1±25,1 and 57,4±19 ml/min, respectively, p=0,006). At 25 months of follow-up, group A mortality was 76%, group B 35,9% and group C 18,9% (Log-rank, p<0,001). When Cox multivariate analysis was performed, the state of malnutrition determined by the MNA test was an independent predictor of mortality (HR 3.75; 95%CI, 1.75-8.02, p=0,001).
Conclusion: We have found that the MNA score retains its influence on long-term mortality in patients with HF and become as a strong independent predictor of mortality in these patients.

P1760 Single centre long term follow-up of undersized mitral annuloplasty for mitral regurgitation in end-stage dilated cardiomyopathy

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Purpose: Heart failure is currently one of the leading causes of death and hospitalization. In patients with dilated cardiomyopathy, functional mitral regurgitation (MR), secondary to left ventricular dilation and dysfunction, is a frequent serious complication that makes the prognosis worse, causing more frequent and more severe episodes of congestive heart failure.
Patients and methods: Between March 1998 and January 2010 at our Centre, 44 patients (30 male, mean age 58.9±10.9 yy) with end-stage dilated cardiomyopathy and • left ventricular echocardiography ejection fraction <30%; • ≥ III+/IV+ mitral regurgitation, with normal mitral leaflet; • LV indexed end-diastolic volume ≥100 ml/m^2 underwent undersized mitral annuloplasty. Their mean duration of documented heart failure was 82.6±75 months. Eleven patients with coronary artery disease underwent concomitant coronary artery bypass graft.
Results: Intra-operative transesophageal echocardiography revealed no or trivial mitral regurgitation in all patients. The average ring size used was 28 mm. There was no intra-operative mortality. In the postoperative period, eleven patients required longer than 24 h of mechanical ventilator support. There were two in-hospital deaths for irreversible low output syndrome, 9 and 23 days after surgery. Forty-two patients have been discharged after a mean hospitalization of 13.8±7 days. All discharged patients have been periodically visit at our Centre, at June 2009 mean follow-up was 59.1±39.1 months (range 3- 128 months). Eleven patients (256%) required readmission for heart failure, six of them were enlisted for heart transplantation (HTx) and five successfully heart transplanted (12%) 21.4±19.2 months after surgery. Eight (19%) late deaths occurred after a mean time from surgery of 31.3±34.7 months. Actuarial survival of all the population is 90.5±4.6%, 83.1±6.0% and 73.9±6.6% respectively after 1, 2 and 5 years. Freedom from cardiac event (death, readmission for heart failure) is 94.8±3.6%, 77.5±6.9% and 67.1±8.3% respectively after 1, 2 and 5 years from surgery. Follow-up echocardiography was available for all patients and shows mean value of EF 34.1±9.4% (pre-op 27.3±3.4%), EdVi 99.6±36 ml/m^2 (pre-op 132.3±28 ml/m^2), pulmonary artery pressure 38.4±7.3 mmHg (pre-op 51.6±11.4 mmHg).
Conclusions: Undersized mitral annuloplasty can be performed in patients with advanced heart failure with low perioperative morbidity and mortality and should be an important and useful procedure in cardiomyopathy patients in an effort to prolong the time to HtTx or even avoid heart transplantation.

P1761 Anemia in heart failure: iron metabolism dictates hepcidin levels in stable outpatients

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Purpose: To study the interaction of iron metabolism, inflammation, renal impairment and bone marrow responses in heart failure-related anemia. While hepcidin inhibits iron intestinal absorption and distribution through the body, positively induced by inflammation in mainly decompensated heart failure scenarios, it is also suppressed by anemia, hypoxia, erythropoietin (EPO), and iron deficiency status. We hypothesized that in stable heart failure patients with anemia, hepcidin is mainly governed by iron stores status. We thus evaluated hepcidin production in heart failure outpatients with and without anemia and explored main factors associated with its profile.
Methods: In this cross-sectional study, stable systolic heart failure outpatients underwent clinical and laboratory evaluation, including complete iron panel and EPO levels. Hepcidin and tumor necrosis factor (TNF)-α were measured by ELISA.
Results: Sixty heart failure outpatients (mean ejection fraction 30±8%, 70% male) were studied. Anemic patients (n=38, mean hemoglobin 11.4±1 g/dL) were older (69.6±9.6 vs. 58±10.8 years old, P< 0.01) and had worse renal function (creatinine 1.4 [0.7 – 4.5] vs. 1.15 [0.6 – 2.2] mg/dL, P<0.04) than non-anemic patients (n=22, mean hemoglobin 13.8±1.1 g/dL). Iron deficiency was present in 42% of patients with anemia and in 27% of non-anemic patients, P=0.25. Levels of TNF-α and hepcidin were 29 and 21% higher in patients with anemia, respectively (P<0.05), compared to non-anemic patients. In the entire group of patients, after adjustment for glomerular filtration rate (GFR) and age, hepcidin remained weakly correlated to transferring saturation (TSAT) (r = 0.27; P=0.04); when the group of patients with anemia and heart failure was separately analyzed, the association of hepcidin and TSAT was also observed, but stronger (r=0.45; P<0.01). However, hepcidin was not associated to TNF-α and to log EPO (r = - 0.11; P=0.53 and r = - 0.24; P=0.19 respectively).
Conclusions: In conclusion, in stable heart failure patients with anemia, hepcidin appears to be mainly governed by iron stores status rather than by inflammation. Our data suggest that iron stores preponderance on hepcidin behavior indicates that optimization of iron availability for erythropoiesis prevails in compensated heart failure.

P1762 Treatment at discharge of acute heart failure: The OFICA study

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Aims: OFICA is a nationwide, observational study of acute heart failure (AHF), which was designed to analyze AHF in the real world. Treatment at discharge was particularly analyzed because of its importance on outcome.
Methods: A single-day snapshot was performed on 2009 in 170 French public and privates hospitals. Investigators were encouraged to include all hospitalized patients with a diagnosis of AHF. Relevant data was recorded about whole hospitalizations, including treatment at discharge.
Results: The survey included 1658 patients with confirmed diagnosis (76±13y, 45% females, 30% of preserved LVEF). In-hospital mortality was 8.2%. Among the 1517 survivors, treatment at discharge included diuretics in 84.0% of cases, ACE-I in 53.1%, ARB in 11.9%, betablockers in 53.5%, aldosterone inhibitors in 17.5%, digoxin in 9.4%, calcium channel blockers in 17.1%, amiodarone in 22.3% and anticoagulants in 43%. Among patients with LVEF ≤0.40, these rates were: diuretics in 87.6% with a mean dose of 138mg/d, ACE-I or ARB in 73.5% with a mean percentage of the target dose of 42%, betablockers in 65.7% with a mean percentage of the target dose of 36%, and aldosterone inhibitors in 25.2% cases. Among patients with history of HF before admission, there was a significant increase in rates of prescription of these drugs between admission and discharge. By using stepwise logistic regression analysis, parameters associated with prescription of ACE-I/ARB were: age (OR 0.98 95CI 0.96-0.99), natriuretic peptides quartiles levels (OR 1.50 95CI 1.10-2.04), LVEF (OR 1.69 95CI 1.10-2.61) as well as renal function (1.02 95CI 1.00-1.04). For betablockers, these parameters were COPD (OR 0.63 95CI 0.51-0.90), age (OR 0.98 95CI 0.96-0.99) and non-ischemic heart disease (1.34 95CI 1.21-2.14). Rate of prescription of aldosterone inhibitors was impacted by age (OR 0.89 95CI 0.85-0.93) and LVEF (OR 0.80 95CI 0.68-0.93).
Conclusion: The OFICA survey is a valuable tool for analyzing the management of AHF in the real world. As compared to guidelines, gaps remain in treatment at discharge, especially for elderly patients and those with COPD, renal insufficiency as well as non-ischemic etiology.

P1763 Percutaneous carbon dioxide gas mist ameliorates cardiac remodeling after myocardial infarction in rats

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Purpose: Carbon dioxide (CO2) bathing has been used to treat some cardiac diseases. However, the effect of CO2 gas mist has not been examined. In this study, we hypothesized that a few micrometers of CO2 particle (CO2 gas mist) would have potential therapeutic benefits on patients who have had myocardial infarctions (MI). We investigated the following issues: (1) whether

percutaneous CO2 gas mist had useful effects compared with CO2 gas, and (2) whether percutaneous CO2 gas mist prevented cardiac remodeling after MI in rats.
Methods: MI was induced by ligation of the left coronary artery in rats. CO2 gas mist was generated using a gas mist production unit, which atomized CO2 gas with H2O by two fluid-nozzles. The whole body of the rat below the axilla was placed in a polyethylene bag filled with percutaneous CO2 gas mist for 30 minutes once a day. In order to compare the effects of CO2 gas mist with CO2 gas, we measured tissue blood flow in the shallow part of the tissue with laser tissue blood oxygenation monitors by near-infrared spectroscopy, and subcutaneous tissue pH using a digital pH-mV meter during the experimental procedure. Moreover, MI rats were divided into 3 groups: (1) no mist group, (2) CO2 gas mist group, and (3) CO2 gas mist and NG-nitro-L-arginine methyl ester (L-NAME) group. At 4 weeks, we assessed cardiac function using echocardiography, serum nitrate concentration, and vascular endothelial growth factor (VEGF) mRNA expression in the myocardium.
Results: The CO2 gas mist group had significantly increased oxygenated hemoglobin levels and tissue saturation, and significantly decreased deoxygenated hemoglobin levels and subcutaneous tissue pH, compared with the no mist group. Moreover, the CO2 gas mist group had a significantly increased ejection fraction compared with the no mist group. Interestingly, the CO2 gas mist group had significantly increased nitrate concentrations and VEGF mRNA expression compared with the no mist group. These improvements were significantly abolished with L-NAME treatment.
Conclusions: Our present study shows for the first time that percutaneous CO2 gas mist can prevent cardiac remodeling after MI, cause the induction of regional VEGF synthesis, result in an increase in NO activity, lower pH conditions, and increase subcutaneous blood flow. These results suggest that percutaneous CO2 gas mist may be a potentially useful therapy for heart failure due to MI.

P1764 Results of a randomized clinical study evaluating nurse-driven telemedicine interventions for high risk chronic heart failure patients with frequent rehospitalizations

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Purpose: A randomized controlled clinical study using Zelen's design was initiated with the aim to improve quality of life (QoL) and reduce rehospitalizations among chronic heart failure (CHF) patients. The hypothesis is to test if an individually customized nurse-managed telephone support program proactively targeting high risk CHF patients could improve quality and efficiency of their care.
Methods: A team of physicians identified and randomized patients with systolic or diastolic CHF, who had been hospitalized $\geq$2 times with the primary diagnosis CHF during the past 12 months. Patients were invited to meet with a specially trained nurse/care manager for a one-hour structured interview investigating possible causes of frequent rehospitalizations. Gaps within the patients' care were identified and specific actions to alleviate the patient's situation (e.g. establishing a primary care contact, booking a specialist or a heart failure nurse appointment, securing home care) were completed. Thereafter regular medical telephone support (structured and planned phone calls) by the same nurse was offered to the patients with the aim to coach and support patients.
Results: The study patients (n=139, median age 82 years [range 44-97], 43% females) had a median of 3 hospital admissions (range 2-17) and 26 outpatient visits to physicians during 12 months before participation at a direct health care cost of 24106 Euros per patient. Data obtained 90 days after initiating the program showed reduced number of rehospitalizations, improved QoL measurements (SF-36) and 16% lower health care costs (randomized program participants vs. control group, n=93 and n=46, respectively). The nurses made 258 health care actions in the intervention group, 160 (62%) concerning self-care, coaching and education, 98 (32%) were contacts with other care givers. A complete evaluation of the entire study (7 month of observation time) will be available at the time of this conference.
Conclusions: Preliminary data indicate that nurse managed telephone support programs can improve quality of care and reduce hospitalizations and costs among high risk CHF patients. Keys to success are (1) an analytically driven selection process identifying patients who benefit from participation (2) customized interventions focusing to close "care gaps" that causes readmission, and (3) rigorous follow-up on results.

P1765 Incidence and predictors of postoperative Heart Failure(HF) in patients undergoing elective noncardiac surgery

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Purpose: Heart Failure is a major concern after surgery. However predictors of Postoperative Heart Failure (HF) after noncardiac surgery (NCS) have not been well studied.
Methods: Patients of age>18 and undergoing elective NCS (from 1/1/2005 yo 12/31/2007) requiring at least an overnight stay were identified. Demographics, diagnoses, labs, medications and primary outcomes, including postoperative HF were obtained from the electronic medical record. All postoperative HF events were validated by individual chart analysis. Missing values in the predictor variables were multiply imputed by chained equations in order to effectively utilize the sample size. A stepwise selection method identified the important predictive variables in the multivariable logistic regression. Concordance indices were calculated for the selected final models to assess predictive accuracy.
Results: 579 (1.7%) developed postoperative new onset or HF exacerbation of which 429 were new onset postoperative HF. All patients required intravenous medications for diuresis. 19 clinical variables were found to be important predictors of postoperative HF in the stepwise multivariable logistic analysis. 13 of them (see Table) were statistically significant (p-values $<$ 0.05). Table).Age, hypertension, hyperlipidemia, insulin dependent diabetes, MI, HF, atrial fibrillation, sleep apnea, vascular surgery, platelet count, hematocrit, glucose and calcium were independent predictors of postoperative HF. The reduced model achieved concordance index of 0.842 for PHF after internal cross-validation

PREDICTOR VARIABLES	P-VALUE	ODDS RATIO
Patient Age: 69 vs 47	<0.001	3.63 (2.84, 4.63)
Hypertension: yes vs no	0.014	0.75 (0.60, 0.94)
Myocardial Infarction: yes vs no	0.002	2.06 (1.31, 3.26)
Heart Failure: yes vs no	<0.001	10.80 (8.36, 13.96)
Atrial Fibrillation: yes vs no	<0.001	1.84 (1.37, 2.47)
Sleep Apnea: yes vs no	0.003	1.88 (1.24, 2.85)
Hyperlipidemia: yes vs no	0.005	0.70 (0.55, 0.90)
Calcium: 12 vs 10	<0.001	0.76 (0.67, 0.86)
Glucose: 114 vs 85	<0.001	0.92 (0.81, 1.06)
Hematocrit: 38 vs 32	<0.001	3.24 (1.80, 5.84)
Platelet Count: 316 vs 210	0.004	0.86 (0.76, 0.97)
Insulin Dependent Diabetes: yes vs no	0.006	1.63 (1.15, 2.32)
Vascular Surgery: yes vs no	<0.001	2.09 (1.67, 2.60)

* restricted cubic splines were applied to numeric predictor variables to relax linearity assumption. Odds ratio for numeric predictors was measured for the amount of the third quartile compared to the first quartile.

Conclusions: A Predictive model of risk for postoperative HF was generated. Components of the model contain easily determined factors that can be entered into risk stratification tools that may be used in preoperative assessments for NCS

P1766 Incidence of cardiotoxicity of trastuzumab in Her2Neu positive breast cancer patients: a retrospective cohort study

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Introduction: HER2neu-receptor blocking agents, such as Trastuzumab, have evolved as promising agent in the treatment of breast cancer with overexpression of the human epidermal growth factor receptor 2 protein (HER2). A well-known downside of treatment with Trastuzumab is the increased incidence of cardiotoxicity. The incidence of cardiotoxic effects of Trastuzumab varies from 2-5% when used as a single agent to 25% when combined with anthracyclines and cyclophosphamide in clinical studies, which is most frequently performed in selected patients. However, the frequency of cardiotoxicity of Trastuzumab in non-selected patients in clinical practice is unknown. Here we describe the cardiotoxicity in a retrospective study of breast cancer patients treated with Trastuzumab.
Materials and methods: In a retrospective single centre study we considered all HER2Neu-receptor positive breast cancer patients who underwent treatment with Trastuzumab from March 2001 until August 2010. Trastuzumab was prescribed in two different settings: adjuvant and palliative. In the adjuvant setting Trastuzumab was preceded by anthracycline containing treatment regiments. After this, Trastuzumab was administered in combination with Paclitaxel, followed by Trastuzumab monotherapy for one year. Whereas in the palliative setting Trastuzumab was administered as initial treatment in combination with Paclitaxel. Afterwards Trastuzumab was continued until relapse in the latter patient population. Left ventricular ejection fraction (LVEF) was assessed by MUGA-scan or 2 or 3D-echocardiography.
Results: In total 215 woman received treatment with Trastuzumab and had received follow-up by MUGA-scan or echocardiography. Two hundred (93%) were treated with Trastuzumab after an anthracycline containing regimen and fifteen (7%) received Trastuzumab without previous treatment with anthracyclines. Sixty-seven of all patients (31%) had a decline in LVEF of more than 10%. Of these

patients 18 demonstrated a decline of 10 to 14% and 49 demonstrated a decline of more than 15%. Seven of the 15 patients treated only with Trastuzumab had a decline in LVEF of more than 10%, of which six had a decline of >15%. Of the patients with a decline in LVEF two patients received angiotensin-converting enzyme inhibitor because of asymptomatic decreased LVEF. Forty-five of the forty-nine patients who had a decline of >15% recovered to an LVEF >45% during and after treatment with Trastuzumab.
Conclusion: Cardiac follow-up is of critical importance in the treatment of patients with Trastuzumab because of the high incidence of cardiotoxicity.

P1767 Gender-dependent characteristics of sleep-disordered breathing in patients with chronic heart failure

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Purpose: Sleep-disordered breathing (SDB) occurs frequently in patients with congestive heart failure (CHF). SDB influences the progression of the disease. The German multi-centre SchlaHF registry is the first registry investigating this topic and providing data on SDB characteristics of stable CHF patients.
Methods: Currently 6657 CHF patients from 53 cardiology departments of hospitals and 97 cardiology practices are included prospectively in the SchlaHF Registry. Inclusion criteria are New York Heart Association (NYHA) ≥II and left-ventricular ejection fraction (LVEF) ≤45%. SDB is determined mainly by two-channel screening (nasal airflow, pulse oximetry) using ApneaLink (ResMed, Sydney, Australia).
Results: SDB prevalence was significantly higher in men compared to women. In the SDB group, age was higher in women than in men. Furthermore, in the SDB group frequency of non-ischemic cardiomyopathy was lower in women compared to men and frequency of ischemic cardiomyopathy was higher.

Demographic and clinical data

	Men		Women	
	AHI ≤15/h	AHI >15	AHI ≤15/h	AHI >15
N (%)	2343 (52.5)	2121 (47.5)	767 (66.1)	393 (33.9)
AHI (1/h)	7.2±4.3[c]	32.3±13.6[d]	6.3±4.2[a]	30.1±13.5[b]
Age (years)	64.7±11.6[b,d]	67.5±10.5[a,c,d]	65.4±11.8[b,d]	70.2±9.7[a,b,c]
BMI (kg/m²)	28.0±4.6[b,d]	28.9±5.1[a]	28.2±5.8[d]	29.6±6.5[a,c]
LVEF (%)	33.6±8.2[c]	33.2±8.3[c,d]	35.5±7.9[a,b]	35.0±8.1[b]
NYHA II/NYHA III+IV (%)	581 (39.2%)/ 903 (60.8%)[b]	457 (33.8%)/ 896 (66.2%)[a]	198 (39.2%)/ 307 (60.8%)	86 (32.5%)/ 179 (67.5%)
Atrial fibrillation (%)	317 (21.1%)[b]	412 (30.1%)[a,c]	89 (17.3%)[b,d]	74 (27.6%)[c]
Ischemic (%)	813 (58.3%)[c,d]	721 (56.0%)[c,d]	192 (42.5%)[a,b]	98 (40.7%)[a,b]
Non-ischemic (%)	499 (41.8%)[c,d]	567 (44.2%)[c,d]	260 (57.5%)[a,b]	143 (59.3%)[a,b]
ACE inhibitors and/or AT1/ receptor blockers (%)	2009 (85.7%)	1869 (88.1%)[c,d]	645 (84.1%)[b]	324 (82.4%)[b]
Beta blockers (%)	2040 (87.1%)	1842 (86.8%)	641 (83.6%)	331 (84.2%)
Diuretics (%)	1770 (75.5%[b,d])	1710 (80.6%[a]	590 (76.9%[d])	330 (84.0%[a,c])
Digitalis (%)	565 (24.1%[b])	441 (20.8%[a])	161 (21.0%)	97 (24.7%)
Aldosteron antagonists (%)	1053 (44.9%)	89542.2%)	33743.9%)	166 (42.2%)

Conclusions: SDB prevalence is higher in stable male CHF patients. In the SDB group, frequency of dilated and hypertensive cardiomyopathy is lower in women compared to men and frequency of ischemic cardiomyopathy is higher.

P1768 Doxorubicin causes downregulation of GRP78 leading to ER-stress induced cell-death and cardiac dysfunction

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Purpose: Anthracycline treatment is accompanied by cardiotoxicity but the underlying mechanisms have not been fully understood up to date. Previously it was shown that anthracycline resistant tumor cell lines upregulated the endoplasmic reticulum (ER) stress sensor glucose-related protein 78 (GRP78/BIP) which binds unfolded proteins and represses adverse ER stress. The present study was designed to determine potential alterations of GRP78/BIP mediated ER stress signaling events induced by and contributing to doxorubicin cardiotoxicity in neonatal cardiac myocytes and mice.
Methods: Neonatal rat ventricular cardiac myocytes were treated with 0,1 μM – 1 μM doxorubicin for 24 h. For knockdown experiments cells were treated with 5nM siRNA. Samples were analyzed by western blotting and semi-quantitative real-time-PCR. Cell death was measured via ToxiLight Assay by determining the amount of adenylate kinase in the cell culture supernatant after 24h of doxorubicin treatment.
Results: We found an initial short upregulation of ER stress markers such as spliced X-box binding protein-1 (Xbp-1) mRNA and GRP78, indicating beneficial ER stress, followed by a strong, dose dependent downregulation of GRP78 and the transcription factor GATA-4. At the same time C/EBP homologous protein (CHOP) expression was upregulated. These events are consistent with late phase adverse ER stress, where cell death mechanisms are activated. In line with this, the anti-apoptotic protein bcl-2 was downregulated and apoptotic cell death enhanced with increasing doxorubicin amounts. Interestingly, siRNA mediated knockdown of GRP78 led to a significant increase in doxorubicin induced cell death. This indicates causality of GRP78 downregulation in promoting doxorubicin cardiotoxicity. Preliminary data from mice indicate that GRP78 overexpression by an adeno-associated-virus mediated gene transfer rescues doxorubicin treated mice from cardiac dysfunction by repression of adverse ER stress events.
Conclusion: In conclusion, doxorubicin cardiomyopathy was linked to downregulation of GRP78/BIP, thereby enhancing an adverse ER stress response resulting in apoptosis and cardiac dysfunction. Gene-therapeutic overexpression of GRP78/BIP might at least in part prevent anthracycline induced cardiomyopathy.

P1769 AAV6 mediated cardiac beta-ARKct gene therapy rescues failing myocardium and normalizes neurohumoral signalling in a pig model of ischemic cardiomyopathy

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Purpose: Chronic heart failure is characterized by beta-adrenergic receptor (betaAR) dysfunction with desensitisation and downregulation of the receptors due to increased levels and activity of G-protein coupled receptor kinase 2 (GRK2) in failing myocardium. The therapeutic miniprotein betaARKct, designed as biological GRK2 inhibitor, has previously shown promising results in rodent heart failure models. The aim of this study was to assess the potential of betaARKct as heart failure therapeutic in a clinically relevant large animal model using adeno-associated virus serotype 6 (AAV6) for cardiac gene delivery.
Methods: A porcine model of left ventricular myocardial infarction by catheter-based occlusion of the left circumflex artery (LCX) was used. Two weeks after myocardial infarction baseline cardiac function (haemodynamics, echocardiography) was assessed and gene delivery by retrograde injection of AAV6-betaARKct or AAV6-Luciferase as control into the anterior interventricular coronary vein was performed. 6 weeks after gene transfer/ 8 weeks after MI final assessment of cardiac function was conducted, and blood and myocardial samples were harvested for further analysis.
Results: We found robust long-term betaARKct expression after retrograde AAV6 mediated delivery throughout the target territory. BetaARKct gene transfer significantly improved left ventricular haemodynamics and the neurohormonal axis - represented by significant reductions in plasma normetanephrine levels as well as metanephrine levels (both direct degradation products of norepinephrine and epinephrine) - was virtually normalized. In contrast AAV6-Luciferase treated control animals showed a significant decline in cardiac function and further increases in plasma normetanephrine levels. Furthermore repression of adverse left ventricular remodelling was observed in AAV6-betaARKct treated animals, as evidenced by reductions in heart to body-weight ratio and repression of fetal gene expression.
Conclusions: Myocardial AAV6-betaARKct gene therapy resulted in sustained improvement of global cardiac function, normalization of the neurohumoral signalling axis and repression of adverse left ventricular remodelling in a pig heart failure model.

P1770 Neural cell adhesion molecule is a cardioprotective factor upregulated by metabolic stress

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Purpose: Failing heart is characterized by alteration in energy metabolism. While, secretory and membrane proteins have been a considerable interest because these proteins are involved in most fundamental biological processes and preferred targets for drug development. To screen for cell-surface proteins whose expressions were enhanced under metabolic stress, we performed a signal sequence trap in combination with a functional cloning method.
Methods and results: We screened for cell-surface proteins whose expressions were enhanced by oligomycin, a mitochondorial respiratory chain inhibitor in H9C2 rat cardiac myoblasts. One of the identified genes was neural cell adhesion molecule (NCAM, CD56). In H9C2 and primary rat cardiac myocytes, oligomycin treatment and glucose deprivation significantly upregulated the mRNA and protein level of NCAM, whereas phenylephrine and AT-II did not. To analyze the expression pattern of NCAM in vivo diseased hearts, we examined the NCAM ex-

pression in mouse MI model. mRNA of NCAM was upregulated in infracted area by 15.2 fold ($P<0.01$). Immunohistochemical analysis revealed that NCAM was strongly expressed in residual cardiac myocytes inside and adjacent infracted scars both at acute and chronic phase, whereas it was detectable only at the intercalated discs in non-infarcted area or sham-operation model. We also examined the NCAM expression pattern in Dahl salt-sensitive (DS) rats at LVH and CHF periods. NCAM expression was enhanced in LVH stage by 3.0 fold ($P<0.01$) and further increased by 24.1 fold ($P<0.001$) in heart failure stage. Immunohistochemical analysis revealed that strong NCAM staining was observed in subendomyocardium surrounding fibrotic area. To investigate the role of NCAM in cardiac myocytes, we introduced siRNA against NCAM by lentivirus. Proliferation of H9C2 was significantly reduced when NCAM was knocked down. Survival rate of cardiac myocytes treated with oligomycin was significantly reduced when NCAM was knocked down (86% to 54.6%, $P<0.05$) suggesting the protective role of endogenous NCAM. Akt activity in NCAM knocked down cardiac myocytes was significantly reduced (42% decrease, $P<0.001$). On the other hand, stimulation of NCAM with synthetic peptide activated AKT and increased the survival rates of cardiac myocytes dose dependently. Finally, immunohistochemical analysis of human cardiomyopathy samples revealed over-expression of NCAM in myocardium surrounding fibrotic area.

Conclusion: NCAM may play a protective role in metabolically stressed heart.

P1771 Prognostic implications of serum heat shock protein 60 levels in patients with acute heart failure

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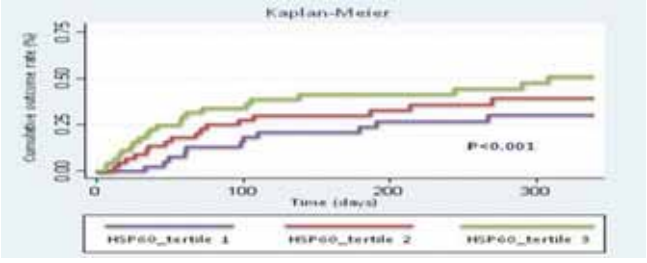
Background: Heat shock protein 60 (HSP60) is primarily a mitochondrial protein that is constitutively expressed in the normal cells, and its expression is upregulated by a variety of stressors. Previous studies have reported that cytosolic proteins leak from cardiomyocytes in patients with heart failure (HF); thus, we speculate serum HSP 60 may be related to ongoing myocardial damage by necrosis or apoptosis. We sought to assess the association between serum HPS 60 level and the composite endpoint of death/acute heart failure (AHF) in patients with an index admission for AHF.

Methods: We analyzed 132 consecutive patients admitted for AHF. We prospectively assessed serum HPS60 levels during hospitalization (median of 48±12 hours after admission). The independent association between serum HPS 60 levels and the endpoint was assessed with Cox regression analysis.

Results: During a median follow-up of 7 months (IQR 2-14 months), 35 (26.5%) deaths, 40 readmission for AHF (30.3%) and 65 (49.2%) deaths/admissions for AHF were identified. Median (IQR) HSP60 were higher in those patients exhibiting the outcome (6.15 ng/ml (8.49) vs 4.71 ng/ml (7.55) p=0.010). A monotonic increase of outcome rates was observed when moving from Q1 to Q3 (38.6%, 47.7% and 61.4%, respectively, p for trend=0.034). After adjusting for established risk factors, including proinflammatory cytokines, patients in the upper tertile showed an adjusted increased risk of death/readmission for AHF (HR=2.63, 95% CI=1.29-5.37; p=0.008).



Conclusions: High serum HSP 60 levels were related to a higher risk for death/readmission for AHF following a previous hospitalization for this condition.

P1772 Prognostic impact of sleep disordered breathing and their treatment in chronic heart failure

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Objective: To determine whether sleep-disordered breathing (SDB) severity, pattern, polygraphic variables and their ventilatory treatment in chronic heart failure (CHF) were associated with adverse CHF outcomes.

Background: SDB are frequent in CHF. The relationships bewteen SDB and outcome in CHF are unknow.

Methods: 384 CHF patients with LVEF <45% were assessed by a polygraphy in our CHF clinic. Ventilatory treatment was started according to SDB severity. Combined endpoint was death, heart tranplant and ventricular assit device implant.

Results: Of the 384 CHF, their mean (SD) age was 59±13, LVEF was 29±9 and 82%% were men. Obstructive sleep apnoea (OSA), central sleep apnoea (CSA) and Cheyne-Stockes respiration (CSR) prevalences were 62%, 26% and 29%. Primary endpoint was observed in 31%. Mean (SD) follow-up for survivors was 47±25 months. Moderate (5.h-120.h-1), OSA and CSA had a similar bad prognostic compared to patients without SDB (respectively p=0.036; p=0.003). 31% of the SDB patients received a ventilatory treatment of whom 98% had severe SDB. Treated SDB had a better outcome than untreated severe SDB after adjustement for cofounding factors (p=0.031; HR: 0.56; 95%CI [0.33-0.95]). Subgroup analysis including only OSA showed a similar result after adjustement (p=0.017; HR: 0.40; 95%CI [0.19-0.95]). In multivariate cox analysis including all the polygraphic variables, only CSR and minimal oxyhemoglobin saturation predicted adverse outcomes in all CHF patients untreated for SDB but AHI.

Conclusion: In patients with CHF, ventilatory treatment of SDB is associated with a better outcome independently of confounding factors.

P1773 Palliative care in chronic heart failure

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Purpose: Heart failure has a worse survival rate than many common cancers, yet few patients receive any palliative during the course of the illness. In response to this, guidelines have been produce, across Europe, to aid both in the identification of those patients who would benefit from palliative care and to describe the role of palliation in end-stage heart failure. These guidelines often recommend clinical prognostic models or general, qualitative "triggers" to identify patients nearing the end of life. The purpose of this study was to compare a simple, clinical set of prognostic criteria for heart failure, the "Gold Standards Framework-Prognostic Indicator Guidance" (GSF), with the "Seattle Heart Failure (SHF) Model", based on their their ability to accurately identify ambulatory heart failure patients in the last year of life.

Methods: Chronic heart failure patients, in NYHA class III or IV, who were being managed by a specialist, heart failure nursing service, were identified from a clinical database. GSF criteria were assessed by interviewing the specialist nurse responsible for each patient's care. The SHF data were used to estimate mean life expectancy and predicted mortality at 1 year. Patients were then followed up, at one year, to evaluate; 1) all cause mortality, 2) place of death, and 3) the sensitivity and specificity of the GSF and SHF to predict death at one year.

Results: 138 NYHA III-IV patients were identified from a total of 368 patients (NYHA II-IV). GSF criteria identified 119/138 (86%) patients that met the minimum requirement for palliative care input. However, the SHF model predicted that only 6/138 patients (4.3%) had a predicted life expectancy of less than one year. At follow up, 43/138 patients had died (31%). Of these, 58% (25/43) died in hospital, following an acute admission. The sensitivity and specificity for the GSF and SHF model were 22%/83% and 98%/12%, respectively. Impaired renal function, defined as an eGFR < 35 (mL/min/1.73m^2), had the best overall sensitivity/specificity of 56%/82%, respectively, with a combined predictive accuracy = 74%.

Discussion: Neither the GSF nor the SHF were very accurate in predicting which patients were in the last year of life, in this selected sample. However, declining renal function does correlate well with mortality at twelve months. The implementation of palliative care in heart failure patients may require a shift away from the traditional "end of life" model developed in cancer treatment, and focus instead on the patient's increasing needs coupled with an understanding that death, itself, may remain unpredictable.

P1774 Acute effects of the targeted anti-cancer agent sunitinib on cardiac contractility

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Background: The potent anti-cancer agent sunitinib elicits cardiotoxicity in a substantial number of treated patients. Most evidence originates from clinical studies in patients treated chronically with this drug. We sought to investigate the acute effects on isolated human myocardium and analyze changes in the microRNA expression pattern, which might be suitable for early detection of cardiotoxicity.

Methods: Human atrial endocardial trabeculae (n=26); modified Tyrode's solution; 37C°, pH 7.4; 2.5mM Ca^{2+}; electrical stimulation with 1 Hz. Analysis of developed force, diastolic tension and twitch kinetics after exposure to sunitinib maleate (0.1-10 μM) or vehicle (DMSO 0.1%).

The murine atrial HL-1 cardiomyocyte cell line was exposed to sunitinib for 24 hours (0.1-1μM). Affymetrix microarrays were used to profile more than 600 microRNAs. RT-PCR was used to confirm differentially expressed microRNAs.

Results: At 0.1μM (which corresponds to normal blood levels) sunitinib had no significant effect on developed force. After preincubation with 1μM and 10μM

sunitinib developed force was decreased to 76.9±2.8% and 54.5±6.3% at 30 minutes compared to 96.1±2.6% in controls ($p<0.05$+$p<0.001$, respectively). No differences in twitch kinetics or diastolic tension could be observed.
The analysed microRNAs showed no difference in their expression compared to untreated cardiomyocytes after exposure to sunitinib for 24 hours.

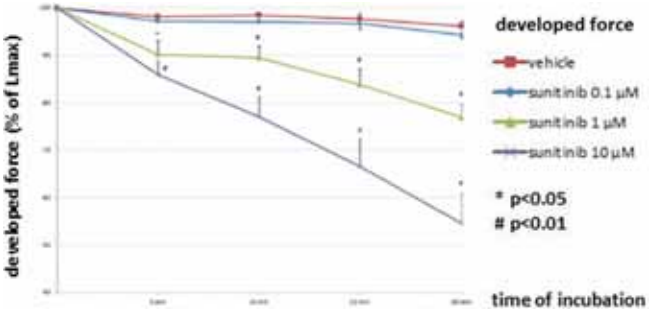

Figure 1

Conclusion: Sunitib may not only induce cardiotoxicity when chronically administered but also elicits a dose-dependent, acute negative inotropic effect in human myocardium, which should be considered when clearance of this drug is decreased (e.g. impaired liver function).
Up- or down regulation of the analysed micoRNAs does not seem to be involved in these acute effects.

P1775 Estrogen therapy reverses chronic heart failure and restores local heart estrogen and aromatase CYP450 levels in mice

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Purpose: Gender differences in the development and progression of certain cardiovascular diseases have been attributed partly to higher circulating estrogen (E2) levels in females. Although the heart has all the machinery necessary to locally synthesize E2 by the help of aromatase CYP450, the role of local heart E2 in heart failure (HF) is not known. We hypothesize that local heart E2 levels are reduced in HF and restoring heart E2 levels by estrogen therapy would rescue HF.
Methods: Young (3-4 month old) ICR male mice were used. Transaortic constriction was used to induce HF (n=25). Serial echocardiography was performed to monitor heart function and when the ejection fraction (EF) reached about 30%, subcutaneous E2 therapy was administered using continuous release pellets (0.012mg/pellet) for 10 days (E2-RESC, n=16). Plasma and local heart E2 concentrations ([E2]) in control (CTRL), HF and E2-RESC were measured. Plasma [E2] was measured by standard radioimmunoassay (RIA). E2 was extracted with diethyl ether from whole heart homogenates and RIA was performed to measure local heart [E2]. Total RNA was isolated using Trizol and reverse transcribed with gene specific primers for Real-Time PCR. GAPDH was used as the reference gene and transcript levels of aromatase were quantified. Data were expressed as mean±SE. $p<0.05$ was considered significant.
Results: HF was associated with the disruption of the heart machinery for E2 biosynthesis, as local heart [E2] was reduced to 5.7±1.5 pg/ml from 16.1±0.7 pg/ml in CTRL. Plasma [E2] on the other hand, was similar in HF and CTRL (28.5±5.9 pg/ml in HF and 29.0±1.3 pg/ml in CTRL). Real-Time PCR showed that aromatase transcripts were about 5-fold downregulated in HF (from 1±0.12 in CTRL to 0.19±0.04 in HF, normalized to CTRL). Next, we examined whether E2 therapy is able to restore aromatase transcripts and to improve cardiac function. E2 therapy fully restored HF-induced downregulation of aromatase expression (to 0.95±0.08 from 0.19±0.04 in HF) and increased local heart [E2] beyond CTRL by about 4-fold. Cardiac function was also significantly improved with E2 therapy, as the EF increased from 33.2±1.1% in HF to 53.1±1.3% after 10 days of treatment. HF was also associated with a 15-fold upregulation of β myosin heavy chain, an established marker of pathological heart hypertrophy, and E2 therapy reversed this upregulation.
Conclusion: Local heart E2 concentration plays a pivotal role in heart function. Local heart E2 levels are reduced in HF and E2 therapy leads to restoration of local heart [E2] and rescue of HF.

P1776 Persistence of viral activity associated with inflammation in endomyocardial biopsy specimens of patients with left ventricular dysfunction predicts better unfavourable outcomes

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Purpose: A significant proportion of patients (pts) with non-ischemic heart failure (NICHF) has viral persistence and/or inflammation in their endomyocardial biopsy (EMB) specimens. EMB is still not routinely used in the evaluation of heart failure pts.The aim of our study was to examine the proportion of viral persistence and/or inflammation and to determine the prognosis in pts admitted for evaluation of NICHF pts by analysing EMB specimens.
Methods: 85 patients with clinically suggested NICHF underwent coronary angiography and endomyocardial biopsy.EMB specimens underwent immunohistological assessment.Polymerase chain reaction (PCR) was performed to detect the genomic sequences of enterovirus (EV), adenovirus (ADV), human cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), parvovirus B-19 (PVB-19), influenza A and B viruses,Chlamydia (trachomatis, psittackie, pneumoniae) and Coxiella burnetii.All pts had markedly reduced LVEF:(25±7%), increased NT-proBNP values (range: 1500-3500pg/ml) and symptoms of heart failure (NYHA functional class II–IV).
Results: In 41 pts viral genome was detected.Chlamydia Trachomatis (n=25), Chlamydia psittaci (n=1), HSV-6 (n=1), Coxsackie B3 (n=2) and CMV (n=1).Coinfections with Chlamydia trachomatis and either HSV-1/HSV-2 or HSV-6 were present in 10 biopsy specimens while coinfection with ParvoB-19 and HSV-1/HSV-2 in 1 biopsy specimen.Inflammation (>14 lymphocytes or macrophages/mm^2, WHF criteria) was observed in 19 patients.Patients were divided into 4 groups:group 1 consisted of pts without any inflammation or virus detection (n=30),group 2 of pts with autoreactive myocarditis (virus-negative,but inflamed myocardium) (n=13),group 3 of virus-positive pts without inflammation (n=29) and pts with virus-positive inflammed myocardium formed group 4 (n=13).All major cardiovascular events [MACE; cardiovascular death (n=3),assist device implantation (n=8), heart transplantation (n=2) and re-hospitalisation due to cardiac decompensation (n=5)] during one year were recorded (n=18).Kaplan-Meier curves demonstrated an increased amount of cardiovascular events in group 4 when compared to the other groups.When patients were divided according to viral status, patients without virus detection tended to have fewer cardiovascular events compared to patients with virus persistence.
Conclusion: Viral persistence in pts with NICHF was associated with increased MACE.Pts with virus-positive inflammed myocardium had the worse short-term prognosis.Data from EMB in pts with reduced left ventricular function is of prognostic relevance.

P1777 Age, but not gender, influences quality of care in heart failure - results from a contemporary U.K. cohort

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Context: Previous studies have reported variation in standards of care in heart failure (HF) according to age, gender and socioeconomic status (SES). We aimed to investigate these inequities in a contemporary cohort.
Methods: Retrospective cohort study of consecutive HF admissions to an acute hospital 2005 - 2007. HF admissions were identified by ICD10 code and these were screened against the ESC criteria for the diagnosis of HF to construct the final cohort. SES was determined by linking postcodes with Index of Multiple Deprivation 2007 scores.
Results: 723 patients were identified for inclusion. The median age was 82 years (range 32.3–100.5). Overall the cohort contained 51% women, and female members of the cohort were significantly older (84 vs 80 years, $p<0.001$). Three age groups were used for the analysis. There was a reversal in the proportion of men and women in the youngest and oldest group with a significant trend of increasing left ventricular ejection fraction (LVEF) and increasing rates of atrial fibrillation (AF) as age increased. Table 1 demonstrates age related differences in care quality. This effect persisted when either only those with LVEF <50%, or with normal renal function were examined. Although men were found to be more often treated with aldosterone antagonists (33.% vs. 21%, $p<0.001$) and have LVEF recorded (69% vs. 56%, $p<0.001$), these effects disappeared after age was taken into account. SES did not appear to influence any marker of care quality at any age.

Table 1. Variation in care quality between young, old and very old patients admitted with heart failure

	<76 years (n=191)	76–85 years (n=280)	≥85 years (n=252)	
Male [n (%)]	128 (67)	142 (51)	82 (33)	p<0.001*
ACEi/ARB prescribed [n (%)]	154 (81)	208 (74)	180 (71)	NS
β-blocker prescribed [n (%)]	68 (36)	43 (15)	27 (11)	p<0.001*
Aldosterone antagonist prescribed [n (%)]	69 (36)	74 (26)	53 (21)	p=0.002*
Echo performed within 6 weeks [n (%)]	98 (51)	101 (36)	72 (29)	p<0.001*
LVEF recorded [n (%)]	140 (73)	185 (66)	127 (50)	p<0.001*

*Chi-square test for trend.

Conclusions: In contrast to earlier reports, we have found little evidence for effects of gender or SES in determining quality of care in HF, but we have observed significant age related inequity in the prescription of disease modifying therapies and access to timely and good quality echocardiography.

P1778 Coronary venous retention - a novel feature in heart failure evidenced by mean of cardiac computed tomography

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Coronary veins (CVs) imaging plays important role in patients with heart failure (HF) considered for electrical devices implantation. It has not been examined whether the functional status of the heart can influence venous system itself. To solve this question we used multi-slice computed tomography imaging.
Purpose: To answer the question - whether the HF is associated with significant anatomical changes of coronary venous system?
Methods: In 179 (aged 57,6±11,4) pts., a 64-slice CT (Aquilion 64) was performed. Patients were dived into 2 groups: with HF (41 pts.) and without HF (138 pts.). In each case nine 3D VR reconstructions, using a 2 mm layer with ECG-gating, were created from 0% to 90% R-R intervals (step 10%). Helical pitch was 12,8; rotation time: 0,4 s, average tube voltage: 135 kV at 380 mA. Visualization of CVs was graded independently by 2 experts trained in MSCT on 0-5 points scale (0-not visible /lack of vein/; 5-smoothly bordered vascular structure).
Results: Average number of visible CVs per case was 3,44 in HF group and 2,98 in pts without HF ($p<0.05$). Proportions of 5 main CVs visibility in groups: with HF and without HF is presented in the table below (%; number of cases where vein was visible). The best quality of visualization was obtained for lateral vein: 2,05±1,53 (HF); 2,49±1,89 (without HF). The worst quality of visualization was obtained for anterolateral vein: 0,59±0,97 (HF); 0,70±1,26 (without HF).

Presence of veins in groups (%; n)

	Without HF group; n=138		HF group; n=41	
	%	cases	%	cases
Posterior vein	43,5%	60	30,0%	12
Posterolateral vein	60,1%	83	80,0%	32
Lateral vein	76,8%	106	85,0%	34
Anterolateral vein	28,3%	39	40,0%	16
Anterior vein	78,3%	108	92,5%	37

Conclusions: Statistically higher number of veins in patients with heart failure may suggest an association between failing heart and cardiac venous retention. The significance and pathophysiological meaning of this finding requires further studies.

P1779 Impact of cardiac contractility modulation on left ventricular global function measured by two-dimensional speckle tracking imaging

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Purpose: As a new device-based therapy for refractory congestive heart failure, cardiac contractility modulation (CCM) has been suggested to improve symptoms and ejection fraction (EF). This study aimed to further explore the impact of CCM on left ventricular (LV) long- and short-axis function and torsion by using two-dimensional (2D) speckle tracking imaging.
Methods: Thirty patients (61±11 years, 82% male) with NYHA class III heart failure, ejection fraction <35% and QRS <120msec were prospectively enrolled, who received the device implantation and had acceptable echocardiographic images. LV global longitudinal, circumferential and radial strain and basal to apical torsion were assessed by 2D speckle tracking imaging at baseline and 3 months after CCM.
Results: Mean LVEF was increased after CCM (28.0±6.3 vs 32.7±6.5%, $p<0.001$). A significant improvement in EF ≥5% was observed in 16 patients (53%) while the other 14 patients (47%) had a change in EF <5%. As shown in the Table, significant improvement in longitudinal ($p<0.01$), circumferential ($p<0.01$) and radial strain ($p<0.001$) were only observed in patients with an increase in EF ≥5%. Furthermore, the correlation between the changes in EF and global longitudinal strain appeared better than other components of LV function (r=0.49, $p<0.01$).

LV function	All patients (n=30)		Patients with change in EF≥5% (n=16)		Patients with change in EF<5% (n=14)	
	Baseline	3-month	Baseline	3-month	Baseline	3-month
Longitudinal strain, %	8.8±2.5	9.5±3.3*	9.3±2.3	10.6±2.3§	8.3±2.6	8.1±3.0
Circumferential strain, %	9.6±3.0	11.1±3.3§	9.6±2.8	12.0±3.4§	9.6±3.4	10.0±3.0
Radial strain, %	13.5±7.5	18.3±7.5†	13.0±7.1	19.1±7.6†	14.1±8.3	17.4±7.7
Torsion, degree	8.0±4.5	10.3±5.5*	8.8±5.1	10.8±6.0	7.1±3.7	9.6±4.9

*$p<0.05$, §$p<0.01$, †$p<0.001$ vs baseline.

Conclusion: In patients with advanced heart failure, CCM induces improvement in LV long- and short-axis function as well as torsion which contribute to gain in LVEF.

P1780 Nexilin deficient neonatal mice display dilated cardiomyopathy and systolic dysfunction

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Background: Dilated cardiomyopathy (DCM) is a leading cause of heart failure. Recently, we identified nexilin (Nex) gene mutations in patients with DCM and showed that loss of Nex in zebrafish leads to impaired cardiac contractile function with instability of the Z-disk and subsequent cardiac dilatation.
Aim: To investigate the role of Nex in the heart with a targeted Nex knockout mouse model.
Material and methods: A constitutive Nex knockout (KO) mice was produced by gene targeting strategy. Cardiac phenotype of neonatal hearts was studied by echocardiography as well as histology, electron microscopy and heart-to-body weight ratio (HW/BW).
Results: Heterozygous (Het) adult mice displayed no apparent phenotype. Homozygous KO mice were produced by mating Het mice. At birth, the ratio of KO: Het: wild-type (WT) mice approximated the expected Mendelian ratios of 1:2:1. After postnatal day 6, survival of KO mice decreased dramatically, and only two out of 250 KO mice remained viable after one month of age. Western blot exhibited the absence of Nex and lower Nex amount in KO and Het mice, respectively. After postnatal day 4, HW/BW was >2.3-fold higher in KO than in WT mice. Between days 4 and 6, KO mice developed a rapidly progressive cardiomyopathy with left ventricular (LV) dilation and wall thinning as determined histologically. Interestingly, echocardiography revealed a LV phenotype in both KO and Het mice characterized by thinning of the walls (lower AWThd and PWThd than in WT littermates) and dilation (higher LVIDd and LVIds than in WT). This resulted in lower ejection fraction in both Het and KO mice. Total LV protein content did not differ between KO and WT mice, suggesting that the higher HW/BW is due to oedema in KO mice. Electron microscopy showed a blurring of the boundary between the I and A bands within the cardiac myocytes.
Conclusion: Both heterozygous and homozygous Nexilin knockout mice developed DCM and systolic dysfunction after birth. The complete absence of nexilin resulted in neonatal lethality, whereas a lower level of nexilin was sufficient to maintain the viability in heterozygous mice.

P1781 Chronic heart failure patients are vitamin D deficient and hyperparathyroid, levels of each relate to markers of severity

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Background: The vitamin D-parathyroid (PTH) axis is increasingly recognised as involved with many of the features of CHF. We aimed to explore vitamin D and PTH levels in CHF patients and relate these to markers of severity.
Methods: We measured 25(OH) vitamin D3 levels in 406 consecutive attendees of the Leeds Comprehensive Heart Failure Clinic (310 men) and correlated these to markers of severity.
Results: Mean age (SE) was 69 (3) years, left ventricular ejection fraction (LVEF) 31 (2)%, creatinine 117μmol/L (2.4), vitamin D levels 21 (1) nmol/L (normal for skeletal health>75nmol/L) and PTH levels 11 (8)pmol/L (normal<6.5pmol/L). Aetiology was ischaemic heart disease in 63% and 23% had diabetes mellitus (DM). Patients were optimally treated (84% beta-blockers (BB), 88% angiotensin-converting enzyme inhibitors (ACEi), 46% spironolactone). The mean daily dose of furosemide was 60 (3)mg. Few patients (5%) were sufficient in vitamin D. Patients with worse NYHA status had lower vitamin D levels and higher PTH levels (ANOVA p=0.06 and <0.001). There was also a negative relationship between furosemide dose and vitamin D (r=0.21; $p<0.0002$) and, in an unselected subset of 160 patients (mean peak oxygen uptake (pVO2) 16.6 (0.5)ml/kg/min), there was a relationship between pVO2 and vitamin D (r=0.16; p=<0.03). Patients with DM had lower vitamin D levels than non-diabetics ($p<0.001$) and there was a negative correlation between vitamin D and fasting glucose levels (r=0.13; p=0.02). There was no relationship between vitamin D levels and age, calcium, creatinine or CRP, and no differences between those patients taking and those not taking BB and ACEi. In 8 unselected patients we found a negative relationship between tumour necrosis factor-alpha (TNF-á) levels and vitamin D (r= -0.62; p=0.05). Although there was no relationship between vitamin D levels and baseline LVEF, in a subgroup of 150 patients followed up one year after titration to optimal CHF therapy, there was a significant positive relationship between change in LV dimensions and vitamin D levels at the time of the baseline scan ($p<0.05$).
Conclusions: The vitamin D-PTH axis is abnormal in CHF, related to the severity of the condition. In addition, reverse remodelling in response to optimal drug titration is greater in those with higher vitamin D levels. Whether vitamin D deficiency is causally related to CHF remains unknown and requires a long-term, randomised, placebo-controlled study in CHF patients with efficacy and mecha-

nistic outcomes, using a dose of vitamin D capable of normalising both vitamin D and PTH levels.

P1782 Galectin 3 predicts mortality and response to statin therapy in chronic heart failure

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Purpose: Galectin-3 is a new biomarker involved in inflammation and fibrogenesis and could therefore contribute to myocardial remodeling. We examined the prognostic value of galectin-3 and its interaction with statin therapy in a sub-study involving approximately 30% of participants in the CORONA study (Controlled Rosuvastatin Multinational Trial in HF).
Methods: Patients (n=1462), >60 years with systolic, ischemic heart failure (HF) were randomized to 10 mg/day rosuvastatin or placebo. The primary composite endpoint was cardiovascular death, nonfatal myocardial infarction or stroke (n=408).
Results: In multi-variable analyses, adjusting for 8 clinical and 2 biochemical variables, higher galectin-3 concentration was associated with a higher risk of the primary end-point [HR 1.16 (1.03-1.31), p=0.012] as well as all cause- and cardiovascular mortality, sudden death, and the composite end-point of all-cause mortality and hospitalization for worsening of heart failure. When N-terminal pro-brain natriuretic peptide (NT-proBNP) was added to the model, the association between galectin-3 and these end-points was attenuated and no longer significant. There was a significant interaction between baseline galectin-3 concentration and the effect of rosuvastatin. In patients with galectin-3 < median (19.0 ng/mL), 72 patients (7.8%) on rosuvastatin and 97 patients (11.2%) on placebo had a primary endpoint: HR 0.65 (0.46-0.92). In patients with galectin-3 >median, 126 patients (15.1%) on rosuvastatin and 116 patients (14.2%) on placebo experienced this outcome: HR 1.07 (0.79-1.45); interaction p=0.019.
Conclusions: Galectin-3 was associated with the primary endpoint, and death in older patients with advanced chronic systolic HF of ischemic etiology. Furthermore, galectin-3 appeared to modify the effect of rosuvastatin, with the benefit from rosuvastatin confined to those with galectin-3 concentration below 19 ng/mL

P1783 The anticancer mTOR-inhibitor temsirolimus induces cardiac dysfunction in mice

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Purpose: The mTOR inhibitor temsirolimus is being evaluated for anticancer efficacy in hundreds of clinical trials and is approved for treatment of advanced renal cell carcinoma. The PI3K/Akt pathway converges on mTOR, which is a central regulator of cell growth, including cardiomyocyte growth. Here, we aim at assessing whether the anticancer mTOR-inhibitor temsirolimus affects cardiac function.
Methods: In vivo cardiac function was measured with Left Ventricular (LV) fractional shortening (FS) by M-mode echocardiography in sedated C57BL/6 mice (2-4 mo. old) at day 0, and after 2, 7, 14, 21 days from a single i.p. administration of temsirolimus (0.1mg/kg, a dose comparable to the one used to treat cancer in humans) or vehicle. Doxorubicin (Doxo, 2.17 mg/kg/day for 7 days) was used as a positive control. With Speckle Tracking echocardiography (ST) we also evaluated radial myocardial strain (%), a very sensitive parameter which can detect subtle changes in cardiac function.
Results: After 2 days, there was no change in FS with temsirolimus, but FS was already reduced with Doxo: 52±0.2%, p=0.0000001 vs sham (60±0.4%). FS was reduced only after 21 days in the temsirolimus group: 50±3%, p=0.009 vs sham. Interestingly, with Speckle Tracking echocardiography we found that radial strain was already decreased at 7 days in the temsirolimus group: 42±5%, p=0.01 vs sham (59±1%).
Conclusions: The mTOR inhibitor temsirolimus induces LV dysfunction in mice. Such dysfunction occurs later than the one observed with Doxo, but can be identified with speckle tracking echocardiography (reduction in myocardial strain) before a decrease in FS is observed with conventional echocardiography. The clear mechanisms of temsirolimus cardiotoxicity are to be elucidated in further experimental studies. We also plan to apply speckle tracking echocardiography to clinical studies, in order to evaluate the impact of early identification of temsirolimus cardiotoxicity in the treatment of renal cell carcinoma.

P1784 The significance of optimal medical therapy before implantation of ICD and CRT-P/CRT-D in the avoidance of non-evidence-based use of the devices

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Background: In the guidelines on device (D) therapy of patients (pts) with chronic heart failure (CHF) optimal medical treatment (OMT) is a key point. However data from a large registry show, that OMT, at least concerning its duration, is a widely neglected factor of indication of D therapy. The large and increasing number of pts with Ds, first of all ICDs, makes reducing unnecessary implantations a question of importance.
Aim: We aimed at investigating the proportion of pts whose parameters improved on OMT to the level making the use of Ds unnecessary, according to the criteria of the 2008 AHA/ACC/ HRS guidelines on D-based therapy.
Patients and methods: Pts from our Heart Failure Clinic who met the LVEF, NYHA class and QRS duration criteria for ICD (258) or CRT-P/CRT-D (204) were evaluated. Majority of them (78%) had long-lasting CHF, while 22% had newly diagnosed CHF. Pts' treatment was optimized: neurohumoral antagonists were titrated to target or highest tolerated doses, preferring beta blockers. Optimal doses of diuretics were applied. 72% of pts were treated with direct vasodilators and 42% with digitalis as well. ICD and CRT-P/CRT-D indications were reassessed after 7.5±6.9 months. Tendency of improvement regarding LVEF and/or NYHA class resulted in delay in decision.
Results: From 258 pts (Age: 59.7±22,3 years, Ischemic: 130 pts, NYHA class: 2.5±0.37, LVEF: 27.5±5.2%) who at the first examination met the criteria for primary prevention ICD, 152 (58%) improved on OMT in respect of LVEF (72%), NYHA class (47%), or both (26%) to a level when ICD was not indicated any longer. Pts who improved beyond ICD indication differed from those not improved in ischemic origin: 43.4% vs. 60.4%; GFR: 75.9±24.1 vs. 63.6±18.6ml/min; heart rate: 85.8±19.7 vs. 78.1±14.8/min; hemoglobin: 143.9±15.6 vs. 137.7±17.7g/l respectively; p<0.05 for all.
Regarding CRT-P/CRT-D, 204 pts (Age: 64.5±11,5 years, Ischemic: 118 pts, NYHA class: 3.6±0.4, LVEF: 24.8±5.9%) who met the criteria for CRT-P and CRT-D at baseline, OMT improved key parameters in 94 pts (46%) beyond the range where D implantation is indicated (LVEF in 45%, NYHA class in 94% or both in 38%). Improved pts differed from those not improved in baseline systolic blood pressure: 129.9±23.2 vs. 110.2±19.1mmHg, p<0.001.
Conclusions: ICD and CRT-P/CRT-D implantations are not in accord with guidelines i.e. they are unnecessary in about 50% of the pts, if the criteria of optimal medical treatment is not fulfilled, and if heart failure symptoms and LVEF are not reassessed 3 months after therapy has been optimized. Early use of D-s is not advised.

P1785 Early vagal stimulation markedly prevented cardiac dysfunction in rats after acute myocardial infarction in addition to suppressing arrhythmic death

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Introduction: We have shown that electrical vagal stimulation (VS) markedly prevented remodeling and death in post-large myocardial infarction (MI) rats survived for 2 weeks. It is well known that deaths within 2 weeks were mainly caused by lethal arrhythmia. In this study, we started VS early phase after acute myocardial infarction (AMI) and examined its additional effects on infarct size reduction, prevention of ventricular remodeling and dysfunction following AMI in rats.
Methods: We implanted a radio-controlled vagal stimulator and an ECG transmitter for VS and monitoring ECG. Intermittent (10s in 60s) VS (0.2ms, 20Hz, 0.1-0.13mA) started 1 hour after left coronary artery ligation. The stimulation intensity was adjusted for each rat to lower heart rate for 10%. At the end of 4-week treatment, the impact of VS was evaluated by death, echocardiography, cardiac catheterization, neurohumoral states and histological examination.
Results: VS-treated MI rats had significantly lower heart rate than sham-stimulated (SS) group (294±36 vs. 328±9bpm, p=0.03). VS significantly suppressed mortality within 24 hours (39% to 7%, p=0.02). VS therapy significantly reduced infarct size (16±5% vs. 22±6%, p<0.05) and prevented the progression of ventricular remodeling and improved indices of cardiac function (table).

Effects of vagal stimulation on cardiac function after acute myocardial infarction

	SS group (n=11)	VS group (n=13)	P-value
Biventricular weight (g/kg BW)	2.57 ± 0.10	2.31 ± 0.05	P<0.05
Ejection fraction (%)	28 ± 1.3	34 ± 3.0	P<0.001
Ees (mm Hg/ml)	215 ± 26	366 ± 49	P<0.01
Cardiac index (ml/min/kg)	106 ± 3	160 ± 4	P<0.01
LVEDP (mm Hg)	29 ± 2	20 ± 1	P<0.01
LV +dp/dt$_{max}$ (mmHg/s)	3529 ± 130	4721 ± 122	P<0.01
LV -dp/dt$_{max}$ (mmHg/s)	3104 ± 201	3913 ± 160	P<0.01
BNP(pg/ml)	413 ± 19	368 ± 9	P<0.05
NE(pg/ml)	2366 ± 831	542 ± 181	P<0.05

Conclusions: Vagal stimulation markedly suppressed arrhythmic death within 24

hours and prevented cardiac remodeling and dysfunction after acute myocardial infarction, suggesting VS is effective both in acute and chronic phase after MI.

P1786 Long-term effects of implantable hemodynamic monitoring in patients with moderate heart failure

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Background: Implantation of a pulmonary artery (PA) sensor as part of a wireless implantable hemodynamic monitoring (W-IHM) system allows physicians to manage patients by treating pressures in addition to standard of care. We previously reported a 30% reduction in the 6-month rate of heart failure related (HFR) hospitalizations in the W-IHM group, the primary endpoint of the CHAMPION (CardioMEMS Heart sensor Allows for Monitoring of Pressures to Improve Outcomes in NYHA class III patients) Trial. We now report the long-term effects of W-IHM on pressures and outcomes in CHAMPION.
Methods: 550 patients were assigned to the W-IHM system (treatment group; 270 patients) or to a control group (280 patients) for at least 6 months. The mean patient follow-up was 15.2±7.0 months with a maximum of 31 months. Heart failure related (HFR) hospitalizations were analyzed using negative binomial regression, and PA pressure changes were analyzed by integrating the area under the curve (AUC) of pressure over time.
Results: Over the full duration of follow-up, there was a 39% reduction in HFR hospitalizations in the W-IHM group compared to the control group (153 vs. 253 hospitalizations, $p<0.001$). The treatment and control patients had similar baseline PA pressures. Over 6 months of follow-up, the treatment group had a reduction in pressures with an AUC of -155.7 mmHg days, compared with an AUC of 33.1 mmHg days in the control group (p=0.008). At 12 months of follow-up, the treatment group had a reduction in pressures with an AUC of -201.5 mmHg days, compared with an AUC of 106.5 mmHg days in the control group (p=0.030).
Conclusion: Patients treated with a W-IHM system had fewer HFR hospitalizations and a decrease in pulmonary pressures when compared to standard of care heart failure management. These reductions were achieved by 6-months and increased through an average of 15.2 months of patient follow-up demonstrating the durability of this approach to HF management.

P1787 Stratifying prognosis in heart failure: nutritional status versus body mass index

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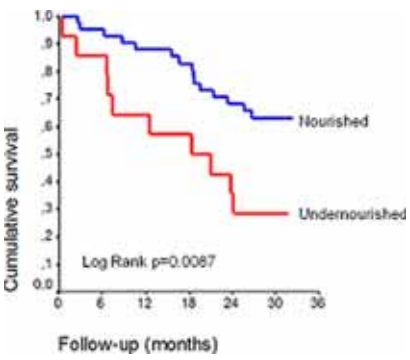
Purpose: Obesity paradox in HF has been criticized in part for the limitation of body mass index (BMI) for a correct classification of overweight/obese patients. A better nutritional assessment is required, so we aimed to assess nutritional status, its relationship with BMI, and its significance in terms of survival.
Methods: Fifty five HF patients were assessed by anthropometry [tricipital skinfold, subscapular skinfold (SS), arm muscle circumference] and biochemical nutritional markers (albumin, total lymphocyte count). Presence of ≥2 of these indexes below normal ranges defined undernourishment. Patients were also stratified by the BMI WHO classification and followed for a median of 26.7[18.4-28.5] months.
Results: Mean age was 73.7±8.7, 65.5% of patients were male, Framingham severity score was 1.6±0.9, and LVEF was 45.6±17.2. Across BMI strata, no patient was underweight, 31% of patients were normal-weight, 42% overweight, and 27% were obese. Nutritional data revealed that 53% of normal-weight patients, 22% of overweight, and none of the obese group were undernourished (p=0.001). Undernourished patients had a significant higher mortality (p=0.0087) (figure).



Survival according to nutritional status.

In the multivariable analysis including age, sex, NYHA functional class, creatinine clearance, hemoglobin, LVEF, NTproBNP, BMI and undernutrition, only the latter (HR=3.149[1.367-7.253]), NYHA class (HR=3.374[1.486-7.659]) and age (HR=1.115[1.045-1.189]), remained in the model. Among the nutritional indicators studied, the best variable for predicting mortality was SS: patients with SS in the 5th percentile had significantly higher mortality (p=0.0001).
Conclusion: BMI does not reveal true nutritional status in HF. Patient classification as nourished/undernourished instead of BMI categories may enable better risk stratification.

P1788 Recent in-hospital mortality trends among patients with heart failure in the netherlands

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Purpose: From 1980 to 1993, in-hospital mortality among heart failure (HF) patients in the Netherlands decreased from 19 to 15%. However, more recent mortality data are lacking. This study described in-hospital mortality rates among patients with HF in the Netherlands from 2005 to 2009.
Methods: The PHARMO database network includes, among other things, hospitalization records of approximately 3.2 million residents in the Netherlands. From this database, all patients with a primary hospital discharge code for HF between 2005 and 2008 were selected. The date of the first HF admission was defined as the index date. Patients hospitalized for HF in the 12 months prior to index date were excluded. Patients were followed from the index date until the end of data collection, death, or a maximum of 12 months, whichever occurred first. Crude mortality rates over time were determined during the index HF admission, during any HF readmission, and during any all-cause readmission (defined as hospitalization for any reason other than HF) during follow-up.
Results: A total of 9,786 patients with an index HF admission between 2005 and 2008 were included in the analyses. Mean (± SD) age was 77 (± 11) years and 52% were female. Overall, during their index HF admission, which had a mean (± SD) length of stay of 11 (± 10) days, 10% of patients died. Hence, 8,850 patients were at risk for a readmission. During follow-up, 1,563 (18%) patients were readmitted for HF and 4,542 (51%) patients had an all-cause readmission. In-hospital mortality during HF readmission, with a mean (± SD) length of stay of 11 (± 9) days, was also 10%. In-hospital mortality during an all-cause readmission, with a mean (± SD) length of stay of 8 (± 10) days, was 5%. Mortality rates over time from 2005 to 2009 were stable. Mean (± SD) number of days between hospital admission and death was 10 (± 13) days for the index HF admission. Mean (± SD) number of days between hospital readmission and death was 12 (± 12) days for HF readmission as well as for all-cause readmission (12 (± 15) days).
Conclusions: Compared to published 1993 data, in-hospital mortality among HF patients in the Netherlands decreased. However, in most recent years, in-hospital mortality remains unchanged with 10% of HF patients dying during HF admission, indicating that there still may be opportunity for improvement of outcomes in this hospitalized population.

P1789 Left ventricular diastolic dysfunction and preceding courses of cardiovascular risk factors: a 17-year follow-up study

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Purpose: Left ventricular (LV) diastolic dysfunction is a progressive condition which predisposes to heart failure. We aimed to investigate whether LV diastolic dysfunction at older age was associated with cardiovascular risk factors up to 17 years prior in a longitudinal population-based study.
Methods: In 1989, individuals aged 50-75 years were included. They were followed-up in 1996-1998, 2000-2001, and 2007-2009. In 2007-2009, LV diastolic dysfunction was assessed using Doppler echocardiography measurement of early diastolic flow and lengthening velocities (E/e') in 334 individuals. Higher E/e' provides an overall estimate of more severe LV diastolic dysfunction. Longitudinal associations between tertiles of E/e' in 2007-2009 and time-dependent HbA1c, total cholesterol, systolic blood pressure, and waist-hip ratio were assessed with multivariate linear mixed models.
Results: Individuals in the highest tertile of E/e' in 2007-2009 had higher HbA1c, total cholesterol, and systolic blood pressure 17 years prior (Table, baseline age 58±5 years). The associations were independent of each other. HbA1c, systolic blood pressure, and waist-hip ratio increased over the 17-year period, while total cholesterol decreased. Total cholesterol and waist-hip ratio became more similar in both tertiles of E/e' after 17 years of follow-up.

Abstract P1786 – Table 1

	HbA_{1c} (%)	Total cholesterol (mmol/L)	Systolic blood pressure (mmHg)	Waist-hip ratio (cm/cm×100)
Baseline group difference (highest vs lowest tertile of E/e')	0.23 (0.05 to 0.40)*	0.32 (0.04 to 0.59)*	5.25 (0.57 to 9.94)*	0.96 (–0.88 to 2.79)
Change over time (in lowest tertile of E/e') per year	0.01 (0.00 to 0.02)*	–0.03 (–0.05 to –0.02)*	0.89 (0.63 to 1.14)*	0.25 (0.17 to 0.33)*
Time × group interaction (= additional change over time in highest tertile of E/e')	0.00 (–0.01 to 0.01)	–0.03 (–0.04 to –0.01)*	0.15 (–0.14 to 0.44)	–0.10 (–0.19 to –0.02)*

Data are reported as regression coefficients with 95% confidence intervals for individuals in the highest and lowest tertiles of E/e' in 2007-2009, *p<0.05. All analyses are adjusted for age, sex, estimated glomerular filtration rate, use of lipid, blood pressure, and/or glucose lowering medication, and the other 3 cardiovascular risk factors. E/e' = the ratio of early diastolic flow velocity (E) and early diastolic lengthening velocity (e'), HbA1c=glycated haemoglobin.

Conclusions: Elevated HbA1c, total cholesterol, and systolic blood pressure around the age of 58 years independently predicted LV diastolic dysfunction 17 years later. Early identification and treatment of high-risk individuals may be of great value for prevention or postponement of developing LV diastolic dysfunction.

SYNCOPE: THE ERA OF IMPLANTABLE LOOP RECORDER

P1790 Pulse generator replacement as a risk factor for cardiac device infection. Pooled analysis of published studies

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Purpose: Cardiac device infection (CDI) is an uncommon but serious complication, necessitating system extraction with associated morbidity/mortality, prolonged hospitalization and increased costs. Pulse generator replacements ("PGR") involve shorter procedures than de novo implants ("New") with fewer re-interventions or temporary pacing wires but the presence of a fibrous capsule may increase CDI risk by impeding access of inflammatory and immune cells. However, the role of PGR as a risk factor for CDI has received limited attention.
Methods: Systematic review of published abstracts and papers since 1990, with data extraction from studies fulfilling the following criteria: [i] consecutive series of pacemaker (PPM), ICD or CRT implants; [ii] CDI rates reported for new implants and PGR subgroups; [iii] only CDIs from denominator population included.
Results: Compared to new implants, PGR was consistently associated with increased risk of CDI across all studies (OR 2.75; 95%CI 2.34-3.23). Subgroup analysis showed that this is not accounted for by combined PGR+lead revision cases. PGR accounted for 44% of all CDIs.

Results

Study	Device Types	New	PGR	P-value
Wunderly 1990	ICD	4/207 (1.9%)	4/56 (7.1%)	0.07
Harcombe 1998	PPM	13/2376 (0.55%)	5/245 (2.00%)	0.02
Mela 2001	ICD*	13/959 (1.30%)	8/447 (1.70%)	0.49
Johansen 2006	PPM	270/36076 (0.75%)	184/8949 (2.06%)	<0.0001
Klug 2007	PPM/ICD/CRT*	24/4461 (0.56%)	18/1858 (0.99%)	0.06
Lekkerkerker 2010	PPM/ICD/CRT*	30/2368 (1.27%)	45/1042 (3.81%)	<0.0001
TOTAL		354/46447 (0.76%)	264/12597 (2.1%)	<0.0001

*Included some patients with lead revisions.

Conclusions: Despite involving a simple operation, PGR carries significantly increased risk of CDI, possibly due to barrier effects of the fibrous capsule. Experience from breast and ophthlamic implant surgery suggests that capsulotomy/capsulectomy can reduce infection risk and should be prospectively evaluated for prevention of CDI after PGR.

P1791 Transvenous lead extraction: current clinical practise with combination of various techniques

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Background: The main indication for pacemaker and ICD lead removal procedure related to infectious complications. Implanted leads are encapsulated by stiff fibrotic tissue and transvenous removal technique using simple polytetrafluoroethylene (PTFE) sheats becomes very often less effective and more risky.
Methods: In our institution 1947 PM and 183 ICD leads were extracted using combination of various methods with success rate of nearly 88% since 1992. The average time from implantation to the extraction procedure was 66.2±13.4 monthshe most frequent indication for lead extraction (97,8%). All procedures are performed in general anestesia in EP lab with cardiac surgery on site. The last five years in all patients we use intracardiac ultrasound to monitor the procedure. In the last three years we combine all the available techniques including EDS – powered by radiofrequency energy (Cook Vascular Inc.), LASER (Spectranetics Inc.) and Rotational dissection sheats (Evolution - Cook Vascular Inc.).
Results: When mechanical extraction sheats were used alone, the success rate was only 79%.When we implemented EDS, the success rate was significantly higher – 94% (p<0,001). Evolution rotational sheats improved the outcome of the extraction for 95% (p<0,54) and Laser system increased our success rate for 97%. Femoral approach used in limited numbers of pts was effetive in 100% cases. In the last 3 years we sent only 12 patients for elective open heart surgery. Rate of complications was minimal for PTFE sheats (only 1 cardiac tamponade) and Evolution rotational sheat (1 tamponade and one SVC perforation). It was significantly higher for Laser (4 tamponades). Alle these patients were sent urgently for open heart surgery. We have only 3 patients where pulmonic embolism was verified and 3 patients with tricuspid valve disruption.
Nobody died due to lead extraction procedure in our institution.
Conclusion: Based on our experiences with combination of the various techniques transvenous lead extraction procedure is reasonable effective and safe.

P1792 Transvenous removal of pacing and implantable cardiac defibrillating leads using single sheath mechanical dilatation and multiple venous approaches: the Pisa experience

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Introduction: Transvenous extraction of Pacing (PL) and Defibrillating Leads (DL) is today a highly effective technique. Device related complications are currently rising the need of Transvenous Lead Removal (TLR). Aim of this report is to analyse the longstanding experience performed in a single Italian Center.
Methods: Since January 1997 to December 2010, we managed 1627 consecutive patients (1238 men, mean age 65.7 years, range 3-95) with 2914 leads (mean pacing period 70.2 months, range 1-420). PL were 2485 (1303 ventricular, 1011 atrial, 171 coronary sinus leads), DL were 429 (409 ventricular, 6 atrial, 14 superior vena cava leads). Indications to TLR were sepsis in in 28%, local infection in 55% and noninfectice indication in 17% of the leads. We performed mechanical dilatation using the Cook Vascular (Leechburg PA, USA) polypropylene sheaths and, if necessary, other intravascular tools (Catchers and Lassos, Osypka, Grentzig-Whylen, G); a Internal Trans-Jugular Approach (JA) through the internal jugular vein was performed in case of free-floating leads or failure of standard approach.
Results: Removal was attempted in 2906 leads because the technique was not applicable in 8 PL. Among these, 2852 leads (2423 PL, all the 429 DL) were completely removed (98.1%), 29 (1%) partially removed, 25 (0.9%) not removed. Among 2825 exposed leads, 434 were removed by manual traction (15.4%), 2117 by mechanical dilatation using the venous entry site (74.9%), 15 by femoral approach (FA) (0.5%) and 205 by JA (7.2%). All the free-floating leads were completely removed, 24.7% by FA and 75.3% by JA. Major complications occurred in 10 cases (0.61%): cardiac tamponade (9 cases, 2 deaths), hemotorax (1 death).
Conclusions: Our experience shows that in centers provided with wide experience, TLR using mechanical dilation has a high success rate and a low incidence of serious complications. The use of the JA allows a very high effectiveness and safety in case of free-floating or difficult exposed leads.

P1793 (W) Patients over 65 years of age with unexplained syncope have a higher risk of recurrent syncope and undergo fewer tests before receiving an implantable loop recorder

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Introduction: Little is known of age as a determinant of presentation, diagnostic pathway and treatment of patients with unexplained syncope. This sub-analysis of the PICTURE international registry aimed to compare older (≥65 years) to younger (<65 years) patients.
Methods: Of the 570 patients who had an implantable loop recorder (ILR) implant (Reveal, Medtronic Inc.) and were followed until the first recurrence of syncope or for at least 12 months after implant, 48.6% were below 65 years of age. The actual follow-up period was 12±10 months. Time to first syncope after implant was analyzed by multivariate regression analysis.
Results: The mean age at first syncope was 41±17 versus 69±13 years, respectively. Patients <65 years had more syncopal events per year, less events without prodromes and were less often hospitalized for syncope. Patients ≥65 years had a higher incidence of hypertension, diabetes and coronary artery disease (all p<0.0001), and their baseline ECG showed more atrial/supraventricular tachycardia (6.8% vs. 1.8%, p<0.01/6.8% vs. 3.6%, p=0.09). There were also higher incidences of atrial fibrillation, or other ECG abnormalities in the older pa-

tients (27% vs. 12%, p<0.0001). Younger patients underwent significantly more tests, e.g. Tilt (40% vs. 30%, p=0.01), exercise test (57% vs. 47%, p=0.02), neurological/psychiatric evaluation (52% vs. 43%, p=0.054) and EEG (45% vs. 33%, p<0.01). Older patients had a higher risk of recurrence of syncope (HR=1.37, 95% CI: 1.01-1.85) and a higher proportion of diagnoses primarily made on Reveal data (68% vs. 52%, p=0.03). Younger patients more often received no specific treatment than older patients (40% vs. 25%, p=0.03).
Conclusions: Older patients were at higher risk of recurrent syncope, had more significant comorbidity and syncopal events without prodromes and had significantly less tests performed before an ILR implant than younger patients. It seems reasonable that patients at the highest risk of recurrence get an ILR sooner, but the number of tests is high in both age groups. Once a diagnosis was made, younger patients were treated less often than older patients, even though there was no difference in the prescribed specific treatment between older and younger patients.

P1794 Asystole during long-term electrocardiographic monitoring in children with unexplained syncope

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Background: Prevalence of unexplained syncope in children is about 5% among all episodes of recurrent loss of consciousness. Although bradiarrhthtmia is the most common arrhythmia event that has been reported during prolonged monitoring with Implantable Loop Recorders (ILR), there is little evidence on prevalence and significance of asystole in children with recurrent syncope of unknown etiology.
Methods: Unexplained syncope (at least two episodes within last 3 years) is considered as an indication for ILR monitoring (Reveal XT). In 2003-2011, ILR was implanted in 160 children younger than 18 years with recurrent syncope that remained unexplained after careful investigation (history of disease, physical examination, ECG, stress-testing, 48-hour ECG (Holter) monitoring (HM), echo, tilt-test, and EP study). Monitoring was completed in 90 pts with syncope on ILR or follow up ≥18 months. 58 pts (65%) aged from 1 to 17 years (12.0±4.4; 46% female) with syncope or significant arrhythmia events registered within 1 to 20 month after ILR implantation were investigated.
Results: Syncope were registered in 40 (69%) of 58 pts: 27 children experienced reflex syncope (RS), 11 – arrhythmogenic (AS) syncope due to asystole, and 2 pts - both AS and RS. Supraventricular tachycardia was documented in 2 pts. Remaining 16 children and 3 pts with RS experienced severe nocturnal asystole. In total, 32 (55%) of all ILR-positive cases are related to asystole with lengths ranging from 3.5 to 30.0 s due to sinus arrest (23) or severe av-block (9). Among all asystole on ILR - 13 (41%) causing syncope. Sinus pause/arrest, sinoatrial exit block or bradycardia ≤40 bpm as asymptomatic features of sinus node dysfunction (SND) have been found on ECG/HM before ILR implantation in 28 (48%) of 58 children. These features were detected in 72% pts with asystole, more frequently in children with symptomatic asystole (85%) compared to those with nocturnal asystole (64%). Among pts with RS signs of SND were found only in 15% (p=0.02) of cases. Asystole on ILR has strong positive association with signs of SND on HM: OR= 2.53 (1.27-3.80, p=0.0001). 28 pacemakers were implanted.
Conclusions: Asystole is the most frequent arrhythmic event in children with S of unknown aetiology. In 72% of cases presence of asystole on ILR is related with asymptomatic SND markers. Detection of potentially life-threatening asystole is one of important goal of the ILR monitoring in pediaty. Whenever unexplained S in a child associated with signs of SND on HM according preliminary investigation, the ILR implantation is strongly recommended.

P1795 Yield of the implantable loop recorder according to clinical indication

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Introduction: Implantable loop recorder (ILR) has proven to be a useful tool in the diagnosis of recurrent syncope (RSyn) in selected populations. However, the spread of its use has expanded indications, and the yield of the device is not well known in real life practice.
Aims: To evaluate the performance of the device according to the reasons for the implant.
Methods: We designed a nation-wide registry of consecutive patients (pts) undergoing implant of an ILR for clinical reasons, between April'2006 and December'2008, with 41 participating centers. A specific form with baseline clinical and ECG data, reason for the implant, events at follow-up (fu.), final diagnosis (DX) and treatment (TX) was prospectively filled for each pt. We analised whether the reasons for the implant in pts with Recurrent syncope (Rsy), Isolated syncope (Isy) or Presyncope (Presy) were predictive of events and DX.
Results: Seven hundred and twenty nine pts (405 men (56%); age 67±15) were included. Seventy three pts were lost to fu. (10%). From the remaining 656, 322 pts (49%) presented a total of 420 events, leading to a final DX in 216 pts (33%). No differences in baseline characteristic were found among the three main indications except for structural heart disease (SHD), less frequent in the group of RSyn (p<0.01). Final DX rates in each subgroup are shown on table. A similar diagnostic power was observed among the different clinical indications in patients with SHD or BBB. However a higher percentage of final DX was obtained in patients with normal heart and RSyn (32.5%) when compared with PSync (19%) or ISyn (17%) (p=0.023).

N=729	Number and % of pts with final DX			P
	Recurrent Syncope	Isolated Syncope	Presyncope	
Global	185 (32%)	20 (19%)	11 (25%)	P=0.017
Normal Heart	133 (32.5%)	10 (17%)	4 (19%)	P=0.023
Bundle Branch Block	48 (34%)	10 (31%)	2 (22%)	P=NS
SHD	49 (31%)	10 (23%)	6 (29%)	P=NS

Conclusions: The rate of final DX is about 1/3 in patients with SHD or BBB, irrespective of the clinical presentation. With normal heart the diagnostic yield is higher in patients with recurrent syncope.

P1796 Prognosis of patients with still unexplained syncope after implantable loop recorder

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Purpose: The implantable loop recorder (ILR) is a useful diagnostic tool in dealing with recurrent syncope in patients, but many patients don't have any recurrence during their monitoring follow-up. The purpose of our study is to determine the prognosis of the patients with still unknown etiology of their syncope after explantation of the ILR.
Methods and results: From July 1999 to May 2008, 132 consecutive patients (age 64±17 years, 57 males) complaining of recurrent unexplained syncope received an ILR (Reveal 9526, Medtronic, Minneapolis, USA) after cardiac and neurological evaluation. According to the ESC guidelines 2009, 42 (31.8%) patients had an abnormal ECG and 35 (26.5%) had a structural heart disease suggesting cardiovascular syncope. At the end of the ILR monitoring (12±5.7 months), 71 (53.7%) patients developed a new syncope, then allowing to diagnose syncope mechanism. An arrhythmic event was observed in 43 (60.5%) after an average period of 176 days (6 months): complete atrioventricular block (n=8), sinus arrest (n=23), ventricular tachycardia (n=5), atrial fibrillation with fast ventricular response (n=1), supraventricular tachycardia (n =6). The 61 (46.3%) patients without recurrence were followed-up during a mean of 39±26 months after explantation of the ILR. We observed in 9 (14.7%) patients recurrence of syncope: 2 (3.2%) with complete atrioventricular block (respectively 1 and 6 years after explantation), 6 (9.8%) with vasovagal syncope and 1 (1.6%) with a final diagnosis of epilepsy. Six (9.8%) patients died of non cardiac causes and 6 (9.8%) were lost to follow-up.
Conclusions: The prognosis of patients without recurrence of syncope before explantation of the ILR is good because most of the syncope by arrhythmic event occurred during the first 6 months after implantation. One year after implantation of the ILR, arrhythmic causes of syncope are very rare.

P1797 Implantable loop recorders in older persons with unexplained syncope

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Introduction: Syncope is common among older persons, with a reported prevalence of 10%. In up to 30%, syncope remains unexplained despite extensive and costly investigations. There is a paucity of data regarding the use of implantable monitoring devices among older patients with unexplained syncope. The purpose of this study was to determine the diagnostic yield of an implantable loop recorder (ILR, Reveal Plus/Reveal DX) in older patients with unexplained syncope.
Methods: Prospective observational data were collected from consecutive patients ≥ 75 years with unexplained syncope who underwent implantation of an ILR and were followed at a single tertiary center between April 2004 and November 2010.
Results: 43 patients, 29 female, were included. The mean age was 82.5 years, ± SD 4.7; range 75 to 95 years. Seventy-seven percent of patients were treated for hypertension, 25% had ischemic heart disease, 16% had cognitive impairment and 14% were treated for diabetes. Prior to assessment, patients had a median of 11 episodes of syncope, range 1-75. Following ILR insertion, the median follow-up time was 12 months (range 1 to 36 months). Twenty-four (55.8%) patients had syncope during the follow-up period; the median time to first syncope was 2.5 months; range 1-16 months. Twenty-two patients achieved symptom-rhythm correlation with an arrhythmia diagnosis in 16 patients; 9 had atrial fibrillation or flutter, 8 with rapid ventricular rates. Significant bradyarrhythmia was documented in 8 patients.

Conclusion: Long-term rhythm monitoring using an implantable loop recorder has a high diagnostic yield in older patients with unexplained syncope. In patients with syncope recurrence during follow-up, 66% had a documented arrhythmia. There was a higher than previously reported incidence of atrial fibrillation as the diagnostic rhythm.

P1798 Implantable loop recorder in patients with structural heart disease

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Introduction: Implantable loop recorder (ILR) may help in diagnosing paroxysmal conditions such as syncope (sync.) or palpitations in the subset of patients (pts) with structural heart disease (SHD). Objective: to evaluate the indications and outcomes of ILR in pts with SHD.
Methods: A national registry of consecutive pts undergoing implant of an ILR for clinical reasons, between April'2006 and Dec'2008, with 41 participating centers. A specific form with baseline clinical and ECG data, events at follow-up (fu), diagnosis (DX) and treatment (TX) was prospectively filled for each pt. All pts had one year fu after the implant. We analized the subset of pts with SHD.
Results: Two hundreds and twenty eight pts (165 men (71%); 68±13 years) were included. Nineteen pts were lost to fu (8.3%). From the remaining 209, 107 pts (51%) presented a total of 122 events, leading to a final DX in 64 pts (31%). In 59 pts (28%) an ILR recorded arrhythmia was considered the diagnostic event. Mean time to diagnosis was 201±145 days.
The most prevalent diagnosis was bradycardia related sync. (58%), followed by neuromediated sync. (19%) and tachycardia related sync. (15%, 7 with VT). The presence of previous bundle branch block was not different among different diagnostic groups. Ten pts (4.8%) died during fu but only in 1 case the cause of death was registered by the device. Sixty two pts (30%) received a specific TX based on the ILR information (36 pacemakers, 7 ICDs, 6 drugs, 2 ablation).

	N=228	%
SHD: Ischemic	132	58
SHD: Valvulopathy	36	16
Abnormal ECG	77	34
Bundle Branch Block	62	27
LVEF under 55%	82	36
Indication: Recurrent Syncope	159	70
Indication: Isolated Syncope	44	19

Conclusion: Main indication for ILR in this subset of pts is recurrent sync. Final diagnosis is obtained in about one third of the pts based on a recorded significant arrhythmia and leading to a specific TX in most of them. Bradycardia related sync. is the most common final DX. No differences among subgroups were found.

P1799 Incidence of detection errors in implantable loop recorders and its impact in the diagnostic yield

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Background: Implantable loop recorders (ILR) are useful tools in the diagnosis of syncope of unknown origin. In addition to manual activation by the patient after symptom recurrence, the ILR can automatically detect and store rhythm disturbances in the absence of manual activation. However, signal artifacts are often mistaken for arrhythmias and stored by the ILR.
Purpose: To assess the incidence of inappropriately stored events in a series of patients with ILR and to evaluate its impact in the diagnostic yield of ILR.
Methods: We retrospectively reviewed a database containing clinical and follow-up data of all consecutive patients who received an ILR for the study of syncope of unknown origin between January 2001 and October 2009. The following data were recorded for analysis: recurrence of syncope, proper manual activation of the ILR by the patient, presence of inappropriately stored events, and final diagnosis.
Results: 173 patients were included in the study (48% male, age 59.7±18.4 years). In 97 patients (56.1%) there was at least one inappropriately stored event due to over- or undersensing of the ECG signal (10.4% had 1-5 false events, 13.3% had 6-20 and 32.3% had >20). There were no significant differences in the incidence of false detections between the different models of ILR implanted during this period. A diagnosis was obtained in 75 patients (43.3%). 50 patients activated manually the ILR after a syncope, with the following diagnoses: asystole in 16 patients, tachycardia in 5, and no significant arrhythmia in 29. Of the 123 patients without manual activation, 25 patients (10 with syncope and 15 asymptomatic) had a relevant arrhythmia detected automatically by the ILR (asystole in 21, tachycardia in 4). Of these 123 patients, 78 had inappropriately stored episodes and 45 did not. A significant arrhythmia was detected in 10 (12,8%) of the 78 patients with inappropriate events and in 15 (33.3%) of the 45 patients without inappropriate events (p=0.006).
Conclusion: The automatic detection feature was useful in the diagnosis of syncope in our series, contributing to one-third of the diagnoses, but it also resulted in a high number of false episodes being inappropriately stored. In patients without symptom recurrence and in those who failed to activate the ILR properly after a syncope, diagnosis relied on the automatic detection of arrhythmias. The presence of inappropriately stored episodes significantly reduced the diagnostic yield of ILR in this group, possibly by overwriting true arrhythmic events or by making its identification more difficult.

P1801 Initial experience of a multi specialty nurse led rapid access blackout clinic: improving patient access and experience

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Introduction: A nurse led rapid access blackout service was developed in 2010. Cardiology and Neurology teams collaborated to develop and deliver the service. The aim was to streamline the patient journey, provide timely assessment, diagnosis and treatment, reduce unnecessary testing and inappropriate referral and meet national guidance on the management of Transient Loss of Consciousness (TLOC). We report our initial experience and outcomes over twelve week period.
Methods: Referral pathways were developed with health care professionals in primary care, accident and emergency, medical admission units and elderly care. All referrals are triaged by arrhythmia/neurology specialist nurses prior to the patients being seen in the blackout clinic by the nurses. The blackout clinic offers a "one-stop-shop" with all patients undergoing comprehensive assessment, clinical examination and 12-lead ECG. Echocardiography, EEG, CT and ambulatory ECG monitoring are available if required. Clinical supervision and review of patient treatment plans when required is provided by consultant cardiologist/neurologists and decisions made for ongoing treatment as necessary. A patient telephone helpline is also provided.
Results: Average waiting time to be seen was one week. Of the number of patients seen (44)100% had 12 lead ECG, (3)7% EEG, (12) 27% echocardiogram, (13) 30% ambulatory ECG, (4) 9% tilt test and (1) 2% of patients had CT scan performed. (26) 59% of patients were diagnosed at first appointment, (18) (41%) required review appointments. Neurology consultant review was required for (6) 14% and cardiology consultant review for (2) 4% of patients. Audit shows 100% compliance with ESC and NICE guidance for TLOC.

Results

Diagnosis	VVS	Orthostatic Hypotension	AF	Epilepsy	NAD	Other Review Review ongoing
Total number of patients 44	(15) 34%	(3) 7%	(2) 4%	(6) 14%	(6) 14%	(12) 27%

Overall patient satisfaction was high 98% of patients were satisfied with the service with 99% indicating they were happy to be seen by a nurse not a doctor.

P1802 Telecardiology for rule-out of patients referred for syncope to public EMS

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Aim: Diagnosis of malignant arrhythmias or severe atrio-ventricular disturbances may be a challenging task in emergency evaluation of subjects referred for syncope. Telecardiology pre-hospital assessment may be helpful in immediate diagnosis of significant arrhythmias needing urgent hospitalization. In this study we therefore aimed to evaluate the rate of incidence of significant arrhythmias in subjects referred for syncope screened at home with telecardiology.
Methods: 2648 consecutive patients (mean age 66±20 years, 53% male gender) referred to public emergency service "118" for syncope were evaluated at home with telecardiology CardioVox P12 device. ECGs were sent to a telecardiology "hub" and immediately read by a team of cardiologists active 24/7. Incidence of any arrhythmias or conduction disturbances was recorded. The study involved the entire Apulia, a region in south-eastern Italy with more than 3-million inhabitants.
Results: In more than 55% of cases ECG findings were normal, in 13% showed sinus tachycardia, in 9% sinus bradycardia. Incidence of ventricular tachycardia was 0.20%, while significant AV disturbances were present in 1.12% of cases (0.11% grade I type 2 AV-block, 0.11% advanced AV-block, 0.19% grade III AV-block, 0.45% junctional rhythm, 0.26% ventricular rhythm).
Limited gender differences were detectable, even though without any clinical relevance. No significant arrhythmias were found in subjects younger than 30 years and no subjects below 30 years needed urgent hospitalization.
Conclusions: Incidence of significant arrhythmias in a context of patients with syncope evaluated at home with telecardiology is very low, and almost absent in subjects below 30 years. Telecardiology screening at home may be helpful in rule-out of patients referred for syncope and in identifying subjects not needing emergency room evaluation or urgent hospitalization.

P1803 Tilt training strikingly reduces syncope recurrence in patients with neurally mediated syncope compared to control subjects during follow up

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Tilt training is considered as a first line treatment for neurally mediated syncope (NMS). In our department tilt training has been performed for about 20 years. This study reports the overall results of a group of 346 patients (mean age: 34.4±21.9 years, range 6.5 – 87 years) with recurrent neurally mediated syncope (S) and a positive tilt test, who underwent a program of tilt training which was started in the hospital. The patients were heavy symptomatic before tilt training: 71% reported 1 S/year, 12% $\geq$ 1 S/month, 13% $\geq$ 1 S/week and 4% $\geq$ 1 S /day.
Methods: Patients were tilted daily on a tilt table (60 ° inclination) until syncope, until severe orthostatic intolerance or until a normal value of 45 min was reached. A group of 324 pts continued tilt training on a regular basis and was compared to a group of 22 patients who discontinued or did not perform TT for logistic reasons. This was considered as the control group. The recurrence rate of syncope was followed at the outpatient clinic.
Results: Almost 80% of patients with NMS and good compliance to therapy remained free of syncope during a one year follow up.

Syncope recurrence during follow up

Recurrence rate of syncope (N per year)	TT continued (N=324)	Control group (N=22)
0	79%	18%
1	9%	41%
$>$ 2	12%	41%

N = number, P=0.001 (Chi square = 69).

Conclusion: Tilt training restores orthostatic tolerance in patients with NMS and should be continued on a regular and long term basis to condition the orthostatic cardiovascular reflexes.

P1804 Does the basal electrocardiogram provide additional prognostic significance in the diagnosis of neurocardiogenic syncope?

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Purpose: We sought to identify common electrocardiographics (ECGs) features potentially associated with neurocardiogenic syncope (NCS) by analyzing the baseline 12-lead standart ECG in a large population of patients with syncope referred for tilt table testing (TTT).
Methods: Observational study including consecutive patients referred to the electrophysiology laboratory of our institution over a 12 year period were enrolled between January 1999 to December 2009. ER pattern was defined as "J" point elevation (J wave) $>$0.05 mV above baseline level, slurred QRS complex (a gradual transition from QRS to ST segment) and ST segment elevation in inferior (II, III, aVF) and lateral (I, aVL, V4 to V6) leads.
Results: A total of 912 patients were included. The mean age was 46.9±22 years, 556 female (61%). Baseline normal ECGs were found in 312 (34.2%). ER prevalence was 20% (182). Right bundle branch block was present in 70 (7.7%) patients. ER was identified in only 29 (5%) of female patients versus 153 (43%, p=0.0001) of males. Most common syncopal pattern was vasodepressor predominance (354 patients, 38.8%), followed by pure vasodepresor (308 patients, 33.8%). Among all patients with ER in the baseline ECG, 160 (87.7%) had a positive TTT for NCS pure vasodepresor type or with vasodepresor predominance, compared with any other type of syncope (22, 12.3%, p=0.04). Logistic regression analysis reported an odds ratio (OR) of 3.97 (95% CI, 1.71-9.21; p=0.001) for NCS vasodepressor type in the subgroup of male patients with ER in comparison with those who did not have this ECG feature, after adjusting for age.
Conclusions: A high incidence of ER pattern was observed in our group of patients with syncope. Male patients with ER pattern had an OR of 3.97 for NCS vasodepressor type in comparison with those male patients who didn't have this ECG feature, orienting to the possible diagnosis and origin of syncope in the initial evaluation of this subgroup of patients.

P1805 Accurate diagnosis of moderate to severe sleep apnea syndrome by analysis of transthoracic impedance signals in patients with permanent pacemaker implantation

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Purpose: There are several reports regarding an excessively high prevalence of undiagnosed sleep apnea syndrome (SAS) in patients with permanent pacemaker implantation. Some programs for pacemakers utilize transthoracic impedance changes between the generator and the electrode tip to derive minute ventilation as a sensor for rate adaptation. We investigated whether this system can detect sleep-related breathing disorders.
Methods: We investigated 39 patients (19 male, 20 female, 78±13 (SD) years) who underwent permanent pacemaker implantation for sick sinus syndrome and advanced or complete atrio-ventricular nodal block. Body mass index of these patients was 23±4 kg/m^2. Chronic heart failure was observed in 10 (26%) of 39 patients. We measured the number of the transthoracic impedance signals remaining unchanged for more than 10 seconds with use of the pacemaker minute ventilation sensor (ELA Medical), and compared with the results of polysomnography (Morpheus C, Teijin). By using polysomnography, we calculated the number of apnea/hypopnea episode per hour (apnea/hypopnea index: AHI). We defined the number of respiratory cycles more than 10 seconds of unchanged transthoracic impedance signals as the respiratory disturbance index (RDI). Receiver operating characteristic (ROC) analysis was performed on the RDI for the diagnosis of moderate to severe SAS (AHI $>$20).
Results: Moderate to severe SAS was diagnosed in 18 (46%) of 39 patients. The area under the ROC curve was 0.87 (95% CI 0.75 to 0.99). Given a cutoff value of 210/hour for the RDI, the RDI can significantly ($p<0.05$) discriminate between patients with and without moderate to severe SAS, and showed 72.2% sensitivity and 90.5% specificity for the diagnosis. The RDI was well correlated with the AHI in patients with moderate to severe SAS (n=15, r=0.771, p=0.0004).
Conclusions: Detection of apnea/hypopnea episode by pacemaker minute ventilation sensor is feasible and accurate for diagnosing SAS in patients with permanent pacemaker implantation.

P1806 Utility of the surface electrocardiogram and fluoroscopy for lead position in right ventricular outflow tract pacing- validation with cardiac computed tomography

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Purpose: Right ventricular outflow tract (RVOT) pacing may have a favourable hemodynamic and electrophysiological profile as compared to apical pacing. Fluoroscopic and electrocardiographic (ECG) landmarks, which are the only guides available to achieve true septal pacing within the RVOT, have not been properly validated. We sought to validate these using cardiac computed tomographic (CT) angiography to confirm lead position within the RVOT.
Methods: 28 patients with pacemaker leads in the RVOT position were subjected to a cardiac CT angiogram (64-slice Dual Source Siemens Definition) for lead localization within the RVOT as anterior, free wall or septal location. 12-lead ECGs were analysed during forced pacing. Fluoroscopic images of the pacemaker leads were also obtained in 4 standard views- AP, LAO, RAO and lateral views.
Results: Cardiac CT angiography was performed in 28 patients with a mean age of 59±13 years (22 males). 14 patients (50%) were found to have an anterior lead location within the RVOT, while 14 (50%) had a septal position. Mean QRS axis and QRS duration did not differ significantly among the two groups (QRS axis: 71±5.4° vs 74±4.3°(P-0.20) and QRS duration: 153±21.1 vs 148±19.3 msec (P-0.55) for anterior versus septal respectively). Notching in none of the limb leads, including inferior leads, was significantly different among the two groups. A negative QRS in lead I could not distinguish an anterior from a septal lead location (9/14 vs 11/14, P-0.67, anterior vs septal). In the fluoroscopic LAO view, the lead was directed rightward in all 14 patients with septal location, but also in 11/14 patients in the anterior location (P-0.22). The lateral view revealed posterior direction of lead in 10/14 patients with septal location, and in only 3/14 patients with anterior lead location (P-0.003).
Conclusions: Accurate localization of lead position using CT angiography revealed that conventional ECG criteria are inaccurate in differentiating septal from anterior RVOT pacing. Similarly, the fluoroscopic LAO view is insufficient in predicting septal location. The left lateral view, as corroborated by CT, was more reliable than the LAO view in confirming septal lead placement.

P1807 The effect of clinical triggers on positive responses of tilt table testing potentiated with nitroglycerin or clomipramine

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Purpose: In this study we evaluated the effect of clinical triggers on the positive responses of tilt table testing (TTT) potentiated with nitroglycerin (which acts mainly through a peripheral dilatation) or clomipramine (which acts mainly through a central serotoninergic mechanism).
Background: The effect of clinical triggers on tilt table testing responses has not been systematically evaluated.
Methods: We enrolled 380 consecutive adult patients: in 66 patients syncope was triggered by emotional distress, in 161 by specific situations or by prolonged standing and in 153 syncope occurred in absence of any detectable trigger. Nitro TTT, performed in 252 patients, consisted of a passive phase of 20 min followed, if negative, by 400 μg nitroglycerin spray sublingually and tilt continued for 15 min;

Clomipramine TTT, performed in 128 patients, consisted of 20 min of tilting with intravenous administration of 5 mg clomipramine during the first 5 min.
Results: The presence of clinical triggers increased the positivity of Nitro TTT (71% central, 75% peripheral) compared with absence of triggers (36%). With Clomipramine TTT the highest positivity rate was observed in patients with central triggers (92%) compared to those with peripheral (45%) and no triggers (30%). Cardioinhibitory forms were more frequent in patients with central trigger than in the other two groups (34% versus 12% and 7%) and with Clomipramine TTT than with Nitro TTT (19% vs 11%). Conversely, mixed or vasodepressor forms were more frequently induced by Nitro TTT (41% vs 24%).
Conclusion: The presence of clinical triggers increases the positivity of TTT and influences the type of responses. Some specificity of nitroglycerin and clomipramine for peripheral and central mechanisms exists.

P1808 Evaluation of possible brain injury caused by vaso-vagal syncope, during head-up tilt test

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Aim of study: Evaluation of injuring influence of vaso-vagal syncope (VVS) during head-up tilt test (HUTT) on the brain by evaluation of myocardial oxygenation and serum level of neuron-specific enolase (NSE), the biochemical marker of brain neurons injury.
Study population: 60 pts (38 women) aged 18-74yrs (mean age 35,6), with VVS, referred to HUTT.
Methods: All pts underwent HUTT according to Westminster protocols. All pts. lies at supine position by 30 minutes after antecubiltal vein canniulation.
During HUTT regional saturation (rSO2) of frontal lobes of brain was measured using INVOS cerebral oximeter in all pts. Baseline value of rSO2 was evaluated during 15 min. supine phase before HUTT. Changes of rSO2 during HUTT was expressed as a relative decrease (in%) of rSO2.
Blood sample for NSE measurement was collected before and 1 hour and 24 hours after HUTT in all pts. An increase of serum level of NSE (dNSE) after HUTT was calculate. All results were analyzed in relation to the type of vaso-vagal response to orthostatic stress during HUTT (acc. to VASIS scale). Serum level of NSE was measured by immunoradiometric method.
Results: HUTT was positive in 51 pts (85,0%). Mixed type of vaso-vagal response was noticed in 28 pts (46,7%), cardiodepressive in 17 pts (28,3%), and vasodepressive – in 6 pts (10%). Significant desaturation preceded syncope induction during HUTT in all pts in comparison to pts with negative test (-29.6 and -31,8% vs -11,4 and -12,1% $p<0,00001$). Serum concentration of NSE before HUTT was in normal range before HUTT.
We observed the significant increase of serum NSE level 1 hour after HUTT in all pts in whom syncope was induced during the test, with normalization after 24 hours (respectively: 3,3; 4,2 and 2,3 ng/ml; $p<0,01$). In 5 pts (8,4%) NSE exceeded normal range (12 ng/ml) 1 hour after HUTT. There were no significant increase of NSE serum levels in pts with negative results of HUTT (respectively: 6,1; 4,1 and 2,7 ng/ml; p=0,27)
NSE increase did not differ significantly between different types of vaso-vagal response.
Increase of serum concentration of NSE during HUTT sigificantely correlate with desaturation (decrease of oxygenation of frontal lobes of the brain) preceeding syncope (r: 0,27; p=0,04). There were no correlation between NSE increase after HUTT and age of pts and HUTT duration.
Conclusions: 1. Cerebral hypoperfusion due to head-up tilt test induced syncope, leads to significant desaturation of the brain as well as to mild release of biochemical markers of brain injury.
2. Vaso-vagal syncope, provoking cerebral hypoperfusion, may led to discrete brain injury.

P1809 Prophylactic pacemaker implantation in familial amyloid polyneuropathy with minor conduction disorders

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Aims: To test the hypothesis that prophylactic pacemaker implantation may protect familial amyloid polyneuropathy (FAP) patients from bradycardia due to transient or permanent AV block.
Methods and results: From January 1999 to January 2010, fifty-one patients with genetically proven FAP (53±13 years old) and minor conduction disorders were implanted with prophylactic dual chamber cardiac pacemaker. Both surface ECG and the complete PM interrogation including temporary pacemaker inhibition and download of the device memory collected at each follow-up visit were retrospectively analyzed over a mean observation period of 43±35 months (cf. Fig. 1). Before pacemaker insertion, ECG was abnormal in 40/51 patients (78%), consisting of intra ventricular conduction disorders (n=20), first degree AV block (n=11) or both (n=9). In the remaining 11 patients, HV interval ranged from 50 to 92 ms. During follow-up, temporary pacemaker inhibition indicated pacemaker dependency with high-degree AV block in 13/51 patients (25%). The time-to-dependency upon pacemaker was 66±42 months (range 5-130).

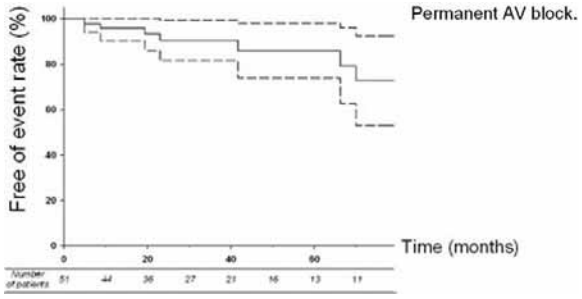

Figure 1

Conclusion: In FAP with minor conduction disorders, prophylactic pacemaker implantation prevented major cardiac events in 25% patients over a 36 months mean follow-up. Prophylactic PM implantation should be strongly considered in these patients.

P1810 Prevalence of cardioinhibitory/mixed form of carotid sinus hypersensitivity in adult patients

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Purpose: Carotid sinus hypersensitivity (CSH) is a well recognized cause of syncope especially in older patients. Recent guidelines recommend performing carotid sinus massage (CSM) in patients over 40 years with syncope of unknown origin and pacing is considered to be an effective treatment option for those with cardioinhibitory/mixed form of the syndrome. The prevalence of carotid sinus hypersensitivity in the general population is not precisely known. The results of previously reported studies vary significantly. The purpose of our study was to determine the prevalence of cardioinhibitory/mixed form of CSH in an unselected community sample of people older than 45 years.
Methods: One hundred forty six (146) individuals randomly sampled from our outpatients department, 69 men, mean age 65.4±10.3 years were finally included in the study. Data concerning their medical history, the presence of syncopal episodes in the past and number and type of prescribed medication were assessed for each individual. All participants underwent supine and upright carotid sinus massage with continuous heart rate monitoring to define the prevalence of cardioinhibitory/mixed type of CSH. A positive response was defined as asystole $\geq$ 3 s.
Results: Seven (5%) out of the 146 individuals demonstrated cardioinhibitory/mixed form of CSH, but only two of them developed pre-syncope or syncope during the test. Six patients reported a history of syncope in the past and of them only one had CSH. The only characteristic that could independently predict a positive cardioinhibitory response to carotid sinus massage was male gender (OR = 6.70 – 95%CI: 1.02 – 54.23, p=0.047). No other differences concerning clinical characteristics and the use of medication were identified between individuals with positive vs negative CSM. When related to previous episodes of syncope, the specificity of a positive cardioinhibitory response in our population was found to be high (95.7%). In the subgroup of 140 individuals with no history of syncope in the past only 6 (4%) demonstrated a positive cardioinhibitory response.
Conclusions: A positive cardioinhibitory response to CSM is uncommon in adult patients over 45 years of age. Only 4% of individuals with no history of syncope in the past demonstrate cardioinhibitory/mixed form of CSH. Male gender is the only characteristic that can predict a positive cardioinhibitory response to CSM.

P1811 The increase in heart rate after vasovagal syncope

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The heart rate rises in substantial percentage of patients after vasovagal syncope. The meaning of this pattern described as peak-2-phenomenon or postvagal tachycardia (PVT) is not known. The aim of the study was to examine the origin of this transient increase in heart rate.
The study group consisted of 562 vasovagal pts aged 43.8±18.2 years (363F, 199M) with positive tilt testing performed according to Italian protocol. The presence of peak-2-phenomenon was assessed by analysis of heart rate trend line obtained from ECG Holter recordings. The results of tilt testing in terms of syncope or presyncope provocation were noted in each case. The logistic regression analysis was performed to find association between presence of presumed postvagal tachycardia and the syncope provocation and pause duration.
The results are presented in the table:

Table 1

	With PVT (n=185)	Without (n=377)	p
Age (years)	40.1±16.8	45.6±15.6	<0.001
Male gender (%)	39	34	NS
Syncope number: median (IQ range)	4 (1–11)	2 (1–6)	<0.001
Traumatic injuries related to syncope (%)	36	29	NS
Blood injury instrumentation phobia (%)	26	16	<0.01
NTG provocation	81	76	NS
VASIS I (%)	32	70	<0.001
VASIS II (%)	67	23	<0.001
VASIS III (%)	1	7	NS
Syncope provocation (%)	95	67	<0.001
Pause (%)	63	16	<0.001

Transient increase in heart rate after neurocardiogenic reflex was observed in 33% of pts. The logistic regression analysis revealed that the pause presence OR 7.0 (CI 4.6-10.6 p<0.001) and syncope provocation OR 5.1 (CI 2.5-10.3 p<0.001) were independently related with transient increase in heart rate after neurocardiogenic reflex provocation.
Conclusions: Profound hypotension is independently related to transient increase in heart rate after neurocardiogenic reflex provocation. The increase in heart rate after vasovagal syncope may be associated with reflex activation of non adrenergic part of sympathetic nervous system.

P1812 Alterations in the expression of genes associated with left ventricular hypertrophy and contractile function after right ventricular apical pacing (preliminary results)

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Purpose: Long term asynchronous ventricular activation from right ventricular apex results in increased wall stress and hypertrophy of the left ventricle (LV), leading to reduced systolic and diastolic function. The purpose of this study is to assess in the peripheral blood alterations of the expression of genes related to LV contractile function and hypertrophy, after right ventricular apical pacing in patients with preserved LV systolic function.
Methods: We enrolled chronically paced patients who were divided into two categories based on the cumulative percentage of ventricular pacing post implant: individuals who were paced due to atrioventricular conduction disturbances and ventricular pacing exceeded 90% (group A) and controls who suffered sinus node dysfunction with preserved intrinsic atrioventricular conduction (group B). At the time of implantation and 3 months later, we evaluated in the peripheral blood concentrations of messenger ribonucleic acid (mRNA) of sarcoplasmic reticulum calcium ATPase (SERCA), and β-myosin heavy chain (β-MHC). We also estimated LV end-diastolic diameter, LV end-systolic diameter and LV ejection fraction echocardiographically.
Results: Up to now, we have collected data from 30 patients during a period of 3-months follow up. In group A (14 patients with QRS 142±12msec) at 3-months follow-up, mRNA levels of SERCA were decreased (9,3±1,49 vs 4,04±1,33 p=0,021) and β-MHC mRNA levels were increased though not signiicantly (62,12±46,97 vs 424±245 p=0,127) while echocardiographic parameters remained unaltered. In controls (16 patients with QRS 85±5msec) all measured parameters showed no signiicant changes.
Conclusions: Permanent right ventricular apical pacing is associated with alterations, in the peripheral blood, in the expression of genes regulating LV function and hypertrophy. These indings are traceable, while at the same time LV function has not deteriorated.

P1813 Cardiac muscarinic receptor overexpression as a possible cause of vagal hyperreactivity

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Purpose: Vagal hyperreactivity associated with baroreflex dysfunction could account for vasovagal syncopes. However, no underlying cardiac abnormality for vagal hyperreactivity has been described so far. The aim of our study was to identify vago-cardiac abnormalities possibly underlying vagal hyperreactivity. To this purpose, we explored cardiac muscarinic receptor and acetylcholinesterase (AchE) expression levels in a rabbit model of vagal hyperreactivity. We also sought blood markers of the observed abnormalities.
Methods: The severity of vagal hyperreactivity was evaluated in conscious animals by measuring the duration of the R-R interval on ECG recording after intravenous injection of phenylephrine. Total, M2 and M3 muscarinic receptor densities were assessed in cardiac tissue using radioligand binding experiments; M2 receptor expression was also determined in peripheral mononuclear white blood cells using quantitative real time PCR (Q-RT-PCR). Cardiac AchE expression was evaluated by Q-RT-PCR and AchE enzyme activity in erythrocytes was assayed colorimetrically.
Results: The R-R interval duration was largely enhanced in hyperreactive rabbits as compared to control animals (10644±878 versus 1867±251 ms). In the hearts of these rabbits, 2.3- to 3-fold increases in total, M2 and M3 muscarinic receptors densities were observed; moreover, muscarinic receptors densities were significantly correlated to the severity of cardiac pauses. The M2 receptor expression was increased similarly in peripheral mononuclear white blood cells. Vagal hyperreactive rabbits displayed an AchE mRNA amplification ratio of 3.6 versus normal rabbits; this was associated with twice the enzyme activity in erythrocytes.
Conclusion: Our results suggest that cardiac muscarinic receptor overexpression plays a critical role in the development of vagal hyperreactivity; increased AchE levels might represent a compensatory consequence of vagal hyperreactivity. They also show that cardiac abnormalities can be inferred with high confidence from muscarinic receptor and AchE expression levels in blood cells, which may be of great practical interest. Finally, these data support the hypothesis that muscarinic receptor overexpression could become a marker of risk among subjects exhibiting vagal or vasovagal syncopes.

P1814 Ultrasound guided puncture of the subclavian vein during pacemaker implantation

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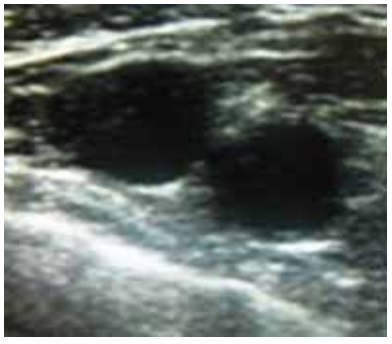
Purpose: Venous access during pacemaker implantation can be challenging when relying solely on anatomical landmarks for guidance. There is also a risk of serious complications. This study evaluates the use of ultrasound to guide puncture of the subclavian vein over the first rib.
Methods: Sixty one consecutive patients (mean age 79 yrs; 29 male) underwent pacemaker implantation by a single operator. Thirty four received a dual chamber device. The subclavian vein and artery were imaged in cross-section over the first rib using a portable ultrasound machine (sonosite micromaxx) equipped with a vascular transducer. The vein was identified by its medial location and its deformation to digital compression. Its diameter (d) and distance (s) from the skin surface were measured. The same needle, guide wire and introducer (9F)were used as for conventional techniques. The needle was advanced towards the vein at a steep angle (70-80 degrees) using continuous ultrasound imaging.
Results: The subclavian vein was clearly imaged and successfully punctured in all patients. Median d and s were 0.9 cm, range 0.5–1.4 and 1.8 cm, range 0.9–2.9 respectively. There was no pneumothorax. No patient required pacemaker revision. In particular there were no cases of lead displacement or wound infection. Further advantages were speed of venous access, minimal discomfort to patients, and smooth passage of introducer and multiple leads underneath the clavicle. Furthermore the presence of marked inspiratory venous collapse on ultrasound imaging allowed identification of patients at risk of air embolism.



Ultrasound of subclavian vessels.

Conclusions: Ultrasound imaging allows safe and reliable puncture of the subclavian vein over the first rib. It should be used routinely in patients undergoing implantation of pacemakers and other devices.

P1815 Recovery of conduction disturbances after complete atrioventricular block induce by transcatheter self expandable aortic valve implantation

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Purpose: Atrioventricular conduction impairment is a well known complication after CoreValve transcatheter aortic valve implantation. Permanent pacemaker implantation is required in around 20-30% of the patients. In this study we assessed the electrocardiographic evolution in the group of patients with complete atrioventricular block after transcatheter aortic valve implantation.
Methods: We analyzed our series of 110 patients, 77±5 years old, with severe aortic stenosis treated with transcatheter aortic valve implantation. Four patients

with previous pacemaker implantation were excluded. All patients were schedule for ECG and clinical control 1 month, 6 month and 1 year thereafter.
Results: Complete atrioventricular block during 72 hours after the procedure needing pacemaker implantation took place in 24 patients (22%). Three additional patients developed late atrioventricular disturbance, requiring pacemaker implantation at 3, 7 and 10 month afterwards. These patients were excluded from the analysis. The only electrocardiographic predictor of pacemaker implantation was the presence of baseline right bundle branch block (76% vs 17%; p<0, 01). Five out of 24 patients with pacemaker implantation died during the follow up. The remaining 19 patients were followed for 16±8 months. Ten of them (42%) fully recovered the atrioventricular conduction (one of them with first degree atrioventricular block, three with atrial fibrillation and adequate ventricular rate and 6 with sinus rhythm and normal PR interval. There were no clinical or echocardiographic variables influencing the full recovery of the atrioventricular conduction. There was a tendency towards a significant difference in the width of baseline QRS complex between patients with and without atrioventricular conduction recovery (109±29 msec vs. 125±32 msec; p= ns). Baseline PR interval or the presence of right bundle branch block or left bundle branch block had no impact on this favourable evolution.
Conclusion: Complete atrioventricular block occurs in a significant number of patients after transcatheter aortic valve implantation, however, full recovery of this transient block takes place during the first year follow up in 42% of patients. Although predicting factors of conduction recovery have not been identified, efforts should be made to avoid unnecessary permanent pacemaker implantation.

P1816 Long-term follow-up of epicardial permanent pacemakers implanted in the neonatal period

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Permanent pacemaker implantation in neonates is infrequently required but represents a challenging problem. The objectives were to define its complications, the freedom from rehospitalisation, reoperation, and the survival of these patients. From 1990 to 2010, epicardial pacemakers were implanted on 58 (21 males) neonates (≤90 days old): 41 congenital rhythm disorders (CONG group) (30 congenital complete heart block, 9 long QT syndrome, and 2 sinus node dysfunction), and 17 postoperative heart block (POSTOP group). Of CONG patients, 20 (49%) presented neonatal lupus. Thirteen (32%) of CONG patients and 2 (12%) of POSTOP were premature babies (p=0.11). CONG group were mainly operated through a sub-xyphoid approach (85%), while POSTOP group were mainly through a thoracotomy (59%) (p=0.0006). Postoperative complications included bleeding (n=1, 1%), effusions (n=4, 7%), infections (n=14, 24%; 3/14, 79% treated conservatively), respiratory distress (n=9, 16%), and hemodynamic instability (n=3, 5%) (CONG=POSTOP, p=NS). The freedom from rehospitalisation for pacemaker complication at 1, 5, 10 and 15 years was 85%, 65%, 47%, and 38% respectively in CONG group, and 94%, 65%, 36% and 36% respectively in POSTOP group (p=0.97). The freedom from reoperation for any pacemaker problem at 1, 5, 10 and 15 years was 88%, 60%, 32%, and 27% respectively in CONG group, and 94%, 51%, 22% and 22% respectively in POSTOP group (p=0.58). The freedom from lead replacement at 1, 5, 10, and 15 years was 93%, 76%, 67%, and 61% respectively in CONG group, and 100%, 75%, 67% and 40% respectively in POSTOP group (p=0.64). The freedom from generator replacement at 1, 5, 10, and 15 years was 95%, 66%, 36%, and 32% respectively in CONG group, and 94%, 57%, 36% and 18% respectively in POSTOP group (p=0.60). The actuarial survival at 5 years was 80% for CONG patients, and 87% for POSTOP patients (p=0.68). Follow-up time was 14.55±5.95 years (range: 8 days to 19 years). Epicardial permanent pacemaker implanted in the neonatal period leads to satisfactory clinical outcome and long-term results. The reoperation rate is high and mainly due to generator end of life.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS: FROM INDICATIONS TO EXTRACTIONS

P1817 Leads extraction in octogenarians: is it safe and effective?

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Purpose: Over 4.3 million people worldwide have been implanted with cardiac rhythm management devices with 500,000 new implantations undertaken per year. More commonly, these devices are being used in more elderly patients with significant comorbidities. We aim to investigate the clinical characteristics and outcome of octogenarians with cardiac device infections undergoing lead extraction.
Methods: A retrospective study was performed to assess the safety and effectiveness of leads extraction in octogenarians with cardiac device infections. Clinical characteristics, procedural features, 30 days-mortality and complication rates were analyzed in two groups of patients: aged ≥80 years (group A) and aged < 80 years (group B).
Results: 115 patients were included in the study group. The mean age was 71±12 years (range 27-96), with males 79,1%. Thirty patients aged ≥ 80 years (85±4 years) (group A) were compared to 85 patients with age < 80 years (66±10,7 years) (group B). At univariate analysis, a significantly higher percentage of patients with age < 80 years presented with heart failure (group B 43.5% versus group A 20%, p=0.02), history of sustained ventricular tachycardia (group B 16.5% versus group A 0%, p=0.01) and more frequently implantation of ICD compared to elderly patients (group B 42.3% versus group A 16.7%, p=0.01). No significant difference based on risk factors, pre-operative medical therapy, lead extraction technique, procedural success rate (93% in group A and 96% in group B) was found. Seven deaths occurred in the 30 days after extraction (6 in group B and 1 in group A); there were 15 (18%) major and 13 (15%) minor complications in group B compared to 1 (3%) and 4 (13%) in group A respectively. No significant difference was found in terms of mortality or complications between the two groups (p=0.41 and p=0.20 respectively).
Conclusions: Older patients may find age-related delay or doubt to lead extraction. Our data confirm that lead extraction can be performed safely and successfully even in octogenarians. Indications for lead extraction should be always carefully considered but age per se should not constitute a limiting and doubtful risk factor.

P1818 Pocket haematoma prevention in patients who required implantation/replacement of a pacemaker or implantable cardiac defibrillator. The PHP Study

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Background: In the last 10 years there is a growth incidence of cardiac implantable electronic device (CIED) procedures. In patients (pts) which cannot discontinue dual-antiplatelet therapy (DAPT) or oral anticoagulant (OAC) the CIED procedures are associated with a high risk of pocket haematoma bleeding complication.
Aim of the study: The aim of our study is to assess the efficacy of a fibrin sealant (Tissucol-Baxter) in preventing pocket haematoma (PH) and subsequent complications in pts undergoing CIED procedures with DAPT or OAC therapy on board.
Methods: In a prospective, randomized, single-centre, open label study, we enrolled consecutively 100 pts undergoing a CIED procedure with DAPT or OAC therapy. 50 pts were allocated to local application of fibrin glue Tissucol treatment (T-Group) into the pocket of CIED and 50 pts to conventional treatment (C-Group): vacuum drainage system application only in case of local bleeding complication. PH was defined as palpable mass that protruded >2 cm anterior to the pulse generator. A blood fluid collected in the drainage system >100 ml were considered equivalent to PH. Follow-up: 45 days. Primary endpoint: to verify the incidence of PH in pts treated with Tissucol compared to conventional treatment. Secondary endpoint: to compare the length of in-hospital stay between the two groups.
Results: 83 pts underwent CIED procedures alone, while 17 (10 pts in the T-group and 7 pts in C-group) underwent other interventions (percutaneous aortic valve implantation;multivessel coronary angioplasty) that resulted in a longer hospitalization. No pts discontinued DAPT or OAC during or after the procedure. No statistically significant baseline differences were observed between the two group in this series. PH occurred in 4 patients (8%) of the T-Group and in 23 patients (46%) of C-Group (P=0.00001). Overall, the in-hospital stay was 2.0±2.3 days for T-group and 2.7±4.9 days for C-group (P=0.401). In the 83 pts undergoing only CIED procedures the in-hospital stay was shorter in the T-group (1.2±1.1 days, n=40) as compared to C-group (1.6±0.9 days, n=43), but this difference didn't reach statistical significance (P=0.062). No adverse effects were observed after the tissucol application.
Conclusions: The use of human fibrin glue, Tissucol, is an effective and safe therapeutic tool in preventing pocket haematoma in patients undergoing CIED procedures with DAPT or OAC therapy on board. In this population the in-hospital stay shows a trend to reduce.

P1819 The prognostic importance of cardiac device infections

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Background: Cardiac Device Infections (CDI) are a serious complication associated with the implantation of cardiac rhythm devices. Although it has been reported that CDI is associated with substantial morbidity and mortality the prognostic importance of CDI has not been reported yet. The objective of this study was to assess the prognostic importance of CDI in implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy – defibrillator (CRT-D) recipients.
Methods: For the current analysis all patients who received their initial ICD/CRT-D between January 2000 and September 2009 were included. During follow up the occurrence of CDI and all-cause mortality were noted. The prognostic impor-

tance of the first CDI was then assessed. CDI was modeled as a time dependent covariate in the Cox proportional hazards model.
Results: A total of 2574 patients (62±13, 78.7% male) were included in this analysis. During follow-up CDI occurred in 66 (2.6%) patients. The 1-year mortality following first CDI was 14.4% ± 9.6%. Experiencing the first CDI was associated with a 1.88-fold increased risk for mortality compared to patients who did not experience CDI. After controlling for possible confounders, this increased to a 2.16-fold higher risk for mortality.

	Univariate			*Multivariate**		
	HR	95% CI	p-value	HR	95% CI	p-value
First CDI	1.88	1.12 - 3.15	0.017	2.16	1.29 – 3.61	0.004

*Adjusted for Age, gender, ejection fraction, diabetes mellitus and renal clearance

Conclusions: In a large cohort of ICD and CRT-D patients, CDI was associated with substantial 1-year mortality. The most important finding is the increased risk for mortality in patients experiencing CDI compared to patients who remain free from CDI.

P1820 Is upgrade to CRT device more likely in pacemaker or defibrillator patients? Insights from the REPLACE Registry

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Introduction: It is unknown which patients with an existing pacemaker (PM) or implantable cardioverter defibrillator (ICD) will require earlier upgrades to cardiac resynchronization therapy (CRT) devices. We examined the clinical characteristics and time to CRT upgrade for patients in the REPLACE Registry.
Methods: All pts in the REPLACE Registry who had a planned upgrade to CRT were included in this analysis. Pts were grouped by existing device type (PM or ICD), and by time to upgrade: early (within 2 yrs) or late (>2 yrs) after original implant. Statistical analysis included the Student's t test for continuous variables and Fisher's Exact or Chi Square Test for categorical variables, and multivariate logistic regression.
Results: Of the 407 pts selected for upgrade to CRT, 167 had an existing PM and 240 had an ICD at entry into REPLACE. Median time to upgrade was 3.6 yrs, and was the same for PM and ICD pts (1 pt with a PM and 2 pts with an ICD had unknown times to upgrade). Of the 166 pts with a PM, 49 (29.5%) had early CRT upgrade and 117 (70.5%) had late upgrade. Of the 238 pts with an ICD, 59 (24.8%) had early upgrade and 179 (75.2%) had late upgrade. Of all clinical variables collected in REPLACE, which included a determination of the Charlson c- morbidity index (CCI) at baseline, only 2 variables were statistically signifiant in univariate analysis: (1) Admission for heart failure in prior 12 months was more common in early vs. late upgrades pts with a PM (41% v. 24%, P=0.039) as well as in pts with an ICD (58% vs. 36%, P=0.004). (2) The CCI was higher in early vs. late upgrade pts with an ICD (3.3 vs. 2.7, P=0.046). Stepwise linear regression confirmed admission for CHF in the 12 months prior to enrollment as a significant predictor of early upgrade in pts with both device types (PM: OR=2.18, P=0.034; ICD: OR=2.44, P=0.004).
Conclusions: One-fourth of pts who underwent upgrade to CRT had the procedure early (within 2 years) of their existing device implant. No meaningful difference was observed in proportions of patients with PMs or ICDs requiring early upgrade to CRT. Admission for heart failure in prior 12 months was the most significant predictor of early upgrade. The higher CCI in ICD pts was an additional factor influencing the probability of early upgrade.

P1821 Time-course of major complications following pacemaker or implantable cardioverter defibrillator generator replacement: results from the REPLACE registry

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Purpose: The prospective REPLACE Registry determined 6-month complication rates after pacemaker (PM) or implantable cardiac defibrillator (ICD) generator replacement only (Cohort 1, 1031 pts) or with a planned lead addition or revision (Cohort 2, 713pts), followed for 6 months. Cohort 2 patients included upgrades from single PM or ICD to dual chamber devices or upgrade to cardiac resynchronization therapy devices or revision of a malfunctioning lead at the time of the generator replacement. Complications were pre-specified and independently adjudicated. We previously reported a patient level major complication rate of 4.0% in Cohort 1 and 15.3% in Cohort 2. The purpose of this study was to examine the time course of the individual major complications.
Methods: All major complications were examined for the time of their occurrence and/or identification referenced to the generator replacement procedure date. Time segments were arbitrarily chosen as 1) within 1 day of the procedure, 2) 2 days to 7 days, 3) 8 days to one month, 4) after one month to 3 months, and 5) after 3 months.
Results: A total of 51 major complications occurred in Cohort 1, and 143 major complications in Cohort 2. Of the total major complications, 3.9% and 12.6% occurred within 1 day of the procedure for Cohorts 1 and 2 respectively. Of the remaining complications occurring after 1 day, 65.3% of Cohort 1 and 67.2% of Cohort 2 were identified between 1 day and 1 month of the procedure, see Table. Although there was a 3.8 fold increase in the observed major complication rate in Cohort 2 vs. Cohort 1, there was no evidence of a difference between cohorts in the distributions of major complications across the follow-up intervals (p=0.134, Wilcoxon-Mann-Whitney Test).

Complications by Time from Replacement

	Total complications N	1 day	>1 day–1 wk	>1 wk–1 mo	>1–3 mo	>3–6 mo
Cohort 1	51	2 (3.9%)	19 (37.3%)	13 (25.5%)	6 (11.8%)	11 (21.6%)
Cohort 2	143	18 (12.6%)	51 (35.7%)	33 (23.1%)	27 (18.9%)	14 (9.8%)

Conclusions: Following PM or ICD generator replacements with or without lead additions or revisions, the majority of the complications occur or are identified within 1 month of the procedure. However, late complications are modest and must be considered when counseling patients. These results are in concordance with other prospective trials and further substantiates the applicability of the REPLACE Registry.

P1822 Single sheath lead extraction, a single centre experience of more than 900 lead extractions

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Our centre is serving most of Norway and Iceland for pacemaker and ICD lead extractions. We have adopted a single sheath technique, a variant of the dilating sheath technique described by Byrd.
Materials and methods: From 1998 to end of August 2010, we treated 551 patients, median age 64 years (range 7-95 years), with 904 leads. Fifty-one percent of the extractions were performed on infections, the rest were elective. Median age of all leads was 5 years (range 0,1 to 42 years). The single sheath technique was used in 69% of the extractions, in 26% we used traction alone, in 5% various fishing techniques and in 1% "Evolution" (Cook).
We start with a gentle traction and then proceed to single sheath technique after applying a locking stylet (Cook/Spectranetics/VascoMed). A single Cook polypropylene sheath is mounted with a Cook Pin Vise and is gently pushed down over the lead with rapid rotation. When serious resistance is met, the sheath size is increased. For larger diameter leads (ICD) we have also used "VisioSheath" (Spectranetics). If hard resistance/calcification is met under the clavicle, a steel sheath is used to gain access into the subclavian vein.
Results: Complete success was achieved with 96% of the leads. "Clinical success" (ie. removal of all of the lead except the distal 4 cm) was achieved in another 3% of the lead extractions. The overall procedural success was 99%. ICD-leads: 154 leads: 99% success, one major complication, resolved without sequelae.
Median "sheath-time" (ie. the time the sheath is applied) is 5 min., range 1 to 300 minutes. Complications: Major complications 2%, one fatal (0,2%). Minor complications 1%.
Conclusion: The single sheath technique was effective, with 99% procedural success. The technique appears to be a quick and effective alternative to laser sheath lead extraction. The complication rate of the single sheath technique was low.

P1823 Predictors of mortality and morbidity in transvenous lead extraction: is it all linked to the procedure?

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Purpose: Transvenous lead extraction is a technically challenging procedure with an associated morbidity and mortality. We reported our 5-year experience of cardiovascular implantable electronic device (CIED) lead removal along with overall major complications and mortality within 30 days from the procedure.
Methods: One hundred and twenty-one patients (pts) were referred to our centre for transvenous lead extraction, aged 70±13 years (range 27-96 ys, 78% males). In our population, procedural indications were pocket infections (46%), sepsis and pocket infection (38%), sepsis (11%) and lead malfunction (5%). Extraction

methods used were: manual traction with locking stylets, mechanical and laser sheaths.
Results: The number of extracted lead were 260, with complete removal in 97%. Mean implantation time was 4.7±5.1 years. Seven pts died but only 1 intraoperatively (cava vein tear), 6 pts died at 14±19 days from the procedure (4 septic shock, 1 pulmonary embolism, 1 acute renal failure). Eight overall complications occurred 6±7 days from the procedure (3 septic shock, 5 pulmonary embolism). At univariate analysis, an higher percentage of pts with complications presented with endocarditic vegetations (72% vs 44%, p=0.01), hemodialysis (22% vs 2%, p=0.002), previous implantation of ICD (60% vs 30%, p=0.01), low use of anticoagulation therapy (13% vs 37%, p=0.03) compared to patients without complications. Multivariate logistic regression demonstrated that previous implantation of ICD (OR 0.20, p=0.005), hemodialysis (OR 13.7, p=0.007) and endocarditic vegetations (OR 4.29, p=0.01) were predictive of in-hospital major complications. In our population, chronic renal failure resulted predictor of mortality at 30 days (OR 12, p=0.02).
Conclusions: Transvenous lead extraction has a prognostic impact on pts with CIED infection, but other clinical variables, not directly linked to the procedure, may affect midterm outcome. In our experience, hemodialysis, previous ICD, presence of endocarditic vegetations and chronic renal failure represent risk factors for morbidity and mortality, independently from the procedure.

P1824 The morphology of far-field electrograms: a new predictor of antitachycardia pacing effectiveness among ischaemic ventricular tachycardias occurring in ICD patients

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Introduction: The ability of antitachycardia pacing (APT) in terminating reentrant VT relies in its capacity to penetrate the circuit during the excitable gap: this depends on the VT cycle length (CL) and on the distance between pacing site and circuit. To date no information is available regarding the ability of the morphology of far-field electrograms (Ff-M) to predict the result of the subsequent ATP. We hypothesized that the Ff-M, as a pseudo-unipolar signal and as hence an indicator of the direction of propagation front, could be related to ATP effectiveness.
Methods: We prospectively studied 308 VT (CL: 332±42 ms) occurring consecutively in 40 ICD patients (LVEF: 31±11; pacing site: right ventricular apex) with Medtronic devices and remote inferior (176 VT) or anterior MI (132 VT). The configuration of Ff-M was ICD can versus ICD right ventricular coil. ICD programming was standardized, including ATP for slow and fast VT (CL: 250-320 ms). VTs were classified as Q-VT (QS, QR) or non-Q-VT (R, RS) depending on the presence or absence of a negative initial deflection in the Ff-M.
Results: The effectiveness of ATP was 84% (81% in inferior and 86% in anterior MI, p=ns). We found four different patterns of Ff-M: QS (n=50), QR (n=137), R (n=80), RS (n=41). R pattern was more frequent in anterior (32 vs. 21%) whereas RS was more frequent in inferior MI (18 vs. 7%), $p<0.05$ for both comparisons. However, the proportion of Q-VT was similar regardless the location of MI: 60% (inferior MI) vs. 61% (anterior MI). ATP was more efficient in Q-VT (94 vs. 74%; $p<0.001$) because the first attempt was more effective: 91 vs. 63% ($p<0.001$). By logistic regression analysis -which included LVEF, CL, etiology, functional class, location of MI, beta-blocker therapy, and indication- the Q-VT pattern was found to be an independent predictor of effective ATP: OR: 7 (95% CI: 3- 16); $p<0.001$. As a result, non Q-VTs need SH to be terminated more frequently: 23 vs. 12% (p=0.001).
Conclusions: Among ischemic VT, non-Q-VTs are less suitable to be terminated by ATP, probably because they are located far from the pacing site. In order to avoid SH, the substrate of non Q-VTs may need a more intensive treatment.

P1825 Follow up of patients with implantable automatic cardioverter defibrillator without defibrillation threshold testing

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Background: Despite intraoperative defibrillation threshold testing (DFT) of implantable cardioverter defibrillators (ICD) is considered of standard practice, ICD implants with no DFT have not been systematically evaluated yet.
Aims: To assess clinical outcomes of patients underwent ICD implantation without performing (DFT) in a mid-term follow-up.
Materials and methods: Retrospective study involving patients who underwent ICD implantation without DFT. Sensing parameters, pacing threshold, and integrity of the system with sub-threshold pulses were tested at implant and at 7 and 30 days and then every 3 months. Clinical outcomes including appropriate and inappropriate therapies, lead dislodgement and ICD failure were evaluated during the follow-up.
Results: A total of 216 patients underwent ICD implantation without DFT. During a follow-up of 34±22 months (3-86); 66 patients (30.55%) presented 199 episodes of ventricular arrhythmia. Almost 45% of the episodes were self limited and required no therapy. Antitachycardia pacing successfully terminated the arrhythmia in 52 episodes. A first shock of 20 Joules (5 episodes) and >30 Joules (38 episodes) correctly treated ventricular arrhythmia. Inappropriate therapy was seen in 6% of the cases. Implant parameters: P wave: 3±1 mV; R wave: 13±4 mV; VD threshold: 0.7±0.3 V; VD impedance: 748±236 Ω; defibrillation integrity system: 48±5 Ω. These values were stable during follow-up. Total mortality during follow-up was 6.8% and none of the deaths were sudden or related to device failure.
Conclusions: ICD implantation without DFT was safe and feasible. No additional complications compared to standard practice were seen. Randomized control trials are needed to confirm this observation.

P1826 Impact of shock testing on the efficiency of the first required ICD therapy

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Background: The study was performed to investigate whether defibrillation threshold testing (DFT) during implantable cardioverter-defibrillator (ICD) implantation is feasible for prediction of the effectiveness of ICD therapy. Defibrillation testing is often performed during insertion of ICDs to confirm shock efficacy. There is no prospective data suggesting that this procedure improves outcomes when modern ICDs are implanted for prevention of sudden cardiac death.
Methods: The retroperspective analysis included patients who received an ICD device with telemedicine capacity. Telemedicine is an excellent tool to follow-up ICD shock therapy because each tachycardia episode requiring ICD therapy can be monitored and evaluated online. In the patients where threshold testing was performed, energy was set 10 J above the successful value. In the non-DFT group, shock energy for the first shock was set to 30-40 J. High energy devices were not used on a regular basis.
Results: A total of 357 ICD patients with telemedicine capacity were enclosed. In 219 patients (61%), DFT testing was performed during implantation. 138 patients were not tested (39%, $p<0.05$). In the DFT group, 124 patients had VT/VF (56.6%) requiring ICD shock therapy. First shock efficacy was 99% for the first VT event in this group, with only one patient undergoing an ineffective first shock delivery; in this patient, the VT could be terminated with the second shock. However, in the long run 7 patients had at least one episode with an ineffective shock, despite the fact that previous shocks had been successful. In the non-DFT group, 76 patients (43.4%, $p<0.05$) required ICD shock therapy and first shock efficacy was 100% (p=n.s.) for the first VT event in this group. There was no significant difference regarding first shock efficacy between patients with ICD for primary or secondary prevention.
Conclusions: First shock efficacy for ventricular tachycardia was high, regardless whether baseline DFT testing was performed or not. This result challenges the current paradigm of ICD shock testing during implantation.

P1827 Long-term follow-up on high-rate cutoff programming for implantable cardioverter defibrillators

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Purpose: Defibrillators are efficient in reducing mortality in patients with left ventricular systolic dysfunction. High-rate cutoff programming may be effective in reducing the rate of both appropriate and inappropriate therapies, but as the long-term consequences on morbidity and mortality remain unclear, it is underutilized.
Methods: We studied 368 consecutive patients (mean age 60±10 years), with ischemic (63%) or non-ischemic cardiomyopathy and left ventricular dysfunction (mean ejection fraction 25±7%), who were implanted with an ICD in primary prevention of sudden cardiac death (40% single chamber, 31% dual chamber, 29% biventricular). All devices were programmed with a shock-only zone over 220 beats per minute (bpm) and a monitor zone between 170 and 220 bpm.
Results: During a median follow-up of 27 months, 35 patients received appropriate shocks (9.5%), while inappropriate shocks were administered to 19 patients (5.2%). Inappropriate therapies were related to supraventricular tachyarrhythmias in 7 patients, and to noise/oversensing in 12 patients. Forty-five patients (12.2%) died, 26 from end-stage heart failure, 18 from a non-cardiac cause, 1 from unexplained sudden cardiac death. Six patients (1.6%) experienced symptomatic untreated ventricular tachycardia episodes in the monitor zone requiring hospitalization and/or device reprogramming.
Conclusions: High-rate cutoff shock-only ICD programming in primary prevention of sudden cardiac death remained safe during a long-term follow-up. It resulted in a low rate of both appropriate and inappropriate shocks, which are known to be deleterious in this population.

P1828 Efficacy and safety of implantable cardioverter-defibrillators in patients with Chagas disease

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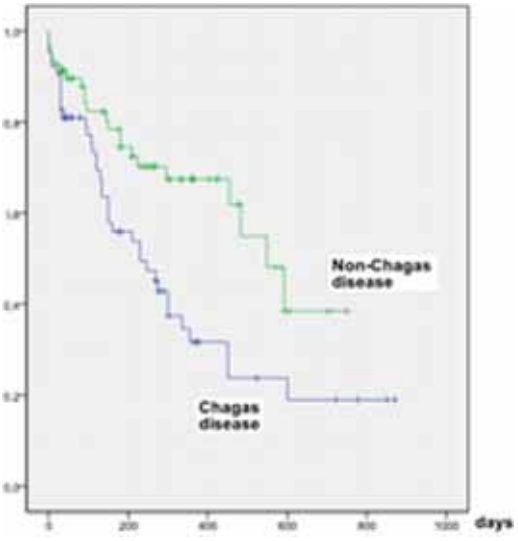
Background: Implantable cardioverter-defibrillators (ICD) are now a first line option for prevention of sudden death in Chagas disease (ChD). However, efficacy and safety of ICD treatment in ChD remains controversial. The aim of our study was to compare in ChD and non-ChD patients their outcome after ICD implantation.
Methods: The study population consists of patients that received ICD implantation in a tertiary Reference Center for ChD in Brazil. The primary outcome of the study was appropriate therapy (appropriate shocks or anti-tachycardia pacing); the secondary outcomes included event-free survival (death or appropriate therapy), mortality and inappropriate shock.
Results: 133 patients were followed for the median time of 266 days. Appropriate ICD therapy occurred in 32 (62.7%) ChD and in 19 (37.3%) non-ChD patients (p=0.005). ChD doubled the risk of receiving appropriate ICD therapy (HR=2.2, 95%CI=1.2-4.3, p=0.01). Moreover, in comparison to non-ChD patients, ChD patients had significantly lower event-free survival (p=0.004). The only independent variable predictive of event-free survival was absence of ChD. During the one year follow-up period there were 16 deaths (11.8%) and five inappropriate shocks (3.7%), with no differences between the two groups.



Event-free survival of ChD and non-ChD

Conclusions: The higher frequency of appropriate ICD therapy and the shorter event free survival in ChD patients are consistent with the presence of an arrhythmogenic substrate that characterizes this cardiomyopathy. ICD implantation in patients with ChD is a safe procedure with low frequency of complications, providing effective protection against arrhythmic death.

P1829 Event-free survival with implantable cardioverter-defibrillators (ICD) and late occurrence of first appropriate ICD therapy (RX)

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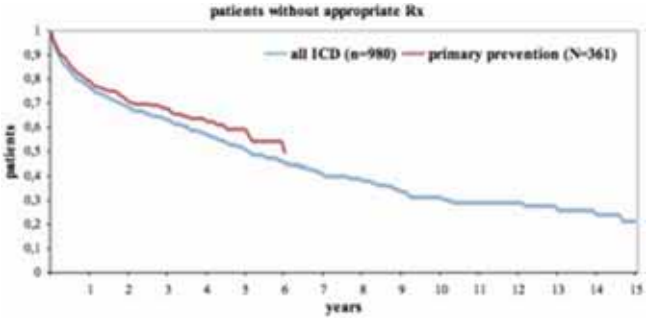
Background: ICD-therapy is an established standard for the prevention of sudden cardiac death (SCD). The indication for implantation is based on the identification of risk factors for SCD without precognition about the exact timing of its occurrence. Some patients (pat.) will never experience arrhythmia, others will only experience complications. This study analyzes the long term probability of the occurrence of ICD-Rx and their properties.
Methods: We investigated data of a single center during a period of >20 years including 980 pat. with 1502 ICD and all of their medical examinations until 08/2010. We analyzed ICD-Rx and complications. We defined appropriate ICD-Rx as the occurrence of ATP or shock triggered by ventricular arrhythmia.
Results: During a mean follow up of 58±51 months, 497 pat. (51%) experienced ICD-Rx: 420 (43%) appropriate and 157 (16%) inappropriate with an overlap of 79 pat. who underwent both. Of note, 68 pat. experienced their first appropriate Rx only after ICD-replacement. This represents 16% of all first appropriate ICD-Rx. Kaplan-Meier-analysis depicts an event free survival rate of only 21% (13%) after 10 (15) years. A total of 139 pat. (14%) did only experience complications (77 with inappropriate shocks), but no appropriate Rx. Out of 168 pat. (17%) who died during FU, 91 died without prior occurrence of adequate ICD-Rx.



Conclusion: ICD therapy is beneficial but it is associated with a relevant percentage of pat. who undergo complication without having profited from any appropriate ICD-intervention before. On the other hand, 6.9% of pat. experience their first appropriate ICD intervention only after the first ICD replacement. We detected the occurrence of first appropriate ICD-Rx even after a long time of follow-up (Figure).

P1830 Relation of ventricular tachycardia/fibrillation to beta-blocker dose maximization guided by pacing mode analysis in non-pacemaker-dependent patients with implantable cardioverter defibrillator

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Background and objective: Current guidelines recommend setting implantable cardioverter defibrillators (ICDs) at a back-up DDDR/VVIR function, at low lower rate limits (about 40 bpm), aiming at minimizing pacing of the right ventricle which can be detrimental for the failing heart. However, in this way the dosage of beta-blocker often remains below clinical-trial-recommended levels. We hypothesized that the up-titration of beta-blockade and adjustment of pacing parameters, with lower rate limit of about 60 bpm, in order to achieve a prevalence of AAIR pacing over indigenous rhythm or DDDR/VVIR pacing in patients with dual-chamber ICDs, would result in maximization of beta-blocker doses and, potentially, reduction of appropriate ICD therapies.
Methods: In this prospective, cohort, crossover study we included patients with ischemic or dilated cardiomyopathy and implanted ICDs, without contraindications to beta-blockers and atrioventricular conduction disturbances. Two 6-month periods were compared: the clinically-guided phase (pacing function set at back-up DDDR mode at a lower rate of about 40 bpm) and the pacing-guided phase, during which beta-blocker dosage was titrated with a target of achieving over 90% AAIR pacing (programmed lower rate 60 bpm with AAIR as primary pacing mode).
Results: 61 patients (age 64.2±8.3 years) were included. During the pacing-guided phase the target of ≥90% AAIR pacing was achieved in 80.3% of patients. The mean daily metoprolol dose during the clinically-guided phase was 96.7±29.4 mg/day versus 127.0±39.6 mg/day in the pacing-guided phase (p<0.001). Appropriate ICD therapies were 35 (57.4%) during the clinically-guided phase, versus 20 (32.8%) during the pacing-guided phase (p<0.001) [1.15 and 0.48 appropriate ICD therapies per patient, respectively (p<0.001)]. In the multivariate analysis, the percentage of AAIR pacing (beta coefficient -0.375; p=0.014) and the beta-blocker dose (beta coefficient -0.351; p=0.001) were independently inversely related to appropriate ICD therapies.
Conclusion: A pacing-guided approach for maximizing beta-blocker doses, aiming at maximizing AAIR pacing, in patients with implanted ICDs, may be beneficial over the conventional strategy. This pacing-guided approach led to higher beta-blocker daily doses, which as expected were correlated to less appropriate ICD therapies.

P1831 Usefulness of magnetic resonance imaging derived left ventricular structure analysis in predicting ICD therapy in patients with hypertrophic cardiomyopathy

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Background: Patients with hypertrophic cardiomyopathy (HCM) are at substantial risk for sudden cardiac death (SCD). Recent study shows the efficacy of prophylactic implantation of Implantable Cardioverter-Defibrillator (ICD) to prevent SCD. However the predictive factor for preventative ICD therapy remains undetermined in these patients. We evaluated possible risk factors for SCD in76 patients with HCM who implanted ICD between May 2000 and August 2010 retrospectively.
Method: Seventy six patients were followed up for 31.1±3.2 months. Study subjects consisted of 50 patients who were implanted ICD for primary prevention, and 26 patients for secondary prevention. Appropriate ICD therapies were recorded in 19 patients (25%). The following variables were evaluated: NYHA functional

class, BNP level, late potential, echo cardiographic parameters such as left ventricular (LV) ejection fraction (EF), LV outflow peak velocity, IVST (interventricular septal thickness)/LVPWT (left ventricular posterior wall thickness) ratio, and max beats and rates of non-sustained ventricular tachycardia (NSVT) on Holter ECG. Cardiac MRI was undertaken for the measurement of LV myocardial mass (MM) (g) and LV end-diastolic volume (LVEDV) (ml). A value of MM/EDV (g/ml) was calculated and utilized as LV Mass Volume (MV) ratio.
Result: High ratio (38%) of ICD therapies was documented in secondary prevention, also primary prevention ICD therapies was recorded in 9 patients (18%). In comparing therapy group with non-therapy group, max NSVT beats (14.5 vs 8.0; P=0.007), LVMM (g) (177 vs 130; P=0.017) and MV ratio (1.79 vs 1.28; P=0.025) are significantly higher in shock therapy group. (values were showed in average). In primary prevention, all patients had NSVT, of which max beats were significantly higher (17.2 vs 8.4; P=0.0017) in therapy group. Furthermore, both max NSVT above 10beats and MV ratio above 1.27 was found highly predictable for appropriate ICD therapies (sensitivity=71%, specificity=91%, PPV=71%, NPV=91%).In the secondary prevention, LVEDV (ml) (145 vs 90; P=0.04), LVMM (g) (202 vs 110; P=0.004) are significantly higher in therapy group.
Conclusion: In HCM patients for ICD, max NSVT beats on Holter ECG, LV Myocardial Mass and MV ratio by MRI suggested useful predictor for ICD therapy, which should be considered for indication to primary ICD implantation.

P1832 Complexity of scar assessed with late gadolinium enhancement cardiovascular magnetic resonance predicts appropriate implantable cardioverter defibrillator therapy delivery

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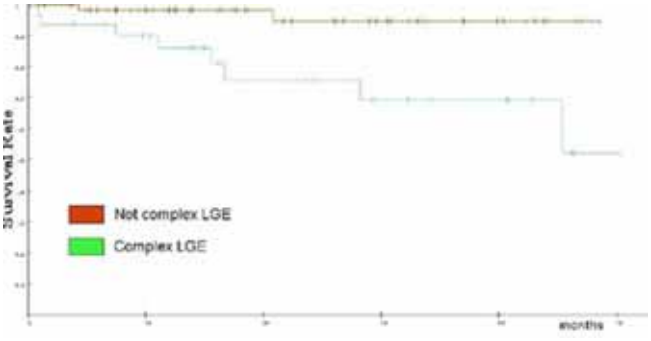
Purpose: To assess late gadolinium enhancement (LGE) cardiovascular magnetic resonance (CMR) imaging characteristics yielding a high risk of ventricular arrhythmias and implantable cardioverter defibrillator (ICD) therapy delivery.
Methods: 99 consecutive patients receiving an ICD and previously evaluated with CMR were enrolled. Left ventricular (LV) and right ventricular (RV) volumes and ejection fraction (EF) were evaluated. LGE was defined "complex" if: 1)ischemic involving $\geq$ 2 different coronary territories; 2) epicardial; 3) "diffuse" subendocardial; 4) $\geq$ 2 different patterns. The primary end-point was the occurrence of a ventricular arrhythmia requiring an ICD therapy. A composite secondary endpoint of cardiovascular death, cardiac transplantation or ventricular assist device implantation was also considered.
Results: During a median follow-up of 15,6 months, 10 and 14 patients reached the primary and secondary end-point, respectively. Complex LGE was highly predictive of primary end-point occurrence (log-rank=8.3, p=0.004), as well as implant in primary or secondary prevention (log-rank=4.5, p=0.033). LV and RV end-diastolic (ED) volume and EF were not statistically associated with arrhythmic events, whereas were predictive of secondary end-point fulfilment (LVEDV: 341±142 mL vs 262±77, p=0.002 - log-rank=4.8, p=0.0283; LVEF: 21±6% vs 28±9%, p=0.006 - log-rank=4.7, p=0.0301; RVEF: 38±20% vs 54±14%, p<0.001 - log-rank=6.3, p=0.012). LGE complexity was not associated with secondary end-point.



Conclusions: CMR has predictive power both for ventricular malignant arrhythmias and hard clinical end-points in dilated cardiomyopathies with current indications to ICD implant. LGE complexity is a strong predictor of ICD intervention both in ischemic and non ischemic etiology.

P1833 ICDs for primary versus secondary prevention in patients with inherited cardiac diseases: efficacy and complications

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Purpose: ICDs are increasingly used in patients with inherited cardiac diseases, whereas data on the yield is scarce and the complication rate presumably substantial. Therefore, we studied the ICD efficacy in primary versus secondary prevention in patients with arrhythmogenic right ventricle cardiomyopathy (ARVC), long QT syndrome (LQTS) and Brugada syndrome (BrS).
Methods: We retrospectively studied all shocks and complications in ICD patients with ARVC, LQTS and BrS in our tertiary referral center. We calculated the number needed to treat (NNT) and number needed to harm (NNH; inappropriate shocks + ICD-related complications).
Results: 19 ARVC, 37 LQTS and 40 BrS patients were followed for a median of 52 (range: 2-167) months after ICD implantation. Patients with ICD implantation for secondary prevention received more appropriate shocks (ARVC 10/15, LQTS 8/28, BrS 3/30; overall 6 shocks/100 patient-years) than patients with a primary prevention indication (ARVC 1/4, LQTS 1/9, BrS 0/10; 2 shocks/100 patient-years) (p=0.05; figure 1). Inappropriate shocks occurred in 14% of patients (11% ARVC, 14% LQTS, 15% BrS). The NNT per year was 8 for ARVC, 20 for LQTS and 62 for BrS. The NNH per year was 28 (ARVC), 14 (LQTS) and 14 (BrS).

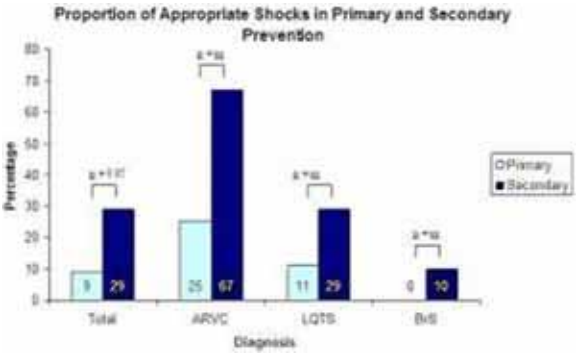

Figure 1

Conclusions: Appropriate shock rates in patients with ARVC, LQTS or BrS treated with an ICD for secondary prevention is considerable (6 shocks/100 patient-years), while it is significantly less in those treated for primary prevention (2 shocks/100 patient-years). However, ICD-related morbidity is substantial and NNH outweighs NNT in patients with LQTS and BrS.

P1834 Indication for implanting an ICD due to primary prevention - How strictly do MADIT criteria have to be met?

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Introduction: According to the criteria of the MADIT-II-study the guidelines recommend implanting an ICD for those patients who not only have a low left ventricular ejection fraction (LVEF<30%) but also have a myocardial infarction in their medical history. As the MI has happened to the MADIT-II patients at the average of 6,8 years ago one may presume that the myocardial infarction was not the reason for the reduced outcome of the MADIT collective but the left ventricular ejection fraction.
Methods: 518 patients suffering from coronary artery disease (CAD) and reduced left ventricular ejection fraction (LVEF<30%) were included in a prospective registry (Institut fuer Herzinfarktforschung, Ludwigshafen). 335/518 (65%) have met the complete MADIT criteria (CAD plus LVEF<30% plus history of MI) (group 1). The remaining 183 patients (35%) did not have a MI in their medical history. (CAD plus LVEF<30% without history of MI) (group 2).
Results: Group 1 and 2 do not differ significantly in age (68 years vs. 69 years), sex (87% vs. 89% male), LVEF (26% vs. 25%), diabetes mellitus (36% vs. 37%), CABG (33% vs. 26%, p=0.07) and NYHA class. There was no difference concerning ICD testing before discharge (16% vs. 24%, p=0.08) or PCI during the stay in hospital (11,9 vs. 12,0%).
Follow up: 165 patients who were included in the registry at least one year ago were followed up. 7,8% of group 1 and 8,2% of group 2 had died (p=ns). 16,1% of group 1 and 16,7% of group 2 were sucessfully shocked by defibrillator (p=ns). Readmission to hospital did not differ either (group 1: 11,7%, group 2: 12,9%, p=ns).
Conclusion: 1. There is a high risk for patients with CAD and LVEF<30% to experience a life threatening arrhythmia even though they did not have a MI in their medical history.
2. The guidelines for implanting an ICD in patients with CAD, strictly based on MADIT criteria, are to be reconsidered.

P1835 Long-term follow up of pacemaker and ICD patients in a national registry

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Background: He Swedish National Pacemaker Registry was started 1989 and now covers all pacemaker (PM) and implantable defibrillator (ICD) implants in Sweden. Up to now 90 000 patients have been entered by 49 implanting and follow up hospitals. The registry is internet based with online access for the users with full search and statistical options available for the users. A yearly report is published on the web.
Methods: Data from 87380 PM and 5929 ICD implants were used to calculate patient survival after first implant. Device longevity was analyzed in all device models implanted in >100 examples. Patient survival and complication rate was analyzed in both PM and ICD patient groups.
Results: Device longevity greatly differed among manufacturers as a whole, fig 1-4, but among models the differences were even more pronounced both as regards to PM and ICD's.
PM patients had generally poorer survival rate than ICD patients and were older at first implant (76/77 years Male/Female vs. 63/60 years M/F). Complication rate in PM implantation was 5,6% and in ICD implantation 6,1%.

Survival probability of ICD device by different manufacturers

Years	Total	Gudiant	Medtronic	St Jude
1	98,7%	98,2%	99,1%	98,7%
2	97,2%	96,4%	97,8%	96,9%
3	89,7%	89,1%	94,2%	81,5%
4	75,3%	61,1%	88,5%	66,2%
5	56,0%	42,0%	74,5%	32,1%
6	42,3%	25,8%	61,2%	18,0%
7	30,8%	5,5%	50,4%	13,1%
8	25,9%	4,7%	42,0%	13,1%
9	19,8%	3,8%	31,1%	13,1%
10	0,0%	0,0%	0,0%	0,0%

Conclusion: Pacemaker and ICD treatment are associated with a reasonable level of perioperative complications. ICD patients generally live longer than pacemker patients and device longevity is of greater importance in ICD than PM patients. Cost efficacy of ICD treatment depends greatly on initial purchase price of the device but also on longevity of the device. Records of longevity gathered by large registries can be used to guide purchase of devices to íncrease cost efficacy.

P1836 Single coil ICD leads are associated with a similar outcome to dual coil ICD leads during median term follow up

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Introduction: The vast majority of ICDs implanted today are attached to dual coil leads. Single coil ICD leads are less commonly used although they may have some advantages; particularly if lead extraction is required in the future. Numerous studies have shown no difference in acute defibrillation thresholds with adequate safety margins, however long term data on outcomes is scarce.
Methods: The outcomes of patients undergoing initial ICD implantation at a single institution since January 2007 were reviewed.
Results: 543 consecutive patients undergoing initial ICD implantation were included. The median age was 62.4 years. The indication for implant was primary prevention in 66% (n=404) and secondary prevention in 34% (n=139). The underlying heart disease included ischaemic heart disease (50%), dilated cardiomyopathy (31%) and other (19%). The median ejection fraction was 30%. Single coil leads were implanted in 49% (268) of patients and dual coil leads in the remaining 51% (275) of patients. High output cans from all manufacturers were used in 100% of patients. The indications for implant, age, ejection fraction, type of ICD, QRS duration, renal function and NYHA class were not significantly different in each group. A greater than 10% safety margin was obtained in >99% of patients with no difference between the groups. One patient crossed over from the single to the dual coil group because of an unacceptable defibrillation threshold at the time of implant. During follow up device complications (not all related to lead problems) requiring lead replacement occurred in 18 patients (12 patients in the dual coil group and 6 patients in the single coil group). During a median follow up period of 24 months, 6 (2.2%) patients with single coil ICD leads and 16 (5.8%) patients with dual coil ICD leads died (p=<0.05).
Conclusions: Implantation of single coil ICD leads is associated with non inferior outcomes as compared to the more commonly implanted dual coil ICD leads at 24 months of follow up. Due to perceived increased problems in extracting long term dual coil ICD leads, it would seem reasonable to implant single coil ICD leads in the majority of patients initially.

P1837 Type of fixation and risk of fracture of Medtronic sprint fidelis ICD lead

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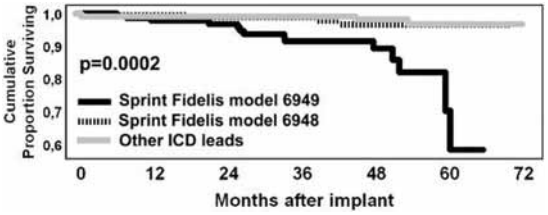
Background: Medtronic Sprint Fidelis (SF) is a small ICD lead presenting an increased incidence of early failure. The impact of the type of fixation of this lead on its risk of fracture is unknown. The aims of this study were: 1) to determine the incidence of the fracture of SF lead after a 60-month follow-up; 2) to evaluate the risk of fracture of the SF model with active fixation and SF model with passive fixation compared to other contemporary ICD leads.
Methods: We retrospectively analysed data from consecutive ICD recipients implanted at our institution. Follow-up was performed with quarterly device interrogation.
Results: Between December 2004 and October 2007, 447 patients (82% male, 65±13 years) underwent ICD leads implantation at our institution: 239 SF leads (46% of which was 6949 model with active fixation and 54% was 6948 model with passive fixation) and 208 leads from other manufacturers. During a median follow-up of 45 months (range 0.3-72 months; interquartile range 38-52 months) a lead failure was detected in 18 (4%) patients: 17 (7%) in SF group and 3 (1%) in the group with other leads. The estimated 60-month incidence of fracture of SF was 15±5%. The survival (Kaplan-Meier) of the 6948 model SF was higher than 6949 model, and it was similar to that of the other leads (Figure).



Conclusions: SF lead shows an important rate of fracture. The model with passive fixation has a lower risk of fracture, similar to that of the leads from other manufacturers implanted in the same period.

P1838 Riata lead failure; A report from Northern Ireland Riata lead screening programme

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The st: Jude Medical Riata family of leads (1560,-61,-62,-70,-71,-72,-80,-81,-82,-90,-91,-92,7000,-01,-02,-10,-11,-12,-40,-41,-42,-50,-51,-52,-20,-21,-22,-70,-71,-30,-31) are high voltage implantable cardioverter defibrillator (ICD) leads. Insulation related inappropriate shocks were noted in a patient in Northern Ireland in November 2006. Lead insulation breach was from internal lumen to external surface. The frequency of lead malfunction in Northern Ireland appeared to exceed the manufacturer quoted values. Active surveillance of all patients with a Riata lead in Northern Ireland was commenced in August 2010. On 16/12/2010 the U.K MHRA issued a medical device alert for Riata and Riata-ST leads. The objectives of the Northern Ireland Riata lead screening programme were to identify insulation defects, risk factors, define prevalence, determine management plan for lead defects, and develop a follow up programme and additional lead screening projects.
Methods: All patients with Riata/Riata-ST and Riata Optim leads in Northern Ireland were invited for screening with high resolution fluoroscopic images at 15fps and ICD lead parameters were checked. Fluoroscopic images were read by two cardiologist blinded to the patient data and insulation breach was identified as negative, positive or borderline.
Results: Two hundred and twelve patients had a Riata lead implanted in Northern Ireland. Of these, 164 were males and 48 females. Mean age at the time of implantation was 62.7±13.40 years. Lead model 1580 was implanted in 16 patients, 1582 in 69, 1570 in 8, 1572 in 5, 7000 in 60, 7002 in 41, 1571 in 2, 1742 in 2, 7040 in 6 and 7022 in 3 patients. One hundred and sixty five out of 212 patients were screened as 28 were dead, 5 had the lead explanted prior screening, 3 patients were excluded and 11 did not attend the screening programme. Mean screening period after implantation was 3.98±1.43 years. After screening 25 (15%) patients were classified as positive, 3 (1.8%) borderline and 137 (83%) negative for insulation breach. Five (3%) out of the 25 patients presented with spontaneous lead issues and 20 (12%) were identified by fluoroscopy. Seven (25%) patients had the defective lead removed. The rest of the patients are closely monitored with surveillance (fluoroscopy and ICD parameter check) every 3 months.
Conclusion: A significant proportion (15%) of patients with Riata and Riata-ST leads had an insulation breach on screening. Clinically significant events was noted in 20% of patients. Further surveillance plans for negative and borderline category need to be developed and agreed internationally.

P1839 Relationship between the notch duration of paced QRS and antitachycardia pacing effectiveness among ICD patients without cardiac resynchronization therapy

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Background: Monomorphic ventricular tachycardias (VT) are the most frequent arrhythmias causing appropriate therapies among ICD patients with left ventricular dysfunction (LVD). Although antitachycardia pacing (ATP) is very effective in terminating VT, 10-30% need shocks (SH), which are associated with an increase in mortality. We speculated that the morphology of paced QRS complex from the right ventricular apex (pQRS) could be a marker of ATP efficiency because the presence of notches reflects delays in the activation of the left ventricle and may therefore be related to the times of conduction of stimulus from the pacing site to the origin of VT. Our aim in the present work was to prospectively determine the relationship between the duration of a notch $>$0.1 mV in the precordial leads of pQRS (DN-pQRS) and the effectiveness of ATP.
Methods: We followed 290 patients with LVD (LVEF: 31$\pm$9, previous myocardial infarction: 66%; pacing site: right ventricular apex; no cardiac-resynchronization therapy) along 28$\pm$20 months. ICD programming was standardized. The pQRS (pacing heart rate: 100 bpm) was obtained at ICD implantation (ECG: 50 mm/s).
Results: We analyzed 947 VT (CL: 333$\pm$45 ms) occurring consecutively in 104 patients. ATP terminated 84% of VT and 14% needed shocks. The adjusted mean ATP effectiveness per patient was 77% (95% CI: 70-84), Generalized Estimated Equation Method (GEEM). DN-pQRS was significantly correlated with the probability of successful ATP (C-coefficient: 0.62; $p<0.001$), the best cut-off point being 50 (sensitivity and specificity of 60% and 70%). Patients with a DN-pQRS$\geq$50 ms (DN50) had a lower ATP efficiency, mean [95% CI]: 65% [53-75] vs. 91% [86-97]- and a higher proportion of VT terminated with SH: 34% [23-45] vs. 9% [2-16]; $p<0.001$ for both, GEEM. By logistic regression - which included LVEF, basal QRS$\geq$120 ms, indication, etiology, functional class, medical therapy and DN50- the latter (DN50) was found to be an independent predictor of the patient presenting with a VT- related SH (OR=3; p=0.02). Among the patients presenting with VT, the mean survival time free of appropriate therapy due to VT was similar in patients with DN50 versus without DN50 (mean (95% CI)): 381 days (200, 400) vs. 404 (82, 313); p=0.8 (log rank test). However, the mean survival time free of VT-related shock was lower in those with a DN50: 795 days (377, 1022) vs. 1559 (324, 3775); p=0.02 (log rank test).
Conclusion: When ATP is applied to the right ventricular apex, the DN-pQRS is a negative and independent predictor of effective ATP. ICD patients with DN50 require shocks more frequently to terminate VT.

P1840 Efficacy and safety of programming a high number of antitachycardia pacing sequences for fast ventricular tachycardia in implantable cardioverter-defibrillators recipients: a single center pilot study

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Purpose: Antitachycardia pacing (ATP) is a painless therapy reducing defibrillation shocks in implantable cardioverter-defibrillator (ICD) recipients. One or 2 ATP sequences are usually programmed to terminate fast ventricular tachycardia (FVT) episodes and avoid shocks without delaying successful therapy in case of ATP failure. Little is known about the optimal number of ATP attempts to program in the FVT zone. We sought to analyze the long-term efficacy and safety of programming a high number of ATP sequences for FVT.
Methods: All patients receiving a first ICD for coronary artery disease (CAD) and dilated cardiomyopathy in primary and secondary prevention indications between 2000 and 2009 were prospectively included in the study. Single chamber, dual chamber and cardiac resynchronization therapy-defibrillator devices capable of delivering ATP for FVT were implanted. Devices were programmed to deliver 10 ATP attempts for FVT cycle lengths (CL) of 250 to 300 ms (200 to 240 bpm) before high energy shock delivery (5 bursts, then 5 ramps; 10 extrastimuli at 81 to 88% of the FVT CL; minimal pacing CL 180 ms).
Results: 770 patients (men 84%; CAD 75.5%; age 63.2$\pm$11 years; secondary indication 54.3%; left ventricular ejection fraction 30.3$\pm$9%) were prospectively included and followed for 40.6$\pm$25.6 months. Among them, 137 patients (17.8%) had a total of 1839 episodes of FVT (mean frequency 209$\pm$9.2 bpm). ATP terminated 1713 episodes of FVT (unadjusted efficacy, 93.1%; GEE adjusted efficacy, 81.7%) and acceleration occurred in 5.8% of episodes. A large majority of episodes were successfully treated (98.3%) by 1 or 2 ATP sequences. Conversely, the patient-based analysis showed that 17 (12.4%), 8 (5.8%) and 5 patients (2.1%) had one episode or more treated by at least 3, 4 or 5 ATP attempts, respectively. These patients would have been shocked with a conventional ICD programming. The benefit of this strategy was reduced for 6 to 10 attempts and only 10 patients were shocks for ATP failure (20 episodes, 1.1%). Despite the high number of attempts programmed, FVT episodes were mainly asymptomatic and found during device interrogation: syncope and pre-syncope occurred in 0.2% and 0.4% of episodes, respectively.
Conclusions: Programming a high number of ATP attempts (at least 4 or 5 ATP sequences) in the FVT zone is both safe and useful. It could prevent painful shocks for FVT in a high proportion of ICD recipients.

P1841 Defibrillator implantation without fluoroscopy

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Purpose: Fluoroscopy is associated with negative effects on patients, fetus, and personnel involved in invasive procedures. Furthermore, these procedures need to be performed with expensive systems and x-ray protection measures. The aim of the present study was to assess the feasibility defibrillator (ICD) implantation without fluoroscopy.
Methods: 11 consecutive patients (9 male, 70$\pm$5 years) referred for ICD implantation (single chamber 9, double chamber 2) were enrolled. A steerable tetrapolar catheter was introduced from the left subclavian vein into the right side of the heart under the guidance of a 3D electroanatomical system (Ensite NavX). This catheter was used for geometrical reconstruction of the right chambers of the heart and then replaced by one or two ICD leads. All electrodes and coils of the leads were connected to the electroanatomical system and guided to their required position. Fluoroscopy was used at the end of the procedure to assess the proper location of the leads and coils.
Results: All devices and leads were implanted without the need of fluoroscopy. Procedure duration was 67$\pm$30 min (range 36-141). Ventricular and atrial leads were implanted in a median of 10$\pm$6,8 min (range 4-29) and 15$\pm$17 min (range 3-27) respectively. Median electrical data at implantation were: successful defibrillation energy 18$\pm$5 J (range 12-16 J), ventricular electrogram amplitude 13$\pm$4,3 mV (range 7-23 mV) and ventricular stimulation threshold $<$1 mV/0.4 ms in all patients. Two patients required relocation of the ventricular and atrial leads respectively from their original position due to inadequate pacing parameters and this was done without fluoroscopy in both of them. One patient needed fluoroscopy to relocate the ventricular lead due to persistent high defibrillation threshold. The proximal coil position needed to be relocated well inside the superior vena cava in 2 patients following X-ray evaluation. Fluoroscopy times in these latter patients were virtually zero. There were no complications.
Conclusions: ICD implantation can be done with the only guidance of an electroanatomical system. However, the proper position of the proximal coil needs to be assessed by fluoroscopy and it is uncertain if this could be avoided with more experience.

P1842 Percutaneous intravascular defibrillator (PICD): Venous anchoring- vessel histology and patency

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Background: A percutaneously placed, implantable intravascular defibrillator has been developed (PICD) with a right ventricular (RV) single coil lead and titanium electrodes in the superior vena cava (SVC) and the inferior vena cava (IVC). The device is secured in the venous vasculature with a self-expanding Nitinol anchor. Little is known regarding the use of such stents in the venous system.
Objective: This study evaluated the anchor/tissue histology and PICD stability in a chronic canine model at 90 days.
Methods: Six Bluetick hounds (wt=30-40kg) were anesthetized and under sterile conditions a custom sheath was introduced into the right femoral vein. The PICD was advanced via the right femoral vein over a wire into the vasculature. Utilizing a delivery catheter the device was positioned such that the titanium electrodes (cathodes) were located in the superior vena cava and the inferior vena cava. A self-expanding Nitinol anchor was advanced from the femoral vein to the jugular via a second wire and deployed in the left jugular to secure the PICD within the vasculature. The protocol required 15-45% over-sizing of the anchor with regard to the target vessel. The catheters, wires, and sheath were removed with an average implant time of under 15 minutes. Animals were examined by a veterinary doctor on a weekly basis to assess their general condition. Venograms were performed at 45 and 90 days to assess luminal patency. All animals were sacrificed at 90 days and histologic evaluation was done of the anchor, surrounding vessel, and adjacent tissues.
Results: All canines recovered from the surgical procedure without serious adverse event. All devices remained in the implanted position without evidence of anchor movement or migration. Venograms revealed wide patency of the jugular veins and IVCs in all animals. General condition of the animals was deemed excellent at 90 days with all routine blood laboratory values within normal range. Histology showed appropriate vessel healing without evidence of hemorrhage, inflammation, or vein perforation in the anchor location. Greater than 98% of all anchor wires were endothelialized and were covered with a mature neointima composed of collagenous fibrovascular tissue generally between 0.1 and 1 mm

thick. There was no collateral injury to adjacent organs or tissues in region of anchor placement.
Conclusions: The PICD can be rapidly implanted and safely anchored in the venous vasculature.

P1843 ICD box-change is required even in patients with no prior appropriate therapies

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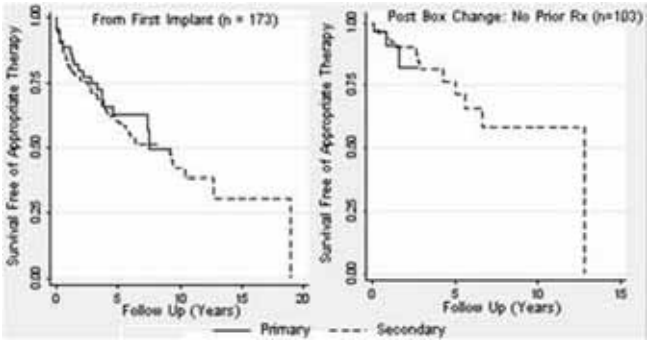
Purpose: Implantable cardioverter defibrillators (ICDs) are an expensive but life saving therapy. The majority of patients receiving ICDs survive to box-change without receiving an appropriate ICD therapy (Rx). This abstract addresses the question: Does a patient who has had no Rx need to have a box-change?
Method: A retrospective audit of our University Hospital's ICD service included analysis of Rx in 174 patients who survived to box-change (first implant date 01/12/1991 to 13/6/2007, median 22/11/02). Mean time to box-change was 5.4 years (SD 1.7 years). ICD was implanted for secondary prevention in 129 and primary prevention in 44 (1 unknown). Mean age at implant was 59.9 years (SD 14.4 years).
Results: Patients who survived to box-change free of Rx had a significant rate of Rx post box-change (Figure). Moreover, in this group the rate of Rx is similar for primary vs. secondary prevention. At 5 years from first implant, 43.2% (95%CI 36.1 to 51.0%) of patients had received appropriate ICD therapy. At 5 years from box-change the rate of Rx in Rx naive patients was 28.0% (CI 15.9% to 46.4%). Analysis of Rx in patients free of Rx at 5 years post implant produced the same result.



Conclusion: The 5 year rate of Rx in patients after ICD box change who have had no Rx before is almost 30%. This data supports box-change, unless continued ICD therapy is inappropriate due to co-morbidities, in both primary and secondary prevention patients.

P1844 Cost-effectiveness of prophylactic cardioverter defibrillator implantation in a large single center cohort

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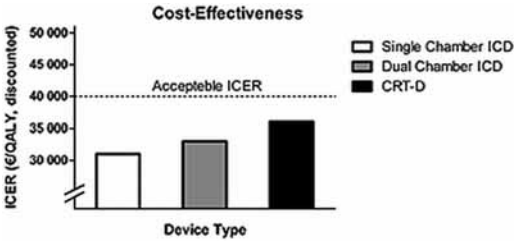
Purpose: Large randomized trials have shown the beneficial effect on survival of an implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRT-D) as primary prevention therapy in selected patients. However, data concerning the cost-effectiveness in routine clinical practice are scarce.
Methods: All patients receiving a prophylactic defibrillator implantation were included in the study. Analyses were stratified for single chamber defibrillator, dual chamber defibrillator, and CRT-D devices. Based on the Markov model, lifetime cost, life years (LY), and gained quality-adjusted life years (QALY) were estimated for device recipients vs. patients receiving conventional treatment. Data on mortality and complication rates, device longevity, and costs were retrieved from our center – without using data from advisory boards or manufacturers – and entered into the Markov model. A cost-effectiveness ratio below € 40,000 per gained QALY was assumed to be acceptable.
Results: A total of 1257 patients were included in the analysis. Single chamber devices increased lifetime cost with € 57,000 and added an estimated average of 2.2 LYs and 1.8 QALYs resulting in an incremental cost-effectiveness rate (ICER) of € 31,000. For dual chamber devices, an increase in lifetime cost of € 58,000 was calculated. Average additional LYs and QALYs were estimated to be 2.1 and 1.7, respectively. This resulted in an ICER of € 33,000. CRT-D patients were estimated to have additional lifetime cost of € 54,000 and added on average 1.8 LYs and 1.5 QALYs. Finally, this resulted in an ICER of € 36,000.



Cost-Effectiveness ICD & CRT-D

Conclusions: Based on the Markov model, prophylactic defibrillator implantation demonstrates to be cost-effective in routine clinical practice.

P1845 Are problems occurring in ICD patients missed during remote management? Conventional follow up compared to automatic remote monitoring in the TRUST trial

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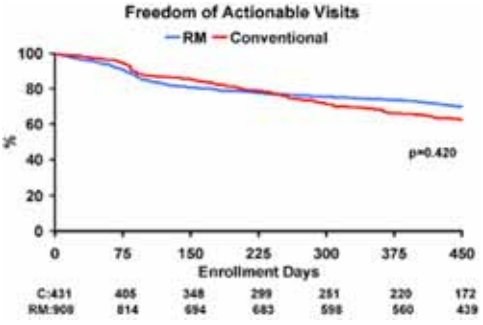
Remote Monitoring (RM) is important in patients with implantable electronic cardiac devices, supplanting most scheduled in-person evaluations (IPE). However, concern exists that lack of frequent IPE may result in missed events that are of clinical significance. TRUST, a multicenter prospective trial, tested this.
Methods: 1,339 patients with ICDs capable of RM were randomized post-ICD implant 2:1 to RM (Biotronik Home Monitoring) or to conventional (C) groups and followed for 15 months. 3 month IPE were scheduled for both groups. Thereafter, RM patients were followed remotely only, for 1 year. In C, IPE were scheduled every 3 months. All scheduled and unscheduled IPE were assessed for "actionability" (ie change(s) in programming/ antiarrhythmic drugs /system components) to measure problem incidence.
Results: Patients were similar (RM vs C = 63±13 vs 64±12 yrs, 72 vs 73% male, NYHA II class 56 vs 60%, LVEF 29±11 vs 29±10%, CAD 65 vs 72%, primary prevention 72 vs 74%, DDD implants 58 vs 57%). 87.2% of patients were enrolled in private hospitals and 12.8% in academic centers. Freedom from actionable events were compared in both groups (figure) and did not differ (p=0.42).



Conclusion: Remote management, compared to traditional frequent in-person evaluations, did not diminish ability for problem discovery in ICD patients. Remote monitoring may be used confidently to manage this high risk population safely.