The heart and other organs

Heart failure and chronic obstructive pulmonary disease: the challenges facing physicians and health services

Nathaniel M. Hawkins[1]*, Sean Virani[2], and Claudio Ceconi[3]

[1]Institute of Cardiovascular Medicine and Science, Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool L14 3PE, UK; [2]Division of Cardiology, University of British Columbia, Vancouver, Canada; and [3]Department of Cardiology and LTTA Centre, University Hospital of Ferrara, Italy

Pulmonary disease is common in patients with heart failure, through shared risk factors and pathophysiological mechanisms. Adverse pulmonary vascular remodelling and chronic systemic inflammation characterize both diseases. Concurrent chronic obstructive pulmonary disease presents diagnostic and therapeutic challenges, and is associated with increased morbidity and mortality. The cornerstones of therapy are beta-blockers and beta-agonists, whose pharmacological properties are diametrically opposed. Each disease is implicated in exacerbations of the other condition, greatly increasing hospitalizations and associated health care costs. Such multimorbidity is a key challenge for health-care systems oriented towards the treatment of individual diseases. Early identification and treatment of cardiopulmonary disease may alleviate this burden. However, diagnostic and therapeutic strategies require further validation in patients with both conditions.

Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are leading causes of death worldwide.[1] Through shared risk factors and pathogenic mechanisms the conditions frequently coexist, presenting diagnostic and therapeutic challenges for physicians.[2,3] Each is an independent predictor of morbidity, mortality, impaired functional status, and health service use. Each is also powerfully associated with socioeconomic deprivation.[4,5] The conditions therefore undermine the two fundamental goals of healthcare: to improve both the overall level and distribution of health. Healthcare internationally is dominated by individual disease approaches, lacking coordination and integration.[6] Multimorbidity is a key challenge for these health systems.[7] We review these challenges and provide direction for future research.

Definitions

The diagnoses of both HF and COPD require typical symptoms combined with objective evidence of organ dysfunction.[8,9] The European Society of Cardiology mandates typical symptoms and signs resulting from any abnormality of cardiac structure or function, including systolic and diastolic dysfunction, valvular, pericardial, and heart rhythm abnormalities.[8] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines airflow obstruction by FEV_1/FVC ratio < 0.70,[9] a consensus definition endorsed by the European Respiratory Society and American Thoracic Society (*Table 1*).[10] This simple definition avoids complex reference equations, is understandable, universal, generalizable, comparable, and lowers barriers to diagnosis.[11] However, the fixed ratio overestimates disease in the elderly relative to lower limit of normal indices,[12] as FEV_1/FVC declines in healthy never smokers with advancing age.[13]

From shared risk factors to pathophysiological mechanisms

Cardiologists readily accept the 'cardiovascular disease continuum', the hypothesis that frames cardiovascular diseases as a chain of events initiated by risk factors and progressing through numerous physiological pathways to the development of end-stage heart disease and HF.[14] Hopefully in coming years, the concept of a

---

* Corresponding author. Tel: +44 151 228 1616, Fax: +44 151 600 1696, Email: nathawkins@hotmail.com

Table I GOLD classification of airflow limitation severity based on post-bronchodilator FEV$_1$

Stage	FEV$_1$/FVC	FEV$_1$ predicted, %
I: Mild	<0.70	FEV$_1 \geq 80$
II: Moderate	<0.70	$50 \leq$ FEV$_1 < 80$
III: Severe	<0.70	$30 \leq$ FEV$_1 < 50$
IV: Very severe	<0.70	FEV$_1 < 30$

FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity.

'cardiopulmonary continuum', as a common ground of heart and lung disease,[15] will be the basis for future achievements. Interest has grown in the association of chronic pulmonary and cardiac diseases; the observation that HF and COPD coexist more frequently than expected from their respective population prevalences being a major reason for this interest. These epidemiological observations encourage new pathophysiological interpretations to understand the connection between the pulmonary and cardiovascular continuum.

Apart from smoking as a common risk factor, patients with COPD share an additional determinant of cardiovascular disease: low-grade systemic inflammation.[16,17] The risk of underlying ischaemic heart disease is greatest in patients with airflow obstruction and elevated C-reactive protein.[18] Furthermore, almost 50% of patients with COPD present coexisting metabolic syndrome as well as increased levels of systemic inflammatory markers, independent of lung function impairment.[19] Diabetes is likewise independently associated with reduced lung function, while obesity may further worsen ventilatory mechanics.[20] Diabetes, metabolic syndrome (and its individual components), and physical inactivity are all major determinants of cardiovascular disease. The fact that each also acts through pro-inflammatory mechanisms strengthens the view that low-grade systemic inflammation is a common pathophysiological link between COPD and cardiovascular diseases.[21]

This concept is substantiated by the observation that direct pro-inflammatory agents, namely cigarette smoking, air pollution, and occupational exposures, induce systemic cellular and humoral inflammation, oxidative stress, striking changes of vasomotor and endothelial function, and enhanced circulating concentrations of several procoagulant factors.[22–25] Thus, 'cardiovascular' and 'pulmonary' risk factors create a 'cardiopulmonary continuum' through shared systemic inflammatory processes, inducing cascades of events which underpin chronic diseases including COPD, coronary disease, and HF.[15,26,27] This pathophysiological relationship revolves around common inflammatory pathways (*Figure 1*). TNF-α plays a central role in chronic inflammatory processes of the pulmonary and cardiovascular system and is involved in the activation of secondary mediators including C-reactive protein and pro-inflammatory cytokines. These in turn mediate the phenotype of syndromes characterized by chronic comorbidities and peripheral abnormalities.[26,28,29]

A challenge for the future will be to understand the role of genetic factors, their genotype–phenotype correlations, and clinical implications. The recent availability of techniques such as genome-wide association studies has increased identification of susceptibility genes for both COPD and cardiovascular disease phenotypes including hypertension, dyslipidaemia, and coronary artery disease.[30,31] A functional link between susceptibility genes has been elucidated only for certain risk factors, such as the low-density lipoprotein receptor defects and other hyperlipidaemia disorders.[31,32] While the association among the most annotated genes and risk factors is defined, heritability and phenotype are less clear: for COPD, several genes are associated with disease susceptibility (e.g. CHRA3–5 or FAM13A9),[30,33,34] but the population attributable risk is limited (approximately below 15%) and no functional link clearly established. Notably, no potential common candidate gene for both COPD and cardiovascular disease phenotypes has yet been identified. The interplay between the two common multigenic diseases remains elusive. Thus far, our understanding of the interaction between cardiovascular and pulmonary disease derives from registries and subgroup analyses. No prospective study has addressed the specific role of pulmonary comorbidity in the treatment and outcomes of cardiovascular disease patients. Nevertheless, in large, retrospective analyses statins and/or angiotensin-converting enzyme inhibitors improve both cardiac and pulmonary outcomes in patients with COPD, with the largest benefits obtained by combining therapies.[35] Cardiovascular medicine has an armamentarium of survival enhancing therapies. These need to be systematically tested in large randomized controlled trials in patients with COPD, with and without overt cardiovascular disease.

Prevalence and prognosis of heart failure and chronic obstructive pulmonary disease

The prevalence of GOLD stage II or higher COPD is ∼5–10% of adults.[36–39] One-year mortality in the community is relatively low (around 3%),[40] but higher following hospitalization (25%).[41,42] Future projections have wide uncertainty intervals, depending on statistical methodology, estimates of prevalence, and associated mortality.[43] Nevertheless, the Global Burden of Disease study anticipates COPD to become the third leading cause of death globally by 2020.[44]

Heart failure is less common, affecting 1–3% of the general population, but carries a worse prognosis.[45] Annual mortality in stable community patients approximates 5–7%,[45–48] while median survival following hospitalization remains just 2 years.[49] Approximately half of patients have HF with preserved ejection fraction and half left-ventricular systolic dysfunction (LVSD).[50] The prevalence of the latter is thus around 1% of the general population.

Prevalence of concurrent heart failure and chronic obstructive pulmonary disease

Prevalence estimates vary widely according to cohort selection, population age structure, risk factor exposure, diagnostic criteria, measurement methods, and surveillance systems.[2,51] From around 10–40% of patients with HF have reported concurrent COPD.[2] However, only a handful of studies employed spirometry.[52–55] In
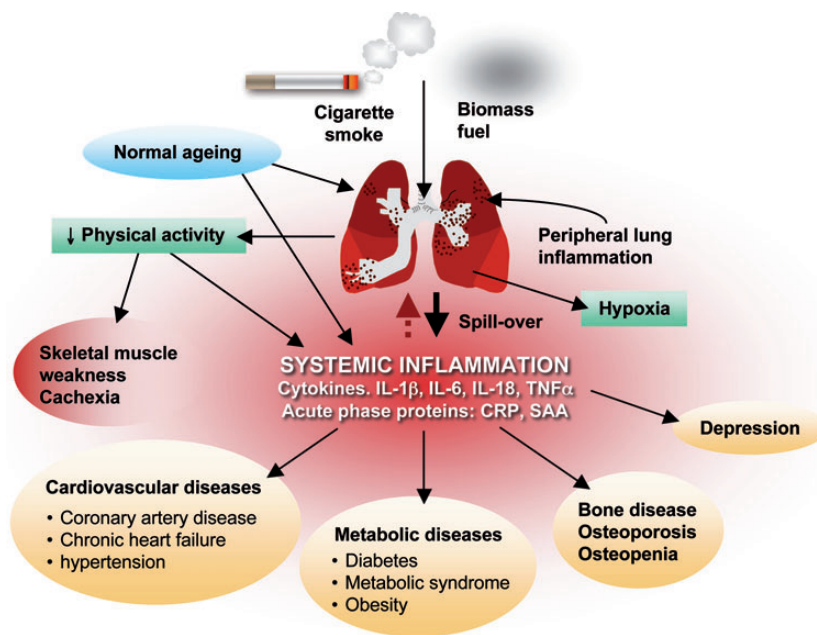
Figure 1 Inflammatory pathways involved in the cardiopulmonary continuum. Patients with chronic obstructive pulmonary disease have peripheral lung inflammation. These patients have also increased circulating cytokines, including interleukin (IL)- 1b, IL-6, IL-18, and TNFa, as well as acute-phase proteins, such as C-reactive protein and serum amyloid A (SAA). This low grade chronic inflammation may represent the link with the increased propensity to cardiovascular, metabolic, bone, neurological diseases as well as the peripheral muscle abnormalities typical of the syndrome (From Boschetto et al., 2012).[27]

the largest of these, COPD was diagnosed in 36% of 532 consecutive patients hospitalized with HF, acknowledging that pulmonary oedema may have contributed to airflow obstruction.[53] A similar proportion (30%) was observed in a recent prospective study of consecutive patients with stable HF.[55]

Estimates of HF prevalence in COPD are likewise sparse though consistent. The prevalence of unrecognized HF was 20.9% in patients with COPD or asthma presenting to the emergency department,[56] 20.5 and 17% in community patients with stable COPD.[57,58] The latter two studies included echocardiography in all patients, detecting LVSD in 10.4 and 13.8%. These findings have significant ramifications. Given COPD is far more prevalent than LVSD in the general population, then COPD is potentially masking a large proportion of patients with LVSD.

Prognosis of concurrent heart failure and chronic obstructive pulmonary disease

Concurrent COPD independently predicts mortality in patients with reduced and preserved ejection fraction (*Table 2*),[2,59] even following adjustment for beta-blocker utilization.[59–65] Furthermore, greater airflow obstruction is associated with worsening survival.[52,62,66] In those studies with sufficient sample size to examine the cause of death, excess non-cardiovascular death predominated.[64,65]

However, a clinical diagnosis of COPD was also associated with sudden death in the Valsartan in Acute Myocardial Infarction Trial.[64]

A single study has examined the prognostic implications of concurrent HF in patients with COPD.[67] Following extensive investigations including echocardiography and pulmonary function tests, 83 of 405 elderly community patients with COPD were diagnosed with HF (20.5%). Patients with HF had double the mortality of those without HF over a mean follow-up of 4.2 years (adjusted HR 2.1 [1.2−3.6]).

Diagnostic challenges

Patients with HF or COPD exhibit a high symptom burden including dyspnoea, orthopnoea, cough, exercise intolerance, fatigue, muscle weakness, disturbed sleep, anorexia, low mood, and anxiety.[68,69] Unfortunately, neither symptoms nor signs are unique to either condition. Chest radiograph may be equally misleading, as pulmonary vascular remodelling in those with COPD either mimics (upper lobe venous diversion)[70] or masks pulmonary oedema (asymmetric, regional, and reticular patterns).[71,72]

Pulmonary function tests

Restrictive ventilation is the hallmark of chronic stable HF,[73,74] reflecting cardiomegaly,[75] respiratory muscle weakness,[76,77] and interstitial fibrosis.[78] Backward transmission of increased left-atrial

Table 2 Studies specifically examining the prognostic implications of chronic obstructive pulmonary disease

References	n	Study design	Prevalence COPD (%)	Spirometry	Mean LVEF (%)	Outcome	Mean follow-up	Adjusted risk (± 95% CI)
Macchia et al.[149]	1020	Retrospective	24	No	—	Mortality	287 days	1.42 (1.09–1.86)
Staszewsky et al.[65]	5010	Prospective	13	No	27	Non-CV mortality	23 months	2.50 (1.58–3.96)
Mascarenhas et al.[52]	186	Retrospective	39	Yes	—	Death/hospitalization	433 days	2.10 (1.05–4.22)
Rusinaru et al.[59]	799	Prospective	20	No	50	Mortality	5 years	1.53 (1.21–1.94)
Hawkins et al.[64]	14 703	Prospective	9	No	35	Mortality	24.7 months	1.14 (1.02–1.28)
Lainscak et al.[150]	638	Retrospective	17	Yes	43	Mortality	1062 days	1.38 (1.04–1.83)
Kwon et al.[66]	184	Retrospective	37	Yes	49	Mortality GOLD III	731 days	3.20 (1.33–7.68)
De Blois et al.[63]	4132	Prospective	17	No	32	Mortality	13.3 months	1.19 (1.02–1.39)
Mentz et al.[151]	20 118	Prospective	25	No	25	Mortality	60 days	0.97 (0.68–1.38)
Mentz et al.[61]	4133	Prospective	10	No	27	Mortality	9.9 months	1.17 (0.96–1.42)
Boschetto et al.[55]	118	Prospective	30	Yes	40	Mortality	1029 days	Non-significant
Arnaudis et al.[62]	348	Prospective	38	Yes	31	Mortality GOLD II	54.9 months	2.27 (1.22–4.25)

pressure disrupts vascular structural integrity and functional properties.[79] Chronic pulmonary capillary stress failure induces local activation of growth stimuli, thickening of the alveolar−capillary and microvascular remodelling. The resulting reduction in alveolar−capillary membrane conductance and lung diffusion capacity impairs gas transfer.[80] Simultaneously, pulmonary hypertension, right-ventricular dysfunction and failure gradually develop. This lung re-modelling is compounded by COPD (*Figure 2*). Compared against 69 matched subjects with HF alone, 69 patients with concurrent COPD exhibited impaired cardiopulmonary exercise response. All variables were poorer, including peak oxygen consumption (12.1 vs. 16.3 mL kg^{-1} min^{-1}), minute ventilation/carbon dioxide production slope (42.7 vs. 33.3), pulmonary artery systolic pressures (51.9 vs. 37.0 mmHg), and 6 min walking distance (295 vs. 367 m) (all $P < 0.001$).[81] A significantly shorter 6 min walking distance was also recently observed in 48 of 174 elderly patients with HF and concurrent COPD (276 vs. 291 m, $P < 0.05$).[54,81]

Airflow obstruction, as opposed to (or superimposed on) restriction, is typical in decompensated acute pulmonary oedema. Interstitial and submucosal oedema compress and obstruct airways, respectively, compounded by bronchial hyperresponsiveness.[82,83] Both misdiagnosis and overestimation of COPD severity may ensue. FEV$_1$ improves by 11−34% with diuresis and often normalizes (*Figure 3*).[83−87] This is particularly relevant for the elderly HF population, in whom the aforementioned fixed FEV$_1$/FVC diagnostic criterion already over diagnoses pulmonary disease.[12,13]

Natriuretic peptides

Natriuretic peptides are raised in pulmonary hypertension,[88] right-ventricular failure or acute stress,[89] and pulmonary disease.[89,90] Typical levels overlap with compensated HF (*Figure 4*). This increases false positive results, thus reducing the specificity and positive predictive value for LVSD. Only one study has examined the ability to detect HF in stable patients with COPD.[90] In 200 elderly patients, four natriuretic peptide assays were comparable and excluded HF with reasonable accuracy (all negative predictive values above 0.85). However, specificity and positive predictive value were much lower, around 0.6 and 0.4, respectively.[90] The logical solution is to apply natriuretic peptides and a more specific test in sequence. To date, this strategy has not prospectively been tested.

Imaging

Echocardiographic acoustic windows may be impeded by air trapping in pulmonary disease. The estimated prevalence of unsatisfactory image quality varies, from 10% in stable primary care patients with COPD[91] to 35% in severe disease and 50% in very severe airflow obstruction.[92,93] The generalizability of these findings is unclear, as most studies utilizing echocardiography in patients with COPD fail to report feasibility. Moreover, the incremental improvement with contrast echocardiography is unknown. Studies are needed comparing echocardiographic modalities with cardiac magnetic resonance imaging in this population.
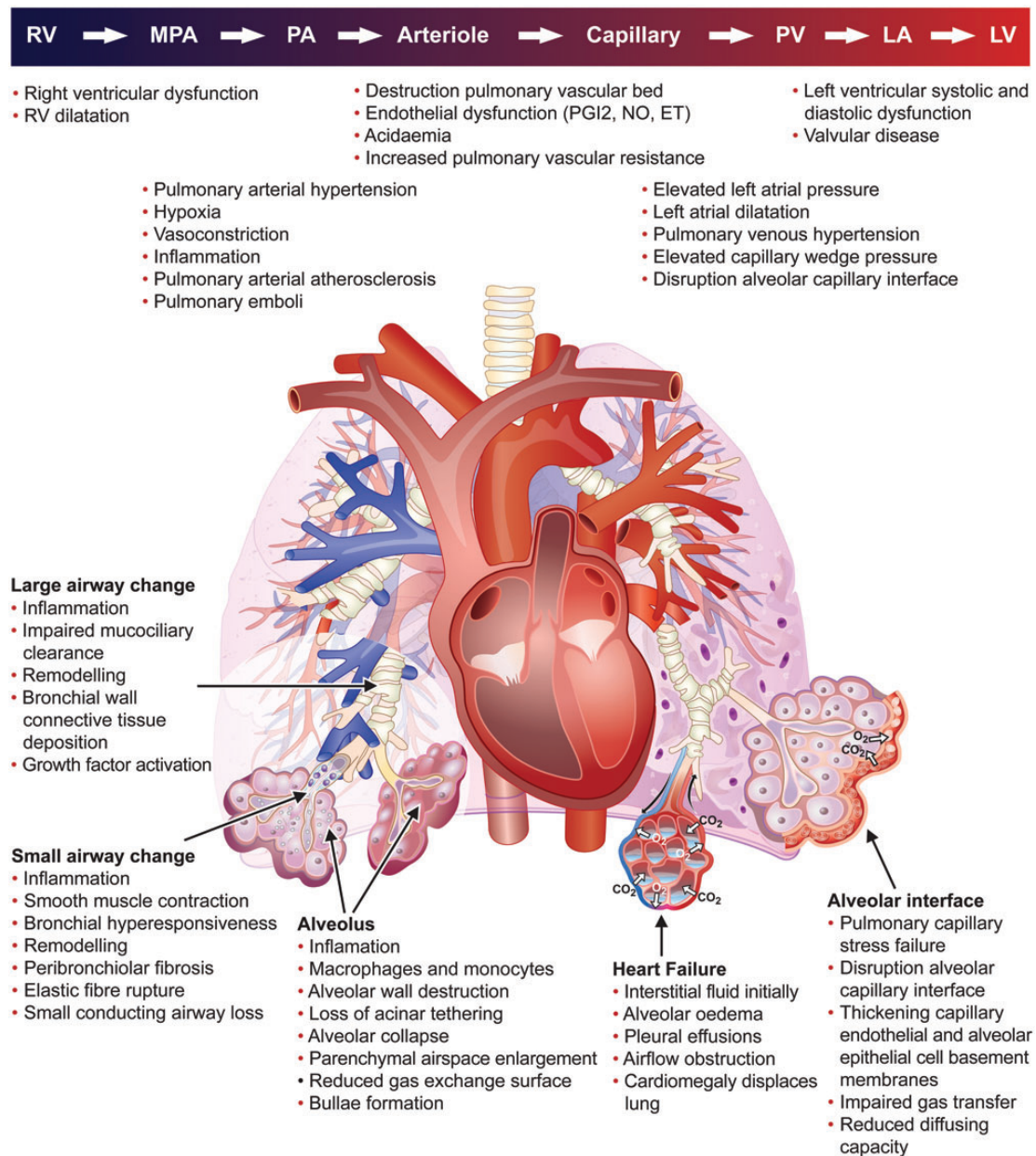
Figure 2 Cardiopulmonary pathophysiology and interactions in patients with heart failure and pulmonary disease.

Should patients with chronic obstructive pulmonary disease be screened for heart failure?

Asymptomatic LVSD fulfils the Wilson–Junger criteria for successful screening:[94] the condition is medically important and clearly defined, with effective treatment, an established natural history and early asymptomatic stage, detectable by an acceptable and safe, valid and reliable test applicable to the target population, resulting in cost-effective screening for which adequate resources exist.[95] The predictive value of screening is critically dependent on disease prevalence.[96] The high prevalence of LVSD in patients with COPD thus favours success. Sequential peptide testing (sensitive to rule out disease) and then echocardiography (specific) may counter the inherent limitations of peptides or echocardiography alone in pulmonary disease. Robust randomized trials are required to determine the efficacy and cost-effectiveness of such screening. Such a trial is currently being planned.

Therapeutic challenges

Beta-blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists reduce hospitalizations, morbidity, and mortality
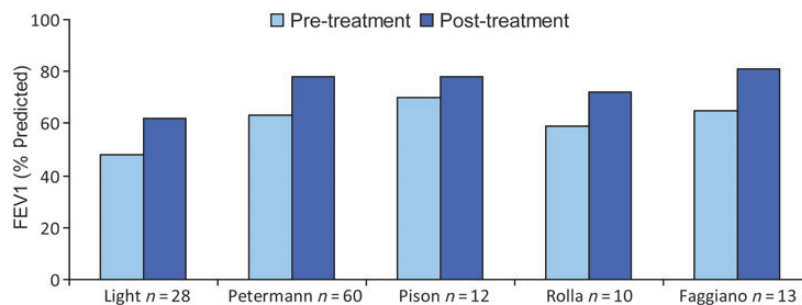
Figure 3 Changes in forced expiratory volume in 1 s following treatment of decompensated heart failure.
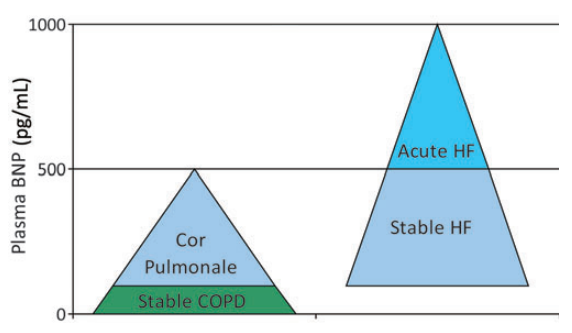

Figure 4 Overlap in natriuretic peptide levels between patients with heart failure and chronic obstructive pulmonary disease.

in HF. The cornerstone of therapy for COPD is long-acting inhaled bronchodilators, either anticholinergic, beta-agonist, corticosteroid, or combination therapy.[97–100] The opposing pharmacological effects of beta-blockers and beta-agonists underpin a reticence to prescribe the former in COPD or the latter in HF.[3]

Beta-blockers and chronic obstructive pulmonary disease

Three recent small randomized controlled trials have examined beta-blockers in patients with HF and concurrent COPD.[101–103] Prior to these, a Cochrane meta-analysis evaluated 20 randomized, controlled, cross-over trials of cardioselective beta-blockers in patients with COPD alone.[104] The included studies were limited in size; some lacked double-blinding or placebo controls; 11 trials involved only a single treatment dose; predominantly young male patients with moderate airflow obstruction were recruited; symptoms were rarely reported; and only one study lasted longer than a month.[3] Within the bounds of these significant limitations, cardioselective beta-blockade exerted minimal impact on reversible or severe airflow obstruction.[104]

The recent trials in patients with both conditions are consistent. In a double-blind, placebo controlled trial in 27 patients with concurrent moderate-to-severe COPD (mean FEV_1 1.3L), FEV_1 was

reduced after 4 months treatment with bisoprolol compared with placebo (-70 vs. $+120$ mL).[101] A subsequent open label triple cross-over trial included 35 patients with coexistent COPD.[103] FEV_1 was highest with bisoprolol (2.0 L), intermediate with metoprolol (1.94 L), and lowest with carvedilol (1.85 L). Finally, FEV_1 increased significantly with bisoprolol but not carvedilol in another open label study recruiting 63 elderly patients with concurrent moderate-to-severe COPD.[102] Without placebo control, the improvement with bisoprolol may simply reflect more intensive medical therapy during the study. Nevertheless, in all three studies, cardioselective beta-blockade was well tolerated. Of note, in all three studies, the FEV_1 reduction of around 150 mL with beta-blockade (either bisoprolol vs. placebo or carvedilol vs. bisoprolol) equals or exceeds the improvement in landmark bronchodilator trials. The recent CIBIS-ELD trial reinforces these observations. Even among elderly patients largely free of pulmonary disease, carvedilol reduced FEV_1 compared with bisoprolol (adjusted mean difference 50 mL).[105] Given mortality was unaltered in any bronchodilator trial, this effect size appears a reasonable exchange for the unequivocal survival benefits of beta-blockade.

The protective effect of beta-blockers may extend across a broad spectrum of patients with COPD (*Table 3*). Ten retrospective cohort studies have demonstrated an association between beta-blockers and improved survival, in patients with COPD and concurrent HF,[65,106] myocardial infarction,[64,107,108] vascular disease,[109] hypertension,[110] and most recently unselected community patients with COPD.[111,112] The pooled relative risk of mortality related to beta-blockers in a recent meta-analysis was 0.69 (95% CI 0.62–0.78).[113] Though observational with obvious confounding, evidence is accumulating to support randomized controlled trials of beta-blockers in COPD. Unthinkable? No more so than the paradigm shift two decades ago with regard to beta-blockers in HF.

Beta-agonists and heart failure

Paradoxically, as evidence accumulates of beta-blocker efficacy in COPD, observational studies point to adverse associations between beta-agonists and HF. Beta-agonists are associated with incident HF in patients with pulmonary disease, and with increased mortality and HF hospitalization in those with existing HF or LVSD (*Table 4*). These observations have sound physiological rationale.

Table 3 Association between beta-blockers and all-cause mortality in patients with chronic obstructive pulmonary disease in observational cohort studies

References	Population	n with COPD	Follow-up	Adjusted risk ($\pm$ 95% CI)
Sin et al.[106]	Heart failure	3834	Median 21 months	0.78 (0.63−0.95)
Staszewsky et al.[65]	Heart failure	628	Median 23 months	0.55 (0.37−0.82)
Hawkins et al.[64]	Myocardial infarction	1258	Median 25 months	0.74 (0.68−0.80)
Gottlieb et al.[108]	Myocardial infarction	41 814	2 years	0.60 (0.57−0.63)
Chen et al.[107]	Myocardial infarction	10 988	1 year	0.86 (0.73−1.00)
Van Gestel et al.[109]	Vascular disease	1205	Median 5 years	0.73 (0.60−0.88)
Au et al.[110]	Hypertension	1966	2 years	0.57 (0.33−0.89)
Rutten et al.[111]	COPD primary care	2230	7.2 years	0.68 (0.56−0.83)
Dransfield et al.[152]	COPD exacerbation	825	—	0.39 (0.14−0.99)
Short et al.[112]	COPD primary care	5977	mean 4.35 years	0.78 (0.67−0.92)

Down-regulation of beta$_1$-receptors with the preservation of the beta$_2$ subpopulation increases the sensitivity of the failing myocardium to beta$_2$-agonists.[114,115] The adverse effects of beta-agonists are numerous: ischaemia, arrhythmias, tachycardia, hypokalaemia, QT prolongation, disturbed autonomic modulation.[116−120] However, association is not causation. The poor outcomes attributed to beta-agonists may reflect the underlying pulmonary disease, smoking burden, and associated pathologies, clustering of cardiovascular risk factors and disease in patients with COPD, or residual confounding by unmeasured covariates. The most recent cohort study supports this standpoint.[121] In 1294 outpatients with HF, beta$_2$-agonist users were older, more often male, with more frequent smoking history, coronary artery disease, pulmonary disease, and higher heart rates. Although unadjusted mortality rates for beta$_2$-agonist users were significantly higher than non-users, adjusted mortality rates were similar after comprehensive multivariable adjustment (HR 1.04 [0.77−1.41]). Nevertheless, doubts regarding the cardiovascular safety of beta-agonists have prompted calls for randomized controlled trials.[3,122] The largest such trial is examining all-cause mortality in 16 000 patients with moderate COPD and established or high risk of cardiovascular disease randomized to four treatment groups: fluticasone/vilanterol combination, fluticasone alone, vilanterol alone, or placebo.[123]

Concurrent beta-blockers and beta-agonists

Beta-blockers and beta-agonists exert opposing pharmacological effects. The immediate clinical impact of this interaction largely depends on cardioselectivity. Non-cardioselective beta-blockers incontrovertibly antagonize beta-agonist-mediated bronchodilatation to varying degrees.[3,104] Conversely, beta-agonist response is preserved alongside cardioselective beta-blockers.[101,103,104,124] The key question is whether any interaction translates into meaningful clinical endpoints. A small number of retrospective cohort studies have tested for statistical interaction between beta-blockers and bronchodilators, with conflicting results.[107,120,125] Unfortunately, the lack of stratification according to cardioselectivity, selection bias, and unavoidable confounding renders such analyses uninterpretable.

Exacerbations

Among patients presenting with acute dyspnoea, prompt diagnosis and treatment is paramount to improved outcomes and decreased healthcare utilization.[126] This is particularly challenging in patients with combined diagnoses of COPD and HF, given the overlapping clinical signs and symptoms which characterize an acute exacerbation of either disease state.[2] Despite these diagnostic pitfalls, a comprehensive history and physical examination has predictive accuracy to identify HF among acutely dyspnoeic patients. In a meta-analysis of 22 publications, a history of HF was associated with a positive likelihood ratio of 5.8, while the presence of classic signs and symptoms of volume overload conveyed likelihood ratios ranging from 2.0 to 11.0 for HF as a cause of the patient's acute dyspnoea.[127] In this regard, clinical gestalt remains an important diagnostic tool for the astute physician.

Natriuretic peptides provide additional diagnostic accuracy and may be the most effective tool in refining the diagnosis for this patient population given the high negative predictive value of a normal result. In the Breath Not Properly study,[128] the negative predictive value of a B-type natriuretic peptide level <50 pg/mL in excluding acute HF was 96%. COPD, through the aforementioned effects on pulmonary pressures and right-ventricular function, may cause elevated circulating levels of natriuretic peptides.[88−90] Despite this potential confounding, the negative predictive accuracy in ruling out acute decompensated HF appears to be preserved even in cohorts of patients with a dual diagnosis.[56,129] Beyond improving diagnostic accuracy, a BNP-guided treatment strategy may also improve patient care through early initiation of targeted treatments and less requirement for confirmatory diagnostic testing.[126] This has significant implications both in terms of patient and system-related outcomes.

Economic costs

Individuals with chronic medical conditions, including HF and COPD, have higher rates of healthcare utilization when compared with age- and sex-matched healthy controls.[130−132] This observation is

Table 4 Association between beta-agonists and incident heart failure, hospitalization, and mortality

References	Population	n	Study design	Bronchodilator and route	Follow-up	Outcome	Risk associated with bronchodilator use [95% CI]	Adjustment includes beta- blockade
Martin et al.[153]	Asthma	8098	Cohort	Bambuterol oral	Median 288 days	Incident HF	RR 3.41 [1.99–5.86], $P < 0.0001$	No
		15 407	Cohort	Salmeterol inhaled	Median 511 days	Incident HF	RR 1.10 [0.63–1.91], $P = 0.7$	No
Coughlin et al.[154]	General population	387	Case–control	β-Agonist oral	20 months	Incident DCM	OR 3.4 [1.1–11.0]	No
		387	Case–control	β-Agonist inhaled/nebule	20 months	Incident DCM	OR 3.2 [1.4–7.1]	No
Sengstock et al.[155]	Cardiology clinic	190	Case–control	β-Agonist inhaled	—	Incident DCM	OR 1.0	No
Macie et al.[156]	COPD or asthma	59 336	Case–control	β-Agonist inhaled	5 years	HF hospitalization	OR 1.74 [1.60–1.91]	Yes
Au et al.[157]	HF	1121	Case–control	β-Agonist inhaled	2.5 years	HF hospitalization	OR 1.5 [0.8–2.8] 1–2 canisters OR 2.1 [1.0–4.3] ≥3 canisters	Yes
	Medical clinics	13 012	Case–control	β-Agonist inhaled	2.5 years	HF hospitalization	OR 1.3 [0.9–1.8] 1–2 canisters OR 1.1 [0.8–1.6] ≥3 canisters	Yes
Au et al.[158]	LVSD	1529	Cohort	β-Agonist inhaled	1 year	Death	RR 0.9 [0.5–1.6] 1 canister/month RR 1.4 [0.9–2.2] 2 canister/month RR 2.0 [1.3–3.2] 3 canister/month	Yes
Singer et al.[159]	Acute HF without COPD	7299	Cohort	Any bronchodilator inhaled	Inpatient	Death IV vasodilator ventilation	OR 1.02 (0.67–1.56) OR 1.40 (1.18–1.67) OR 1.69 (1.21–2.37)	Yes
Bermingham et al.[121]	HF	1294	Cohort	β-Agonist inhaled	Mean 2.9 years	Mortality	HR 1.04 (0.77–1.41)	Yes

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCM, idiopathic dilated cardiomyopathy; HF, heart failure; HR, hazard ratio; IV, intravenous; LVSD, left ventricular systolic dysfunction; OR, odds ratio; RR, relative risk.

consistent across healthcare systems globally despite variations in clinical practice patterns, the patient population being evaluated, the cost of tests and services employed, and the underlying strategy for provider reimbursement.[51,133–135] Given that the natural history of both HF and COPD is characterized by frequent episodes of acute exacerbation, increased healthcare utilization is primarily attributable to unplanned admission for disease decompensation.[132,136,137] This is particularly apparent in patients with more advanced symptoms and/or those with a dual diagnosis, who are at highest risk for hospitalization.[138–145] Diagnostic testing, medications, out-patient clinical services, and medical provider visits also contribute significantly to system related costs for both disease states.[134,141]

To provide granularity to this issue of increased healthcare utilization, in 2005, the US Congressional Budget Office confirmed that high-cost Medicare beneficiaries were responsible for 85% of the expenditures associated with this entitlement program but comprised only 25% of the beneficiaries. Moreover, 30% of high-cost beneficiaries had a combined diagnosis of HF and COPD and ~75% of this group had at least one hospitalization episode over the course of a given year.[146] These findings highlight the impact of co-existent HF and COPD with respect to clinical outcomes, risk of hospitalization, and healthcare expenditures.

Understanding the type and frequency of healthcare utilization among patients with multiple chronic disease diagnoses is paramount to developing strategies which improve patient- and system-related outcomes. Developing such strategies entails a robust characterization of patients, their co-morbidities, and the mechanisms through which they interact. Given the high prevalence and risk of hospitalization among individuals with a combined COPD and HF diagnosis, interventions to reduce unscheduled admission can lead to major cost savings for healthcare systems. To achieve this end, an emphasis on chronic disease management strategies which encompass patient self-management and evidence-based treatment algorithms, and which reduce the frequency of disease exacerbation must be employed to ensure efficient resource utilization.

Clinical guidance

The diagnostic and therapeutic complexity of the cardiopulmonary continuum is best addressed through simple clinical measures. In patients with suspected or established cardiopulmonary disease, clinical acumen should be reinforced by natriuretic peptides and objective measures of organ dysfunction. Pulmonary function testing when euvolaemic is mandatory, as is echocardiographic or cardiac magnetic resonance imaging. Beta-blockers markedly improve symptoms and survival across the cardiovascular spectrum, from coronary disease to HF. The European Society of Cardiology guidelines are explicit on this matter: COPD is not a contraindication to beta-blockade.[8] Moreover, severe airflow obstruction is actually uncommon, mild and moderate airways disease being the norm.[62] In patients with symptomatic LVSD and heart rate ≥70 beats per min receiving the maximum tolerated dose of beta-blocker (or truly intolerant), ivabradine should be considered to reduce the risk of HF hospitalization.[8,147] Beta-agonists remain a cornerstone of symptomatic relief. However, it seems sensible to base treatment regimens on long-acting anti-muscarinic agents, given the superiority of tiotropium to salmeterol in reducing exacerbations.[3,100]

Conclusion and direction for future research

The interaction between the heart and lungs is complex and incompletely understood. As with the kidney, direct physical connection and systemic neurohormonal and inflammatory activation are responsible.[148] Understanding these pathways may yield novel therapies. However, many of the challenges facing physicians and healthcare systems have potential to be addressed through existing resources. Comprehensive large-scale cohort studies and trials are required: establishing the prevalence and clinical consequences of the respective coexistent condition; prospectively testing diagnostic strategies; establishing the efficacy and cost-effectiveness of screening; undertaking randomized controlled trials of beta-blockers and beta-agonists across a spectrum of pulmonary and cardiovascular diseases, respectively; and determining the efficacy of integrated chronic disease management strategies. Such far reaching studies require closer collaboration between the cardiovascular and pulmonary communities. They also require greater financial support from governments, research funders, and healthcare payers. Translational medicine is expensive; so too are the consequences of ignoring the challenges of multimorbidity.

Funding

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De Leon FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012;**380**:2095–2128.

2. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail* 2009;**11**:130–139.

3. Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, Wikstrand J, McMurray JJ. Heart failure and chronic obstructive pulmonary disease the quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol* 2011;**57**:2127–2138.

4. Hawkins NM, Jhund PS, McMurray JJ, Capewell S. Heart failure and socioeconomic status: accumulating evidence of inequality. *Eur J Heart Fail* 2012;**14**:138–146.

5. Gershon AS, Dolmage TE, Stephenson A, Jackson B. Chronic obstructive pulmonary disease and socioeconomic status: a systematic review. *COPD* 2012;**9**:216–226.

6. Hawkins NM, Wright DJ, Capewell S. Heart failure services in the United Kingdom: rethinking the machine bureaucracy. *Int J Cardiol* 2013;**162**:143–148.

7. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;**380**:37–43.

8. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Guidelines ESCCfP, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document R, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the heart failure association (HFA) of the ESC. *Eur Heart J* 2012;**33**:1787–1847.

9. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;**187**:347–365.

10. Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, Marciniuk DD, Denberg T, Schunemann H, Wedzicha W, MacDonald R, Shekelle P, American College of Physicians, American College of Chest Physicians, American Thoracic Society, European Respiratory Society. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Intern Med* 2011;**155**:179–191.

11. Celli BR, Halbert RJ. Point: should we abandon fev(1)/fvc <0.70 to detect airway obstruction? No. *Chest* 2010;**138**:1037–1040.

12. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. *Eur Respir J* 2005;**26**:948–968.

13. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, Jensen RL, Falaschetti E, Schouten JP, Hankinson JL, Stocks J, Quanjer PH. Using the lower limit of normal for the fev1/fvc ratio reduces the misclassification of airway obstruction. *Thorax* 2008;**63**:1046–1051.

14. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: Part i: pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). *Circulation* 2006;**114**:2850–2870.

15. Ukena C, Mahfoud F, Kindermann M, Kindermann I, Bals R, Voors AA, van Veldhuisen DJ, Bohm M. The cardiopulmonary continuum systemic inflammation as 'common soil' of heart and lung disease. *Int J Cardiol* 2010;**145**:172–176.

16. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;**2**:8–11.

17. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;**105**:1135–1143.

18. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;**107**:1514–1519.

19. Watz H, Waschki B, Kirsten A, Muller KC, Kretschmar G, Meyer T, Holz O, Magnussen H. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009;**136**:1039–1046.

20. Poulain M, Doucet M, Major GC, Drapeau V, Series F, Boulet LP, Tremblay A, Maltais F. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. *CMAJ* 2006;**174**:1293–1299.

21. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007;**370**:797–799.

22. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. *Chest* 2007;**131**:1557–1566.

23. Agusti A. Chronic obstructive pulmonary disease: a systemic disease. *Proc Am Thorac Soc* 2006;**3**:478–481.

24. Viegi G, Maio S, Pistelli F, Baldacci S, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease: health effects of air pollution. *Respirology* 2006;**11**:523–532.

25. Hoffmann B, Moebus S, Dragano N, Stang A, Mohlenkamp S, Schmermund A, Memmesheimer M, Brocker-Preuss M, Mann K, Erbel R, Jockel KH. Chronic residential exposure to particulate matter air pollution and systemic inflammatory markers. *Environ Health Perspect* 2009;**117**:1302–1308.

26. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;**31**:204–212.

27. Boschetto P, Beghe B, Fabbri LM, Ceconi C. Link between chronic obstructive pulmonary disease and coronary artery disease: implication for clinical practice. *Respirology* 2012;**17**:422–431.

28. Sevenoaks MJ, Stockley RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity—a common inflammatory phenotype? *Respir Res* 2006;**7**:70.

29. Ceconi C, Boraso A, Mele D, Guardigli R, Ferrari R. Tnfalpha in patients with congestive heart failure. *Basic Res Cardiol* 2004;**99**:12–17.

30. Todd JL, Goldstein DB, Ge D, Christie J, Palmer SM. The state of genome-wide association studies in pulmonary disease: a new perspective. *Am J Respir Crit Care Med* 2011;**184**:873–880.

31. Zeller T, Blankenberg S, Diemert P. Genomewide association studies in cardiovascular disease—an update 2011. *Clin Chem* 2012;**58**:92–103.

32. Sandhu MS, Waterworth DM, Debenham SL, Wheeler E, Papadakis K, Zhao JH, Song K, Yuan X, Johnson T, Ashford S, Inouye M, Luben R, Sims M, Hadley D, McArdle W, Barter P, Kesaniemi YA, Mahley RW, McPherson R, Grundy SM, Wellcome Trust Case Control C, Bingham SA, Khaw KT, Loos RJ, Waeber G, Barroso I, Strachan DP, Deloukas P, Vollenweider P, Wareham NJ, Mooser V. LDL-cholesterol concentrations: a genome-wide association study. *Lancet* 2008;**371**:483–491.

33. Pillai SG, Ge D, Zhu G, Kong X, Shianna KV, Need AC, Feng S, Hersh CP, Bakke P, Gulsvik A, Ruppert A, Lodrup Carlsen KC, Roses A, Anderson W, Rennard SI, Lomas DA, Silverman EK, Goldstein DB, Investigators I. A genome-wide association study in chronic obstructive pulmonary disease (copd): Identification of two major susceptibility loci. *PLoS Genet* 2009;**5**:e1000421.

34. Cho MH, Boutaoui N, Klanderman BJ, Sylvia JS, Ziniti JP, Hersh CP, DeMeo DL, Hunninghake GM, Litonjua AA, Sparrow D, Lange C, Won S, Murphy JR, Beaty TH, Regan EA, Make BJ, Hokanson JE, Crapo JD, Kong X, Anderson WH, Tal-Singer R, Lomas DA, Bakke P, Gulsvik A, Pillai SG, Silverman EK. Variants in fam13a are associated with chronic obstructive pulmonary disease. *Nat Genet* 2010;**42**:200–202.

35. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* 2006;**47**:2554–2560.

36. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765–773.

37. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E. International variation in the prevalence of COPD (the bold study): a population-based prevalence study. *Lancet* 2007;**370**:741–750.

38. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, Montes de Oca M, Talamo C, Hallal PC, Victora CG. Chronic obstructive pulmonary disease in five Latin American cities (the Platino study): a prevalence study. *Lancet* 2005;**366**:1875–1881.

39. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006;**28**:523–532.

40. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, Nordestgaard BG. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new gold classification: A study of the general population. *Am J Respir Crit Care Med* 2012;**186**:975–981.

41. Lykkegaard J, Sondergaard J, Kragstrup J, Romhild Davidsen J, Knudsen T, Andersen M. All Danish first-time COPD hospitalisations 2002–2008: incidence, outcome, patients, and care. *Respir Med* 2012;**106**:549–556.

42. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of copd. *Chest* 2003;**124**:459–467.

43. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V, Buist S. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006;**27**:397–412.

44. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: global burden of disease study. *Lancet* 1997;**349**:1498–1504.

45. Hawkins NM, Scholes S, Bajekal M, Love H, O'Flaherty M, Raine R, Capewell S. Community care in England: reducing socioeconomic inequalities in heart failure. *Circulation* 2012;**126**:1050–1057.

46. Ezekowitz JA, Kaul P, Bakal JA, Quan H, McAlister FA. Trends in heart failure care: has the incident diagnosis of heart failure shifted from the hospital to the emergency department and outpatient clinics? *Eur J Heart Fail* 2011;**13**:142–147.

47. Lowrie R, Mair FS, Greenlaw N, Forsyth P, Jhund PS, McConnachie A, Rae B, McMurray JJ. Pharmacist intervention in primary care to improve outcomes in patients with left ventricular systolic dysfunction. *Eur Heart J* 2012;**33**:314–324.

48. Nielsen OW, McDonagh T, Cowburn P, Blue L, Robb SD, Dargie H. Patient differences related to management in general practice and the hospital: a cross-sectional study of heart failure in the community. *Eur Heart J* 2004;**25**:1718–1725.

49. Jhund PS, MacIntyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009;**119**:515–523.

50. Lenzen MJ, Scholte op Reimer WJ, Boersma E, Vantrimpont PJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function: a report from the Euroheart failure survey. *Eur Heart J* 2004;**25**:1214–1220.

51. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, Connell C, Jemal A, Lee TA, Miravitlles M, Aldington S, Beasley R. Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* 2006;**27**:188–207.

52. Mascarenhas J, Lourenco P, Lopes R, Azevedo A, Bettencourt P. Chronic obstructive pulmonary disease in heart failure. Prevalence, therapeutic and prognostic implications. *Am Heart J* 2008;**155**:521–525.

53. Iversen KK, Kjaergaard J, Akkan D, Kober L, Torp-Pedersen C, Hassager C, Vestbo J, Kjoller E. Chronic obstructive pulmonary disease in patients admitted with heart failure. *J Intern Med* 2008;**264**:361–369.

54. Apostolovic S, Jankovic-Tomasevic R, Salinger-Martinovic S, Djordjevic-Radojkovic D, Stanojevic D, Pavlovic M, Stankovic I, Putnikovic B, Kafedzic S, Catovic S, Tahirovic E, Dungen HD. Frequency and significance of unrecognized chronic obstructive pulmonary disease in elderly patients with stable heart failure. *Aging Clin Exp Res* 2011;**23**:337–342.

55. Boschetto P, Fucili A, Stendardo M, Malagu M, Parrinello G, Casimirri E, Potena A, Ballerin L, Fabbri LM, Ferrari R, Ceconi C. Occurrence and impact of chronic obstructive pulmonary disease in elderly patients with stable heart failure. *Respirology* 2013;**18**:125–130.

56. McCullough PA, Hollander JE, Nowak RM, Storrow AB, Duc P, Omland T, McCord J, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003;**10**:198–204.

57. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, Hoes AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005;**26**:1887–1894.

58. Macchia A, Rodriguez Moncalvo JJ, Kleinert M, Comignani PD, Gimeno G, Arakaki D, Laffaye N, Fuselli JJ, Massolin HP, Gambarte J, Romero M, Tognoni G. Unrecognised ventricular dysfunction in COPD. *Eur Respir J* 2012;**39**:51–58.

59. Rusinaru D, Saaidi I, Godard S, Mahjoub H, Battle C, Tribouilloy C. Impact of chronic obstructive pulmonary disease on long-term outcome of patients hospitalized for heart failure. *Am J Cardiol* 2008;**101**:353–358.

60. Lainscak M, Hodoscek LM, Dungen HD, Rauchhaus M, Doehner W, Anker SD, von Haehling S. The burden of chronic obstructive pulmonary disease in patients hospitalized with heart failure. *Wien Klin Wochenschr* 2009;**121**:309–313.

61. Mentz RJ, Schmidt PH, Kwasny MJ, Ambrosy AP, O'Connor CM, Konstam MA, Zannad F, Maggioni AP, Swedberg K, Gheorghiade M. The impact of chronic obstructive pulmonary disease in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the Everest trial. *J Card Fail* 2012;**18**:515–523.

62. Arnaudis B, Lairez O, Escamilla R, Fouilloux A, Fournier P, Monteil B, Bouisset F, Arnal JF, Elbaz M, Carrie D, Roncalli J, Pathak A, Galinier M. Impact of chronic obstructive pulmonary disease severity on symptoms and prognosis in patients with systolic heart failure. *Clin Res Cardiol* 2012;**101**:717–726.

63. De Blois J, Simard S, Atar D, Agewall S, Norwegian Heart Failure Registry. COPD predicts mortality in HF: the Norwegian Heart Failure Registry. *J Card Fail* 2010; **16**:225–229.

64. Hawkins NM, Huang Z, Pieper KS, Solomon SD, Kober L, Velazquez EJ, Swedberg K, Pfeffer MA, McMurray JJ, Maggioni AP. Chronic obstructive pulmonary disease is an independent predictor of death but not atherosclerotic events in patients with myocardial infarction: analysis of the valsartan in acute myocardial infarction trial (VALIANT). *Eur J Heart Fail* 2009;**11**:292–298.

65. Staszewsky L, Wong M, Masson S, Barlera S, Carretta E, Maggioni AP, Anand IS, Cohn JN, Tognoni G, Latini R. Clinical, neurohormonal, and inflammatory markers and overall prognostic role of chronic obstructive pulmonary disease in patients with heart failure: data from the val-heft heart failure trial. *J Card Fail* 2007;**13**:797–804.

66. Kwon BJ, Kim DB, Jang SW, Yoo KD, Moon KW, Shim BJ, Ahn SH, Cho EJ, Rho TH, Kim JH. Prognosis of heart failure patients with reduced and preserved ejection fraction and coexistent chronic obstructive pulmonary disease. *Eur J Heart Fail* 2010;**12**:1339–1344.

67. Boudestein LC, Rutten FH, Cramer MJ, Lammers JW, Hoes AW. The impact of concurrent heart failure on prognosis in patients with chronic obstructive pulmonary disease. *Eur J Heart Fail* 2009;**11**:1182–1188.

68. Janssen DJ, Spruit MA, Uszko-Lencer NH, Schols JM, Wouters EF. Symptoms, comorbidities, and health care in advanced chronic obstructive pulmonary disease or chronic heart failure. *J Palliat Med* 2011;**14**:735–743.

69. Walke LM, Byers AL, Tinetti ME, Dubin JA, McCorkle R, Fried TR. Range and severity of symptoms over time among older adults with chronic obstructive pulmonary disease and heart failure. *Arch Intern Med* 2007;**167**:2503–2508.

70. Milne EN. Correlation of physiologic findings with chest roentgenology. *Radiol Clin North Am* 1973;**11**:17–47.

71. Hublitz UF, Shapiro JH. Atypical pulmonary patterns of congestive failure in chronic lung disease. The influence of pre-existing disease on the appearance and distribution of pulmonary edema. *Radiology* 1969;**93**:995–1006.

72. Gehlbach BK, Geppert E. The pulmonary manifestations of left heart failure. *Chest* 2004;**125**:669–682.

73. Naum CC, Sciurba FC, Rogers RM. Pulmonary function abnormalities in chronic severe cardiomyopathy preceding cardiac transplantation. *Am Rev Respir Dis* 1992;**145**:1334–1338.

74. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, Lubarsky L, Agostoni PG. Lung function and exercise gas exchange in chronic heart failure. *Circulation* 1997; **96**:2221–2227.

75. Hosenpud JD, Stibolt TA, Atwal K, Shelley D. Abnormal pulmonary function specifically related to congestive heart failure: comparison of patients before and after cardiac transplantation. *Am J Med* 1990;**88**:493–496.

76. Daganou M, Dimopoulou I, Alivizatos PA, Tzelepis GE. Pulmonary function and respiratory muscle strength in chronic heart failure: comparison between ischaemic and idiopathic dilated cardiomyopathy. *Heart* 1999;**81**:618–620.

77. Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kubler W, Haass M. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. *Circulation* 2001;**103**:2153–2158.

78. Guazzi M. Alveolar-capillary membrane dysfunction in heart failure: evidence of a pathophysiologic role. *Chest* 2003;**124**:1090–1102.

79. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation* 2012;**126**:975–990.

80. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail* 2008; **14**:695–702.

81. Guazzi M, Myers J, Vicenzi M, Bensimhon D, Chase P, Pinkstaff S, Arena R. Cardiopulmonary exercise testing characteristics in heart failure patients with and without concomitant chronic obstructive pulmonary disease. *Am Heart J* 2010; **160**:900–905.

82. Anonymous. Cardiac asthma. *Lancet* 1990;**335**:693–694.

83. Pison C, Malo JL, Rouleau JL, Chalaoui J, Ghezzo H, Malo J. Bronchial hyperresponsiveness to inhaled methacholine in subjects with chronic left heart failure at a time of exacerbation and after increasing diuretic therapy. *Chest* 1989;**96**:230–235.

84. Light RW, George RB. Serial pulmonary function in patients with acute heart failure. *Arch Intern Med* 1983;**143**:429–433.

85. Petermann W, Barth J, Entzian P. Heart failure and airway obstruction. *Int J Cardiol* 1987;**17**:207–209.

86. Rolla G, Bucca C, Brussino L, Gallo W, Malara D. Bronchodilating effect of ipratropium bromide in heart failure. *Eur Respir J* 1993;**6**:1492–1495.

87. Faggiano P, Lombardi C, Sorgato A, Ghizzoni G, Spedini C, Rusconi C. Pulmonary function tests in patients with congestive heart failure: effects of medical therapy. *Cardiology* 1993;**83**:30–35.

88. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000;**102**:865–870.

89. Bozkanat E, Tozkoparan E, Baysan O, Deniz O, Ciftci F, Yokusoglu M. The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease. *J Int Med Res* 2005;**33**:537–544.

90. Rutten FH, Cramer MJ, Zuithoff NP, Lammers JW, Verweij W, Grobbee DE, Hoes AW. Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease. *Eur J Heart Fail* 2007;**9**:651–659.

91. Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuithoff NP, Lammers JW, Hoes AW. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *BMJ* 2005; **331**:1379.

92. Boussuges A, Pinet C, Molenat F, Burnet H, Ambrosi P, Badier M, Sainty JM, Orehek J. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *Am J Respir Crit Care Med* 2000;**162**:670–675.

93. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. *Chest* 1998;**113**:576–583.

94. McMurray JV, McDonagh TA, Davie AP, Cleland JG, Francis CM, Morrison C. Should we screen for asymptomatic left ventricular dysfunction to prevent heart failure? *Eur Heart J* 1998;**19**:842–846.

95. Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease*. Public health papers no 34. Geneva: World Health Organization; 1968.

96. Grimes DA, Schulz KF. Uses and abuses of screening tests. *Lancet* 2002;**359**:881–884.

97. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**:775–789.

98. Karner C, Cates CJ. The effect of adding inhaled corticosteroids to tiotropium and long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011;**9**:CD009039.

99. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**:1543–1554.

100. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, Rabe KF, Fabbri LM. Tiotropium versus salmeterol for the prevention of exacerbations of copd. *N Engl J Med* 2011;**364**:1093–1103.

101. Hawkins NM, Macdonald MR, Petrie MC, Chalmers GW, Carter R, Dunn FG, McMurray JJ. Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial. *Eur J Heart Fail* 2009;**11**:684–690.

102. Lainscak M, Podbregar M, Kovacic D, Rozman J, von HS. Differences between biso-prolol and carvedilol in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized trial. *Respir Med* 2011;**105** (Suppl. 1):S44–S49.

103. Jabbour A, Macdonald PS, Keogh AM, Kotlyar E, Mellemkjaer S, Coleman CF, Elsik M, Krum H, Hayward CS. Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial. *J Am Coll Cardiol* 2010;**55**:1780–1787.

104. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005:CD003566.

105. Dungen HD, Apostolovic S, Inkrot S, Tahirovic E, Topper A, Mehrhof F, Prettin C, Putnikovic B, Neskovic AN, Krotin M, Sakac D, Lainscak M, Edelmann F, Wachter R, Rau T, Eschenhagen T, Doehner W, Anker SD, Waagstein F, Herrmann-Lingen C, Gelbrich G, Dietz R. , investigators C-E, Project Multicentre Trials in the Competence Network Heart F. Titration to target dose of bisoprolol vs. Carvedilol in elderly patients with heart failure: The CIBIS-ELD trial. *Eur J Heart Fail* 2011;**13**:670–680.

106. Sin DD, McAlister FA. The effects of beta-blockers on morbidity and mortality in a population-based cohort of 11,942 elderly patients with heart failure. *Am J Med* 2002;**113**:650–656.

107. Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol* 2001;**37**:1950–1956.

108. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med* 1998;**339**:489–497.

109. van Gestel YR, Hoeks SE, Sin DD, Welten GM, Schouten O, Witteveen HJ, Simsek C, Stam H, Mertens FW, Bax JJ, van Domburg RT, Poldermans D. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. *Am J Respir Crit Care Med* 2008;**178**:695–700.

110. Au DH, Bryson CL, Fan VS, Udris EM, Curtis JR, McDonell MB, Fihn SD. Beta-blockers as single-agent therapy for hypertension and the risk of mortality among patients with chronic obstructive pulmonary disease. *Am J Med* 2004;**117**:925–931.

111. Rutten FH, Zuithoff NP, Hak E, Grobbee DE, Hoes AW. Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010;**170**:880–887.

112. Short PM, Lipworth SI, Elder DH, Schembri S, Lipworth BJ. Effect of beta blockers in treatment of chronic obstructive pulmonary disease: a retrospective cohort study. *BMJ* 2011;**342**:d2549.

113. Etminan M, Jafari S, Carleton B, Fitzgerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. *BMC Pulm Med* 2012;**12**:48.

114. Bristow MR, Ginsburg R, Umans V, Fowler M, Minobe W, Rasmussen R, Zera P, Menlove R, Shah P, Jamieson S. Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. *Circ Res* 1986;**59**:297–309.

115. Packer M. Pathophysiological mechanisms underlying the effects of beta-adrenergic agonists and antagonists on functional capacity and survival in chronic heart failure. *Circulation* 1990;**82**:I77–I88.

116. Cazzola M, Matera MG, Donner CF. Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease. *Drugs* 2005;**65**:1595–1610.

117. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004;**125**:2309–2321.

118. Bremner P, Woodman K, Burgess C, Crane J, Purdie G, Pearce N, Beasley R. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir J* 1993;**6**:204–210.

119. Jartti T, Kaila T, Tahvanainen K, Kuusela T, Vanto T, Valimaki I. The acute effects of inhaled salbutamol on the beat-to-beat variability of heart rate and blood pressure assessed by spectral analysis. *Br J Clin Pharmacol* 1997;**43**:421–428.

120. Au DH, Curtis JR, Every NR, McDonell MB, Fihn SD. Association between inhaled beta-agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002;**121**:846–851.

121. Bermingham M, O'Callaghan E, Dawkins I, Miwa S, Samsudin S, McDonald K, Ledwidge M. Are beta2-agonists responsible for increased mortality in heart failure? *Eur J Heart Fail* 2011;**13**:885–891.

122. Mentz RJ, Fiuzat M, Kraft M, Lindenfeld J, O'Connor CM. Bronchodilators in heart failure patients with COPD: is it time for a clinical trial? *J Card Fail* 2012;**18**:413–422.

123. Vestbo J, Anderson J, Brook RD, Calverley PM, Celli BR, Crim C, Haumann B, Martinez FJ, Yates J, Newby DE. The study to understand mortality and morbidity in COPD (summit) study protocol. *Eur Respir J* 2013;**41**:1017–1022.

124. Agostoni P, Contini M, Cattadori G, Apostolo A, Sciomer S, Bussotti M, Palermo P, Fiorentini C. Lung function with carvedilol and bisoprolol in chronic heart failure: is beta selectivity relevant? *Eur J Heart Fail* 2007;**9**:827–833.

125. Hawkins NM, Wang D, Petrie MC, Pfeffer MA, Swedberg K, Granger CB, Yusuf S, Solomon SD, Ostergren J, Michelson EL, Pocock SJ, Maggioni AP, McMurray JJ. Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators in the charm programme. *Eur J Heart Fail* 2010;**12**:557–565.

126. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004;**350**:647–654.

127. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005;**294**:1944–1956.

128. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;**347**:161–167.

129. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;**39**:202–209.

130. Simon-Tuval T, Scharf SM, Maimon N, Bernhard-Scharf BJ, Reuveni H, Tarasiuk A. Determinants of elevated healthcare utilization in patients with COPD. *Respir Res* 2011;**12**:7.

131. Sharafkhaneh A, Petersen NJ, Yu HJ, Dalal AA, Johnson ML, Hanania NA. Burden of COPD in a government health care system: a retrospective observational study using data from the us veterans affairs population. *Int J Chron Obstruct Pulmon Dis* 2010;**5**:125–132.

132. Mapel DW, Hurley JS, Frost FJ, Petersen HV, Picchi MA, Coultas DB. Health care utilization in chronic obstructive pulmonary disease. A case-control study in a health maintenance organization. *Arch Intern Med* 2000;**160**:2653–2658.

133. Sullivan SD, Ramsey SD, Lee TA. The economic burden of COPD. *Chest* 2000;**117**:5S–9S.

134. Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. *Eur J Heart Fail* 2001;**3**:283–291.

135. Priest JL, Cantrell CR, Fincham J, Cook CL, Burch SP. Quality of care associated with common chronic diseases in a 9-state medicaid population utilizing claims data: an evaluation of medication and health care use and costs. *Popul Health Manag* 2011;**14**:43–54.

136. Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the national health service in the UK. *Eur J Heart Fail* 2002;**4**:361–371.

137. Foster TS, Miller JD, Marton JP, Caloyeras JP, Russell MW, Menzin J. Assessment of the economic burden of COPD in the U.S.: a review and synthesis of the literature. *COPD* 2006;**3**:211–218.

138. Liao L, Anstrom KJ, Gottdiener JS, Pappas PA, Whellan DJ, Kitzman DW, Aurigemma GP, Mark DB, Schulman KA, Jollis JG. Long-term costs and resource use in elderly participants with congestive heart failure in the cardiovascular health study. *Am Heart J* 2007;**153**:245–252.

139. Davey PG, Clarkson PB, McMahon A, MacDonald TM. Costs associated with symptomatic systolic heart failure. *Pharmacoeconomics* 1999;**16**:399–407.

140. Hilleman DE, Dewan N, Malesker M, Friedman M. Pharmacoeconomic evaluation of COPD. *Chest* 2000;**118**:1278–1285.

141. Gerdtham UG, Andersson LF, Ericsson A, Borg S, Jansson SA, Ronmark E, Lundback B. Factors affecting chronic obstructive pulmonary disease (COPD)-related costs: a multivariate analysis of a swedish COPD cohort. *Eur J Health Econ* 2009;**10**:217–226.

142. Lin PJ, Shaya FT, Scharf SM. Economic implications of comorbid conditions among medicaid beneficiaries with COPD. *Respir Med* 2010;**104**:697–704.

143. Hutchinson A, Brand C, Irving L, Roberts C, Thompson P, Campbell D. Acute care costs of patients admitted for management of chronic obstructive pulmonary disease exacerbations: contribution of disease severity, infection and chronic heart failure. *Intern Med J* 2010;**40**:364–371.

144. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003; **42**:1226–1233.

145. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among medicare beneficiaries. *Arch Intern Med* 1997;**157**:99–104.

146. Office CB. High-Cost Medicare Beneficiaries. *Congress of the United States Congressional Budget Office*.

147. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (shift): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.

148. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. *Eur Heart J* 2012;**33**:2135–2142.

149. Macchia A, Monte S, Romero M, D'Ettorre A, Tognoni G. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalised for chronic heart failure. *Eur J Heart Fail* 2007;**9**:942–948.

150. Lainscak M, Hodoscek LM, Dungen HD, Rauchhaus M, Doehner W, Anker SD, von HS. The burden of chronic obstructive pulmonary disease in patients hospitalized with heart failure. *Wien Klin Wochenschr* 2009;**121**:309–313.

151. Mentz RJ, Fiuzat M, Wojdyla DM, Chiswell K, Gheorghiade M, Fonarow GC, O'Connor CM. Clinical characteristics and outcomes of hospitalized heart failure patients with systolic dysfunction and chronic obstructive pulmonary disease: findings from optimize-HF. *Eur J Heart Fail* 2012;**14**:395–403.

152. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of copd. *Thorax* 2008;**63**:301–305.

153. Martin RM, Dunn NR, Freemantle SN, Mann RD. Risk of non-fatal cardiac failure and ischaemic heart disease with long acting beta 2 agonists. *Thorax* 1998; **53**:558–562.

154. Coughlin SS, Metayer C, McCarthy EP, Mather FJ, Waldhorn RE, Gersh BJ, DuPraw S, Baughman KL. Respiratory illness, beta-agonists, and risk of idiopathic dilated cardiomyopathy. The Washington, DC, dilated cardiomyopathy study. *Am J Epidemiol* 1995;**142**:395–403.

155. Sengstock DM, Obeidat O, Pasnoori V, Mehra P, Sandberg KR, McCullough PA. Asthma, beta-agonists, and development of congestive heart failure: results of the ABCHF study. *J Card Fail* 2002;**8**:232–238.

156. Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. *Int J Chron Obstruct Pulmon Dis* 2008;**3**: 163–169.

157. Au DH, Udris EM, Curtis JR, McDonell MB, Fihn SD. Association between chronic heart failure and inhaled beta-2-adrenoceptor agonists. *Am Heart J* 2004; **148**:915–920.

158. Au DH, Udris EM, Fan VS, Curtis JR, McDonell MB, Fihn SD. Risk of mortality and heart failure exacerbations associated with inhaled beta-adrenoceptor agonists among patients with known left ventricular systolic dysfunction. *Chest* 2003; **123**:1964–1969.

159. Singer AJ, Emerman C, Char DM, Heywood JT, Kirk JD, Hollander JE, Summers R, Lee CC, Wynne J, Kellerman L, Peacock WF. Bronchodilator therapy in acute decompensated heart failure patients without a history of chronic obstructive pulmonary disease. *Ann Emerg Med* 2008;**51**:25–34.