Metadata of the article that will be visualized in OnlineFirst

1	Article Title	**Dipeptidyl-peptidase-4 Inhibitors and Heart Failure: Class Effect, Substance-Specific Effect, or Chance Effect?**	
2	Article Sub- Title		
3	Article Copyright - Year	**Springer Science+Business Media New York 2014 (This will be the copyright line in the final PDF)**	
4	Journal Name	Current Treatment Options in Cardiovascular Medicine	
5	Corresponding Author	Family Name	**Standl**
6		Particle	
7		Given Name	**Eberhard**
8		Suffix	
9		Organization	Munich Diabetes Research Group e.V. at Helmholtz Centre
10		Division	
11		Address	Ingolstaedter Landstrasse 1, Neuherberg 85764, Germany
12		e-mail	eberhard.standl@lrz.uni-muenchen.de
13	Author	Family Name	**Erbach**
14		Particle	
15		Given Name	**Michael**
16		Suffix	
17		Organization	Sciarc Institute
18		Division	
19		Address	Baierbrunn, Germany
20		e-mail	
21	Author	Family Name	**Schnell**
22		Particle	
23		Given Name	**Oliver**
24		Suffix	
25		Organization	Munich Diabetes Research Group e.V. at Helmholtz Centre
26		Division	
27		Address	Ingolstaedter Landstrasse 1, Neuherberg 85764, Germany

28		e-mail
29		Received
30	Schedule	Revised
31		Accepted
32	Abstract	
33	Keywords separated by ' - '	Heart failure - DPP-4 inhibitors - Diabetes therapy - Side effects - Cardiovascular safety of diabetes drugs
34	Foot note information	This article is part of the Topical Collection on *Prevention*

Curr Treat Options Cardio Med (2014) 16:353
DOI 10.1007/s11936-014-0353-y

Prevention (L Sperling and D Gaita, Section Editors)

Dipeptidyl-peptidase-4 Inhibitors and Heart Failure: Class Effect, Substance-Specific Effect, or Chance Effect?

Eberhard Standl[1,*]
Michael Erbach[2]
Oliver Schnell[1]

Address
[*,1]Munich Diabetes Research Group e.V. at Helmholtz Centre, Ingolstaedter Landstrasse 1, 85764, Neuherberg, Germany
Email: eberhard.standl@lrz.uni-muenchen.de
[2]Sciarc Institute, Baierbrunn, Germany

This article is part of the Topical Collection on *Prevention*

Keywords Heart failure · DPP-4 inhibitors · Diabetes therapy · Side effects · Cardiovascular safety of diabetes drugs

Opinion statement

The increased risk of heart failure hospitalizations related to treatment with the DPP-4 inhibitor saxagliptin observed in the SAVOR TIMI 53 trial, is likely not to be a chance effect, but rather a previously unrecognized side effect of this drug, as this risk was very consistently apparent across all subgroups of this large multicenter, prospective, randomized trial. Whether this side effect might represent a class effect of all DPP-4 inhibitors remains to be seen. Results of randomized prospective multicenter trials with the DPP-4 inhibitors alogliptin and vildagliptin have in fact generated new uncertainties and clearly not totally excluded the possibility of a class side effect. A meta-analysis of 59 randomized controlled trials with various DPP-4 inhibitors evaluating data from 36,620 patients with diabetes and a minimal observation period of 24 weeks, confirmed a 21 % increase of heart failure events compared to placebo treatment, however, not in comparison to treatment with other blood glucose lowering drugs. German registry data also did not show an increased risk for heart failure for the latter comparison. Potential interactions of DPP-4 inhibitors with other drugs, e.g. ACE inhibitors, have been discussed in relation to the increased heart failure risk, as well as interactions with peptides regulating cardiovascular functions that are also

split by DPP-4 enzymes such as BNP, substance P, and NPY. Results from ongoing large multicenter trials with the DPP-4 inhibitors sitagliptin and linagliptin are expected to clarify the potential heart failure issue related to treatment with DPP-4 inhibitors.

Introduction

Chronic heart failure develops rather frequently in patients with diabetes mellitus, i.e. some 30 % more often compared to non-diabetic subjects [1, 2, 3••, 4]. Thus, heart failure has emerged as a clinically important issue in the context of diabetes-associated cardiac complications [1, 2, 3••, 4]. Heart failure, however, has also attracted wide attention in relation to the development of innovative blood glucose-lowering drugs for people with diabetes, e.g. dual PPAR alpha/gamma agonists ("glitazars") and the thiazolidindiones or PPAR gamma agonists ("glitazones"). Because of the negative experience with muraglitazar and a doubling of the rate of heart failure and cardiovascular complications in the published labelling studies [5], the American Food and Drug Administration and the European Medicines Agency have updated their labelling rules for new diabetes drugs, particularly focusing on cardiovascular safety [6]. This is further augmented by similar adverse results obtained from randomized, placebo-controlled, prospective cardiovascular outcome studies with rosiglitazone [7–9], but also with pioglitazone [10, 11]. The disadvantageous outcome results with aleglitazar in the recently stopped Aleglitazar to Reduce Cardiovascular Risk in Coronary Heart Disease Patients with a Recent Acute Coronary Syndrome Event and Type 2 Diabetes Mellitus (ALECARDIO) Study seem to underpin the validity of the new regulatory measures [12]. The debate over an increased heart failure risk connected with the use of blood glucose-lowering drugs, however, has entered a new phase, after the results of the randomized, placebo-controlled Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) Study became available. Unexpectedly, the authors found a 27 % increased risk for heart failure hospitalizations in the group on treatment with saxagliptin, a dipeptidyl-peptidase-4 (DPP-4) inhibitor, compared to the placebo group [13•]. Furthermore, results of randomized, prospective, multicenter trials with other DPP-4 inhibitors, i.e. with alogliptin and vildagliptin have in fact generated new uncertainties and clearly not excluded the possibility that an increased heart failure risk may comprise a previously unrecognized side effect of the whole class of DPP-4 inhibitors [14, 15•, 16].

The mini-review presented here attempts to evaluate whether the increased risk of heart failure hospitalizations seen in SAVOR-TIMI 53 represents a class side effect of DPP-4 inhibitors, a saxagliptin specific side effect, or a "chance" effect.

Evidence from randomized cardiovascular outcome trials

SAVOR-TIMI 53 randomized 16,492 patients with type 2 diabetes and a history of cardiovascular (CV) events or at high CV risk either to saxagliptin or placebo and followed them for a median of 2.1 years [13•]. A primary endpoint event (i.e. a composite of CV death, myocardial infarction, or stroke) occurred in 613 patients of the saxagliptin group and 609 patients of the placebo group. In other words, the CV event rate was identical in both groups [hazard ratio (HR) for saxagliptin 1.00; 95 % confidence interval (CI) 0.89 – 1.12; p=0.99 for superiority and p<0.001 for non-inferiority]. An increased CV risk from saxagliptin treatment, therefore, appeared to be excluded. On the other hand, an advantage of saxagliptin treatment in terms of CV complications could not be substantiated either. Looking at the

predefined and adjudicated secondary endpoints, however, an imbalance in heart failure events requiring hospitalization became apparent. More patients in the saxagliptin group had been hospitalized for heart failure compared to the placebo group (3.5 % vs. 2.8 %; HR 1.27; 95 % CI 1.07 – 1.51; p=0,007). This result was unexpected and could have also reflected a chance finding in the context of multiple statistical comparisons [13•]. Meanwhile, however, it is clear [15•] that this imbalance in heart failure hospitalizations had occurred both in the 2,105 patients with a prior history of heart failure, i.e. a high risk group for heart failure, as well as in the remaining patients without a prior history of heart failure (11.7 vs. 10.2 % in patients with prior heart failure, HR 1.21; 95 % CI 0.93 – 1.58 vs. 2.3 and 1.7 in patients without prior heart failure, HR 1.32; 95 % CI 1.04 – 1.65; p=0.68 for interaction). Conversely, looking at the concentrations of NT-pro-BNP measured at baseline, it was revealed that the excess of heart failure hospitalizations had happened more or less exclusively in the highest NT-pro-BNP quartile (10.9 vs. 9.0 %; HR 1.31; 95 % CI 1.0 – 1.6; p=0.021), suggesting a role of "subclinical" heart failure as a risk factor of the untoward effect of saxagliptin. Beyond that, the increased heart failure risk in the saxagliptin group was consistently seen in all of subgroups. The result was independent of demographic or biochemical variables such as age, gender, BMI, renal function, glycemic, and lipid parameters, as well as a concurrent therapy with diabetes drugs like insulin, metformin, or sulphonylureas or with the various classes of antihypertensive drugs, including ACE inhibitors or angiotensin receptor blockers, or with aspirin or statins. Thus, the increased heart failure risk seems likely not to be a chance effect, but rather a previously unrecognized side effect of saxagliptin, although it is important to note that it had no impact on the overall primary CV outcome in SAVOR-TIMI 53.

In parallel to SAVOR-TIMI 53, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) Trial was published, another randomized and placebo-controlled study evaluating the DPP-4 inhibitor alogliptin in 5,380 patients with diabetes and recent myocardial infarction or unstable angina, respectively, with a mean follow-up of 18 months [14]. Similar to SAVOR-TIMI 53, EXAMINE was focused on CV safety in a cohort of diabetic patients at high risk for CV complications. Again, the primary outcome was defined as a composite of CV death, nonfatal myocardial infarction, or stroke and showed no difference between the two treatment groups. Three hundred and five patients in the alogliptin group (11.3 %) and 316 patients in the placebo group (11.8 %) had developed a primary endpoint event (HR 0.96; 95 % CI upper limit 1.16; p<0.001 for non-inferiority, p=0.32 for superiority). Surprisingly, no results with regard to heart failure events were released in the primary publication despite the fact that some 28 % of patients in both study arms had a prior history of heart failure [14]. In published responses to enquiries about heart failure, a statement was made by the investigators of EXAMINE that no significant differences had been observed for heart failure between the two treatment groups of the trial [15•]; this statement was not qualified further. According to presentations of the EXAMINE data at large international meetings such as EASD or ACC, however, the situation seems to be less clear [17]. Looking at a newly

defined explorative composite endpoint (all-cause mortality, non-fatal myocardial infarction or stroke, emergency revascularization for instable angina, or hospitalization for heart failure) no significant differences were found (HR 0.98; 95 % CI 0.86 – 1.12) and the frequency of heart failure within this composite endpoint amounted to 3.1 % in the alogliptin group compared to 2.9 % in the placebo group (HR 1.07; 95 % CI 0.79 – 1.46). However, this contrasts with the tendency that all patients requiring hospitalization for heart failure in the trial were considered irrespective of other prior events. One hundred and six patients were contained in the alogliptin group compared to 89 patients in the placebo group (HR 1.19; 95 % CI 0.89 – 1.58). A full publication of these data is urgently needed. For the time being, a preliminary meta-analysis looking at all heart failure in SAVOR-TIMI 53 and EXAMINE (Table 1) fosters the suspicion that an increased heart failure risk might be an emerging side effect of the whole class of DPP-4 inhibitors, not just of saxagliptin (a total of 395 patients with hospitalization requiring heart failure on DPP-4 inhibitors in comparison to 317 patients on placebo, HR 1.24; 95 % CI 1.07 – 1.44).

Another DPP-4 inhibitor, vildagliptin, has been investigated in terms of cardiac safety in diabetic heart failure patients in the Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) Trial [16]. Again, only information derived from congressional presentations is currently available and a full publication is eagerly awaited. The VIVIDD Trial had enrolled 254 patients with diabetes and chronic heart failure NYHA class I-III and randomized them to either vildagliptin or placebo therapy. The echocardiographic ejection fraction was determined as primary endpoint and measured at baseline and at 1-year follow-up. Both groups showed significant improvement of some 4 % at 1 year with no significant difference existing between the two groups. Unexpected, however, was the finding of a significant increase of the left-ventricular end-diastolic and end-systolic volume as well as of the stroke volume in the vildagliptin arm compared to placebo. Conversely, plasma BNP concentrations had fallen by 28 % in the vildagliptin group, and by 14 % in the placebo group. The difference, however, was not statistically significant. Likewise, no significant difference was seen in terms of all-cause mortality (four patients on placebo vs. 11 patients on vildagliptin). The trial, however, was not powered to detect differences in clinical endpoints and conclusions regarding cardiac safety of vildagliptin are, therefore, limited. Hence, uncertainties remain which would need to be addressed in a much larger trial with a much

Table 1. Heart failure requiring hospitalization in prospective, randomized studies evaluating DPP-4 inhibitors and cardiovascular outcomes – a Meta-Analysis

Study	DPP-4 inhibitor	Placebo	OR (95 % CI)
SAVOR-TIMI 53	289	228	1.27 (1.06–1.52)
EXAMINE	106	89	1.19 (0.89–1.58)
Combined	395	317	1.24 (1.07–1.44)

longer follow-up. The finding of larger hearts after a 1 year of therapy with vildagliptin does not exclude an increased heart failure risk, but might be rather suggestive for it.

Potential pathophysiologic links

DPP-4 inhibitors inhibit more or less specifically the enzyme DPP-4 that exists as trans-membranous exo-peptidase in many cells of the body and splits off dipeptides at the N-terminal end of proteins or peptides immediately after a proline of alanine residue (sometimes also after other amino acid residue) in position 2 [18]. Among a wide scope of aspects, DPP-4 has turned out to be an important regulator of the incretin effect, as it spits the two main incretin hormones released from the L- or K-cells, respectively, in the small intestines, i.e. glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In the case of GLP-1, the hormone loses its capacity to bind to the GLP-1 receptor of cells and to induce signal transduction by the removal of the dipeptide. Inhibition of GLP-1 degradation by DPP-4 inhibitors increases the GLP-1 receptor-dependent effects and is the basis of the mode of action of the class of blood glucose-lowering drugs called DPP-4 inhibitors. On the other hand, the GLP-1 molecule shortened by the dipeptide seems to have physiologic albeit GLP-1 receptor-independent effects, e.g. at the heart [18]. DPP-4 inhibitors, therefore, shift the effects of the original peptide and the shortened peptide in favor of the original peptide. Whether this shift also impacts the biological action of the shortened peptide is unclear, but might, however, be of importance in the context of a potential link between the use of DPP-4 inhibitors and the occurrence of heart failure.

Meanwhile, it has become apparent that the DPP-4 enzyme splits a multitude of biologically important peptides that exert effects on the heart [18, 19]. An incomplete list of these peptides (the number of the amino acid residues is shown in brackets) summarizes their cardiac effects (other effects are again shown in brackets):

- GLP-1 (**GLP-1 7–36**): increased cardiac function, glucose uptake, decreased contractility, apoptosis (blood vessels: increased NO-production, decreased inflammation)
- B-Type Natriuretic Peptide (**BNP 1–32**): decreased LV-remodeling (blood vessels: increased vasodilatation; kidney: increased natriuresis)
- Substance P (**SP 1–11**): decreased chronotropy and inotropy (brain: altered cardiac adrenergic tone)
- Neuropeptide Y (**NPY 1–36**): increased Ca2+i-voltage
- Peptide YY (**PYY 1–36**): (blood vessels: increased collateral blood flow)
- GLP2 (**GLP-1 1–33**): (blood vessels: increased blood flow, blood pressure and heart frequency)
- Stromal-derived factor 1 alpha (**SDF1 alpha 1–68**): (progenitor cells: increased homing of progenitor cells in ischemic myocardium, increased angiogenesis)

- GIP (**GIP 1–42**): in rodents, receptors detected in the atrium and ventricle (lipogenesis?, but also effects on signal transduction pathways of endothelial cells)

An enhancement of these effects, therefore, could exhibit substantial modulations of heart function, and a connection with the increased occurrence of heart failure cannot primarily be excluded. Our current knowledge of this area of research, however, is rather limited. Studies are certainly warranted about whether circulating concentrations of BNP and their measurement are affected by DPP-4 inhibition, especially in patients with heart failure. In addition, the DPP-4 enzyme splits the basic fibroblast growth factor (bFGF), perhaps anchoring proteins for cytokines within the extracellular matrix (18). Conversely, some of the cleavage products of DPP-4 induced degradation exert profound cardiac effects. They are summarized below:

- **GLP-1 9–36:** increased cardiac function, glucose uptake, decreased apoptosis (blood vessels: increased vasodilatation)
- **BNP 3–32**: (kidney: increased natriuresis)
- **NPY 3–36**: (blood vessels: increased angiogenesis)

Whether these effects might be modified in the context of therapeutic DPP-4 inhibition is again unclear and merits scientific attention. It is also noteworthy in this connection that PYY 3–36 in comparison to PYY 1–36 penetrates the blood brain barrier much more easily and induces anorexic effects in the brain. Moreover, PYY 3–36 represents an anti-secretory and pro-absorptive hormone and regulates the postprandial water and sodium influx into the gut, especially in the ileum and colon [19]. Obviously, therapeutic usage of DPP-4 inhibition might influence a multitude of biological processes in a very complex way, not to mention the various affinities and specificities in regulating signal transduction pathways and partial inhibitory effects of the enzymes DPP-8 and DPP-9. Hence, not only do potential connections with the occurrence of heart failure need further clarification, but also aspects beyond.

Discussion

In aggregate, weighing the evidence in relation to the increased occurrence of heart failure requiring hospitalization while on therapy with saxagliptin, one seems to deal with a previously unknown side effect of a blood glucose lowering DPP-4 inhibitor, as this signal appears to be very consistent and robust in the huge data base of SAVOR-TIMI 53 [13•, 15•]. It is important in terms of clinical relevance, however, that this increased risk for heart failure had no effect on the primary endpoint and by an independent committee adjudicated endpoint which comprised a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [13•]. The NT-pro-BNP concentrations measured in SAVOR should have been unaffected by therapy with the DPP-4 inhibitor and suggest a role of "subclinical" heart failure as a risk factor for the observed side effect. NT-pro-BNP is produced in equimolar

amounts when BNP is generated from pro-BNP. Conversely, it remains to be determined whether the BNP concentrations measured in the VIVIDD trial might have been influenced by the administration of the DPP-4 inhibitor vildagliptin, and if so, whether such an effect might have had an effect on cardiac function [16]. Among a number of effects, BNP is involved in left-ventricular remodeling [18], and an increase of left-ventricular end-diastolic and end-systolic volume was seen in VIVIDD connected with the use of the DPP-4 inhibitor vildagliptin, although the primary endpoint, i.e. the ejection fraction, showed a very similar improvement as in the placebo arm [16].

Potential interactions with ACE inhibitors have also been discussed in the context of possible pathogenic links [20–22]. Paradoxical increases of blood pressure and heart rate have been described at higher doses of ACE inhibitors which might have been induced by interactions with SP1-11 or NPY1-36 [19–22]. Increased concentrations of norepinephrine and signs of enhanced vaso-constrictory effects of angiotensin II have been observed [21, 23, 24]. Vildagliptin has been associated with cardiac arrhythmias in experiments with dogs and an increased number of first degree AV blocks has been noted in humans [25].

At present, however, it has neither been confirmed nor excluded by the results of the VIVIDD as well as the EXAMINE study whether the heart failure findings in SAVOR may represent a class side effect of all DPP-4 inhibitors. A recent meta-analysis has raised new serious concerns. Fifty-nine available prospective and randomized studies evaluating DPP-4 inhibitors for at least 24 weeks have gathered a data base of a total of 36,620 patients with a mean follow-up time of 46.7 weeks [26]. A highly significant increase of heart failure hospitalizations were reported on treatment with DPP-4 inhibitors compared to placebo therapy (n=24,111, RR 1.21, 1.03 – 1.42), whereas no significant differences were found in terms of all-cause mortality, CV mortality, myocardial infarction, or stroke. In comparison to other blood glucose-lowering agents, however, DPP-4 inhibitors showed comparable clinical outcomes including heart failure [26]. Trends in favor of DPP-4 inhibitors regarding all-cause mortality, myocardial infarction, and stroke did not reach the level of significance. These observations are in agreement with 1-year follow-up data of a large German registry, called DiaRegis, enrolling non-insulin requiring patients with type 2 diabetes [27]. Although add-on treatments were at the discretion of the individual physician and were not allocated randomly, patients on new DPP-4 inhibitor therapy as compared to new sulphonylurea therapy exhibited some non-significant trends for lower rates of stroke and unstable angina, like in the meta-analysis, but no difference was noted in terms of heart failure. Conflicting data were also recently reported at the Joint Meeting of the International Society of Endocrinology and the American Endocrine Society [28]. In a retrospective cohort study using the Cleveland Clinic electronic health record system, patients with type 2 diabetes who received a prescription for metformin plus a DPP-4 inhibitor had a significant, albeit small, increased risk for heart failure compared with those who received metformin and other oral antidiabetic agents [28]. In contrast, a large data base of "real world" type 2 diabetic patients obtained at the Joslin Diabetes Center, Boston, did not find an adverse heart failure signal in

patients starting DPP-4 inhibitor therapy, but rather the opposite, i.e. a less frequent rate of heart failure [28].

Thus, in all, important arguments exist at present, not to take the heart failure findings seen in SAVOR-TIMI 53 as unequivocally granted as being indicative for a class side effect of all DPP-4 inhibitors.

Perspectives

Regarding DPP-4 inhibitors and heart failure, the book is not closed yet. The much larger and longer ongoing randomized controlled trials evaluating the DPP-4 inhibitors sitagliptin and linagliptin and looking at hard CV outcomes will probably be key [29, 30]. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) and the Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA), in which more than 20,000 patients with diabetes have been enrolled, are expected to clarify the issue [29, 30]. Finally, likewise, still ongoing large multicenter studies with GLP-1 receptor agonists might contribute new notions on the topic.

Acknowledgments

This activity was supported by an Educational Grant of the Association for the Support of International Scientific Communication in Diabetology e.V., Munich, Germany

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Eberhard Standl, Dr. Michael Erbach, and Dr. Oliver Schnell each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Standl E, Schnell O. A new look at the heart in diabetes mellitus: from ailing to failing. Diabetologia. 2000;43(12):1455–69.
2. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007;28(1):88–136. doi:10.1093/eurheartj/ehl260.

3.•• Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035–87. doi:10.1093/eurheartj/eht108.

most recently updated comprehensive guideline on heart failure & diabetes mellitus.

4. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Early online. Lancet Diabetes Endocrinol. 2014. doi:10.1016/S2213-8587(14)70031-2.

5. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. JAMA. 2005;294(20):2581–6. doi:10.1001/jama.294.20.joc50147.

6. Center for Drug Evaluation and Research. Guidance for industry diabetes mellitus: evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. 2008. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf (accessed May 1, 2014).

7. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457–71. doi:10.1056/NEJMoa072761.

8. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427–43. doi:10.1056/NEJMoa066224.

9. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373(9681):2125–35. doi:10.1016/S0140-6736(09)60953-3.

10. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279–89. doi:10.1016/S0140-6736(05)67528-9.

11. Erdmann E, Charbonnel B, Wilcox RG, Skene AM, Massi-Benedetti M, Yates J, et al. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). Diabetes Care. 2007;30(11):2773–8. doi:10.2337/dc07-0717.

12. Lincoff AM, Tardif JC, Schwartz GG, Nicholls SJ, Rydén L, Neal B, et al. Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus. The AleCardio Randomized Clinical Trial. JAMA. 2014;311(15):1515–25.

13.• Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26. doi:10.1056/NEJMoa1307684.

detailed information on fully published randomized controlled trials on DPP4 inhibitors & heart failure.

14. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35. doi:10.1056/NEJMoa1305889.

15.• Standl E. Saxagliptin, alogliptin, and cardiovascular outcomes. N Engl J Med. 2014;370(5):483. 10.1056/NEJMc1313880#SA1.

detailed information on fully published randomized controlled trials on DPP4 inhibitors & heart failure.

16. McMurray J. The Vildagliptin in Ventricular Dysfunction Diabetes (VIVIDD) trial. Presented at the Heart Failure Congress 2013, Lissabon, Portugal. 2013;99. abstract.

17. Nainggolan L. Heart-failure data for alogliptin prompt more debate at ACC. Medscape. March 31, 2014. Available at http://www.medscape.com/viewarticle/822849 (accessed 14-05-05).

18. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. Endocr Rev. 2012;33(2):187–215. doi:10.1210/er.2011-1052.

19. Parker SL, Balasubramaniam A. Neuropeptide Y Y2 receptor in health and disease. Br J Pharmacol. 2008;153(3):420–31. doi:10.1038/sj.bjp.0707445.

20. Fadini GP, Avogaro A. Cardiovascular effects of DPP-4 inhibition: beyond GLP-1. Vasc Pharmacol. 2011;55(1–3):10–6. doi:10.1016/j.vph.2011.05.001.

21. Marney A, Kunchakarra S, Byrne L, Brown NJ. Interactive hemodynamic effects of dipeptidyl peptidase-IV inhibition and angiotensin-converting enzyme inhibition in humans. Hypertension. 2010;56(4):728–33. doi:10.1161/HYPERTENSIONAHA.110.156554.

22. Jackson EK, Dubinion JH, Mi Z. Effects of dipeptidyl peptidase iv inhibition on arterial blood pressure. Clin Exp Pharmacol Physiol. 2008;35(1):29–34. doi:10.1111/j.1440-1681.2007.04737.x.

23. Jackson EK, Mi Z. Sitagliptin augments sympathetic enhancement of the renovascular effects of angiotensin II in genetic hypertension. Hypertension. 2008;51(6):1637–42. doi:10.1161/HYPERTENSIONAHA.108.112532.

24. Boschmann M, Engeli S, Dobberstein K, Budziarek P, Strauss A, Boehnke J, et al. Dipeptidyl-peptidase-IV

inhibition augments postprandial lipid mobilization and oxidation in type 2 diabetic patients. J Clin Endocrinol Metab. 2009;94(3):846–52. doi:10.1210/jc.2008-1400.

25. Vildagliptin. Arznei-Telegramm 2008; Jg. 39, Nr. 6, 66–67.

26. Krum H, Skiba M, Wu S, Hopper I. Heart failure and dipeptidyl peptidase-4 inhibitors. Eur J Heart Fail. 2014. doi:10.1002/ejhf.90.

27. Gitt AK, Bramlage P, Binz C, Krekler M, Deeg E, Tschope D. Prognostic implications of DPP-4 inhibitor vs. sulfonylurea use on top of metformin in a real world setting - results of the 1 year follow-up of the prospective DiaRegis registry. Int J Clin Pract. 2013;67(10):1005–14.

28. Naingolan L. Conflicting data on sitagliptin and heart failure in diabetes. Medscape 2014, July 1. Available at http://www.medscape.com/viewarticle/827653 (accessed 14-07-02).

29. Green JB, Bethel MA, Paul SK, Ring A, Kaufman KD, Shapiro DR, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. Am Heart J. 2013;166(6):983–9 e7. doi:10.1016/j.ahj.2013.09.003.

30. CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. ClinicalTrials.gov Identifier: NCT01243424 (accessed May 1, 2014)

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES.

Q1. Please check the suggested running page title if appropriate. Otherwise, please provide short running title with maximum of 65 characters including spaces.
Q2. Degree is mandatory. Please provide.
Q3. Please provide complete bibliographic details of this reference.
Q4. Please check if the page range here is correct.