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EDITORIAL

Heart failure and dipeptidyl peptidase-4 inhibitors

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Background

Heart failure is a major co-morbid association of diabetes mellitus. The incidence of heart failure in diabetic vs. control subjects is 2- to 3-fold greater in every decade of life.[1] Similar data on prevalence have also been observed in the Framingham study.[2] Conversely, diabetes represents a major co-morbidity in patients with heart failure. In both clinical trials and registries of heart failure patients, between 24% and 44% have known diabetes mellitus.[3]

A key epidemiological issue in the context of discussion of therapies for diabetes and the associated risk of heart failure is the impact of glycaemic control on heart failure risk. Both UKPDS[4] and a large cohort investigated by Iribarren *et al.*[5] have demonstrated a close positive linear relationship between haemoglobin A_{1c} levels and rate of heart failure development. Specifically, poorest glycaemic control was associated with greatest risk of heart failure. However, studies such as UKPDS demonstrated that more intensive glycaemic control was not associated with reduced development of heart failure.[6] More contemporaneous meta-analyses have supported this observation,[7] albeit potentially driven by drug treatments such as thiazolidinediones which may contribute to heart failure development.

Cardiovascular actions of dipeptidyl peptidase-4 inhibitors

Based on pre-clinical and early clinical work, dipeptidyl peptidase-4 (DPP-4) inhibitors should, in theory, have beneficial rather than adverse effects on progression of LV remodelling and therefore delay development of symptomatic heart failure[8] (*Figure 1*).

Dipeptidyl peptidase-4 is involved in the enzymatic breakdown of glucagon-like peptide (GLP)-1; thus, DPP-4 inhibition augments circulating GLP-1 levels, which appears to have beneficial effects upon the heart in animal models as well as in the post-myocardial infarction and established heart failure settings in man.[9] DPP-4 stimulates activation of proinflammatory cytokines,[9] independent drivers of progression of LV systolic dysfunction due to their prohypertrophic and profibrotic effects.[10]

Inhibition of DPP-4 augments circulating levels of soluble-derived factor (SDF)-1 α,[9] a stimulant of bone marrow production of erythroid precursor cells, which should contribute to improved vascular and myocardial function. Finally, DPP-4 inhibition should direct BNP metabolism towards an increase in active BNP rather than biologically inactive BNP precursor fragments.[9]

Pre-clinical studies with DPP-4 inhibitors in animal models of LV systolic dysfunction[11] support a beneficial effect on LV remodelling and survival in comparison with controls.

Major outcome trials with dipeptidyl peptidase-4 inhibitors

Published and ongoing major cardiovascular outcome trials with DPP-4 inhibitors are summarized in *Table 1*. Three major DPP-4 inhibitor trials have recently reported, all with implications for heart failure, and these are examined in greater detail below.

SAVOR-TIMI 53

The SAVOR-TIMI 53 trial compared the DPP-4 inhibitor, saxagliptin, with placebo in the setting of patients with a history of, or who are at risk of, cardiovascular events.[12] There was no overall effect of saxagliptin vs. placebo on the primary endpoint of time to first event of cardiovascular death, myocardial infarction, or ischaemic stroke. However, patients in the saxagliptin group were more likely to be hospitalized for heart failure than those in the placebo group [3.5 vs. 2.8%, hazard ratio (HR) 1.27, 95% confidence interval (CI) 1.07–1.51, $P = 0.007$]. A Kaplan–Meier plot of accrual of heart failure hospitalizations over time showed an early divergence of the curves which continued to diverge slightly beyond the first 180 days of treatment.[13]

A Forrest plot of key baseline variables that may influence risk of heart failure hospitalization according to treatment did not

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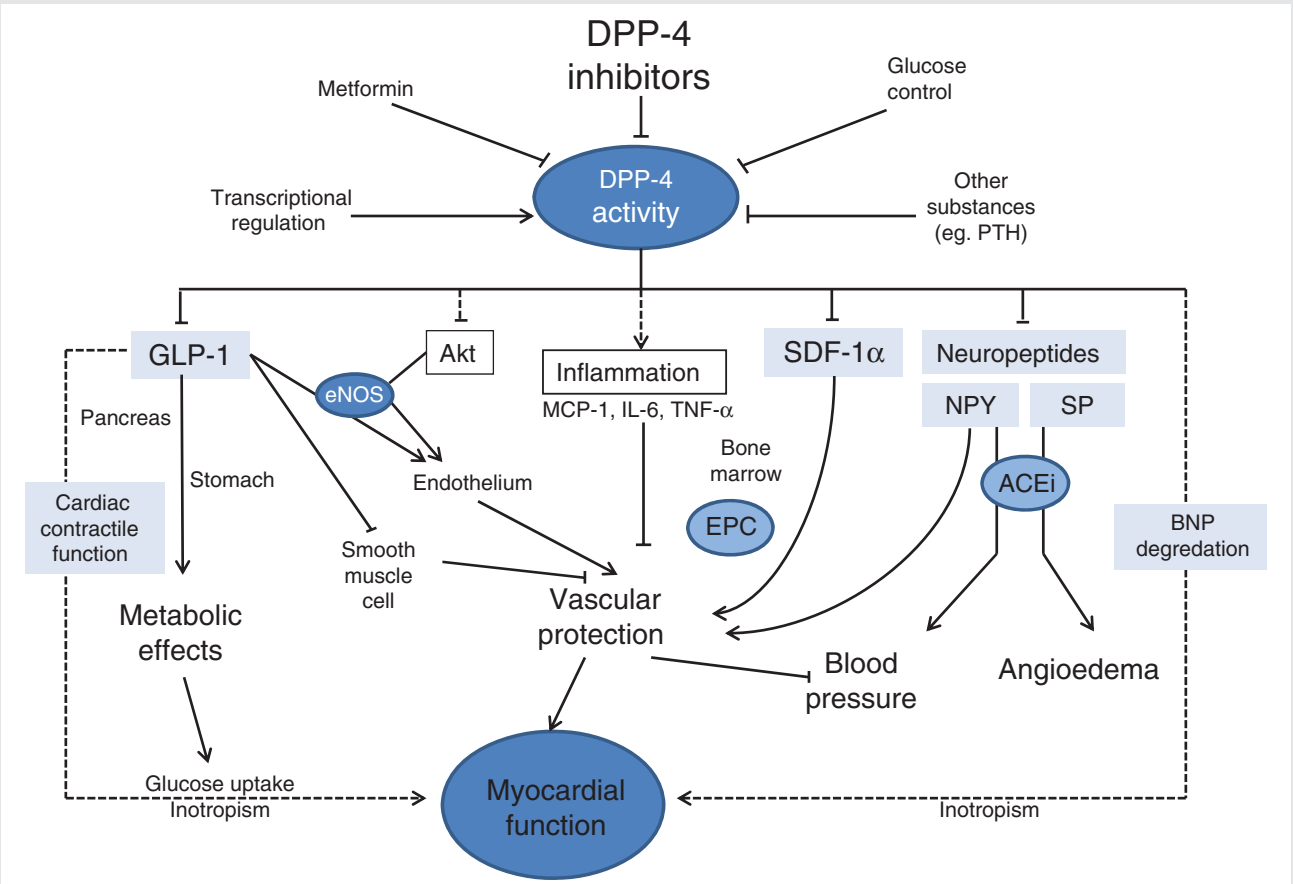

Figure 1 Cardiovascular actions of dipeptidyl peptidase-4 (DPP-4) and DPP-4 inhibitors. In the context of heart failure, these include glucagon-like peptide (GLP) and eNOS (endothelial nitric oxide synthase) metabolism, activation of proinflammatory cytokines, inhibition of soluble-derived factor-1 α (SDF-1α)-mediated endothelial progenitor cell (EPC) production, breakdown of neuropeptide Y (NPY) and substance P (SP), as well as conversion of BNP to inactive fragments. Adapted from: Fadini GP, Avogaro A. Cardiovascular effects of DPP-4 inhibition: beyond GLP-1. *Vascul Pharmacol* 2011;55:10–16.[9]

demonstrate any heterogeneity, with all pre-defined subgroups trending towards an excess of primary endpoint events with saxagliptin vs. placebo. One exception may be baseline plasma NT-proBNP levels. In those patients within the highest BNP quartile (333–46627 pg/mL), 10.9% of saxagliptin and 8.9% of placebo patients had a hospitalization for heart failure ($P = 0.024$).

EXAMINE

The EXAMINE study assessed the DPP-4 inhibitor, alogliptin, in patients who had recently had an acute coronary syndrome.[14] As with saxagliptin in SAVOR, there was no significant effect of this class on the primary endpoint (death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke). In EXAMINE, 3.9% of alogliptin-treated and 3.3% of placebo-treated patients had a hospitalization for heart failure (HR 1.19, 95% CI 0.89–1.58, $P = $ NS).[15] This was a pre-defined exploratory endpoint that was independently adjudicated.

In EXAMINE, 28% of patients had a history of congestive heart failure at baseline. The primary EXAMINE endpoint was reduced with alogliptin vs. placebo, HR 0.82, $P = 0.20$[15], in these patients. Data on recurrent heart failure hospitalizations within this subgroup have not as yet been reported.

VIVIDD

The Vildagliptin In Ventricular Dysfunction Diabetes (VIVIDD) trial has been presented[16] but not yet published. All patients in VIVIDD had evidence of symptomatic systolic heart failure with an LVEF <35% as well as diabetes requiring glucose-lowering therapy. There was no difference in adjudicated heart failure events between vildagliptin ($n = 128$, 18%) and placebo ($n = 125$, 17.6%) patients over the 52 weeks of the study.

The primary endpoint of the VIVIDD study was change in LVEF, with no difference observed between treatment groups (+0.54, 95% CI −1.97 to 3.06, $P = 0.67$). Interestingly, plasma BNP levels were reduced in both groups: vildagliptin, ratio of 0.72 vs. baseline; placebo, 0.86 vs. baseline. Somewhat surprisingly, LV diastolic and systolic volumes were both increased with vildagliptin compared with placebo.

Table 1 Recent and ongoing major placebo-controlled dipeptidyl peptidase-4 inhibitor cardiovascular trials

Trial	DPP-4 inhibitor	Patient population	Primary CV efficacy endpoint	Key findings	HF effects
SAVOR-TIMI 53[12]	Saxagliptin	T2DM, established CVD, or multiple CV risk factors ($n = 16\,492$)	CV death, MI, or ischaemic stroke	Not superior, HR 1.00 (0.89–1.12) Met non-inferiority criteria	↑HF hospitalization with saxagliptin (3.5% vs. 2.8%)
EXAMINE[14]	Alogliptin	T2DM, AMI, or UAP requiring hospitalization in previous 15–90 days ($n = 5380$)	CV death, non-fatal MI, non-fatal stroke	Not superior, HR 0.96 (–1.16) Met non-inferiority criteria	↑HF hospitalization with alogliptin (3.9% vs. 3.3%)
VIVIDD[16]	Vildagliptin	T2DM, systolic chronic HF ($n = 254$)	Change in LVEF	No change in LVEF (non-inferior) Non-significant ↓BNP, ↑LV volume with vildagliptoin vs. PBO	No ↑in adjudicated worsening HF with vildagliptin (18% vs. 17.6%)
TECOS	Sitagliptin	T2DM, >50 years, documented CVD ($n = 14\,000$)	CV death, non-fatal MI, non-fatal stroke, hospitalization for UAP	Study ongoing	Study ongoing
CARMELINA	Linagliptin	T2DM, previous CV complications, albuminuria, CKD ($n = 8000$)	CV death; non-fatal MI, CVA, hospitalization for UAP (+ renal co-primary endpoint)	Study ongoing	Study ongoing

AMI, acute myocardial infarction; CKD, chronic kidney disease; CV, cardiovascular; CVA, cerebrovascular accident; CVD, cardiovasular disease; DPP-4, dipeptidyl peptidase-4; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; PBO, placebo; T2DM, type 2 diabetes mellitus; UAP, unstable angina pectoris.

Dipeptidyl peptidase-4 inhibitor meta-analysis

Our group recently performed a meta-analysis of heart failure outcomes with DPP-4 inhibitors, including the above studies. Forest plots of these data, comparing DPP-4 inhibitor with placebo and an active comparator, are shown in *Figure 2*. A sensitivity analysis was also undertaken, with thiazolidenediones included and excluded as comparator. With thiazolidenediones included, the risk ratio for heart failure with DPP-4 inhibitors was 0.80, 95% CI 0.35–1.81, $P = 0.59$. With thiazolidenediones removed as comparator, the risk ratio for heart failure was 1.15, 95% CI 1.00–1.33, $P = 0.04$.

Mechanisms underlying dipeptidyl peptidase-4 inhibitor-related increases in heart failure

It is not entirely certain whether DPP-4 inhibitors directly or even indirectly cause heart failure, but if one accepts the premise that this is the case, then a number of potential explanations need to be considered.

Play of chance

It is entirely plausible that the increase in heart failure events observed, particularly in SAVOR,[12] represents the play of chance. There is a long history of 'play of chance' influencing cardiovascular trials. This is particularly true of subgroup analysis, but would equally apply to analysis of 'off-target' effects of drugs.[17] Nevertheless, there are hints with DPP-4 inhibitors that this may not be the case, especially given the numerical increase in events in EXAMINE[14] and the odd remodelling effects of vildagliptin in VIVIDD.[16] Furthermore, there was an excess (not significant) of all-cause mortality events with vildagliptin amongst patients in VIVIDD.[24]

Imbalance between groups

Although SAVOR and EXAMINE were large trials and baseline characteristics appear to be well balanced, it is certainly possible that there were imbalances at baseline between groups, which may have led to an increase in risk of heart failure hospitalization with the DPP-4 inhibitor. Specifically, there may be imbalances in background medications that are known to retard heart failure progression, such as ACE inhibitors. It would certainly be prudent to look at the patients who did have a heart failure hospitalization to see if there are baseline imbalances within this specific subgroup.

Excess hypoglycaemia with dipeptidyl peptidase-4 inhibitors

Hypoglycaemia stimulates the sympathetic and renin–angiotensin–aldosterone systems and, thus, with chronic stimulation, may have adverse consequences including progression to symptomatic heart failure. However, the increase in rates of hypoglycaemia in both SAVOR and EXAMINE were very modest compared with the placebo group. An increase in relative risk for hypoglycaemia with saxagliptin in SAVOR was noted in patients on background sulfonylureas.[12] However, when this subgroup was examined, there was no increase in risk of heart failure hospitalization with saxagliptin.[13] Similarly, in EXAMINE, differences in hypoglycaemia were very minor between the alogliptin and placebo groups.[14]

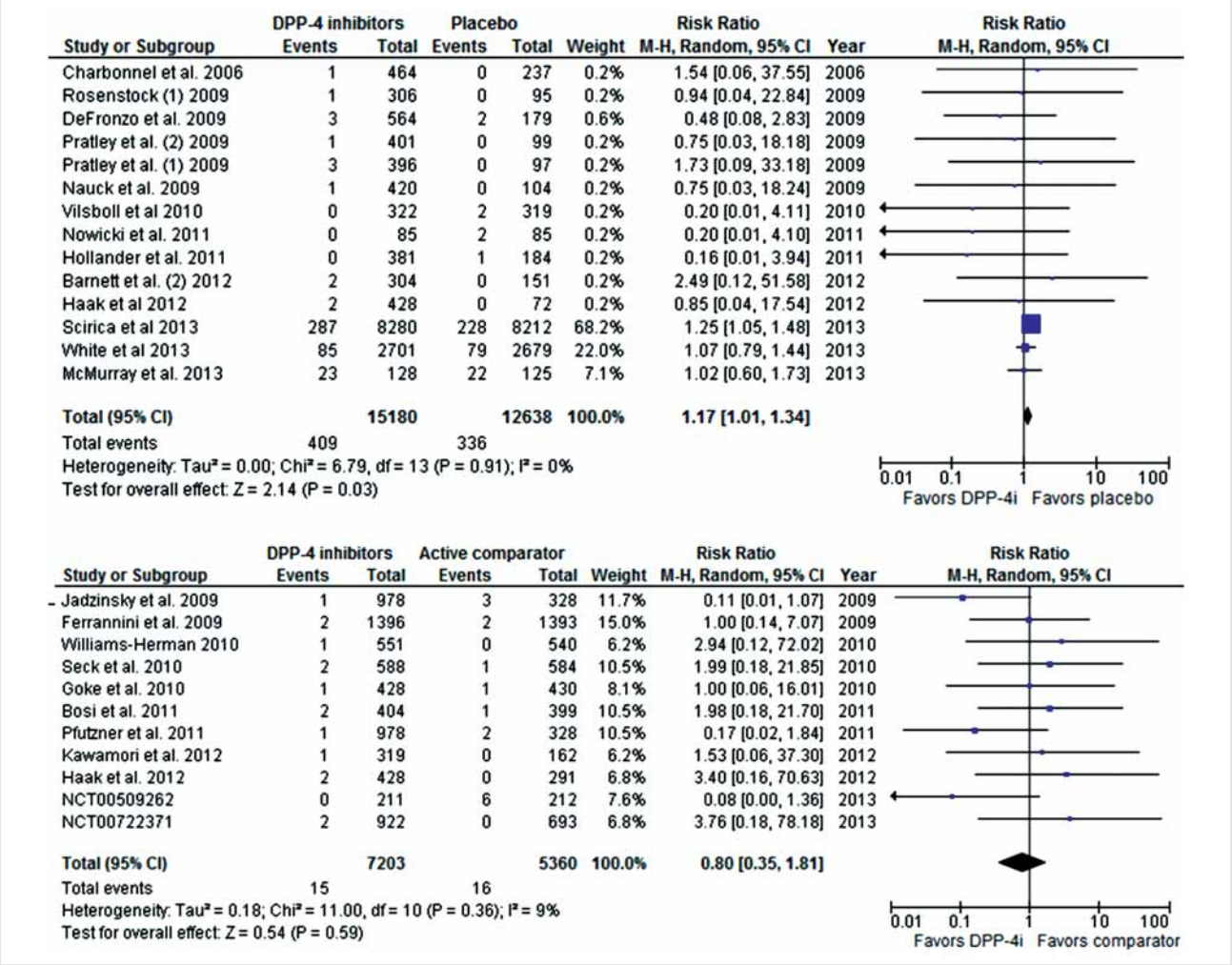

Figure 2 Forest plots of risk of heart failure with dipeptidyl peptidase-4 (DPP-4) inhibitors in trials vs. placebo (top panel) and active (lower panel) comparators. CI, confidence interval.

Interaction with angiotensin-converting enzyme inhibitors/vasoconstrictor effects

Marney *et al.*[18] suggested that sitagliptin interacted with high-dose enalapril to increase rather than decrease blood pressure levels in metabolic syndrome patients. This was associated with an increase in heart rate and plasma norepinephrine levels that was significant at the highest dose of enalapril. The mechanisms underlying this interaction are unclear but may relate to blockade of the peptides substance P and/or neuropeptide Y with DPP-4 inhibitors, leading to sympathetically mediated vasoconstriction. Similarly, Jackson *et al.*[19] demonstrated that, in a renal perfusion model, enhancement of angiotensin II-mediated constrictor responses due to increasing neuropeptide Y administration could be exacerbated by sitagliptin and blocked if sitagliptin is given with a neuropeptide Y inhibitor.

If the above are correct, then attention to heart rate and blood pressure responses in the major DPP-4 outcome trials would be of considerable interest. However, an analysis of earlier, much smaller saxagliptin studies[20] suggested that (either as monotherapy or in combination) there was little impact on blood pressure with the DPP-4 inhibitor in comparison with placebo or metformin.

Discussion

The recent major DPP-4 inhibitor outcome studies have raised the hypothesis that heart failure may be precipitated and/or exacerbated with the use of these agents in the management of patients with diabetes. This is surprising given that preceding DPP-4 inhibitor data suggested potential for theoretical benefit with regard to HF, on the basis of the mechanisms outlined above.[8,9] This may represent play of chance and/or imbalances across study groups, but, if real, mechanisms urgently need to be elucidated.

Until more data are available, guideline recommendations should be followed, but undoubtedly greater vigilance should be applied to recognizing the development of clinically significant HF in DPP-4 inhibitor-treated patients, including careful clinical assessment of

heart failure symptoms and signs, together with (as required) ancillary objective assessments of heart failure status including measurement of plasma BNP levels and echocardiography.

Two large-scale, placebo-controlled outcome trials, TECOS (with sitagliptin) and CARMELINA (with linagliptin), are due to report in the next few years, which should provide important data to support or refute the above hypothesis. In the meantime, a mechanistic explanation for this potential link should be further explored.

Conflict of interest: none declared.

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