Original Article
Cardiovascular safety of dipeptidyl peptidase-4 inhibitors: recent evidence on heart failure

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Abstract: The cardiovascular safety of DPP4 inhibitors as a class, especially in regards to heart failure, has been questioned after the publication of first trials (SAVOR-TIMI 53 and EXAMINE) assessing the cardiovascular risks of DPP4 inhibitors alogliptin and sitagliptin in 2013. Although there were no increased risks in composite cardiovascular outcomes, the SAVOR-TIMI 53 trial reported a 27% increase in hospitalization for heart failure in diabetic patients who received the DPP4 inhibitor saxagliptin. There has been substantial increase in knowledge on the heart failure effect of DPP4 inhibition since 2013. This review will summarize the role of the DPP4/incretin axis in heart failure and discuss the findings from recent large scale clinical trials assessing the effects of DPP4 inhibitors on heart failure.

Keywords: DPP4, incretin, heart failure, cardiovascular outcomes

Introduction

Dipeptidyl peptidase-4 (DPP4) inhibitors are a novel class of oral anti-diabetic agents. The first two large clinical trials assessing the cardiovascular safety of DPP4 inhibitors (EXAMINE and SAVOR-TIMI 53) suggest DPP4 inhibitors are safe from a cardiovascular perspective. Both alogliptin and saxagliptin neither increase nor decrease the risk of cardiovascular disease [1, 2]. However, the SAVOR-TIMI 53 trial reported a 27% increase in hospitalization for heart failure in diabetic patients who received saxagliptin, raising concern of DPP4 inhibitors in heart failure. Outcomes with respect to heart failure were not mentioned in the initial report of the EXAMINE trial by White et al., although 28% of patients had congestive heart failure at baseline. Two other trials assessing cardiovascular outcomes of incretin-based drugs (sitagliptin and lixisenatide) were recently completed [3, 4]. In addition, the heart failure data of EXAMINE trials was also reported last year. In this review, we will summarize the role of the DPP4/incretin axis in heart failure and discuss the findings from recent large scale clinical trials assessing the effects of DPP4 inhibitors on heart failure.

Diabetes as a risk factor for heart failure

Type 2 diabetes has been associated with increased risk for heart failure [5-7]. Almost 50% of patients with type 2 diabetes develop heart failure, and those with both diabetes and established heart failure have more severe outcomes [8, 9]. This is largely due to type 2 diabetes' ability to accelerate coronary artery disease. Diabetic patients are more likely to develop coronary artery atherosclerosis at an early stage and affect distal coronary segments [5, 10]. Patients with diabetes develop fewer collateral vessels in response to ischemia [11], and this can be attributed to impaired production or responsiveness to angiogenic growth factors [12]. In addition, hypertension, dilated cardiomyopathy and extracellular fluid volume expansion are also important pathogenic factors for the development of heart failure in individuals with diabetes [13-15].

Anti-diabetic drugs and heart failure

Diabetes has been widely regarded as a major risk factor for cardiovascular disease, with doubled cardiovascular risk in patients with diabetes [16-18]. Interestingly, a large scale clinical

trial in 2008 suggested intensive glycemic control increase, rather than decreased cardiovascular mortality in patients with diabetes (Hazard ratio: 1.35; 95% CI: 1.04-1.76; p = 0.02) [19]. The Food and Drug Administration (FDA) therefore recommends manufacturers to assess cardiovascular safety for all new anti-diabetic drugs.

The cardiovascular side effects of anti-diabetic drugs are believed to be an important reason for the increased heart failure risk in intensive glycemic control patients. Most of the currently available oral anti-diabetic drugs have more or less shown adverse cardiovascular side effects. In addition to DPP4 inhibitors, commonly used oral anit-diabetes agent categories include biguanides, thiazolidinediones, and sulfonylureas.

Metformin is the most commonly used biguanide for the treatment of diabetes. It decreases hepatic glucose production, improves glucose uptake and utilization, and improves insulin sensitivity [20]. Metformin has been contraindicated in diabetic patients with heart failure because it may increase the risk of lactic acidosis [21-23]. However, later studies demonstrated that metformin is safe and may be associated with lower morbidity and mortality in diabetic patients with established heart failure when compared to other diabetic therapy, although no placebo-controlled large scale trials on heart failure are available [24, 25].

Thiazolidinediones, such as rosiglitazone and pioglitazone, enhance insulin sensitivity by activating nuclear peroxisome proliferator activated receptor γ (PPAR-γ). However, they have been associated with both fluid retention and increased risk for heart failure [26, 27]. The use of rosiglitazone has been reported to cause diabetic macular edema-related vision lost in several cases [28, 29] and it increases the risk of fractures in women [30]. In a study involving 30 diabetic patients who used pioglitazone or rosiglitazone and had both lower extremity edema and macular edema, Ryan et al. reported that thiazolidinedione use may be the cause of fluid retention in certain patients and that drug cessation could result in rapid resolution of both peripheral and macular edema [31]. Moreover, in 2007 Nissen and Wolski [32] found that rosiglitazone was associated with an increased risk of myocardial infarction and a

borderline increased risk of cardiovascular death, although this finding could not be confirmed in an interim analysis of the RECORD study (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of glycaemia in Diabetes; a company-sponsored clinical trial evaluating cardiovascular outcomes of rosiglitazone) at that time [33]. Analysis of other recent studies by the European Medicines Agency (EMA)'s Committee for Medicinal Products for Human Use (CHMP) also suggests an increased risk of cardiovascular diseases in rosiglitazone users [34-37].

Sulfonylureas such as glipizide, glyburide, and glimepiride have been widely used for hypoglycemic management of type 2 diabetes. Clinical evidence has shown that sulfonylurea treatment increases the risks of heart failure [38, 39]. Compared to metformin, the 2nd generation sulphonylureas (glipizide, gliquidone, glimepiride, glibenclamide, and gliclazide) increased the risk of developing congestive heart failure by 18% (hazard ratio, 95% CI: HR 1.18, 1.04-1.34) in a retrospective cohort study involving 91,521 diabetic patients in the UK. All-cause mortality also increased in patients treated with either 1st or 2nd generation sulphonylureas [38]. In another study following 4,902 diabetic women for a mean duration of 11 years, Li et al. reported that sulfonylurea increased the risks of coronary heart disease and a longer duration of sulfonylurea use was associated with a higher risk of coronary heart disease [40]. Furthermore, metformin/sulfonylurea combination therapy increased the risk of coronary heart disease by 3.27-fold compared with users of metformin monotherapy (relative risk, 95% CI: 3.27, 1.31-8.17) [40]. Patients treated with high-dose sulfonylurea also showed higher risks for heart failure than those with low-dose sulfonylurea [39]. These results suggest sulfonylureas dose-dependently and time-dependently increase the risk of heart failure.

DPP4 and incretin hormones in diabetes

DPP4 is an enzyme that cleaves N-terminal dipeptides from proteins with alanine, proline or serine at the penultimate position. It is widely expressed in a variety of cell types including T cells, macrophages, dendritic cells, adipocytes, hepatocytes, endothelial cells and epithelial cells [41, 42]. The substrates of DPP4

Table 1. Completed cardiovascular outcome trials for DPP4 inhibitors and GLP-1R agonist

Study	Drug (Sponsor)	Phase	Study Design	Duration (weeks)	Intervention Arms Dosage (N)+	Hazard Ratio, 95% CI, (*p* value)
DPP4 Inhibitors						
SAVOR-TIMI 53	Saxagliptin (AstraZeneca)	4	RCT/DB	104	Saxagliptin 5 mg or 2.5 mg (8280) Placebo (8212)	1.00, 0.89-1.12, (0.99)
EXAMINE	Alogliptin (Takeda)	3	RCT/DB	160	Alogliptin 25/12.5/6.25 mg (2701) Placebo (2679)	0.96, 1.16*, (0.32)
TECOS	Sitagliptin (Merck Sharp & Dohme Corp.)	3	RCT/DB	156	Sitagliptin 100 mg or 50 mg (7332) Placebo (7339)	0.98, 0.88-1.09, (NS)
GLP-1 Receptor Agonists						
ELIXA	Lixisenatide (Sanofi)	3	RCT/DB	108	Lixisenatide 10-20 µg (3034) Placebo (3034)	1.02, 0.89-1.17, (NS)

DB, double blind; NS, not significant; RCT, randomized control trial; *, the upper boundary of the one-sided repeated confidence interval, at an alpha level of 0.01.

include various regulatory peptides (eg. glucagon-like peptide-1 [GLP-1], GLP-2, gastric inhibitory polypeptide [GIP], etc), chemokines/cytokines (eg. stromal cell-derived factor 1 [SDF-1], eotaxin, RANTES, GM-CSF, interleukin-3 [IL-3], etc), and neuropeptides (eg. neuropeptide Y, peptide YY, etc). Cleavage of N-terminal dipeptides by DPP4 changes the bioactivity of its substrates. In addition to its enzymatic activity, DPP4 also interacts with many ligands. For example, it provides co-stimulatory signals to T cells via interacting with adenosine deaminase (ADA) and it also serves as the entry protein for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) by interacting with spike protein located on the envelope of the virus [43-46].

Incretin hormones, such as Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are short peptide hormones secreted by the gut in response to nutrients. GLP-1(7-36), the active form of GLP-1, is secreted by L cells located in the ileum and colon, while GIP is secreted by intestinal K cells which are located in the proximal small intestine. These incretin hormones are released into circulation within minutes of meal ingestion and promote insulin secretion by activating their receptors located on the pancreatic β cells. Incretin-receptor activation leads to glucose-induced insulin secretion and stimulates β-cell proliferation. GLP-1 also induces glucose-dependent inhibition of glucagon, promotes satiety, and delays gastric emptying, which are responsible for the weight loss observed from persistent use of GLP-1 analogs. GIP also promotes adipose tissue energy storage and augments bone formation by stimulating osteoblast proliferation. Both GLP-1(7-36) and GIP(1-42), the active forms of GLP-1 and GIP respec-

tively, are rapidly degraded by DPP4, resulting in very short half-lives (minutes long) in vivo [47, 48]. DPP4 inhibitors and DPP4 resistant GLP-1R agonists are increasingly used in clinic as anti-diabetic drugs due to their weight neutral/weight loss effect, and good safety and tolerability profiles [42, 49]. DPP4 inhibitors are a novel class of oral anti-diabetic drugs. Since the first DPP4 inhibitor, sitagliptin, was approved by FDA in 2006, 8 more DPP4 inhibitors have entered the market for the treatment of diabetes: three approved by the FDA (saxagliptin, linagliptin, and alogliptin), one approved by the EU (vildagliptin), and four approved in Japan (anagliptin, teneligliptin, trelagliptin, and omarigliptin). DPP4 inhibitors have modest effects on glycemic control, resulting in a 0.2-0.8% reduction in glycated hemoglobin (HbA1c) [50-52].

Clinical trials on DPP4 inhibitors and heart failure

DPP4 inhibitors have been increasingly used in clinic due to a low incidence of hypoglycemia, and weight neutrality. Although animal studies suggest a beneficial effect of DPP4 inhibition on cardiovascular disease, their cardiovascular safety, especially in regards to heart failure of DPP4 inhibitors as a class, has been questioned after the completion of the first of two large clinical trials (EXAMINE and SAVOR-TIMI 53) assessing the cardiovascular risks of DPP4 inhibitors [1, 2]. While both trials showed no increased risks in composite cardiovascular outcomes (**Table 1**), the SAVOR-TIMI 53 trial reported a 27% increase in hospitalization for heart failure, without excess heart failure related mortality, among diabetic patients who received saxagliptin as compared with those

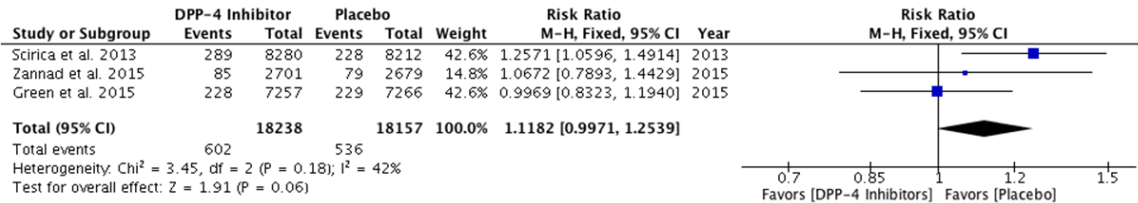| Study or Subgroup	DPP-4 Inhibitor Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Scirica et al. 2013	289	8280	228	8212	42.6%	1.2571 [1.0596, 1.4914]	2013
Zannad et al. 2015	85	2701	79	2679	14.8%	1.0672 [0.7893, 1.4429]	2015
Green et al. 2015	228	7257	229	7266	42.6%	0.9969 [0.8323, 1.1940]	2015
Total (95% CI)		18238		18157	100.0%	1.1182 [0.9971, 1.2539]	
Total events	602		536				

Heterogeneity: Chi² = 3.45, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 1.91 (P = 0.06)

Figure 1. Effects in trials of incretin therapies on heart failure hospitalization. The risk ratios are given for DPP4 inhibitors versus placebo. The diamond indicates the overall risk and 95% CI for heart failure hospitalization.
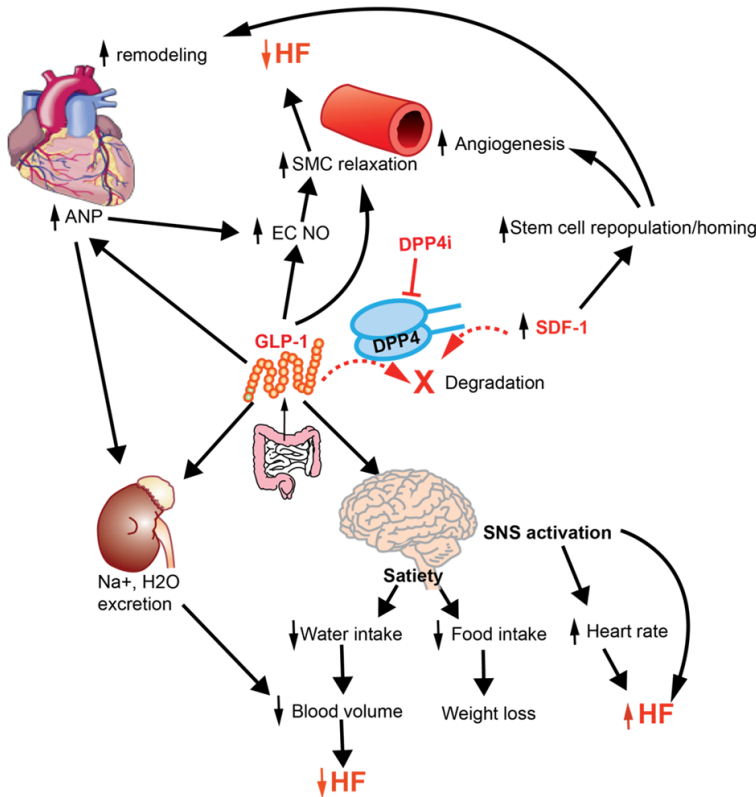

Figure 2. Cardiovascular Effects of DPP4 inhibition. DPP4 inhibition modulates cardiovascular function by preserving GLP-1 and SDF-1. ANP, Atrial natriuretic peptide; EC, endothelial cell; GLP-1, glucagon-like peptide-1; HF, heart failure; NO, nitric oxide; SDF-1, stromal cell-derived factor 1; SMC, smooth muscle cell; SNS, sympathetic nervous system.

who received placebo (3.5% vs. 2.8%; hazard ratio, 95% CI: 1.27, 1.07-1.51; P = 0.007). In a later analysis, findings suggested that previous history of heart failure, eGFR<60 ml/m, elevated BNP and albumin/creatinine ratio were the strongest predictors of heart failure hospitalization [53]. Outcomes with respect to heart failure were not mentioned in the initial report of EXAMINE trial by White et al., although 28% of patients had congestive heart failure at baseline. There have been two other large scale trials, one on DPP4 inhibitor sitagliptin (TECOS) and one on GLP-1R agonist lixisenatide (ELIXA), which reported the cardiovascular outcomes of these two drugs including effects on heart failure hospitalization in 2015 [3, 4]. There was no excess heart failure risk noted with sitagliptin or lixisenatide. In TECOS, the hospitalization rate for heart failure was identical with sitagliptin and placebo (3.1 vs. 3.1%; HR, 1.00, 0.83-1.20; P = 0.98). Randomized controlled clinical trial evidence for lixisenatide also showed similar heart failure hospitalization rates compared to placebo (HR = 0.96; 95% CI, 0.75-1.23). In addition to these two trials completed this year, the EXAMINE group also published heart failure hospitalization data earlier this year [54]. First occurrences of heart failure hospitalization for alogliptin and placebo groups were 3.1 and 2.9% respectively (HR 1.07, 0.79-1.46, p = 0.68). Further investigation is still needed to conclude if there is an excess heart failure risk in DPP4 inhibition therapy as there is a marginal effect based on currently available trials (overall risk 1.12, 0.99-1.25; P = 0.06, **Figure 1**). However, it must be noted that the weight of SAVOR-TIMI 53 trial is over 40% in this analysis. The heart failure effects of gliptins and GLP-1R agonists need further confirmation in ongoing cardiovascular outcome trials, including two trials on linagliptin and several trials on incretin therapies.

Possible cardiovascular mechanisms of DPP4 inhibition in heart failure

GLP-1R is widely expressed in cardiovascular system such as endothelium, vascular smooth muscle, and cardiac atrium [55, 56]. GLP-1R activation on endothelial cells has been shown to be able to increase cAMP, followed by the activation of Protein kinase A (PKA) and endothelial nitric oxide synthase (eNOS) [57]. The activation of eNOS subsequently results in the release of nitric oxide (NO) and vessel relaxation. Studies in humans also confirmed the vasodilatory effect of GLP-1 [58, 59]. GLP-1 analogs are also able to reduce blood pressure by increasing urinary sodium excretion [60], promoting Atrial natriuretic peptide (ANP) release from atrium [61], and relaxing vascular smooth muscle cells [62]. The activation of GLP-1R in the central nervous system induces satiety and thus reduces body weight and cardiovascular risk [63]. In addition to enhancing GLP-1 effect, DPP4 inhibitors also increases SDF-1, a chemoattractant for many types of hematopoietic cells including cardiac stem cells, endothelial progenitor cells, and mesenchymal stem cells [64]. Preservation of SDF-1 by DPP4 inhibition enhances chemotaxis and repopulation ability of hematopoietic progenitor cells and stem cells, increasing the neovascularization of injured tissues [65-69].

However, GLP-1R activation has also been shown to increase heart rate and blood pressure by activating sympathetic nervous system [70]. A recent study also showed DPP4 inhibitor MK-0626 impaired cardiac function accompanied by modest cardiac hypertrophy, while genetic DPP4 deficiency improved cardiac function after transverse aortic constriction surgery [71], suggesting drug related unspecific effects may play a role in cardiac function. Therefore, DPP4 inhibition modulates cardiovascular function by mechanisms involving multiple organs (**Figure 2**).

Conclusions

The cardiovascular safety, especially in regards to heart failure, of DPP4 inhibitors has gained much attention since 2013. The heart failure assessments on three out of the four FDA-approved DPP4 inhibitors showed saxaglitpin, but not alogliptin and sitagliptin, may increase the risks of heart failure. These results suggest this might not be a class effect of all DPP4 inhibitors. Furthermore, meta-analysis of these 3 trials indicates a marginal effect on hospitalization rate for heart failure. Further investigations are required to come to a conclusion on whether DPP4 inhibition may result in increased risk of heart failure.

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Disclosure of conflict of interest

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