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STATE-OF-THE-ART REVIEW

Worsening Heart Failure During the Use of DPP-4 Inhibitors

Pathophysiological Mechanisms, Clinical Risks, and Potential Influence of Concomitant Antidiabetic Medications

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ABSTRACT

Although dipeptidyl peptidase (DPP)-4 inhibitors have been reported to have a neutral effect on thromboembolic vaso-occlusive events in large-scale trials, they act to potentiate several endogenous peptides that can exert deleterious cardiovascular effects. Experimentally, DPP-4 inhibitors may augment the ability of glucagon-like peptide-1 to stimulate cyclic adenosine monophosphate in cardiomyocytes, and potentiation of the effects of stromal cell–derived factor-1 by DPP-4 inhibitors may aggravate cardiac fibrosis. These potentially deleterious actions of DPP-4 inhibitors might not become clinically apparent if these drugs were to promote sodium excretion. However, the natriuretic effect of DPP-4 inhibitors is modest, because they act on the distal (rather than proximal) renal tubules. Accordingly, both clinical trials and observational studies have reported an increase in the risk of heart failure in patients with type 2 diabetes who were receiving DPP-4 inhibitors. This risk may be muted in trials with a high prevalence of metformin use or with low and declining background use of insulin and thiazolidinediones. Still, the most vulnerable patients (i.e., those with established heart failure) were not well represented in these studies. The only trial that specifically evaluated patients with pre-existing left ventricular dysfunction observed important drug-related adverse structural and clinical effects. In conclusion, an increased risk of worsening heart failure appears to be a class effect of DPP-4 inhibitors, even in patients without a history of heart failure. Additional clinical trials are urgently needed to elucidate the benefits and risks of DPP-4 inhibitors in patients with established left ventricular dysfunction. (J Am Coll Cardiol HF 2018;6:445–51)

Because of their ease of use and tolerability, dipeptidyl peptidase (DPP)-4 inhibitors are commonly prescribed to lower blood glucose in patients with type 2 diabetes, particularly as an adjunct to first-line therapy with metformin (1,2). Unlike other agents that signal through the incretin pathway (i.e., long-acting glucagon-like peptide [GLP]-1 analogs), DPP-4 inhibitors do not require parenteral administration, and their use is associated with fewer gastrointestinal adverse effects (1). Unlike older antidiabetic drugs, the use of DPP-4 inhibitors is not accompanied by weight gain and carries a low risk of hypoglycemia (2). In contrast to sodium-glucose transporter 2 (SGLT2) inhibitors, DPP-4 inhibitors do not increase the risk of genitourinary infections or have adverse effects on lipid metabolism. Taken together, these features have contributed to the popularity of DPP-4 inhibitors among practitioners who treat patients with type 2 diabetes.

However, DPP-4 inhibitors may precipitate heart failure in patients at increased cardiovascular risk or may worsen the clinical course in patients with pre-existing left ventricular dysfunction. Heart failure is the most important and preventable macrovascular

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ABBREVIATIONS AND ACRONYMS

AMP = adenosine monophosphate

DPP = dipeptidyl peptidase

GLP = glucagon-like peptide

SDF = stromal cell-derived factor

SGLT2 = sodium-glucose transporter 2

complication of diabetes; diabetes and heart failure frequently coexist, and the clinical courses of the 2 disorders often progress in parallel (3). Given the clinical overlap between these 2 disorders, it is relevant to ask, Is worsening heart failure a class effect of DPP-4 inhibitors? Can patients with both diabetes and heart failure be treated safely with this class of drugs? In this article I describe the pathophysiological pathways that may be relevant to the use of DPP-4 inhibitors in patients with known or clinically inapparent left ventricular dysfunction, critically examine the findings of randomized clinical trials and community-based observational studies, and identify important concerns that warrant urgent attention in future research.

EXPERIMENTAL ACTIONS OF DPP-4 INHIBITORS THAT ARE RELEVANT TO HEART FAILURE

DPP-4 inhibitors are incretins that lower blood glucose because of their ability to augment the release of insulin from the pancreas (1). Experimentally, potentiation of insulin signaling can cause adverse cardiac remodeling, deleterious effects on vascular structure and function, and sodium retention by the kidney (4–6). These pathophysiological responses likely explain why antidiabetic medications that enhance hyperinsulinemia or augment insulin signaling are associated with an increased risk of heart failure in clinical trials (7).

The action of DPP-4 inhibitors as insulin secretagogues results from their ability to potentiate of GLP-1 and glucose-dependent insulinotropic polypeptide (1). Endogenous GLP-1 is wholly responsible for the hypoglycemic actions of DPP-4 inhibitors (8). However, DPP-4 inhibitors also act to enhance the effects of many other substrates that rely on DPP-4 for their degradation, particularly stromal cell-derived factor (SDF)-1 (9,10). Many of the nonhypoglycemic actions of DPP-4 inhibitors are mediated by their effect to potentiate endogenous SDF-1. SDF-1 is a stem cell chemokine that acts to channel mesenchymal cells to sites of tissue injury, thereby promoting inflammation, regeneration, and repair (11,12). Conventional incretins (i.e., long-acting GLP-1 analogs) do not potentiate the actions of SDF-1 (1).

ACTIONS OF DPP-4 INHIBITORS ON THE HEART IN EXPERIMENTAL STUDIES. The noninsulin peptides that are potentiated as a result of DPP-4 inhibition have diverse actions on the heart. Experimentally, DPP-4 inhibitors have positive inotropic effects that are mediated by their ability to enhance the actions of GLP-1 to stimulate cyclic adenosine monophosphate (AMP) in cardiomyocytes (13). Furthermore, in experimental heart failure, potentiation of SDF-1 promotes the outflow of sympathetic activity from the central nervous system, thus further augmenting the increase in myocardial cyclic AMP (14). These 2 actions, working in concert in the clinical setting of heart failure, might be expected to lead to calcium overload and serious deleterious effects in patients with heart failure and reduced ejection fraction.

However, whereas signaling through the GLP-1 receptor (acting through a cyclic AMP–dependent mechanism) increases heart rate in clinical trials, the use of DPP-4 inhibitors is not accompanied by a meaningful chronotropic response in patients with type 2 diabetes (1). Some researchers have hypothesized that the increases in cyclic AMP produced by DPP-4 inhibitors are compartmented into microdomains, which are not coupled to a chronotropic effect (15). Additionally, potentiation of SDF-1 may lead to uncoupling of beta-adrenergic receptors and interference with cyclic AMP messaging in the heart (16,17). Accordingly, DPP-4 inhibitors attenuate the ability of sympathetic activation to promote myocardial hypertrophy and cardiac arrhythmias (18,19). Furthermore, SDF-1 may act directly on the heart to suppress cardiac force and frequency (16). These effects appear to offset any increases in cardiac contractility or sinus rate that might be expected to occur from potentiation of endogenous GLP-1 (13).

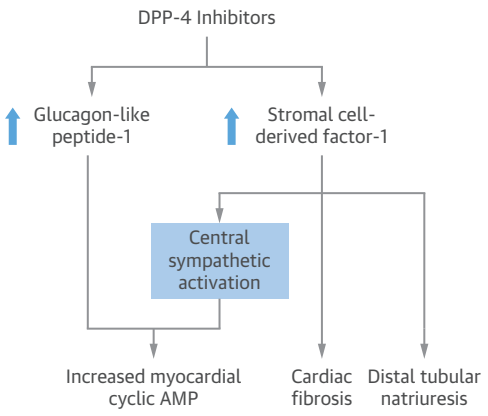
However, the action of DPP-4 inhibitors on the heart is further complicated by the fact that SDF-1 can mediate the body's response to cardiac injury by its influence on the process of repair. Patients with heart failure have increased levels of SDF-1 and exhibit enhanced expression of the cardiac receptors for the chemokine (20,21). The release of SDF-1 by the heart acts as a homing signal to direct mesenchymal stem cells to the injured myocardium (12). Although this response has conventionally been regarded as having regenerative potential, in diabetes and other states of cardiac stress, mesenchymal stem cells that are recruited through actions of SDF-1 may be transformed into fibroblasts rather than cardiomyocytes, and thus, potentiation of SDF-1 by DPP-4 inhibitors may lead to cardiac fibrosis (**Central Illustration**) (22–24). The aggravation of fibrosis may be particularly relevant to patients with type 2 diabetes, who are prone to the development of heart failure with preserved ejection fraction (25), a disorder in which cardiac fibrosis likely plays a critical role in limiting cardiac distensibility (26). Additionally, patients with diabetes have excessive

quantities of biologically active epicardial fat (27), which can act as an important source of mesenchymal stem cells (28). Increases in SDF-1 activity can enhance adipose tissue inflammation and promote fibrosis in experimental diabetic cardiomyopathy (24,29).

ACTIONS ON THE KIDNEY AND VASCULATURE IN EXPERIMENTAL STUDIES. Any potentially detrimental effects of DPP-4 inhibition on the heart might not become clinically important if DPP-4 inhibitors were to exert meaningful natriuretic effects, which would act to ameliorate cardiac loading conditions. DPP-4 inhibitors promote sodium excretion by the kidney (30), but in the clinical setting, this effect appears to be modest when compared with other antidiabetic drugs that exert direct actions on the renal tubules. In contrast to the natriuretic effects of GLP-1 receptor agonists and SGLT2 inhibitors, the increase in urinary sodium excretion produced by DPP-4 inhibitors does not lead to a decrease in body weight (31–35); moreover, unlike SGLT2 inhibitors, the use of DPP-4 inhibitors is not accompanied by hemoconcentration and the potential for clinically important volume depletion (31,32,36). The modest nature of the natriuretic effects of DPP-4 inhibitors can be explained by their unique site of action. Both GLP-1 receptor agonists and SGLT2 inhibitors act primarily on the proximal renal tubule, where the majority of sodium reabsorption takes place (37,38). In contrast, the effect of DPP-4 inhibitors on the proximal tubule appears to be minor and is not mediated by the GLP-1 receptor (30,39). Instead, these drugs exert their natriuretic effects primarily by an action on the distal renal tubules, an effect that is mediated through potentiation of SDF-1 (30).

Conceivably, the risk of developing heart failure could also be ameliorated if DPP-4 inhibition were to exert important systemic vasodilator effects that might reduce loading conditions in the heart. DPP-4 may contribute to the breakdown of endogenous natriuretic factors that have vasodilator actions (10). In addition, DPP-4 inhibition may mediate vasodilation through a nitric oxide–dependent mechanism (40). Experimentally, the vasodilator effect of DPP-4 inhibitors may be a prerequisite for the ability of SDF-1 to promote neovascularization and thereby promote both myocardial and renal repair (41). However, these nitric oxide–dependent pathways are attenuated in diabetes, and thus, they may not be capable of exerting adaptive effects on the circulation (42).

CENTRAL ILLUSTRATION Actions of Dipeptidyl Peptidase-4 Inhibitors That Are Relevant to Their Effects in Patients With Chronic Heart Failure



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AMP = adenosine monophosphate; DPP = dipeptidyl peptidase.

EFFECT OF DPP-4 INHIBITORS ON THE CLINICAL COURSE OF HEART FAILURE

Four large-scale cardiovascular outcomes trials with DPP-4 inhibitors have been completed, and their findings have been published (**Table 1**) (31–34). In 2 studies (with saxagliptin and alogliptin), DPP-4 inhibition was accompanied by an increased risk of heart failure (**Table 1**), which prompted the U.S. Food and Drug Administration to mandate warnings about this risk in the labeling for both drugs (43). In a trial with saxagliptin (SAVOR-TIMI 53 [Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus-Thrombolysis In Myocardial Infarction 53]) (44), patients treated with the drug experienced a significant increase in the risk of hospitalization for heart failure (hazard ratio: 1.27; 95% confidence interval: 1.07 to 1.51; $p = 0.007$), which was seen early following initiation of treatment and was observed primarily in patients with biomarker evidence for elevated cardiac filling pressures at study entry but without symptoms of heart failure. In a trial with alogliptin (EXAMINE [Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome]) (45), patients who were randomized to active therapy were hospitalized for heart failure more frequently than those assigned to placebo; this difference was nominally significant in patients without a history of heart

TABLE 1 Effects of Dipeptidyl Peptidase-4 Inhibitors on the Risk of Hospitalization for Heart Failure in Large-Scale Cardiovascular Outcomes Trials in Patients With Type 2 Diabetes

Drug (Ref. #) (Trial)	Study Features	Proportion of Patients With Heart Failure at Study Entry	Use of Nonstudy Antidiabetic Medications	Total Number of Heart Failure Hospitalizations Following Randomization	HR (95% CI) for Effect of DPP-4 Inhibitor
Sitagliptin (31,46) (TECOS)	14,735 patients with T2D with CVD followed for 3.0 yrs	18.0%	Metformin 81.6% Insulin 23.2% TZD 2.7% (30% reduced risk of starting insulin)	457	1.00 (0.83–1.19) (no data for subgroup with no baseline HF)
Saxagliptin (32,44) (SAVOR-TIMI 53)	16,492 patients with T2D with CVD or with multiple CV risk factors followed for 2.1 yrs	12.8%	Metformin 69.5% Insulin 41.1% TZD 6.0% (modest insulin sparing; NS during first year)	517	1.27 (1.07–1.51) (in patients with no baseline HF: 1.30 [2.03–2.65], p = 0.03)
Alogliptin (33,45) (EXAMINE)	5,380 patients with T2D with ACS followed for 1.5 yrs	27.9%	Metformin 66.2% Insulin 29.9% TZD 2.4% (no data on post-randomization insulin)	195	1.19 (0.90–1.58) (in patients with no baseline HF: 1.76 [1.07–2.90], p = 0.03)
Omarigliptin (34) (Protocol 018)	4,202 patients with T2D with CVD followed for 1.8 yrs	15.2%	Metformin 77.4% Insulin 34.9% TZD 1.1% (no data on post-randomization insulin)	53	0.60 (0.35–1.05) (no data for subgroup with no baseline HF); potential concern about competing risk

Definition of heart failure at baseline was not standardized across the trials. Number of heart failure hospitalizations following randomization includes both treatment groups. In the omarigliptin trial, the hazard ratio for heart failure hospitalization should be interpreted in light of a potential competing risk of death (higher in the omarigliptin group; HR: 1.28).

ACS = acute coronary syndrome; CV = cardiovascular; CVD = cardiovascular disease; EXAMINE = Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; HF = heart failure; NS = not significant; SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis In Myocardial Infarction 53; T2D = type 2 diabetes; TECOS = Trial Evaluating Cardiovascular Outcomes With Sitagliptin; TZD = thiazolidinedione.

failure (hazard ratio: 1.76; 95% confidence interval: 1.07 to 2.90; p = 0.026), who constituted the majority of the patients in the study. In contrast, no increase in the risk of hospitalization for heart failure was reported in trials with sitagliptin (TECOS [Trial Evaluating Cardiovascular Outcomes With Sitagliptin]) and omarigliptin (**Table 1**) (34,46). However, the omarigliptin trial was terminated early, and the thoroughness of follow-up is uncertain; furthermore, the number of heart failure events in the trial was too small for reliable interpretation, and the hazard ratio may have been distorted by a higher risk of death in the omarigliptin group (34).

What can explain the lack of an increased risk of heart failure hospitalization in the TECOS trial with sitagliptin? Compared with other large-scale trials, the patients in TECOS were more likely to be treated with metformin and less likely to be treated with insulin and thiazolidinediones at the time of randomization; furthermore, during follow-up, treatment with insulin was initiated 30% less frequently in the sitagliptin than placebo group (31). These characteristics differ meaningfully from those in the SAVOR-TIMI 53 trial with saxagliptin, which had a lower prevalence of metformin use and a higher prevalence of the use of insulin and thiazolidinediones at the start of the study; furthermore, the prevalence of insulin use was only modestly different between the 2 groups after randomization, particularly during the first year of the trial (32). In the SAVOR-TIMI 53 trial, the risk of heart failure was directly associated with the use of insulin and inversely associated with the use of metformin (44). These observations are noteworthy, because in large-scale studies of antidiabetic medications other than DPP-4 inhibitors, metformin has been associated with favorable effects on the clinical course of heart failure (47) (potentially due to benefits on autophagy-mediated cardiac remodeling [48]), whereas both insulin and thiazolidinediones have increased the risk of heart failure (in part related to their antinatriuretic actions) (6,7,49,50). Importantly, concurrent treatment with insulin and thiazolidinediones mutually reinforces the risk of each agent; combined therapy markedly accentuates the likelihood of worsening heart failure in clinical practice (51,52), possibly because the sodium-retentive actions of thiazolidinediones within the renal tubules are insulin dependent (53). It is therefore likely that concomitant treatment with antidiabetic medications can modulate the pathophysiological mechanisms of DPP-4 inhibitors that lead to heart failure. In the TECOS trial, the high prevalence of metformin use and the low and declining use of insulin in sitagliptin-treated patients may have

spared them from experiencing adverse clinical consequences from the pathophysiological actions of DPP-4 inhibitors that can predispose to heart failure.

The totality of evidence from randomized clinical trials supports the premise that worsening heart failure is a class effect of DPP-4 inhibitors. A meta-analysis by Verma et al. (54) of 100 randomized controlled clinical trials reported that the use of DPP-4 inhibitors was accompanied a significant 13% increase in the risk of blindly adjudicated heart failure hospitalizations, with no significant heterogeneity across members of the drug class. This estimate was confirmed by Li et al. (55) in their meta-analysis of 5 randomized controlled trials. Monami et al. (56) observed a 19% significant increase in the risk of events classified as acute heart failure that were observed in 84 randomized clinical trials, again without evidence of heterogeneity among members of the drug class. Finally, a meta-analysis by Clifton (57) reported a 24% increase in the risk of heart failure endpoints in DPP-4 inhibitor-treated patients, and the estimate remained nearly significant in its own right even when the results of SAVOR-TIMI 53 were removed from the analysis. None of these meta-analyses were carried out using patient-level data, and thus, they could not determine if the reported risks were modulated by the concurrent use of other antidiabetic medications (i.e., insulin and metformin).

Concerns that DPP-4 inhibitor can increase the risk of heart failure have been reinforced by the results of nonrandomized studies carried out in the community. Post-marketing analyses by the Food and Drug Administration have suggested a disproportionate reporting of adverse heart failure events among users of DPP-4 inhibitors across all members of the drug class (58), and an increased risk of hospitalization for heart failure has been observed early following the initiation of treatment in a nonrandomized cohort of patients receiving these drugs (59), a pattern similar to that seen in the SAVOR-TIMI 53 trial (44). Other observational studies have also reported an increase in risk (60–62). Several retrospective population-based studies have concluded that DPP-4 inhibitors do not precipitate or worsen heart failure; however, these reports have been difficult to interpret, either because they did not focus on new users or because they showed no difference with comparator groups that are known to increase the risk of heart failure in their own right (63,64). If the incidence of heart failure in patients receiving DPP-4 inhibitors is comparable with that seen with rosiglitazone and pioglitazone, the study implies an increased risk, rather than a neutral effect. Interestingly, in the only observational study that used SGLT2 inhibitors as a comparator, the risk of hospitalization for heart failure in users of DPP-4 inhibitors was increased (65). The totality of evidence from meta-analyses of randomized trials and observational studies is consistent with an increased risk and supports the premise that worsening heart failure represents a class effect.

It is important to note that concerns about an increased risk of worsening heart failure with DPP-4 inhibitors have been based on evidence from trials that were carried out not in patients with established heart failure but in patients who largely had clinically stable type 2 diabetes, who typically did not have clinically overt evidence of cardiac dysfunction. If DPP-4 inhibitors adversely affect the pathophysiological mechanisms that can lead to heart failure, this finding might be most apparent in patients with existing diagnoses. This possibility is supported by experience with other incretin-based drugs. Whereas GLP-1 receptor agonists did not increase the risk of heart failure in large-scale trials of patients without clinically apparent cardiac dysfunction (35), the use of liraglutide in patients with moderate to severe heart failure was accompanied by clinically important deleterious effects (66,67). This observation suggests that the risks of DPP-4 inhibitors in patients with established heart failure, although poorly investigated, are being underestimated.

The possibility of harm with DPP-4 inhibitors in patients with clinically overt heart failure has been recently highlighted by the results of the VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial (68), the only trial to date that has been designed to evaluate the effects of a DPP-4 inhibitor in patients with established left ventricular dysfunction. In the trial, 254 patients with diabetes with chronic heart failure and left ventricular ejection fractions $<40\%$ were randomly assigned (double-blind) to placebo and vildagliptin for 1 year. The background use of metformin was low ($\leq 35\%$). Left ventricular chamber size increased significantly in the patients treated with the DPP-4 inhibitor compared with placebo. Furthermore, 14.8% of the vildagliptin group and 11.1% of the placebo group experienced cardiovascular hospitalizations; 8.6% of the vildagliptin group, but only 3.2% of the placebo group, died. The number of clinical events was too small to interpret reliably. Nevertheless, these results are not reassuring, and they heighten concerns that physicians know little about the use of DPP-4 inhibitors in patients with clinically important left ventricular dysfunction. Interestingly, a review of studies registered at ClinicalTrials.gov does not identify any planned or ongoing randomized controlled clinical trials of

DPP-4 inhibitors in patients with established heart failure.

SUMMARY AND CONCLUSIONS

It is well known that the treatment of diabetes may worsen the clinical course of patients with heart failure, but large-scale cardiovascular safety trials in these patients have enrolled few individuals with clinically overt cardiac dysfunction. The limited evidence to date suggests that DPP-4 inhibitors may precipitate symptoms of heart failure, which are severe enough to require hospitalization. The evidence from clinical trials and observational studies is consistent with increased risk, especially following initiation of therapy, even in patients without a history of heart failure. Experimental studies have identified several potential mechanisms that may be responsible for these clinical observations. Given their current popularity and growing use, randomized clinical trials of DPP-4 inhibitors in patients with established heart failure are urgently needed. Until such studies are performed, clinicians should be mindful of the fact that favorable perceptions of cardiovascular profile of DPP-4 inhibitors in patients with diabetes ignore the risk of heart failure and that the safety of these drugs in patients with concurrent heart failure has not been established.

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