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Review

Mechanism by which dipeptidyl peptidase-4 inhibitors increase the risk of heart failure and possible differences in heart failure risk

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ABSTRACT

Dipeptidyl peptidase-4 (DPP-4) inhibitors are oral antidiabetic drugs that safely reduce the blood glucose level over the long term. In Japan, DPP-4 inhibitors have become the oral antidiabetic drugs most frequently prescribed for patients with type 2 diabetes. However, the results of several cardiovascular outcomes studies have suggested that some DPP-4 inhibitors may increase the risk of hospitalization for heart failure. In patients with diabetes, heart failure is the most frequent cardiovascular condition, and it has a negative impact on the quality of life as well as being a potentially fatal complication. Therefore, it is important to determine whether an increased risk of heart failure is associated with certain DPP-4 inhibitors or is a class effect of these drugs. This review explores the mechanism by which DPP-4 inhibitors may increase the risk of heart failure and possible differences among these drugs. The available research suggests that DPP-4 inhibitors cause sympathetic activation as a class effect and this may increase the risk of heart failure. Unlike other DPP-4 inhibitors, sitagliptin and alogliptin are mainly excreted in the urine and suppress renal sodium-hydrogen exchanger 3 activity. These two drugs did not increase the risk of hospitalization for heart failure in large-scale cardiovascular outcomes studies.

Contents

Introduction

There is a close association between diabetes and heart failure (HF). The prevalence of diabetes was approximately 30% in large-scale clinical trials recently initiated in patients with HF. In addition, the prevalence of HF was reported to be higher than that of myocardial infarction or stroke among patients with type 2 diabetes [1,2]. Complications of HF can have a severe impact on the quality of life in patients with diabetes [3] and HF is a frequent cause of death for these patients [4]. Conversely, complications of diabetes are independent prognostic factors for a fatal outcome in patients with HF [5].

Cardiovascular outcomes trials of dipeptidyl dipeptidase-4 inhibitors

In the American Diabetes Association guidelines and the 2018 European Association for the Study of Diabetes guidelines, saxagliptin and alogliptin are classified as “having potential risk of heart failure” [6]. Also, the American Heart Association has previously stated (in 2016) that dipeptidyl peptidase (DPP)-4 inhibitors are associated with a potential risk of HF [7]. These

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statements were triggered by the fact that the US Food and Drug Administration (FDA) requires the performance of large-scale clinical studies to evaluate the cardiovascular safety of oral antidiabetic agents. In 2005, it was reported that pioglitazone (a thiazolidinedione) reduced cardiovascular events, albeit for secondary endpoints. As a result, the reputation of thiazolidinediones for safety received a huge boost [8]. However, a meta-analysis of rosiglitazone (another thiazolidinedione) was published in 2007 that showed a significant increase in cardiovascular events [9]. The FDA noted these opposite outcomes for cardiovascular events, despite the two drugs having the same mechanism of action. Therefore, the FDA announced that novel oral antidiabetic drugs would only be approved if a cardiovascular outcomes trial provided satisfactory evidence of safety in relation to major adverse cardiovascular events other than hospitalization for HF, i.e. cardiovascular death, myocardial infarction, and stroke [10]. Subsequently, the safety of DPP-4 inhibitors with respect to cardiovascular events was evaluated by the following large-scale clinical studies according to this FDA guideline: the SAVOR trial (Saxagliptin Assessment of Vascular Outcomes Recorded) for saxagliptin [11], the EXAMINE trial (EXamination of cArdiovascular outcoMes with AlogliptIN versus Standard of carE) for alogliptin [12], the TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) for sitagliptin [13], and the CARMELINA trial (CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin) for linagliptin. Three of these trials have already been completed and the results have been published, while the results of the CARMELINA trial will be published in 2018 [14]. Vildagliptin has not been approved by the FDA because there has been no large-scale clinical trial to evaluate cardiovascular events [15]. The three published trials have demonstrated that DPP-4 inhibitors did not increase the risk of cardiovascular death, myocardial infarction, or stroke. However, the SAVOR trial showed a significant increase in hospitalization for HF by 1.27-fold [confidence interval (CI): 1.07–1.51]. In addition, the first report on the EXAMINE trial suggested that hospitalization for HF was increased by alogliptin [12], although the effect was not significant. However, subsequent analysis using the composite endpoint of cardiovascular death and hospitalization for HF found no difference between the placebo group and the alogliptin group [16]. Since there were few deaths from cardiovascular events in the alogliptin group, it was suggested that some of the patients treated with alogliptin avoided death and were hospitalized for HF instead, thus elevating the HF hospitalization rate. In this review, I will discuss the EXAMINE trial by using the increase of 1.07-fold (CI: 0.78–1.46) in the risk of hospitalization for HF that was reported in *The Lancet*. Pooled analysis of clinical studies has shown that hospitalization for HF is increased by 1.31-fold (CI: 0.53–3.12) in patients treated with vildagliptin and by 1.88-fold (CI: 0.84–4.16) in patients using linagliptin [17], although these data are not from large-scale prospective studies. In contrast, the TECOS trial showed that sitagliptin did not increase the risk of hospitalization for HF. Based on the above results, it has been suggested that an increased risk of HF may be a class effect of DPP-4 inhibitors [7]. Therefore, we need to consider the mechanism by which DPP-4 inhibitors may increase the risk of HF.

Class effect of DPP-4 inhibitors on HF

DPP-4 inhibitors were developed as oral antidiabetic drugs that regulate the blood glucose level by preventing the breakdown of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, thus enhancing incretin activity. In addition, injectable GLP-1 receptor agonists (GLP-1RAs) have been developed that also increase the incretin effect. Reports on four large-scale cardiovascular outcomes trials of GLP-1RAs have been published: the LEADER trial [18] (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) on liraglutide, the SUSTAIN 6 trial [19] (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) on semaglutide, the EXSCEL trial [20] (Exenatide Study of Cardiovascular Event Lowering) on exenatide, and the ELIXA trial [21] (Evaluation of Lixisenatide in Acute Coronary Syndrome) on lixisenatide. In all four trials, GLP-1RA treatment did not increase the risk of hospitalization for HF compared with placebo, but each of the GLP-1RAs caused a significant increase in the heart rate. It has been reported that GLP-1 receptors are expressed in the myocardium, sinus node, and other regions [22], and it is thought that GLP-1RAs can increase both myocardial contractility and the heart rate. In HF patients with left ventricular dysfunction, the risk of cardiac adverse events was found to be increased by liraglutide in the LIVE trial (A Randomized, Double-blind, Placebo-controlled Study of The Effect of LIraglutide on Left VEntricular Function in Chronic Heart Failure Patients With and Without Type 2 Diabetes) [23] and the FIGHT trial (Functional Impact of GLP-1 for Heart Failure Treatment) [24], but these were small-scale studies.

However, the heart rate is not increased by administration of DPP-4 inhibitors, suggesting that the higher risk of HF in patients taking these drugs may be related to DPP-4 substrates other than incretin hormones [25]. Substance P is also degraded by DPP-4 and it increases sympathetic activity [26,27], so there has been concern that elevation of the circulating substance P level by administration of DPP-4 inhibitors may increase the risk of HF by accelerating the heart rate through sympathetic activation. In fact, when degradation of substance P was completely inhibited by concomitant administration of a DPP-4 inhibitor and an angiotensin-converting enzyme (ACE) inhibitor, the noradrenaline level and heart rate were significantly increased in several placebo-controlled clinical studies [28]. Neuropeptide Y is another peptide degraded by DPP-4, and it also increases sympathetic activity [26]. Accordingly, it is possible that the increased risk of hospitalization for HF may be related to elevation of the plasma levels of DPP-4 substrates such as substance P and/or neuropeptide Y that stimulate sympathetic activity, and this would represent a class effect of DPP-4 inhibitors [29]. Interestingly, the rate of hospitalization for HF was significantly increased by treatment with saxagliptin throughout the SAVOR trial. However, subanalysis showed that hospitalization for HF was not increased in patients receiving concomitant treatment with beta-blockers, supporting the hypothesis that saxagliptin increased the risk of HF via sympathetic activation [30]. ACE inhibitors were reported to be not inferior to angiotensin II receptor blockers (ARBs) with regard to improving the prognosis of HF patients despite the fact that ACE inhibitors increase the blood levels of substance P and neuropeptide Y [31]. The effect of increased blood levels of substance P or neuropeptide Y associated with ACE inhibitor therapy is considered to have a minor influence on the prognosis of HF. It is speculated that potential aggravation of HF due to sympathetic activation by substance P or neuropeptide Y is less significant compared with inhibition of HF due to suppression of angiotensin II production by ACE inhibitors. In contrast, elevation of the blood levels of substance P or neuropeptide Y by DPP-4 inhibitors may become significant because DPP-4 inhibitors do not inhibit ACE.

The severity of diabetes mellitus and use of concomitant medications differed between the SAVOR trial and the TECOS trial. The percentage of patients receiving concomitant insulin was higher in the SAVOR trial (41.2% in the placebo group and 41.6% in the saxagliptin group) than in the TECOS trial (22.9% in the placebo group and 23.5% in the sitagliptin group). On the other hand, the percentage of patients receiving concomitant sulfonylureas (SUs) was approximately 40% in both trials. In the SAVOR trial, the

incidence of hypoglycemia was significantly higher in the saxagliptin group than in the placebo group, which may have increased the risk of hospitalization for patients with HF in the former group. Although the risk of hospitalization was not analyzed in relation to hypoglycemia in that trial, analysis stratified by concomitant use of insulin or SUs, which are likely to cause hypoglycemia, revealed that the risk of hospitalization for HF was similar regardless of concomitant use of insulin or SUs [30]. This suggests the possibility that factors other than hypoglycemic events associated with aggravation of HF may have influenced the results of the SAVOR and TECOS trials.

Next, I will discuss why the risk of hospitalization for HF was significantly increased in patients taking saxagliptin, but not in those using sitagliptin or alogliptin [32].

Mechanism underlying differences in the risk of HF among DPP-4 inhibitors

Sodium-hydrogen exchanger 3 (NHE3) is involved in sodium reabsorption from the proximal renal tubules and its expression is enhanced in both HF and diabetes [33]. NHE3 forms a complex with DPP-4 [34] and inhibition of DPP-4 reduces NHE3 activity, thus suppressing sodium reabsorption and causing sodium diuresis [35]. When alogliptin was administered to GLP-1 receptor knock-out mice, sodium diuresis was detected in these mice as in wild-type mice [36], suggesting that alogliptin causes sodium diuresis by inhibiting DPP-4 rather than by increasing GLP-1 activity.

Complexes formed by NHE3 and DPP-4 have been detected in the luminal membrane of the proximal tubules. Therefore, it has been suggested that certain DPP-4 inhibitors, which are mainly excreted unchanged in the urine, may cause sodium diuresis by inhibiting luminal NHE3 activity in the renal tubules. Among the various DPP-4 inhibitors, sitagliptin and alogliptin are mainly excreted in the urine, while there is little urinary excretion of saxagliptin, linagliptin, and vildagliptin [37]. This suggests that sitagliptin and alogliptin are more likely to suppress renal DPP-4 activity and enhance sodium excretion compared with the other DPP-4 inhibitors. In fact, it was recently reported that urinary sodium excretion was significantly higher in patients treated with sitagliptin than in those receiving placebo [38]. Sodium diuresis could reduce the blood pressure. Interestingly, systolic blood pressure was significantly lower in the alogliptin group than in the placebo group during the EXAMINE trial [39]. My colleagues and I have also confirmed that sitagliptin can significantly reduce blood pressure [40]. In addition, a hypotensive effect of sitagliptin was demonstrated by a placebo-controlled study [41] and multicenter observational studies [42–45]. Furthermore, Kanozawa et al. reported that both sitagliptin and alogliptin caused a significant increase in urinary sodium excretion and reduced the systolic blood pressure, while vildagliptin did not have these effects [46]. Moreover, the Kurume University group found that treatment with sitagliptin reduced blood pressure, which returned to the baseline level after patients were switched to linagliptin [47]. The MARLINA-T2D trial performed in patients with early diabetic kidney disease found no significant differences in blood pressure, estimated glomerular filtration rate, and albuminuria between the linagliptin group and the placebo group [48], while the TECOS trial identified a significant decrease in the estimated glomerular filtration rate and albuminuria with sitagliptin therapy [49]. Finally, an observational study of 247 patients performed in Japan showed that sitagliptin decreased the estimated glomerular filtration rate slightly while improving albuminuria [50]. These findings were interpreted as indicating that sitagliptin may improve glomerular hyperfiltration through tubuloglomerular feedback by promoting sodium excretion. In addition, it seems that the renal effects of DPP-4 inhibitors differ between those mainly excreted in the urine and those with low urinary excretion, depending on differential suppression of tubular NHE3 activity. Furuki et al. performed an analysis of DPP-4 inhibitors, which indicated that the odds ratio for hospitalization due to HF increased as the urinary excretion rate of the unchanged drug decreased (Fig. 1) [51]. A pooled analysis of clinical studies of linagliptin, which is not excreted in the urine, showed that cardiac failure occurred in 0.5% (26/5488) of the patients treated with linagliptin versus 0.2% (8/3290) of those receiving placebo [52], so the incidence of cardiac failure was higher with linagliptin although it was low in both groups. In this context, the CARMELINA trial is important because it is evaluating the safety and efficacy of linagliptin in patients with advanced diabetic nephropathy [14], and the results are awaited. In the VIVIDD (Vildagliptin in Ventricular Dysfunction Diabetes) trial, the safety of vildagliptin was assessed in patients who had type 2 diabetes and reduced left ventricular contractility, with an increase in left ventricular end-diastolic volume being observed in the vildagliptin group [53]. On the other hand, the 3D trial (Effect of a DPP-4 inhibitor on left ventricular diastolic dysfunction in patients with type 2 diabetes and diabetic cardiomyopathy) compared sitagliptin with the

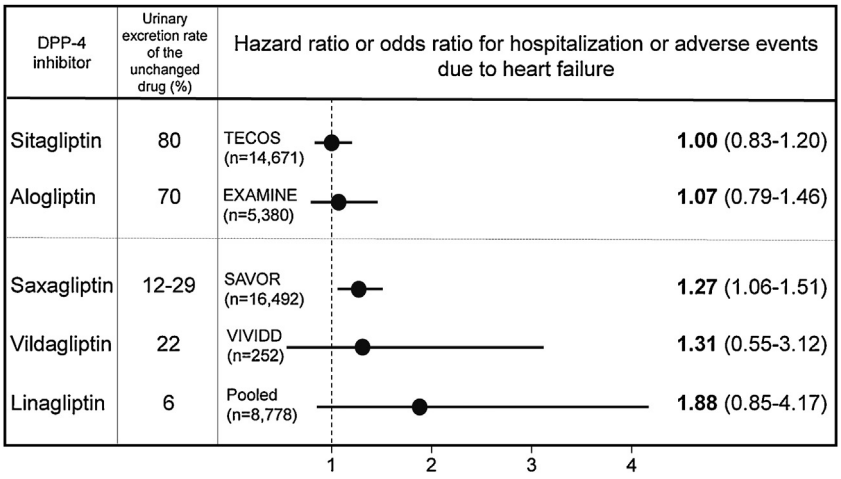

Fig. 1. Hazard ratio or odds ratio for hospitalization or for adverse events related to heart failure. Hospitalization for heart failure (hazard ratio) was adjudicated by an independent clinical event committee in the trials of sitagliptin (TECOS), alogliptin (EXAMINE), and saxagliptin (SAVOR-TIMI 53). Hospitalization for heart failure (odds ratio) was also adjudicated by an independent clinical event committee in the trial of vildagliptin (VIVIDD). Adverse cardiac events related to heart failure (odds ratio) was not adjudicated by an independent clinical event committee in the trials of linagliptin. Reproduced with permission from Furuki et al. [51].

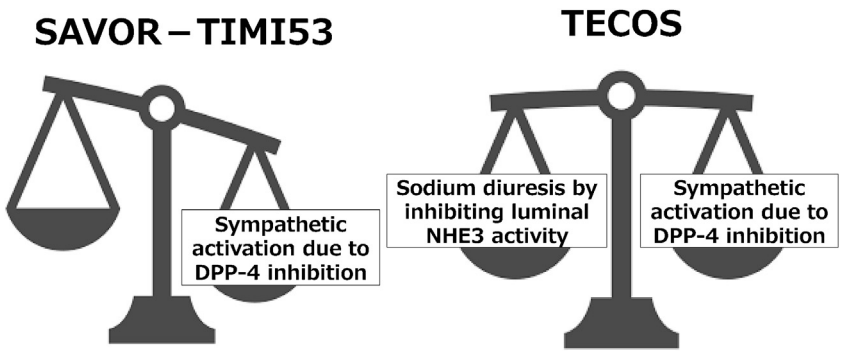

Fig. 2. Potential mechanism for differences in the risk of heart failure among DPP4 inhibitors. DPP-4 inhibitors tend to exacerbate heart failure through sympathetic activation as a class effect. However, it is thought that sitagliptin and alogliptin do not increase the risk of heart failure because these drugs are mainly excreted in the urine and suppress renal NHE3 activity to promote sodium diuresis. In contrast, saxagliptin shows low urinary excretion and may increase the risk of heart failure. DPP-4, dipeptidyl peptidase-4; NHE3, sodium-hydrogen exchanger 3.

alpha-glucosidase inhibitor voglibose in patients who had type 2 diabetes and reduced left ventricular contractility, revealing no changes in left ventricular contractility evaluated by echocardiography in either group [54].

Taken together, the available research suggests that DPP-4 inhibitors cause sympathetic activation as a class effect and this can increase the risk of HF. However, sitagliptin and alogliptin, which are mainly excreted in the urine and suppress renal NHE3 activity, did not increase hospitalization for HF in large-scale cardiovascular outcomes studies. In contrast, saxagliptin has a low urinary excretion rate and saxagliptin treatment is associated with an increased risk of hospitalization for HF. Fig. 2 shows a mechanism that could possibly explain the differing effects of these DPP-4 inhibitors on HF.

Conclusion

Unlike DPP-4 inhibitors, sodium glucose cotransporter 2 inhibitors have been reported to decrease the risk of hospitalization for HF as a class effect [55–59]. Three cardiovascular outcomes trials of DPP-4 inhibitors have been completed, revealing different results with regard to the risk of HF. It is difficult to conclude that the increased risk of hospitalization for HF associated with saxagliptin in the SAVOR trial was only incidental. This trial revealed that the risk of HF was higher in the saxagliptin group than in the placebo group, particularly in patients with renal dysfunction and patients with a higher urinary microalbumin excretion rate. Assuming that the results of the cardiovascular outcomes trials published so far are correct, sodium glucose cotransporter 2 inhibitors rather than DPP-4 inhibitors should preferentially be used to treat patients with diabetes who have a high risk of HF. When DPP-4 inhibitors are used, it seems important to consider potential differences among these drugs and select those associated with a lower risk of HF.

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Conflict of interest

The author declares that there is no conflict of interest.

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