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DPP4 inhibitors and Cardiovascular Outcomes: Safety on Heart Failure

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Abstract

Diabetes is an important risk factor for cardiovascular disease. However, clinical data suggests intensive glycemic control significantly increase rather than decrease cardiovascular mortality, which is largely due to the fact that a majority of oral anti-diabetic drugs have adverse cardiovascular effect. There are several large scale clinical trials evaluating the cardiovascular safety of DPP4 inhibitors, a novel class of oral anti-diabetic medications, have been recently completed. They were proven to be safe with regards to cardiovascular outcomes. However, concerns on the safety of heart failure have been raised as the SAVOR-TIMI 53 trial reported a 27% increase in the risk for heart failure hospitalization in diabetic patients treated with DPP4 inhibitor saxagliptin. In this review, we will discuss recent advances in the heart failure effects of DPP4 inhibition and GLP-1 agonism.

Keywords

DPP4; incretin; heart failure; cardiovascular outcomes

Introduction

Diabetes mellitus, a chronic metabolic disorder of glucose-insulin homeostasis, is an epidemic in today's world. As of 2015, the prevalence was estimated to be about 415 million worldwide with about 85–95% of them being patients with type 2 diabetes mellitus.[1] Diabetes accounts for significant morbidity and mortality and is a major risk factor for coronary artery disease, cerebrovascular disease, chronic kidney disease, peripheral vascular disease and microvascular damage in terms of nephropathy, neuropathy and retinopathy.[2] This translates into a discouraging economic burden of about 673 billion US dollars spent in the management of diabetes mellitus.[1]

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Pharmacological management of diabetes has seen a dramatic change over the past few decades. Apart from oral single agents, today, we not only have combination oral therapies but also injectable medications other than insulin. These include biguanides, sulfonylurea insulin secretagogues, meglitinides, thiazolidinediones, Glucagon-like peptide-1(GLP-1) receptor agonist, didpetidyl peptidase IV (DPP4) inhibitor, alpha-glucosidase inhibitor, bile acid sequestrants and exogenous insulin. The ability of these medications to lower HbA1c levels ranges from 0.5% – 1.5% depending on the particular agent.[3]

Diabetes has a clear association with cardiovascular diseases and heart failure. However, some of the medications used to treat diabetes can potentially exacerbate heart failure. One such class of drugs are the thiazolidinediones, which by way of sodium and water retention can cause increase in plasma volume and worsen heart failure symptoms.[4] Another medication that has come under the radar is the DPP4 inhibitors after a major clinical trial (SAVOR-TIMI 53) reported an increased rate of hospitalizations for heart failure in patients taking Saxagliptin.[5] However, several subsequent trials failed to observe the same phenomenon in patients treated with other DPP4 inhibitors. There have been growing studies investigating the effects of DPP4 inhibitor on heart failure since the first report in 2013. In this review, we aim to discuss the cardiovascular effects of DPP4 inhibitors, especially their potential association with heart failure.

Diabetes as a Risk Factor for Heart Failure

Diabetes mellitus is not only a well-known risk factor for heart disease, but for many years has also been considered equivalent to coronary heart disease for cardiovascular risk prediction and prevention.[6]It was demonstrated that about 40% of those treated for acute congestive heart failure had diabetes.[7] The presence of heart failure in a diabetic population portends a 10-fold increase in mortality and the 5-year survival rate is only 12.5%, with a median survival of 1.1 year.[8, 9] The risk of heart failure was higher if there were other comorbidities such as ischemic heart disease and hypertension, but this incremental risk was evident even after adjusting for these two variables. [10, 11]

Hyperglycemia is directly related to heart failure. There is a graded association between these two. This was shown by Iribarren C. and co-workers who demonstrated that for every 1% increase in HbA1c, there was an 8% increase in the risk of heart failure. An HbA1c of 10% compared to 7% had a 1.56-fold greater risk of heart failure.[12] The mechanisms of heart failure are varied. The most widely studied and established cause of heart failure in diabetes is ischemic heart disease. Accelerated coronary atherosclerosis may have a role to play here.[13] There are considerable levels of protein-bound advanced glycation end products (AGEs) circulating in the serum of diabetic patients. These compounds are highly reactive and tend to modify the apoprotein B (Apo B) and the phospholipid components of LDL leading to oxidation of LDL and subsequent atherosclerosis and eventually ischemic heart disease.[14] In addition, endothelial dysfunction is also potential trigger for atherosclerosis. Hyperglycemia induced non-enzymatic glycation of proteins can lead to increased production of oxygen-derived free radicals which then suppresses endothelium-dependent vasodilation thus causing endothelial dysfunction.[15] However, cardiomyopathy in diabetic patients can also occur by virtue of direct damage to the heart muscle caused by

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cellular changes in calcium transport and fatty acid metabolism. [12] On the other hand, heart failure condition may also promote hyperglycemia through multiple mechanisms. [16, 17] Patients with chronic heart failure showed increased insulin levels and reduced insulin sensitivity compared to control subjects. [18, 19] Reduction of peak oxygen consumption is related to enhanced insulin resistance in patients with heart failure. [18] Sympathetic activation in heart failure could increase insulin resistance, inhibit insulin secretion from β cells, increase hepatic glucose production, and glucagon production release of from the pancreatic beta cells, which induce the production of the hepatic glucose and glucagon by stimulating both gluconeogenesis and glycogenolysis. [17] The reduced physical activity in heart failure patients may also contribute to diabetes. [20, 21]

Left ventricular hypertrophy leading to diastolic dysfunction may occur in diabetic patients in the absence of hypertension. This may be related to the presence of a greater degree of interstitial connective tissue deposition and cardiac myocyte loss in such patients and these changes are compounded by the presence of hypertension. Another possible mechanism is that of restrictive cardiomyopathy in patients with normotensive type I and type II diabetes mellitus which has not yet been universally validated. [11] Somaratne et al. reported that prevalence of left ventricular hypertrophy in type 2 diabetic patients was as high as 56% as determined by echocardiography. [22] In a multi-ethnic population study, Eguchi et al. indicated that type 2 diabetes increased the risk of left ventricular hypertrophy by 46% after adjusting for a number of factors including age, sex, race, body mass index, systolic blood pressure, education, history of coronary artery disease, physical activity and alcohol consumption. [23] In addition, patients with chronic heart failure often show enhanced inflammation, an important risk factor for diabetes. [24]

Glucose-lowering Therapy Adverse Effects and Heart Failure

Compared with non-diabetic individuals, the risk of developing cardiovascular disease is doubled in diabetic patients.[25–27] Unexpectedly, a large scale clinical trial in 2008 evaluating the effects of glycemic control on cardiovascular disease showed that intensive glycemic control using anti-diabetic medications was significantly increased rather than decreased cardiovascular mortality in patients with diabetes (Hazard ratio: 1.35; 95% CI: 1.04–1.76; p=0.02).[28] Except few anti-diabetic medications such as metformin and SGLT2 inhibitors, a new class of anti-diabetic drugs that have been recently shown to reduce cardiovascular death by 38% [29], most oral anti-diabetic medications have adverse cardiovascular effects. The improvement in cardiovascular outcomes by SGLT2 inhibitors is probably associated with their reduction effects on blood pressure, [30] kidney hyperfiltration, [31, 32] and body weight. [33] In contrast, many other oral anti-diabetic drugs increase the risks of cardiovascular disease. For example, sulphonylureas have been shown to induce weight gain and other metabolic fuels. Evidence showed that long-term use of sulfonylureas was associated with an increased risk of coronary heart disease in diabetic females. [34] By following up 4,902cases of women with diabetes up to 10 years, Li et al. reported that 1–5 years of sulfonylurea use increased coronary heart disease by 24% (95% CI 0.85–1.81), 6–10 years of sulfonylurea therapy increased coronary heart disease by 51% (95% CI 0.85–1.81) 51% (95% CI 0.94–2.42), and over 10 years of sulfonylurea increased the risk by 115% (95% CI1.31–3.54). [34]Glitazones have also been shown to have potential

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adverse effects on heart failure.[35] Therefore, development of novel anti-diabetic drugs is urgently needed for controlling cardiovascular complications of diabetes. FDA thereby revised their guidelines in 2008, encouraging manufacturers to assess cardiovascular safety for newly developed anti-diabetic therapies.

DPP4 Inhibitors

There has been a paradigm shift in the management of diabetes mellitus with new classes of drugs becoming available to physicians in clinical practice, one of which is the DPP4 inhibitors. These drugs received FDA approval as early as 2006 and have been provided promising results since then. The mechanism of action of this class of drugs is diverse and has been widely studied. The DPP4 protein is a ubiquitous serine protease that is present in various cells of the body. Thus, the efficacy and adverse effects caused by DPP4 inhibitors is explicable by the influence these medications have on the particular tissue that it acts upon. The DPP4 is not only available as a circulatory form but is also expressed on endothelial cells, liver, gut, kidney, lungs and T-lymphocytes.[2] Within these tissues, the enzyme acts on multiple substrates of which the most widely studied ones are GLP-1and glucose-dependent insulinotropic polypeptide (GIP).[36] GLP-1 and GIP proteins act by means of a feedback loop that is based on levels of serum glucose. Hyperglycemia serves as a stimulus for GLP-1 secretion which then acts upon the pancreatic β-cells to release insulin and also simultaneously inhibit hepatic glucagon secretion.[37] The DPP4 inhibitors by virtue of inhibiting the breakdown of GLP-1 assist in more intense glycemic control. Ancillary mechanisms involved in glycemic control include reduction in gastrointestinal motility and slowing of gastric emptying. It has also been postulated that these drugs act at the level of the hypothalamus to regulate satiety. [2] Given their overall action, it was demonstrated that the DPP4 inhibitors were effective glucose lowering agents and significantly reduced HbA1c values by 0.6% at 24 weeks into treatment. [38] They pose a low risk of hypoglycemia and are weight neutral, which also adds to their safety profile.[39] However, as with any other drugs, these medications are not without side-effects. Notable adversities include increased prevalence of upper respiratory tract infections, reduction in T-lymphocyte counts, hypertension, pancreatitis and hepatic enzyme elevations.[37] Until recently, it was thought that DPP4 inhibitors did not increase the risk of cardiovascular events.[40] However, evidence from the SAVOR-TIMI 53 Randomized Trial indicated otherwise as is outlined in the section to follow.[41]

Clinical Trials on DPP4 Inhibitors and Heart Failure

Due to the increasing attention on the cardiovascular impact of glucose lowering strategies, there have been a number of clinical trials investigating the cardiovascular safety of DPP4 inhibitors, a novel class of oral anti-diabetic drugs. SAVOR-TIMI 53(ClinicalTrials.gov Identifier: NCT01107886), a large clinical trial evaluating the risk of cardiovascular outcomes assessed safety and efficacy of saxagliptin in patients with type 2 diabetes, included a total of 16,492 patients and followed up to 2.9 years. A significant observation of this trial was that saxagliptin treatment increased hospitalization for acute heart failure by 27%(3.5% vs. 2.8%; hazard ratio, 95% CI: 1.27, 1.07 – 1.51; P = 0.007) although no excess heart failure related mortality was noticed.[42] They also indicated in a later report that

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elevated BNP and albumin/creatinine ratio, eGFR<60 ml/m, and previous history of heart failure may be risk factors for increased heart failure hospitalization in saxagliptin treatment group. [41] However, another initial report of EXAMINE trial failed to observe adverse effect of alogliptin, another DPP4 inhibitor, on heart failure although there were 28% of patients had congestive heart failure at baseline.[43] There were no differences in composite events of cardiovascular death and hospital admission for heart failure between alogliptin and placebo groups (HR 1.00, 95% CI 0.82–1.21). [43] In addition, TECOS trial completed in 2015 also reported that no significant heart failure risk was observed in type 2 diabetic patients treated with sitagliptin. [44] The hospital admission rate for heart failure was the same in sitagliptin group in a medium follow up duration of 3 years, compared with placebo group. [44]

Therefore, current results do not support adverse effect on heart failure is a class effect of DPP4 inhibitor. However, DPP4 inhibition therapy may also do not possess beneficial cardiovascular effect. [45] Interestingly, the LEADER trial completed recently to evaluate the cardiovascular safety of liraglutide, a GLP-1R agonist, indicates GLP-1R liraglutide reduced both cardiovascular mortality and all cause death in patients with type 2 diabetes. Moreover, fewer hospitalizations for heart failure in liraglutide group were noticed compared with placebo group, although the difference did not reach statistical significance (1.2% vs. 1.4%; HR 0.87, 95% CI 0.73–1.05, p=0.14).[46] The SUSTAIN trial assessing the cardiovascular safety of semaglutide, another GLP-1R agonist, reported semaglutide reduced primary composite outcome(HR 0.74, 95% CI 0.58–0.95, P<0.001) and nonfatal stroke (HR 0.61, 95% CI 0.38–0.99, P=0.04). However, the hospitalization rate for heart failure was not different (HR 1.11, 95% CI 0.77–1.61, P=0.57). [47] Therefore, current results of the cardiovascular disease outcome safety trials indicate incretin-based therapies including DPP4 inhibition and GLP-1R agonist appear to be safe with regard to the cardiovascular outcome. This will be further tested in the ongoing trials assessing the cardiovascular outcomes, including 2 trials on DPP4 inhibition and several trials on GLP-1 agonists (Table 1).

Conclusions

DPP4 as a class of drugs have served as a useful adjunct in lowering HbA1c levels in the diabetic population.[3] Regulatory agencies such as the FDA raised concerns over the cardiovascular safety of these diabetic medications. Hence, multiple cardiovascular variables were included in the randomized clinical trials on DPP4 inhibitors. However, all of these studies are heterogeneous in their structure, which poses a serious challenge to data interpretation. So far, only the SAVOR-TIMI trial has hinted towards a possible increase in the rates of heart failure exacerbations in patients taking saxagliptin. The authors noted that 3.5% of the patients treated with saxagliptin were hospitalized for heart failure as compared to 2.8% of the patients treated with placebo (HR, 1.27; 95% confidence interval, 1.07–1.51; P=0.007).[5] Other trials such as the EXAMINE, TECOS and VIVIDD that studied alogliptin, sitagliptin and vildagliptin respectively have failed to demonstrate similar results. [44, 48, 49]It is unclear at this time if the results obtained from the SAVOR-TIMI trial reflect a side effect of saxagliptin in particular or if this is a class effect or merely just a chance phenomenon or a difference in the baseline characteristics of enrolled patients.

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One of the plausible theories that aim to explain this discrepancy is that the patients readmitted for heart failure in the SAVOR-TIMI trial may have been sicker at baseline as reflected by their previous history of heart failure, renal dysfunction and elevated baseline levels of NT-proBNP.[5] Another hypothesis is that in the other clinical trials such as the EXAMINE, patients with heart failure were medically optimized with beta blockers unlike the patients enrolled in the SAVOR-TIMI trial. This could potentially explain the difference in the rates of heart failure exacerbations seen with saxagliptin but not alogliptin.[36] Although a few meta-analyses have also shown an increase in the rates of heart failure exacerbation with the use of DPP4 inhibitors, these results may be skewed by the sample size of the SAVOR-TIMI trial that were taken into consideration when analyzing the results because the SAVOR-TIMI population represented the largest cohort in these meta-analyses.[50] However, if truly saxagliptin is associated with heart failure exacerbations, a few authors have postulated that this could be secondary to elevated end-diastolic volumes and worsening endothelial dysfunction caused by the DPP4 inhibitors.[51]

Further randomized double blind clinical trials are necessary to determine if the results of the SAVOR-TIMI trial represent a side effect of saxagliptin per se or if this is class effect of the DPP4 inhibitors. The results from the on-going CAROLINA trial (CARdiovascular Outcome Trial of LINAgliptin Versus Glimepride in Type 2 Diabetes) will be instrumental in obtaining clarification on the various mechanisms of action of DPP4 inhibitors and their association with heart failure, if any.

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Table 1

Ongoing trials evaluating the effect of incretin therapy on cardiovascular safety

Agent	Drug Class	Study Name	ClinicalTrials.gov identifier	Sponsor	Phase	N	Study Description	Completion Date
Exenatide	GLP-1R Agonist	EXSCEL	NCT01144338	AstraZeneca	3	9500	Exenatide Study of Cardiovascular Event Lowering Trial: A Randomized, Placebo-Controlled Clinical Trial to Evaluate CV Outcomes after Treatment with ExQW in Patients with T2DM	Apr, 2018
Dulaglutide	GLP-1R Agonist	REWIND	NCT01394952	Eli Lilly	3	9622	Researching Cardiovascular Events With a Weekly Incretin in Diabetes	Apr, 2019
Linagliptin	DPP4 inhibitor	CAROLINA	NCT01243424	BoehringerIngelheim	3	6000	Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with Type 2 Diabetes	Sep, 2018
Linagliptin	DPP4 inhibitor	CARMELINA	NCT01897532	BoehringerIngelheim	4	8300	Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in patients with Type 2 Diabetes Mellitus at High Vascular Risk	Jan, 2018