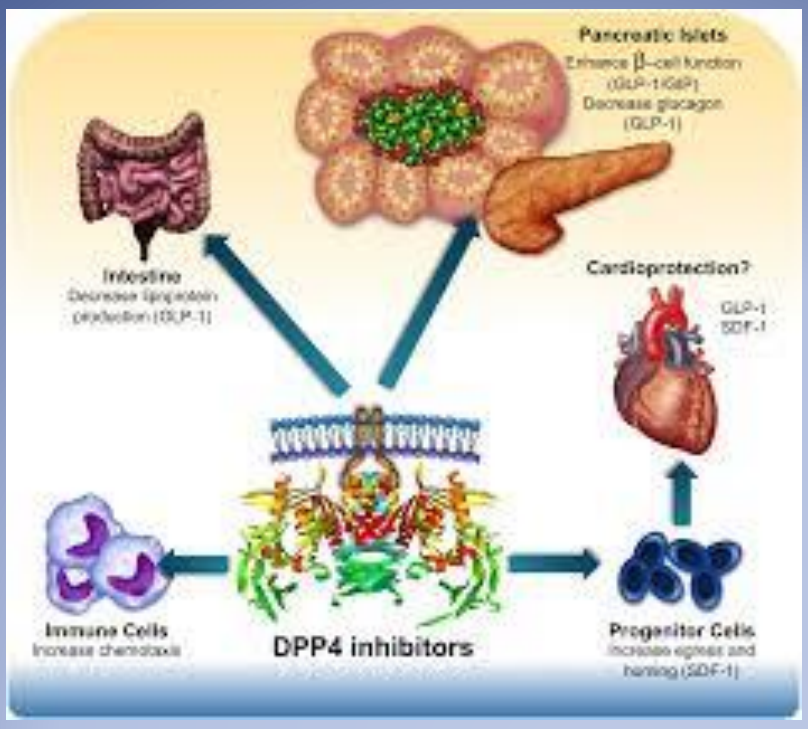

Dipeptidyl peptidase 4 (DPP-4) inhibitors and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM)

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Abstract

To review the current studies investigating the effects of dipeptidyl peptidase-4 (DPP-4) inhibitors on the outcome of patients with cardiovascular disease (CVD) and their associated risk factors. The majority of the recent clinical studies have demonstrated that DPP-4 inhibitors have beneficial effects on the cardiovascular (CV) system. These agents may have the potential to lower blood pressure, improve lipid profile and endothelial dysfunction, decrease the macrophage-mediated inflammatory response, and prevent myocardial injury. DPP-4 inhibitors have some CV protective effects in type 2 diabetes mellitus (T2DM) in addition to their antidiabetic actions. Long-term outcome clinical trials are underway to investigate the effects of the DPP-4 inhibitors on elevated CV risks in patients with T2DM. Further investigation in a large cohort is needed to assess the exact mechanisms of CV protective effects of DPP-4 inhibitors.

Introduction:

Type 2 diabetes is a chronic disease. It is characterized by high levels of sugar in the blood. Type 2 diabetes is also called type 2 diabetes mellitus and adult-onset diabetes. This is because it is almost always in middle- and late adulthood. However, more and more children and teens are developing this condition. Type 2 diabetes is much more common than type 1 diabetes and is a different disease. However, they share the results of high blood sugar levels and the complications of high glucose in the blood. Type 2 diabetes occurs when the body cells resist the normal effect of insulin, which is to drive glucose in the blood into the inside of the cells. (1) This condition is called insulin resistance. As a result, glucose starts to build up in the blood. As a result, the pancreas responds by making extra insulin to maintain normal blood sugar. After a long period of time, the body's insulin resistance gets worse. In response, the pancreas makes more and more insulin. Finally, the pancreas gets "exhausted“; therefore, it cannot keep up with the demand for more and more insulin. As a result, blood glucose levels start to rise. (2)

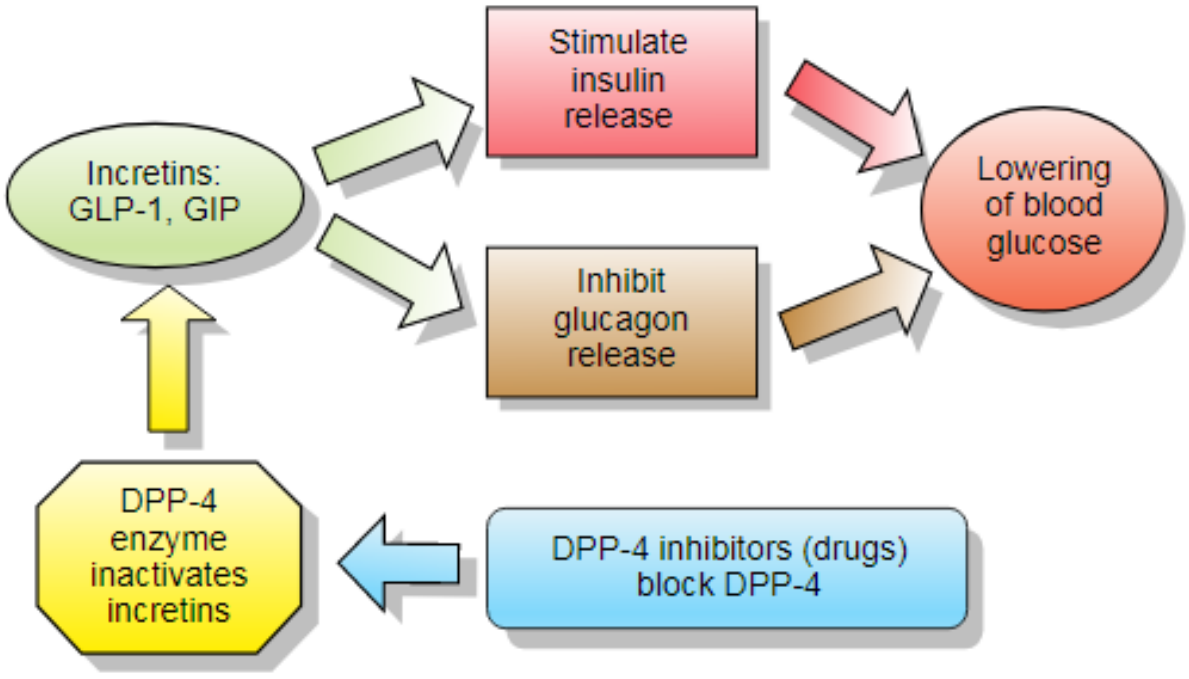
T2DM is a well-studied chronic metabolic disease that, when left untreated or insufficiently managed can cause serious microvascular and macrovascular complications. The blood glucose-lowering agents such as metformin, sulfonylurea derivatives, and insulin all can improve glycemic control in patients with T2DM. However, these agents have limited or no effect on the associated CV risk factors accompanying T2DM, including dyslipidemia, hypertension, and obesity. Treatment with both sulfonylurea derivatives and insulin has been associated with weight gain, which may diminish any positive effects on vascular endpoints. (3) Thiazolidinediones have

even been associated with an increased risk of CVD. (4) Therefore, there is a need to ensure that any new medication for T2DM is not associated with a deleterious effect on CV outcomes.

Glucose homeostasis is achieved by a complex interaction of hormones, principally insulin, glucagon, amylin, and incretins. Incretins are secreted from the gastrointestinal tract in response to food intake and have several systemic effects, including glucose-dependent stimulation of insulin secretion by pancreatic beta-cells. Two incretins have been discovered: glucagon-like peptide-1 (GLP-1), derived from the L-cells of the distal small intestine and large bowel, and glucose-dependent insulinotropic polypeptide (GIP) derived from the K-cells of the proximal small intestine. (5) Additional effects of GLP-1 include suppressing postprandial glucagon secretion from pancreatic alpha-cells, slowing gastric emptying, and enhancing satiety at a hypothalamic level, leading to reduced food intake. GLP-1 and GIP are glucose-lowering agents that can interfere with postprandial hyperglycemia, which has been associated with CV complications. G-protein-coupled receptors for GLP-1 are present in other tissues, including cardiac myocytes, (6) but their physiological action at these other sites remains unknown.

Inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors or gliptins) are a class of oral hypoglycemic agents that block the enzyme dipeptidyl peptidase-4 (DPP-4). They are used to treat diabetes mellitus type 2. The enzyme dipeptidyl peptidase- (DPP-) 4, also known as adenosine deaminase complexing protein 2, degrades both GLP-1 and GIP to their inactive metabolites. (7) Pharmacological competitive inhibition of DPP-4 increases the half-life and bioavailability of active incretins, enhancing their physiological effect. Currently available DPP-4 inhibitors include sitagliptin(The first

agent of the class approved by the FDA in 2006), saxagliptin, linagliptin, alogliptin, and vildagliptin. The first four are approved in the USA and throughout much of the world to treat T2DM; vildagliptin has been approved for use in Europe and Latin America. Other chemicals that may inhibit DPP-4 include Berberine, an alkaloid found in plants of the genus Berberis, inhibiting dipeptidyl peptidase-4, (8-10) partly explaining its antihyperglycemic activity. With daily doses ranging from 100 mg for sitagliptin to 5 mg for saxagliptin and linagliptin, the drugs are all similar in their efficacy in lowering HbA1c levels, safety profiles, and patient tolerance. DPP-4 inhibitors result in a mean decrease in A1C ranging between 0.5% and 1%. In this review will focus on the cardiovascular safety of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus.



The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels.

Previous Evidence on CV Safety of Dipeptidyl Peptidase-4 Inhibitors

DPP4 inhibitors prevent the rapid degradation of incretin levels (glucagon-like peptide [GLP]-1 and gastric inhibitory polypeptide [GIP]) which in turn increases insulin secretion and inhibits glucagon secretion by pancreatic β-cells. Although the FDA released the guidelines outlining specific cardiovascular (CV) safety assessment requirements before and after approval of new anti-diabetic drugs, many safety concerns of DPP4 inhibitors remain unclear. In fact, after the approval of DPP4 inhibitors for the treatment of type 2 diabetes mellitus, the interest in the DPP4 enzyme and its effects on CV disease rose substantially due to an effect of degradation of natriuretic peptides, left ventricular (LV) diastolic function, and anti-inflammatory, antioxidant, and antiapoptotic effects in the vasculature(11). To date, there remains contradicting evidence regarding the CV effects of DPP4 activities and, in particular, their role in heart failure development. In studies carried out around the world, there have been significant controversies on the class effect of DPP4 inhibitors on cardiovascular outcomes. Currently available DPP4 inhibitors in India are sitagliptin (USapproved 2006), vildagliptin (EU approved 2007), alogliptin (FDA approved 2013), saxagliptin (US approved 2009), linagliptin (US approved 2011), gemigliptin (Director General of Health Services (DCGI) approved 2015), and teneligliptin (DCGI approved 2015), trelagliptin (approved for use in Japan in 2015) and dutogliptin (being developed by Phenomix Corporation) Phase III. (12)

Associated benefits with the use of DPP-4 inhibitors such as little evidence of hypoglycemia have been reported, Weight neutral, ability to reliably lower blood glucose with oral administration, one dose per day, well-tolerated, and decreases blood pressure, makes these agents the best choice for patients with type 2 diabetes. In addition, DPP-4 inhibition has been shown experimentally to increases myocardial cAMP, which is related to the potentiation of endogenous GLP-1 (glucagon-like peptide-1). Although sustained increases in cAMP may exacerbate the clinical course of heart failure, the increase produced by modest GLP-1 receptor signaling might be confined to intracellular microdomains that are not linked to pathways that cause deleterious effects on cardiomyocytes. Such compartmentation may help to explain why DPP-4 inhibitors do not increase heart rate, unlike long-acting GLP-1 analogs. (13)

However, in a recent study documented in the USA, a post hoc assessment of CV safety in patients with type 2 diabetes mellitus was performed by taking data from 25 double-blind studies, which randomized patients at baseline to sitagliptin or a nonsitagliptin comparator. The studies were limited to those ranging from 12 to 104 weeks in duration. Major adverse cardiovascular events, including ischemic events and CV deaths were analyzed. In the entire cohort analysis, 78 patients had at least 1 reported MACE-related event, with 40 in the sitagliptin group and 38 in the nonexposed group. In this analysis, the exposure-adjusted incidence rate was 0.65 per 100 patient-years in the sitagliptin group and 0.74 in the nonexposed group; comparing sitagliptin to placebo, the exposure-adjusted incidence rate was 0.80 per 100 patient-years with sitagliptin and 0.76 with placebo; comparing sitagliptin to sulfonylurea, the exposure-adjusted incidence rate was 0.00 per 100 patient-years with sitagliptin and 0.86 with

sulfonylurea. In conclusion, a pooled analysis of 25 randomized clinical trials did not indicate that treatment with sitagliptin increases CV risk in patients with T2DM. In a subanalysis, a higher rate of CV-related events was associated with sulfonylurea relative to sitagliptin. (14)

Current Status on Cardiovascular Safety of DPP-4 Inhibitors

Although the cardiovascular effect of DPP4 inhibition has been substantially studied, the exact role of DPP4 in cardiovascular disease, especially in humans, remains elusive. Previous small studies and meta-analyses have suggested a benefit in both surrogate outcomes and cardiovascular events for these agents. However, there was growing evidence in recent years questioning the cardioprotective effect of DPP4 inhibitors. Furthermore, the path for DPP4 inhibitors during the 2010s was documented on the several cardiovascular outcome trials performed with DPP4 inhibitors. (15) Between the period of 2013 and 2019, five of the studies were published or reported. The studies were all performed in subjects at risk for cardiovascular diseases and were initially designed and powered for cardiovascular safety. However, the results are also important for documenting the long-term general safety of the DPP4 inhibitors and discussing a potential beneficial cardiovascular effect of glucose-lowering therapies.

The table below compare between five different globalized studies which compare the number of patients and the period of their follow up

DPP-4 inhibitor	Name of trial	Number of subjects	Median follow up period (year)	Hazard ratio for primary endpoint (95% CI*)	References
Saxagliptin	SAVOR-TIMI	16,492	2.1	1.00 (0.89; 1.12)	(94)
Alogliptin	EXAMINE	5,280	1.5	0.96 (0.76; 1.16)	(95)
Sitagliptin	TECOS	14,671	3.0	0.98 (0.88; 1.09)	(96)
Linagliptin	CARMELINA	6,979	2.2	1.02 (0.89; 1.17)	(97)
Linagliptin	CAROLINA	6,033**	6.0**	Not reported	(98)

*CI, confidence interval. **These results reported in a press release from Boehringer Ingelheim, February 19, 2019.
Primary endpoint: composite of cardiovascular death, myocardial infarction, or ischemic stroke (94), composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (95), composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (96), or time to first occurrence of the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (97), respectively.

SAVOR-TIMI (Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications?) is an interventional long-term multicenter trial that is currently enrolling and plans to enroll 16,492 patients with a completion date in April 2014. TECOS (Randomized, Placebo-Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients With T2DM and Inadequate Glycaemic Control) is a phase III noninferiority trial designed to assess CV outcomes of long-term treatment with sitagliptin in patients with T2DM (HbA1c of 6.5–8.0%) and a history of CVD. The study group will be compared with those patients treated with the usual standard of care. The primary outcome measure will be the first confirmed CV event, a composite of CV-related death, nonfatal MI, nonfatal stroke, or unstable angina requiring hospitalization. Fourteen thousand participants are estimated to be recruited into TECOS, with an estimated study completion date of December 2014. Also, the interim analysis of results of SITAGRAMI (Safety and Efficacy of Sitagliptin plus Granulocyte Colony-Stimulating Factor in Patients Suffering from Acute Myocardial Infarction), a phase III multicenter trial testing the myocardial regenerating effects after an acute MI of the combination of sitagliptin

with G-CSF, are encouraging but need to be confirmed with completion of the long-term study . (16-18)

CAROLINA (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with T2DM) is a long-term multicenter study currently enrolling and plans to enroll 6,033 patients with a completion date in September 2018. The primary outcome of cardiovascular death, myocardial infarction, or stroke occurred in 11.8% of the linagliptin group compared with 12.0% of the glimepiride group (p for noninferiority < 0.001, p for superiority = 0.76). Secondary outcomes:Cardiovascular death: 4.3% with linagliptin vs. 4.2% with glimepiride ,Myocardial infarction: 4.7% with linagliptin vs. 4.6% with glimepiride ,Stroke: 2.8% with linagliptin vs. 3.4% with glimepiride,Hypoglycemia: 10.6% with linagliptin vs. 37.7% with glimepiride (p < 0.001),Weighted average mean difference in body weight: -1.54 kg for linagliptin vs. glimepiride (p < 0.05). **In a nutshell**, Among patients with type 2 diabetes and elevated cardiovascular risk, the DPP4 inhibitor linagliptin was non-inferior to the sulfonylurea glimepiride to prevent major adverse cardiovascular events over a median of 6.3 years. Linagliptin was not superior to glimepiride in preventing major adverse cardiovascular events; however, it was associated with a lower frequency of hypoglycemia and less weight gain than glimepiride. Admittedly, metformin remains the first-line agent for the treatment of type 2 diabetes. Options for a second-line agent include a sulfonylurea or a DPP4 inhibitor. The lower cost would favour the former category, while less hypoglycemia and weight gain would favour the latter category.

Heart Failure Occurrence under the effect of DPP-4i drugs

What are the consequences of the sympathetic system overactivity produced by DPP4 inhibitors? Prolonged activation of β-adrenergic receptors can aggravate heart failure through 2 potential mechanisms. On the one hand, β-receptor stimulation can increase cAMP, signalling through protein kinase A and cardiotoxicity. However, this response seems to be attenuated by SDF-1, possibly because the chemokine acts (through a G_i protein-coupled mechanism) to inhibit the cAMP response to β-receptor stimulation. Interference with cAMP signalling may explain the action of DPP4 inhibition to attenuate adrenergically mediated hypertrophy and arrhythmias. It may contribute to the lack of a positive chronotropic response to DPP4 inhibitors in clinical trials. (19)

On the other hand, β-receptor stimulation leads to increased signalling through CaMKII (Ca++/calmodulin-dependent protein kinase II), which may be the primary mechanism by which sympathetic overactivity causes calcium overload cardiomyocyte apoptosis and adverse cardiac remodelling. Interestingly, this effect on CaMKII does not seem to be attenuated by SDF-1; in fact, potentiation of SDF-1 and other peptides by DPP-4 inhibitors is likely to increase the activity of CaMKII because of increased sympathetic nerve traffic. This may explain why experimental suppression of SDF-1 and CXCR7 acts to attenuate the response to β-adrenergic receptor stimulation and ameliorate adverse cardiac remodelling after myocardial infarction; additionally, high levels of SDF-1 may act directly to cause apoptosis in the myocardium. These deleterious actions could be further augmented by an effect of DPP4 inhibitors to potentiate NPY and substance P. Stimulation of the NPY-Y1 receptor leads to detrimental effects on the structure and function of cardiomyocytes, and potentiation of substance P can also accelerate cardiomyocyte apoptosis. (20)

Conclusion

DPP-4 inhibitors have some CV protective effects in type 2 diabetes mellitus in addition to their antidiabetic actions. Additional benefits include lowering the blood pressure, improving the lipid profile and the endothelial dysfunction, decreasing the macrophage-mediated inflammatory response, and reducing myocardial injury. Further investigation in a large cohort is needed to assess the exact mechanisms of cardiovascular protective effects of DPP4 inhibitors.

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