

<b>MEDICAL OUTCOMES</b>
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# Diabetes Mellitus: Dipeptidyl Peptidase 4 Inhibitors and Cardiovascular Outcomes

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## A B S T R A C T

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### ABBREVIATIONS

ACE = angiotensin converting enzyme  
 CHD = coronary heart disease  
 CV = cardiovascular  
 DPP-4 = dipeptidyl peptidase 4  
 G-CSF = granulocyte colony-stimulating factor  
 GIP = insulinotropic polypeptide  
 GLP-1 = glucagon-like peptide-1  
 MACE = major adverse cardiovascular events  
 MI = myocardial infarction  
 SDF1 $\alpha$  = stromal cell-derived factor 1 $\alpha$   
 T2DM = type 2 diabetes mellitus

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Dipeptidyl peptidase 4 (DPP-4) inhibitors represent a new pharmacological class of glucose – lowering agents, mainly used as add-on therapy, after metformin or combination of metformin with sulfonylurea or metformin with a thiazolidinedione. Over the last few years, several DPP-4 inhibitors, also called gliptins, have been approved and introduced into clinical practice such as sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin. Their mechanism of action relates to the inhibition of the DPP-4 enzyme which degrades the incretin hormones, e.g. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), released from the small intestine into the circulation during a meal, potentially capable to stimulate the release of insulin from pancreatic beta cells, thus affording a glucose-lowering action. However, these incretins are swiftly degraded by the DPP-4 enzyme. Gliptins, therefore, inhibit this enzyme, enhancing the bioavailability of GLP-1 and GIP. They have been approved for better glycemic control in type 2 diabetic patients.

Although, these new agents have been heralded as safe agents conferring pleiotropic or cardioprotective effects, recent studies showed that the new DPP-4 inhibitors may not have serious adverse cardiovascular effects, but have failed to show any pleiotropic actions or favorable cardiovascular effects. Additional data from ongoing studies may shed further light on this issue.

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## I N T R O D U C T I O N

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Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease associated with an increased rate of mortality and morbidity, mainly due to microvascular and macrovascular disease.<sup>1</sup> Adequate glycemic control with classical drugs, such as metformin, sulfonylurea derivatives, and insulin all can improve glycemic control and reduce, mainly, the microvascular complications. However, these therapies have not shown a similar improvement in the reduction of macrovascular complications, including coronary heart disease (CHD) and peripheral artery disease (PAD).<sup>2</sup> Moreover, the available data from large clinical trials have shown controversial effects of the tight glycemic control concerning the reduction of all-cause mortality in patients with T2DM.<sup>3</sup> All the above therapies have shown no significant reduction of cardiovascular risk beyond glycemic control and additionally thiazolidinediones have been associated with an increased risk of cardiovascular mortality.<sup>4</sup>

Conflict of Interest: none declared

Dipeptidyl peptidase 4 (DPP-4) inhibitors represent a newly introduced pharmacological class of glucose – lowering agents predominantly used as second- or third-line agents, typically after metformin or the combination of metformin – sulfonylurea or metformin – thiazolidinedione. Their mechanism of action relates to the inhibition of the DPP-4 enzyme which degrades incretins. Two of the most recognized gut-secreted incretins are the glucagon-like peptide-1 (GLP-1), which is a specific ligand for the G protein-coupled GLP-1 receptor (GLP-1R) and the glucose-dependent insulinotropic polypeptide (GIP), which control the postprandial glucose-dependent stimulation of insulin secretion by pancreas.<sup>5,6</sup> The activity of GIP in patients with T2DM is lost whereas that of GLP-1 is weak.<sup>7</sup> Although the administration of GLP-1 analogues has been shown to have a positive effect on plasma glucose regulation, the final therapeutic result is limited mainly due to the degradation activity of the DPP-4 enzyme. Over the last few years, several DPP-4 inhibitors, also called gliptins, have been approved and introduced into clinical practice such as sitagliptin, linagliptin, saxagliptin, vildagliptin and alogliptin. These compounds result in a mean decrease in glycated hemoglobin (HbA1C) ranging between 0.5% and 1% having additionally a minor risk of hypoglycemia and body weight gain. Furthermore, clinical studies have shown that gliptins increase the concentration of other peptides with cardioprotective effects independently of their action on the GLP-1 receptors, which are also located on the cardiovascular system (Fig. 1).<sup>8</sup> This review will focus on the potential effects of the DPP-4 inhibitors on the cardiovascular system.

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#### IMPACT OF DPP-4 INHIBITORS ON CARDIOVASCULAR RISK FACTORS

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Many antidiabetic drugs have been shown to have beneficial effects on diabetic dyslipidemia, in both fasting and

postprandial state.<sup>9</sup> Experimental studies with either GLP-1 receptor agonists or DPP-4 inhibitors have indicated that GLP-1 could have an inhibitory effect on the intestinal production of triglyceride-rich lipoproteins independently of weight changes.<sup>10</sup> Therapy with vildagliptin has been shown to improve the postprandial triglyceride and apolipoprotein B-48 particle metabolism.<sup>11</sup> This enhancement of postprandial lipid mobilization and oxidation seems to be caused by an increase in postprandial adipose tissue lipolysis via activation of the sympathetic nervous system rather than via a direct effect on metabolic status.<sup>12</sup> A retrospective analysis based on the General Electric Centricity database from 1996 to 2008, included 5,861 patients who were treated with the DPP-4 inhibitor sitagliptin. These patients showed decreases in low-density lipoprotein cholesterol, total cholesterol, and triglycerides.<sup>13</sup> Moreover, the results from a metaanalysis showed that patients under DPP-4 inhibitor treatment had a significant difference in total cholesterol compared to controls before and after treatment.<sup>14</sup>

With regards to hypertension, which commonly coexists in patients with T2DM, DPP-4 inhibitors may decrease the blood pressure either directly through DPP-4 inhibition or via the modulation of incretin hormone physiology. A small study, which enrolled non diabetic patients with mild to moderate hypertension, showed that sitagliptin produced slightly statistically significant reductions of 2–3 mmHg systolic and 1.6–1.8 mmHg diastolic blood pressure as assessed by 24-hour ambulatory blood pressure monitoring.<sup>15</sup> The favorable effect of sitagliptin on blood pressure seems to be reversed when a high dose of angiotensin-converting-enzyme inhibitor (ACE-I) is co-administrated. Marney et al<sup>16</sup> suggested that high levels of substance P and decreased degradation of neuropeptide Y, because of the double blockade of ACE (enalapril 10 mg) and DPP-4 (sitagliptin), caused the activation of the sympathetic nervous system eliminating thus the vasodilatory effects. Additional data support a dose-dependent reduction in blood

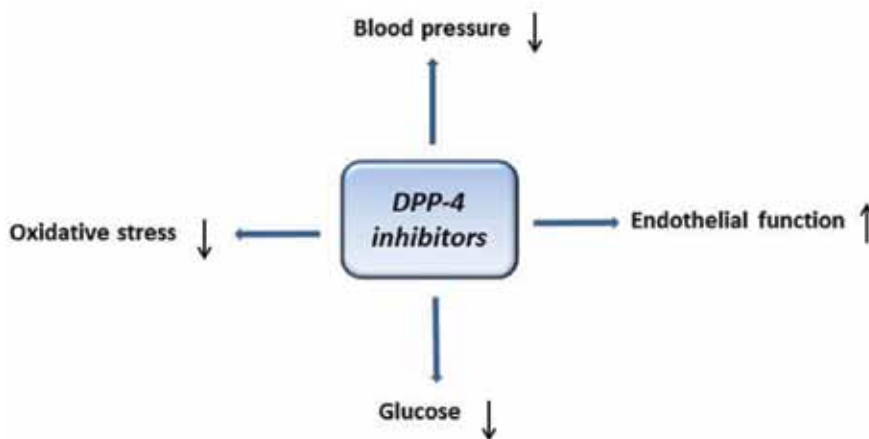


FIGURE 1. Pleiotropic effects of DPP-4 inhibitors on cardiovascular risk factors. DPP-4 = dipeptidyl peptidase 4.

pressure since patients receiving 100 mg vildagliptin vs 50 mg vildagliptin had significantly greater reduction in diastolic blood pressure compared to placebo.<sup>17</sup> The novel mechanisms underlying the effects of DPP4 inhibitors on lipid metabolism, fasting and postprandial, remain to be explored through more extensive prospective clinical studies.

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### EFFECT OF DPP-4 INHIBITORS ON PROCESS OF ATHEROSCLEROSIS AND CORONARY HEART DISEASE

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#### ENDOTHELIAL DYSFUNCTION AND INFLAMMATION PROCESS

It is well known that endothelial dysfunction is common in T2DM and is considered an independent cardiovascular risk factor. Increasing evidence exists that GLP-1 analogues administration might ameliorate endothelial dysfunction in patients with T2DM reducing the coronary heart disease risk.<sup>18</sup> Experimental data in mice show that DPP-4 inhibitors reduce inflammation via inhibition of monocyte activation and chemotaxis.<sup>19</sup> Furthermore, data from patients with T2DM receiving sitagliptin show an increase in the levels of circulating vasculoprotective endothelial progenitor cells and a concomitant upregulation of stromal cell-derived factor 1 $\alpha$  (SDF1 $\alpha$ ), which is a substrate of DPP4.<sup>20</sup> Diabetic patients who were receiving vildagliptin for one month, had a better endothelium-dependent vasodilatation compared to acarbose therapy.<sup>21</sup> Moreover, after six months of therapy with sitagliptin, a significant reduction of microalbuminuria was reported in patients with T2DM, which is considered a specific marker of endothelial dysfunction.<sup>22</sup>

#### CORONARY HEART DISEASE (CHD)

Although data from human studies concerning the impact of DPP-4 inhibitors on ischemic heart disease is limited, there is evidence from small studies that these drugs have a beneficial protective anti-ischemic effect independently of their hypoglycemic action. Read et al studied the effect of sitagliptin on left ventricular function in patients suffering from CHD who underwent dobutamine stress echocardiography, based on the hypothesis that increasing the plasma concentration of GLP-1 by DPP-4 inhibition would protect the heart from ischemic left ventricular dysfunction. At peak stress and during the phase of recovery, researchers observed that the increase of plasma levels of GLP-1 was accompanied by an enhancement on left ventricular response to stress, both globally and regionally in the 12 paired non-apical segments as assessed by peak systolic tissue Doppler. In the recovery phase, sitagliptin attenuated the post ischemic stunning seen after the control study.<sup>23</sup>

After myocardial infarction DPP-4 inhibition can reduce the size of the infarct and reverse left ventricular remodeling.<sup>24</sup> A trial studied 100 patients with acute myocardial infarction

after successful percutaneous coronary intervention who were randomized to placebo or granulocyte colony-stimulating factor (G-CSF) for 5 days plus sitagliptin for 28 days. The objective was to examine the effects of the combination of G-CSF plus sitagliptin on myocardial regeneration process by studying the improved myocardial homing of the mobilized stem cells. The process of myocardial stem cell homing involves the interaction of SDF-1 $\alpha$ , which is cleaved by the enzyme DPP-4, and the cellular homing receptor C-X-C chemokine receptor type 4. Preliminary results confirm that a high level of cellular DPP-4 expression after myocardial infarction decreases the migration of peripheral blood mononuclear cells towards SDF-1 $\alpha$ , and negatively influences cardiac function after a myocardial infarction.<sup>25</sup> Sitagliptin has also been shown to have an inhibitory effect on the platelet aggregation in both healthy individuals and diabetic patients. This seems to be caused primarily via the inhibitory effect of sitagliptin on intracellular free calcium and tyrosine phosphorylation.<sup>26</sup>

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### CURRENT EVIDENCE FOR CARDIOVASCULAR OUTCOMES AND SAFETY

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A recent study assessed the cardiovascular safety of sitagliptin in patients with T2DM from 25 double-blind studies, which randomized patients at baseline to sitagliptin or a non-sitagliptin comparator. The main objective was to assess the major adverse cardiovascular events (MACE) including ischemic event and cardiovascular death rates. Analysis of the results showed that 40 patients in the sitagliptin group and 38 in the non-sitagliptin group had at least one reported MACE-related event. In this analysis, the exposure adjusted incidence rate was 0.65 per 100 patient-years in the sitagliptin group and 0.74 in the non-sitagliptin group. Therefore, this pooled analysis did not indicate that treatment with sitagliptin increases cardiovascular risk in patients with T2DM.<sup>27</sup> Similarly, a meta-analysis of 53 randomized clinical trials reported that DPP-4 inhibitors had a similar risk of MACE, cancer or pancreatitis compared with placebo or other treatment.<sup>28</sup> The safety of vildagliptin was assessed regarding cardiovascular and cerebrovascular events. Categories included in the composite endpoint were acute coronary syndrome, transient ischemic attack with imaging evidence of infarction, stroke, and cerebrovascular death. The risk ratios (RR) for the composite endpoint were <1 for both vildagliptin 50 mg qd and vildagliptin 50 mg bid. These results were consistent across subgroups defined by age, gender, and cardiovascular risk status. The investigators concluded that vildagliptin was not associated with an increased risk of adjudicated cerebrovascular events relative to all comparators in the broad population of T2DM including patients at increased risk of cerebrovascular events.<sup>29</sup>

Recently, results were presented and published from two

major cardiovascular (CV) outcomes trials, EXAMINE and SAVOR-TIMI 53 Trials,<sup>30-32</sup> showing that the new DPP-4 inhibitors, saxagliptin and alogliptin, may not have serious adverse CV effects, but failed to show any pleiotropic actions or favorable CV effects.<sup>33</sup> In the EXAMINE study,<sup>31</sup> a total of 5380 patients with T2DM and either an acute MI or unstable angina within the previous 15-90 days underwent randomization to alogliptin or placebo and were followed for up to 40 months (median, 18 months). A primary end-point event (CV death, MI or stroke) occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio-HR, 0.96). Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, -0.36 percentage points;  $P < 0.001$ ). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

In the SAVOR-TIMI 53 study,<sup>32</sup> 16,492 patients with T2DM with history of, or at risk for, CV events were randomly assigned to receive saxagliptin or placebo. At 2 years, a primary end-point event (CV death, myocardial infarction-MI, or ischemic stroke) occurred in 613 patients (7.3%) in the saxagliptin group and in 609 patients in the placebo group (7.2%) ( $P = \text{NS}$ ). The major secondary end point (CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure) occurred in 1059 patients (12.8%) in the saxagliptin group and in 1034 patients in the placebo group (12.4%) ( $P = \text{NS}$ ). More patients in the saxagliptin group (3.5%) than in the placebo group (2.8%) were hospitalized for heart failure (hazard ratio-HR, 1.27;  $P = 0.007$ ). Rates of pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1% in the two groups, respectively).

At present, the safety and any potential cardioprotective effects of DPP-4 inhibitors are being tested further in ongoing multicenter clinical trials, whereby the primary MACE end-point considered is a cardiovascular safety outcome to reduce the risk of events. TECOS (Randomized, Placebo-Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients With T2DM and Inadequate Glycemic Control) is a phase III non-inferiority trial designed to assess cardiovascular outcomes of long-term treatment with sitagliptin in patients with T2DM (HbA1c of 6.5–8.0%) and a history of cardiovascular disease. Finally, CAROLINA (Cardiovascular Outcome Study of Linagliptin versus Glimepiride in Patients with T2DM) is a multicenter study planning to enroll about 6,000.<sup>34</sup>

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## CONCLUSION

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All the above data demonstrate that DPP-4 inhibitors are promising antidiabetic drugs with potential pleiotropic effects

on the cardiovascular system. Beyond their hypoglycemic action, they may improve the lipid profile and the endothelial dysfunction decreasing the inflammatory response, and reducing myocardial injury. However, although safety of these agents seems to have been documented by recent trials, the alleged cardioprotective effects of DPP-4 inhibition have not been confirmed by initial cardiovascular outcomes studies. According to the regulatory requirements and for the cardiovascular safety of all new anti-diabetic drugs, more clinical trials involving different DPP-4 inhibitors and cardiovascular outcomes are currently underway. These trials do not allow direct comparison between specific agents, but they may provide new data regarding the exact mechanisms of cardiovascular effects of DPP-4 inhibitors. Finally, gliptins do not seem to increase the cardiovascular risk, nor do they appear to reduce it, thus leading us to seek other approaches to reduce this risk, refocusing back at conventional risk factors, such as control of hyperlipidemia, hypertension, smoking, and obesity, rather than relying on glycemic control as a proxy of reduced cardiovascular risk.<sup>34</sup>

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