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VASCULAR BIOLOGY (RS ROSENSON, SECTION EDITOR)

Antiatherothrombotic Effects of Dipeptidyl Peptidase Inhibitors

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Abstract Atherothrombotic cardiovascular events are a leading cause of morbidity and mortality in patients with type 2 diabetes (T2D). A number of factors beyond hyperglycemia contribute to this increased risk of cardiovascular events in T2D, including elevated blood pressure, dyslipidemia, inflammation, endothelial dysfunction, and enhanced platelet activation. Importantly, most currently available antihyperglycemic treatments for T2D do not address these additional mechanisms. Indeed, we posit that this may explain why more intensive treatment of hyperglycemia has not contributed to a reduced incidence of cardiovascular events in subjects with T2D. Incretin-targeted therapies, such as dipeptidyl peptidase 4 inhibitors, are a relatively new class of antidiabetic treatments, and preclinical as well as small mechanistic clinical studies suggest that they exert beneficial cardiovascular effects. This review focuses specifically on the potential antiatherothrombotic effects of dipeptidyl peptidase 4 inhibitors.

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Introduction

Atherosclerosis is the result of a slowly progressive disease process that includes endothelial dysfunction, inflammation, thickening of the arterial wall, and the hallmark lesion known as an atherosclerotic plaque [1]. Modifiable risk factors for atherosclerosis include hypertension, dyslipidemia, smoking, and diabetes. Metabolic syndrome, which is characterized by hyperglycemia, obesity, high lipid and triglyceride levels, and elevated systolic blood pressure, has also been shown to accelerate atherosclerosis [2]. In patients with type 2 diabetes (T2D), the combination of insulin resistance and endothelial dysfunction is a major risk factor for the development of atherosclerosis [3]. Indeed, as the incidence of T2D rises around the world, so will the burden of atherosclerosis. Although conventional antidiabetic treatment agents such as sulfonylureas, thiazolidinediones, and insulin are effective glucose-lowering agents, there is little or no evidence supporting their ability to benefit other aspects of metabolic syndrome such as obesity, dyslipidemia, and elevated blood pressure. As such, their impact on the risk and progression of atherosclerosis may be muted [4, 5]. In contrast, the newly available incretin-based therapies display advantages beyond regulating hyperglycemia, including weight-neutral or weight-losing effects, lowering blood lipid levels, and reducing blood pressure [6, 7]. These agents therefore have the potential to prevent the progression of atherosclerosis in high-risk patients with T2D and beyond.

Two classes of incretin-targeted therapies are currently prescribed as antidiabetic agents: glucagon-like peptide 1

receptor (GLP-1R) agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors. GLP-1R agonists (e.g., liraglutide and exenatide) are molecules that are resistant to degradation and mimic the actions of endogenous glucagon-like peptide 1 (GLP-1) by binding to GLP-1R. In contrast, DPP-4 inhibitors increase endogenous levels of GLP-1 by inhibiting the enzyme responsible for its degradation and thus prolonging its action. DPP-4 inhibitors currently approved by the FDA include saxagliptin, sitagliptin, alogliptin, and linagliptin, and vildagliptin is approved for use in Europe. This review focuses mainly on DPP-4 inhibitors and critically evaluates the literature on the potential use of these agents in the prevention of atherosclerosis and thrombus formation. More specifically, we examine preclinical and clinical studies evaluating the effects of these agents on factors associated with atherosclerotic plaque development, such as blood pressure, lipid profile, inflammation, endothelial dysfunction, and platelet activation. Finally, we also briefly review studies aimed at addressing the long-term cardiovascular safety of DPP-4 inhibitors in patients with T2D, and other studies currently under way.

Blood Pressure

Hypertension is a well-established risk factor for atherosclerosis, and is two times more likely to occur in patients with T2D than in those without T2D [8]. Evidence available from animal and human studies suggests that DPP-4 inhibitors could have beneficial effects on lowering blood pressure.

In Zucker diabetic fatty rats, sitagliptin (10 mg/kg body weight/day) was shown to inhibit the development of hypertension associated with the progression of diabetes [9]. In another model of L-NAME (a nitric oxide synthase inhibitor)-induced hypertensive nephropathy in Wistar rats, sitagliptin treatment significantly improved hypertension, and resulted in an upregulation of renal GLP-1R expression and increased serum nitric oxide (NO) levels. In addition, pathological changes to the kidney associated with L-NAME administration were reduced in sitagliptin-treated rats [10].

Small but significant effects on blood pressure have also been observed in short-term studies in humans. A double-blind, placebo-controlled, three-period-crossover study was initiated to assess the effects of sitagliptin on patients with mild to moderate hypertension. In this study, 19 patients were randomized to receive sitagliptin (50 mg/day or 100 mg/day) or placebo for 5 days, with 7-day washout periods between. Treatment with both doses of sitagliptin resulted in small but significant reductions (approximately 2–3 mmHg) in 24-h ambulatory systolic and diastolic blood pressure acutely (day 1) and at the steady state (day 5) [11]. Another short-term study also suggested that sitagliptin (100 mg/day for 5 days) can interact with angiotensin-converting enzyme (ACE) inhibitors in hemodynamic control. At a submaximal (5-mg) dose of the ACE inhibitor enalapril, sitagliptin enhanced the reduction in blood pressure exerted by enalapril alone; however, at a maximal dose of enalapril (10 mg), sitagliptin *attenuated* the hypotensive response to enalapril. The proposed mechanism behind this modulation was that sitagliptin was activating the sympathetic nervous system at high doses of enalapril [12]. This interesting observation begs the question as to what the effects of DPP-4 inhibitors might be in diabetic subjects taking higher doses of ACE inhibitors. Indeed, we speculate that this and related lines of investigation are needed to help unravel the unexpected increase in heart failure hospitalizations observed in SAVOR-TIMI 53, the recently published long-term cardiovascular safety study of saxagliptin [13••].

The effect of DPP-4 inhibitors on blood pressure has also been investigated in longer-term studies. One such study included 17 hypertensive Japanese men with T2D who had exhibited little variation in their blood pressure profiles over the preceding 6 months. When they were treated with sitagliptin (50 mg/day on alternate days) for 6 months, their systolic blood pressure was significantly reduced, and remained so for the duration of the study. A similar effect on diastolic blood pressure was not observed. This reduction in blood pressure was not correlated with the decrease in hemoglobin A_{1c} (HbA_{1c}) levels associated with sitagliptin treatment, suggesting that the effect on blood pressure was not a result of better glycemic control [14].

These results have also been repeated on a larger scale. A retrospective, observational study of 940 T2D patients investigated the effects of sitagliptin on blood pressure over a 12-week period. These patients were either not being treated with antihypertensive agents (n=619), or were receiving unaltered antihypertensive agents throughout the duration of the study (n=314). Again, significant decreases in systolic and diastolic blood pressure were observed in the patients receiving sitgaliptin [15]. Although the effects of DPP-4 inhibitor treatment on blood pressure have been small, they have been consistent.

Lipid Profile

T2D is often associated with dyslipidemia, including elevated levels of triglycerides, particularly postprandial triglycerides, higher levels of low-density lipoprotein (LDL), and low levels of high-density lipoprotein. Indeed, dyslipidemia in diabetes is a particularly strong risk factor for cardiovascular disease and atherothrombotic events [16, 17]. Treatment with DPP-4 inhibitors has been associated with improved dyslipidemia.

A small study of 31 patients found that treatment with vildagliptin (50 mg twice daily) for 4 weeks reduced postprandial proatherogenic triglyceride levels as compared with

placebo [18]. Another randomized, double-blind crossover study of 20 obese patients examined the effect of vildagliptin (100 mg/day) for 7 days versus placebo. This study found that treatment with the DPP-4 inhibitor resulted in increased postprandial adipose tissue lipid mobilization, which was associated with an increase in postprandial systemic lipid oxidation rate. As plasma levels of norepinephrine were elevated after treatment with the DPP-4 inhibitor, the authors of the study hypothesized that a mechanism underlying the "lipolytic" effect of vildagliptin was GLP-1-mediated activation of the sympathetic nervous system [19]. A study of 36 subjects investigated the effects of sitagliptin (100 mg/day) treatment for 6 weeks on dyslipidemia. Treatment with sitagliptin resulted in a significant reduction in fasting cholesterol, apolipoprotein B, and LDL cholesterol levels, as well as postprandial levels of triglycerides and free fatty acids [20]. Similar results have also been demonstrated with alogliptin [21].

In the retrospective observational study of 940 patients with T2D discussed previously, patients treated with sitagliptin also showed a significant reduction in total cholesterol and postprandial triglyceride levels after 4 and 12 weeks of treatment compared with the baseline [15]. Together these studies suggest that DPP-4 inhibitors improve dyslipidemia, which may contribute to potential long-term cardiovascular benefits.

Inflammation

The biology of inflammation includes the expression of adhesion molecules on the endothelium, inflammatory cell infiltration, and the ultimate formation, growth, and rupture of atherosclerotic plaques [22, 23]. Chronic, low-grade inflammation is often present in T2D, and subjects with T2D have been shown to express inflammatory cytokines and manifest endothelial dysfunction [24, 25]. Contributing to this phenotype, T2D is often associated with obesity, and inflammatory cells are known to accumulate in obese adipose tissue [26]. DPP-4 was first identified for its role in the immune system, where it was designated as cell surface marker CD26. The CD26 marker is expressed at relatively low levels on T cells, but its expression is rapidly upregulated with T-cell activation. CD26 is involved in the co-stimulatory signal necessary for T-cell activation, as well as in signal transduction pathways leading to cytokine proliferation and production [27]. Given a role for CD26 in immune signaling, it is perhaps not surprising that DPP-4 inhibitors have been found to exert immunological effects. One meta-analysis has shown that patients treated with DPP-4 inhibitors have an increased incidence of infection. However, the studies included in this meta-analysis were of relatively short duration (mostly under 30 weeks), with longer-term effects on immune function remaining unstudied. This having been said, the long-term SAVOR-TIMI 53 study found no significant increase in the incidence of infection in patients treated with saxagliptin [13••]. Another study also showed that patients treated with sitagliptin for at least 6 months had no significant difference in T-cell activation compared with untreated controls [28]. One study in humans compared the levels of C-reactive protein (a general marker of inflammation) in patients with T2D treated for 6 months with either sitagliptin or aggressive conventional treatments. This study found that sitagliptin treatment was associated with a significant reduction in C-reactive protein levels [29]. Together, the animal studies and this human study suggest a potential beneficial role of DPP-4 inhibitor treatment in T2D- and obesity-related inflammation.

T-cell expression of CD26 has also been correlated with metabolic parameters, with higher expression levels in patients with higher HbA_{1c} levels, and higher expression in patients with T2D than in nondiabetic controls [30]. Excluding patients treated with thiazolidinediones and metformin, another study also showed that T2D was associated with higher serum levels of CD26, and that treatment with DPP-4 inhibitors decreased the expression of T-cell CD26 [30]. The clinical relevance of this observation is uncertain.

In LDL-receptor-deficient ($LDLR^{-/-}$) mice receiving a high-fat diet, alogliptin caused reduced recruitment of inflammatory macrophages and monocytes to visceral adipose tissue. As well, treatment with the DPP-4 inhibitor decreased atherosclerotic plaque burden in the aortic sinus, and reduced proinflammatory macrophage infiltration in these plaques [31]. An examination of C57BL/6 mice fed a high-fat diet showed that treatment with sitagliptin reduced inflammatory cytokine expression [interleukin (IL)-6, IL-12, monocyte chemoattractant protein 1] in pancreatic islets. Additionally, these mice showed reduced expression of inflammatory markers [IL-6, IL-12, tumor necrosis factor (TNF)-α] in their adipose tissue, as well as decreased macrophage infiltration [32]. Yet another study showed similar reductions in the levels of inflammatory macrophage and $CD8^{+}$ cells in adipose tissue, with improved fatty liver phenotype of high-fat-fed mice treated with desfluorositagliptin (mixed in with the diet to 1.1 % concentration) [33]. Finally, a study in high-fat-fed apolipoprotein $E^{-/-}$ mice also showed that sitagliptin treatment for 12 weeks reduced plaque monocyte infiltration and stabilized plaques through a GLP-1-dependent mechanism [34]. Together, these animal studies suggest that treatment with DPP-4 improves inflammation in several tissues throughout the body. Whether DPP-4 inhibitors have an effect on the immune system through direct inhibition of CD26 on immune cells or by upregulating GLP-1 to increase GLP-1R activation, remains unknown. For example, the GLP-1R agonist liraglutide has been shown to decrease inflammation in the hearts of high-fat-fed mice, and GLP-1 has been shown to inhibit the interaction between TNF-α-activated human umbilical vascular endothelial cells and monocytes (THP-1) [35].

Endothelial Dysfunction

Endothelial dysfunction causes the endothelium to become proinflammatory and proatherogenic, and is a major contributor to atherosclerosis and atherothrombotic events. When the endothelium is dysfunctional, as in T2D, secretion of the vasodilators NO and prostacyclin is reduced [36]. Some studies have shown that DPP-4 inhibitor treatment is associated with improved endothelial function, which may attenuate the risk of atherosclerosis.

In preconstricted aortic segments from C57BL/6 mice, alogliptin treatment resulted in dose-dependent vasorelaxation. The mechanism behind this effect was mediated through increased secretion of nitric oxide, generated by the Src–Akt–endothelial nitric oxide synthase pathway. Pretreating the arteries with exendin(9-39), a GLP-1R antagonist, did not inhibit the alogliptin-induced vasorelaxation, suggesting that the effect was independent of GLP-1R [37•]. A study in obese Zucker diabetic fatty rats treated with saxagliptin (10 mg/kg/day) for 4 and 8 weeks showed significant and progressive increases in NO generation from glomerular and aortic endothelial cells. This effect was not accompanied by significant changes in fasting blood glucose levels, indicating that the improved endothelial function was not a result of better glycemic control [38]. In another study, sitagliptin (10 mg/kg/day) treatment improved endothelial function in renal arteries of spontaneously hypertensive rats [39]. These studies suggest a beneficial effect of DPP-4 inhibition on endothelial function.

A study of DPP-4 expression on human endothelial cells in intramyocardial blood vessels showed that DPP-4 expression is decreased in infarct areas after myocardial infarction (MI). Further, this decrease in DPP-4 was associated with an increase in expression of tissue factor in the endothelium, suggesting that endothelial DPP-4 may serve to increase the endothelial thrombogenicity and increase the risk of atherothrombotic events [40]. In another study, 40 patients with coronary artery disease, uncontrolled T2D, and endothelial dysfunction were randomized to receive either sitagliptin (50 mg/day) treatment or intensified conventional treatment for 6 months. Patients receiving sitagliptin showed a significantly greater improvement in endothelial function compared with controls (62.4±59.2 % vs 15.9±22.0 %, $p<0.01$), as measured by reactive hyperemia peripheral artery tonometry. Improvements in endothelial function were not correlated with improvements in HbA_{1c} levels [29]. In contrast, one study showed that treatment with sitagliptin (50 mg/day) and alogliptin (25 mg/day) for 6 weeks attenuated endothelial function, as measured by flow-mediated vasodilation in the brachial artery [41]. Although mechanistic studies in animals and some studies in humans seem to show improvements in endothelial dysfunction with DPP-4 inhibitor treatment, other studies in humans have found the opposite. More research is necessary to determine whether the effect of DPP-4 inhibitor treatment on the endothelium is actually beneficial, and what the factors are that might explain some of these discrepant results to date.

Platelet Function

Platelets play a crucial role in thrombosis and hemostasis, and are involved in atherogenesis and plaque rupture. Patients with T2D exhibit a prothrombic state, consisting of increased levels of coagulation factors, hyperactive platelets, and increased surface expression of integrins [42–44]. This contributes to the increased incidence of atherothrombotic events in T2D [42, 45]. Our laboratory has shown that megakaryocytes (the cellular precursors to platelets) express GLP-1R, and that GLP-1 and the GLP-1R agonist exendin-4 inhibit thrombin-induced platelet aggregation in vitro [46]. Another group has demonstrated that sitagliptin has an inhibitory effect on platelets isolated from patients with T2D, as well as on platelets isolated from healthy volunteers and subsequently incubated with sitagliptin [47]. If DPP-4 inhibitors are antiplatelet agents, they could exert beneficial effects on both plaque formation and rupture.

DPP-4 Inhibitor Treatment and Cardiovascular Outcomes

Numerous studies have been conducted to assess the cardiovascular consequences of DPP-4 inhibition, and the effects of their use on the risk of atherothrombotic events (Table 1).

Large-scale studies have shown beneficial effects of DPP-4 inhibitor treatment on cardiovascular outcomes. A 2-year double-blind parallel-group study investigated the efficacy and safety of linagliptin ($n=777$) versus glimepiride ($n=775$). Both groups showed similar reductions in HbA_{1c} levels; however, the linagliptin group had significantly fewer cardiovascular events [relative risk 0.46; 95 % confidence interval (CI) 0.23–0.91; $p=0.0213$] [48•]. Similar results were observed in a meta-analysis that combined the results of eight phase 3 studies investigating the effects of linagliptin versus a comparator, and included a total of 3,319 patients receiving linagliptin, and 1,920 receiving a comparator. The primary end point of this meta-analysis was fatal or nonfatal MI or stroke and unstable angina. The linagliptin group had a significantly lower incidence of meeting the primary end point (hazard ratio 0.34; 95 % CI 0.16–0.70) [49]. The DiaRegis registry, a prospective, observational and noninterventional study of 3,810 patients, investigated the effects of DPP-4 inhibitors on cardiovascular outcomes. Patients were randomized to receive either DPP-4 inhibitors or sulfonylureas on top of metformin monotherapy, and baseline characteristics were recorded. At 12 months after randomization to either

Table 1 Summary of completed dipeptidyl peptidase 4 (*DPP-4*) inhibitor cardiovascular safety clinical trials

Drug	Study design	No. of patients (DPP-4 inhibitor)	No. of patients (comparator)	Duration	Outcome
Linagliptin vs glimepiride [48•]	Double-blind	777	775	2 years	Decreased number of CV events
Linagliptin vs placebo, glimepiride, voglibose [49]	Meta-analysis of phase 3 trials	3,319	1920	>12 weeks	Decreased inidence of fatal/nonfatal MI, stroke, unstable angina
DPP-4 inhibitor vs sulfonylurea [50]	Observational, noninterventional	463	153	1 year	Decreased incidence of stroke, transient ischemic attack
DPP-4 inhibitors vs comparator [51]	Meta-analysis	41,959		>24 weeks	Decreased risk of MACE, all-cause death
Saxagliptin vs placebo, metformin, uptitrated glyburide [52]	Systematic overview of phase 2/3 trials	3,356	1,251	–	Decreased risk of CV events
Sitagliptin vs comparator [54]	Post hoc analysis of double-blind trials	7,726	6,885	12 weeks–2 years	Decreased risk of MACE
Sitagliptin vs metformin [55]	Retrospective cohort study	1,228	83,528	4 years	No difference for all-cause mortality, acute MI, stroke
Saxagliptin vs placebo [13••]	Double-blind, placebo-controlled	16,492		Median 2.1 years	Noninferior for CV death, MI, stroke, increased hospitalization for HF
Alogliptin vs placebo [56]	Double-blind, placebo-controlled	5,380		Median 18 months	No difference in MACE

CV cardiovascular, *HF* heart failure, *MACE* major adverse cardiovascular events, *MI* myocardial infarction

sulfonylureas (n=153) or DPP-4 inhibitors (n=463), DPP-4 inhibitor-treated patients had a significantly lower incidence of stroke and transient ischemic attack, and a trend towards a reduction in the incidence of nonfatal vascular events. This was not associated with a significant difference in HbA_{1c} levels or body weight between groups [50]. Another recent meta-analysis of all randomized trials (70 trials and 41,959 patients) with a duration longer than 24 weeks comparing DPP-4 inhibitors with either placebo or a comparator found that treatment with a DPP-4 inhibitor reduced the risk of major adverse cardiovascular events (MACE), reaching statistical significance for saxagliptin and vildagliptin [51]. Fewer studies included in this meta-analysis investigated the risk of MI and stroke; however, those that did reported significantly lower risk of MI, but not stroke. Additionally, the risk of all-cause death, but not cardiovascular death, was significantly decreased [51].

Several studies have also shown that treatment with a DPP-4 inhibitor has neutral or only small beneficial effects on cardiovascular outcomes. A study led by Bristol-Myers Squibb investigating the cardiovascular outcomes associated with saxagliptin treatment compiled the results of eight short-term phase 2/3 clinical trials studying the efficacy and safety of saxagliptin. Across these trials, no increase in the risk of cardiovascular death, MI, or stroke was reported, with the unexpected finding that risk of cardiovascular events was actually reduced [52]. A study led by Merck investigated the cardiovascular outcomes of patients treated with sitagliptin (100 mg/day). This study combined 19 double-blind clinical trials with durations of 12 weeks to 2 years, including 10,246 patients with T2D. The study also found no increased incidence of MACE in subjects treated with sitagliptin (risk ratio 0.68; 95 % CI 0.41–1.12) [53]. This study was then updated to include results up until December 2011, encompassing 25 clinical trials and 14,611 patients. Post hoc analysis aimed at specifically assessing the incidence of MACE in these studies found a slightly reduced risk of MACE in sitagliptin-treated patients (adjusted incidence rate ratio 0.87; 95 % CI 0.56–1.35) [54]. A 4-year retrospective cohort of Danish subjects was used to investigate the cardiovascular effects associated with sitagliptin monotherapy (n=1,228) versus metformin monotherapy (n=83,528). There was no statistically significant difference between these groups for all-cause mortality, or for a composite end point of all-cause mortality, acute MI, and stroke [55].

Recently, the results of two large safety studies specifically designed to investigate the cardiovascular outcomes of high-risk diabetic subjects treated with saxagliptin versus placebo (SAVOR-TIMI 53) and alogliptin versus placebo (EXAMINE) became available. SAVOR-TIMI 53 was a multicenter, double-blind, placebo-controlled phase 4 trial that included 16,492 patients randomly assigned to treatment with either saxagliptin (5 mg/day or 2.5 mg/day in patients with a glomerular filtration rate of 50 ml/min or less) or placebo. As stated, the patients selected for this study had a history of or were at a high-risk of cardiovascular events. This study found that treatment with saxagliptin was noninferior, but not

superior, to placebo for the composite end point of cardiovascular death, MI, and stroke. However, the risk of hospitalization for heart failure was increased in the saxagliptin group (3.5 % vs 2.8 %; hazard ratio 1.27; 95 % CI 1.07–1.51; p= 0.007) [13••]. Of note, just over 50 % of the study population were taking an ACE inhibitor. As mentioned earlier, sitagliptin has been shown to attenuate the hypotensive response to high-dose enalapril [12]. We have speculated on whether this or other perturbations in cardiorenal function caused by saxagliptin in vulnerable subjects could underlie this unexpected observation.

The EXAMINE study investigated the effects of alogliptin on cardiovascular outcomes in patients who had recently had acute coronary syndrome. In this study, 5,380 patients were randomized to receive either alogliptin (12.5–25 mg/day depending on kidney function) or placebo for a median duration of 18 months (maximum 40 months). The primary end point was a composite of death from cardiovascular causes, and nonfatal MI or stroke. As in SAVOR-TIMI 53, there was no difference between alogliptin and placebo in the primary end point [56]. Again, in a population at high risk of cardiovascular events, the very high frequency of concomitantly administered cardioprotective medications such a statins, beta-blockers, aspirin, and inhibitors of the renin–angiotensin system may have reduced the opportunity for DPP-4 inhibitors to manifest cardiovascular benefits.

Clinical Trials Under Way

Several studies are currently under way to understand further the cardiovascular consequences of DPP-4 inhibitor treatment (Table 2). The Sitagliptin Cardiovascular Outcome Study (MK-0341-082) (TECOS) is a 5-year study with an estimated enrollment of 14,000 patients and an expected completion date of December 2014. The primary outcome measure of this study is the time to the first cardiovascular event (NCT00790205) [57]. The CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes began in October 2010, and is expected to conclude in September 2018 with an enrollment of 6,000 patients. The primary outcome measure is a composite end point of cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina (NCT01243424) [58].

Saxagliptin and Atherosclerosis (SAXATH) is a study that is currently recruiting, and is aimed at investigating the effects of saxagliptin on atherosclerosis. The estimated enrollment for SAXATH is 50 patients, and the primary outcome measure is a change in a selection of atherosclerosis biomarkers from the baseline to 3 months of saxagliptin treatment (NCT01552018) [59]. Effects of Vildagliptin/Metformin Combination on Markers of Atherosclerosis, Thrombosis, and Inflammation in Diabetics with Coronary Artery Disease (VAAST) will include an estimated 60 patients, and is estimated to be completed by December 2014. The primary outcome measure of this study is a reduction in serum levels of IL-6 (NCT01604213) [60]. Another prospectively designed retrospective database study, Risk of Cardiovascular Events in Patients with Type 2 Diabetes Initiating Oral Antidiabetic Treatments, is investigating the effects of saxagliptin on cardiovascular events compared with

Table 2 Clinical trials currently under way investigating the cardiovascular safety of DPP-4 inhibitors

Trial name	Drug	Duration	Enrollment	Primary outcome measures	Expected completion date
Sitagliptin Cardiovascular Outcome Study (MK-0431-082) (TECOS) (NCT00790205)	Sitagliptin vs placebo	5 years	14,000	Time to 1st CV event	December 2014
CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (NCT01243424)	Linagliptin vs glimepiride	400 weeks	6,000	Composite end point of cardiovascular death, nonfatal MI, nonfatal stroke, unstable angina	September 2018
Saxagliptin and Atherosclerosis (SAXATH) (NCT01552018)	Saxagliptin vs placebo	3 months	50	Change in a selection of biomarkers for atherosclerosis	TBD
Effects of Vildagliptin/Metformin Combination on Markers of Atherosclerosis, Thrombosis, and Inflammation in Diabetics with Coronary Artery Disease (VAAST) (NCT01604213)	Vildagliptin/metformin vs metformin monotherapy	3 months	60	Reduction in serum levels of IL-6	December 2014
Risk of Cardiovascular Events in Patients with Type 2 Diabetes Initiating Oral Antidiabetic Treatments (NCT01086280)	Saxagliptin vs comparator	18–54 months	113,505	MACE	April 2015

IL interleukin

other oral antidiabetic agents, with an estimated enrollment of 113,505 patients and the primary outcome measure of major cardiovascular events The estimated completion date of this study is April 2015 (NCT01086280) [61].

Conclusion

To date, a major challenge of antidiabetic treatments has been to reduce the incidence of atherothrombotic cardiovascular events. The development of new drugs, such as DPP-4 inhibitors, has allowed a reexamination of the effects of antidiabetic treatments on risk factors beyond hyperglycemia. However, despite preclinical, small mechanistic clinical studies, and meta-analyses suggesting a potent variety of beneficial cardiovascular effects of DPP-4 inhibitors, two initial longer-term safety studies of DPP-4 inhibitors in patients with T2D at high risk of cardiovascular events have failed to show any benefits associated with their use. We believe this may be due to the difficulty of demonstrating cardiovascular benefits in study populations receiving aggressive risk factor modification. We believe this is a more likely explanation than the possibility that previous meta-analyses were systematically flawed, or that the beneficial effects of DPP-4 inhibitors documented in lower-risk populations are somehow lost in high-risk subjects.

Compliance with Ethics Guidelines

Conflict of Interest Alison Cameron-Vendrig and Mansoor Husain report grants from Merck during the duration of the study. Dhanwantee Mundil declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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