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**Cardiovascular effects of DPP-4 inhibitors : from risk factors to clinical
outcomes**

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Introduction

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular (CV) disease¹. Because of the presence of chronic hyperglycemia and a segregation of various cardiometabolic abnormalities linked to insulin resistance (so-called metabolic syndrome), patients with T2DM carry a poor prognosis with increased CV morbidity, CV mortality and all-cause mortality². Nevertheless, a meta-analysis of results from large interventional clinical trials suggests that tight glucose control does not reduce the risk of macrovascular events in T2DM and even may cause harm³. This may reflect the adverse consequences of increased hypoglycemia and/or the negative effects of many antidiabetic agents on weight gain^{4,5}. Indeed, metformin, which does not induce hypoglycemia nor weight gain, appears to be more beneficial than sulfonylureas or insulin in reducing the incidence of CV events⁶. Furthermore, the CV consequences of intensive therapy may also depend on the specific mechanism of action of the antidiabetic agent(s) used to achieve tight glycemic control⁷⁻⁹. In this regard, metformin is considered to offer some CV favorable pleiotropic effects, independently of its glucose-lowering activity¹⁰, although its protective CV effect has been challenged recently¹¹. Interestingly, observational studies showed that the protective effects of metformin may also be observed in patients with T2DM who are generally considered as at risk and for whom metformin is officially contraindicated¹².

Dipeptidyl peptidase-4 (DPP-4) inhibitors, also called gliptins, are a promising pharmacological class of glucose-lowering agents that open new perspectives for the management of T2DM¹³. Several DPP-4 inhibitors are already commercialized, sitagliptin (FDA approval October 2006),¹⁴ vildagliptin (not approved in US but available in most other countries, including Europe)^{15,16}, saxagliptin (FDA approval July 2009)¹⁷, linagliptin (FDA approval May 2011)¹⁸ and alogliptin (FDA approval January 2013)^{19,20}, and several other compounds are in current development. Although they produce slightly lower or rather similar reductions in blood glucose concentrations and glycated hemoglobin (HbA1c) levels as compared with other antihyperglycemic agents^{21,22}, DPP-4 inhibitors may offer several clinical advantages²²⁻²⁴, including a negligible risk of hypoglycemia, especially much lower than that observed with sulfonylureas²⁵⁻²⁷, and an absence of weight gain (rather a slight

weight reduction may occur), contrasting with the increase of body weight generally observed with sulfonylureas, glinides, thiazolidinediones and insulin therapy^{25,27-29}. These advantages have been recognized in a recently updated position statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for the management of hyperglycemia in T2DM³⁰.

DPP-4 inhibitors increase glucagon-like peptide-1 (GLP1) levels by blocking the degradation of this gastrointestinal hormone into inactive products. Because GLP-1 may exert positive effects on CV system^{31,32}, incretin-based therapies may open new perspectives in the management of T2DM by providing some CV protection³³⁻³⁸. GLP-1 levels are increased to a lesser magnitude with oral DPP-4 inhibitors than GLP-1 receptor agonists (exenatide, liraglutide)^{39,40}, but DPP-4 cleaves multiple other peptides and numerous DPP-4 substrates have been identified to act on multiple peripheral tissues that influence the CV system^{31,37}. These pleiotropic effects associated with DPP-4 inhibitors may result in favorable CV outcomes, independently of GLP-1 and GLP-1 receptor^{31,38}.

The present review provides an updated evaluation of the CV effects of DPP-4 inhibitors or gliptins in patients with T2DM. The review, which is restricted to human data only, is divided into three main parts. The first part consists of a systematic description of the effects of gliptins on various CV risk factors that may contribute to favorably influence the CV prognosis of patients with T2DM. The second part analyzes some surrogate endpoints in patients with coronary artery disease, with a special focus on the effects of DPP-4 inhibitors on cardiomyocyte metabolism and myocardial ischemic preconditioning. The third part reports the available preliminary data from phase II-III trials suggesting that DPP-4 inhibitors are safe and may reduce the incidence of CV events; it also briefly describes the ongoing prospective trials with CV outcomes designed to prove this hypothesis in T2DM patients with a high CV risk profile.

Material and methods

To identify relevant studies, an extensive literature search of MEDLINE was performed from January 2005 to February 2013, with the term “DPP-4 inhibitors” or the generic names “sitagliptin”, “vildagliptin”, “saxagliptin”, “alogliptin”, “linagliptin” combined with cardiovascular, coronary heart disease, stroke, atherosclerosis. No language restrictions were imposed. References of original studies, narrative reviews and previous systematic reviews were also carefully examined.

Results

1. Effects on cardiovascular risk factors

The accelerated atherosclerosis and CV disease in T2DM is likely to be multifactorial and therefore several mechanisms may be targeted by pharmacological interventions¹. Besides their incretin effects and beyond their effects on glucose control, DPP-4 inhibitors can influence some CV risk factors, which may contribute to a potential anti-atherogenic activity in T2DM (Table 1)⁴¹.

1.1. Blood glucose control

In a recent meta-analysis of 62 evaluated articles concerning trials of at least 12 weeks, DPP-4 inhibitors lowered glycated hemoglobin (A1c) significantly more than placebo (weighted mean difference [WMD] -0.76%; 95% confidence interval or CI -0.83 to -0.68)⁴². In the 17 active comparator trials, there was no significant difference in A1c reduction (WMD 0.04%; 95% CI -0.09 to 0.16)⁴². No clinically relevant difference in A1c was observed in comparison with thiazolidinediones, α -glucosidase inhibitors or sulfonylureas, whereas metformin produced a slightly greater reduction in A1c^{21,43-45}. DPP-4 inhibitors showed a similar efficacy in monotherapy and in combination with other agents^{21,22}. They appear to be more effective in older patients with mild/moderate fasting hyperglycemia⁴³. No major differences could be found between the various available DPP-4 inhibitors regarding the reduction in A1c levels⁴⁴⁻⁴⁶. However, as reviewed recently²¹, head-to-head comparisons are scarce and only one trial of > 12 weeks may be found in the literature⁴⁷. In an 18-week non-inferiority trial in T2DM patients whose glycemia was inadequately controlled with metformin, saxagliptin 5 mg showed non-inferiority compared to sitagliptin 100 mg⁴⁷. In a recent paper, a novel model-based meta-analysis to indirectly estimate the comparative efficacy of two medications showed a similar A1c reduction with linagliptin 5 mg and sitagliptin 100 mg at 24 weeks⁴⁸.

Incretins play a major role in glucose homeostasis⁴⁹. In general, an almost twofold reduction in postprandial glucose concentrations compared with the corresponding reduction in fasting plasma glucose levels has been reported with the various DPP-4 inhibitors^{50,51}. This more portent effect after a meal may be of interest considering the potential deleterious impact of postprandial hyperglycemia on oxidative stress and atherothrombosis⁵². Reduction of glucose excursion by DPP-4 inhibition may prevent the progression of carotid intima-

media thickness, a surrogate marker for early atherosclerosis, in patients with T2DM, probably through the reduction of daily silent inflammation and oxidative stress (see below 1.5 and 1.6)⁵³.

1.2. Body weight

In most cases, T2DM is associated with overweight or obesity⁴ so that weight management may be an essential factor when selecting an appropriate antidiabetic therapy in T2DM⁵⁴. Except metformin, traditional pharmacotherapies for T2DM (insulin, sulfonylureas, glinides, glitazones) can further increase body weight, making management of overweight or obese patients with T2DM quite challenging^{4,55}. A systematic review and meta-analysis selected 27 reports of 19 studies including 7,136 patients randomized to a DPP-4 inhibitor and 6,745 patients randomized to another anti-hyperglycemic drug. DPP-4 inhibitors had a favorable weight profile compared with sulfonylureas (WMD -1.92 kg, 95% CI -2.34 to -1.49) or pioglitazone (-2.96 kg, 95% CI -4.13 to -1.78), but not compared with GLP-1 receptor agonists (1.56 kg, 95% CI 0.94 to 2.18)²⁷.

The weight gain observed with many glucose-lowering agents may undermine the cardiometabolic benefits of improved glycemic control.^{28,29} Consequently, while reduction in hyperglycemia remains the foremost goal in the treatment of patients with T2DM, the avoidance of weight gain may be a clinically important secondary objective and this might be taken into account when selecting glucose-lowering therapies^{28,56}. Because they improve glucose control while being weight-neutral, DPP-4 inhibitors represent a potentially important addition to the oral treatment options currently available for the management of T2DM⁵⁷, even if the precise underlying mechanisms require further investigation^{58,59}.

No specific study investigated changes in fat distribution (subcutaneous/visceral fat) or body composition (fat/muscle components) with DPP-4 inhibitors. A study evaluated patients with T2DM who initiated an incretin-based (exenatide or sitagliptin) or insulin-based regimen to analyze the relationship between weight change and glycemic control and improvement in CV risk biomarkers in a real-world setting. Compared to insulin, weight reductions with incretin-based therapies were associated with shifts toward a more favorable CV risk profile with a lowering of blood pressure (BP) and a significant improvement of lipid profile⁶⁰.

1.3. Blood pressure

Preclinical and clinical studies investigating the antihypertensive effects of incretins were recently reviewed^{61,62}. Overall, DPP-4 inhibition may contribute to a small reduction in

BP, although the effect was less marked than with GLP-1 receptor agonists (exenatide, liraglutide)⁶³⁻⁶⁵. In most phase 2-3 trials with DPP-4 inhibitors, no consistent effect on BP (systolic BP : -0.1; 95% CI -1.2 to +0.8 mmHg) has been recorded⁶⁶. However, none of these trials was designed to specifically evaluate the effects on BP, which was measured routinely, as part of the safety assessment, and in T2DM patients not specifically selected for hypertension⁶⁶. Nevertheless, sitagliptin has some more specific data. It produced small but statistically significant reductions of 2-3 mmHg in 24-hour ambulatory BP measurements in nondiabetic patients with mild to moderate hypertension⁶⁴. Sitagliptin also lowered systolic BP without reducing body mass index, independent of the blood glucose reduction, in Japanese hypertensive patients with T2DM⁶⁷. Recent experimental data suggested that the local actions of incretins may be via their key role in regulating natriuresis, thereby lowering BP, especially in individuals with salt-sensitive hypertension⁶⁸.

1.4. Lipid profile

The lipid effects of some antihyperglycemic agents may influence CV risk beyond glucose-lowering actions⁶⁹. This may be a matter of concern for CV prognosis as recently demonstrated by the experience with rosiglitazone⁷⁰. Of potential interest, incretin-based therapies may target postprandial lipid metabolism and thereby may favorably influence several endothelial and CV functions in patients with T2DM⁷¹⁻⁷³.

DPP-4 inhibitors have been found to have an effect on postprandial lipid levels⁵¹. Treatment with sitagliptin for 6 weeks reduced postprandial plasma levels of triglyceride-rich lipoproteins of both intestinal and hepatic origin, most likely by increasing incretin hormone levels, reducing circulating plasma free fatty acid concentrations and improving insulin sensitivity and β -cell function⁷⁴. Treatment with vildagliptin for 4 weeks improved postprandial plasma triglyceride and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal^{75,76}. In an experimental study assessing changes in adipose tissue and skeletal muscle metabolism induced in T2DM patients, vildagliptin augmented postprandial lipid mobilization and oxidation, possibly by sympathetic activation rather than a direct effect on metabolic status⁷⁷. One-week treatment with alogliptin treatment significantly suppressed the postprandial elevation in serum triglycerides, apoB-48, and remnant lipoprotein cholesterol both in non-diabetic subjects⁷⁸ and in patients with T2DM⁷⁹. The mechanisms underlying the effects of DPP-4 inhibitors on lipid

metabolism, especially in the postprandial phase, and their potential relationships with weight regulation remain to be explored⁵⁹.

Lipid profile after an overnight fast may also be improved by DPP-4 inhibition. In patients initiating sitagliptin, change in body weight was significantly associated with improvements in fasting triglycerides and total cholesterol⁶⁰. When added to previously taken antidiabetic agents, sitagliptin after 2 years of therapy reduced body weight and insulin resistance and improved lipid profile (reduction in total and LDL cholesterol, lowering of triglycerides and augmentation in HDL cholesterol)⁸⁰. A meta-analysis suggested a possible beneficial effect of DPP-4 inhibitors on cholesterol, which, although small, could contribute to the reduction of CV risk⁸¹. In a recent meta-analysis of 70 trials with DPP-4inhibitors, a significant reduction in total cholesterol was observed (-0.28; 95% CI -0.46 to -0.10 mmol/l), with no significant changes in HDL cholesterol (-0.02; 95% CI -0.04 to +0.01 mmol/l)⁶⁶.

The data support the concept that incretins not only modulate glucose metabolism but also influence lipid metabolism, in general, and chylomicron metabolism in intestinal cells and postprandial lipemia, in particular. However, further human studies are needed to better establish the impact of DPP-4 inhibition on dyslipidemia and the potential contribution of the lipid modulation to the potential overall CV benefit of gliptins.

1.5. Silent inflammation

Sitagliptin has been shown to reduce high-sensitive C-reactive protein (hsCRP) level, similarly as metformin, in T2DM patients already treated with pioglitazone⁸². Significant reductions in hsCRP and soluble vascular cell adhesion molecule 1 were also observed at 6 months of a treatment with sitagliptin in Japanese T2DM patients⁸³. In another study in such a population, sitagliptin reduced inflammatory cytokines and improved the unfavorable M1/M2-like phenotypes of peripheral blood monocytes⁸⁴. A potent and rapid antiinflammatory effect of sitagliptin has been reported in patients with T2DM with a significant fall in both mRNA expression and protein expression of several proinflammatory markers after 12 weeks of sitagliptin⁸⁵.

In patients with T2DM inadequately controlled by metformin, reduction in glucose variability by a DPP-4 inhibitor was associated with reductions of markers of systemic inflammation, such as IL-6 and IL-18 levels⁸⁶. In a study comparing the two DPP-4 inhibitors, the same group reported significant correlations between change in daily acute glucose fluctuations, change in carotid intima-media thickness and change in fasting and interprandial

(180 min after meals) inflammation score (combining IL-6, IL-18 and TNF- α changes) and nitrotyrosine plasma levels⁵³.

1.6. Oxidative stress

During a meal, glycemia, nitrotyrosine, and plasma 8-iso prostaglandin F₂ α (8-iso-PGF₂ α) remained unchanged in the control subjects, whereas these markers of oxidative stress increased in T2DM patients, despite the fact that GLP-1 increased in both groups⁸⁷. DPP-4 inhibition by vildagliptin may blunt daily acute glucose fluctuations in patients with T2DM and this effect was associated and significantly correlated with a reduction in nitrotyrosine, a marker of oxidative stress^{53,86}. In another study, however, oxidative stress, assessed by the marker STAT-8-isoprostane, was not significantly affected by adding sitagliptin to metformin-treated T2DM patients for 3 months⁸⁸.

1.7. Endothelial function

Endothelial dysfunction is an early component of atherosclerosis and appears to be a critical determinant of CV events in patients with T2DM. Post-meal GLP-1 secretion can simultaneously exert an incretin effect on insulin secretion and a protective effect on endothelial function, reasonably controlling oxidative stress generation⁸⁷. The ability of GLP-1 in protecting endothelial function seems to depend on the level of glycemia⁸⁷.

There is increasing evidence that at least pharmacologic concentrations of GLP-1 or GLP-1 mimetics may improve endothelial function and have direct vascular-protective effects^{89,90}. Intravenous infusion of GLP-1 improved endothelial dysfunction in T2DM patients with coronary heart disease⁹¹. It remains questionable whether physiological levels of GLP-1, as those achieved after DPP-4 inhibition, are high enough to exert similar favorable effects on endothelial function. However, DPP4 inhibitors may increase the availability of endothelial progenitor cells (EPCs), via a GLP-1 receptor-independent pathway⁹². Several DPP-4 inhibitors have shown positive effects on endothelial function^{78,93,94}.

Four weeks' treatment with vildagliptin improved endothelium-dependent vasodilatation in subjects with T2DM, compared to therapy with acarbose, an alpha-glucosidase inhibitor targeting postprandial hyperglycemia⁹³. One-week treatment with alogliptin significantly improved postprandial endothelial dysfunction in non-diabetic subjects, an effect that may be explained by concomitant improvement of postprandial lipemia⁷⁸. The treatment of T2DM patients with sitagliptin also reversed vascular endothelial

dysfunction, as evidenced by increase in the flow-mediated dilation⁹⁴. In patients with coronary artery disease and T2DM, sitagliptin significantly improved endothelial function and inflammatory markers, beyond its hypoglycemic action⁹⁵. Sitagliptin was shown to increase circulating vasculoprotective EPCs in T2DM patients with concomitant upregulation of stromal-derived factor-1alpha (SDF-1 α), which is a substrate of DPP-4⁹⁶. The modulation of EPCs, as well as inflammatory pathway and ischemic response, emerges as a major CV target of DPP-4 inhibitors⁹⁷.

Recent experimental observations provide a molecular explanation, involving transcriptional regulation of gene expression, for in vivo studies suggesting DPP-4 inhibitors may have novel, GLP-1 independent, effects in acting to attenuate endothelial cell dysfunction and atherogenesis⁹⁸.

1.1.8 Antiplatelet activity

Sitagliptin has been shown to inhibit platelet aggregation in both healthy individuals and patients with T2DM. The concentration-dependent antiplatelet activity was attributed to the inhibitory effect of sitagliptin on intracellular free calcium and tyrosine phosphorylation⁹⁹. The potential effects of vildagliptin, compared to those of pioglitazone, on coagulation cascade in T2DM, thus targeting thrombogenesis, have been recently reviewed¹⁰⁰.

2. Surrogate endpoints in patients with coronary artery disease

Intriguing findings showed significantly lower fasting levels of active GLP-1 in patients with coronary artery disease than those without¹⁰¹. Available experimental evidence, together with a few pilot studies in humans, showed that GLP-1 receptor agonists and DPP-4 inhibitors are capable of ameliorating myocardial function and protect cardiocytes from ischemic damage, independent of their glucose-lowering effects⁹². A large body of animal experiments now provides compelling evidence for the advantageous impact of DPP-4 inhibition in the ischemia/reperfusion injury model¹⁰². Human data showed that vildagliptin does not damage the protective mechanism of myocardial ischemic preconditioning in patients with T2DM and coronary artery disease, in contrast to repaglinide, a glucose-lowering agent acting as K(ATP) channel blocker (a mechanism shared by sulfonylureas)¹⁰³.

Sitagliptin improved beta-cell function and glucose perturbations in patients with acute coronary syndrome and newly diagnosed glucose disturbances¹⁰⁴. Short-term studies appeared

to demonstrate modest yet beneficial actions of DPP-4 inhibition on cardiac function in subjects with ischemic heart disease³¹. The augmentation of GLP-1 by inhibition of DPP-4 by sitagliptin improved global and regional left ventricular performance in response to dobutamine stress and mitigated postischemic stunning in patients with coronary artery disease¹⁰⁵. Preliminary results from the REPERATOR study suggested that high cellular CD26 expression decreases the migration of peripheral blood mononuclear cells towards SDF-1 α and high cellular CD26 expression negatively influences cardiac function post-MI. Treating patients shortly post-MI with sitagliptin to inhibit CD26 may therefore increase mononuclear cells homing to the infarct area and could improve cardiac recovery and repair¹⁰⁶. A first interim analysis demonstrated that the combined application of sitagliptin and Granulocyte-Colony Stimulating Factor (G-CSF) seems to be safe on the short term and feasible after acute MI and may represent a new therapeutic option in future, which is currently tested in the SITAGRAMI trial¹⁰⁷.

3. CV clinical outcomes

Regulatory agencies such as the US Food and Drug Administration actually now mandate that all new glucose-lowering medications undergo thorough CV safety assessment before marketing approval¹⁰⁸. New therapeutic approaches, such as incretin-based therapies in general and DPP-4 inhibitors in particular, should ideally also target CV risk, beyond glucose control¹⁰⁹. CV safety was evaluated through the examination of CV adverse event reports in phase 2-3 trials performed with any of the five DPP-4 inhibitors. Pooled and meta-analyses of clinical trial data have shown no increase in major adverse CV events, but rather suggest a potential CV benefit to such DPP-4 inhibition therapy¹¹⁰. Available analyses for each DPP-4 inhibitor are summarized in Table 2¹¹¹⁻¹¹⁶.

According to a Cochrane review, long-term data, especially on CV outcomes and safety, are urgently needed before widespread use of these new agents¹¹⁷. Whether gliptins actually decrease CV outcomes remains to be confirmed by large randomized placebo-controlled trials specifically designed for such demonstration¹¹⁸. Several prospective trials are ongoing in order to demonstrate the CV safety (non-inferiority analysis versus placebo) and possibly the superiority of DPP-4 inhibitors to reduce the incidence of CV events in T2DM patients at high risk of CV disease (Table 3)¹¹⁹⁻¹²¹. All trials are comparing the DPP-4 inhibitor with a placebo, except CAROLINA that will compare linagliptin with the sulfonylurea glimepiride¹²². Furthermore, all studies are investigating T2DM patients with

high CV risk but with a stable disease, except EXAMINE with alogliptin specifically devoted to T2DM patients with recent acute coronary syndrome¹²¹.

3.1.Sitagliptin

3.1.1 Pooled phase II-III trials

A first pooled analysis of data from 10,246 patients with T2DM demonstrated the safety and tolerability of sitagliptin in clinical studies¹¹¹. These data were confirmed by a post hoc assessment of CV safety in 14,611 patients. This further analysis pooled data from 25 double-blind studies (duration : 12 to 104 weeks), which randomized patients at baseline to sitagliptin 100 mg/day or a non-sitagliptin comparator (i.e., non-exposed). Patient-level data were used in this analysis of major adverse cardiovascular events (MACE) including ischemic events and CV deaths. Analyses were performed in three cohorts: the entire 25-study cohort, the cohort from placebo-controlled portions of studies (n=19), and the cohort from studies comparing sitagliptin to a sulfonylurea (n=3). The exposure-adjusted incidence rate was 0.65 per 100 patient-years in the sitagliptin group versus 0.74 in the non-exposed group (RR = 0.83; 95% CI 0.53 to 1.30) in the entire cohort analysis, 0.80 per 100-patient-years with sitagliptin versus 0.76 with placebo (RR = 1.01 ; 95% CI 0.55 to 1.86) in the analysis comparing sitagliptin to placebo (thus an almost similar risk with sitagliptin and placebo), and 0.00 per 100 patient-years with sitagliptin versus 0.86 with sulfonylurea (RR = 0.00, 95% CI 0.00 to 0.31) in the analysis comparing sitagliptin to sulfonylurea. Thus, this pooled analysis does not indicate that treatment with sitagliptin increases CV risk in patients with T2DM, but rather suggests that sitagliptin may be associated with a lower CV risk compared to a sulfonylurea¹²³.

3.1.2. TECOS with sitagliptin

The purpose of TECOS is to evaluate the potential impact of sitagliptin when used in addition to usual diabetes care on CV outcomes and clinical safety in a multinational (around 30 countries), randomized, double-blind, placebo-controlled trial¹¹⁹. TECOS is a pragmatic, academically run trial that will recruit approximately 14,000 patients with T2DM who are ≥ 50 years old, have documented CV, and who have an A1c ≥ 6.5 and $\leq 8\%$ on stable doses of any one or two of three oral antihyperglycemic agents (metformin, sulfonylurea, pioglitazone). Randomization will be 1:1 to the addition of double-blind sitagliptin (100 mg/day, reduced to 50 or 25 mg/day in case of renal impairment) or matching placebo to a patient's existing diabetes care regimen in a usual care setting, with the aim of achieving glycemic equipoise in

the two groups. The primary endpoint will be the time to the first occurrence of a composite CV outcome (CV death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina). CV events will be adjudicated by an independent committee, blinded to study therapy. In this non-inferiority trial, follow up will be a minimum of four years or until 1300 primary endpoints have occurred¹¹⁹. This study is projected to be completed in 2015.

3.2. Vildagliptin

3.2.1 Pooled phase II-III trials

Data were pooled from 25 phase 3 studies of vildagliptin, used either as monotherapy or combination therapy, with durations of 12 weeks to $>$ or $=$ 2 years¹¹². The safety of vildagliptin (50 mg qd, $n = 1,393$ or 50 mg bid, $n = 6,116$) was assessed relative to a pool of all comparators (both placebo and active comparators, $n = 6,061$). CV and cerebrovascular events were adjudicated in a prospective, blinded fashion by an independent adjudication committee. Categories included in the composite endpoint were acute coronary syndrome, transient ischaemic attack (with imaging evidence of MI), stroke and CV and cerebrovascular death. Relative to all comparators, the RRs for the composite endpoint were < 1 for both vildagliptin 50 mg qd (RR = 0.88, 95% CI 0.37 to 2.11) and vildagliptin 50 mg bid (RR = 0.84, 95% CI 0.62 to 1.14). The results were consistent across subgroups defined by age, gender and CV risk status. The exposure-adjusted incidences of each component of the composite endpoint for vildagliptin 50 mg bid were also lower than or similar to those of all comparators. Thus, in a large meta-analysis, vildagliptin was not associated with an increased risk of adjudicated CV and cerebrovascular events relative to all comparators¹¹².

3.2.2. CV outcome study

Vildagliptin, in contrast to other DPP-4 inhibitors, is not currently evaluated in a large prospective CV outcome study.

3.3. Saxagliptin

3.3.1 Pooled phase II-III trials

The RR for CV events has been assessed across all 8 randomized phase 2/3 trials evaluating saxagliptin in patients with T2DM. CV events (death, MI, stroke, revascularization procedures, and cardiac ischemia) were reported by investigators through standard adverse event reporting procedures and were systematically identified. Post hoc blinded adjudication of all deaths, MIs, and strokes was performed using prespecified endpoint definitions by an

independent clinical events committee. A total of 4,607 randomized and treated patients (n = 3,356 treated with saxagliptin 2.5-100 mg/day versus n = 1,251, comparator [n = 656, placebo; n = 328, metformin; n = 267, uptitrated glyburide]) were included. The clinical events committee reviewed 147 patients with potential CV events and identified a total of 40 patients with CV death/MI/stroke: 22 (0.7%), saxagliptin; 18 (1.4%), comparator; RR = 0.43 (95% CI 0.23 to 0.80). No increased risk of CV death/MI/stroke was observed in patients randomly assigned saxagliptin across a broad drug development program. In contrast, although this systematic overview has inherent and important limitations, the data support a potential reduction in CV events with saxagliptin^{113,114}.

3.3.2. SAVOR-TIMI 53 with saxagliptin

SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus-Thrombolysis In Myocardial Infarction) is a phase 4, randomized, double-blind, placebo-controlled trial conducted in 25 countries that is designed to evaluate the safety and efficacy of saxagliptin during long-term treatment of approximately 16,500 patients with T2DM¹²⁰. Eligible patients who are either treatment naive or on any background antidiabetic treatment (except incretin therapy) with history of established CV disease or multiple risk factors are randomized 1:1 to saxagliptin 5 mg qd (2.5 mg in subjects with moderate/severe renal impairment) or matching placebo, stratified by qualifying disease state. The primary end point is the composite of CV death, nonfatal MI, or nonfatal ischemic stroke. The trial will continue until approximately 1,040 primary end points accrue. Thus, SAVOR-TIMI 53 is testing the hypothesis that treatment with saxagliptin is safe and reduces CV events in high-risk patients with T2DM¹²⁰. The results of this trial should be already available during the second part of 2013.

3.4. Alogliptin

3.4.1 Pooled phase II-III trials

To determine whether alogliptin affects CV risk, the incidence of CV events in patients treated with alogliptin, placebo or comparator anti-hyperglycemic drugs was evaluated in the clinical trial database for alogliptin using the composite major adverse cardiovascular event (MACE) end points of CV death, nonfatal myocardial infarction and nonfatal stroke¹¹⁵. The pooled analysis included 4,168 patients exposed to alogliptin 12.5 and 25 mg daily for 2023 patient-years compared to 691 patients treated with placebo for 263 patient-years and 1,169 patients treated with other anti-diabetic agents (metformin,

sulfonylureas, and thiazolidinediones) for 703 patient-years. Cardiovascular events were adjudicated by an expert endpoint committee blinded to treatment allocation. The incidence rates of the combined MACE were not significantly different between patients treated with alogliptin and comparator therapies (HR = 0.635, 95% CI 0.0 to 1.41). Additionally, other types of serious CV events were not significantly different between patients treated with alogliptin and comparator therapies¹¹⁵.

3.4.2. EXAMINE with alogliptin

Long-term CV safety of alogliptin is being established in a randomized, placebo-controlled clinical study in T2DM patients with acute coronary syndrome using an analytical approach that has both an interim and final assessment (EXAMINE : EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome)¹²¹. The primary CV end point for this trial is a composite of CV death, nonfatal MI, and nonfatal stroke. Approximately 5,400 men and women with T2DM and acute coronary syndrome (acute MI or unstable angina) are being recruited and will be followed up for up to 4.5 years postrandomization. The statistical plan for the trial uses a design that evaluates the HR of alogliptin to placebo first based on the primary CV composite end point after accrual of 80 to 150 primary CV events and again when there are 550 to 650 primary CV events. In the first series of analyses, the upper bound of a group-sequential 1-sided repeated CI for the HR must be ≤ 1.8 for registration in the United States¹⁰⁸. At end of study, the upper bound of a subsequent group-sequential 1-sided repeated CI for the HR must be ≤ 1.3 . EXAMINE will define the CV safety profile of alogliptin in patients at high risk for CV events¹²¹. This study is projected to be completed in 2014.

3.5. Linagliptin

3.5.1 Pooled phase II-III trials

In a pre-specified meta-analysis of CV events in linagliptin or comparator-treated patients with T2DM from eight phase 3 studies, all suspected CV events were prospectively adjudicated by a blinded independent expert committee¹¹⁶. The primary endpoint was a composite of CV death, stroke, MI, and hospitalization for unstable angina. Of 5,239 treated patients, 3,319 received linagliptin once daily (5 mg, n = 3,159; 10 mg, n = 160) and 1,920 received comparators (placebo, n = 977; glimepiride 1-4 mg, n = 781; voglibose 0.6 mg, n = 162). Primary CV events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%)

receiving comparators¹¹⁶. The HR for the primary endpoint showed significantly lower risk with linagliptin than comparators (HR = 0.34, 95% CI 0.16 to 0.70) as did estimates for all three secondary endpoints (HR ranging from 0.34 to 0.55 for CV death, non-fatal stroke, and non-fatal MI, all adjudicated CV events or FDA-defined custom MACE ; all upper 95% CIs < 1.0)¹¹⁶. The results from this large phase 3 program support the hypothesis that linagliptin may have CV benefits in patients with T2DM¹¹⁶. These findings were confirmed in a recently published 2-year trial comparing linagliptin against a commonly used sulfonylurea (glimepiride); the DPP-4 inhibitor was associated with significantly fewer CV events (12 vs 26 patients; RR=0.46, 95% CI 0.23 to 0.91, p=0.0213)¹²⁴.

3.5.2. CAROLINA with linagliptin

CAROLINA is an active comparator CARdiovascular Outcome study of the DPP-4 Inhibitor LINAgliptin in patients with T2DM at high CV risk¹²². The aim this multicentre, international, randomized, parallel group, double blind study, is to investigate the long-term impact on CV morbidity and mortality of treatment with linagliptin (5 mg od) in patients with T2DM at elevated CV risk receiving usual care, and compare outcome against glimepiride (1-4 mg once daily) used as reference. To be included T2DM patients should have elevated HbA1c and pre-existing CV disease or specified diabetes end-organ damage or age ≥ 70 years or two or more specified CV risk factor. The primary outcome measure is the time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death, non-fatal MI, non-fatal stroke and hospitalisation for unstable angina pectoris. CAROLINA is currently the largest head-to-head CV outcome trial that involves a comparison of a sulfonylurea (glimepiride) with a DPP-4 inhibitor (linagliptin) and will provide a unique perspective with respect to CV outcomes with these two commonly used agents¹²². This study is projected to be completed in 2018.

3.6. Meta-analyses

Several meta-analyses pooling data from all DPP-4 inhibitors together have been published^{45,66,125}. In a first meta-analysis of 41 randomized controlled trials, the relative risk of CV events and all-cause death with DPP-4 inhibitors was 0.76 (95% CI 0.46 to 1.28) and 0.78 (95% CI 0.40 to 1.51), respectively, compared with placebo or an active comparator⁴⁵. A more recent meta-analysis by the same group included a total of 70 trials with a duration ≥ 24 weeks enrolling 41,959 patients with a mean follow-up of 44.1 weeks⁶⁶. When comparing DPP-4 inhibitors with placebo or other glucose-lowering agents, the ORs were 0.71 (95% CI

0.59 to 0.86), 0.64 (95% CI 0.44 to 0.94), 0.77 (95% CI 0.48 to 1.24) and 0.60 (95% CI 0.41 to 0.88) for MACE, MI, stroke and mortality, respectively (Table 2). These favorable results were consistent across subgroups defined by age, gender and CV risk status. The reduction in the incidence of MI was greater than what predicted on the basis of conventional risk factors, suggesting a role for other mechanisms of DPP-4 inhibition⁶⁶.

A meta-analysis was performed by another group using fixed and random effects to specifically determine risk ratio (RR) for adverse CV events with DPP-4 inhibitor monotherapy compared to other oral diabetic medications or to placebo¹²⁵. Eighteen controlled trials met inclusion criteria, comprising 4,998 patients who were randomized to DPP-4 inhibitors and 3,546 to a comparator, with a median duration of therapy of 46.4 weeks. In pooled analysis, the RR of any adverse CV event with a DPP-4 inhibitor was 0.48 (95% CI 0.31 to 0.75), and the RR for nonfatal MI or acute coronary syndrome was 0.40 (95% CI 0.18 to 0.88)¹²⁵.

In these three meta-analyses, comparison groups comprised T2DM patients treated with placebo or an active glucose-lowering agent, cardiac and vascular events were combined, and trials with all DPP-4 inhibitors were pooled together. A recent systematic review and meta-analysis restricted its analysis to placebo-controlled trials only (thus excluding comparison with sulfonylureas), tried to analyze separately cardiac versus vascular events and aimed at comparing the findings of each DPP-4 inhibitor¹²⁶. Generally speaking, the results were less favorable. However, data should be taken cautiously because of a rather low number of events in all subgroups of patients. Finally, it is noteworthy that none of the studies included in all these meta-analyses have been designed to specifically assess the CV efficacy of DPP-4 inhibitors.

Conclusion

Numerous clinical trials demonstrated that DPP-4 inhibitors provide effective and consistent glycemic control with a good tolerability profile, especially no severe hypoglycemia and no weight gain. Additional non-glycemic favorable effects on some well recognized CV risk factors have been also reported in patients with T2DM, such as reductions in BP, postprandial lipemia, silent inflammation, oxidative stress, endothelial dysfunction and possibly platelet aggregation. Although each individual effect may appear somewhat modest, their combination may lead to a significant reduction in atherothrombosis and associated complications in patients with T2DM. DPP-4-inhibitors not only block the degradation of GLP-1, but also the inactivation of several other peptides that may have vasoactive and

cardioprotective effects. Post-hoc analyses of phase 2-3 controlled trials support the CV safety of DPP-4 inhibitors and suggest a possible CV protection compared to placebo or an active comparator (sulfonylurea in most instances). Large prospective trials with CV outcomes are ongoing to demonstrate first the non-inferiority and possibly the superiority of DPP-4 inhibitors compared to placebo (or a sulfonylurea in CAROLINA) in patients with T2DM and high CV risk.

SUMMARY (max 300 words)

Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) are oral incretin-based glucose-lowering agents with proven efficacy and safety in the management of type 2 diabetes mellitus (T2DM). In addition, pre-clinical data and mechanistic studies suggest a possible additional non-glycemic beneficial action on vessels and heart, via both glucagon-like peptide-1 (GLP-1)-dependent and GLP-1-independent effects. As a matter of fact, DPP-4 inhibitors improve several cardiovascular risk factors; they improve glucose control (mainly by reducing postprandial glycemia) and are weight neutral, they may somewhat lower blood pressure, improve postprandial (and even fasting) lipemia, reduce inflammatory markers, diminish oxidative stress, improve endothelial function and reduce platelet aggregation in patients with T2DM. In addition, positive effects on the myocardium have been described in patients with ischemic heart disease. Results of post-hoc analyses of phase 2-3 controlled trials suggest a possible cardioprotective effect with a trend (sometimes significant) to lower incidence of major cardiovascular events with sitagliptin, vildagliptin, saxagliptin, linagliptin or alogliptin compared to placebo or other active glucose-lowering agents. However, the definite relationship between DPP-4 inhibition and better cardiovascular outcomes remains to be proven. Major prospective clinical trials involving various DPP-4 inhibitors with predefined cardiovascular outcomes are underway in patients with T2DM and a high risk cardiovascular profile : TECOS with sitagliptin, SAVOR-TIMI 53 with saxagliptin, EXAMINE with alogliptin and CAROLINA with linagliptin. If these trials confirm that a DPP-4 inhibitor can reduce the cardiovascular burden of T2DM, it would be a major progress that will dramatically influence the management of the disease.

Key-words : Cardiovascular outcomes – Dipeptidyl peptidase-4 inhibitor – Gliptin – Glucagon-like peptide-1 – Type 2 diabetes mellitus

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Table 1 : Incretin-based and pleiotropic effects of dipeptidyl peptidase-4 (DPP-4) inhibitors on various cardiovascular risk factors in patients with type 2 diabetes mellitus (T2DM).

Abnormalities in T2DM	Favorable effects of DPP-4 inhibitors
Impaired insulin secretion	Increased (glucose-dependent) insulin secretion ³⁹
Increased glucagon levels	Decreased (glucose-dependent) glucagon levels ³⁹
Increased hepatic glucose production	Decreased hepatic glucose production ³⁹
Hyperglycemia	Reduction in fasting and postprandial glycemia ^{50,51} Reduction in HbA1c ^{21,42}
Body weight excess	Weight neutrality (or small reduction) ^{21,27}
Elevated blood pressure	Modest reduction or no change in blood pressure ^{62,64,67}
Dyslipidemia	Reduction in postprandial lipemia ^{74,76,77,79} Mild improvement in fasting lipid profile ⁸¹
Silent inflammation	Reduction in inflammatory markers (hs-CRP, IL-6, IL-18) ^{85,86}
Oxidative stress	Reduction in nitrotyrosine ^{53,86}
Endothelial dysfunction	Improved flow-mediated dilation ^{78,93,94}
Platelet hyperactivity	Reduction of platelet aggregation ⁹⁹

Table 2 : Relative risk (RR) of cardiovascular (CV) events in T2DM patients receiving a DPP-4 inhibitor (exposed) versus a comparator (placebo or active drug : non exposed) in pooled phase 2-3 trials. MI : Myocardial Infarction. MACEs : Major Adverse Cardiovascular Events. CV : confidence interval.

DPP-4 inhibitor	References	N Trials N Patients	Events Per 100 patient.years	CV Events RR (95% CI)
Sitagliptin	Williams- Herman et al 2010 ¹¹¹ Engel et al 2013 ¹²³	19 trials N=10,246 25 trials N= 14,611	0.6 vs 0.9 MACEs 0.65 vs 0.74 MACEs	0.68 (0.41, 1.12) 0.83 (0.53-1.30)
Vildagliptin	Schweizer et al 2010 ¹¹²	25 trials N=10,988	1.32 vs 1.64 % MACEs (*)	0.84 (**) (0.62, 1.14)
Saxagliptin	Frederich et al 2010 ¹¹³ Cobble et al 2012 ¹¹⁴	8 trials N=4,607	0.7 vs 1.4 CV deaths, MI,stroke	0.43 (0.23, 0.80)
Alogliptin	White et al 2013 ¹¹⁵	11 trials N=6,028	0.3 vs 0.5	0.635 (0, 1.406)
Linagliptin	Johansen et al 2011 ¹¹⁶	8 trials N=5,239	0.53 vs 1.68 MACEs (*)	0.34 (0.16, 0.70)
All gliptins (pooled analysis)	Monami et al 2013 ⁶⁶	70 trials N=41,959	MACEs MI Stroke CV mortality Total mortality	0.71 (0.59, 0.86) 0.64 (0.44, 0.94) 0.77 (0.48, 1.24) 0.67 (0.39, 1.14) 0.60 (0.41, 0.88)

(*) For this analysis, a blinded committee adjudicated all events.

(**) Data in patients receiving vildagliptin 50 twice daily (for vildagliptin 50 mg once daily : RR = 0.88; 95% CI 0.37, 2.11)

Table 3 : Ongoing prospective clinical trials specifically designed to analyze CV outcomes.

No such trial is underway with vildagliptin.

DPP-4 inhibitor (ClinicalTrials.gov identifier)	Ongoing CV trials Acronyms	N (drug comparison)	Population	Primary endpoint	Expected results Year
Sitagliptin (NCT00790205)	TECOS : <u>T</u> rial <u>E</u> valuating <u>C</u> ardiovascular <u>O</u> utcomes with <u>S</u> itagliptin ¹¹⁹	N = 14,000 50/100 mg vs placebo Non-inferiority trial	HbA1c 6.5-8% CV disease history	Time to first confirmed CV event (nonfatal MI, nonfatal stroke, or hospitalization for unstable angina)	2015
Saxagliptin (NCT01107886)	SAVOR-TIMI53 : <u>S</u> axagliptin <u>A</u> ssessment of <u>V</u> ascular <u>O</u> utcomes <u>R</u> ecorded in Patients with Diabetes Mellitus Trial ¹²⁰	N = 16,500 2.5/5 mg vs placebo Non inferiority/ superiority trial	HbA1c ≥ 6.5% High CV risk	Time to first confirmed CV event (nonfatal MI, nonfatal ischemic stroke, or CV death)	2013
Alogliptin (NCT00968708)	EXAMINE : <u>E</u> Xamination of <u>C</u> ardiovascular <u>O</u> utcomes: Alogliptin vs. Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome ¹²¹	N = 5,400 6.25/12.5/25 mg vs placebo Superiority trial	HbA1c 6.5-11% Recent acute coronary syndrome	Time from randomization to the first occurrence of a primary major adverse cardiac event (nonfatal MI, nonfatal stroke, or CV death)	2014
Linagliptin (NCT01243424)	CAROLINA : Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes ¹²²	N = 6,000 5 mg vs glimepiride 1-4 mg Non-inferiority/ Superiority trial	HbA1c 6.5-8.5% High CV risk	Time to the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or CV death	2018

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