A review of gliptins for 2011

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Review
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ABSTRACT

Introduction : Dipeptidylpeptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes (T2DM).

Areas covered : This paper is an updated review, providing an analysis of both the similarities and differences between the various compounds known as gliptins, currently used in the clinic (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin). This paper discusses: the pharmacokinetic and pharmacodynamic characteristics of gliptins; both the efficacy and safety profiles of gliptins in clinical trials (compared to classical glucose-lowering agents), given as monotherapy or in combination, including in special populations; the positioning of DPP-4 inhibitors in the management of T2DM in recent guidelines; and various unanswered questions and perspectives.

Expert opinion: The role of DPP-4 inhibitors in the therapeutic armamentarium of T2DM is evolving, as their potential strengths and weaknesses become better defined. Future critical issues may include the durability of glucose control, resulting from better β-cell protection, positive effects on cardiovascular outcomes and long-term safety issues.

Key-words : Clinical trial – DPP-4 inhibitor – Gliptin – Pharmacodynamics – Pharmacokinetics –Type 2 diabetes mellitus

ARTICLE HIGHLIGHTS BOX

- Dipeptidylpeptidase-4 (DPP-4) inhibitors (gliptins) are incretin-based therapies that play an increasing role in the management of type 2 diabetes (T2DM), especially in combination with other glucose-lowering agents.
- All compounds (sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin) act as oral selective DPP-4 inhibitors (thereby inhibiting GLP-1 and GIP metabolism), but differ by some important pharmacokinetic properties that may be clinically relevant in some patients.
- By stimulating insulin secretion and reducing glucagon secretion, in a glucose-dependent manner, DPP-4 inhibitors diminish both fasting and postprandial glucose levels, without inducing hypoglycemia, and reduce HbA1c levels by about 0.6-0.8 %.
- DPP-4 inhibitors are weight neutral (contrasting with the weight gain reported with many other glucose-lowering agents) and may exert some favorable effects on cardiovascular risk markers.
- Preliminary encouraging results obtained in phase 3 trials initiated large prospective (ongoing) trials to demonstrate non-inferiority/superiority of a DPP-4 inhibitor (mostly versus a placebo) as far as cardiovascular outcomes are concerned.
- Overall, the tolerance/safety profile of DPP-4 inhibitors is excellent. Some concern regarding a possible higher risk of pancreatitis or even of pancreatic cancer with incretin-based therapies has been raised, which requires careful long-term postmarketing surveillance.
- Because of their favorable efficacy/safety profile, DPP-4 inhibitors are best suited for special populations of T2DM patients such as elderly people, patients with renal impairment or patients at risk of hypoglycemia.

1. Introduction

Dipeptidylpeptidase-4 (DPP-4) inhibitors are a promising pharmacological class of glucose-lowering agents that open new perspectives for the management of type 2 diabetes (T2DM). These agents inhibit the DPP-4 enzyme that rapidly degrades two major gastrointestinal hormones into inactive products, thereby increasing the active levels of these so-called incretin hormones, i.e. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The mechanism of action of DPP-4 inhibitors is distinct from any existing class of oral glucose-lowering agents [1]. Although they produce similar reductions in blood glucose concentrations and glycated hemoglobin (HbA1c) levels, DPP-4 inhibitors offer several clinical advantages [2]. The most important ones are a negligible risk of hypoglycemia, especially much lower than that observed with sulfonylureas, and a weight neutrality, contrasting with the weight gain generally observed with sulfonylureas and thiazolidinediones (TZDs). Therefore, this pharmacological class is expected to play an increasing role in the management of T2DM and several DPP-4 inhibitors ("gliptins") are already available or in current development.

The present review provides an updated evaluation of DPP-4 inhibitors. The following topics will be more particularly covered : 1) an analysis of both similarities and differences between the various compounds regarding pharmacokinetic (PK) and pharmacodynamic (PD) characteristics; 2) an evaluation of both the efficacy and safety profiles of gliptins in clinical trials, as monotherapy or in combination, compared to placebo or an active drug, including in special populations; 3) the positioning of DPP-4 inhibitors in the management of T2DM in recent guidelines; and 4) a brief discussion regarding unanswered questions and perspectives. To identify relevant studies, an extensive literature search of MEDLINE was performed from January 2005 to July 2011, with the term "DPP-4 inhibitors" or the generic names "sitagliptin", "vildagliptin", "saxagliptin", "alogliptin", "linagliptin". No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

2. The family of DPP-4 inhibitors (Fig 1)

The 'first-in-class' DPP-4 inhibitor, sitagliptin, was approved in 2006 and is now available worldwide [3, 4]. It was followed by vildagliptin, available in the EU and many other countries since 2007, although approval by the US Food and Drug Administration (FDA) is

still pending [5-7]. More recent compounds are saxagliptin (in 2009) [8-10], alogliptin (in 2010, presently only in Japan) [11] and linagliptin, which recently received approval in the US, Europe and Japan [12]. Several other DPP-4 inhibitors are still in development (dutogliptin, gemigliptin, …) [13, 14]. The chemical structures of the first five DPP-4 inhibitors are depicted in Figure 1. All have a common mechanism of action and thereby share similar properties regarding clinical efficacy and safety profiles. However, DPP-4 inhibitors also show significant structural heterogeneity that could translate into different pharmacological, both pharmacokinetic (PK) and pharmacodynamic (PD), properties [15].

2.1. PK/PD similarities between gliptins

Although they differ in terms of their chemistry, DPP-4 inhibitors are all small molecules which are orally available (Table 1). They are similar when comparing their mode of action ("incretin enhancers"), efficacy regarding lowering HbA_{1c} levels, safety profile, and patient tolerance [15, 16].

At therapeutic doses, all DPP-4 inhibitors reduce plasma DPP-4 activity by 70-90% in a sustained manner (over 24 hours) and provide a clinically meaningful increase in GLP-1 levels (1.5-4 fold) (Table 2) [15]. By inhibiting enzymatic degradation and thereby increasing circulating levels of incretin hormones, DPP-4 inhibitors control elevated blood glucose by triggering pancreatic insulin secretion and suppressing pancreatic glucagon secretion (both in a glucose-dependent manner, therefore not exposing T2DM patient to hypoglycemia). They are able to reduce both fasting plasma glucose and postprandial glucose levels, in monotherapy and in combination, especially with metformin [17]. While they do not lower glucose to a greater extent than existing therapies, all DPP-4 inhibitors offer many potential advantages, including the ability to achieve sustainable reductions in HbA1c levels with a once-daily (except vildagliptin, which is preferably given twice daily) oral agent that has a low risk of hypoglycemia, is not associated with weight gain and has an apparently benign adverse event profile. At present, according to indirect comparisons reported in several meta-analyses [15, 18-21], there seems to be little to distinguish between the different DPP-4 inhibitors in terms of their efficacy as glucose-lowering compounds ("antidiabetic agents"), both as monotherapy or in combination, and their overall safety profile (see below).

2.2. PK/PD differences between gliptins

As the number of DPP-4 inhibitors on the market increases, potential differences among the different members of the class may become important when deciding which agent is best suited for an individual patient [15, 22]. There are some differences between them in terms of their absorption, distribution, metabolism and elimination, as well as in their potency and duration of action. At the PK level, DPP-4 inhibitors have important differences, including half-life, systemic exposure, bioavailability, protein binding, metabolism, presence of active metabolites, excretion routes and potential for drug-drug interactions (Table 1) [23, 24]. The different DPP-4 inhibitors are distinctive in their metabolism (saxagliptin and vildagliptin are metabolized in the liver whereas sitagliptin is not), their excretion (linagliptin is excreted mostly unchanged by the liver, in contrast to other DPP-4 inhibitors that are mainly eliminated via the kidneys), and the potential of cytochrome-mediated drug-drug interactions (observed with saxagliptin, but not with other gliptins). Certain of these differences may be clinically relevant, especially in patients with renal or hepatic impairment (see below : special populations), and when considering combination therapy , especially in patients with cardiovascular disease (CVD) receiving multiple drugs (Table 2) [25].

There are important differences in the kinetics of the interaction of different gliptins with the catalytic site of DPP-4, which may lead to varying PK, PD and dosing regimens. The recommended daily dosage that is required for effective treatment is different, varying from 5 mg for saxagliptin and linagliptin to 100 mg for sitagliptin and vildagliptin (Table 2). It has been pointed out that vildagliptin offers the advantage of a tight binding and slow dissociation characteristics that lead to a sustained overnight inhibitory effect on DPP-4 enzyme and glucose-lowering activity [17]. Furthermore, it has binding characteristics that ensure inhibition of the DPP-4 enzyme beyond the presence of detectable drug levels in plasma. Nevertheless, it is recommended to give vildagliptin as a twice daily administration whereas other DPP-4 inhibitors are given once daily.

DPP-4 may also be compared as far as their selectivity for DPP-4 compared to other DPP enzymes (Table 2). Selectivity for the DPP-4 enzyme may have implications for tolerability as suggested by animal experiments. However, most available data suggest that non selective DPP inhibition should not lead to clinical consequences [26]. However, further studies are needed to determine whether higher selectivity for DPP-4 in some compounds will offer a clinical advantage over other agents in the class.

Even if the expanding evidence base suggests that certain differences between DPP-4 inhibitors may prove to be clinically significant [22], only long-term accumulated clinical experience and data from large prospective clinical trials will reveal whether compound-related characteristics lead to any clinically relevant differences [15, 16].

3. Clinical efficacy of gliptins

3.1. Blood glucose control

DPP-4 inhibitors significantly reduced HbA1c at 24 weeks by 0.6 (0.5-0.7) % when compared with placebo; they showed a similar efficacy in monotherapy and in combination with other agents [20]. No clinically relevant difference in HbA1c was observed in comparisons with TZDs, α-glucosidase inhibitors or sulfonylureas, whereas metformin produced a slightly greater reduction in HbA1c, at least in the short term [27]. Initial observations suggested than DPP-4 inhibitors were less potent than TZDs to control blood glucose, but these differences almost disappear when between-study differences in treatment effects are adjusted for baseline differences in HbA1c levels [28, 29]. Although drugs for T2DM are studied in heterogeneous samples of patients, their efficacy can be predicted by some clinical parameters. DPP-4 inhibitors appear to be more effective in older patients with mild/moderate fasting hyperglycemia [27]. No major differences could be found between DPP-4 inhibitors regarding the reduction in HbA1c levels. For instance in a meta-analysis of 12 trials with sitagliptin and 11 trials with vildagliptin , the weighted mean differences versus placebo were -0.79 (95% CI = -0.93 to -0.65) for sitagliptin and -0.67 (95% CI = -0.83 to -0.52) for vildagliptin [18, 20, 21]. However, head-to-head comparisons are scarce. In an 18-week non-inferiority trial comparing the efficacy of saxagliptin and sitagliptin in T2DM patients whose glycemia was inadequately controlled with metformin, the adjusted mean changes in HbA1c were - 0.52 and - 0.62%, respectively. The between-group difference was 0.09% (95% CI, -0.01 to 0.20%), demonstrating non-inferiority of saxagliptin 5 mg versus sitagliptin 100 mg [30].

A recent meta-analysis of 43 randomized controlled trials assessed the efficacy of DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin and alogliptin) to reach the HbA1c target of <7% in people with T2DM and compared the results with those obtained in patients treated with placebo or another active glucose-lowering agent. A greater proportion of patients can achieve the HbA1c goal <7% with DPP-4 inhibitors compared to placebo, with

no weight gain, and no hypoglycemic risk when used alone. The reduction of the HbA1c level and the rate of HbA1c goal attainment were not different with DPP-4 inhibitors from that observed with active comparator drugs [18].

Incretins play a major role in glucose homeostasis [31]. Both fasting and postprandial glucose levels are significantly reduced by vildagliptin [32-34], as by all available DPP-4 inhibitors. Generally the reduction in postprandial glucose is almost twofold the diminution in fasting plasma glucose, with almost similar results reported with the various DPP-4 inhibitors [15]. Glucagon secretion plays an essential role in the regulation of hepatic glucose production, and elevated fasting and postprandial plasma glucagon concentrations in patients with T2DM contribute to their hyperglycemia [35]. DPP-4 inhibition results in a significant reduction in plasma glucagon levels, which may contribute to reduce postprandial glucose levels as suggested by the significant correlation between reductions in plasma glucagon and 2h-postmeal glucose levels [32, 33]. However, in case of hypoglycemia, glucagon secretion is not inhibited anymore by GLP-1, an important finding contributing to the absence of severe hypoglycemia reported with DPP-4 inhibitors [31].

3.2. Body weight

The vast majority of patients with T2DM are overweight or obese. Lifestyle intervention to lose weight is recommended in most diabetic patients to improve glycemic control and reduce associated risk factors. Furthermore, many agents used to target hyperglycemia (insulin, sulfonylureas, TZDs) are associated with weight gain, making management of overweight or obese patients with T2DM quite challenging[36, 37]. 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 T2DM [38], even if the precise underlying mechanisms require further investigation[39, 40].

3.3. Cardiovascular risk factors

In addition to their glucose-lowering and weight-neutral (or even mild weight-reducing) actions, DPP-4 inhibitors may exert some anti-atherogenic effects : decreased

systolic blood pressure (BP), improved postprandial lipid parameters, reduced high-sensitivity C-reactive protein (hsCRP) levels and improved endothelial dysfunction have been reported [41]. Yet, their long-term effects on subclinical or clinical atherosclerosis remain to be established by future studies (see below).

DPP-4 may contribute to a reduction in BP [42-44]. Sitagliptin produced small but statistically significant reductions of 2-3 mmHg in 24-hour ambulatory BP measurements acutely and at steady state, in nondiabetic patients with mild to moderate hypertension [43]. Sitagliptin also lowered systolic BP without reducing body mass index, independent of the blood glucose reduction, in Japanese hypertensive patients with T2DM [45]. 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 hypertension [46]. A recent study provided the first evidence for a complex interactive hemodynamic effect of DPP-4 and ACE (Angiotensin Converting Enzyme) inhibition in humans. Indeed, sitagliptin lowered BP during placebo or submaximal ACE inhibition whereas sitagliptin activated the sympathetic nervous system to diminish hypotension when ACE was maximally inhibited [42].

DPP-4 inhibitors have also been found to have an effect on postprandial lipid levels [15]. 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 function [47]. Treatment with vildagliptin for 4 weeks improves postprandial plasma triglyceride and apolipoprotein B-48-containing triglyceride-rich lipoprotein particle metabolism after a fat-rich meal [48]. 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 status [49]. The mechanisms underlying the effects of DPP-4 inhibitors on postprandial lipid metabolism and their potential relationships with weight regulation remain to be explored [40]. It has been suggested that vildagliptin may exert more favorable effects on plasma lipid profile than sitagliptin[15]. However, in absence of head-to-head trials, caution and further investigation are required.

Sitagliptin has been shown to reduce hsCRP level without any significant difference compared to metformin in T2DM patients already treated with pioglitazone [50]. Recent animal

data demonstrated that DPP-4 inhibition exerts antiatherosclerotic effects and reduces inflammation via inhibition of monocyte activation/chemotaxis, although the underlying mechanisms require further investigation [51]. Significant reductions in HsCRP, soluble vascular cell adhesion molecule 1 and microalbuminuria were also observed at 6 months of a treatment with sitagliptin 50 mg in Japanese T2DM patients [52]. Microalbuminuria in T2DM is considered not only as a marker of early nephropathy but also as a marker of endothelial dysfunction. Therefore, reduced microalbuminuria may also reflect improvement of endothelial function with DPP-4 inhibitors.

Endothelial dysfunction is a common finding in T2DM patients and is considered as an independent CV risk factor. Sitagliptin was shown to increase circulating vasculoprotective endothelial progenitor cells in T2DM patients with concomitant upregulation of stromal-derived factor-1alpha, which is a substrate of DPP-4 [53]. A recent study demonstrated that four weeks' treatment with vildagliptin improves endothelium-dependent vasodilatation in subjects with T2DM, compared to therapy with acarbose [54]. A recent experimental study showed that DPP-4 inhibition by alogliptin mediates rapid vascular relaxation via GLP-1 independent, Src-Akt-eNOS mediated NO release and the activation of vascular potassium channels [55]. These findings should be confirmed in humans as well as the relevance of these underlying mechanisms. However, the modulation of endothelial progenitor cells, inflammatory pathway and ischemic response emerges as a major CV target of DPP-4 inhibitors [56].

3.3. Beta-cell function and preservation

There is a progressive deterioration in β-cell function and mass in T2DM. Impaired β-cell function and possibly decreased β-cell mass might be reversible, particularly at early stages of the disease. In preclinical studies, DPP-4 inhibitors promoted β-cell proliferation, neogenesis, and inhibition of apoptosis in rodents [57]. Even if meal tolerance tests showed improvement in postprandial β-cell function with DPP-4 inhibitors, it is difficult to estimate the protective effects of incretin enhancers on β-cells in humans, and there is no clinical evidence yet that DPP-4 inhibitors really have such protective effects [57, 58].

In a model-based analysis of a meal tolerance test, sitagliptin improved β-cell function relative to placebo in both fasting and postprandial states in patients with T2DM treated with metformin monotherapy [59]. However, in a pilot study, improved HbA1c with sitagliptin could not be attributed to a significant effect on preservation of β-cell function [60]. Vildagliptin monotherapy consistently produced robust improvements in both fasting and meal test-

derived measures of β-cell function across a broad spectrum of drug-naïve patients with T2DM [34]. One year treatment with vildagliptin significantly increased β-cell secretory capacity. However, this effect was not maintained after the washout, indicating that this increased capacity was not a disease modifying effect on β-cell mass and/or function [61].

4. Clinical safety of gliptins

DPP-4 is a member of a family of ubiquitous atypical serine proteases with many physiological functions beyond incretin degradation, including effects on the endocrine and immune systems. Therefore, possible adverse effects resulting from DPP-4 inhibition cannot be excluded. However, the preponderance of available data suggests that non selective DPP inhibition is probably without clinical consequence, even if further surveillance is still required [26].

The tolerability profile of the DPP-4 inhibitors is generally considered as excellent, with the incidence of adverse events similar to that of placebo in phase 3 clinical trials. There was a suggestion of a slightly increased incidence of nasopharyngitis versus placebo (5-6% versus 3-4%) with sitagliptin and urinary tract infection (6.8 versus 6.1% with placebo) and headache with saxagliptin (6.5 versus 5.9% with placebo) [62]. A nested case-control study was conducted using VigiBase, the World Health Organization-Adverse Drug Reactions (WHO-ADR) database, and indicated an increased reporting of infections (reporting odds ratio : 2.3), in particular upper respiratory tract infections (reporting odds ratio : 12.3), for users of DPP-4 inhibitors compared with users of other antidiabetic drugs. However, because of the limitations of spontaneous reporting systems, further research is needed to evaluate this suspicion and the underlying mechanism [63].

The safety and tolerability of sitagliptin was assessed by pooling 19 double-blind clinical studies up to 2 years in duration in 10,246 patients with T2DM. Summary measures of overall adverse events were similar in the sitagliptin and non-exposed groups, except for an increased incidence of drug-related adverse events in the non-exposed group. Incidence rates of specific adverse events were also generally similar between the two groups, except for increased incidence rates of hypoglycemia, related to the greater use of a sulfonylurea, and diarrhea, related to the greater use of metformin, in the non-exposed group and constipation in the sitagliptin group [64].

Because of safety concern the US FDA declined approval of vildagliptin, requiring more data on adverse effects, notably possible liver and skin toxicities. However, a meta-analysis indicated that vildagliptin is not associated with increased risk of hepatic events or hepatic enzyme elevations indicative of drug-induced liver injury, skin-related toxicity or infections [65]. The overall good tolerance of vildagliptin was recently confirmed in another pooled analysis of 38 studies of 12-104 weeks' duration in which adverse event profiles of vildagliptin (50 mg twice daily) were evaluated relative to a pool of comparators (placebo and active comparators) [66].

The risk of acute pancreatitis with DPP-4 therapy remains a controversial and debated topic. A pooled analysis of controlled clinical trials revealed similar incidence rates of pancreatitis in patients treated with sitagliptin compared with those not treated with sitagliptin (0.08 events per 100 patient-years vs. 0.10 events per 100 patient-years, respectively). The conclusion was that clinical trial data with sitagliptin to date confirm preclinical observations and do not indicate an increased risk of pancreatitis in patients with T2DM treated with sitagliptin [67]. A similar conclusion was drawn from a meta-analysis of clinical trials with vildagliptin [65]. In a study population derived from a large US commercial health insurance transaction database using an active drug safety surveillance system, data did not provide evidence for an association of acute pancreatitis among initiators of sitagliptin compared to metformin/glyburide (glibenclamide) initiators [68]. A retrospective cohort study of a large medical and pharmacy claims database demonstrated increased incidence of acute pancreatitis in diabetic versus nondiabetic patients but did not find an association between the use of sitagliptin and acute pancreatitis. However, the limitations of this observational claims-based analysis cannot exclude the possibility of an increased risk [69].

In a recent controversial paper that examined the US FDA database of reported adverse events, the use of sitagliptin was shown to increase the odds ratio for reported pancreatitis 6-fold as compared with other therapies. A further astonishing observation was that pancreatic cancer was also more commonly reported among patients who took sitagliptin as compared with other therapies, while all other cancers occurred similarly among patients who took sitagliptin compared with other therapies [70]. Surprisingly also, this huge increase in relative risk of pancreatitis and pancreatic cancer reported with sitagliptin was almost similar to that noticed with exenatide. Reporting bias may be suspected to explain these unexpected observations. Nevertheless, further investigation is needed and long-term careful postmarketing surveillance is mandatory. Indeed, various experimental data in animal models

suggested that there are grounds for concern that the GLP-1 class of drugs may induce asymptomatic pancreatitis and, perhaps over time in some individuals, induce pancreatic cancer [71]. However, at present, these concerns are based on limited data.

A meta-analysis summarized multiple studies reporting that DPP-4 inhibitors affect the risk for clinical angioedema. Using clinical trials data from about 14,000 patients taking vildagliptin, 19 cases of angioedema were confirmed. Three-quarters of patients exhibiting angioedema were also taking an ACE inhibitor at the time of diagnosis [72]. In the Adverse Event Reports System database of the FDA, a search for all reports of potential drug allergy identified 4 cases of angioedema in patients treated with sitagliptin, besides other allergic reactions [73]. An altered immune function status was suspected as the underlying mechanism for angioedema and other hypersensitivity reactions to DPP-4 inhibitors. However, currently, despite the increasing use of DPP-4 inhibitors, few data are available to confirm the clinical impact and associations of DPP-4 inhibitors and angioedema, including any additive or synergistic angioedema risk in patients taking inhibitors of the renin-angiotensin system and DPP-4 inhibitors [74].

Thus, despite their good tolerance and safety profile, some concerns remain over long-term safety of DPP-4 inhibitors, as for other new drugs [75]. This must be weighed against any potential clinical benefit such as weight neutrality, low risk of hypoglycemia and improved CV surrogated risk factors.

5. Place of gliptins in the management of type 2 diabetes

5.1. DPP-4 inhibitors in DT2M patients

A recent review summarized the benefits and harms of different glucose-lowering agents, including DPP-4 inhibitors, as monotherapy and in combination, to treat adults with T2DM [76]. A composite endpoint for HbA1c reduction, lack of hypoglycemia and no body weight gain may be used to combine both efficacy and safety criteria and provide an integrated benefit/risk ratio for clinical use. Compared to sulfonylureas, significantly more patients treated by a DPP-4 inhibitor achieved an HbA1c reduction of >0.5% without hypoglycemia and without an increase in body weight [77] and compared to TZDs, significantly more patients receiving a DPP-4 inhibitor achieved an HbA1c reduction of >0.5% without an increase in body weight [27]. This advantage was confirmed in monotherapy in drug-naive T2DM patients as well as in combination therapy, essentially with metformin. Interestingly,

decreased risk for hypoglycemia and weight gain may help avoid physician's clinical inertia [78] and improve patient's adherence to drug therapy [79].

5.1.1 Gliptins as monotherapy

DPP-4 inhibitors as monotherapy are almost as effective as current glucose-lowering treatments in patients inadequately controlled with diet and exercise provided that HbA1c reductions were adjusted for baseline values [28, 29]. All gliptins have proven their superiority to placebo and showed slightly less reductions in HbA1c levels compared to metformin and quite similar improvements compared to a sulfonylurea, a TZD or acarbose in 24-week randomized controlled trials (Table 3) [76]. A few direct comparative trials confirmed that DPP-4 inhibitors are slightly less effective relative to metformin [80]. Hypoglycemic events were rare with both a DPP-4 inhibitor and metformin. Weight loss tended to be slightly greater with metformin than with any tested gliptin. Thus, available data do not support the initial use of a DPP-4 inhibitor instead of the reference drug metformin, except in patients for whom metformin is either not tolerated (gastrointestinal adverse events) or contraindicated (for instance, renal insufficiency). Scarce head-to-head trials showed that DPP-4 inhibitors were non inferior to a TZD (pioglitazone 30 mg or rosiglitazone 8 mg) regarding HbA1c reduction, with the advantage of no weight gain[80].

5.1.2. Gliptins combined to metformin

As metformin therapy is considered as the first-line drug in T2DM, most combination trials tested the efficacy and safety of adding a DPP-4 inhibitor to a baseline metformin monotherapy and showed that it was superior to placebo with a mean reduction in HbA1c of 0.6-0.8 % [81]. Head-to-head trials versus sulfonylureas demonstrated that DPP-4 inhibitors induced a similar reduction in HbA1c as glipizide, glimepiride or gliclazide, with no weight gain and a much lower incidence of reported hypoglycemic episodes (< 3-5 % versus 30-35%). Those versus a TZD showed that DPP-4 inhibitors were non inferior to piogliazone 30-45 mg regarding HbA1c reduction, with the advantage of no weight gain (Table 3) [80].

Several fixed-dose combinations have been developed and/or commercialized : sitagliptin-metformin [82, 83], vildagliptin-metformin [84, 85], saxagliptin-metformin [86, 87]. The initial combination of a DPP-4 inhibitor and metformin provided substantial and additive glycemic improvement and was generally well tolerated in patients with T2DM. The potential dose-sparing effect of adding a DPP-4 inhibitor to a rather low-dose metformin in preference

to the up-titration of metformin may allow patients to achieve equivalent or superior HbA1c lowering without the gastrointestinal tolerability issues associated with higher doses of metformin [88].

5.1.2. Gliptins combined to a sulfonylurea

Several trials have also evaluated the efficacy and safety of adding a DPP-4 inhibitor to a sulfonylurea. This may be of interest in patients who cannot be treated with metformin. Sitagliptin 100 mg, vildagliptin 50 or 100 mg, saxagliptin 2.5 or 5 mg and alogliptin 12.5 or 25 mg significantly improved glycemic control (reduction in HbA1c : 0.4-0.6%) in patients with T2DM who had inadequate glycemic control with glimepiride or glyburide (glibenclamide) [80]. Whereas the association gliptin-metformin does not lead to hypoglycemia, hypoglycemic events may occur with the combination gliptin-sulfonylurea. In T2DM patients with not very high HbA1c levels (7-8%) on sulfonylurea monotherapy, it may be cautious to somewhat reduce the dose of sulfonylurea when a DPP-4 inhibitor is added in order to minimize the risk of hypoglycemia, especially in elderly people.

5.1.3. Gliptins combined to a thiazolidinedione

Owing to the pathophysiology of T2DM, the combination of a DPP-4 inhibitor, an insulin secretagogue that does not promote weight gain, and a TZD, an insulin sensitizer that favours weight increase, seems an appealing approach [89].The addition of a DPP-4 inhibitor (sitagliptin 100 mg, vildagliptin50-100 mg, saxagliptin 2.5-5 mg, linagliptin 5 mg and alogliptin 12.5-25 mg) to patients inadequately controlled on pioglitazone reduced HbA1c levels by 0.7-1.4% from a baseline of 8.0-8.5% [80]. Such combination was well tolerated, did not increase the incidence of hypoglycemia, and did not substantially worsen the weight-gain induced by pioglitazone. The combination of a DPP-4 inhibitor with pioglitazone can be a useful therapeutic approach in patients with T2DM who cannot tolerate metformin or a sulfonylurea [90]. This combination may offer a valuable additive initial treatment option for T2DM, particularly where metformin is contraindicated, such as in patients with renal impairment.

5.1.4. Gliptins as triple oral therapy

The availability of DPP-4 inhibitors offered a new alternative for triple oral therapy at a time when only the combination of metformin plus a sulfonylurea plus a TZD was available [91]. The addition of a DPP-4 inhibitor could provide a valuable treatment option, in place of a

TZD, for individuals with inadequate glycemic control despite metformin plus sulfonylurea therapy [80, 92, 93]. Reductions in HbA1c between 0.4 and 0.9% have been reported, although the reduction with the addition of a gliptin appears less effective than that observed with the addition of a TZD [80]. Alternatively, adding alogliptin 25 mg to an existing metformin-pioglitazone regimen provided superior glycemic control and potentially improved β-cell function versus uptitrating pioglitazone in patients with T2DM, with no clinically important differences in safety [94].

5.1.5. Gliptins combined to insulin in T2DM

Favorable results with additional 0.3-0.6% reductions in HbA1c have been reported with the addition of sitagliptin 100 mg once daily, vidagliptin 50 mg twice daily, saxagliptin 5 mg once daily or alogliptin 12.5 mg or 25 mg once daily with a low rate of hypoglycemia and slight weight reduction [80]. Thus, adding a DPP-4 inhibitor to insulin therapy may be useful in T2DM patients in order to improve glucose control, without increasing hypoglycemia, and possibly limiting weight gain. Of note, in the study combining vildagliptin with insulin, hypoglycemic events were less common and less severe in patients receiving vildagliptin than in those receiving placebo [95]. Further studies are warranted to explore the role of a DPP-4 inhibitor added to optimized insulin regimens as available studies were performed in patients on basal insulin therapy.

5.2. DPP-4 in special populations

5.2.1. Renal impairment

Therapeutic options for patients with T2DM and chronic kidney disease are limited because a reduced glomerular filtration rate (GFR) results in the accumulation of certain drugs and/or their metabolites [96]. The PK characteristics of five DPP-4 inhibitors have been studied in subjects with varying degrees of renal impairment (RI) [24].

PK characteristics of DPP-4 inhibitors have been evaluated in patients with various degrees of RI : mild RI (creatinine clearance 50–80 ml/min), moderate RI (30–50 ml/min), severe RI (<30 ml/min), end-stage renal disease (ESRD) on hemodialysis, and normal renal function (>80 ml/min : controls) : after single doses of sitagliptin [97], saxagliptin (and its pharmacologically active metabolite, 5-hydroxy saxagliptin) [98], vildagliptin [99], alogliptin [100] and, finally, linagliptin under single-dose and steady-state conditions (Table 4) [101]. Potentially clinically relevant increases in maximal plasma concentrations, elimination half-life and total

exposure (more than twofold increase) have been reported for sitagliptin, the active metabolite of saxagliptin and alogliptin.

Based on these findings, sitagliptin dose adjustments are recommended for patients with moderate RI (50 mg daily) or severe RI or ESRD (25 mg daily) to provide plasma sitagliptin exposure comparable to patients with normal renal function. When using such dose adjustment in a 54-week trial, sitagliptin was generally well tolerated and provided effective glycemic control in patients with T2DM and moderate to severe RI, including patients with ESRD on dialysis [102]. However, in a study assessing dose adjustment of glucose-lowering agents in T2DM patients with moderate RI to ESRD from a large outpatient electronic medical records database, only 15% of patients with orders for sitagliptin received doses of the drug appropriate for their degree of RI. Thus, in clinical practice, sitagliptin is frequently used at inappropriate doses in patients with RI, an observation similar to that noticed with metformin [103].

One-half the usual dose of saxagliptin 5 mg (i.e. 2.5 mg orally once daily) is recommended for patients with moderate (30-50 mL/min) or severe (<30 mL/min not on dialysis) RI or ESRD, but no dose adjustment is recommended for those with mild RI. Saxagliptin 2.5 mg once daily has been shown to be a well-tolerated treatment option for patients with inadequately controlled T2DM and various degrees of RI, incidences of adverse events and hypoglycemic events being similar to those noticed with placebo [104]. The reduction in HbA1c was greater with saxagliptin than with placebo in the subgroups of patients with moderate and severe RI, but not in the subgroup with ESRD on hemodialysis, both after 12 weeks [104] and after 52 weeks [105].

Half of all patients in the global development program exposed to the marketed doses of vildagliptin as monotherapy had either mild or moderate RI at study baseline. Data pooled from 38 studies where vildagliptin was given for 12 to 104 weeks in patients with T2DM showed that it was effective and well tolerated in presence of mild or moderate RI [65]. According to the labeling, no dosage adjustment of vildagliptin is required in patients with mild RI. Vildagliptin is, however, not recommended in patients with moderate or severe RI or ESRD on hemodialysis due to limited experience. Nevertheless, in a recent 24-week study of 515 patients with T2DM and moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to placebo. Further, relative to placebo, vildagliptin elicited a statistically and clinically significant decrease in HbA1c in patients with

moderate or severe RI [106]. These data confirmed those from a retrospective analysis, which demonstrated similar assessed safety and tolerability of vildagliptin as an add-on to metformin in T2DM patients with normal renal function and mild RI (GFR: >50 to ≤80mL/min/1.73m²) [107].

Despite the fact that a single dose PK study demonstrated that alogliptin exposure increases according to the severity of RI (Table 4) [100], no clinical trials in patients with T2DM and RI have been published yet demonstrating how to use this drug effectively and safely in this population (a reduction of the daily dose by half would probably be recommended). Because RI only has a minor effect on linagliptin PK [101], there will be no need for adjusting the linagliptin dose in patients with RI. The efficacy (reduction in HbA1c levels) and safety of linagliptin 5 mg was confirmed in T2DM patients with mild or moderate RI in a pooled analysis of 3 randomized, placebo-controlled, Phase 3 clinical trials, as well as in T2DM patients with severe RI (GFR <30 mL/min/1.73 m^2) in a randomized, double-blind, placebo-controlled trial targeting specifically this population [108].

5.2.2. Liver impairment

The PK characteristics of five DPP-4 inhibitors have been studied in subjects with varying degrees of hepatic impairment (HI) : sitagliptin [109], saxagliptin (and its pharmacologically active metabolite, 5-hydroxy saxagliptin) [98], vildagliptin [110], alogliptin[111] and linagliptin [112]. Because there was no significant difference in exposure to any tested DPP-4 inhibitor in patients with mild, moderate or even severe HI, no dose adjustment seems necessary in patients with liver disease, even for linagliptin despite its specific biliary excretion [24, 108].

However, according to the labeling, vildagliptin is not recommended in patients with HI including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal. Although a slightly higher risk of mild hepatic enzyme elevations was observed with vildagliptin 100 mg per day, this does not translate into an increased incidence of actual hepatic adverse events [65].

5.2.3. Elderly patients

Oral DPP-4 inhibitors are promising new therapies for use in older patients because of their consistent efficacy and low risk of hypoglycemia. However, data with these new agents are still scarce in this population, which has not been particularly well represented in clinical trials, highlighting the need for additional specific studies. There are few published trials to date dedicated to this population, although a few studies are currently ongoing [80]. Data from elderly subgroups of individual studies were reviewed when available, as well as pooled analyses by age subgroups across clinical programs conducted with DPP-4 inhibitors [113]. For elderly patients with T2DM (> 65 years or even > 75 years), reductions in HbA1c after treatment with a DPP-4 inhibitor were not significantly different from those in younger patients. In a pooled analysis from 10 clinical trials, vildagliptin 50 mg twice daily was effective and well-tolerated in above 300 T2DM patients >/=75 years (mean age 77 years) [114]. Use of DPP-4 inhibitors in these studies was associated with a low risk of hypoglycemia, and these agents were weight neutral [115]. Only one randomized controlled trial is available, which specifically targeted T2DM patients older than 65 years. In this 24-week study, sitagliptin treatment (100 or 50 mg, depending on renal function) significantly and rapidly improved glycemic measures (reductions in HbA1c from 0.5% to 1.6% depending on baseline levels), and was well tolerated with no adverse events of hypoglycemia in patients aged ≥ 65 years with T2DM without severe RI [116].

5.3. DPP-4 inhibitors in current guidelines

As any novel glucose-lowering compound, DPP-4 inhibitors will not fully disclose their spectrum of beneficial and adverse activity before long-term trials with clinical endpoints are available. Nevertheless, several authors tried to describe the current state-of-the-art of using DPP-4 inhibitors in clinical practice, including an attempt to suggest their place in treatment algorithms for T2DM patients.

The recommendations, as set by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) [117], the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) [118], and the Canadian Diabetes Association [119], are similar in their emphasis on lifestyle modification but differ in specific pharmacological approaches. While both ADA/EASD and AACE/ACE treatment guidelines recommend starting metformin in most patients on diagnosis of T2DM, they differ in terms of which agents are preferred as second-line therapies. The ADA/EASD so-called "consensus statement" recommended a tiered approach to treatment, starting with well-

validated second-line agents, such as sulfonylureas and basal insulin for patients unable to achieve target glucose levels with metformin alone. The higher cost of DPP-4 inhibitors, coupled with an absence of long-term safety and clinical outcome data, was the reason why DPP-4 inhibitors were not selected in the ADA-EASD algorithm. However, this position was criticized because it does not offer physicians and patients the appropriate selection of options to individualize and optimize care [120]. The AACE/ACE recommendations[118], as well as the updated NICE guidelines[121], include a broader range of first- and second-line therapies and combinations, including DPP-4 inhibitors because of their low risk of hypoglycemia and weight neutrality. An "HbA1C and ABCD" strategy of glycemia management in T2DM has been published to guide clinicians in the use of therapeutic agents more effectively, efficiently and safely [122]. While no regulatory-approved drug can be excluded, given its proven efficacy, there is a need to better phenotype patients, paying particular attention to ABCD (Age, Body weight, Complications and Disease Duration). Based on these parameters, physicians can select the therapeutic approach with minimum risk and maximum benefit for each individual, and DPP-4 inhibitors should play an increasing role in such a strategy because of their attractive efficacy/safety balance.

6. Unresolved questions and perspectives

6.1. DPP-4 inhibitors versus GLP-1 receptor agonists

Incretin-based agents include GLP-1 receptor agonists, which mimic endogenous GLP-1, and DPP-4 inhibitors which inhibit the breakdown of endogenous incretin hormones [123-125]. GLP-1 receptor agonists are more effective in lowering blood glucose and result in substantial weight loss, whereas therapy with DPP-4 inhibitors lowers blood glucose levels to a lesser degree, and they are weight neutral, as show in a meta-analysis of indirect comparative trials [21]. Such differences were confirmed in a few head-to-head trials comparing sitagliptin 100 mg versus exenatide twice daily, exenatide once weekly or liraglutide once daily [80, 124].

Although GLP-1 receptor agonists demonstrate superiority compared to DPP-4 inhibitors, the average differences in HbA1c and weight reductions were not huge compared to several disadvantages of GLP-1 receptor agonists (injectable versus oral, more nausea, increased cost). Further advantages might be expected but remain to be demonstrated such as a better CV protection or a longer durability of glucose control with GLP-1 receptor agonists (possibly favoured by weight loss) compared to DPP-4 inhibitors [126].

6.2. DPP-4 inhibitors and cardiovascular protection

T2DM is a well-established risk factor for CVD and new therapeutic approaches, such as incretin-based therapies, should ideally also target CVD risk, beyond glucose control [127]. In a meta-analysis of 41 RCTs (9 of which are unpublished), the risk of CV events and all-cause death with DPP-4 inhibitors was 0.76 [95%CI 0.46-1.28] and 0.78 [0.40-1.51], respectively [20].

Available analyses for each DPP-4 inhibitor are summarized in Table 5. A pooled analysis included data from 19 double-blind, randomized studies including 10,246 T2DM patients who received either sitagliptin 100 mg/day or a comparator agent (placebo or an active comparator). Treatment with sitagliptin was not associated with an increased risk of major adverse CV events versus comparator (0.6 versus 0.9 %) [64]. A large meta-analysis pooled data from 25 Phase III studies of vildagliptin, used either as monotherapy or combination therapy, with durations of 12 weeks up to 2 years. Relative to all comparators, the relative risk (RR) for the composite endpoint was < 1 for both vildagliptin 50 mg once daily (RR = 0.88) and vildagliptin 50 mg twice daily (RR = 0.84). The results were consistent across subgroups defined by age, gender and CV risk status, including the higher CV risk subgroups of elderly patients, males or patients with a high CV risk status [128]. Similarly, no increased risk of CV death/myocardial infarction/stroke was observed in patients randomly assigned saxagliptin across a broad drug development program including all 8 randomized phase 2/3 trials. Although this systematic overview has inherent and important limitations, the data support a potential reduction in CV events with saxagliptin compared with non-saxagliptin comparator [129]. Similar reduction in RR of CV events were reported in two abstracts only for alogliptin [130] and linagliptin [131] (Table 5).

Whether gliptins actually decrease CVD outcomes remains to be confirmed by large randomized placebo-controlled trials. Several prospective trials are ongoing in order to demonstrate the CV safety (most trials have non-inferiority outcome versus placebo) and possibly the superiority of DPP-4 inhibitors to reduce the incidence of CV events in T2DM patients at high risk of CVD (Table 5).

6.3. DPP-4 inhibitors, beta-cell protection and durability of glucose control

Studies in humans with T2DM have indicated improvement of islet-cell function, both in the fasted state and under postprandial conditions, and these beneficial effects were sustained in studies with a duration up to two years. However, there is at present no evidence

in humans to suggest that DPP-4 inhibitors have durable effects on β-cell function after cessation of therapy [57, 58].

In patients with T2DM, adding sitagliptin 100 mg to metformin monotherapy improved glycemic control over 2 years, similar to the glucose-lowering efficacy observed with adding glipizide 5 mg/day (up-titrated up to 20 mg/day based upon prespecified glycemic criteria), but with greater durability and generally better maintenance of β-cell function [132]. The rise in HbA1c from week 24 to week 104 was smaller with sitagliptin (0.16%/year compared with glipizide, 0.26%/year). In another 2-year randomized, double-blind, active-comparator study of patients with T2DM inadequately controlled by metformin monotherapy, patients received vildagliptin (50 mg twice daily) or glimepiride (up to 6 mg/day) added to metformin. The initial response was significantly more sustained with vildagliptin than with glimepiride, again suggesting a better durability of the glucose-lowering effect with the DPP-4 inhibitor [133]. However, the duration of these two trials was too short to draw any definite conclusion. The effects of DPP 4 inhibitors on β-cell mass in humans and the durability of the glucose-lowering effect of gliptins (as opposed to the escape phenomenon reported with sulfonylureas) are still unresolved issues. To our knowledge, there are no long-term controlled ongoing trials specifically designed to answer this question with any of the five DPP-4 inhibitors considered in the present review. Perhaps, post-hoc analyses of large CV ongoing trials (Table 5) will provide interesting additional information regarding the durability of glucose control with gliptins.

6.4. Better understanding of mechanisms of action of DPP-4 inhibitors

Although the mechanism of the glucose-lowering effect appears quite simple, several unresolved questions still persist. For instance, the relative contributions of the enhancement of insulin secretion and the inhibition of glucagon secretion in the glucose-lowering effects observed in both fasting and postprandial states remain to be better explored [32, 33, 35]. Exactly how DPP 4 inhibitors lead to a decline in fasting plasma glucose levels without an increase in insulin secretion need further research [125]. The effects of saxagliptin 5 mg on β-cell function of T2DM patients were assessed at baseline and week 12 by intravenous hyperglycemic clamp (fasting state) and intravenous-oral hyperglycemic clamp following oral ingestion of 75 g glucose. DPP-4 inhibition with saxagliptin improves pancreatic β-cell function in both postprandial and fasting states. Given the magnitude of enhancement of the insulin response in the fasting state, further study into the effect of DPP-4 inhibition on the β-cell is warranted

[134]. In another recent intriguing study, DPP-4 inhibition augmented insulin secretory responses both after oral glucose and during isoglycemic intravenous glucose infusions, with no net change in the incretin effect. It was hypothesized that DPP-4 inhibitor-induced changes in the incretin-related environment of islets may persist overnight, augmenting insulin secretory responses to intravenous glucose as well. Alternatively, yet unidentified mediators of DPP-4 inhibition may have caused these effects [135].

As already mentioned, other effects of DPP-4 inhibitors have been suspected beyond glucose control, especially on the CV system [41]. Favorable effects may be expected, through the activation of GLP-1 receptors but also via other hypothetical mechanisms. Indeed, while GLP-1 signaling has been shown to be active in both the heart and vessels, where it may exert beneficial effects, DPP-4 enzyme has several non-incretin substrates, and its immunomodulatory activity is known from decades. DPP-4 physiologically cleaves cytokines, chemokines and neuropeptides involved in inflammation, immunity, and vascular function. Owing to these off-target mechanisms, DPP-4 inhibitors hold promise for CV protection, but may also face unexpected side effects [56].

7. Conclusion

The role of DPP-4 inhibitors in the therapeutic armamentarium of T2DM is evolving as their potential strengths and weaknesses become better defined. 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. These agents are active as monotherapy in drug-naïve T2DM patients and in combination therapy with metformin, a sulfonylurea and/or a TZD, and even as add-on therapy to insulin. Combination therapy with a DPP-4 inhibitor can thus offer a potential advantage in achieving glycemic goals for the majority of patients withT2DM without additional tolerability concerns. However, only large long-term clinical trials and careful post-marketing surveillance in real life conditions will be able to confirm the good safety profile of this novel pharmacological class. What so ever, DPP-4 inhibitors are already considered as an important pharmacological class for the management of T2DM and will probably increase their impact in a near future, considering the commercialization of several new compounds very soon as well as the recognition of additional indications for available gliptins.

8. EXPERT OPINION SECTION

Type 2 diabetes mellitus (T2DM) develops as a consequence of progressive β-cell dysfunction in the presence of insulin resistance. Therefore, therapy should be aimed at correcting underlying pathophysiological defects, including β-cell failure and insulin resistance. Traditional treatment has focused on correcting hyperglycemia. However, T2DM is often accompanied by other conditions (i.e. overweight/obesity with associated metabolic syndrome), which are considered as risk factors and thereby could further affect both morbidity and mortality. A broader view toward treating the array of physiological derangements may provide significant long-term outcomes benefits in patients with T2DM.

The four most important unmet needs associated with the current management of T2DM are (1) the failure to target all primary abnormalities of the disease; (2) the lack of lasting efficacy in reducing hyperglycemia; (3) the high residual cardiovascular risk; and (4) the presence of deleterious side effects with many antidiabetic therapies.

(1) T2DM is a multifaceted disease involving multiple pathophysiological defects that are not all addressed by traditional oral glucose-lowering agents. Cumulatively, available drugs address the influx of glucose from the gastrointestinal tract, impaired insulin action, and acute β-cell dysfunction; however, there are not able to deal with the inappropriate hyperglucagonemia or progressive β-cell-decline.

(2) None of the currently available glucose-lowering therapies is able to change the course of T2DM by halting the relentless decline in β-cell function. Typically, the effects of metformin, the first-choice pharmacological intervention, are of limited durability to control glycemia adequately and the secondary addition of a sulfonylurea is generally associated with a rapid escape of blood glucose control. Thiazolidinediones appear to offer a better durability, but induce weight gain and raised other safety concern.

(3) Most patients with T2DM die from a cardiovascular complication. Thus, therapy should also correct underlying risk factors for cardiovascular disease whenever possible. Controversy over the choice of antidiabetic therapy for lowering macrovascular events has existed for nearly four decades, beginning with the potential risk of increased cardiovascular mortality with sulfonylureas and continuing with the increased risk of coronary heart disease attributed to rosiglitazone. Additionally, positive results for metformin in reducing

macrovascular events have not been clearly substantiated. In absence of outcome studies, the impact of various agents on known cardiovascular risk factors may be considered when selecting a therapeutic regimen.

(4) Some conventional glucose-lowering drugs are associated with inconvenient side effects such as hypoglycemia and weight gain for sulfonylureas/glinides and weight gain and fluid retention for thiazolidinediones. These adverse events may retard intensifying therapy by the physician despite persistent poor glucose control and/or may reduce patient's compliance to drug therapy. Furthermore, weight gain could worsen some cardiovascular risk factors while severe hypoglycemia may be associated with major cardiovascular events in high risk patients (elderly, patients with long-lasting T2DM). Other safety concerns have been raised especially for thiazolidinediones (congestive heart failure, bone fractures, bladder cancer, ..).

The recently introduced new glucose-lowering agents, especially incretin-based therapies, may serve to address some of the challenges associated with traditionally available oral antidiabetic agents. Because of their favorable properties (extensively reviewed in the main paper), DPP-4 inhibitors may offer an attractive alternative, although they are not more efficacious for reducing HbA1c than conventional pharmacological agents. The complex pathological mechanisms responsible for development of T2DM are not fully addressed by conventional drugs, thus opening the door to various combination therapies. In addition to stimulating insulin secretion and inhibiting glucagon secretion (both in a glucose-dependent manner, thus limiting the risk of hypoglycemia), DPP-4 inhibitors somewhat reduce appetite, thereby stabilizing weight and/or slightly promoting weight loss despite better glucose control and reduced glucosuria. These agents might have the opportunity to interfere with the disease progression if used as an early intervention, when enough β-cell mass/function can still be preserved or restored. However, there is at present no evidence in humans to suggest that DPP-4 inhibitors have durable effects on β-cell function after cessation of therapy.

Another potential advantage of DPP-4 inhibitors would concern their positive effects on cardiovascular profile, which might contribute to reduce the incidence of cardiovascular events, as suggested in pooled analyses of phase III trials and currently tested in large placebo-controlled prospective trials. Unfortunately, most ongoing studies are non-inferiority trials and none will directly compare a gliptin with an active comparator (except one that is comparing linagliptin with glimepiride).

Although head-to-head clinical trials comparing various DPP-4 inhibitors are scarce (only one published trial), the amount of data referring to indirect comparisons suggests that the class effect is largely predominant and that all available DPP-4 inhibitors have almost the same efficacy/safety profile. However, substantial differences have been reported regarding their pharmacokinetic properties, which may influence the use of one molecule rather the other in special populations, for instance in case of renal impairment. In patients with high risk of hypoglycemia, DPP-4 inhibitors clearly offer clinically relevant advantage over other insulin secretagogues such as sulfonylureas. This diversity may offer the possibility to personalize glucose-lowering therapy. It should be pointed out, however, that little data is available yet to evaluate the long-term effectiveness and safety of DPP-4 inhibitors compared with more established treatments, limiting our ability to determine how to best incorporate these newer medications into clinical practice.

Declaration of interest

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Figure 1 : Chemical structures of DPP-4 inhibitors

Table 1 : Main PK characteristics of five DPP-4 inhibitors. Data were obtained in separate studies allowing only indirect comparisons. NA : information not available. Adapted from references [15, 24]

Parameters	**Sitagliptin MK-0431**	**Vildagliptin LAF237**	**Saxagliptin BMS-477118**	**Alogliptin SYR-322**	**Linagliptin BI1356**
Absolute bioavailability (%) (*)	87	85	67 (**)	➢ 70	30
T_{max} (h)	1-4	1-2	2 4 (BMS-510849)	1-2	1-3
Volume distribution (L)	198	71	151	300	368-918
Fraction bound to protein (%)	38	9.3	< 10	20	➢ 70
Terminal $t_{1/2}$ (h)	12.4	2-3	2.5 3.1 (BMS-510849)	21.4	120
Total plasma clearance (mL/min)	416	683	NA	NA	140-314
Renal clearance (mL/min)	350	217	230	163-218	NA
Renal clearance (%)	70	31	NA	NA	< 5
Primary metabolites	6 (inactive)	LAY 151 (inactive)	BMS-510849 (active)	Minimally metabolized (inactive)	CD179 (inactive)
Excreted in feces (%)	13	4.5	22 (oxidative metabolites)	13	85 (mostly unchanged)
Excreted in urine (%)	87	85	75	76	5
Proportion excreted unchanged (%)	79	23	24 (36 % as BMS-510849)	95	(mostly unchanged)
Substrate for P-gp	yes	yes	yes	NA	NA
Substrate for CYP3A4	low	no	yes	no (minimally	no

CYP3A5 CYP2C8	no very low	no no	yes no	metabolized	(minimally metabolized)

(*) No significant effect of food (**) Predicted instead of measured [57]

Table 2 : Main PD properties of five DPP-4 inhibitors. Data were obtained in separate studies allowing only indirect comparisons. NA : information not available. Adapted from reference [15].

Parameters	**Sitagliptin MK-0431**	**Vildagliptin LAF237**	**Saxagliptin BMS-477118**	**Alogliptin SYR-322**	**Linagliptin BI1356**
Therapeutic dose (mg/day)	100	100	**5**	25	5
Administration	Once daily	Twice	Once daily	Once daily	Once daily
Dose reduction if renal impairment	Yes (25/50	No	Yes (2.5)	Yes (12.5)	No
Dose reduction if hepatic impairment	No	No	No	No	No
Dose reduction if CYP3A inhibitors	No	No	Yes (2.5)	No	No
Affinity constant for inhibitor binding (Ki) nmol	18	13	1.3	NA	NA
In vitro DPP-4 inhibition (IC50, nmol/L) (*)	19	62	50	24	1
Effect on plasma DPP-4 activity (% inhibition over 24 h)	➢ 80	➢ 80	➢ 70	➢ 80	➢ 80
Increase in active GLP-1 levels	2-fold	3-fold	1.5- to 3-fold	2- to 3-fold	4 -fold (25 mg)
In vitro selectivity (**) vs DPP-8 or DPP-9	➢ 2600	< 100	< 100	➢ 14000	➢ 10000
vs DPP-2	➢ 5550	➢ 10000	➢ 50000	➢ 14000	➢ 100000
vs Fibroblast Activation protein	➢ 5550	➢ 300	➢ 4000	➢ 14000	< 100

(*) IC50 : concentration at which there is 50% inhibition of measured enzyme activity in vitro.

(**) concentration at which there is inhibition of the corresponding enzyme divided by the concentration at which DPP-4 is inhibited.

Table 3 : Reductions in HbA1c levels and changes in body weight with DPP-4 inhibitors versus metformin in drug-naive patients, versus a sulfonylurea in metformin-treated patients and versus a thiazolidinedione in pooled drug-naive and metformin-treated patients with type 2 diabetes in 12-104 weeks head-to-head trials (adapted from reference Scheen 2011 [80]). NA : Not available.

COMPARISON	Number of trials	Reduction in HbA1c % (95% CI)	Between-treatment P value	Changes in body weight Kg (95% CI)	Between-treatment P value
DPP-4 inhibitors (*) Metformin 1000-2000 mg/day	10	-1.01 (-0.92,-1.09) -1.31 (-1.22,-1.41)	0.00017	-0.11 (0.01,-0.24) -1.70 (-1.59,-1.80)	0.00037
DPP-4 inhibitors Sulfonylureas (**)	8	-0.56 (-0.51,-0.61) -0.61 (-0.55,-0.67)	0.06042	-0.75 (-0.60,-0.90) +1.12 (1.05,1.20)	0.00001
DPP-4 inhibitors Thiazolidinediones (***)	8	-0.87 (-0.83,-0.92) -1.00 (-0.93,1.08)	0.03861	-0.21 (-0.12,-0.31) +1.80 (1.61-1.99)	0.00024

(*) Pooled data of trials with sitagliptin 100 mg, vildagliptin 100 mg (except 50 mg in one trial) mg, saxagliptin 10 mg, alogliptin 25 mg and linagliptin 5 mg

(**) Sulfonylureas : Glimepiride (1- 6 mg), glipizide (5-20 mg) or gliclazide(80-320 mg)

(***) Thiazolidinediones : Pioglitazone (30 or 45 mg) or rosiglitazone (8 mg)

Table 4 : Exposure to the DPP-4 inhibitor (assessed by the geometric mean ratio of the area under the curve of plasma concentrations from 0 to infinity : AUC0-∞) after a single dose administration (except if otherwise specified) in subjects with mild, moderate or severe renal and hepatic impairment, respectively, and in patients with end-stage renal disease (ESRD) on hemodialysis.

Exposure (AUC0-∞)	RENAL IMPAIRMENT						HEPATIC IMPAIRMENT				
	Reference	Dose mg	Mild	Moderate	Severe	ESDR	Reference	Dose mg	Mild	Moderate	Severe
SITAGLIPTIN	Bergman et al 2007[97]	50	1.6	2.3	3.8	4.5	Migoya et al 2009[109]	100	NA	1.21	NA
VILDAGLIPTIN	He et al 2007[99]	25 or 50	2.01	1.32	2.34	1.42	He et al 2007[136]	100	0.80	0.92	1.22
SAXAGLIPTIN	Boulton et al 2011[98]	10						10			
Parent drug			1.16	1.41	2.08	0.79	Boulton et al 2011[98]		1.10	1.38	1.77
Active metabolite			1.67	2.92	4.47	4.09			0.78	0.93	0.67
LINAGLIPTIN											
Single dose	Grefe-Mody et al 2011[101]	5	1.3	1.6	1.4	1.5	Grefe-Mody et al 2011[112]		NA	NA	NA
Multiple doses (7-10 days)			1.1	1.7	NA	NA		5	1.25	0.86	≈1.00
ALOGLIPTIN	Karim et al 2008[100]	50	1.7	2.1	3.2	3.8	Karim et al 2007[111]	50		No significant change	

Table 5 : 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 II-III trials and ongoing prospective clinical trials specifically designed to analyze CV outcomes.

	References	CV EVENTS IN PHASE II-III TRIALS RR (95% CI)	ONGOING CLINICAL TRIALS WITH CV OUTCOMES
SITAGLIPTIN	Williams-Herman et al 2010[64]	0.68 (0.41, 1.12)	**TECOS** : Trial Evaluating Cardiovascular Outcomes with **Sitagliptin**
VILDAGLIPTIN	Schweizer et al 2010[128]	0.84 (0.62, 1.14)	NONE
SAXAGLIPTIN	Frederich et al 2010[129]	0.43 (0.23, 0.80)	**SAVOR** : **Saxagliptin** Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Trial
ALOPGLIPTIN	White et al 2010[130]	0.63 (0.21, 1.91)	**EXAMINE** : EXamination of CArdiovascular OutcoMes: **Alogliptin** vs. Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome
LINAGLIPTIN	Johansen et al 2011[131]	0.34 (0.16, 0.70)	**CAROLINA** : Cardiovascular Outcome Study of **Linagliptin** Versus Glimepiride in Patients With Type 2 Diabetes

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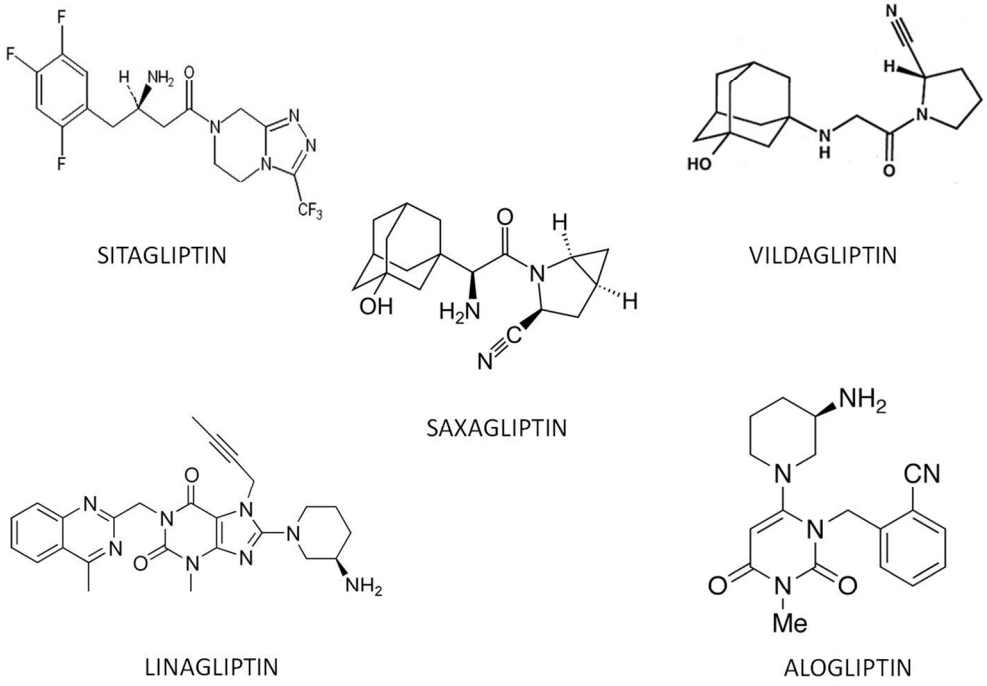

Figure 1 : Chemical structures of DPP-4 inhibitors
242x172mm (150 x 150 DPI)