Dipeptidyl peptidase 4 inhibitors in the treatment of type 2 diabetes mellitus

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Abstract | Dipeptidyl peptidase 4 inhibitors (DPP4i) have been available for treating type 2 diabetes mellitus since 2006. Although they are a diverse group, DPP4i are all small, orally available molecules that interact with the catalytic site of DPP4 without disturbing any of its other known functions, including its effects on the immune system. DPP4i have no intrinsic glucose-lowering activity, so their efficacy as anti-diabetic agents is related directly to their ability to inhibit DPP4 activity and is mediated through the effects of the substrates they protect. Of these, the incretin hormone, glucagon-like peptide 1, is probably the most important. As the effects of glucagon-like peptide 1 are glucose-dependent, the risk of hypoglycaemia with DPP4i is low. Class effects, which are directly related to the mechanism of action, are common to all DPP4i; these include their overall good safety profile and tolerability, as well as their efficacy in improving glycaemic control, but also, potentially, a small increased risk of acute pancreatitis. Compound-specific effects are those related to their differing chemistries and/or pharmacokinetic profiles. These compound-specific effects could affect the way in which individual DPP4i are used therapeutically and potentially explain off-target adverse effects, such as hospitalization for heart failure, which is seen only with one DPP4i. Overall, DPP4i have a favourable therapeutic profile and are safe and effective in the majority of patients with type 2 diabetes mellitus.

Twenty-five years ago, the idea of inhibiting the activity of the enzyme dipeptidyl peptidase 4 (DPP4) as a novel way to treat type 2 diabetes mellitus (T2DM) was first published[1] and, since then, DPP4 inhibitors (DPP4i) have become firmly established in treatment algorithms[2–4] and national guidelines for managing T2DM. The basis for this approach lies with the finding that DPP4 has a key role in determining the clearance of the incretin hormone, glucagon-like peptide 1 (GLP1)[5]. GLP1 is an intestinal peptide, which was known to have a role in glucose homeostasis[6] via actions that include the potentiation of glucose-induced insulin secretion and the suppression of glucagon secretion[7] (FIG. 1). The finding that exogenously infused GLP1 could normalize fasting blood levels of glucose in patients with T2DM[8] had already sparked interest in its therapeutic potential[9]. However, this interest was tempered by the discovery that GLP1 was a substrate for DPP4 (which cleaves a dipeptide from the amino terminus of the intact peptide, GLP1 7–36 amide, to form a metabolite, GLP1 9–36 amide)[10], and that both exogenous[1,11] and endogenous GLP1 (REF.[12]) were extensively degraded in vivo. It follows, therefore, that an intervention to reduce GLP1 degradation should enhance its anti-hyperglycaemic effects and lead to improved glycaemic control[5].

Accordingly, preclinical studies showed that DPP4 inhibition prevented the degradation of GLP1 and enhanced its insulinotropic effects[13] and was associated with improved glucose homeostasis in animal models of T2DM[14]. These findings were quickly followed by clinical proof-of-concept studies demonstrating that DPP4i improved metabolic control in patients with T2DM[15] and led to statistically significant reductions in HbA_{1c} levels over the longer term[16]. Moreover, as the actions of GLP1 are strictly glucose-dependent (effects on insulin and glucagon levels being seen only at euglycaemia and above[8]), DPP4i are typically not associated with any increased risk of hypoglycaemia[17,18]. These features, together with the good tolerability and safety profiles of DPP4i, their oral availability and the fact that they are small molecules (BOX 1) have combined to make the so-called gliptin class highly successful. As a testament to this success, at least 11 different DPP4i have received regulatory authority approval worldwide and are now available as therapeutic options for managing patients with T2DM.

All the DPP4i work by inhibiting the catalytic activity of DPP4; however, they do differ in terms of their pharmacological and therapeutic profiles. Broadly speaking, these can be divided into differences related to the mechanism of action (that is, their efficacy as

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https://doi.org/10.1038/s41574-020-0399-8

Key points

- Dipeptidyl peptidase 4 inhibitors (DPP4i) were rationally designed based on the prior knowledge of the physiology of glucagon-like peptide 1 and an understanding of the role of DPP4 in its metabolism.
- DPP4i are all small molecules that inhibit the catalytic activity of the enzyme without affecting any of the other known functions of the DPP4 protein.
- The DPP4i class comprises a heterogeneous group of unrelated compounds with differing pharmacokinetic profiles.
- Potential risks and benefits of DPP4i can be divided into class effects, occurring directly as a consequence of the inhibition of DPP4 activity, and compound-specific effects, related to the individual chemical entities.
- DPP4i have a favourable therapeutic profile and are proven not to increase cardiovascular risk; they are safe and effective in the majority of patients with type 2 diabetes mellitus.

DPP4i) and differences that are completely unrelated to the inhibition of DPP4 per se, but that might arise because of intrinsic differences related to the individual chemical entities. Regarding the former, any difference in terms of extent and/or duration of DPP4 inhibition will clearly directly affect the clinical efficacy to reduce HbA_{1c} levels (and could potentially be relevant should any tolerability or safety issues directly related to inhibition of the catalytic activity of the DPP4 protein be identified). For the latter, the fact that the DPP4i comprise a chemically diverse class of agents might give rise to differences in metabolism and elimination, which might affect their clinical application. It also opens up the possibility for compound-specific pharmacology and/or toxicology of the parent compound and/or of any metabolites, which could lead to off-target or unwanted adverse effects.

This Review discusses the use of DPP4i in the treatment of T2DM, highlighting their benefits and risks. The article will focus primarily on the five DPP4i (TABLE 1) with the widest geographical distribution: alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin (albeit that vildagliptin is not marketed in the USA or Canada).

Mechanisms of action of DPP4i

DPP4i themselves do not possess inherent glucose-lowering activity; rather, their anti-hyperglycaemic efficacy arises secondarily from the actions of endogenous substrates, levels of which are altered once the catalytic activity of DPP4 is inhibited (FIG. 2). To date, the major player in mediating the therapeutic effect of DPP4i is believed to be GLP1 (REF.[19]). GLP1 has been clearly established as a physiological DPP4 substrate[19,20], and levels of the endogenous, intact, biologically active peptide are increased following DPP4 inhibition in vivo and are associated with improved glucose homeostasis[21,22]. Moreover, studies using the GLP1 receptor antagonist, exendin 9–39, have demonstrated that the glycaemic efficacy of DPP4i is reduced if GLP1 signalling is eliminated[23,24], thereby confirming a role for GLP1 in the mechanism of action of DPP4i. However, these same studies also indicated that GLP1 could not be the only mediator involved as some residual glucose-lowering activity was still evident even in the absence of GLP1 receptor activation[23,24].

The second incretin, glucose-dependent insulinotropic polypeptide (GIP), is also a physiological substrate of DPP4 and levels of GIP rise when DPP4 activity is inhibited[21,22]. Furthermore, like GLP1, GIP has a glucose-dependent insulinotropic action[7], raising the possibility that GIP might be involved in the anti-hyperglycaemic effect of DPP4i. Classically, the notion that GIP might be therapeutically useful had largely been dismissed as early studies had shown that its ability to stimulate insulin secretion is severely impaired in T2DM[25], while studies aiming to explore this finding further in humans with T2DM were hampered by the lack of suitable GIP receptor antagonists. However, the subsequent demonstration that the insulinotropic effect of GIP is at least partially restored by improving glycaemic control in patients with T2DM[26,27], together with the development of novel antagonists[28] that can be used in clinical studies, is leading to a reappraisal of the role of GIP in mediating the glycaemic effects of DPP4i therapy. Furthermore, while the ability of GLP1 to suppress glucagon secretion diminishes once blood levels of glucose fall below usual fasting levels[8], GIP actually enhances glucagon responses to low glucose levels[29]. Thus, as GIP administration during insulin-induced hypoglycaemia results in increased glucagon secretion[30], it follows that the elevated levels of intact GIP observed after DPP4 inhibition might contribute to the preserved glucagon counter-regulatory responses seen when blood levels of glucose are clamped at hypoglycaemic levels[31,32]. Accordingly, therefore, the effects of GIP in improving glucagon counter-regulation might further contribute to the minimal hypoglycaemia risk associated with DPP4i.

Whether other DPP4 substrates also contribute to the therapeutic actions of DPP4i remains to be established. Numerous peptide hormones and chemokines have been identified as being susceptible to DPP4 cleavage when incubated at a high concentration with the enzyme in vitro[20,33]. However, for most of them, no evidence suggests that their endogenous levels are altered by DPP4 inhibition in humans[19,20], and no adverse effects or safety issues have thus far been identified as being due to off-target effects of DPP4i on other endogenous substrates.

DPP4 inhibitors

After the discovery of DPP4 in 1966 (REF.[34]), its substrate preferences were described[35], which soon led to a number of DPP4i being found, many of which were based on a dipeptide scaffold. Although these inhibitors could be used in vitro[36], most were unsuitable for in vivo studies. However, once DPP4 had been identified as a therapeutic target, detailed structure–activity screening was used to find compounds that were suitable for clinical use, leading to the development of inhibitors such as vildagliptin[37] and saxagliptin[38]. The finding that DPP4 belonged to a family of related enzymes, and the publication of the crystal structure[39] of the DPP4 protein, permitted further optimization, resulting in inhibitors such as sitagliptin[40], alogliptin[41] and linagliptin[42]. The class now consists of a number of DPP4i spanning a range of unrelated compounds, giving it a diverse chemical and pharmacokinetic profile[43] (TABLE 1).

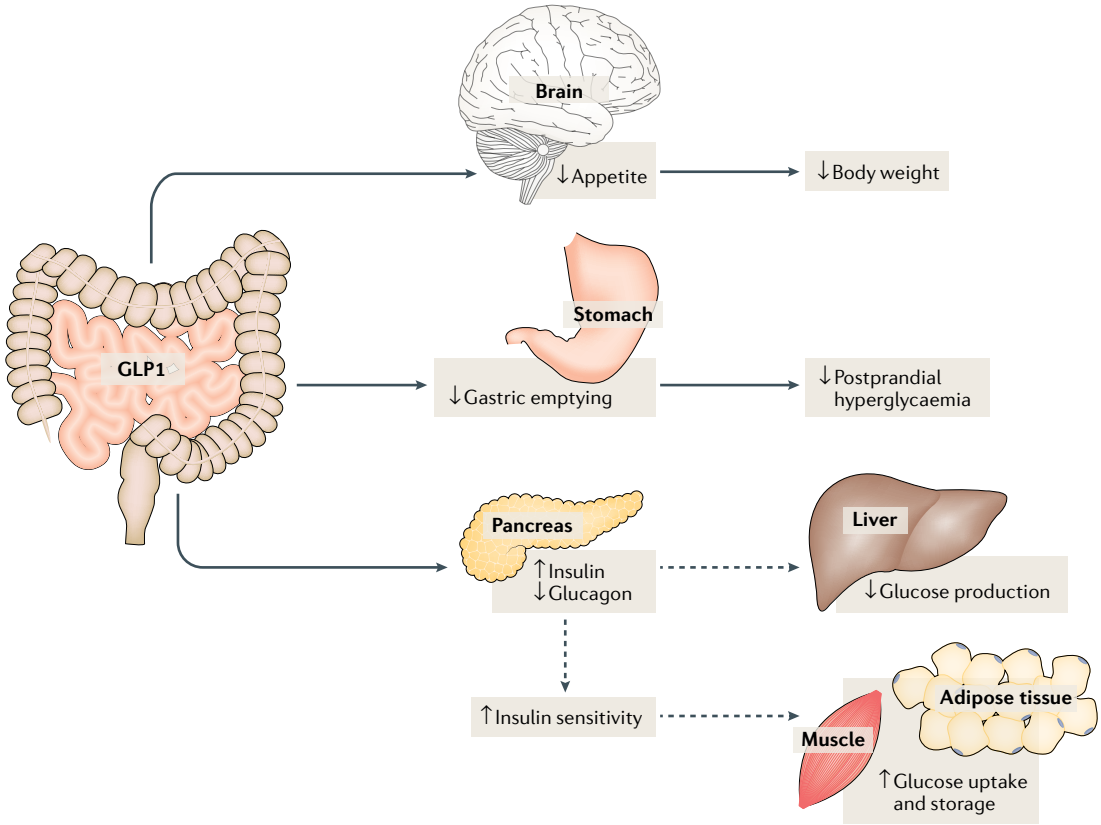


Fig. 1 | **Anti-diabetic actions of GLP1.** Glucagon-like peptide 1 (GLP1) is released after nutrient ingestion and exerts its effects via interaction with GLP1 receptors in target tissues[7]. In the islets of Langerhans, GLP1 glucose-dependently stimulates secretion of insulin from β-cells and suppresses the release of glucagon from α-cells, which results in decreased hepatic glucose production and increased glucose uptake in muscle and adipose tissue. The rate of gastric emptying is decreased, leading to smaller postprandial glucose excursions, while appetite is decreased, leading to reduced food intake and body weight loss. Solid arrows indicate effects mediated directly by GLP1. Dashed arrows indicate effects mediated secondarily to GLP1-induced effects on pancreatic islet activity.

Sitagliptin. Sitagliptin was the first DPP4i to receive marketing approval, and was launched in the USA in 2006. It is a β-amino acid-based triazolopiperazine derivative[40], which does not undergo substantial metabolism, giving it a half-life of around 12.5 h[43]. The kidneys are the main clearance route, with more than 80% of the administered dose being eliminated unchanged in the urine; renal clearance exceeds the glomerular filtration rate, indicating that both passive filtration and active secretion are involved[44,45]. Accordingly, once renal function declines, exposure to the drug begins to increase[46], providing the rationale for the dose reduction in patients with moderate or severe renal impairment[45] (see a subsequent section).

Vildagliptin. Vildagliptin was the second DPP4i to be approved and belongs to the cyanopyrrolidine chemical class[37]. Vildagliptin is subject to substantial hydrolysis (cytochrome-independent), generating an inactive molecule (LAY151), which is the predominant circulating form and accounts for 57% of the dose; only around 18% circulates as the active drug[43,47]. Accordingly, the half-life (~2 h) is much shorter than that of sitagliptin, and vildagliptin is used in a twice daily dosing regimen. This metabolism is the main route of elimination of the parent drug, and, consequently, exposure to the active molecule is only modestly increased with falling creatinine clearance[43,47]. However, LAY151 is renally eliminated, and exposure to LAY151 increases in patients with impaired renal function[48].

Saxagliptin. Like vildagliptin, saxagliptin is also a cyanopyrrolidine[38] and also undergoes substantial metabolism. However, unlike vildagliptin, this metabolism is mediated in the liver by cytochrome P450 3A4 or P450 3A5, and generates a metabolite (5-hydroxy-saxagliptin) that also has DPP4 inhibitory activity (around half the potency of the parent molecule). Approximately 25% of circulating saxagliptin-related material consists of the parent drug (half-life 2.5 h) and 50% as the primary metabolite (half-life 3 h)[43,49]. The parent saxagliptin molecule is eliminated via metabolism in the liver with some limited renal clearance, while the metabolite in cleared via filtration in the kidneys[50,51]. However, hepatic impairment has only modest effects on drug exposure, meaning that no change in the therapeutic dose is required whereas, in line with other renally eliminated DPP4i, some dose reduction is recommended when renal function declines[51] (see a subsequent section).

Alogliptin. Whereas sitagliptin, vildagliptin and saxagliptin can all be described as being peptidomimetics (their structure resembles a dipeptide structure), alogliptin is a non-peptidomimetic, being a modified pyrimidinedione[41]. Like sitagliptin, it is not appreciably metabolized, giving it a half-life of around 20 h[43,52]. Alogliptin is eliminated predominantly through the kidneys unchanged, via mechanisms involving both glomerular filtration and active secretion, and, therefore, dose reduction is recommended in patients with reduced renal function to avoid any increase in exposure to the drug[53].

Linagliptin. Of the five most commonly used DPP4i, linagliptin is the most recent to come to market, receiving regulatory approval in 2011. As a methyl xanthine derivative[42], it also falls into the group of non-peptidomimetics. Linagliptin does not undergo notable metabolism and has a long half-life (effective half-life ~12 h, terminal half-life >100 h)[43,54] but, in contrast to the other four DPP4i, the kidney has only a minor role in its elimination[43,55]. The high degree of protein binding of linagliptin (to DPP4 itself as well as to other unidentified plasma proteins) minimizes glomerular filtration, so that less than 6% of the drug is cleared renally and the majority of the dose is instead excreted into the bile and eliminated in the faeces[43,54]. Consequently, exposure to linagliptin is unaffected by changes in renal function and so, unlike the other four DPP4i, the dose is not adjusted according to renal function[56] (see a subsequent section). Despite its biliary route of elimination, drug exposure is not altered in a clinically meaningful way in patients with hepatic impairment[57], and no dose adjustment is necessary[56].

Efficacy

As discussed already, the efficacy of DPP4i to inhibit the catalytic activity of the DPP4 enzyme will clearly correlate with their efficacy as anti-diabetic agents. All of the DPP4i currently being used therapeutically interact with the catalytic site of the DPP4 molecule in a reversible manner to block substrate entry, albeit with some differences in the underlying kinetics. Sitagliptin, alogliptin and linagliptin interact non-covalently with residues in the catalytic pocket before dissociating unchanged as the parent inhibitor molecules, which are then free to interact with the enzyme again[58,59]. This feature, together with their inherent long half-lives, results in sustained DPP4 inhibition, and is compatible with a once daily dosing regimen. By contrast, both vildagliptin and saxagliptin bind covalently via their cyanopyrrolidine moiety[58,59], which has the effect of prolonging the inhibitor–enzyme interaction until the bonds are hydrolysed, releasing their primary metabolites, LAY151 (inactive; vildagliptin) and 5-hydroxy-saxagliptin (active; saxagliptin). This feature, therefore, provides the explanation for why, despite their fairly short half-lives of just a few hours, vildagliptin is fully effective when used twice daily whereas saxagliptin can still be used once daily.

Accordingly, in short-term studies (1–9 days in duration), head-to-head comparisons in patients with T2DM have shown that when used at their therapeutic doses, sitagliptin (100 mg once daily), vildagliptin (50 mg twice daily) and saxagliptin (5 mg once daily) all achieve the same maximal and trough levels of DPP4 inhibition[60] and are associated with similar enhancements of intact incretin hormone concentrations[61,62]. It follows, therefore, that if the extent and duration of DPP4 inhibition is similar, the improvement in glycaemic control should also be similar. Indeed, in the few studies in which direct comparisons have been made, glucose excursions[61,62] and HbA_{1c} levels[63–65] are reduced to similar extents. Two longer-acting once-weekly DPP4i, namely trelagliptin (half-life 54 h) and omarigliptin (half-life ~63 h), are also marketed, albeit with a more restricted geographic availability than the other DPP4i (mainly confined to Japan)[66]. These inhibitors achieve similar degrees of DPP4 inhibition to the shorter-acting DPP4i discussed already[67,68] and, in line with this finding, head-to-head comparisons have also shown them to be non-inferior with respect to glycaemic control[67,69].

Some reports indicate that DPP4i might have greater efficacy in Asian populations than in white populations[70,71] based on retrospective analyses of clinical trials. It has been suggested that this difference might be related to differences in the pathology of T2DM in the two populations (a lean with impaired β-cell function phenotype in Asian patients versus an obese insulin-resistant phenotype in white patients). However, other studies have failed to find any association between efficacy and ethnicity[72,73]. Prospective trials designed specifically to address this issue are therefore required to resolve whether or not ethnicity has a role in the response to DPP4i.

Box 1 | **Attributes of small molecule drugs**

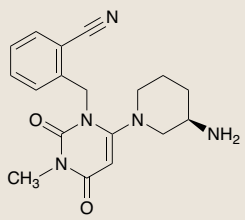
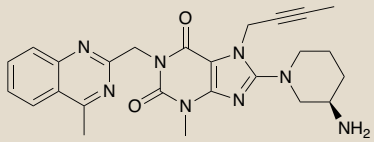
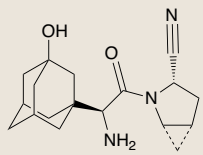
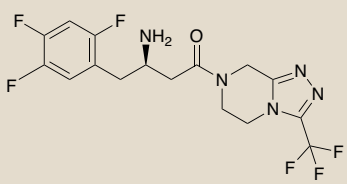
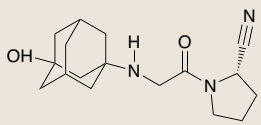
In terms of drug development, small molecules, including dipeptidyl peptidase 4 inhibitors (DPP4i), might share a number of features that contribute to making them commonly used and successful therapeutic agents[134,135].

- Usually chemically and thermally stable, requiring no special storage conditions
- Designed to be well absorbed, which helps to ensure reproducible pharmacokinetic and pharmacodynamic profiles with low inter-patient variability
- Low risk of triggering immune response (for example, immuno-neutralizing antibody formation)
- Can often be co-formulated with other agents in a single pill
- Oral delivery addresses often-held physician preferences and patient preferences for pills rather than injectable drugs
- Often fairly simple and inexpensive to make

Potential risks of DPP4i

The fact that both the functions of DPP4 and the underlying endocrinology of the incretin system were already understood has meant that DPP4i could be rationally designed based on a known target, rather than being developed secondarily to observations of a glucose-lowering effect. This feature has contributed to the relative lack of unwanted off-target or adverse effects associated with the DPP4i that are used therapeutically, which are characterized by their overall good tolerability and placebo-like safety profile[18] (a feature that also seems to be shared by the once-weekly DPP4i, although these are less widely available than other DPP4i[67,69]). Nevertheless, adverse effects associated with DPP4i have

Table 1 | **Characteristics of commonly used dipeptidyl peptidase 4 (DPP4) inhibitors**

DPP4 inhibitor	Chemistry	Structure	Half-life	Absolute bioavailability	Dose	Plasma protein binding	Metabolism	Elimination route
Alogliptin[43,52,53]	Modified pyrimidinedione		20 h	100%	25 mg once daily	20–30%	Minimal	Predominantly (>70%) renal
Linagliptin[43,54,56]	Xanthine based		~12 h (effective), >100 h (terminal)	~30%	5 mg once daily	>90%	Minimal	Predominantly biliary (<6% renal)
Saxagliptin[43,49,51]	Cyanopyrrolidine		2.5 h (parent), 3 h (metabolite)	~75%	5 mg once daily	Negligible	Hydrolysis (cytochrome P450 3A4 or P450 3A5) to form an active metabolite	Metabolism (parent) and renal (metabolite)
Sitagliptin[43–45]	β-amino acid based		12.5 h	~87%	100 mg once daily	38%	Minimal	Predominantly (>80%) renal
Vildagliptin[43,47,48]	Cyanopyrrolidine		~2 h	85%	50 mg twice daily	~9%	Hydrolysis (cytochrome-independent) to form an inactive metabolite	Metabolism (parent) and renal (metabolite)

been reported, albeit that these tend to be uncommon, and they can be classified as being either class effects or adverse effects confined to individual DPP4i.

Class effects. Class effects are any potential risks related directly to the mechanism of action (that is, the inhibition of the catalytic activity of DPP4), which will, by definition, affect all members of the DPP4i class. As already alluded to, the DPP4 enzyme is capable of cleaving numerous substrates in the test tube[20,33]. Moreover, the DPP4 protein (also referred to as CD26) is known to have a role in regulating T cell immune responses[74]. Together, these features raise the possibility that inhibiting the enzymatic activity of DPP4 could be associated with unwanted off-target adverse effects and/or outright safety issues arising from impaired immune function and/or from changes in concentrations of these other substrates.

Regarding effects in the immune system, there is little evidence that immune function is impaired by DPP4 inhibition. Although the DPP4 protein can enhance the activity of T cells it is not essential, and several other molecules also serve as T cell activators[75]. Moreover, the T cell stimulatory effect does not involve the enzymatic activity of DPP4 (REF.[76]), but is mediated indirectly via the interaction of DPP4 with other cell surface proteins[75]. This means that DPP4i, which are all small molecules with molecular weights under 500 Da, can interact with the catalytic site to inhibit the enzyme without interfering with the ability of the molecule to function as a co-stimulatory factor. Accordingly, DPP4i do not impair innate or adaptive immune responses[77] and have no adverse effects on viral load or markers of immune cell activation even in patients with compromised immune systems (such as patients with human immunodeficiency virus infection[78,79]). Moreover, pooled safety analyses[80–84] and large cardiovascular outcome trials (CVOTs)[85–89] have not revealed any signals for increased infection rates, further supporting the suggestion that DPP4 inhibition does not adversely affect immune function.

With respect to potential adverse effects related to DPP4i-mediated changes in substrate levels, in practice the effects of only a few of the identified in vitro substrates are actually influenced by DPP4 inhibition in vivo[19,20]. This finding can be explained in three ways.

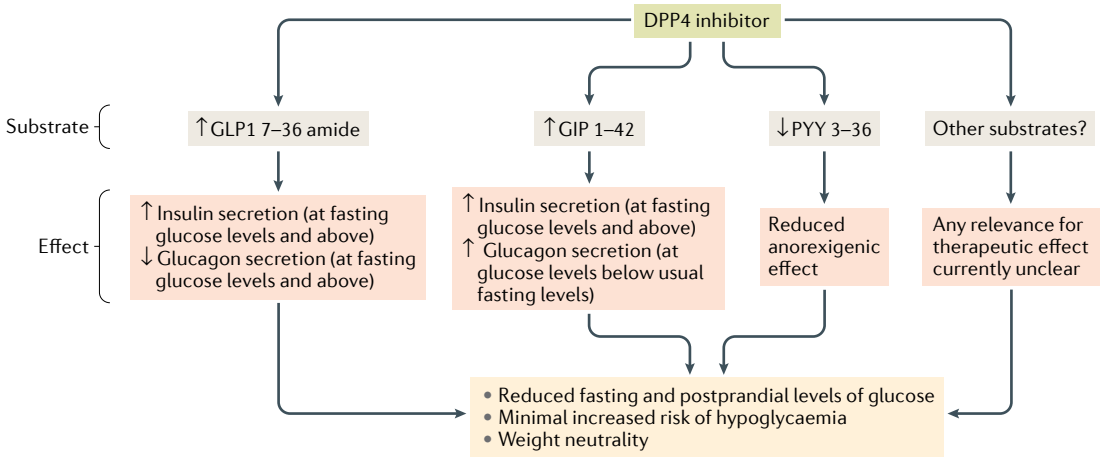


Fig. 2 | **Mechanism of action of DPP4i.** The therapeutic effects of dipeptidyl peptidase 4 inhibitors (DPP4i) are mediated secondarily via the substrates they protect from degradation. Increased levels of intact, biologically active glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) affect insulin and glucagon secretion in a glucose-dependent manner. Reduced degradation of peptide tyrosine tyrosine (PYY) 1–36 results in lower levels of the anorexigenic metabolite PYY 3–36. This effect might counterbalance any appetite-suppressing effect of the increased GLP1 levels, thereby resulting in minimal effects on body weight. Very few other potential substrates have been shown to be affected by DPP4 inhibition in humans[19,20], and whether they might contribute to the anti-diabetic effects of DPP4i remains to be established.

First, substrates identified in vitro never actually come into contact with the enzyme under physiological circumstances (for example, substrates with an intracellular distribution will not meet DPP4, which has an extracellular localization). Second, DPP4 is not the substrate's primary route of metabolism (for example, the substrate might have already been degraded by other enzymes or it might have multiple clearance pathways that can take over if DPP4 activity is blocked). Third, the actions of the substrates are not altered by DPP4 cleavage (for example, the biological activity resides in the central or carboxy-terminal portions of the molecule and will be unaffected by the loss of the N-terminal dipeptide).

It follows, therefore, that inhibiting the activity of DPP4 will not have any meaningful effect on these 'pharmacological' substrates in the in vivo setting. Of the known physiological substrates, the effects of DPP4 inhibition have been most clearly described for the incretin hormones[19,20] where, as discussed already, the effects of DPP4i on the pancreatic islets mediate the glucose-lowering action of DPP4i. However, appetite loss and/or weight loss and gastrointestinal adverse effects such as nausea, vomiting and diarrhoea, which are seen with GLP1 receptor agonists, are not generally associated with DPP4i[18]. This finding might partly be explained by the fact that circulating levels of intact endogenous GLP1 after DPP4 inhibition are still substantially lower than the pharmacological concentrations of the GLP1 agonists. However, it has also been argued that altered levels of another DPP4 substrate, the intestinal hormone peptide tyrosine tyrosine (PYY), might contribute. Thus, DPP4 inhibition reduces conversion of intact PYY 1–36 to its anorexigenic metabolite PYY 3–36 (REF.[90]) so that the resultant reduced levels of PYY 3–36 might counterbalance any weight loss effect due to the increased levels of intact GLP1, thereby explaining the weight neutrality of DPP4i.

Over the years, there has been some controversy over whether incretin therapies increase the risk of acute pancreatitis[91,92]; however, currently, little evidence exists to support a direct causal relationship[93,94]. Nevertheless, although not statistically significant, numerical imbalances in pancreatitis events (but not pancreatic cancer) were noted in the individual large CVOTs with four DPP4i (sitagliptin[87], saxagliptin[85], alogliptin[86] and linagliptin[88]; there is no equivalent trial with vildagliptin) in which pancreatic adverse effects were adjudicated (that is, rigorously evaluated by a panel of independent experts in a blinded fashion). Subsequently, a meta-analysis has suggested that the risk of acute pancreatitis is increased in the specific populations included in these outcome trials, albeit that the absolute risk was small (0.117% per patient-year of observation for patients on DPP4i versus 0.067% per patient-year of observation for those on placebo)[95]. Given that there was no similar association of acute pancreatitis with GLP1 agonists in the CVOTs with those agents, the authors of the meta-analysis speculated that perhaps another DPP4 substrate, rather than GLP1, could be the mediator[95], but this idea remains to be explored. In the more general T2DM population, retrospective database analyses have given conflicting results over whether an association between DPP4i and acute pancreatitis truly exists[96,97]. This inconsistency might, to some extent, be driven by reporting and/or channelling bias (a larger proportion of 'sicker' patients being prescribed DPP4i because of their good tolerability and/or because other agents might be contraindicated). Published in 2020, an extensive meta-analysis of 165 randomized clinical trials with a duration of at least 24 weeks, including the CVOTs, failed to find any association between DPP4i and acute pancreatitis; however, the authors did not rule out that such an association might potentially exist in selected populations,

such as those with an increased risk of pancreatitis[98]. On balance, therefore, acute pancreatitis might occur as an uncommon adverse effect with a low frequency, albeit that for the vast majority of patients the anti-hyperglycaemic benefit of DPP4i far outweighs any potential risk[99].

Pharmacoepidemiological database analyses and isolated case reports have reported associations of other rare adverse effects, such as arthralgia[100] and bullous pemphigoid (an autoimmune skin disease)[101,102], with all the individual DPP4i, which is suggestive of possible class effects. However, the very fact that these adverse effects are rare means that any causal relationship (or indeed, whether individual members of the DPP4i class differ in this respect) is difficult to establish, but cannot be excluded. In addition, there are currently no convincing mechanistic explanations to explain the associations.

Compound-specific effects. Remarkably, perhaps, given the diverse chemistry of DPP4i, very few adverse effects linked to individual inhibitors have been reported. Of these, heart failure has received the most attention, following the finding of a small, but statistically significant, increased risk of hospitalization for heart failure (HHF) in SAVOR-TIMI[85], the saxagliptin CVOT. Although the underlying cause has not yet been identified (and could just be a chance finding), a class effect related to the mechanism of action of DPP4i can probably be ruled out given that event rates in TECOS[87] (sitagliptin), EXAMINE[86] (alogliptin) and in both CARMELINA[88] and CAROLINA[89] (linagliptin) were not increased (TABLE 2). Nevertheless, it remains possible that the association between saxagliptin and HHF could be an off-target effect related to the saxagliptin molecule and/or its metabolite (or metabolites), and there has been some speculation that inhibition of another member of the DPP4 enzyme family, namely DPP9, might be responsible. In this respect, saxagliptin inhibits DPP9 activity in vitro and is associated with changes in cardiac electrophysiology and adverse effects on cardiomyocyte contractility[103,104], whereas similar effects were not seen with a highly selective DPP4i (sitagliptin)[104]. However, it is unknown whether there is any alteration in DPP9 activity when saxagliptin is used therapeutically, and this hypothesis remains to be tested in humans. Nonetheless, even though no mechanism to explain the association between saxagliptin and HHF has been identified, treatment guidelines are differentiating DPP4i according to the risk of heart failure. Thus, the consensus report of the American Diabetes Association and the European Association for the Study of Diabetes and the position paper from the European Society of Cardiology and Heart Failure Association both recommend that saxagliptin should not be used in patients with heart failure because of the risk of HHF[105,106].

As already mentioned, vildagliptin belongs to the same chemical group (cyanopyrrolidine) as saxagliptin and is also extensively metabolized. Like saxagliptin, vildagliptin can also inhibit DPP9 in vitro[107], raising a question mark over whether vildagliptin might also be associated with HHF. However, no large CVOT with vildagliptin exists, meaning there is no equivalent randomized controlled study that might shed light on this question; however, a non-interventional database safety analysis highlighted no cardiovascular safety issues[108]. In a small ($n = 254$) 1-year placebo-controlled study (the VIVIDD trial) in patients with T2DM and pre-existing heart failure, vildagliptin had no effect on left ventricular ejection fraction compared with placebo. Left ventricular volumes were, however, increased, but no evidence was found of deterioration in heart failure status[109]. Although HHF was not increased in patients given vildagliptin, it should be noted that event rates were low (13 versus 10 events) and the trial was not designed to examine any potential link between vildagliptin and HHF[109]. The clinical implications of the increased ventricular volumes are not known, and any causal relationship with vildagliptin remains to be clarified.

A small number of other adverse effects, which seem to be linked with an individual DPP4i, have also been reported, but so far these remain associations rather than adverse effects that can be definitively attributed to a specific compound. Thus, safety analyses have revealed that vildagliptin is associated with small increases in hepatic transaminase levels; however, this effect does not seem to be related to any increases in the number of actual hepatic adverse effects[110], and an underlying mechanism has not been established. Nonetheless, prescribing information for vildagliptin includes the recommendation to monitor liver function and not to use this particular DPP4i in patients with any degree of hepatic insufficiency or in those with elevated transaminase levels at baseline[48]. Isolated cases of liver injury in patients receiving alogliptin have been reported and, although whether hepatoxicity is associated with alogliptin has been the subject of debate[111,112], the use of alogliptin is not specifically contraindicated in patients with mild or moderate liver disease[53].

Table 2 | **Cardiovascular outcome trials with dipeptidyl peptidase 4 inhibitors**

Inhibitor	CVOT	Comparator	Cardiovascular safety (MACE), (HR; primary end point)	Risk of hospitalization for heart failure (HR)
Alogliptin	EXAMINE[86]	Placebo	0.96	1.07 ($P = 0.66$)
Linagliptin	CARMELINA[88]	Placebo	1.02	0.90 ($P = 0.26$)
	CAROLINA[89]	Glimepiride	0.98	1.21 ($P = 0.18$)
Saxagliptin	SAVOR-TIMI[85]	Placebo	1.00	1.27 ($P < 0.007$)
Sitagliptin	TECOS[87]	Placebo	0.98	1.00 ($P = 0.98$)
Vildagliptin	None planned[a]	NA	No data	No data

Cardiovascular safety outcomes: hazard ratios (HRs) for major adverse cardiovascular events (MACE) and hospitalization for heart failure. CVOT, cardiovascular outcome trial; NA, not applicable. [a]CVOT was not mandatory because vildagliptin is not marketed in the USA.

Benefits of DPP4i

DPP4i all benefit by being highly orally available and well tolerated anti-hyperglycaemic medications. They are also easy to use, requiring no dose titration and can be taken at any time of day without regard to meal times. Their mechanism of action, involving both

Table 3 | **Primary effects of anti-diabetic agents, illustrating their complementary mechanisms of action**

Anti-diabetic agents	Improved insulin levels	Improved insulin resistance	Reduced hepatic glucose overproduction	Reduced glucose absorption or reabsorption
Metformin	NA	Improves hepatic and muscle insulin sensitivity	Decreases gluconeogenesis	NA
Sulfonylureas	Increase insulin exocytosis	NA	NA	NA
Glinides	Increase insulin exocytosis	NA	NA	NA
Thiazolidinediones	NA	Improve insulin sensitivity in adipose tissue, muscle and liver	NA	NA
DPP4i	Increase insulin biosynthesis and secretion (glucose-dependent). Indirect effect via enhancing incretin levels to improve β-cell function	NA	Decreases glycogenolysis and gluconeogenesis. Indirect effect via enhancement of GLP1 levels resulting in suppression of glucagon (glucose-dependent)	NA
SGLT2i	NA	NA	NA	Reduce renal reabsorption
α-glucosidase inhibitors	NA	NA	NA	Reduce intestinal uptake
GLP1 agonists	Improve β-cell function by increasing insulin biosynthesis and secretion (glucose-dependent)	NA	Decrease glycogenolysis and gluconeogenesis. Indirect effect via suppression of glucagon (glucose-dependent)	NA
Insulin	Exogenous administration	NA	NA	NA

DPP4i, dipeptidyl peptidase 4 inhibitors; GLP1, glucagon-like peptide 1; NA, not applicable; SGLT2i, sodium–glucose transporter 2 inhibitors.

insulinotropic and glucagonostatic effects, means that they combine well with other anti-diabetic agents to give additional HbA_{1c}-lowering efficacy (TABLE 3). In this regard, the individual DPP4i have a low propensity for drug–drug interactions, meaning that they can be used with any other medications without the need for dose adjustment (however, owing to its route of metabolism, the efficacy of saxagliptin might be reduced if used together with strong inducers of P450 3A4, such as rifampicin[51]). Similarly, doses of other agents used together with DPP4i do not generally require adjustment; however, reduction of concomitant sulfonylurea or insulin doses is recommended to minimize the hypoglycaemic risk associated with sulfonylureas and insulin[45,48,51,53,56]. The discovery that metformin can stimulate GLP1 secretion[113,114] and that this effect contributes to the action of metformin[115] further explains the particular effectiveness of the metformin and DPP4i combination. Moreover, the dual effects of DPP4i on α-cells and β-cells means that they also combine well with the pancreatic islet-independent action of sodium–glucose transporter 2 inhibitors (SGLT2i). Furthermore, the reduction in hepatic glucose production caused by DPP4i due to the suppression of glucagon secretion provides a complementary effect when DPP4i are used with insulin secretagogues or insulin itself (TABLE 3), and also means that beneficial effects on glycaemic control can still be obtained, even if β-cell function is reduced.

As noted already, the effects of DPP4i on glucose homeostasis are not direct, but are mediated secondarily via the actions of the substrates they protect, notably the incretin hormones (FIG. 2). Consequently, given that DPP4 activity is already fully inhibited when the DPP4i are used at their therapeutic doses, it follows that any increase in exposure to the drug (for example, after accidental overdose or as a consequence of reduced clearance; see later discussion) will have no further glucose-lowering effect (because the enzyme cannot be inhibited by more than 100%). Combined with the fact that the actions of both GLP1 and GIP are themselves glucose-dependent, the inherent risk of hypoglycaemia with DPP4i therapy is therefore particularly low[17,18].

In common with all the latest anti-diabetic agents, the DPP4i that are also marketed in the USA (alogliptin, linagliptin, saxagliptin and sitagliptin) have had their cardiovascular safety evaluated in large CVOTs. These trials, carried out in patients with established cardiovascular disease or in high-risk individuals with several cardiovascular risk factors, have included tens of thousands of patients, with median follow-up durations of 1.5–6.3 years[85–89]. Uniformly, they have demonstrated that the risk of major adverse cardiovascular events is not increased with any of the DPP4i tested (TABLE 2). However, despite encouraging early signs from meta-analyses of phase III clinical trials[116], there was no risk reduction in the CVOTs.

These features combine to make DPP4i especially suitable for use in elderly, frail and/or vulnerable patients, who are often on polypharmacy because of longstanding T2DM and multiple comorbidities, and in those with renal impairment, where other anti-diabetic medications might be contraindicated. While such patients are often excluded from clinical trials, it is noteworthy that DPP4i tend to be preferentially prescribed for older patients, particularly for those above 75 years of age who have a history of comorbidities[117]. Nevertheless, a few studies have specifically investigated DPP4i in elderly individuals with T2DM (aged 65 years[118] or 70 years

and above[119,120]), and these have shown that DPP4i are safe and effective in this population. Moreover, the large CVOTs with DPP4i included considerable numbers of older patients (≥75 years) with comorbidities (around 15% of all participants), demonstrating the safety of DPP4i in these patients[121,122] while also showing that glycaemic efficacy was similar to that obtained in the younger participants[121].

DPP4i have been studied in patients with reduced kidney function, including those with end-stage renal disease on dialysis, showing DPP4i to be effective and well tolerated, which was also true for DPP4i with clearance pathways involving the kidney[123]. As noted previously, exposure to the parent inhibitor (sitagliptin and alogliptin) or the primary metabolite (vildagliptin and saxagliptin) increases with falling glomerular filtration rates. Accordingly, therefore, DPP4i dose reductions are recommended[45,48,51,53] to maintain plasma levels of the drug (or its primary metabolite) similar to those in individuals with normal renal function (linagliptin, with its biliary route of elimination, does not require any change in dose[56]). However, patients whose renal status is not regularly reviewed might unwittingly be receiving inappropriately high DPP4i doses. It is also apparent that dosing recommendations might not always be followed in patients with known renal impairment, with studies revealing that considerable numbers of patients are prescribed doses higher than those recommended[124]. It is, therefore, reassuring that the dose adjustments for the renally eliminated DPP4i are based on pharmacokinetic profiles, and are not because of safety concerns. As already discussed, any increase in exposure will not lead to hypoglycaemia or other mechanism-based adverse effects because the enzyme is already maximally inhibited, and compound-specific adverse effects are unlikely because of the wide dosing safety margins; early dose-finding studies, using doses of 4–32 times the therapeutic doses, found no dose-related increases in the incidence of adverse effects[125–127].

Conclusions

Although members of the DPP4i class differ in their chemical and pharmacokinetic characteristics, which can influence the way in which the individual drugs are used in clinical practice, as a class they have proved to be a well-tolerated and easy-to-use addition to the therapeutic options for managing T2DM. Their low risk of causing hypoglycaemia and their complementary mechanism of action has meant that they have become widely used second-line agents, and their benign profile means that they are particularly suited when other agents might not be preferred (for example, because of adverse effects or issues with route of administration) or are contraindicated (for example, because of pre-existing comorbidities or concomitant medication). As discussed, DPP4i are not generally associated with drug–drug interactions, and the fact that they are small molecules has facilitated co-formulation of fixed-dose combinations of DPP4i with other commonly used agents such as metformin, SGLT2i and pioglitazone[128–130]. Accordingly, the adverse effect profiles of the fixed-dose combinations resemble what is seen when the individual components are used together, while the complementary mechanisms of action (TABLE 3) means that additional glycaemic efficacy can be obtained without increasing the pill burden.

Like all the new anti-diabetic agents, DPP4i were required to demonstrate their cardiovascular safety, and large CVOTs have confirmed that the risk of major adverse cardiovascular events is not increased. However, unlike members of the GLP1 receptor agonist and SGLT2i classes, for which cardiovascular benefits were seen[131], DPP4i were neutral in this respect. Nevertheless, it should perhaps be emphasized that trial data should be interpreted in the context of the actual populations of patients studied (for example, those with established cardiovascular disease and/or high-risk individuals with multiple cardiovascular risk factors), which might not be fully representative of the general T2DM population. Accordingly, the latest American Diabetes Association and the European Association for the Study of Diabetes consensus statement provides separate recommendations for those with or without "indicators of high risk or established atherosclerotic cardiovascular disease, chronic kidney disease or heart failure"[132]. However, it should also be recognized that any choice of anti-diabetic agent based on its potential for cardiovascular risk reduction should not be at the expense of glucose regulation, because good glycaemic control is important for the prevention of microvascular complications[133]. Thus, even though DPP4i did not improve cardiovascular outcomes in the CVOTs, they do remain recommended options in those with high cardiovascular risk or established disease if HbA_{1c} is not at target levels with GLP1 agonists or SGLT2i[132]. The requirement for CVOTs has also had the added benefit of providing large databases, meaning that any less common tolerability issues and/or adverse effects might be easier to detect than in smaller studies. Reassuringly, these trials, which included many thousands of patients and typically had longer durations of follow-up than most phase III clinical trials, have not uncovered any new safety issues with DPP4i.

At the end of the day, however, the benefits of any drug are dependent on the patient actually taking the medication. DPP4i are safe and effective in the majority of patients with T2DM, and it is to be hoped that with their overall favourable therapeutic profile DPP4i might contribute to helping patients achieve glycaemic targets. Moreover, with some patents approaching their expiry dates, DPP4i might become more accessible as they transition from the proprietary to the generic phase of their drug life.

Published online: 14 September 2020

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Competing interests
No writing assistance or financial support was used in the preparation of this article. C.F.D. has received consultancy and/or lecture fees from companies with an interest in developing and marketing incretin-based therapies for treatment of type 2 diabetes mellitus (Boehringer Ingelheim, Lilly, Merck/MSD and Novo Nordisk). C.F.D.'s spouse is employed by, and holds stock in, Merck/MSD.

Peer review information
Nature Reviews Endocrinology thanks G. Mingrone, who co-reviewed with L. Gissey, P. Flatt and K. Kaku, for their contribution to the peer review of this work.