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DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials

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Abstract

Dipeptidyl peptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes. Direct comparisons with active glucose-lowering comparators in drug-naive patients have demonstrated that DPP-4 inhibitors exert slightly less pronounced HbA_{1c} reduction than metformin (with the advantage of better gastrointestinal tolerability) and similar glucose-lowering effects as with a thiazolidinedione (TZD; with the advantage of no weight gain). In metformin-treated patients, gliptins were associated with similar HbA_{1c} reductions compared with a sulphonylurea (SU; with the advantage of no weight gain, considerably fewer hypoglycaemic episodes and no need for titration) and a TZD (with the advantage of no weight gain and better overall tolerability). DPP-4 inhibitors also exert clinically relevant glucose-lowering effects compared with a placebo in patients treated with SU or TZD (of potential interest when metformin is either not tolerated or contraindicated), and as oral triple therapy with a good tolerability profile when added to a metformin-SU or pioglitazone-SU combination. Several clinical trials also showed a consistent reduction in HbA_{1c} when DPP-4 inhibitors were added to basal insulin therapy, with no increased risk of hypoglycaemia. Because of the complex pathophysiology of type 2 diabetes and the complementary actions of glucose-lowering agents, initial combination of a DPP-4 inhibitor with either metformin or a glitazone may be applied in drug-naive patients, resulting in greater efficacy and similar safety compared with either drug as monotherapy. However, DPP-4 inhibitors were less effective than GLP-1 receptor agonists for reducing HbA_{1c} and body weight, but offer the advantage of being easier to use (oral instead of injected administration) and lower in cost. Only one head-to-head trial demonstrated the non-inferiority of saxagliptin *vs* sitagliptin. Clearly, more trials of direct comparisons between different incretin-based therapies are needed. Because of their pharmacokinetic characteristics, pharmacodynamic properties (glucose-dependent glucose-lowering effect) and good overall tolerability profile, DPP-4 inhibitors may have a key role to play in patients with renal impairment and in the elderly. The role of DPP-4 inhibitors in the therapeutic armamentarium of type 2 diabetes is rapidly evolving as their potential strengths and weaknesses become better defined mainly through controlled clinical trials.

Keywords: Clinical trial-DPP-4 inhibitor; Alogliptin; Linagliptin; Saxagliptin; Sitagliptin; Vildagliptin; Type 2 diabetes mellitus; Review

Résumé

Les inhibiteurs de la DPP-4 dans le traitement du diabète de type 2 : revue critique des essais cliniques contrôlés.

Les inhibiteurs de la dipeptidylpeptidase-4 (DPP-4) offrent de nouvelles options pour le traitement du diabète de type 2. Des comparaisons directes avec d'autres médicaments antidiabétiques chez des patients naïfs de tout traitement ont démontré que les inhibiteurs de la DPP-4 étaient un peu moins puissants pour diminuer le taux d'HbA_{1c} que la metformine (avec l'avantage d'une meilleure tolérance digestive) et aussi puissants que les thiazolidinediones (avec l'avantage d'une neutralité pondérale). Chez les patients déjà traités par metformine, les gliptines entraînent une baisse des taux d'HbA_{1c} similaire à celle observée avec les sulfamides (mais sans prise de poids, sans hypoglycémie et sans nécessité de titration) ou avec les thiazolidinediones (avec l'avantage de l'absence de prise de poids et d'un meilleur profil de tolérance). Les inhibiteurs de la DPP-4 améliorent aussi le contrôle glycémique par rapport à un placebo chez les patients traités avec un sulfamide ou une thiazolidinedione (ce qui peut être intéressant chez les patients pour lesquels la metformine est non tolérée ou contre-indiquée) ou encore en triple thérapie orale en étant ajoutés à une combinaison metformine-sulfamide ou pioglitazone-sulfamide, avec toujours un bon profil de tolérance. Plusieurs essais cliniques ont montré une diminution consistante des taux d'HbA_{1c} lorsqu'un inhibiteur de la DPP-4 était ajouté à une insulinothérapie basale, sans accroître le risque d'hypoglycémie. En raison de la physiopathologie complexe du diabète de type 2 et de la complémentarité d'action des médicaments hypoglycémiants, une combinaison initiale d' un inhibiteur de la DPP-4 avec soit la metformine, soit une glitazone peut être proposée chez les patients insuffisamment contrôlés par régime et exercice, avec une meilleure efficacité et une aussi bonne tolérance qu'une monothérapie

pharmacologique initiale. Les inhibiteurs de la DPP-4 sont moins efficaces que les agonistes des récepteurs du *glucagon-like peptide-1* en ce qui concerne la diminution des taux d'HbA_{1c} et du poids, mais offrent le bénéfice d'un usage plus facile (prise orale au lieu d'une injection) et d'un coût moins élevé. Un seul essai clinique comparatif direct a été publié à ce jour entre deux inhibiteurs de la DPP-4, démontrant une non infériorité de la saxagliptine par rapport à la sitagliptine. De toute évidence, davantage d'essais cliniques devraient offrir une comparaison directe entre les différents traitements fondés sur l'effet incrétine. En raison de leurs caractéristiques pharmacocinétiques, de leurs propriétés pharmacodynamiques (effet hypoglycémiant glucose-dépendant) et de leur bon profil de tolérance, les gliptines devraient occuper une place de choix chez les patients avec une insuffisance rénale ou chez les sujets âgés. Le rôle des inhibiteurs de la DPP-4 dans l'arsenal thérapeutique du diabète de type 2 évolue rapidement au fur et à mesure que leurs avantages et inconvénients apparaissent mieux définis, essentiellement grâce aux essais cliniques contrôlés.

Mots clés : Diabète de type 2 ; Essai clinique ; Inhibiteur de la DPP-4 ; Alogliptine ; Linagliptine ; Saxagliptine ; Sitagliptine ; Vildagliptine ; Revue générale

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a novel pharmacological class of glucose-lowering agents that open up new perspectives for the management of type 2 diabetes mellitus (T2DM). The mechanism of action of DPP-4 inhibitors is distinct from any existing class of oral glucose-lowering agents [1]. Although they are not more potent in lowering blood glucose concentrations and reducing glycated haemoglobin (HbA_{1c}) levels [2], DPP-4 inhibitors nevertheless offer several clinically relevant advantages [3-5]. Among the most important benefits are a negligible risk of hypoglycaemia that is considerably lower than that observed with sulphonylurea (SU), and a weight-neutral profile in contrast to the weight gain generally observed with SU and thiazolidinedione (TZD). DPP-4 inhibitors have been evaluated as monotherapy and in various combinations with other glucose-lowering agents, and compared with either a placebo or an agent of another glucose-lowering pharmacological class as an active comparator [6].

The present review is an updated evaluation of five DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin) in randomized clinical trials in the literature so far, and focuses particularly on the following topics:

- direct comparisons with active glucose-lowering comparators in drug-naive or metformin-treated patients;
- comparisons with placebo or active comparators in more unusual indications as an add-on to SU or TZD, as oral triple therapy or as an add-on to insulin;
- use as the initial combination with metformin or TZD in drug-naive patients;
- comparisons with glucagon-like peptide-1 (GLP-1) receptor agonists or other gliptins in head-to-head trials;
- use of DPP-4 inhibitors in special populations, especially patients with renal impairment and the elderly.

2. Methods

To identify the relevant studies, an extensive literature search of Medline was performed from January 2005 to August 2011, using the term "DPP-4 inhibitors", and the generic names "sitagliptin", "vildagliptin", "saxagliptin", "alogliptin" and "linagliptin". No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined. Only clinical trials that randomized at least 100 T2DM patients and lasted at least 12 weeks were considered. Most of the studies ran for 24-26 weeks, with a maximum follow-up duration of 104 weeks in a few cases.

3. Results

3.1. Gliptins as monotherapy or as add-ons to metformin

Numerous placebo-controlled trials have demonstrated both the efficacy and safety of DPP-4 inhibitors in patients with T2DM treated with diet and exercise (drug-naive patients), and in patients treated with metformin monotherapy, the first-line drug choice for T2DM. All of these trials showed that DPP-4 inhibitors reduced HbA_{1c}, fasting plasma glucose and postprandial glucose levels without inducing hypoglycaemia, with near weight neutrality and a tolerability profile that did not differ from that of placebo. These trials have already been summarized in various reviews [7] and meta-analyses [2,8]. Clinically relevant reductions in HbA_{1c} were obtained with a gliptin across a wide range of T2DM patient subgroups examined by either specific baseline

demographic characteristics or β-cell function indices such as the homoeostatic model assessment (HOMA)-β [9]. Our present report has specifically compared DPP-4 inhibitors with active glucose-lowering comparators (instead of a placebo) to better delineate the potential advantages (and disadvantages) of DPP-4 inhibitors in clinical use.

3.1.1. Gliptins as monotherapy

As metformin is considered the first-line drug therapy for the management of T2DM [10,11], it is of interest to compare the efficacy (and safety) of aDPP-4 inhibitor with that of metformin in drug-naive T2DM patients insufficiently controlled with diet and exercise [12-21]. Overall, metformin (1000-2000 mg/day) demonstrated slightly (but significantly) greater reductions in both HbA_{1c} and body weight (Table 1, Fig. 1). However, the DPP-4 inhibitor showed superior gastrointestinal tolerability compared with metformin. Nevertheless, these comparative results 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 well tolerated (gastrointestinal adverse events) or is contraindicated (for instance, renal insufficiency).

Only three head-to-head trials have compared a DPP-4 inhibitor with a TZD (two with pioglitazone 30 mg and one with rosiglitazone 8mg) [22-24]. Overall, the reduction in HbA_{1c} was similar with the two pharmacological approaches, with a low incidence of hypoglycaemic events. However, the TZDs were associated with significant weight gain in contrast to the weight neutrality of gliptins (Table 1, Fig. 1).

Two studies compared a DPP-4 inhibitor with an alpha-glucosidase inhibitor as monotherapy in patients with T2DM. One trial compared vildagliptin 50 mg with acarbose (titrated up to 3x100mg) and reported similar HbA_{1c} reductions with the two compounds [25], while the other trial demonstrated that linagliptin (5 or l0mg once a day) had greater efficacy than voglibose (3 × 0.2 mg/day) for improving glycaemic control [26]. In both these studies, drug-related gastrointestinal disorders were more common with the alpha-glucosidase inhibitor than with the DPP-4 inhibitor (Table 1).

3.1.2. Gliptins combined with metformin

As metformin is considered the first-line drug in T2DM, most combination trials have tested the efficacy and safety of adding a DPP-4 inhibitor to baseline metformin monotherapy, and found that adding any gliptin was superior to a placebo, with a mean reduction in HbA_{1c} of 0.6-0.8% [7]. However, in the present review, only head-to-head trials *vs* active comparators are presented in brief. Gliptins have also been compared with SUs (glimepiride, glipizide, gliclazide) [27-34], TZDs (pioglitazone 30 mg, rosiglitazone 8 mg) [35-39] and GLP-1 receptor agonists (exenatide, liraglutide) [36,40,41]. However, only one head-to-head study compared two different DPP-4 inhibitors in the same trial: saxagliptin 5 mg with sitaglitptin 100 mg as add-ons to basal metformin therapy [42].

Compared with SU, a DPP-4 inhibitor generally led to a similar reduction in HbA_{1c} levels and a similar increase in the proportion of patients achieving HbA_{1c} levels < 7% (53 mmol/mol; Table 2, Fig. 1), but with a much lower incidence of hypoglycaemic events. SU therapy was associated with modest weight gain, whereas the administration of a gliptin resulted in no weight change or even modest weight loss (Table 1, Fig. 1). In the two longest-running trials, the 'escape phenomenon', assessed by a secondary increase in HbA_{1c} levels between weeks 24 and 104 following a good initial HbA_{1c} reduction, was significantly less pronounced with sitagliptin 100 mg or vildagliptin 100 mg than with glipizide or glimepiride, respectively [28,31], suggesting better β-cell protection and durability of glucose control with a DPP-4 inhibitor.

Compared with a TZD, a DPP-4 inhibitor was not inferior as regards improvement of glucose control (Table 2, Fig. 1). Initial observations had suggested that DPP-4 inhibitors might be less potent than TZDs. However, when considering the results of different trials in indirect comparisons, it is crucial to adjust treatment-induced HbA_{1c} reductions in relation to baseline values [43,44]. In this case, the differences between gliptins and TZDs that had initially appeared almost disappeared and, thus, were in agreement with the head-to-head comparisons analyzed in the present report. However, there was a clear-cut difference between the two pharmacological classes in terms of body-weight changes. A significant weight increase was observed in all trials with TZDs in contrast to the weight neutrality seen with DPP-4 inhibitors (Table 2, Fig. 1).

3.2. Gliptins in special combinations

3.2.1. Gliptins combined with sulphonylureas

Several trials have evaluated the efficacy and safety of adding a DPP-4 inhibitor *vs* a placebo to SU monotherapy (glimepiride or glyburide). This may be of interest in patients who cannot be treated with metformin. Compared with a placebo, sitagliptin 100 mg (once daily) [45] and vildagliptin (50 or 100 mg daily) [46] significantly

improved glycaemic control and β-cell function, and were well tolerated in T2DM patients with inadequate glycaemic control with glimepiride alone. Similar results were reported in T2DM patients with the addition of alogliptin (12.5 mg or 25 mg) to glyburide [47] and the addition of linagliptin (5mg) to a SU [48]. In addition, saxagliptin (2.5 or 5 mg) added to submaximum glyburide (5 or 7.5 mg) therapy led to statistically significant improvements *vs* upti-tration of glyburide alone (up to 15 mg) across key glycaemic parameters, with no significant differences in the reported incidences of hypoglycaemic events after a follow-up of 24 weeks [49] and 76 weeks [50]. However, while the association of gliptin-metformin did not lead to hypoglycaemia, hypoglycaemic events may arise with the combination of gliptin-SU. This means that, in T2DM patients with moderately increased HbA_{1c} levels taking SU as monotherapy, it may be safer to reduce the SU dose when a DPP-4 inhibitor is added to minimize the risk of hypoglycaemia, especially in elderly patients.

Table 1 : *Head-to-head trials comparing a DPP-4 inhibitor and an active glucose-lowering agent (metformin, a thiazolidinedione or acarbose) in drug-naive type 2 diabetes mellitus (T2DM) patients.*

	Reference	***n***	**Period (weeks)**	**Intervention (mg/day)**	**Δ HbA_{1c} (%)**	**HbA_{1c} <7 %[a] (% patients)**	**Δ BW (kg)**
Sitagliptin	Goldstein et al., 2007 [13]	1091	24	Sitagliptin 100	-0.66	20	0
				Metformin 1000	-0.82	23	-0.6
				Metformin 2000	-1.13	38	-1.3
	Williams-Herman et al., 2009 [14]	885	54	Sitagliptin 100	-0.80	23	+0.6
				Metformin 1000	-1.00	25	-1.0
				Metformin 2000	-1.30	44	-1.5
	Williams-Herman et al., 2010 [15]	454	104	Sitagliptin 100	-1.20	32	+0.5
				Metformin 1000	-1.10	28	-0.8
				Metformin 2000	-1.30	45	-2.4
	Aschner et al., 2010 [16]	1050	24	Sitagliptin 100	-0.43	69	-0.6
				Metformin 2000	-0.57	76	-1.9
Vildagliptin	Schweizer et al., 2007 [12]	780	52	Vildagliptin 100	-1.0	35	+0.3
				Metformin 2000	-1.4	45	-1.9
	Göke et al., 2008 [17]	305	104	Vildagliptin 100	-1.0	NA	+0.5
				Metformin 2000	-1.5	NA	-2.5
	Schweizer et al., 2009 [18]	335	24	Vildagliptin 100	-0.64	49	-0.45
				Metformin 1500	-0.75	61	-1.25
	Bosi et al.,2009 [19]	589	24	Vildagliptin 100	-1.1	40	-0.59
				Metformin 2000	-1.4	44	-1.62
	Rosenstock et al., 2007 [24]	786	24	Vildagliptin 50	-1.1	NA	-0.3
				Rosiglitazone 8	-1.3	NA	+ 1.6
	Rosenstock et al., 2007 [22]	607	24	Vildagliptin 100	-1.1	42	+0.2
				Pioglitazone 30	-1.4	43	+ 1.5
	Pan et al., 2008 [25]	661	24	Vildagliptin 100	-1.4	46	-0.4
				Acarbose (up to 300)	-1.3	47	-1.7
Saxagliptin	Jadzinsky et al., 2009 [20]	663	24	Saxagliptin 10	-1.7	32	-1.1
				Metformin 500-2000	-2.0	41	-1.6
	Pfützner et al., 2011 [21]	428	76	Saxagliptin 10	-1.55	25	-0.3
				Metformin 500-2000	-1.79	35	-1.0
Alogliptin	Rosenstock et al., 2010 [23]	327	26	Alogliptin 25	-0.96	24	-0.3
				Pioglitazone 30	-1.15	34	+2.2
Linagliptin	Kawamori et al., 2010 [26]	481	26	Linagliptin 5	-0.44	30	NA
				Linagliptin 10	-0.48	34	NA
				Voglibose 0.6	-0.10	22	NA

Δ: change *vs* baseline; BW: body weight; NA: not available. [a] 53 mmol/mol.

3.2.2. Gliptins combined with thiazolidinediones

Given the pathophysiology of T2DM, the combination of an insulin secretagogue, such as a DPP-4 inhibitor, and an insulin sensitizer, such as TZD, may appear to be an appealing approach [51]. In fact, each of the five studied DPP-4 inhibitors was able to further reduce HbA_{1c} levels by almost 1% and increase the proportion of patients

with HbA_{1c} levels < 7% (53 mmol/mol) by 15-20% when added to pioglitazone, without increasing hypoglycaemic episodes and with minimal weight increases (Table 3). All these studies compared the effect of adding a DPP-4 inhibitor *vs* a placebo [52-58].

Only one study used an active comparator instead of a placebo to evaluate the DPP-4 inhibitor added to TZD. In this controlled trial, the effects of the addition of sitagliptin (100 mg once a day) or metformin (850 mg twice a day) to pioglitazone monotherapy in poorly controlled T2DM patients showed improvements in HbA_{1c}, fasting plasma glucose and postprandial glucose levels with both interventions. However, metformin also led to a decrease in body weight, and to faster and better improvements in insulin resistance and inflammatory state parameters, even though sitagliptin led to better protection of β-cell function. However, an important limitation of the study was that the dose of piogliazone was different between the two arms (15 mg with metformin and 30 mg with sitagliptin; Table 3) [59]. In another study from the same group, a pioglitazone plus vildagliptin combination was more effective in preserving β-cell function, and reducing insulin resistance and inflammatory state parameters, despite similar improvements in glucose control parameters compared with the glimepiride plus vildagliptin combination [60].

Thus, the combination of a DPP-4 inhibitor with piogli-tazone may be an effective and safe therapeutic approach in patients with T2DM who cannot tolerate either metformin or SU [61].

Fig. 1. *Mean changes (95% confidence interval) in HbA_{1c} (upper) and body weight (lower) in head-to-head trials comparing a gliptin and metformin in drug-naive patients (10 trials), a gliptin and a sulphonylurea (SU) in metformin-treated patients (eight trials), and a gliptin and a glitazone (TZD) in both drug-naive and metformin-treated patients (eight trials). P values are for between-treatment differences. Note that some trials were computed twice or three times, as specific reports were published after various follow-up durations (24, 54 and/or 104 weeks).*

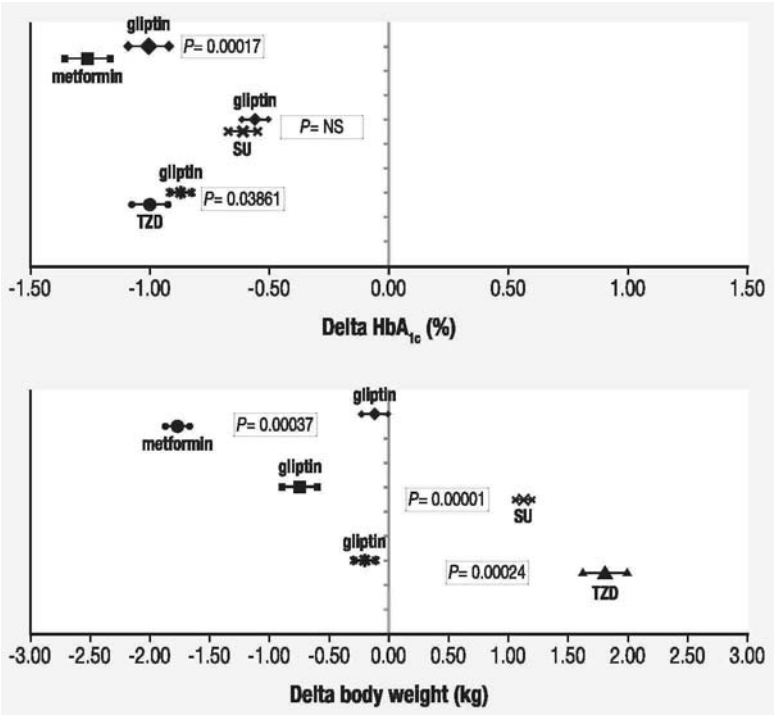

Table 2 : *Head-to-head trials comparing a DPP-4 inhibitor and an active glucose-lowering agent (sulphonylurea, thiazolidinedione, exenatide or liraglutide), and one trial of sitagliptin vs saxagliptin, in type 2 diabetes mellitus (T2DM) patients already treated with metformin (≥ 1500 mg/day).*

	Reference	*n*	Period (weeks)	Intervention (mg/day)	Δ HbA_{1c} (%)	HbA_{1c}< 7%[a] (% patients)	Δ BW (kg)
Sitagliptin	Nauck et al., 2007 [27]	1172	52	Sitagliptin 100	-0.67	63	-1.5
				Glipizide 5-20	-0.67	59	+1.1
	Seek et al., 2010 [28]	1172	104	Sitagliptin 100	-0.54	63	-1.6
				Glipizide 5-20	-0.51	59	+0.7

	Arechavaleta et al., 2011 [29]	1035	30	Sitagliptin 100	-0.47	52	-0.8
				Glimepiride 1-6	-0.54	60	+1.2
	Scott et al., 2008 [35]	273	18	Sitagliptin 100	-0.73	55	-0.4
				Rosiglitazone 8	-0.79	63	+1.5
	Bergenstal et al., 2010 [36]	514	26	Sitagliptin 100	-0.9	30	-0.8
				Pioglitazone 45	-1.2	43	+2.8
				Exenatide 2 once weekly sc	-1.5	59	-2.3
	Pratley et al., 2010 [40]	665	26	Sitagliptin 100	-0.9	21	-0.96
				Liraglutide 1.2	-1.24	44	-2.86
				Liraglutide 1.8	-1.50	55	-3.38
	Pratley et al., 2011 [41]	497	52	Sitagliptin 100	-0.88	27	-1.16
				Liraglutide 1.2	-1.29	50	-2.78
				Liraglutide 1.8	-1.51	63	-3.68
Vildagliptin	Ferrannini et al., 2009 [30]	2789	52	Vildagliptin 100	-0.44	54	-0.2
				Glimepiride 1-6	-0.53	56	+1.6
	Matthews et al., 2010 [31]	3118	104	Vildagliptin 100	-0.1	37	-0.3
				Glimepiride 1-6	-0.1	38	+1.2
	Filozof et al.,2010 [32]	1007	52	Vildagliptin 100	-0.81	30	+0.08
				Gliclazide 80-320	-0.85	32	+1.36
	Bolli et al., 2008 [37]	576	24	Vildagliptin 100	-0.9	27	+0.3
				Pioglitazone 30	-1.0	36	+1.9
	Bolli et al., 2009 [38]	576	52	Vildagliptin 100	-0.6	NA	+0.2
				Pioglitazone 30	-0.6	NA	+2.6
	Blonde et al., 2009 [39]	2478	12	Vildagliptin 100	-0.68	60	-0.6
				TZD (variable)	-0.57	52	+0.3
Saxagliptin	Göke et al., 2010 [33]	858	52	Saxagliptin 5	-0.74	43	-1.1
				Glipizide 5-20	-0.80	48	+1.1
Alogliptin	No published trial						
Linagliptin	Forst et al., 2010 [34]	333	12	Linagliptin 1	-0.40	15	-0.15
				Linagliptin 5	-0.73	15	-0.57
				Linagliptin 10	-0.67	21	-1.27
				Glimepiride 1-3	-0.90	NA	+0.73
Saxa- *vs* Sitagliptin	Scheen et al.,2010[42]	801	18	Sitagliptin 100	-0.62	39	-0.4
				Saxagliptin 5	-0.52	33	-0.4

Δ: change *vs* baseline; BW: body weight; se: subcutaneous; NA: not available; TZD: thiazolidinedione (pioglitazone or rosiglitazone). [a] 53 mmol/mol.

Table 3 : *Head-to-head trials comparing a DPP-4 inhibitor and a placebo or an active glucose-lowering agent (uptitration of initial dose of sulphonylurea [SU] or metformin) in type 2 diabetes mellitus (T2DM) patients already treated with a SU or a thiazolidinedione (TZD).*

	Reference	***n***	**Period (weeks)**	**Baseline (mg/day)**	**Intervention (mg/day)**	**Δ HbA_{1c} (%)**	**HbA_{1c} < 7%[a] (% patients)**	**ΔBW (kg)**
Add-on to SU								
Sitagliptin	Hermansen et al., 2007 [45]	212	24	Glimepiride ≥4	Sita 100	-0.30	11	+ 1.1
					Placebo	+0.27	9	0
Vildagliptin	Garber et al.,2008 [46]	515	24	Glimepiride 4	Vilda 50	-0.58	21	-0.1
					Vilda 100	-0.63	25	+ 1.3
					Placebo	+0.07	12	-0.4
Saxagliptin	Chacra et al.,2009 [49]	768	24	Glyburide 7.5	Saxa 2.5	-0.54	22	+ 0.7
					Saxa 5	-0.64	23	+0.8
					SU uptitration 15	+0.08	9	+0.3
	Chacra et al.,2011 [50]	557	76	Glyburide 7.5	Saxa 2.5	+0.11	27	+0.8
					Saxa 5	+0.03	24	+ 1.0
					SU uptitration 15	+0.69	14	+0.3
Alogliptin	Pratley et al., 2009 [47]	500	26	Glyburide ≥ 10	Alo 12.5	-0.38	30	+0.6
					Alo 25	-0.52	35	+0.7
					Placebo	+0.01	18	-0.2

Linagliptin	Lewin et al., 2010 [48]	240	18	SU (variable)	Lina 5	-0.57	15	≈0
					Placebo	-0.10	4	≈0
Add-on to TZD								
Sitagliptin	Rosenstock et al., 2006 [52]	175	24	Pioglitazone 30-45	Sita 100	-0.85	45	+ 1.8
					Placebo	-0.15	23	+ 1.5
	Derosa et al., 2010 [59]	151	52	Pioglitazone 30	Sita 100	-1.4	NA	-1.6
				Pioglitazone 15	Metformin 1700	-1.4	NA	-2.8
Vildagliptin	Garber et al.,2007[53]	463	24	Pioglitazone 45	Vilda 50	-0.8	29	+ 1.5
					Vilda 100	-1.0	36	+2.7
					Placebo	-0.3	15	+ 1.4
Saxagliptin	Hollander et al., 2009 [54]	565	24	TZD (variable)[b]	Saxa 2.5	-0.66	42	+ 1.3
					Saxa 5	-0.94	42	+ 1.4
					Placebo	-0.30	26	+0.9
	Hollander et al., 2011 [57]	360	76	TZD (variable)[b]	Saxa 2.5	-0.59	35	+2.0
					Saxa 5	-1.09	41	+2.2
					Placebo	-0.2	24	+ 1.6
Alogliptin	Pratley et al., 2009 [55]	493	26	Pioglitazone 30-45	Alo 12.5	-0.66	NA	NA
					Alo 25	-0.80	NA	NA
					Placebo	-0.19	NA	NA
	Kaku et al., 2011 [56]	329	12	Pioglitazone 15-30	Alo 12.5	-0.91	49	+0.5
					Alo 25	-0.97	50	+0.5
					Placebo	-0.19	20	0
Linagliptin	Gomis et al., 2011 [58]	389	24	Pioglitazone 30[c]	Lina 5	-1.06	43	+2.3
					Placebo	-0.56	30	+ 1.2

Δ: change *vs* baseline; BW: body weight; NA: not available. [a] 53 mmol/mol.
[b] pioglitazone 30-45 mg or rosiglitazone 4-8 mg. [c] TZD as initial treatment.

3.2.3. Gliptins as oral triple therapy

The arrival of DPP-4 inhibitors offered a new alternative for oral triple therapy (Table 4) at a time when only the combination of metformin plus SU plus TZD was available [62]. Again, most studies, except one [63], were randomized clinical trials comparing the addition of a gliptin *vs* a placebo on top of a dual combination of either metformin-SU [45,64] or metformin-TZD [65]. Sitagliptin 100mg once daily significantly improved glycaemic control and β-cell function in patients with T2DM who had inadequate glycaemic control with glimepiride plus metformin therapy [45]. Similarly, adding linagliptin 5 mg to metformin in combination with SU significantly improved glycaemic control in T2DM patients and was well tolerated [64]. Adding alogliptin 25 mg to a metformin-pioglitazone regimen provided superior glycaemic control and potentially improved β-cell function *vs* uptitrating pioglitazone in T2DM patients, with no clinically important differences in safety [65]. One study compared two modalities of triple therapy. Among ethnic-minority T2DM patients poorly controlled with the maximum tolerated doses of metformin and SU, third-line add-on therapy with TZD (rosiglitazone 8mg or pioglitazone 45 mg) was found to control hyperglycaemia more effectively than sitagliptin 100 mg after 4 months [63].

Table 4 : *Head-to-head trials comparing a DPP-4 inhibitor and an active glucose-lowering agent in type 2 diabetes mellitus (T2DM) patients already treated with a combined oral therapy [sulphonylurea (SU) + metformin or SU + thiazolidinedione (TZD)] or insulin (with or without metformin).*

	Reference	***n***	**Period (weeks)**	**Baseline**	**Intervention (mg/day)**	**Δ HbA_{1c} (%)**	**HbA_{1c} <7%[a] (%patients)**	**Δ BW (kg)**
Triple therapy								
Sitagliptin	Hermansen et al., 2007 [45]	229	24	Metformin + glimepiride	Sita 100	-0.59	23 1	+0.4
					Placebo	+0.30		-0.7
	Hsia et al., 2011 [63]	212	16	Metformin + SU	Sita 100	-1.3	46[b]	+ 1.1
					TZD	-2.0	62[b]	NA
Vildagliptin	No published trial							
Saxagliptin	No published trial							
Alogliptin	Bosi e tal., 2011 [65]	803	52	Metformin + pioglitazone	Alo 25	-0.70	33 21	+ 1.1
					Placebo	-0.29		+ 1.6

Linagliptin	Owens et al., 2011 [64]	1058	24	Metformin + SU	Lina 5	-0.72	29 8	+0.27
					Placebo	-0.10		-0.06
Add-on to insulin								
Sitagliptin	Visboll et al., 2010 [67]	641	24	Insulin	Sita 100	-0.6 0	13	+0.1
					Placebo		5	+0.1
Vildagliptin	Fonseca et al.,2007 [66]	296	24	Insulin ≥ 30 units	Vilda 100	-0.5	NA	+ 1.3
					Placebo	-0.2	NA	+0.6
Saxagliptin	Barnett et al., 2011 [69]	455	52	Insulin	Saxa 5	-0.80	21	+0.8
				30-150 units	Placebo	-0.40	9	+0.5
Alogliptin	Rosenstock et al., 2009 [68]	390	26	Insulin ± metformin	Alo 12.5	-0.63	NA	+0.68
					Alo 25	-0.71	NA	+0.60
					Placebo	-0.13	NA	+0.63
Linagliptin	No published trial							

Δ: change vs baseline; BW: body weight; NA: not available. [a] 53 mmol/mol. [b] < 7.5% (58 mmol/mol) instead of < 7% (53 mmol/mol).

3.2.4. Gliptins combined with insulin in type 2 diabetes mellitus

Insulin therapy in T2DM patients is frequently initiated while oral glucose-lowering agents (most often metformin, sometimes SU) are maintained, at least in part. Therefore, it may also be possible to speculate on the clinical efficacy of combining a DPP-4 inhibitor with insulin. Four placebo-controlled trials have investigated the clinical efficacy and safety of adding a DPP-4 inhibitor to a basal insulin regimen (with or without metformin or SU; Table 4) [66-69]. All studies reported consistent results, with a reduction in HbA_{1c} levels of 0.5-0.6% on average if daily insulin dosages were maintained unchanged. These favourable results were obtained with no weight gains or increases in the incidence of hypoglycaemia. A reduction in severe hypoglycaemic episodes was reported in one trial of insulin plus vildagliptin in T2DM patients poorly controlled with high doses of insulin, presumably because of an individual reduction in daily insulin dosage (which resulted in a smaller HbA_{1c} reduction of only 0.3%) [66]. In the TRANSITION randomized controlled trial [70], significantly greater reductions in HbA_{1c} (-1.44% *vs* -0.89%; $P<0.001$) and plasma glucose levels were achieved with the combination of insulin detemir + sitagliptin + metformin compared with sitagliptin + metformin ± SU, with no increases in the rate of hypoglycaemia.

Thus, adding a DPP-4 inhibitor to insulin therapy may be useful in T2DM patients for improving glucose control without increasing hypoglycaemia, and possibly for limiting weight gain. Further studies are warranted to explore the role of a DPP-4 inhibitor added to optimized insulin regimens (premixed insulin preparations or a basal-bolus insulin scheme), as the available studies only involved patients using basal insulin therapy.

3.3. Gliptins as the initial combination

Because of the complexity of the pathophysiology of T2DM and the frequently observed primary or secondary failure of monotherapy, initial combination treatment may be considered to offer more efficacious management of T2DM [51]. Several clinical trials have evaluated initial combinations of either metformin + gliptin [13-15,19-21,71] or TZD + gliptin [22,23,58,72] and compared the results with an initial monotherapy (Table 1). However, none of these trials evaluated an initial combination including a DPP-4 inhibitor *vs* another initial combination not including a gliptin in a head-to-head comparison.

The initial combination of sitagliptin (2 × 50 mg) or vildagliptin (2 × 50 mg) with metformin (low dose of 2 × 500 mg or high dose of 2 × 1000 mg) had superior efficacy compared with monotherapy treatments, with comparable overall tolerability profiles and low risk of hypoglycaemia [13-15,19-21,71]. Similar results were obtained with the initial combination of saxagliptin 5 or 10 mg plus metformin 500 mg uptitrated to 2000 mg [20,21]. These favourable results were observed in both short-term (18-24 weeks) and long-term (54-104 weeks) clinical trials. The potential dose-sparing effect of adding a DPP-4 inhibitor to relatively low-dose metformin in preference to metformin uptitration may allow patients to achieve equivalent or superior HbA_{1c}-lowering without the gastrointestinal tolerability issues associated with higher doses of metformin [73].

Similar results have been reported with the initial combination of TZD-gliptin [22,23,58,72]. Reductions in HbA_{1c} of 1-2.4% *vs* baseline have been reported and were always significantly greater than those observed with monotherapy with either TZD or a DPP-4 inhibitor. In addition, first-line combined treatments had minimal risks of hypoglycaemia, led to similar or only slightly more weight gain than pioglitazone on its own and offered a tolerability profile comparable to component monotherapy. Thus, such combinations may offer a valuable adjunctive initial treatment option for T2DM, particularly in cases where metformin is contraindicated, as in patients with renal impairment.

3.4. Head-to-head trials comparing incretin-based therapies

3.4.1. DPP-4 inhibitors vs 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 [74,75]. This means that both GLP-1 receptor agonists and DPP-4 inhibitors elevate GLP-1 activity and substantially improve glycaemic control. Indirect comparisons reported in meta-analyses of randomized controlled trials have shown that 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 is weight-neutral [8]. However, head-to-head comparisons of the two therapies are scarce, and only one DPP-4 (sitagliptin) has been so evaluated. Two trials compared sitagliptin 100 mg *vs* exenatide either twice daily [76] or once weekly [36], and a further trial compared sitagliptin 100 mg with liraglutide once daily [40] (Table 2).

In a trial comparing short-term (2-week) treatment with exenatide (5 µg twice daily for 1 week, then 10 µg twice daily for 1 week) *vs* sitagliptin 100 mg once daily, the results were better with exenatide treatment, as assessed in terms of lowering postprandial glucose, increasing insulin levels, decreasing glucagon levels and decreasing caloric intakes [76]. A 26-week, randomized, double-dummy superiority trial assessed the safety and efficacy of exenatide 2mg once a week *vs* sitagliptin 100 mg once a day in patients treated with metformin. Treatment with exenatide reduced HbA_{1c} significantly more than did sitagliptin, with greater weight loss and no episodes of major hypoglycaemia (Table 2). However, exenatide was associated with more nausea and diarrhoea than sitagliptin [36]. Also, an extension of the study showed that patients who switched to once-weekly exenatide from daily sitagliptin had improved or sustained glycaemic control (HbA_{1c}-0.3%) and weight loss (-1.1 %) [77]. In a 24-week prospective trial comparing treatment with liraglutide (1.2 or 1.8 mg once daily) *vs* sitagliptin 100 mg in metformin-treated patients with T2DM, reductions in HbA_{1c} and body weight were significantly greater with both dosages of liraglutide than with sitagliptin, but at the cost of an increased incidence of minor side-effects such as nausea and vomiting (Table 2) [40]. Incidences of hypoglycaemic events were low (5%) and similar in all treatment groups. These data were also confirmed after 1 year [41].

Although GLP-1 receptor agonists demonstrate superiority compared with DPP-4 inhibitors, the average modest differences in HbA_{1c} and weight reductions may be counterbalanced by several disadvantages of GLP-1 receptor agonists (injected *vs* oral, more nausea, more expensive). Other possible additional advantages remain to be demonstrated, such as better cardiovascular protection and longer duration of glucose control [5,74,75].

3.4.2. Head-to-head comparisons among gliptins

As DPP-4 inhibitors have heterogeneous chemical structures and various pharmacokinetic characteristics, this raises the question of possible between-gliptin differences in efficacy and safety profiles [78]. The different DPP-4 inhibitors are distinctive in their metabolism (saxagliptin and vildagliptin are metabolized in the liver whereas sitagliptin is not), excretion (linagliptin is excreted mostly unchanged by the liver, unlike other DPP-4 inhibitors, which are mainly eliminated *via* the kidneys) and potential for 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 impairment (see below). Nevertheless, all DPP-4 inhibitors are similar when comparing their mode of action (as 'incretin enhancers'), efficacy in lowering HbA_{1c} levels, safety profile (no risk of severe hypoglycaemia) and patient tolerability. Also, as there were no significant differences seen with exposure to any tested DPP-4 inhibitor in patients with mild, moderate or even severe hepatic impairment, it appears that no dose adjustment is necessary in patients with liver disease, not even for linagliptin despite its specific biliary excretion [5,78,79].

In the absence of head-to-head comparative randomized trials of different DPP-4 inhibitors (for instance, sitagliptin *vs* vildagliptin), any information can only be found through indirect comparisons. In a meta-analysis of 12 trials with sitagliptin and 11 trials with vildagliptin, the weighted mean differences *vs* 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 [8]. In a matching-adjusted indirect comparison of trials in Japanese patients with T2DM, vildagliptin 50 mg twice daily was associated with a slightly but significantly greater HbA_{1c} reduction than sitagliptin 50 mg (difference: 0.28%) or 100 mg (difference: 0.35%) once daily [80].

However, head-to-head comparisons are scarce, and only one trial has been published as a full report so far. In this 18-week non-inferiority trial comparing the efficacy of saxagliptin 5mg once daily and sitagliptin 100 mg once daily in T2DM patients with glycaemia inadequately controlled by metformin, the adjusted mean changes in HbA_{1c} were - 0.52% and -0.62%, respectively (Table 2). The between-group difference was 0.09% (95% CI: -0.01 to 0.20%), demonstrating non-inferiority. The safety profile was similar for the two DPP-4 inhibitors, with modest weight loss and almost no increase in the incidence of reported or documented hypoglycaemic episodes [42].

3.5. Gliptins in special populations

3.5.1. Patients with 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 [81]. The pharmacokinetic characteristics of five DPP-4 inhibitors have been studied in subjects with varying degrees of renal impairment (RI): mild = creatinine clearance 50-80 mL/min; moderate = 30-50 mL/min; and severe = < 30 mL/min, including patients with end-stage renal disease (ESRD) [5,82]. According to the results, dose adjustment according to creatinine clearance is recommended for sitagliptin (50 mg in cases of moderate RI and 25 mg in cases of severe RI), saxagliptin (2.5 mg instead of 5 mg in cases of moderate or severe RI) and vildagliptin (50 mg once a day instead of 50 mg twice a day). However, no dose adjustments are recommended for linagliptin.

Several post-hoc analyses of phase-III or specific clinical trials have also evaluated both the efficacy and safety of DPP-4 inhibitors in T2DM patients with various degrees of RI. With dose adjustment in a 54-week trial, sitagliptin was generally well tolerated and provided effective glycaemic control in patients with T2DM and moderate-to-severe RI, including patients with ESRD on dialysis [83]. However, in a study assessing dose adjustments of glucose-lowering agents in T2DM patients with moderate to end-stage RI from a large outpatients electronic medical records database, only 15% of patients with prescriptions for sitagliptin received dosages of the drug appropriate for their degree of RI. Thus, in clinical practice, sitagliptin was frequently used at inappropriate dosages in patients with RI [84].

Saxagliptin 2.5 mg once daily proved to be a well-tolerated treatment option for patients with inadequately controlled T2DM and various degrees of RI, with incidences of adverse events and hypoglycaemic events similar to those with a placebo [85]. In a 12-week study, the reduction in HbA_{1c} was greater with saxagliptin than with a placebo in subgroups of patients with moderate and severe RI, but not in the subgroup with ESRD on haemodialysis. These observations were recently confirmed in a longer follow-up of 52 weeks [86].

A retrospective analysis demonstrated similar safety and tolerability of vildagliptin as an add-on to metformin in T2DM patients with normal renal function and mild RI [87]. Data pooled from 38 studies in which vildagliptin was given for 12 to 104 weeks in patients with T2DM showed that it was effective and well tolerated in the presence of mild or moderate RI [88]. In a recent 24-week study of 515 T2DM patients with moderate or severe RI, vildagliptin added to ongoing antidiabetic therapy had a safety profile similar to that with a placebo. Furthermore, compared with a placebo, vildagliptin resulted in a statistically and clinically significant decrease in HbA_{1c} in patients with moderate or severe RI [89].

In a large phase-III 24-week study comparing linagliptin 5 mg once daily with a placebo in patients with T2DM, having mild or moderate RI did not influence trough plasma levels of linagliptin [90]. Also, the efficacy (reduction of HbA_{1c} levels) and safety of linagliptin 5 mg was confirmed in T2DM patients with mild or moderate RI in a pooled analysis of three randomized, placebo-controlled, phase-III clinical trials, as well as in T2DM patients with severe RI (GFR<30mL/min/1.73m^2) in a randomized, double-blind, placebo-controlled trial specifically targeting such a population [79].

3.5.2. Elderly patients

Oral DPP-4 inhibitors are promising new therapies for older patients because of their consistent efficacy and low risk of hypo-glycaemia. However, data for these new agents are still scarce in this population, which has not been particularly well represented in initial clinical trials, highlighting the need for additional specific studies [5]. However, where available, data from elderly subgroups in individual studies are included in this present review along with pooled analyses by age subgroups in clinical programmes involving DPP-4 inhibitors [91]. For elderly patients with T2DM, reductions in HbA_{1c} after treatment with a DPP-4 inhibitor were not significantly different from those seen in younger patients. This was demonstrated in post-hoc pooled analyses of 24-week trials with vildagliptin 100 mg monother-apy in treatment-naive patients aged > 65 years *vs* those < 65 years [92], and with vildagliptin 100 mg as monotherapy or as add-on therapy to metformin in patients aged > 75 years *vs* those < 75 years [93]. The safety profile of vildagliptin was similar in older and younger patients overall. Use of DPP-4 inhibitors in these studies was associated with a low risk of hypoglycaemia, and the agents were weight-neutral [94].

Similar observations have been reported with saxagliptin 5 mg once-daily as monotherapy or as add-on therapy [95], and with alogliptin [47] in T2DM patients aged > 65 years.

So far, only one clinical trial has been specifically performed in elderly T2DM patients. In this placebo-controlled, 24-week study, sitagliptin treatment (100 or 50 mg, depending on renal function) significantly and rapidly improved glycaemic measures (reductions in HbA_{1c} from 0.5% to 1.6%, depending on baseline levels),

and was well tolerated with no adverse episodes of hypoglycaemia in patients aged > 65 years with T2DM without severe RI [96].

Although, so far, there are no available studies of elderly individuals with linagliptin, a specific trial is currently ongoing. However, because of the unique pharmacokinetic characteristics of the compound (in particular, its non-renal elimination route), it is unlikely that any clinically relevant efficacy/safety differences in older *vs* younger patients with T2DM will be seen with linagliptin therapy [79].

4. Pharmacoeconomic evaluation

Although newer incretin-based therapies offer more options for glycaemic control in T2DM and certain advantages compared with other classical glucose-lowering agents [3,4], the cost of the therapy needs to be taken into account when making global comparisons for clinical use [97]. DPP-4 inhibitors are clearly more expensive than SUs, but less expensive than GLP-1 receptor agonists [98]. This means that demonstrable gains in quality of life and/or longevity with these new agents are necessary to prove their economic value to both patients and healthcare systems [99]. Although there are favourable cost-effectiveness and cost-utility data for DPP-4 inhibitors compared with SUs, only scanty preliminary data are currently available [100]. Thus, more economic analyses are required to establish when it will become more cost-effective to switch from SUs to DPP-4 inhibitors [97].

5. Conclusion

Despite the wide structural heterogeneity among gliptins and differences in their pharmacokinetic profiles, the data available so far indicate similar glucose-lowering efficacy with DPP-4 inhibitors as either monotherapy or in combination with other hypoglycaemic drugs, similar weight-neutral effects, and comparable safety and tolerability profiles. A composite endpoint including HbA_{1c} reduction, no hypoglycaemia and no weight gain could be used to combine both efficacy and safety criteria, and so provide an integrated benefit/risk ratio for clinical use. Significantly more patients treated by a DPP-4 inhibitor achieved an HbA_{1c} level < 7% (53mmol/mol) or an HbA_{1c} reduction > 0.5%, with no hypoglycaemia and no increase in body weight compared with a SU, and with no weight gain compared with a TZD. This advantage was confirmed with monotherapy in drug-naive T2DM patients as well as with combination therapy mainly with metformin, and the potential advantages of initiating combined metformin-gliptin therapy have been demonstrated in several trials. DPP-4 inhibitors also showed good efficacy as dual therapy in combination with SU or TZD and as oral triple therapy, and when added to basal insulin treatment in T2DM patients. Thus, combination therapy with a DPP-4 inhibitor offers the potential advantage of achieving glycaemic control with no additional tolerability concerns.

Prospective long-term clinical trials are ongoing to confirm the safety/efficacy of DPP-4 inhibitors added to any type of glucose-lowering therapies as regards cardiovascular outcomes [5]. However, it is noteworthy that most of these studies are placebo-controlled trials, and none will directly compare two incretin-based therapies. Nevertheless, as these trials plan to recruit more than 50,000 T2DM patients and to follow them for 4-5 years, they should provide further valuable information on the long-term efficacy/safety of this new incretin-based class of pharmacological agents.

Disclosure of interest

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