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REVIEW

DPP-4 inhibitor plus SGLT-2 inhibitor as combination therapy for type 2 diabetes: from rationale to clinical aspects

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SUMMARY

Introduction : Type 2 diabetes (T2D) is a complex disease with multiple defects, which generally require a combination of several pharmacological approaches to control hyperglycemia. Combining a dipeptidyl peptidase-4 inhibitor (DPP-4i) and a sodium-glucose cotransporter type 2 inhibitor (SGT2i) appears to be an attractive approach.

Area covered: An extensive literature search was performed to analyze the pharmacokinetics, pharmacodynamics and clinical experience of different gliptin-gliflozin combinations.

Expert opinion: There is a strong rationale for combining a DPP-4i and a SGLT2i in patients with T2D because the two drugs exert different and complementary glucose-lowering effects. Dual therapy (initial combination or stepwise approach) is more potent than either monotherapy in patients treated with diet and exercise or already treated with metformin. Combining the two pharmacological options is safe and does not induce hypoglycemia. The additional glucose-lowering effect is more marked when a gliflozin is added to a gliptin than when a gliptin is added to a gliflozin. Two fixed-dose combinations (FDCs) are already available (saxagliptin-dapagliflozin and linagliptin-empagliflozin) and others are in current development. Bioequivalence of the two compounds given as FDC tablets was demonstrated when compared with coadministration of the individual tablets. FDCs could simplify the anti-hyperglycaemic therapy and improve drug compliance.

Keywords: Combined therapy, DPP-4 inhibitor, fixed-dose combination, SGLT2 inhibitor, type 2 diabetes mellitus

Drug Summary box

Drug name	Saxagliptin / dapagliflozin
	Linagliptin / empagliflozin
Phase	Available separately
	Available as FDC (Qtern®, Glyxambi®)
Indication	Treatment of patients with type 2 diabetes
Pharmacology description	Saxagliptin, linagliptin : DPP-4 inhibitors
	Dapagliflozin, empagliflozin : SGLT2 inhibitors
Route administration	Oral
Chemical structure	

Pivotal trial(s)

Pharmacokinetic interactions: [25,33]

Clinical trials: [27, 28, 29, 35, 36]

Article highlights box

- Type 2 diabetes (T2D) often requires the combination of several medications with complementary actions to reach glucose control targets while limiting side effects
- The combination of a dipeptidyl peptidase-4 inhibitor (DPP-4i) and a sodium-glucose cotransporter type 2 inhibitor (SGLT2i)-is an attractive approach for the management of T2D.
- Both saxagliptin plus dapagliflozin and linagliptin plus empagliflozin combined therapies have been tested as separate tablets (no clinically relevant pharmacokinetic drug-drug interactions) and as fixed-dose combination (FDC : bioequivalence studies).
- DPP-4i – SGLT2i combined therapies are more efficacious than either monotherapy to control blood glucose, without worsening of the safety profile.
- Initial DPP-4i – SGLT2i combination may be considered or one compound may the added to the other. However, which one should be used in first place remains an open question.

1. Introduction

Type 2 diabetes (T2D) is a complex disease with different pathophysiological defects [1]. If metformin, combined with lifestyle, is considered as the first pharmacological option, monotherapy fails to reach or maintain target glycated haemoglobin (HbA1c) when the disease progresses with time in a majority of T2D patients. Thus combination therapy is recommended soon or later in T2D. Various pharmacological approaches may be added to metformin as dual therapies or combined together as triple therapies, among which dipeptidyl peptidase inhibitors (DPP-4i) and/or sodium-glucose cotransporter type 2 inhibitors (SGLT2i) [2-5].

DPP-4i as oral incretin-based therapy are increasingly used in the management of T2D as an alternative or add-on therapy to other glucose-lowering agents, especially sulphonylureas [6]. They offer the advantage of an excellent safety profile with no increased risk of hypoglycaemia, weight gain and cardiovascular events (however, concern about a possible greater risk of hospitalization for congestive heart failure remains controversial) when compared to placebo [7]. SGLT2i, which target the kidney and promote glucosuria, belong to the newest pharmacological class of glucose-lowering agents [8]. Both their efficacy and safety have been recently reviewed [9, 10]. The demonstration of a remarkable reduction in cardiovascular and all-cause mortality with empagliflozin in T2D patients with history of cardiovascular disease in the EMPA-REG OUTCOME trial [11] raised considerable interest among diabetologists and cardiologists, although the underlying mechanisms of protection remain largely unknown [12].

DPP4i and SGLT2i exert their glucose-lowering effects via different and complementary mechanisms. When one single pharmacological class does not reach HbA1c target as monotherapy or even when added to metformin, a combination of a DPP-4i and a SGLT2i could be helpful in the management of patients with T2D [5, 13, 14]. Fixed-dose combinations (FDCs) have been recently commercialized, which could facilitate therapy and improve compliance of patients with T2D [15, 16].

The main aims of this review are the following ones: 1) to summarize the arguments supporting a combined used of a DPP-4i and a SGLT2i for the management of T2D; 2) to analyze the pharmacokinetic (PK) characteristics of gliptin-gliflozin administered separately or as FDCs; and 3) to describe the clinical efficacy and safety of DPP-4i-SGLT2i combinations, especially saxagliptin-dapagliflozin and linagliptin-empagliflozin, two FDCs recently available for the management of T2D. To identify relevant studies, an extensive literature search in MEDLINE was performed from January 2010 to April 2016, with the

terms of DPP4i, alogliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, SGLT2i, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, combined therapy and FDC. No language restrictions were imposed. Reference lists of original studies, narrative reviews and previous systematic reviews were also carefully examined.

2. Rationale of DPP-4 inhibitor plus SGLT2 inhibitor combination

Together, DPP-4i and SGLT2i fulfil a need for pharmacological agents with complementary mechanisms of action that can be used in combination to improve glucose control in a wide spectrum of patients with T2D, with a low risk of adverse events, such as hypoglycaemia or weight gain and the potential of cardiovascular protection (Table 1, Figure 1) [5, 13, 14].

DPP-4i enhance postprandial insulin secretion and suppress glucagon secretion by preventing the degradation of endogenously released incretin hormones [glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)], two intestinal peptides whose concentrations physiologically increase after food intake [5]. Of major interest, DPP-4 inhibitors stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, thus reducing hyperglycaemia while minimizing hypoglycaemia [6]. Furthermore, they do not induce weight gain and have proven their cardiovascular safety in several large prospective cardiovascular outcome studies [7].

SGLT2i, by specifically targeting the kidney, inhibit glucose reabsorption at the proximal tubule and thereby promote glucosuria, an effect independent of insulin. Because of the progressive deterioration of beta-cell function that characterizes T2D, a pharmacological mechanism of action that is independent of pancreatic beta-cell function makes SGLT2i an appropriate option for patients with advanced T2D, particularly if their glycaemic control is inadequate with other oral glucose-lowering agents. By promoting glucosuria and reducing hyperglycaemia, SGLT2i dampen glucotoxicity, which indirectly results in an improvement of beta-cell function and peripheral insulin sensitivity [17-19]. However, treatment with SGLT2i resulted in an increase in plasma glucagon concentrations, which was accompanied by a substantial increase in endogenous (hepatic) glucose production [17, 18]. The latter has been estimated to offset approximately half of the glucose excreted in the urine as a result of SGLT2i [17]. Thus, the addition of a DPP-4 inhibitor which inhibits glucagon and stimulates insulin secretion may have the potential to block the increase in endogenous glucose production and enhance the glucose-lowering ability of SGLT2i (Figure 1). Taken together,

these findings suggest that the combination of a DPP-4i with a SGLT2i would potentially provide additional help to individuals with T2D in reaching their glycaemic goal. Beyond a glucose-lowering effect, SGLT2i have some added value with reductions in body weight (including abdominal adiposity), blood pressure and serum uric acid, all markers considered as independent cardiovascular risk factors (Table 1) [8]. In EMPA-REG OUTCOME trial, empagliflozin, a selective SGLT2i, was associated with a remarkable reduction in cardiovascular and all-cause mortality in T2D patients with antecedents of cardiovascular disease [11, 12]. Because a marked reduction in the incidence rate of hospitalisation for heart failure was also reported with empagliflozin in EMPA-REG OUTCOME [20], contrasting with a higher rate of hospitalisation for heart failure with the DPP-4i saxagliptin in SAVOR-TIMI 53 [21], one may speculate that combining a DPP4-i and a SGLT2i would be of potential interest regarding the risk of heart failure in patients with T2D [22].

Thus, combination treatment with a DPP-4i and/or SGLT2i appears to be an attractive option for patients with T2D starting pharmacological therapy, or for patients who are already treated with a glucose-lowering agent, especially metformin, but require additional medications to further improve glycaemic control. Available findings indicate that the underlying mechanisms of action of DPP-4i and SGLT2i not only complement a variety of other oral antidiabetics agents but also are complementary by themselves (Table 1, Figure 1) [5, 13, 14].

3. Saxagliptin plus dapagliflozin

The potential therapeutic value of a combination therapy with saxagliptin and dapagliflozin for the treatment of T2D has been recently reviewed [23].

3.1 Pharmacokinetics

The absolute oral bioavailability of saxagliptin and dapagliflozin was determined using simultaneous intravenous ^{14}C-microdose/therapeutic oral dosing in healthy volunteers [24]. The geometric mean point estimates (90% confidence interval – CI –) values for saxagliptin and dapagliflozin were 50% (48, 53%) and 78% (73, 83%), respectively. The arithmetic mean half-life values for the intravenous and oral doses were similar (for saxagliptin: 7.5±0.6 and 5.7±0.4 h, respectively; for dapagliflozin: 12.2±5.3 and 13.7±3.4 h, respectively) and the plasma concentration-time terminal elimination phases for each route

were parallel. Overall, the intravenous microdosing had similar pharmacokinetics to the therapeutic oral dosing [24].

The bioequivalence of saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets compared with coadministration of the individual tablets was evaluated in an open-label, randomised, single-dose crossover study in 72 healthy subjects [25]. Saxagliptin/dapagliflozin 2.5/5 mg and 5/10 mg FDC tablets were bioequivalent to coadministration of the individual components in healthy subjects under fasted conditions (Table 2). Furthermore, this study investigated the potential influence of food and concluded that food had no clinically meaningful effect on the bioavailability of saxagliptin/dapagliflozin FDC [25].

3.2 Pharmacodynamics

A study analyzed changes in plasma glucose, insulin, and glucagon in relation to glycaemic response after a liquid meal tolerance test during treatment with dual add-on of saxagliptin plus dapagliflozin to metformin extended release compared with saxagliptin add-on or dapagliflozin add-on alone in patients with T2D poorly controlled with metformin [26]. The combination of saxagliptin plus dapagliflozin provided additional reductions in glucose area under the curve from 0 to 180 minutes (AUC0-180 min) and HbA1c without the increase in plasma insulin seen with saxagliptin and without the increase in plasma glucagon seen with dapagliflozin. Changes in plasma insulin and glucose but not glucagon AUC0-180 min correlated with change in HbA1c [26].

3.3 Efficacy in clinical trials

A double-blind trial randomised adults with poorly controlled T2D on background metformin to saxagliptin 5 mg/day plus dapagliflozin 10 mg/day, or saxagliptin 5 mg/day and placebo, or dapagliflozin 10 mg/day and placebo [27]. As a primary objective, changes from baseline in HbA1c were compared with the triple therapy versus each dual therapy at week 24. Greater improvements in glycaemic control were obtained with the triple therapy by the dual addition of saxagliptin and dapagliflozin than dual therapy with the addition of saxagliptin or dapagliflozin alone to background metformin monotherapy. The positive impact concerned the reduction in HbA1c, the proportion of patients reaching an HbA1c target < 7%, and the reductions in both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) (Table 3). The reduction in body weight was greater with the triple therapy

than with metformin plus saxagliptin but not than the reduction seen with metformin plus dapagliflozin. Even if the objective was not to compare metformin plus saxagliptin versus metformin plus dapagliflozin, it appears that the difference in blood glucose control was greater when the triple therapy was compared with the dual therapy metformin + saxagliptin than when compared with the dual therapy metformin plus dapagliflozin [27].

Two other randomised, double-blind, phase 3 trials in T2D patients evaluated the efficacy of a triple therapy combing metformin plus saxagliptin plus dapagliflozin but using a different protocol. One study tested the efficacy of adding dapagliflozin 10 mg versus placebo to a saxagliptin plus metformin background therapy [28] whereas the other investigated the efficacy of adding saxagliptin 5 mg versus placebo to a dapagliflozin plus metformin background therapy [29] (Table 3). Treatment with dapagliflozin add-on to saxagliptin plus metformin resulted in a greater mean HbA1c reduction than placebo (-0.82 vs. -0.10%, $P < 0.0001$) [28] whereas treatment with saxagliptin add-on to dapagliflozin plus metformin resulted in a less marked reduction in HbA1c (-0.51% versus -0.16% with placebo), but still highly significant ($P < 0.0001$) (Table 3) [29]. These differences translate into higher proportions of T2D patients reaching a target HbA1c < 7 % among those treated with the triple therapy compared to those receiving pacebo added to the background dual therapy [28, 29].

3.4 Safety in clinical trials

In a study comparing triple therapy by the dual addition of saxagliptin and dapagliflozin to dual therapies with the addition of saxagliptin or dapagliflozin alone in patients not well controlled by metformin, the proportion of patients with adverse events was similar across treatment groups [27]. Despite large decreases in HbA1c, hypoglycaemic event rates were low (around 1%) and similar across treatment groups, with no episodes of major hypoglycaemia [27]. Similar reassuring findings regarding the risk of hypoglyacemia were reported in two other studies having evaluated the safety of the triple therapy metformin-saxagliptin-dapagliflozin [28, 29].

Urinary and genital infections occurred less frequently in patients receiving the triple therapy than in those receiving any of the dual therapies [27]. This unexpected finding was also observed in another study reporting a lower rate of genital infections when a saxagliptin was added to dapagliflozin compared with the SGLT2 inhibitor alone [29]. When dapagliflozin was added to saxagliptin plus metformin, a higher proportion of patients, all of

whom were women, had genital infections (5%) compared with those receiving placebo add-on to saxagliptin plus metformin therapy (0.6%); however, the occurrence of urinary tract infections was similar for the dapagliflozin add-on to saxagliptin plus metformin group (5%) and placebo add-on to saxagliptin plus metformin group (6.3%) [28].

No severe adverse effects such as pyelonephritis, acute pancreatitis or hospitalisation for heart failure were reported with the triple therapy metformin-saxagliptin-dapagliflozin in these three clinical trials of 24 weeks [27-29].

4. Linagliptin plus empagliflozin

The potential therapeutic value of a combination therapy with linagliptin and empagliflozin for the treatment of T2D has been recently reviewed [30, 31]. The single-pill combination (FDC) of linagliptin and empagliflozin, with their complementary mechanisms of action, is a promising treatment option for patients with T2D [15, 16, 32].

4.1 Pharmacokinetics

In an open-label, randomised, multiple-dose, crossover study, sixteen healthy male subjects received empagliflozin 50 mg once daily for 5 days, both empagliflozin 50 mg once daily and linagliptin 5 mg once daily for 7 days, and linagliptin 5 mg once daily for 7 days [33]. Linagliptin total exposure and peak concentration was unaffected by coadministration of empagliflozin (Table 2). Similarly, empagliflozin total exposure was unaffected by coadministration of linagliptin. There was a reduction in empagliflozin peak exposure when linagliptin was coadministered, which was not considered clinically meaningful (Table 2). Thus, these data support the coadministration of empagliflozin and linagliptin without dose adjustments [33].

4.2 Pharmacodynamics

Both empagliflozin and linagliptin improve glucose tolerance to a standardized test meal in patients with T2D, although via different mechanisms that may be complementary, as already discussed. After meal ingestion, empagliflozin 25 mg promoted glucosuria and was associated with significant reductions in plasma glucose and insulin AUC, which may be explained by improved beta-cell function and insulin sensitivity. In contrast, the glucagon response increased contributing to a significant rise in endogenous glucose

production [18]. Following a meal tolerance test, linagliptin 5 mg significantly increased the two incretin hormones intact GLP-1 and GIP, but significantly lowered glucagon. These changes contributed to reduce postprandial hyperglycaemia in patients with T2D (Figure 1) [34].

4.3 Efficacy in clinical trials

The efficacy of linagliptin/empagliflozin was evaluated in two studies of up to 52 weeks duration (primary endpoint assessed at week 24) in patients with T2D treated with diet and exercise [35] or with a metformin monotherapy [36]. In both studies, the single-pill combination of linagliptin and empagliflozin produced clinical improvements in glycaemic control that were generally superior to the improvements seen with each individual component, either linagliptin or empagliflozin alone.

T2D patients not receiving antidiabetes therapy for at least 12 weeks were randomised to empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks [35]. Reductions in HbA1c at week 24 were significantly greater for empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg ($P < 0.001$) but not compared with empagliflozin 25 mg, and were significantly greater for empagliflozin 10 mg/linagliptin 5 mg compared with the linagliptin 5 mg and empagliflozin 10 mg individual components ($P < 0.001$ for both). These changes translated in different proportions of patients with baseline HbA1c ≥ 7% who reached HbA1c < 7% at week 24 (Table 4). Similar differences were noticed for FPG levels (Table 4). Overall, efficacy was maintained at week 52. Thus, in this study, reductions from baseline in HbA1c with empagliflozin/linagliptin were significantly greater versus linagliptin 5 mg and empagliflozin 10 mg but not versus empagliflozin 25 mg [35].

To evaluate the efficacy of combinations of empagliflozin/linagliptin as second-line therapy, subjects with T2D inadequately controlled on metformin were randomised to a combination of empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg as add-on to metformin for 52 weeks [36]. At week 24, reductions in HbA1c with empagliflozin/linagliptin were superior to those with empagliflozin or linagliptin alone when added to metformin (Table 4). With the triple therapy, more subjects with baseline HbA1c ≥ 7% had HbA1c <7% at week 24 compared with each dual therapy. The same trends were observed regarding reductions in

FPG levels (Table 4). Again, glucose-lowering efficacy was maintained at week 52. Thus, combinations of empagliflozin/linagliptin as second-line therapy for 52 weeks significantly reduced HbA1c compared with the individual components [36].

4.3 **Safety in clinical trials**

The overall safety profile of empagliflozin/linagliptin was similar to the known safety profiles of the individual components. In drug-naïve T2D patients, the proportion of subjects with adverse events over 52 weeks was similar across the three groups of patients treated with empagliflozin alone, linagliptin alone or a combination of the two glucose-lowering agents [35]. Adverse events leading to discontinuation, severe adverse events, and serious adverse events were noticed in slightly higher percentages of subjects with empagliflozin/linagliptin or empagliflozin alone compared with linagliptin alone [35]. However, overall the three treatments were well tolerated. Empagliflozin and linagliptin were associated with a low risk of hypoglycaemia when given as monotherapy, and no confirmed hypoglycaemic episodes were observed with empagliflozin/linagliptin combination [35]. In metformin-treated T2D patients, the proportion of subjects with one or more adverse events was similar across treatment groups receiving empagliflozin, linagliptin and the combination therapy [36]. Confirmed hypoglycaemic episodes (none requiring assistance) were reported in 3.6% of subjects on empagliflozin 25 mg/linagliptin 5 mg, 2.2% on empagliflozin 10 mg/linagliptin 5 mg, 3.5% on empagliflozin 25 mg, 1.4% on empagliflozin 10 mg, and 2.3% on linagliptin 5 mg. Interestingly, slightly lower rates of genital infections and urinary tract infections were reported when linagliptin was added to empagliflozin compared with the SGLT2 inhibitor alone [36]. In these two trials, no episodes of ketoacidosis were reported over a period of 52 weeks, whatever the treatment arm considered, and only one case of pancreatitis has been noticed (among drug-naïve patients receiving empagliflozin 25mg/linagliptin 5mg) [35, 36].

5. DPP-4i plus canagliflozin

Besides dapagliflozin and empagliflozin, another SGLT2i canagliflozin is commercialized both in the US and in Europe [37]. However, no specific studies evaluated the efficacy and safety of canagliflozin combined with a DPP-4i and no FDC is available yet.

Of the 4330 patients in the large prospective cardiovascular outcome trial CANVAS, 316 were taking DPP-4i (75.6 % sitagliptin and 22.5 % vildagliptin). At 18 weeks, canagliflozin provided significant placebo-subtracted reductions in HbA1c in patients taking DPP-4i : -0.56% (95% CI -0.77, -0.35) with canagliflozin 100mg and -0.75% (95% CI -0.95, -

0.54) with canagliflozin 300 mg [38]. Placebo-subtracted reductions in body weight (-2.0 kg with canagliflozin 100 mg and -2.7 kg with canagliflozin 300 mg) and systolic blood pressure (-4.7 mm Hg with both dosages) were noticed in patients already treated with DPP-4i. Higher incidences of genital mycotic infections and osmotic diuresis-related adverse events were seen with canagliflozin compared with placebo. Although the incidence of hypoglycaemia was numerically higher with canagliflozin versus placebo, nearly all events occurred in patients on background insulin or insulin secretagogues (sulphonylureas) [38]. In patients on background DPP-4i, canagliflozin improved HbA1c, body weight and systolic blood pressure, with an increased incidence of known adverse events related to SGLT2i.

A 52-week open-label study performed in Japanese T2D evaluated the efficacy and safety of adding canagliflozin 100 mg or 200 mg once daily (doses used in Japan) to different background glucose-lowering therapies, including DPP-4i (sitagliptin, vildagliptin or alogliptin) [39]. The baseline to end-point change in HbA1c was -1.04% with canagliflozin 100 mg (n=71) and -1.26% with canagliflozin 200 mg (n=74) in patients already treated with DPP-4i. These reductions were almost similar or slightly greater when compared with other subgroups receiving non-DPP-4i background glucose-lowering therapies. The addition of canagliflozin to a DPP-4i was also associated with significant reduction in FPG, body weight and systolic blood pressure. As expected from the properties of the combination drugs, the incidence of hypoglycaemia was much lower in patients treated with DPP-4i than in those treated with a sulphonylurea [39].

Oral teneligliptin is a DPP-4i indicated for the treatment of adults with T2D but it is commercialized only in some countries, i.e. in Japan (trade name: Tenelia®) [40] and Argentina (trade name: Teneglucon®) [41]. Pharmacokinetic interactions of canagliflozin and teneligliptin were investigated in Japanese healthy adult men in an open-label, one-way crossover study using canagliflozin (200 mg/day) and teneligliptin (40 mg/day) [42]. A single dose of object drug (either canagliflozin or teneligliptin) was administered on day 1 followed by washout. After a continuous administration of precipitant drug (days 1 - 9), both drugs were concomitantly administered on day 7. No changes in exposure (AUC0 - 72h) and peak concentrations (Cmax) were observed for canagliflozin+teneligliptin versus monotherapy; geometric mean ratios for AUC0 - 72h and Cmax were 0.982 and 0.982 for the plasma concentration of canagliflozin and 0.983 and 0.976 for the plasma concentration of teneligliptin, respectively (Table 2). Thus, results showed no PK interaction between canagliflozin and teneligliptin [42].

6. SGLT2i combined with sitagliptin

Other combinations have been investigated but only limited data are available yet and mainly restricted to pharmacokinetic studies looking for possible drug-drug interactions. Sitagliptin, the most widely used DPP4i worldwide [43], has been used as the reference DPP4i for such drug-drug interaction studies or clinical trials with various SGLT2i.

6.1 Trials demonstrating the absence of drug-drug interactions

Several studies investigated the potential pharmacokinetic drug-drug interactions between a SGLT2i and sitagliptin : no significant and clinically relevant interactions were reported as far as dapagliflozin [44], ipragliflozin [45], tofogliflozin [46] and ertugliflozin [47] were concerned.

6.2 Dapagliflozin added to sitagliptin

A randomised trial assessed the efficacy and safety of dapagliflozin 10 mg (n=225) versus placebo (n=226) as add-on therapy to sitagliptin 100 mg with or without metformin in patients with inadequately controlled T2D (mean baseline HbA1c 7.9%) [48]. At 24 week add-on treatment with dapagliflozin provided additional clinical benefit with a significant reduction in HbA1c (-0.5% versus 0% with placebo) and body weight (-2.1kg versus -0.3 kg). Dapagliflozin also decreased HbA1c significantly versus placebo when added to sitagliptin alone (placebo-subtracted, –0.6%) or to sitagliptin plus metformin (placebo-subtracted, –0.4%; both $p<0.0001$). Glycaemic and weight benefits observed at week 24 were maintained through week 48 and fewer patients receiving dapagliflozin were discontinued or rescued for failing to achieve glycaemic targets compared with placebo. Combined therapy was well tolerated except an increase in genital infections (9.8% with dapagliflozin versus 0.4% with placebo [48].

6.3 Ertugliflozin added to sitagliptin

Pfizer and Merck have a joint venture that is investigating an ertugliflozin/sitagliptin combination product. A clinical trial recently evaluated the efficacy and safety of a co-administration of ertugliflozin (MK-8835/PF-04971729) and sitagliptin given together or alone along with metformin in participants with T2D and inadequate glycaemic control on metformin monotherapy (ClinicalTrials.gov Identifier: NCT02099110). At 26 weeks, the co-administration of ertugliflozin and sitagliptin was significantly more effective than ertugliflozin or sitagliptin alone in reducing HbA1c (primary endpoint), which resulted in a

greater proportion of patients achieving an HbA1c treatment goal of less than 7.0%), and FPG; furthermore, ertugliflozin-sitagliptin combined therapy was significantly more effective in reducing body weight and systolic blood pressure compared to sitagliptin alone, which were secondary endpoints [49].

6.4 Innovative combination

In patients with T2D, the combination of LX4211, a dual SGLT1/SGLT2 inhibitor, plus sitagliptin was associated with significantly increased active GLP-1, total GLP-1, and total peptide YY, with a significant reduction in total GIP, and with a significantly improved blood glucose level, with less insulin, compared with sitagliptin monotherapy. The dual SGLT1/SGLT2 inhibitor alone was associated with a significant increase in total GLP-1 and peptide YY and a reduced total GIP, likely due to a reduction in SGLT1-mediated intestinal glucose absorption, whereas sitagliptin alone was associated with suppression of all three peptides relative to baseline. All treatments were well tolerated, with no evidence of diarrhea (due to intestinal SGLT1 inhibition) with LX4211 treatment [50]. Although a dual SGLT1/SGLT2 inhibitor + DPP-4 inhibitor combination may provide an option in patients with T2D, the potential clinical benefits of such combination therapy need to be confirmed in further studies.

7. Conclusion

Treatment of T2D most often requires the combination of several glucose-lowering agents to tackle the various pathophysiological defects of the disease and maximize the chance of reaching individual HbA1c targets. The combination of a DPP-4i and a SGLT2i is attractive because their complementary modes of action contribute to improve blood glucose control in patients with T2D without deteriorating the safety/tolerance profile of each compound (on the contrary, a reduction in some adverse events may be expected). FDC formulations combining saxagliptin plus dapagliflozin and linagliptin plus empagliflozin are already commercialized and others combinations are currently investigated for the management of T2D. Although the precise positioning of a DPP-4i-SGLT2i combination should be better delineated by further studies, this approach appears to be a new option for the management of patients with T2D, with a good efficacy/safety ratio but at a higher cost.

8. Expert opinion

The potential complementary mechanisms of action of DPP-4i and SGLT2i make these agents attractive treatment options for combination therapy. Theoretically, they could be used with any of the existing glucose-lowering agents in patients with T2D (except GLP-1 receptor agonists), from metformin to insulin. Most available studies were performed in metformin-treated patients [27, 36] and there is a need for specific studies for instance in insulin-treated patients. Better glucose control was observed with combined DPP-4i and SGLT2i therapy in diet-treated [35] and metformin-treated [27, 36] patients when compared with individual component add-on therapy. Of potential interest may be the inhibitory effect on glucagon secretion exerted by the DPP-4i, which opposes to the stimulatory effect on glucagon secretion described with SGLT2i [17, 18]. Such SGLT2i-induced rise in glucagon secretion contributes to increase endogenous glucose production, which could somewhat limit the glucose-lowering effect resulting from enhanced glycosuria [17]. Furthermore, increased glucagon secretion was suspected to contribute to the development of ketoacidosis in T2D patients treated with SGLT2i, at least under special circumstances [51]. Thus, adding a DPP-4i that reduces glucagon secretion in a glucose-dependent fashion may be a valuable option in T2D patients treated by SGLT2i. However, the opposite effects of DPP-4i and SGLT2i on glucagon secretion deserve further specific studies to better understand the potential benefit of this combination in this regard. Together, DPP-4i and SGLT2i fulfill a need for treatments with mechanisms of action that can be used in combination with a good safety profile and a low risk of adverse events, such as hypoglycaemia or weight gain.

The safety profiles of DPP-4i [7] and SGLT2i [9] are well known. The safety profile of the DPP-4i-SGLT2i combination is comparable with that of each component prescribed separately. DPP-4i are generally well tolerated [7] while genital mycotic infections, predominantly in women, and, to a less extent, urinary tract infections are the most common reported adverse effects of SGLT2i [9]. Interestingly, urinary and genital infections were less frequently observed with the addition of a DPP-4i to a SGLT2i in clinical trials with the combination saxagliptin-dapagliflozin [27, 29] or linagliptin-empagliflozin [36]. These observations may lead to speculation that DPP-4i could, by an unknown mechanism (either related to or independent of the additional glucose-lowering effect), protect against SGLT2i–induced urinary and genital infections. None of these two pharmacological classes by itself is associated with a higher risk of hypoglycaemia although some hypoglycaemic episodes may be observed when each of them is added to a background therapy of sulphonylureas or insulin. A low risk of hypoglycaemic adverse events with a DPP-4i-SGLT2i combination, even when added to metformin, is a particularly important finding for clinicians [27, 36]. The

DPP-4i saxagliptin has been suspected to increase the risk of heart failure [21] whereas SGLT2i exert an osmotic diuretic effect that could prevent the development of heart failure [20]. Although the risk of heart failure associated with DPP-4i remains uncertain [52], if present, it should be minimized by the addition of a SGLT2i, which has the capacity to promote both diuresis and natriuresis [12, 22].

The place of DPP-4i-SGLT2i combined therapy remains to be more precisely defined in the management of T2D [2, 3]. The glucose-lowering effect of the combined therapy was clearly greater with saxagliptin/dapagliflozin [27] or with linagliptin/empagliflozin [35, 36] than with each individual component. Furthermore, a single-pill combination of a DPP-4i and a SGLT2i, as recently commercialized for saxagliptin/dapagliflozin and linagliptin/empagliflozin, would reduce the daily pill burden in patients with T2D, potentially improving adherence to, and optimizing the benefits of therapy [15, 16]. However, the glucose-lowering effects of the two compounds were far from being additive and the final results, as far as the primary endpoint was concerned (HbA1c reduction at week 24), were somewhat disappointing. Overall, the added reduction in HbA1c when comparing DPP-4i-SGLT2i combined therapy with SGLT2i alone was rather limited (only 0.2-0.4 %) in diet-treated patients [35] or in metformin-treated patients [27, 36]. Consequently the add-on value of a DPP-4i appears less marked when it was added to a background therapy with metformin plus SGLT2i than when it was added to metformin alone. Indeed, in metformin-treated T2D patients, adding a DPP-4i has been shown to reduce HbA1c by about 0.6-0.8% [53] and be almost as effective as adding a sulphonylurea [54]. Despite the complementary mechanisms of DPP-4i and SGLT2i, it is thus difficult to systematically recommend the initiation of a combined therapy after failure of metformin monotherapy. The question that thus arises is which of the two pharmacological agents should be added first, either SGLT2i or DPP-4i, in T2D patients who do not reach individual HbA1c targets with metformin [55]. According to the results of a recent systematic review and network meta-analysis of clinical trials and compared to DPP-4i, almost similar reductions in HbA1c were reported with dapagliflozin and empagliflozin but a greater reduction in HbA1c was observed with canagliflozin, especially at the dosage of 300 mg [10]. Superiority of canagliflozin versus DPP-4i was confirmed in a recent real-world study [56]. When a SGLT2i was combined to metformin first, the additional glucose-lowering effect of prescribing a DPP-4i afterwards was rather limited [29]. In contrast, when a DPP-4i was combined to metformin first, the additional glucose-lowering effect of prescribing a SGLT2i afterwards was more clinically relevant [28].

These findings may help the physician in his/her therapeutic choice. However, secondary and tertiary add-on drug therapy should be individualized based not only on efficacy but also on tolerance and personal preferences, taking into account the wishes and priorities of the patient [2, 3, 57]. DPP-4i have a better tolerance profile than SGLT2i and have proven to be well tolerated in elderly patients [7] while SGLT2i should be used with caution in this more fragile population [9]. Another advantage of DPP-4i is that these oral antidiabetic agents may be used in patients with renal impairment [58], whereas SGLT2i are contraindicated in patients with estimated glomerular filtration rate below 45 or 60 ml/min/1.73m² (depending on the medication) [59]. Nevertheless, recent results from EMPA-REG OUTCOME showed that empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care in patients with T2D at high cardiovascular risk, and these findings may open new perspectives [60]. SGLT2i offer some advantages beyond the glucose-lowering effect, such as inducing weight loss, reducing systolic blood pressure, and improving cardiovascular outcomes in at risk patients, especially when heart failure is present. Therefore, SGLT2i may be preferred in T2D patients with obesity, hypertension, congestive heart failure and/or antecedents of cardiovascular events. Past history of cardiovascular disease or congestive heart failure may represent a key criterion of choice considering the remarkable efficacy of the SGLT2i empagliflozin in EMPA-REG OUTCOME [11, 12], contrasting with previous mitigated results reported with other glucose-lowering agents, including DPP-4i [61]. Thus, in clinical practice, the choice should be individualized according to individual characteristics of the patient [62].

Finally, DPP-4i and SGLT2i are rather new oral antidiabetic agents that are more expensive than older compounds such as metformin and sulphonylureas. In order for healthcare decision makers to ensure patients receive the highest standard of care within the available budget, the clinical benefits of each treatment option must be balanced against the economic consequences [63]. In patients with T2D treated with metformin, DPP-4i as add-on treatment may represent a cost-effective option compared with sulphonylureas [64]. Pharmaco-economic assessment of SGLT2i should take into account not only the magnitude of the glucose-lowering response [65], but also the potential benefits resulting from reduction in diabetes complications, including cardiovascular events [11, 12]. Further pharmaco-economic analyses are needed to investigate the cost-effectiveness and cost-utility of a DPP-4i-SGLT2i combination in the management of T2D.

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Figure 1: Illustration of the complementary glucose-lowering activities of DPP-4 inhibitors (DPP-4i) and SGLT2 inhibitors (SGLT2i) in type 2 diabetes. DPP-4 : dipeptidyl peptidase-4. SGLT2: Sodium-glucose cotransporter type 2. GIP: glucose-dependent insulinotropic polypeptide. GLP-1: glucagon-like peptide-1. SBP : systolic blood pressure.

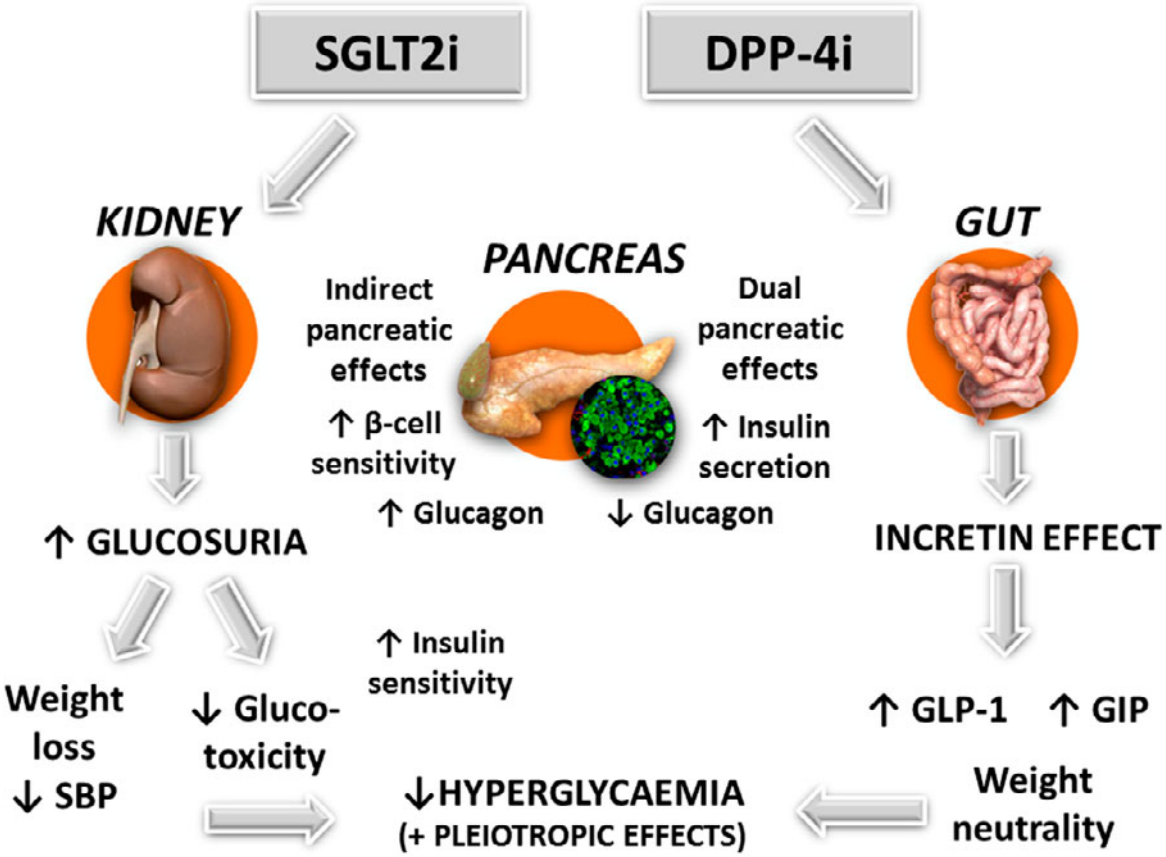

Table 1: Comparison of the metabolic, hormonal and clinical effects of DPP-4 inhibitors and SGLT2 inhibitors in patients with type 2 diabetes.

Parameters	DPP-4 inhibitor	SGLT2 inhibitor
Medications (*)	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	Canagliflozin, dapagliflozin, empagliflozin
Target organ	Gut	Kidney
Mode of action	Inhibition of degradation of GLP-1 and GIP (incretins)	Inhibition of tubular reabsorption of glucose
Glucosuria	Unchanged/decreased (due to reduced hyperglycaemia)	Increased (primary effect)
Caloric intake	Slightly decreased (GLP-1-related)	Slightly increased (compensatory)
Insulin secretion	Increased (incretin effect, post-meal)	Decreased (sparing effect)
Glucagon secretion	Decreased	Increased
Endogenous glucose production	Decreased	Increased
Peripheral insulin sensitivity	Unchanged	Increased
Fasting plasma glucose	Slightly decreased	Decreased
Postprandial plasma glucose	Decreased	Decreased
HbA1c	Decreased	Decreased
Body weight	Unchanged	Decreased
Systolic blood pressure	Unchanged	Decreased

Lipid profile	Almost unchanged	Almost unchanged
Serum uric acid	Unchanged	Decreased
Cardiovascular outcomes	Non-inferiority versus placebo (three trials) (**)	Superiority versus placebo (in EMPA-REG OUTCOME)
Hospitalisation for heart failure	Increased (in SAVOR-TIMI 53)	Decreased (in EMPA-REG OUTCOME)
Mortality (cardiovascular and all-cause)	Unchanged (three non-inferiority trials) (**)	Decreased (in EMPA-REG OUTCOME)
Renal events	Not reported (three non-inferiority trials) (**)	Decreased (in EMPA-REG OUTCOME)

(*) Medications available in United States and Europe

(**) EXAMINE (alogliptin), SAVOR-TIMI 53 (saxagliptin), TECOS (sitagliptin)

GLP-1 : glucagon-like peptide. GIP : glucose-dependent insulinotropic polypeptide

Table 2: Results of pharmacokinetic interactions in studies combining saxagliptin plus dapagliflozin, linagliptin plus empagliflozin and teneligliptin plus canagliflozin. Data are adjusted geometric mean ratios (90% confidence interval).

Single dose [25]	n	Dapagliflozin		Saxagliptin	
		C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
Saxagliptin 2.5 mg /Dapagliflozin 5 mg FDC vs Saxagliptin 2.5 mg plus Dapagliflozin 5 mg	36	1.093 (1.013-1.178)	1.006 (0.982-1.030)	1.047 (0.967-1.133)	1.040 (1.006-1.075)
Saxagliptin 5 mg /Dapagliflozin 10 mg FDC vs Saxagliptin 5 mg plus Dapagliflozin 10 mg	35	0.946 (0.878-1.019)	1.036 (1.010-1.062)	1.059 (0.993-1.129)	1.007 (0.973-1.042)
Multiple dose (5-7 days) [33]	n	Empagliflozin		Linagliptin	
		$C_{max,ss}$	$AUC_{tau,ss}$	$C_{max,ss}$	$AUC_{tau,ss}$

Linagliptin 5 mg/Empagliflozin 50 mg vs Linagliptin 5 mg	16	NA	NA	1.01 (0.87-1.19)	1.03 (0.96-1.11)
Linagliptin 5 mg /Empagliflozin 50 mg vs Empagliflozin 50 mg	16	0.88 (0.79-0.99)	1.02 (0.97-1.07)	NA	NA
Single dose [42]	n	Canagliflozin		Teneligliptin	
		C_{max}	AUC $_{0-72h}$	C_{max}	AUC $_{0-72h}$
Teneligliptin 40 mg /Canagliflozin 200 mg vs Teneligliptin 40 mg	19	NA	NA	0.983 (0.940-1.028)	0.976 (0.903-1.056)
Teneligliptin 40 mg /Canagliflozin 200 mg vs Canagliflozin 200 mg	25	0.982 (0.880-1.095)	0.982 (0.955-1.011)	NA	NA

AUC : area under the plasma concentration-time curve

C_{max} : maximum observed plasma concentration

FDC : fixed dose combination

NA : not applicable

Table 3: Results of clinical trials with the combination saxagliptin-dapagliflozin in patients with type 2 diabetes.

Reference	Background therapy	Duration weeks	Treatment	Patients n	ΔBW kg	ΔFPG mg/dl	Baseline HbA1c %	ΔHbA1c %	% patients < 7%	ΔPPG mg/dl
Rosenstock et al 2015 [27]	Metformin	24	Saxagliptin 5 mg + Dapagliflozin 10 mg	179	-2.1 p=NA p=NA	-38 ± 2.8 p=NA p=NA	8.92 ± 1.18	-1.47 ± 0.08 p<0.0001 [a] p=0.0166 [b]	41 p=NA p=NA	-80 p<0.0001 [a] p=0.06 [b]
			Saxagliptin 5 mg	176	0	-14 ± 2.9	9.03 ± 1.05	-0.88 ± 0.08	18	-36
			Dapagliflozin 10 mg	179	-2.4	-32 ± 2.8	8.87 ± 1.16	-1.20 ± 0.08	22	-70

Mathieu et al 2015 [28]	Metformin + Saxagliptin 5 mg	24	Dapagliflozin 10 mg	160	-1.9 p<0.0001 [c]	-33 p<0.0001 [c]	8.17 ± 0.98	-0.82 ± 0.07 p<0.0001 [c]	38.0 p<0.0001 [c]	-74 p<0.0001 [c]
			Placebo	160	-0.4	-5	8.24 ± 0.96	-0.10 ± 0.07	12.4	-38
Matthaei et al 2015 [29]	Metformin + Dapagliflozin 10 mg	24	Saxagliptin 5 mg	153	-0.53 NS	-9 NA	7.97 ± 0.83	-0.51 ± NA p<0.0001 [c]	35.3 NA	-37 p=0.2014 [c]
			Placebo	162	-0.51	-5	7.86 ± 0.93	-0.16 ± NA	23.1	-31

a : versus Saxagliptin

b: versus Dapagliflozin

c : versus placebo

NA : not available

NS : not significant

Delta : change from baseline

BW : body weight

FPG : fasting plasma glucose

HbA1c : glycated haemoglobin

PPG : postprandial glucose

Table 4: Results of clinical trials with the combination linagliptin-empagliflozin in patients with type 2 diabetes.

Reference	Background therapy	Duration weeks	Treatment	Patients n	ΔBW kg	ΔFPG mg/dl	Baseline HbA1c %	ΔHbA1c %	% patients < 7%
Lewin et al 2015 [35]	Diet + exercise	24	Linagliptin 5 mg + Empagliflozin 25 mg	134	-2.0 p=0.801 [a] p=0.018 [b]	-29.6 p=0.161 [a] p<0.001 [b]	7.99 ± 0.95	-1.08 ± 0.06 p=0.179 [a] p<0.001 [b]	55.4 p=0.022 [a] p<0.001 [b]
			Linagliptin 5 mg + Empagliflozin 10 mg	135	-2.7 p=0.362 [a] p<0.001 [b]	-28.2 p=0.125 [a] p<0.001 [b]	8.04 ± 0.96	-1.24 ± 0.06 p<0.001 [a] p<0.001 [b]	62.3 p<0.001 [a] p<0.001 [b]
			Empagliflozin 25 mg	133	-2.1	-24.2	7.99 ± 0.97	-0.95 ± 0.06	41.5
			Empagliflozin 10 mg	132	-2.3	-22.4	8.05 ± 1.03	-0.83 ± 0.06	38.8
			Linagliptin 5	133	-0.8	-5.9	8.05 ± 0.89	-0.67 ± 0.06	32.3

			mg						
DeFronzo et al 2015 [36]	Metformin	24	Linagliptin 5 mg + Empagliflozin 25 mg	134	-3.0 p=0.660 [a] p<0.001 [b]	-35.3 p<0.001 [a] p<0.001 [b]	7.9 ± 0.79	-1.19 ± 0.06 p<0.001 [a] p<0.001 [b]	61.8 p<0.001 [a] p<0.001 [b]
			Linagliptin 5 mg + Empagliflozin 10 mg	135	-2.6 p=0.876 [a] p<0.001 [b]	-32.2 p<0.002 [a] p<0.001 [b]	7.95 ± 0.80	-1.08 ± 0.06 p<0.001 [a] p<0.001 [b]	57.8 p<0.001 [a] p<0.001 [b]
			Empagliflozin 25 mg	140	-3.2	-18.8	8.02 ± 0.83	-0.62 ± 0.06	32.6
			Empagliflozin 10 mg	137	-2.5	-20.8	8.00 ± 0.93	-0.66 ± 0.06	28.0
			Linagliptin 5 mg	128	-0.7	-13.1	8.02 ± 0.90	-0.70 ± 0.06	36.1

a: Versus Empagliflozin alone at corresponding dosage

b: Versus Linagliptin 5 mg

Delta : change from baseline

BW : body weight

FPG : fasting pasma glucose

HbA1c : glycated haemoglobin

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