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## DPP-4 Inhibitors vs. SGLT-2 Inhibitors; Cons and Pros

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### Abstract

Type 2 diabetes mellitus (T2DM) is a progressive, chronic disease characterized by hyperglycemia. Despite recent advances to early diagnosis and prevention, its prevalence is rising worldwide. More than half of the T2DM patients do not achieve optimal glycemic control according to current guidelines. It is obvious that the need for new antidiabetic treatment and the achievement of therapeutic targets is of great importance in order to prevent micro- and macrovascular complications as well as morbidity and mortality. The most recent therapeutic choices for the management of T2DM are dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT-2) inhibitors. In this article, we summarize the mechanism of action, the advantages and disadvantages of SGLT-2 and DPP-4 inhibitors, their effect on cardiovascular (CV) events, their role in current guidelines for T2DM treatment and how they are implemented in daily clinical practice.

**Keywords:** Type 2 diabetes; Hyperglycemia; Hypoglycemia; Dipeptidyl peptidase 4; Glucagonlike peptide.

### Introduction

T2DM is continually increasing in prevalence worldwide and is expected to affect 440 million people by 2030, with significant implications to diabetic patient's quality of life [1]. T2DM is associated with increased morbidity and mortality due to two categories of complications, microvascular and macrovascular [1]. Hyperglycemia is the main pathogenetic risk factor for T2DM complications by inducing increased polyol pathway flux, increased advanced glycation end-product (AGE) formation, activation of protein kinase C (PKC) and increased hexosamine pathway flux [2]. Therefore, achieving normal ranges of blood glucose levels is of main importance for the prevention of diabetic complications [2]. For this reason, different antidiabetic agents are available, including insulin and oral drugs some of which are biguanides, thiazolidinediones, sulfonylureas, alpha-glucosidase inhibitors

and the newer GLP-1 analogues and dipeptidyl peptidase 4 inhibitors. These agents may be associated with significant side effects such as hypoglycemia (sulfonylureas, insulin), weight gain (sulfonylureas, thiazolidinediones, and insulin), edema (thiazolidinediones), and adverse CV outcomes (thiazolidinediones). A far more important point of focus is that more than half of the patients treated with oral agents cannot reach optimal HbA1c target values [3,4]. Therefore, the formulation of newer approaches in the treatment of T2DM patients with oral agents should be prioritized by all researchers. Two novel approaches in reducing hyperglycemia are targeting the modulation of renal glucose excretion by inhibiting sodium-coupled glucose transporters (SGLTs) and exploiting the incretin effect with dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists [5-7].

### DPP-4 inhibitors

DPP-4 inhibitors are oral antihyperglycemic agents, enhancing insulin secretion by reducing degradation of endogenous GLP-1. The effectiveness of delayed degradation of substances such as GLP-1 is based on a phenomenon named the "incretin effect". The basis of this theory is relatively simple: orally administered glucose seems to induce a far more notable insulin excretion peak in comparison to the intravenous (IV) route. The difference between the two has been explained by existence of substances named "incretins" (GLP-1, GIP) that mediate pancreatic insulin release whenever glucose is received orally [8]. Members of the DPP-4 inhibitors category are sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin [3].

According to clinical trial data from the development of various DPP-4 inhibitors, their induction of HbA1c value reduction seems to average at about -0.74% depending on their use as monotherapy or in combination with other antidiabetic agents [4]. Sitagliptin and vildagliptin are highly efficient in achieving glycemic control, more so when combined with metformin, sulfonylureas, and/or thiazolidinediones [4].

DPP-4 inhibitors are metabolized by renal excretion; therefore, it is necessary to adjust their dose in patients with moderate or severe renal impairment accordingly [9,10]. An exception to this is linagliptin, which is mainly metabolized

though the biliary route, with only a very small fraction (<6%) being excreted through the kidneys [9].

This drug class has a neutral effect on patients' weight and a very low risk of hypoglycemia. However, in patients previously treated with insulin or sulfonylurea it is advised to proceed to dose adjustments of the substance, and keep caution during administration of a DPP-4 inhibitor [11]. Adverse reactions such as anaphylaxis and angioedema have been reported with the use of DPP-4 inhibitors. In more detail, use of vildagliptin was correlated with the presence of angioedema in individuals receiving an angiotensin-converting enzyme (ACE) inhibitor [12,13]. Vildagliptin has been, also, linked to some cases of hepatic dysfunction [11]. As a result, its use should be avoided in diabetics with alanine aminotransferase or aspartate aminotransferase values equal or greater than three times the higher normal value.

There is raised concern for pancreatic adverse reactions with DPP-4 inhibitors since there have been reports of acute pancreatitis, including fatal hemorrhagic or necrotizing pancreatitis, in studies with sitagliptin, vildagliptin, and saxagliptin [14-17]. However, analyses of studies with patients treated with sitagliptin [18] did not show an increased prevalence of acute pancreatitis as compared to others receiving other antidiabetic agents. The same finding was observed in an analysis including vildagliptin and alogliptin showing no increased prevalence of pancreatic adverse events [19,20]. At this point it must be mentioned that diabetic patients show a higher risk of pancreatitis and pancreatic cancer in comparison to non-diabetics [21].

DPP-4 inhibitors have demonstrated a lower risk of hypoglycemia along periods of fasting that concern many ethnic groups and pose a challenge for physicians (ie. Ramadan fasting). Specifically, vildagliptin has been compared to sulphonylurea and was linked to far fewer episodes on hypoglycaemia during Ramadan fasting [22-27].

CV safety trials conducted on patients treated with DPP-4 inhibitors suggest a rather neutral effect on CV event incidence and severity of outcome [28-31].

**SAVOR-TIMI study:** Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) study included 16,492 patients with T2DM and previous incidents and/or risk factors of CV disease. The conclusion of the study revealed that both primary and secondary CV end points were statistically similar between the saxagliptin and the placebo group (non-inferiority of saxagliptin in comparison to placebo). Similarly, adverse event reports were nearly equal for the two groups (72.5% for saxagliptin, 72.2% for placebo). However, after 2.1 years of monitoring, the prevalence of patient admission for CV events was notably higher for the patients receiving saxagliptin (3.5% for saxagliptin, 2.8% for placebo,  $p=0.007$ ) [29].

**EXAMINE study:** EXAMINE included 5,380 patients with T2DM diagnosed with acute coronary syndrome (ACS) in a period of 90 days or less prior to admission to the study. Both primary and secondary endpoints were similar between

alogliptin and placebo users (non-inferiority of alogliptin in comparison to placebo). Specifically, patients receiving alogliptin presented with a prevalence of 11,3% for major CV events, while the placebo users rated at 11,8% [30].

**VIVID study:** Vildagliptin in Ventricular Dysfunction Diabetes (VIVID) study, included 254 patients with T2DM and CV disease classified as type I, II and III by the New York Heart Association. The subjects were randomized in order to receive either vildagliptin or placebo. The two groups showed no difference in left ventricle functionality and/or prevalence of hospital admission for CV events. However, despite the significant reduction of their natriuretic peptide plasma levels, patients on vildagliptin presented with an increase in end-diastolic left ventricular volume. Another point of interest is that there were more patient deaths on the group receiving vildagliptin, though one should mention that this finding was not statistically significant [31,32].

**TECOS study:** Trial Evaluating Cardiovascular Outcome with Sitagliptin (TECOS) study included 14,671 patients with T2DM and CV disease. The patients were randomized in order to receive sitagliptin (100 mg, once daily) or placebo. After a mean follow-up period of 3 years, the prevalence of a primary end-point was similar across both groups (11,4 and 11,6% respectively). The percentage of hospitalisation for CV events was the same for both groups (3,1%) as was the risk for hypoglycaemia, acute pancreatitis or pancreatic cancer. TECOS study results proved the safety of sitagliptin in comparison to other antidiabetic regimens as far as CV disease was concerned [31].

## SGLT-2 inhibitors

It is well known that kidneys have an important role in the control of blood glucose levels. In healthy humans, about 180 g/day of glucose is filtered through the renal glomerulus, more than 99% of which is reabsorbed along the tubular system. The result is that no glucose is excreted in the urine. When the capacity of glucose reabsorption has been exceeded, the surplus glucose is excreted in the urine and glucosuria develops [11].

The sodium-coupled glucose transporters (SGLTs) are membrane proteins involved in the transport of glucose, amino acids, vitamins, osmolytes, and ions [33]. SGLT-2 transporter is found mainly in the kidney and is responsible for most of glucose reabsorption [34]. SGLTs couple glucose reabsorption to sodium reabsorption, and in this way mediate renal glucose reabsorption. The early convoluted segment (S1) of the proximal tubule reabsorbs approximately 90% of the filtered renal glucose. This is accomplished by the high-capacity, low-affinity SGLT-2 transporter. The remaining 10% of the filtered glucose is reabsorbed by the high-affinity, low-capacity SGLT-1 transporter in the distal straight segment (S3) of the proximal tubule [35]. During periods of hyperglycemia, the glucose reabsorptive capacity of the kidney increases in proportion to the plasma glucose concentration. However, as plasma glucose concentrations increase, the filtered glucose load increases in a linear manner. When the rate of glucose entering the nephron rises above 260-350 mg/min/1.73 m<sup>2</sup>,

for example in subjects with diabetes, the excess glucose outstrips restorative capacity and appears in the urine. In healthy subjects, this equates to a blood glucose concentration of approximately 200 mg/dL [36].

Dapagliflozin, empagliflozin and canagliflozin are the three SGLT-2 inhibitors currently used widely in clinical practice. They can be administered once-daily and produce a dose-dependent increase in glucosuria. HbA1c reduction by SGLT-2 inhibitors varies from 0.6 to 1%, depending on the patient's initial HbA1c value [37].

SGLT-2 inhibitors have several positive effects, such as weight loss, low risk of hypoglycemia and blood pressure values (BP) reduction. It is known that urinary loss of 60 to 80 g of glucose per day equates to 240 to 320 cal/day, resulting in patients losing weight, a phenomenon observed in all clinical studies with SGLT2 inhibitors [38,39]. As it is previously mentioned early decreases in weight may be the result of the osmotic diuretic effect of the agents, whereas weight loss over subsequent weeks may be the result of caloric loss. Weight loss of 2–3 Kg has been demonstrated in 12-week trials of dapagliflozin, canagliflozin and empagliflozin [38,39]. Another finding in SGLT-2 inhibitors studies is the mild reduction in systolic and diastolic blood pressure [38] that is attributed to the fluid/sodium deficit that occurs during the first several days of dapagliflozin treatment [38,39].

Preclinical and early clinical studies showed that SGLT2 inhibitors do not cause hypoglycaemia. This is explained by the fact that SGLT2 inhibitors decrease the plasma glucose concentration without augmenting insulin secretion by the pancreatic  $\beta$ -cells and because of the renal threshold of glycaemia, below which SGLT2 inhibitors would not be expected to cause further urinary glucose excretion. According to the data by the clinical trials, the prevalence of hypoglycemic events in subjects treated with SGLT2 inhibitors was like that in people receiving placebo [40]. However, when SGLT2 inhibitors are used in combination with sulfonylurea or insulin, physicians should consider reducing the dose of sulfonylurea or insulin in order to avoid possible hypoglycemic events.

Adverse effects reported with SGLT2 inhibitors include constipation, diarrhea, and nausea, urinary and genitourinary infections. In clinical studies, a small (3–5%) increase in the rate of UTIs has been reported in subjects receiving SGLT2 inhibitors compared to placebo. Most of these infections involved cystitis, vulva-vaginitis and balanitis and have responded to standard antibiotic and local anti-fungal treatment [39]. In trials where dapagliflozin was used there was a small increase to the incidence of UTIs compared with placebo and metformin [40]. It is known that diabetic women are more prone to UTIs than nondiabetic subjects. In addition, recurrent vaginal candidiasis is more prevalent in diabetic subjects [39]. However, a prospective study with 600 diabetic women showed that glucosuria did not increase the risk for developing asymptomatic bacteriuria or UTIs [41].

Another risk with treatment with SGLT2 inhibitors is a possible increase in urine volume as well as loss of

electrolytes, and a 400 to 500 ml negative fluid balance occurs during the first 2–3 days of therapy. However, when dapagliflozin was administered to humans, urine volume increased only modestly during the first 2 to 3 days after initiation of therapy. Excessive urine loss of sodium, potassium, and other electrolytes was not observed [40]. This mild volume contraction was followed by a small rise in hematocrit and plasma urea nitrogen to creatinine ratio as well as a decrease in blood pressure. Finally, plasma electrolyte concentrations did not change in dapagliflozin group [39,40]. Tachycardia and orthostatic hypotension (clinical signs of volume depletion) and hyponatremia (laboratory evidence of water depletion) have not been reported in subjects treated with SGLT2 inhibitors [39,40]. According to studies, SGLT2 inhibitors do not have any deleterious effect on renal function in subjects with T2DM with normal levels of GFR, electrolyte disturbances, acid-base balance, hypertension and patient's quality of life. At this point it must be mentioned that all these studies were performed in subjects with normal renal function, and further studies are needed to clarify the effects of SGLT2 inhibitors in subjects with impaired renal function.

An increased incidence of bladder and breast cancer was observed in phase III studies of dapagliflozin [42]. There were 9 cases of breast cancer in the dapagliflozin group (2223 patients) compared to 1 case in placebo (1053 patients), all diagnosed within the first year of the studies [42]. Bladder cancers were reported in 9 cases in the dapagliflozin group (5478 patients) compared to 1 case in the control group (3156 patients) [42]. All were men and 6 patients had a history of hematuria before receiving the study drug [42]. In preclinical studies of dapagliflozin in rodents there was no evidence of carcinogenicity. It is important to notice that the significance of the increased incidence of these tumors observed in dapagliflozin studies remains uncertain and further studies are needed to be determined [42].

Small reductions in GFR occur shortly after the initiation of the therapy, returning to normal after a few weeks [42,43]. In addition, because of their mechanism of action, the efficacy of SGLT2 inhibitors to reduce the plasma glucose levels is highly dependent upon renal function. In subjects with GFR levels between 60–90 ml/min, the glucosuria produced by dapagliflozin [42] was decreased by 40% and the reduction in HbA1c was decreased by about 20%. Among subjects with similarly impaired renal function, ipragliflozin was reported to produce comparable glucosuria to subjects with GFR greater than 90 ml/min [43]; however, the decrease in fasting blood glucose levels was decreased by 50%. In subjects with GFR levels between 30–59 ml/min, the glucosuria produced by both ipragliflozin and dapagliflozin was reduced but the decrease in fasting blood glucose levels and HbA1c was clinically insignificant.

Another point of interest concerning the use of SGLT-2 inhibitors as part of a treatment regimen is their association to episodes of diabetic ketoacidosis (DKA) at a notably higher rate than DPP-4 inhibitors [44]. DKA is an acute complication of DM that can become life threatening. It is caused by the deficiency of insulin action in an individual, more often presenting in type

1 DM (T1DM) subjects with little to no control of the disease or in T2DM subjects with poor insulin regulation, often triggered by extreme stress. DKA often presents with notable hyperglycemia and dehydration, though it can rarely present with little to no increase in blood glucose (BG) levels, an instance known as euglycemic or normoglycemic DKA (DKA with a blood glucose level of below 250 mg/dL) [45]. SGLT-2 inhibitors have been interestingly linked to numerous cases of euglycemic DKA, deeming it a necessity for physicians to be aware of such risk and monitor patients initiating said therapy more closely [44,45].

T2DM patients also seem to present with a higher prevalence of bone fractures, that some classes of medication (i.e., thiazolidinediones) could further increase [46]. From the SGLT-2 inhibitors, canagliflozin has been flagged by the FDA as a possible agent that could amplify the issue. Treatment with canagliflozin and dapagliflozin showed a rise in bone resorption marker beta-CTx and minimal decline in procollagen type 1 N-terminal propeptide (P1 NP), a bone formation marker [34]. The lipid profile of patients treated with SGLT-2 inhibitors seems to vary considerably. Canagliflozin administration, in a dose of 300 mg/day appeared to improve lipid control [47], while dapagliflozin did not show similar action on lipid values [48].

**EMPA-REG OUTCOME Trial:** Empagliflozin cardiovascular outcome event trial in Type 2 diabetes mellitus patients (EMPA-REG OUTCOME) trial, included 7,020 patients with T2DM and CV disease, randomized in order to receive either empagliflozin (10 mg or 25 mg, once daily) or placebo therapy [49]. After a mean follow-up period of 3 years, there was a notable and statistically significant difference as far as the primary endpoint was concerned between subjects receiving empagliflozin of any dosage and those treated with placebo (-14% deaths on the empagliflozin group). Empagliflozin reduced deaths by CV causes by 38%, deaths by any cause by 32% and hospitalisation for CV incidents by 38%. Genital tract infections were more common among patients receiving empagliflozin vs. placebo (5.0 vs. 1.5% for men and 10.0 vs. 2.6% for women, respectively). The risk for urinary tract infections, hypoglycaemia, DKA or bone fractures was the same across the two groups [49].

**CANVAS Program:** Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes (CANVAS) program included 10,142 patients with T2DM and high CV risk, 65% of which had reported previous CV incidents and 35% of which had 2 or more CV risk factors and were over 50 years of age [50,51]. The follow-up period averaged 188 weeks while the mean age across participants was 63.3 years and their mean disease duration neared 13.5 years. The primary endpoint was significantly reduced on the group receiving Canagliflozin (-14%, HR=0.86, p<0.001 for non-inferiority and p=0.02 for inferiority to placebo). CANVAS-RENAL also revealed a decline in death by renal causes (drop of GFR by 40%, need for dialysis) HR=0.73 (CI 0.67-0.79). As far as secondary endpoints are concerned, CV related deaths, myocardial infarction incidences, strokes and hospitalisation for CV failure were reduced for the canagliflozin group [51].

Adverse effects included fungal infections of the female genital tract (at a rate nearing 3 times that of the placebo group), higher risk of amputation (HR=1.97) (mainly for fingers, with higher absolute risk for amputation in patients having undergone previously similar procedures or with peripheral arterial disease) and higher risk for bone fractures (HR=1.23) for patients of the canagliflozin group [51].

## Comparison between DPP-4 and SGLT-2 inhibitors

There are several studies comparing DPP-4 and SGLT-2 inhibitors. In one such study, empagliflozin (10 mg and 25 mg) was compared both with sitagliptin 100 mg and placebo in patients with HbA1c levels of 7.5–10%. HbA1c appeared reduced by almost 0.8% (95% CI -0.88 to -0.59; P<0.0001) in the group treated with empagliflozin 10 mg, 0.85% (-0.99 to -0.71; P<0.0001) in the one with 25 mg, and 0.73% (-0.88 to -0.59; P<0.0001) for treatment with sitagliptin at 24 weeks [52].

In another trial, drug-naïve T2D patients were divided into five groups; received empagliflozin and linagliptin combination therapy (25 mg and 5 mg, respectively, or 10 mg and 5 mg), treated with empagliflozin (25 mg or 10 mg) or linagliptin (5 mg) monotherapy (53). Both single-pill combinations significantly reduced HbA1c from baseline (from 7.99 to 8.05%) compared with linagliptin monotherapy (25 mg/5 mg, difference -0.4%; P<0.001; 10 mg/5 mg, difference -0.6%; P<0.001). HbA1c reductions were more significant with empagliflozin/linagliptin 10 mg/5 mg than with empagliflozin 10 mg (difference -0.41%; P<0.001), but were not notably varying between empagliflozin/linagliptin 25 mg/5 mg and empagliflozin 25 mg (difference -0.14%; p = non-significant). The single-pill combinations showed greater reductions in FPG and body weight than linagliptin monotherapy. Hypoglycemic incidents (glucose ≤ 70 mg/dL) were reported in two subjects on empagliflozin 25 mg and one each on empagliflozin 10 mg and linagliptin 5 mg.

Canagliflozin (100 mg and 300 mg) was compared to sitagliptin in diabetic patients with HbA1c levels from 7–10.5%. Canagliflozin 100 mg was neutral, while canagliflozin 300 mg demonstrated superiority to sitagliptin in lowering HbA1c (0.88 vs. 20.73%) at a 52 weeks' period of treatment. In contrast to sitagliptin, canagliflozin showed both weight loss and systolic BP drop, while UTIs, osmotic diuresis-related adverse events, and hypoglycemia incidents were also higher in the canagliflozin group [50-53].

In another study, canagliflozin (300 mg) was compared with sitagliptin (100 mg) in diabetics that could not achieve optimal glucose control solely with metformin and sulfonylurea, demonstrating noninferiority at 52 weeks and superiority in a subsequent assessment (HbA1c 21.03 vs. 20.66%, respectively). Patients reporting incidents of hypoglycemia were almost equal, either receiving canagliflozin (43.2%) or sitagliptin (40.7%). Canagliflozin was shown to produce FPG levels improvement, as well as weight loss and systolic BP moderation in comparison to sitagliptin (P<0.001). Adverse

effects reported were about equal in both groups (canagliflozin: 76.7%, sitagliptin: 77.5%). Importantly, serious adverse events and, as a result, treatment discontinuation were low for both groups. UTIs had a higher prevalence, in both genders, in the canagliflozin group. Same was the case with osmotic diuresis-related adverse events. Cases of hypoglycemia showed a similar likelihood of occurrence in both groups [54]. All previously stated, study derived, information supports the addition of canagliflozin in triple combination therapy with metformin plus a sulfonylurea for the treatment T2D patients.

A 24-week, randomized, double-blind, placebo-controlled study assessed dapagliflozin 10 mg as a part of combination therapy with sitagliptin, 100 mg, and with and without metformin,  $\geq 1500$  mg/day, in 447 participants [55]. At the end of the study, dapagliflozin was shown to reduce mean HbA1c concentration as opposed to placebo, excluding data after rescue [placebo-corrected difference  $-0.5\%$ ; 95% confidence interval (CI),  $-0.6$  to  $-0.3$ ;  $p < 0.0001$ ], even in a subset of subjects with increased HbA1c baseline ( $\geq 8\%$ ). Treatment with dapagliflozin showed significant decrease of FPG (placebo-corrected difference  $-1.55$  mmol/l; 95% CI  $-1.92$  to  $-1.19$ ;  $p < 0.0001$ ) and weight loss (placebo-corrected difference  $-1.9$  kg; 95% CI  $-2.4$  to  $-1.4$ ;  $p < 0.0001$ ). There was no group showing superiority in adverse incident reports while discontinuation rates were low for all as well.

Recently, the combination of dapagliflozin with saxagliptin compared to saxagliptin or dapagliflozin monotherapy, was examined in a 24-week, randomized, active-controlled study having 534 subjects with T2D previously receiving only metformin [56]. After 24 weeks, the reduction in HbA1c from baseline (8.9%, 9.0% and 8.9%, respectively), was higher in the group treated with the combination therapy (saxagliptin 5 mg plus dapagliflozin 10 mg; adjusted mean change from baseline  $-1.5\%$ ) when compared with the groups receiving monotherapy (saxagliptin  $-0.9\%$ ; difference  $-0.6\%$ ;  $P < 0.0001$ ; dapagliflozin  $-1.2\%$ ; difference  $-0.3\%$ ;  $P < 0.02$ ). The moderated proportion of participants reaching HbA1c levels of  $< 7\%$  was 41% with combination therapy vs. 18 and 22% with saxagliptin or dapagliflozin alone, respectively. UTIs rates did not deviate from what was expected from past studies.

In combination, DPP-4 and SGLT2 inhibitors can be used to improve glucose control in numerous patients with T2DM, carrying a relatively low risk of adverse events, such as hypoglycaemia or weight gain and offering cardiovascular protection at the same time. 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 sulphonyl ureas or insulin.

An interesting point of discussion is the inhibitory effect on glucagon secretion exerted by the DPP-4 inhibitors as opposed to the contradictory stimulatory effect by SGLT-2 inhibition [25,47,57,58]. The glucagon secretion regulated by SGLT-2 inhibition stimulates body glucose production, which could antagonize the glucose-lowering effect resulting from enhanced glycosuria [58]. DKA in T2DM patients associated

with SGLT-2 inhibition, as discussed before, could be linked to said regulation of glucagon secretion [44,45]. Thus, combining DPP-4 and SGLT-2 inhibition can favor optimal glucagon regulation. Furthermore, combination therapy with DPP-4 and SGLT-2 inhibitors also seems to have other benefits such as the reduction of urinary and genital tract infections prevalence [34,59].

One of the differences between the two drug categories is that DPP-4 inhibitors seem to be better tolerated by the elderly (in stark contrast to SGLT-2 inhibitors) [13,14]. Another point where the two categories diverge is their safety as far as administration in patients with renal impairment is concerned. DPP-4 inhibitors are safe to use in patients with renal impairment, whereas SGLT2 inhibitors should not be used in patients with estimated glomerular filtration rate below 60 ml/min/1.73 m<sup>2</sup> or slightly less in some cases (different lower limits of administration, depending on the specific substance) [10,60-62].

## Conclusion

SGLT-2 inhibitors alone seem to achieve better control of blood glucose levels along with greater weight loss than DPP-4 inhibitors do. On the other hand, both pharmacological groups seem to have similar effects on the lipid profile of patients, with SGLT-2 inhibitors being slightly more beneficial in patients with low HDL-C. Yet, the potential complementary mechanisms of action of DPP-4 and SGLT-2 inhibitors make these agents attractive treatment options for combination therapy. Both SGLT-2 inhibitors and DPP-4 inhibitors can be used to treat patients with T2D unable to achieve normoglycemia, as they are well tolerated, do not induce weight gain and have low chance of hypoglycemia. Furthermore, combination of a DPP-4 and a SGLT-2 inhibitor has potential benefits beyond lowering glucose, such as beneficial effects on CV and renal risk factors, including albuminuria, and lowering body weight and systolic blood pressure.

## Conflict-of-Interest

Authors declare no conflict of interests for this article

## Authors Contributions

Karampousli E, Papazafiropoulou AK and Xourgia E wrote the paper; Melidonis A performed the revision.

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