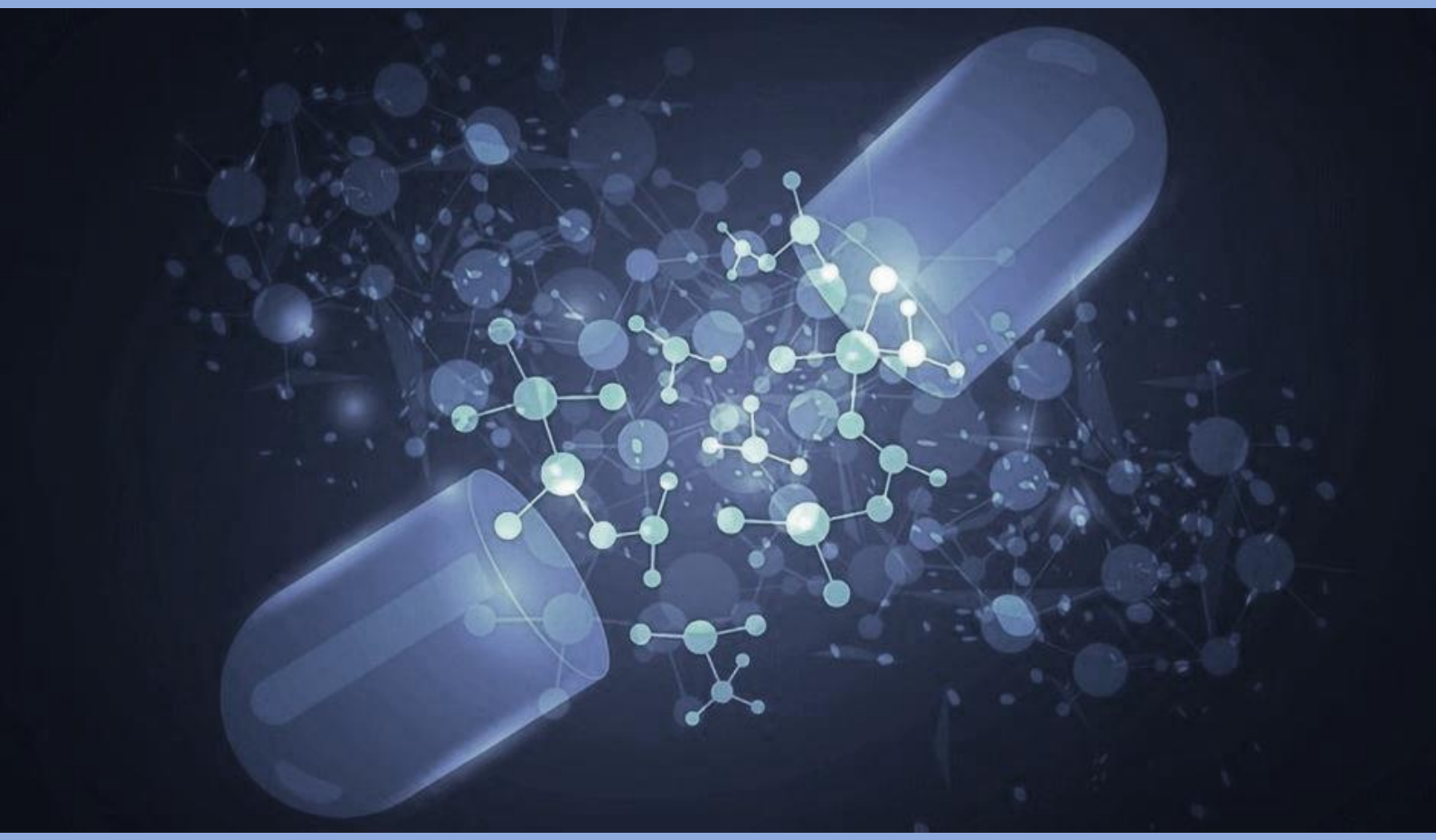
IMPACT OF COMBINATION THERAPY ON SITAGLIPTIN + DAPAGLIFLOZIN



Content

Background and Objective of the Survey

Combination therapy with sitagliptin and dapagliflozin has emerged as a promising approach in the management of type 2 diabetes mellitus (T2DM), offering synergistic effects that address multiple pathophysiological pathways. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, works by enhancing the action of incretin hormones, thereby increasing insulin secretion and decreasing glucagon levels, leading to improved glycemic control. Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, acts by promoting urinary glucose excretion, thereby reducing plasma glucose levels independently of insulin action.

Clinical studies evaluating the combination therapy of sitagliptin and dapagliflozin have demonstrated significant reductions in HbA1c levels, fasting plasma glucose, and body weight compared to monotherapy with either agent. Additionally, this combination therapy has shown favorable effects on cardiovascular outcomes and renal function, making it a valuable option for patients with T2DM, particularly those with comorbidities such as obesity, hypertension, and cardiovascular disease. Overall, combination therapy with sitagliptin and dapagliflozin represents a promising strategy for achieving comprehensive glycemic control and reducing the risk of diabetes-related complications.

The objective of the survey is:

To evaluate the impact of combination therapy on sitagliptin + dapagliflozin

Methodology of the Survey

A survey was conducted to evaluate the impact of combination therapy on sitagliptin + dapagliflozin. A total of 160 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Dapagliflozin
- Clinical pharmacology
- Therapeutic use of dapagliflozin in patients with T2DM
- Benefits of dapagliflozin
- Current guidance for Dapagliflozin
- Sitagliptin
- Pharmacokinetics and pharmacodynamics
- Clinical efficacy
- Safety and tolerability
- Combination of SGLT2 inhibitor and DPP-4 inhibitor
- Dapagliflozin plus Sitagliptin

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Type 2 diabetes mellitus (T2DM) is on the rise and is closely associated with various cardiovascular and renal complications. A range of medications is employed to manage and prevent these complications in T2DM patients. According to current guidelines, metformin is typically recommended as the initial pharmacological treatment for T2DM. However, a significant number of patients either fail to reach glycemic targets or experience intolerable side effects with metformin therapy, necessitating the addition of a second oral agent, such as a glucagon-like peptide 1 (GLP-1) receptor agonist or insulin. Besides metformin, available oral agents include sulphonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, and the newer selective inhibitors of sodium–glucose linked transporter type 2 (SGLT2). These medications offer diverse mechanisms of action and are often utilized in combination to achieve optimal glycemic control and minimize the risk of complications associated with T2DM.

Dapagliflozin[1]

Dapagliflozin, a selective inhibitor of sodium-glucose linked transporter type 2 (SGLT2), has garnered recent approval for managing patients with type 2 diabetes mellitus (T2DM). This review aims to provide an overview of the pharmacokinetic properties, metabolic impacts, and adverse effects associated with dapagliflozin.

Mechanism of action

Sodium-glucose linked transporter type 2 (SGLT2) plays a pivotal role in renal glucose reabsorption, accounting for around 90% of active reabsorption in the early proximal tubule's S1 segment. Dapagliflozin, a selective and reversible SGLT2 inhibitor, disrupts this process, leading to a notable decline in glucose reabsorption and subsequent reductions in serum glucose levels, independent of insulin action. While dapagliflozin enhances insulin sensitivity, it paradoxically increases endogenous glucose production in individuals with type 2 diabetes mellitus (T2DM). This inhibition of glucose reabsorption by dapagliflozin has been linked to

reductions in body weight, likely attributed to decreased caloric load. Additionally, the drug demonstrates efficacy in reducing blood pressure, functioning as an osmotic diuretic and contributing to weight loss.

Clinical pharmacology[1]

Dapagliflozin, an orally administered medication, is a reversible and highly selective inhibitor of sodium-glucose linked transporter type 2 (SGLT2), typically prescribed in once-daily doses. In humans, it boasts an impressive absolute bioavailability of 78%. Rapid absorption occurs, with a time to reach maximum plasma concentration ranging from 0.5 to 1.3 hours post-administration. The drug exhibits extensive extravascular distribution, with a mean volume of distribution of 118 liters. Notably, factors such as body weight, age, race, sex, or the presence of type 2 diabetes mellitus (T2DM) do not significantly influence dapagliflozin's exposure. However, due to limited evidence, caution is advised when initiating dapagliflozin therapy in patients aged over 75 years or under 18 years. Importantly, food consumption does not substantially alter the pharmacokinetics or efficacy of dapagliflozin.

Dapagliflozin undergoes hepatic and renal metabolism, primarily via uridine diphosphate glucuronosyltransferase 1A9 (glucuronidation) in the liver and kidney, leading to the formation of its major inactive metabolite, dapagliflozin 3-O-glucuronide (D3OG), which is predominantly cleared through renal excretion. Hepatic impairment can influence dapagliflozin's plasma concentration, with a single 10 mg oral dose study revealing a 12% lower maximum plasma concentration in subjects with mild hepatic impairment, while those with moderate or severe impairment exhibited 12% and 40% higher concentrations, respectively. Dosage adjustment is unnecessary for patients with mild or moderate hepatic impairment, but caution is advised in severe cases, with a recommended starting dose of 5 mg, potentially titrated to 10 mg if tolerated well.

In terms of renal impairment, dapagliflozin and its metabolite clearance predominantly occur via the kidneys. Studies indicate a progressive increase in maximum plasma concentration levels of dapagliflozin and D3OG with mild, moderate, and severe renal impairment, along with a corresponding decrease in pharmacodynamic effects, leading to reduced efficacy in these patients. Dapagliflozin is indicated for patients with mild renal impairment, but contraindicated in those with moderate to severe impairment (creatinine clearance <60 ml/min or estimated glomerular filtration rate < 60 ml/min/1.73 m2).

Therapeutic use of dapagliflozin in patients with T2DM[1]

Monotherapy

A phase III, double-blind, placebo-controlled study enrolled 282 treatment-naive patients with T2DM (glycosylated hemoglobin HbA1c ⩾7.0% and ⩽10.0%) and randomized them to receive dapagliflozin at doses of 1, 2.5, or 5 mg/day, or placebo for 24 weeks (Table 1). The primary efficacy measure was the change in HbA1c from baseline. Dapagliflozin treatment resulted in a significant decrease in HbA1c (-0.68% with 1 mg, -0.72% with 2.5 mg, -0.82% with 5 mg) compared to placebo (+0.02%, $p < 0.0001$). Similarly, dapagliflozin led to a notable reduction in fasting plasma glucose levels and body weight, significantly more than placebo ($p < 0.02$ and $p < 0.003$, respectively). These substantial benefits of dapagliflozin translated into lower rates of rescue medication addition or discontinuation due to inadequate glycemic control. Overall, adverse effects were comparable across treatment groups.

Table 1. Selected studies showing the effects of dapagliflozin compared with placebo on anthropometric, glycemic and atherosclerosis-related variables.

Study	**Effects***
Dapagliflozin 1 mg *versus* dapagliflozin 2.5 mg *versus* dapagliflozin 5 mg *versus* placebo in treatment naïve patients with T2DM (*n* = 282, duration 24 weeks)	HbA1c (−0.68 *versus* −0.72 *versus* −0.82 *versus* +0.02%, $p < 0.001$), fasting plasma glucose (−10.8 *versus* −21.6 *versus* −28.4 *versus* +4.1 mg/dl, $p < 0.01$), body weight (−2.69 *versus* −2.64 *versus* −2.69 *versus* −0.96 kg, $p < 0.01$)
Dapagliflozin 2.5 mg *versus* dapagliflozin 5 mg *versus* dapagliflozin 10 mg *versus* placebo in treatment naïve patients	HbA1c (−0.58 *versus* −0.77 *versus* −0.89 *versus* −0.23%, $p < 0.001$ for 5 and 10 mg), fasting plasma glucose (−15.2 *versus* −24.1 *versus* −28.8 *versus* −4.1 mg/dl, $p < 0.001$ for 5 and 10 mg), body weight (−3.3 *versus* −2.8 *versus* −3.2 *versus* −2.2 kg, *p* =NS)

with T2DM (*n* = 485, duration 24 weeks)	
Dapagliflozin 5 mg *versus* dapagliflozin 10 mg *versus* placebo in drug-naïve Asian patients with T2DM (*n* = 393, duration 24 weeks)	HbA1c (−1.04 *versus* −1.11 *versus* −0.29%, $p < 0.001$), fasting plasma glucose (−25.1 *versus* −31.6 *versus* +2.5 mg/dl, $p < 0.001$), patients with HbA1c < 7% at week 24 (42.6 *versus* 49.8 *versus* 21.3%, $p < 0.001$), 2 h postprandial glucose (−46.8 *versus* −56.9 *versus* +1.1 mg/dl, $p < 0.001$), body weight (−1.64 *versus* −2.25 *versus* −0.27 kg, $p < 0.001$), patients with >5% reduction in body weight (20.8 *versus* 29.6 *versus* 5.6%; $p < 0.05$), HDL-C (+9.55 *versus* +11.52 *versus* +4.24%, *p* not mentioned), triglycerides (−19.11 *versus* −16.47 *versus* −6.95%, *p* not mentioned), fasting C peptide (−0.36 *versus* −0.40 *versus* +0.03 ng/ml, *p* not mentioned)
Dapagliflozin 10 mg (one of multiple dosage schemes in this study) *versus* metformin 1500 mg/day *versus* placebo (*n* = 389, duration 12 weeks)	HbA1c (−0.85 *versus* −0.83 *versus* −0.18%, $p < 0.001$), fasting plasma glucose (−21 *versus* −18 *versus* −6 mg/dl, $p = 0.002$), systolic blood pressure (−6.4 *versus* −0.4 *versus* +2.4 mmHg, $p = 0.001$), diastolic blood pressure (−2.6 *versus* −0.6 *versus* +0.3, $p = 0.07$), serum creatinine (−0.02 *versus* −0.02 *versus* 0.0 mg/dl, $p = 0.34$), blood urea nitrogen (+2.3 *versus* −0.18 *versus* −0.96 mg/dl, $p < 0.001$), serum sodium (−0.15 *versus* −0.06 *versus* +0.93 mEq/liter, $p = 0.05$), potassium (−0.0 *versus* −0.04 *versus* −0.01 mEq/liter, $p = 0.88$), calcium (−0.12 *versus* −0.09 *versus* −0.10 mg/dl, $p = 0.88$), magnesium (+0.12 *versus* −0.3 *versus* +0.04 mEq/liter, $p = 0.03$), phosphate (+0.12 *versus* −0.08 *versus* +0.08 mg/dl, $p = 0.73$), uric acid (−0.98 *versus* +0.18 *versus* −0.16 mg/dl, $p < 0.001$), hematocrit (+1.95 *versus* −1.12 *versus* −0.08%, $p < 0.001$)
Dapagliflozin 2.5 mg *versus* dapagliflozin 5 mg *versus* dapagliflozin	HbA1c (−0.67 *versus* −0.70 *versus* −0.84 *versus* −0.30%, $p < 0.001$), fasting plasma glucose (−17.8 *versus* −21.4 *versus* −23.4 *versus* −5.9 mg/dl, $p < 0.002$),

10 mg *versus* placebo on top of metformin (*n* = 546, duration 24 weeks)	patients with HbA1c <7.0% at week 24 (33.0 *versus* 37.5 *versus* 40.6 *versus* 25.9%, $p < 0.05$ for 5 and 10 mg), body weight (−2.2 *versus* −3.0 *versus* −2.9 *versus* −0.9 kg, $p < 0.001$)
Dapagliflozin 2.5 mg *versus* dapagliflozin 5 mg *versus* dapagliflozin 10 mg *versus* placebo on top of metformin (*n* = 546, extension for 78 weeks of the above study)	HbA1c (−0.48 *versus* −0.58 *versus*−0.78 *versus* +0.02%, $p < 0.001$), fasting plasma glucose (−19.3 *versus* −26.5 *versus* −24.5 *versus* −10.4 mg/dl, $p < 0.002$ for 5 and 10 mg), percentage of patients with HbA1c < 7% (20.7 *versus* 26.4 *versus* 31.5 *versus* 15.4%, $p < 0.02$ for 5 and 10 mg), body weight (−1.1 *versus* −1.7 *versus* −1.74 *versus* +1.36 kg, $p < 0.001$), uric acid (−0.6 *versus* −0.5 *versus* −0.6 *versus* −0.02 mg/dl, $p < 0.006$), hematocrit (+0.84 *versus* +1.35 *versus* +1.84 *versus* −1.43%, $p < 0.0001$), hemoglobin (+1.5 *versus* +3.1 *versus* +4.1 *versus* −4.9 g/l, $p < 0.0001$), systolic blood pressure (+0.7 *versus* −1.1 *versus* −0.3 *versus* +1.5 mmHg, $p < 0$ .05 for 5 and 10 mg)
Dapagliflozin 10 mg *versus* placebo on top of sitagliptin ± metformin (*n* = 432, duration 24 weeks)	HbA1c (−0.5 *versus* 0.0%, $p < 0.001$), HbA1c in patients with baseline HbA1c ⩾ 8% (−0.8 *versus* 0.0%, $p < 0.001$), body weight (−2.1 *versus* −0.3 kg, $p < 0.001$), fasting plasma glucose (−24.1 *versus* −3.8 mg/dl, $p < 0.001$), hematocrit (+2.2 *versus* −0.5, *p* not mentioned), uric acid (−0.76 *versus* +0.1 mg/dl, *p* not mentioned)
Dapagliflozin 5 mg *versus* dapagliflozin 10 mg *versus* placebo on top of pioglitazone (*n* = 420, duration 24 weeks)	HbA1c (−0.82 *versus* −0.97 *versus* −0.42%, $p < 0.001$), fasting plasma glucose (−24.9 *versus* −29.6 *versus* −5.5 mg/dl, $p < 0.001$), 2 h postprandial glucose (−65.1 *versus* −67.5 *versus* −14.1 mg/dl, $p < 0.001$), body weight (+0.09 *versus* −0.14 *versus* +1.64 kg, $p < 0.001$), uric acid (−0.2 *versus* −0.3 *versus* +0.1 mg/dl, $p =$ NS), sodium (+0.4 *versus* +0.7 *versus* −0.2 mEq/liter, $p =$ NS), parathyroid hormone (+4.6 *versus* +4.2 *versus* +0.4 pg/ml, $p =$ NS)

Dapagliflozin 2.5 mg *versus* dapagliflozin 5 mg *versus* dapagliflozin 10 mg *versus* placebo on top of glimepiride (*n* = 597, duration 24 weeks)	HbA1c (−0.58 *versus* −0.63 *versus* −0.82 *versus* −0.13%, $p < 0.001$), body weight (−1.18 *versus* −1.56 *versus* −2.26 *versus* −0.72 kg, $p < 0.01$ for 5 and 10 mg), systolic blood pressure (−4.7 *versus* −4.0 *versus* −5.0 *versus* −1.2 mmHg, $p < 0.05$), diastolic blood pressure (−1.1 *versus* −1.7 *versus* −2.8 *versus* −1.4 mmHg; p = NS), uric acid (−0.36 *versus* −0.44 *versus* −0.44 *versus* +0.02 mg/dl, *p* not mentioned), triglycerides (−5.25 *versus* −3.99 *versus* −10.56 *versus* +0.29%, $p < 0.05$ for 10 mg)
Dapagliflozin 2.5 mg *versus* dapagliflozin 5 mg *versus* dapagliflozin 10 mg *versus* placebo on top of insulin plus oral antidiabetic drugs (*n* = 804, duration 48 weeks)	HbA1c (−0.79 *versus* −0.96 *versus* −1.01 *versus* −0.47%, $p < 0.001$), body weight (−1.78 *versus* −1.82 *versus* −2.43 *versus* +0.82 kg, $p < 0.001$), uric acid (−0.13 *versus* −0.14 *versus* −0.16 *versus* +0.04 mg/dl, *p* not mentioned), urinary albumin/creatinine ratio (−22.1 *versus* −24.8 *versus* −17.3 *versus* −1.6 mg/g, *p* not mentioned), magnesium (+0.16 *versus* +0.12 *versus* +0.18 *versus* −0.12 mEq/liter, *p* not mentioned)

[*] *p* denotes significance *versus* placebo.

HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; NS, nonsignificant; T2DM, type 2 diabetes mellitus.

Another 24-week, double-blind trial randomized 485 patients with T2DM to placebo or dapagliflozin 2.5, 5 or 10 mg once daily in the morning (main cohort) or evening (exploratory cohort). In the main cohort, mean HbA1C changes from baseline at week 24 were significantly greater with dapagliflozin (−0.58%, −0.77%, −0.89% with 2.5, 5 and 10 mg, respectively) compared with placebo (−0.23%, $p < 0.001$ *versus* 5 and 10 mg). Similar results were observed in the exploratory evening dose cohort. In patients with high HbA1c at enrolment (10.1–12.0%, *n* = 73), dapagliflozin administration induced numerically greater reductions in HbA1C

compared with those observed in patients with lower baseline HbA1c levels (−2.88% with 5 mg and −2.66% with 10 mg).

The effects of the drug on blood pressure were investigated in a randomized, double-blind trial which randomized 75 patients with T2DM for 12 weeks to dapagliflozin 10 mg/day, hydrochlorothiazide 25 mg/day or placebo. The 24 h ambulatory mean systolic blood pressure (SBP) decreased by −3.3 mmHg with dapagliflozin [95% confidence interval (CI) −6.8 to +0.2 mmHg], −6.6 mmHg with hydrochlorothiazide (95% CI −9.9 to −3.2 mmHg) and −0.9 mmHg with placebo (95% CI −4.2 to +2.4 mmHg) (all values are adjusted for baseline SBP). The greater effect of dapagliflozin compared with placebo was observed during daytime SBP but not during night-time SBP. Dapagliflozin also resulted in a greater decrease in in-office SBP by −12.3 mmHg (95% CI −17.8 to −6.8 mmHg) compared with hydrochlorothiazide [−1.1 mmHg (95% CI −2.2 to 0.0 mmHg)] or placebo [−0.1 mmHg (95% CI −10.8 to +0.6 mmHg)]. The effects of dapagliflozin or hydrochlorothiazide were independent from concurrent antihypertensive drug use. In a substudy of 30 patients, dapagliflozin treatment resulted in a reduction in plasma volume by −7.3% [median (interquartile range) −12.4% to −4.8%] compared with hydrochlorothiazide [+2.8% (−10.6% to +25.7%)] or placebo [+5.2% (−2.5 to +8.7)]. Dapagliflozin treatment resulted in a greater decrease in glomerular filtration rate [−10.8% (95% CI −14.6% to −6.7%)] compared with hydrochlorothiazide [−3.4% (−7.3% to +0.6%)] or placebo [−2.9% (−6.9% to +1.2%)].

Addition to DPP-4 inhibitors

In a 24-week, double-blind trial with a 24-week blinded extension period, 432 patients with T2DM receiving sitagliptin (100 mg/day) with or without metformin (⩾1500 mg/day) were randomized to dapagliflozin 10 mg/day or placebo (). The administration of dapagliflozin resulted in a significant reduction in HbA1c levels (−0.5%) and body weight (−1.8 kg) compared with placebo, independently of the background treatment. These results were maintained throughout the extension period. During the trial, patients receiving dapagliflozin experienced signs and symptoms suggestive of genital infection more frequently (9.8% *versus* 0.4%), but not of urinary tract infection (6.7% *versus* 6.2%), compared with placebo.

Benefits of dapagliflozin[2]

Dapagliflozin has proved to be an effective therapeutic agent improving glycemic control in a diverse range of people with T2DM. It is effective when used as monotherapy, and in combination with metformin, glimepiride, pioglitazone, sitagliptin and insulin. Additionally, dapagliflozin acts independently of insulin secretion or action and is thus unlikely to cause hypoglycemia.

Although not fully understood, SGLT2 inhibition caused by dapagliflozin sequentially corrects and effects multiple metabolic and hemodynamic risk factors particularly associated with diabetes and CVD. In addition to plasma glucose reduction, glucosuria produces a negative energy balance and in combination with fluid loss secondary to osmotic diuresis contributes to weight reduction. Previous studies have shown a total bodyweight loss of over 2 kg in 24 weeks following a combination of dapagliflozin 10 mg and metformin. It also promotes urinary excretion of sodium, which in turn reduces plasma volume and blood pressure. Systolic blood pressure has been reduced by 3–5 mmHg compared with placebo in those taking dapagliflozin 10 mg. Dapagliflozin is also associated with lowering of uric acid levels and albuminuria.

Clinical efficacy of SGLT2i[2]

Following the controversy surrounding rosiglitazone over a decade ago, the Centre for Drug Evaluation and Research at the FDA in the USA published guidance mandating any new glucose-lowering drugs intended for the treatment of Type 2 diabetes to rule out a statistically significant unacceptable increase in CV risk. Prespecified primary composite end point outcomes required for evaluation of CV risk included CV mortality, nonfatal MI and nonfatal stroke. This is known as the classic three-point Major Adverse Cardiovascular Events (MACE). Often other end points are included under the umbrella term of MACE including hospitalization for HF, unstable angina and overall mortality. More recent trials use the three-point MACE system, particularly as different end points and heterogeneity among trials makes comparison of similar studies difficult and superiority is difficult to ascertain. Since the release of FDA guidance in 2008, multiple large-scale CV outcome trials have provided new insights into how the disease process can be modified by some treatment approaches, causing a dramatic shift in therapeutic approach in T2DM from a focus on reducing HbA1c to recognition of the importance of reducing CV risk.

Unlike many earlier glucose-lowering drugs, the associations of cardiometabolic and hemodynamic advantageous characteristics of SGLT2 inhibitor treatment, alongside supporting evidence raised the hypothesis that they would reduce the CV risk in T2DM independently of their glucose-lowering effects. This meant that while fulfilling the requirements set out by the FDA, some of the CV outcomes trials with SGLT2i were powered for superiority as well as noninferiority with placebo. Prior to the results of the Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58 trial (DECLARE-TIMI 58), the Phase II and III trials with dapagliflozin, collected information on CV events. In a meta-analysis investigating CV outcomes from these studies, there was no suggestion of increased risk for major adverse CV events; furthermore, there was evidence of potential CV benefit, particularly reduction in hospitalization for HF and a decreased incidence of MI and other MACE events in patients with pre-existing CVD.

While the DECLARE-TIMI 58 trial was ongoing, two other SGLT2i CV outcome trials were published, with empagliflozin (the EMPA-REG OUTCOME trial) and canagliflozin (the CANVAS trials), respectively. EMPA-REG OUTCOME included 7020 patients with T2DM and established CVD, randomized to 10 or 25 mg of empagliflozin or placebo and followed for a median time of approximately 3 years. There was a 14% relative risk reduction (RRR) of the three-point MACE primary outcome in patients on empagliflozin therapy versus placebo (hazard ratio [HR]: 0.86; 95% CI: 0.74–0.99; p = 0.04 for superiority). Considerable benefit was seen in the empagliflozin group with respect to CV mortality (38% RRR), any-cause death (32% RRR) and hospitalization secondary to HF (35% RRR). No statistically significant differences were seen with rates of MI or stroke. The CANVAS trials included 10,142 patients with T2DM. Unlike EMPA-REG OUTCOME, 65.6% of participants had established CVD and the remainder were at high risk of CVD with multiple risk factors. Canagliflozin reduced the three-point MACE primary outcome by 14% (HR: 0.86; 95% CI: 0.75–0.97; p = 0.02 for superiority). It also observed a 33% RRR in HF-associated hospitalization. No statistically significant reduction in CV-related mortality was seen. In both trials, the efficacy of three-point MACE outcomes was more apparent in patients with pre-existing CVD. On the other hand, further subanalysis of the trials confirmed the reduction of HF hospitalization was beneficial among a wide range of patients including those without established CVD.

CV outcomes with dapagliflozin in the DECLARE-TIMI 58 trial[2]

DECLARE-TIMI 58 was a multicenter, randomized, double-blind, placebo-controlled, Phase III trial designed to evaluate the effect of dapagliflozin 10 mg once daily on CV outcomes in patients with T2DM with either established atherosclerotic CVD or with risk factors. The trial was originally designed with the primary hypothesis that dapagliflozin does not increase incidence of MACE and will reduce the incidence of CV events. As described previously, published data from the EMPA-REG study revealed significant benefit with regard to RRR of hospitalization secondary to HF- and CV-related death. In response, the primary outcome was amended to include hospitalization due to HF and CV death and thus there were two coprimary end points; MACE and the composite of hospitalization for HF and CV death. Secondary outcome measures included time to all-cause mortality and time to first event of renal composite end point (confirmed sustained ≥40% decrease in estimated glomerular filtration rate [eGFR] to eGFR < 60 ml/min/1.73 m^2 and/or ESRD and/or renal or CV death) within a time frame of up to 6 years. From 2013 to 2018 (median of 4.2 years), 17,160 participants with T2DM and either established CVD (n = 6974) or multiple risk factors (n = 10,186) were studied. Patients treated with dapagliflozin achieved better glucose control during the trial (0.42%; 95% CI: 0.40–0.45) versus placebo, but the differences tended to attenuate over time. A placebo-subtracted weight reduction of 1.8 kg was seen in those on dapagliflozin and placebo-subtracted systolic and diastolic blood pressure reduction of 2.7 and 0.7 mmHg, respectively.

Although dapagliflozin was noninferior for MACE events, there was no statistically significant reduction (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR: 0.93; 95% CI: 0.84–1.03; p = 0.17). However, among patients with established CVD the rate of MACE was lower in the dapagliflozin group (13.9%) compared with placebo (15.3%); which is of interest although not statistically significant. The same benefit was not seen in those without established CVD.

For the other coprimary end point, patients treated with dapagliflozin had a lower rate of the composite outcome of CV mortality and hospitalization for HF (HR: 0.83; 95% CI: 0.73–0.95; p = 0.005). This was largely driven by the reduction in hospitalization for HF (HR: 0.73; 95% CI: 0.61–0.88), with a RRR of 17 and 27%, respectively, which was consistent across an extensive range of patients irrespective of a history of atherosclerotic disease or HF, whereas the reduction in CV death was not significant.

A prespecified subgroup analysis of DECLARE specifically focused on patients within the trial with a history of MI (n = 3584). Due to their high baseline risk, it was hypothesized that this secific group would gain an even greater benefit from dapagliflozin therapy. In patients with prior MI, there was a 16% RRR and 2.6% absolute risk reduction of MACE, whereas no significant risk reduction was noted in those without a history of MI including those with established CVD. There was also a 19% RRR of CV death and a 15% RRR of hospitalization for HF in those with a prior MI.

Another subanalysis of DECLARE explored the effect of dapagliflozin on HF and mortality, found that HF was reduced in patients with T2DM with or without HF and reduced ejection fraction and reduced CV mortality in those with T2DM with HF and reduced ejection fraction

Renal & other outcomes in DECLARE-TIMI 58[2]

In a prespecified secondary analysis, the incidence of cardiorenal events, defined as a sustained decline of at least 40% in eGFR to less than 60 ml/min per 1.73 m^2, end-stage renal disease or death from renal or CV causes was 4.3% in those taking dapagliflozin and 5.6% in those taking placebo (HR: 0.76; 95% CI: 0.67–0.87). Excluding CV death, the HR for the renal composite outcome was 0.53; 95% CI: 0·43–0·66; this lower rate of renal disease progression was consistent among those with and without established CVD, HF and or chronic kidney disease.

In previous trials of SGLT2i, there have been conflicting data reports of some infrequent adverse events, notably amputations, bladder cancer, fractures and severe genital and urinary tract infections, making it difficult to ascertain genuine conclusions. The DECLARE trial specifically reported these events including incidence of amputations, fractures, stroke, severe genital and urinary tract infections, diabetic ketoacidosis (DKA) and bladder cancer. Compared with placebo, rates of major hypoglycemia, acute kidney injury and bladder cancer were lower with dapagliflozin and no statistical difference was found between the two groups in the incidence of amputations, fractures, stroke, volume depletion or hypersensitivity. Higher rates of DKA were seen in patients on dapagliflozin (0.3 vs 0.1%; p = 0.02) of which more than 80% were using insulin at baseline. Genital infections that led to discontinuation of dapagliflozin or thought to be serious adverse events in both male and female patients were seen more frequently with dapagliflozin treatment (0.9 vs 0.1%; HR: 8.36; 95% CI: 4.19–16.68; p < 0.001), albeit serious adverse events were rare with only two events occurring in each group.

Out of the six reported cases of Fournier's gangrene, only one was within the dapagliflozin group.

New evidence on dapagliflozin in HF: the DAPA-HF trial[2]

During the European Society of Cardiology (ESC) Congress in September 2019, the results of the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction Trial (DAPA-HF) were presented for the first time and results subsequently published. DAPA-HF was a randomized, placebo-controlled Phase III trial lasting a median of 18.2 months involving 4744 patients with New York Heart Association (NYHA) class II, III or IV HF and an ejection fraction of 40% or less. Prior to the completion of the trial, most evidence surrounding dapagliflozin and HF reduction was obtained from populations who for the large part did not have HF at baseline. The trial, completed across 410 centers in 20 countries, was thus designed to measure the efficacy and safety of dapagliflozin in subjects with pre-existing HF with reduced ejection fraction irrespective of a diagnosis of T2DM.

Assigned treatment of dapagliflozin 10 mg once daily or placebo was given in conjunction with recognized standard drug therapy for HF including angiotensin-converting enzyme inhibitor, angiotensin receptor blocker or sacubitril/valsartan; and a β-blocker (unless contraindicated or not tolerated); as well as a mineralocorticoid receptor antagonist, if indicated. Patients requiring standard HF device therapy such as an implantable cardioverter defibrillator (26%) and/or cardiac resynchronization therapy (8%) were also included.

The primary outcome included a composite of CV death or worsening HF defined as hospitalization or an urgent visit resulting in intravenous therapy for HF. Secondary outcomes included a composite of hospitalization for HF or CV death, total number of hospitalizations for HF, CV death, a composite of worsening renal function and death from any cause.

The primary composite outcome (worsening HF or death from CV causes) favorably with dapagliflozin, occurring in 16.3% of dapagliflozin patients compared with 21.2% of placebo patients (HR: 0.74; 95% CI: 0.65–0.85; $p < 0.001$). It was recorded within the trial duration that 21 patients would need to be treated with dapagliflozin to prevent one primary event.

A first event of worsening HF was seen in 10% of patients on dapagliflozin versus 13.7% of patients on placebo (HR: 0.70; 95% CI: 0.59–0.83). Less than 10% of dapagliflozin patients were hospitalized for HF compared with over 13% of placebo patients. Death from CVD occurred in 9.6% of the dapagliflozin group compared with 11.5% of the placebo group, while death from any cause occurred in 11.6 and 13.9%, respectively. Incidence for secondary outcomes of hospitalization for HF- or CV-related death was lower in those taking dapagliflozin. Between the treatment groups, no difference was seen in renal composite outcomes.

Initially, 42% of all patients had T2DM, with a new diagnosis of T2DM later being made in around 3% of patients in each cohort. Notably, primary outcomes were consistent among patients with and without diabetes. NYHA classes III and IV seemed to benefit less compared with NYHA class II.

No statistically significant side effects were observed, and adverse events rarely required the discontinuation of treatment.

Impact of dapagliflozin[2]

Although dapagliflozin did not result in three-point MACE reduction across the general population, it did suggest modest benefit in those who had pre-existing CVD. Importantly, dapagliflozin did produce superior outcomes to placebo in prevention of HF hospitalization and improved renal outcomes among a broad range of patients with T2DM, irrespective of prior CVD, HF or renal disease. Moreover, most of the patients did not have a known history of HF, so the prevention of new clinical HF is notable. Additional benefits of dapagliflozin therapy as validated by DECLARE included lowering plasma glucose, blood pressure reduction and weight loss. Notably, all of which positively contribute to the metabolic syndrome and pathophysiological processes related to complications and CV events.

More recently, the results of DAPA-HF, which shows a reduction for risk of worsening HF and CVD, present a clear benefit of dapagliflozin therapy in patients with HF and reduced ejection fraction irrespective of the presence or absence of diabetes. The effectiveness of dapagliflozin in patients with and without diabetes supports the idea that it has benefits beyond those directly related to glucose lowering.

Dapagliflozin and other drugs of the class have more notable dominance in impacting HF and renal disease due to their action on the kidneys. This is also true for many features of the metabolic syndrome by which dapagliflozin and other SGLT2i impact. The chain of events grossly simplified relates to glycosuria and natriuresis. Whereby downstream effects involving natriuresis lower blood pressure and plasma volume, which in turn reduces arterial stiffness and reduces myocardial stretch. Natriuresis also increases tubuloglomerular feedback, causing afferent arteriole constriction, which then triggers a reduction in intraglomerular hypertension and hyperfiltration. The impact of glycosuria on the other hand includes weight loss through negative energy balance, which also impacts blood pressure. Weight loss also contributes to a reduction in epicardial fat, helping to increase cardiac contractility and reduce inflammation and fibrosis. The modest reduction in plasma uric acid may also impact atherosclerosis risk. Glycosuria also reduces HbA1c, the core purpose of treatment which as already known reduces atherosclerosis, inflammation and glucose toxicity. The collective features together create a unique cardiac and renal protective system.

Current guidance for Dapagliflozin[2]

Dapagliflozin was formally approved by the EMA for use in the European Union in 2012, followed by the US FDA in 2014. Known by its brand names Farxiga (the USA) and Forxiga (EU), it is licensed as 5 or 10 mg doses for the use in adults with T2DM to improve glycemic control in conjunction with diet and exercise. Dapagliflozin 10 mg is contraindicated for the use in patients with Type-1 diabetes due to risk of hypoglycemia and DKA as per FDA and EMA guidance. However, based on emerging research, EMA has approved the use of dapagliflozin 5 mg for the treatment of uncontrolled Type-1 diabetes despite optimal insulin therapy and a BMI $\geq$27 kg/m^2 to be used in conjunction with insulin and appropriate guidance and risk awareness. As mentioned, most common side effects include urinary tract and genital mycotic infections with a specific warning and awareness against less likely but possible DKA.

Currently, the management of T2DM UK guidance published by the National Institute of Clinical Excellence has not incorporated the most recent evidence of the use of dapagliflozin or other SGLT2i in the realm of CV risk protection, but an update is planned for 2020. However, as data have been released from SGLT2i trials and related research over the years, their benefits in reducing major CV events in patients with pre-existing CVD have been increasingly recognized internationally. In 2016, European guidelines for CVD prevention

were revised to include consideration of early SGLT2i use in the course of diabetes management in those with established CVD. Last year, the American Diabetes Association and the European Association for the Study of Diabetes released a consensus statement on management of hyperglycemia in T2DM. The report recommends using a SGLT2i in patients with pre-existing CVD irrespective of glucose control due to the benefits of MACE reduction. Following the findings from DECLARE of a reduction in progression of chronic kidney disease, the American Diabetes Association and FDA, respectively, updated its position statement and drug label, lowering the eGFR threshold to 45 from 60 ml/min/1.73 m^2 in an attempt to provide safe beneficial outcome to a wider patient group. In addition, the DECLARE subanalysis mentioned earlier that focuses on patients with previous history of MI adds to current recommendations encouraging that patients with T2DM and previous MI be considered for SGLT2i to reduce CV risk.

Despite DECLARE evidently demonstrating reduction of hospitalization for HF regardless of previous CV history, the present guidelines have largely focused on initiating treatment in those established CVD. The data suggest that dapagliflozin could also be considered in patients with T2DM without pre-existing CVD or HF. However, in August 2019, the ESC-released guidelines in collaboration with the European Association for the Study of Diabetes recommending the use of dapagliflozin or other SGLT2i in those with T2DM and CV or in those with T2DM who are at high risk of CV or HF. Following this and based on the results from DECLARE in October 2019, the FDA approved dapagliflozin in reducing risk of HF-associated hospitalization in adults with T2DM and multiple CV risk factors or pre-existing CVD.

In 2019, a systematic review by Zelniker et al. compared the effects of GLP-1 RA and SGLT2i for prevention of major adverse CV events and renal outcomes in T2DM. The study concluded that in trials which had been reported to date, similar reduction of MACE was achieved in both groups in patients with established CVD. However, SGLT2i have a higher impact in preventing hospitalization for HF and progression of kidney disease. Renoprotection was also confirmed in the recent CREDENCE trial, which compared the renal outcomes of patients with T2DM and albuminuric chronic kidney disease taking 100 mg of canagliflozin versus placebo.

The latest DAPA HF data suggest that dapagliflozin could be used as an adjunct to standard HF therapy in those with HF and a reduced ejection fraction (±T2DM) and should be considered in future HF guidance.

Sitagliptin[3]

The ever-increasing burden of type 2 diabetes mellitus (T2DM) and inadequate control in the majority of patients has led to a quest for newer therapeutic options. There have been recent exciting advances in the treatment of T2DM, targeting the enteroinsular axis with incretin-based therapies that include the dipeptidyl peptidase IV (DPP-IV) inhibitors. Sitagliptin (MK-0431 [(2R)-4-oxo-4-(3-[trifluoromethyl]-5,6-dihydro[1,2,4]triazolo[4,3-a]-pyrazin-7[8H]-yl)-1-(2,4,5-trifluorophenyl) butan-2-amine]) is an orally active, potent and selective inhibitor of DPP-IV.

Pharmacokinetics and pharmacodynamics[3]

Plasma sitagliptin is well absorbed, with an oral bioavailability of about 87%. The administration of food before dosing showed no significant difference in peak drug levels. Area under the plasma time--concentration curve (AUC) increased dose proportionally over the dose range studied (1.5 -- 600 mg). The half-life for sitagliptin is ~ 8 -- 14 h. Median time to maximal concentration in plasma values (Tmax) across doses ranged from 1 to 6 h. A trend towards a shorter Tmax was noted with increasing sitagliptin dose. Sitagliptin is predominantly cleared by the kidney, with ~ 80 -- 87% of the drug excreted unchanged in urine. Sitagliptin is probably actively secreted since the renal clearance of sitagliptin is 388 ml/min, much higher than the normal glomerular filtration rate. Approximately 2.3-, 3.8- and 4.5-fold exposure was demonstrated in patients with moderate (creatinine clearance (CrCl) 30 -- 49 ml/min) and severe (CrCl < 30 ml/min) renal insufficiency and end-stage renal disease (ESRD) on dialysis respectively. Dose adjustment of 50 mg daily in patients with moderate renal insufficiency and 25 mg daily in those with severe renal dysfunction or ESRD has been recommended.

About 16% of the drug is metabolized by the liver. A study looking at the pharmacokinetics of sitagliptin in moderate hepatic dysfunction (Child--Pugh's scores ranging from 7 to 9) compared with healthy control subjects found that the mean AUC and Cmax for sitagliptin were numerically, but not significantly, higher in patients with moderate hepatic insufficiency compared with healthy matched control subjects. There was no statistically significant effect on the Tmax, half-life or fraction of the oral dose excreted into urine and renal clearance of sitagliptin. Sitagliptin was well tolerated in this patient population.

Sitagliptin is not a substrate, inducer or inhibitor for cytochrome P450. Age, sex and obesity did not impact the pharmacokinetics of sitagliptin in healthy subjects. Phase I studies in normoglycemic volunteers and patients with diabetes provided proof of predicted pharmacologic characteristics for sitagliptin in humans. Near-maximal glucose-lowering efficacy after single oral doses of sitagliptin was associated with inhibition of plasma DPP-IV activity of ‡ 80%, which occurred at plasma sitagliptin concentrations of ‡ 100 nmol and an augmentation of active GLP-1 and GIP levels of twofold or higher. When the assay is corrected for plasma dilution, the level of DPP-IV inhibition is estimated to be ~ 96%. This degree of DPP-IV inhibition occurred at doses of ‡ 100 mg over a 24-h period, supporting the use of a 100-mg once-daily dosing regimen.

Clinical efficacy[3]

Phase II studies

The safety and efficacy of different doses of sitagliptin were compared with placebo in randomized controlled trials and are summarized in Table 1.

Table 1. Phase II trials.

Study	Baseline therapy	Intervention	Duration (weeks)	n	Average baseline A1c (%)	A1c change (%) compared to placebo	Weight change compared to placebo
Scott, 2007 [56]	Diet and exercise	Sitagliptin 5 – 50 mg b.i.d. Glipizide 5 – 20 mg/day Placebo	12	743	7.9	-0.38 (5 mg) to 0.77 (50 mg b.i.d.) -1 (glipizide)	No significant change (sitagliptin) +1.3 kg (glipizide)
Hanefeld, 2007 [57]	No treatment or drug washout	Sitagliptin 25, 50, 100 mg/day Sitagliptin 50 mg b.i.d. Placebo	12	555	7.7	-0.39 (25 mg) to -0.56% (100 mg)	No significant change
Nonaka, 2008 [58]	Diet and exercise; drug washout	Sitagliptin 100 mg/day Placebo	12	151	7.6	-1.06	-0.7 kg

Phase III studies

Sitagliptin has been evaluated in a number of trials as monotherapy and combination therapy.

In a 24-week, randomized, double-blind study, 1091 drug-naive patients with a mean baseline HbA1c of 8.8% on diet and exercise were randomized to sitagliptin 100 (S100), metformin 1000 or 2000 mg (M1000/M2000), metformin in combination with sitagliptin, or placebo. The

placebo-subtracted HbA1c change from baseline was -2.07% (S100/M2000), -1.57% (S100/M1000), -1.30% (M2000), -0.99% (M1000) and -0.83% (S100). The incidence of gastrointestinal adverse experiences as well as amount of weight loss for combination therapy was similar to that with metformin monotherapy at the same dose. There was additive glycemic improvement with the combination therapy with no increase in the adverse events.

Migoya et al. demonstrated that metformin increases total GLP-1 plasma concentrations, possibly by enhancing GLP-1 secretion from enteroendocrine L-cells, while sitagliptin inhibits the degradation of active GLP-1. Thus, the combination of a DPP-IV inhibitor and metformin results in additive increases in active GLP-1 concentrations.

Long-term safety and efficacy of adding sitagliptin or glipizide to ongoing metformin therapy were established in a study with 1072 patients who were randomized to receive sitagliptin or glipizide. After 2 years, the change in HbA1c from baseline of 7.3% was -0.54% with sitagliptin (n = 248) and -0.51% with glipizide (n = 256). The rise in HbA1c from week 24 to week 104 (coefficient of durability; COD) was smaller with sitagliptin (COD (95% CI) 0.16%/year) compared with glipizide (0.26%/year).

A 26-week parallel-group, open-label trial involving patients with T2DM on metformin (‡ 1500 mg daily for ‡ 3 months) with HbA1c between 7.5 and 10.0% evaluated the efficacy of liraglutide and sitagliptin. Change in HbA1c was -1.50% and -1.24% with 1.8-mg and 1.2-mg doses of liraglutide respectively, compared with -0.90% with sitagliptin. Nausea was more common with liraglutide (27% patients on 1.8 mg and 21% on 1.2 mg) than with sitagliptin (5%). There was no difference in the incidence of hypoglycemia between the groups.

In a double-blind, cross over, randomized study with exenatide and sitagliptin in metformin-treated patients, reduction in fasting glucose was similar in the two groups (-15 +/- 4 mg/dL vs. -19 +/- 4 mg/dL) while 2-h postprandial was lower with exenatide compared to sitagliptin (133 +/- 6 mg/dL vs. 208 +/- 6 mg/dL). Exenatide significantly improved the insulinogenic index of insulin secretion, reduced postprandial triglycerides, slowed gastric emptying and reduced total caloric intake compared to sitagliptin. The incidence of nausea and vomiting in the sitagliptin group was 12% and 3% compared to 34% and 24% in the exenatide group.

In a 26-week randomized, double-blind, double-dummy superiority trial in patients treated with metformin, treatment with exenatide once weekly achieved HbA1c reduction of -1.5% from mean baseline of 8.5, compared to -0.9% for sitagliptin and -1.2% for pioglitazone. Change from baseline weight was -2.3 kg with exenatide, -0.8 kg with sitagliptin and +2.8 kg with

pioglitazone. Significant hypoglycemia was not reported in any of the groups. Nausea and diarrhea were the most common side effects, with a greater number reported for exenatide (24 and 18%) compared with sitagliptin (10 and 10%).

The superior glucose lowering with the GLP-1 receptor agonists is believed to be due to the pharmacologically high levels of receptor agonism achieved, with concentrations six- to tenfold that of physiological GLP-1 in addition to slowed gastric emptying. DPP-IV inhibitors, by contrast, achieve a more modest twofold augmentation of GLP-1 levels with sitagliptin and do not significantly impact gastric emptying.

Postmarketing surveillance (Phase IV) studies of interest

Fadini et al. looked at the effect of sitagliptin in modulating endothelial progenitor cell (EPC) levels in patients with T2DM in a controlled, nonrandomized clinical trial. Stromalderived factor-1-alpha (SDF-1a) is a substrate of DPP-IV. Vasculoprotective endothelial progenitor cells (EPCs) are regulated by SDF-1a, which is reduced in T2DM. Patients on metformin and/or secretagogues who received sitagliptin (n = 16) were compared with 16 patients who received no additional treatment. At baseline, there was no difference between the two groups. After 4 weeks, patients receiving sitagliptin showed a significant increase in EPCs and SDF-1a and a decrease in monocyte chemoattractant protein-1. It was speculated that this effect of DPP-IV inhibition may potentially have favorable cardiovascular implications.

Other ongoing studies that are of considerable clinical interest include those looking at the utility of sitagliptin in adult patients with type 1 diabetes and its potential use in the treatment of reactive hypoglycemia secondary to hyperinsulinism.

Safety and tolerability[3]

Drug interactions

Sitagliptin is free from major drug interactions. Pharmacokinetics and pharmacodynamics were not meaningfully altered following coadministration of multiple-dose sitagliptin and single-dose warfarin, indicating that no dosage adjustment for warfarin is necessary when coadministered with sitagliptin.

The administration of sitagliptin did not alter the pharmoacokinetics of glyburide in an open-label, randomized, two-period, crossover study involving eight healthy subjects. However, dose reduction is recommended because of the increased potential for hypoglycemia with the combination of glyburide and sitagliptin. When digoxin 0.25 mg was coadministered with sitagliptin 100 mg for 10 days, an 11% increase in AUC and an 18% increase in C_{max} were noted. This was felt to be not significant enough to warrant dose adjustment. However, close monitoring of digoxin levels is recommended.

There have been case reports about interaction of rhabdomyolysis associated with the use of DPP-IV inhibitors with statins. In one of the case reports, the use of amiodarone may have been a confounding factor. A study that evaluated the effect of sitagliptin on the pharmacokinetics of simvastatin did not show an interaction.

The coadministration of sitagliptin 200 mg/day with an oral contraceptive for 21 days did not lead to significant alterations in the AUC(0 -- 24 h) or C_{max} of 17 α-ethinyl estradiol and norethindrone in a randomized, placebo-controlled, two-period, crossover study in 18 healthy female patients. Coadministration of a single oral dose of cyclosporine with a single dose of sitagliptin modestly increased maximal plasma concentration of sitagliptin without a meaningful effect on overall exposure. No dosage adjustment has been recommended by the manufacturer.

Experiments in transfected CHO-1 cells demonstrated that the transport of sitagliptin in the kidney was mediated by human organic anion transporter 3 (hOAT 3), organic anion transporting polypeptide 4C1 (OATP4C1) and multidrug resistance P-glycoprotein (Pgp). Inhibitors of hOAT 3 such as probenecid, ibuprofen and fenofibrate inhibited sitagliptin uptake. However, this is probably of no clinical relevance since, even if the active renal secretion were to be completely blocked, the increase in the plasma concentration of sitagliptin would not be more than twofold. Sitagliptin is known to have a large therapeutic window with large clinical trials showing 200 mg daily to be well tolerated.

Adverse events

Adverse events that occurred in a greater frequency in the sitagliptin group compared with controls in clinical trials are nasopharyngitis (5.2 vs 3.3%), upper respiratory infection (6.3 vs 3.4%) and headache (5.1 vs 3.9%). Risk of hypoglycemia is minimal with monotherapy. As

might be expected, the risk of hypoglycemia does not increase when combined with metformin or pioglitazone, but is increased with glimepiride and insulin. An increase in neutrophils of ~ 200 cells/µl versus placebo, with a mean baseline white blood cell count of ~ 6600 cells/µl noted in four pooled placebo-controlled clinical studies, is not considered to be clinically relevant. Postmarketing reports have identified hypersensitivity reactions and pancreatitis. However, there was no suggestion of increased risk of pancreatitis in clinical trials. In a pooled analysis of 19 randomized, double-blind clinical trials that included data from 10 246 patients, the incidence of acute pancreatitis was 0.10/100 patient-years in the placebo group and 0.08/100 patient-years in the sitagliptin group. Therefore, it is likely that sitagliptin does not play a causal role in the reported instances of pancreatitis.

DPP-IV inhibitors are thought to increase the risk of angioedema in patients treated with angiotensin converting enzyme (ACE) inhibitors. A recent study indicated that vildagliptin use may be associated with increased risk of angioedema among patients taking ACE inhibitors. ACE normally inactivates substance P, which is thought to be a mediator of angioedema. Substance P is also a substrate for DPP-IV. Thus, when ACE is inhibited, the concern is that degradation of substance P becomes more dependent on DPP-IV activity. However, neutral endopeptidase (NEP) also inactivates substance P. A randomized, double-blind, crossover pilot study in six volunteers assessed the effect of a single dose of sitagliptin compared with placebo on substance-P-induced skin inflammation. There was no difference between the skin responses to substance P when sitagliptin was administered compared with placebo, suggesting that proteolytic cleavage of substance P by ACE and NEP compensate for the blockade of DPP-IV to prevent an augmentation of its proinflammatory action. There is a case report of angioedema associated with the use of sitagliptin in conjunction with an angiotensin receptor blocker (ARB) with recurrence when the patient was rechallenged with sitagliptin. This is postulated to be mediated by bradykinin, which again is degraded by DPP-IV.

The aforementioned pooled analysis of data from 10,246 patients from double-blind, randomized studies that included patients treated with sitagliptin 100 mg/day up to 2 years showed no significant difference in the incidence rates of angioedema. (0.06 and 0.08 per 100 patient-years while on an ACE inhibitor and 0.03 and 0.04 while not on an ACE inhibitor in the sitagliptin and non-exposed groups, respectively).

There have been recent postmarketing reports of worsening renal function with the use of sitagliptin, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal insufficiency, some of whom were prescribed inappropriate doses of sitagliptin. In these patients, a return to baseline levels of renal insufficiency was observed with supportive treatment and discontinuation of potentially causative agents. The package insert has been revised by the manufacturer and recommends assessment of renal function prior to starting sitagliptin and periodically thereafter, and emphasizes dose adjustment for the degree of renal impairment. Clinical trials have not demonstrated increased risk of renal failure.

Combination of SGLT2 inhibitor and DPP-4 inhibitor[4]

Combination therapy is recommended after failure of metformin monotherapy for the management of hyperglycaemia in type 2 diabetes (T2D). Various pharmacological approaches may be added to metformin as dual therapies or combined together as triple therapies, including sodiumglucose cotransporter type 2 inhibitors (SGLT2I) and dipeptidyl peptidase inhibitors (DPP-4Is).

SGLT2Is (also known as gliflozins), which target the kidney and promote glucosuria, belong to the newest pharmacological class of glucose-lowering agents. In T2D patients with a history of cardiovascular disease, the demonstration of a remarkable reduction in cardiovascular and renal events with empagliflozin in the EMPA REG OUTCOME trial raised huge interest among the medical community; however, the underlying mechanisms of protection of empagliflozin remain unknown and controversial. SGLT2Is, by specifically targeting the kidney, inhibit glucose reabsorption at the proximal tubule and thereby promote glucosuria, an effect independent of insulin. By reducing hyperglycaemia, SGLT2Is dampen glucotoxicity, which indirectly results in an improvement of both b-cell function and peripheral insulin sensitivity. However, treatment with SGLT2Is resulted in an increase in plasma glucagon concentrations, which was accompanied by a substantial increase in endogenous (hepatic) glucose production. Increased glucagon secretion has also been implicated in the occurrence of euglycaemic ketoacidosis episodes reported with SGLT2Is. Thus, the addition of a DPP-4I, which inhibits glucagon and stimulates insulin secretion, may have the potential to block the increase in endogenous glucose production and thereby enhance the glucose-lowering ability of SGLT2I while reducing the risk of ketoacidosis, although this remains to be proven. Beyond a glucose-lowering effect, SGLT2Is 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. In the EMPA-REG OUTCOME trial, empagliflozin was associated not only with a remarkable reduction in cardiovascular and all-cause mortality in T2D patients with antecedents of cardiovascular disease but also with a marked reduction in the incidence rate of hospitalization for heart failure. Because of their specific mode of action, some limitations exist in using SGLT2I in patients with renal impairment.

DPP-4Is (also known as gliptins) are increasingly used in the management of T2D as an alternative or add-on therapy to other glucose-lowering agents. As oral incretin-based therapy, they offer an excellent safety profile, with no increased risk of hypoglycaemia, weight gain and cardiovascular events when compared with placebo. DPP-4Is 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. Of major interest, DPP-4Is stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, thus reducing hyperglycaemia while minimizing hypoglycaemia. Furthermore, they do not induce weight gain and have proven their cardiovascular safety in several large, prospective, cardiovascular outcome studies. A higher rate of hospitalization for heart failure with the DPP-4I saxagliptin was reported in the SAVOR-TIMI 53 trial. Because this adverse event was not observed with Sitagliptin in the TECOS trial, it remains controversial whether it is specific to saxagliptin, whether it is only a chance effect, or whether it might be a class effect. Moreover, because of the marked reduction in the rate of hospitalization for heart failure with empagliflozin in the EMPA-REG OUTCOME trial, one may speculate that adding an SGLT2I to a DPP-4I would be of potential interest with regard to the risk of heart failure in patients with T2D. DPP-4Is keep good efficacy, together with a favourable safety profile, in patients with renal impairment, although the dose should be reduced according to the glomerular filtration rate (for most of the DPP-4Is, except for linagliptin, which is not excreted in the urine) in order to maintain similar total exposure as in subjects with normal renal function They may be used in patients with mild to moderate hepatic impairment but are contraindicated in patients with severe hepatic failure. Detailed pharmacokinetic characteristics of available DPP-4Is have been reported in two previous papers.

DPP-4Is and SGLT2Is exert their glucose-lowering effects via different and complementary mechanisms. When one single pharmacological class does not reach the glycated haemoglobin (HbA1c) target as monotherapy, or even when added to metformin, a combination of a DPP-4I and an SGLT2I could be helpful in the management of patients with T2D. Fixed-dose combinations (FDCs) have recently been commercialized, which should facilitate therapy and improve compliance of patients with T2D.

Dapagliflozin plus Sitagliptin[4]

Pharmacokinetics

The study by Kasichayanula et al. assessed the potential for pharmacokinetic DDIs between Dapagliflozin and different glucose-lowering agents, including Sitagliptin, in healthy subjects. In this open-label, randomized, crossover study, 18 subjects received a single-dose of Sitagliptin 100 mg or Sitagliptin 100 mg plus Dapagliflozin 20 mg. The mean Dapagliflozin plasma concentration versus time profile was similar with and without coadministration of Sitagliptin. The pre-specified criteria to conclude a lack of interaction between Dapagliflozin and Sitagliptin were met for Cmax and AUC as the 90% CIs were within the no-effect interval of 0.8–1.25. The tmax and t for Dapagliflozin were also unaffected by coadministration of Sitagliptin. The median (range) tmax for Dapagliflozin was 1.5 h (1.0–4.0) without and 1.7 h (1.0–6.0) with Sitagliptin coadministration. Furthermore, the mean t values for Dapagliflozin were 14.3 ± 10.1 h without and 15.9 ± 7.1 h with Sitagliptin coadministration. Similarly, no meaningful differences in Cmax and AUC were observed for Sitagliptin in the presence of Dapagliflozin as the 90% CIs were within the no-effect interval. Again, the tmax and t for Sitagliptin were unaffected by coadministration of Dapagliflozin. The median tmax for Sitagliptin was 3.0 h (0.5–5.8) without Dapagliflozin, and 4.0 h (1.5–8.0) with Dapagliflozin. The respective t values for Sitagliptin were 14.2 ± 2.0 h and 14.4 ± 2.0 h in the absence and presence of Dapagliflozin, respectively.

Clinical Efficacy

The RCT by Jabbour et al. 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. At 24 weeks, add-on treatment with Dapagliflozin

provided additional clinical benefit, with a significant reduction in HbA1c (-0.5 vs. 0% with placebo) and body weight (-2.1 vs. -0.3 kg). Dapagliflozin also decreased HbA1c significantly versus placebo when added to Sitagliptin alone (placebo-subtracted -0.6%; p\0.0001) or to Sitagliptin plus metformin dual therapy (placebo-subtracted -0.4%; p\0.0001). Glycaemic and body 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.

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Abstracts:

Macrovascular Complications of Type 2 Diabetes Mellitus

Abstract

Background: Type 2 diabetes mellitus (T2DM) has emerged as a pandemic. It has different complications, both microvascular and macrovascular.

Objective: The purpose of this review is to summarize the different types of macrovascular complications associated with T2DM.

Methods: A comprehensive review of the literature was performed to identify clinical studies, which determine the macrovascular complications associated with T2DM.

Results: Macrovascular complications of T2DM include coronary heart disease, cardiomyopathy, arrhythmias and sudden death, cerebrovascular disease and peripheral artery disease. Cardiovascular disease is the primary cause of death in diabetic patients. Many clinical studies have shown a connection between T2DM and vascular disease, but almost always other risk factors are present in diabetic patients, such as hypertension, obesity and dyslipidaemia.

Conclusion: T2DM causes a variety of macrovascular complications through different pathogenetic pathways that include hyperglycaemia and insulin resistance. The association between T2DM and cardiovascular disease is clear, but we need more clinical studies in order to identify the pure effect of T2DM.

Reference: Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular Complications of Type 2 Diabetes Mellitus. *Curr Vasc Pharmacol*. 2020;18(2):110-116.

Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study

Abstract

Objective: To assess the efficacy and safety of dapagliflozin as add-on therapy in patients with type 2 diabetes who were inadequately controlled with a dipeptidyl peptidase-4 inhibitor with or without metformin.

Research design and methods: In this 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study with a 24-week blinded extension period, 432 patients were randomized to receive dapagliflozin 10 mg/day or placebo added to sitagliptin (100 mg/day) ± metformin (≥1,500 mg/day).

Results: Baseline HbA1c and FPG levels were 7.9% (63.0 mmol/mol) and 162.2 mg/dL (9.0 mmol/L) for the dapagliflozin group and 8.0% (64.0 mmol/mol) and 163 mg/dL (9.0 mmol/L) for placebo. At week 24, dapagliflozin significantly reduced mean HbA1c levels (-0.5% [-4.9 mmol/mol]) versus placebo (0.0% [+0.4 mmol/mol]). Dapagliflozin reduced body weight versus placebo (-2.1 and -0.3 kg) and reduced HbA1c levels in patients with baseline values ≥8.0% (-0.8% [8.7 mmol/mol] and 0.0% [0.3 mmol/mol]) and fasting plasma glucose levels (-24.1 mg/dL [-1.3 mmol/L] and 3.8 mg/dL [0.2 mmol/L]). Similar results were observed when data were stratified by background therapy. Glycemic and weight benefits observed at week 24 were maintained through week 48. Changes from baseline in systolic blood pressure at week 8 were not significantly different between treatment groups. Over 48 weeks, fewer patients receiving dapagliflozin were discontinued or rescued for failing to achieve glycemic targets compared with placebo. Adverse events were balanced between groups, and discontinuation rates were low. At week 48, signs and symptoms suggestive of genital infection were more frequent with dapagliflozin (9.8%) than with placebo (0.4%). Signs and symptoms suggestive of urinary tract infection were balanced between dapagliflozin (6.7%) and placebo (6.2%).

Conclusions: These results suggest that in patients with type 2 diabetes, inadequately controlled on sitagliptin with or without metformin, add-on treatment with dapagliflozin provides additional clinical benefit and is well tolerated.

Reference: Jabbour SA, Hardy E, Sugg J, Parikh S; Study 10 Group. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care*. 2014;37(3):740-750.

Development and optimization of sitagliptin and dapagliflozin loaded oral self-nanoemulsifying formulation against type 2 diabetes mellitus

Abstract

Control of hyperglycemia and prevention of glucose reabsorption (glucotoxicity) are important objectives in the management of type 2 diabetes. This study deals with an oral combined dosage form design for two anti-diabetic drugs, sitagliptin and dapagliflozin using self-nanoemulsifying drug delivery systems (SNEDDS). The SNEDDS were developed using naturally obtained bioactive medium-chain/long-chain triglycerides oil, mixed glycerides and nonionic surfactants, and droplet size was measured followed by the test for antioxidant activities. Equilibrium solubility and dynamic dispersion experiments were conducted to achieve the maximum drug loading. The *in vitro* digestion, *in vivo* bioavailability, and anti-diabetic effects were studied to compare the representative SNEDDS with marketed product Dapazin®. The representative SNEDDS containing black seed oil showed excellent self-emulsification performance with transparent appearance. Characterization of the SNEDDS showed nanodroplets of around 50–66.57 nm in size (confirmed by TEM analysis), in addition to the high drug loading capacity without causing any precipitation in the gastro-intestinal tract. The SNEDDS provided higher antioxidant activity compared to the pure drugs. The *in vivo* pharmacokinetic parameters of SNEDDS showed significant increase in C_{max} (1.99 ± 0.21 μg mL^{-1}), AUC (17.94 ± 1.25 μg mL^{-1}), and oral absorption (2-fold) of dapagliflozin compared to the commercial product in the rat model. The anti-diabetic studies showed the significant inhibition of glucose level in treated diabetic mice by SNEDDS combined dose compared to the single drug therapy. The combined dose of sitagliptin-dapagliflozin using SNEDDS could be a potential oral pharmaceutical product for the improved treatment of type 2 diabetes mellitus.

Reference: Kazi M, Alqahtani A, Ahmad A, Noman OM, Aldughaim MS, Alqahtani AS, Alanazi FK. Development and optimization of sitagliptin and dapagliflozin loaded oral self-nanoemulsifying formulation against type 2 diabetes mellitus. Drug Deliv. 2021 Dec;28(1):100-114.

Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes

Abstract

Importance: Additional treatments are needed for heart failure with reduced ejection fraction (HFrEF). Sodium-glucose cotransporter 2 (SGLT2) inhibitors may be an effective treatment for patients with HFrEF, even those without diabetes.

Objective: To evaluate the effects of dapagliflozin in patients with HFrEF with and without diabetes.

Design, setting, and participants: Exploratory analysis of a phase 3 randomized trial conducted at 410 sites in 20 countries. Patients with New York Heart Association classification II to IV with an ejection fraction less than or equal to 40% and elevated plasma N-terminal pro B-type natriuretic peptide were enrolled between February 15, 2017, and August 17, 2018, with final follow-up on June 6, 2019.

Interventions: Addition of once-daily 10 mg of dapagliflozin or placebo to recommended therapy.

Main outcomes and measures: The primary outcome was the composite of an episode of worsening heart failure or cardiovascular death. This outcome was analyzed by baseline diabetes status and, in patients without diabetes, by glycated hemoglobin level less than 5.7% vs greater than or equal to 5.7%.

Results: Among 4744 patients randomized (mean age, 66 years; 1109 [23%] women; 2605 [55%] without diabetes), 4742 completed the trial. Among participants without diabetes, the primary outcome occurred in 171 of 1298 (13.2%) in the dapagliflozin group and 231 of 1307 (17.7%) in the placebo group (hazard ratio, 0.73 [95% CI, 0.60-0.88]). In patients with diabetes, the primary outcome occurred in 215 of 1075 (20.0%) in the dapagliflozin group and 271 of 1064 (25.5%) in the placebo group (hazard ratio, 0.75 [95% CI, 0.63-0.90]) (P value for interaction = .80). Among patients without diabetes and a glycated hemoglobin level less than 5.7%, the primary outcome occurred in 53 of 438 patients (12.1%) in the dapagliflozin group and 71 of 419 (16.9%) in the placebo group (hazard ratio, 0.67 [95% CI, 0.47-0.96]). In patients with a glycated hemoglobin of at least 5.7%, the primary outcome occurred in 118 of 860 patients (13.7%) in the dapagliflozin group and 160 of 888 (18.0%) in the placebo group (hazard ratio, 0.74 [95% CI, 0.59-0.94]) (P value for interaction = .72). Volume depletion was

reported as an adverse event in 7.3% of patients in the dapagliflozin group and 6.1% in the placebo group among patients without diabetes and in 7.8% of patients in the dapagliflozin group and 7.8% in the placebo group among patients with diabetes. A kidney adverse event was reported in 4.8% of patients in the dapagliflozin group and 6.0% in the placebo group among patients without diabetes and in 8.5% of patients in the dapagliflozin group and 8.7% in the placebo group among patients with diabetes.

Conclusions and relevance: In this exploratory analysis of a randomized trial of patients with HFrEF, dapagliflozin compared with placebo, when added to recommended therapy, significantly reduced the risk of worsening heart failure or cardiovascular death independently of diabetes status.

Reference: Petrie MC, Verma S, Docherty KF, et al. Effect of Dapagliflozin on Worsening Heart Failure and Cardiovascular Death in Patients With Heart Failure With and Without Diabetes [published correction appears in JAMA. 2021 Apr 6;325(13):1335]. *JAMA.* 2020;323(14):1353-1368.

Survey Form

1) How frequently do you prescribe the combination therapy of Sitagliptin + Dapagliflozin for your patients?

a. Very frequently
b. Frequently
c. Occasionally
d. Rarely

2) What factors influence your decision to opt for the combination therapy of Sitagliptin + Dapagliflozin?

a. High HbA1c levels and poor glycemic control
b. Concerns about cardiovascular risk reduction
c. Desire to achieve rapid improvement in glucose control
d. Patient's willingness to try aggressive therapy
e. Presence of comorbidities (e.g., obesity, hypertension)

3) In your clinical experience, how effective is the combination therapy of Sitagliptin + Dapagliflozin in achieving glycemic control?

a. Very effective
b. Effective
c. Moderately effective
d. Not effective

4) Have you observed any significant differences in cardiovascular outcomes or risk reduction among patients using Sitagliptin + Dapagliflozin as Combination therapy?

a. Yes, there are noticeable cardiovascular benefits
b. No significant cardiovascular benefits observed

5) What are the main challenges, if any, you have encountered when using the combination therapy of Sitagliptin + Dapagliflozin?

a. Concerns about potential side effects
b. Patient compliance and adherence issues
c. Managing drug interactions with other medications
d. Explaining the rationale to patients

6) How do you monitor and assess the response of patients on the combination therapy of Sitagliptin + Dapagliflozin?

a. Regularly monitor HbA1c levels and adjust treatment
b. Check for changes in weight and blood pressure
c. Assess improvement in cardiovascular risk factors
d. Evaluate patient-reported outcomes and satisfaction

7) In your opinion, what additional benefits or improvements have you observed in patients on the combination therapy of Sitagliptin + Dapagliflozin?

a. Weight loss
b. Blood pressure reduction
c. Improvement in kidney function
d. Decreased insulin requirements

8) How frequently do you involve a multidisciplinary healthcare team when initiating and monitoring patients on the combination therapy of Sitagliptin + Dapagliflozin?

a. Always
b. Frequently
c. Occasionally
d. Rarely

9) In your experience, do you find that the combination therapy of Sitagliptin + Dapagliflozin is better suited for specific patient populations?

a. Yes, for patients with type 2 diabetes and cardiovascular risks
b. Yes, for patients with specific metabolic profiles (e.g., obesity)
c. No, it is equally effective for all eligible patients

10) In your clinical experience, have you observed any differences in the response to the combination therapy of Sitagliptin + Dapagliflozin between younger and older patients?

a. Yes, younger patients tend to respond more favourably
b. Older patients tend to have better responses
c. No significant age-related response differences observed

11) Do you consider the combination therapy of Sitagliptin + Dapagliflozin as a potential first-line treatment option for patients with newly diagnosed type 2 diabetes?

a. Yes, I often consider it as a first-line option
b. Yes, I consider it occasionally as a first-line option
c. No, I generally reserve it for patients with inadequate response to other treatments
d. No, I do not consider it as a first-line option

12) In your experience, what are the key patient education topics that you prioritize when initiating the combination therapy of Sitagliptin + Dapagliflozin?

a. Importance of regular glucose monitoring
b. Dietary modifications and carbohydrate counting
c. Signs and symptoms of hypoglycaemia and adverse events associated with this combination
d. Potential benefits of weight loss and blood pressure reduction

13) In your opinion, what are the most significant advantages of the combination therapy of Sitagliptin + Dapagliflozin for patients with type 2 diabetes?

a. Simultaneous improvement in glycemic control and cardiovascular risk factors
b. Reduced need for additional antihyperglycemic medications
c. Potential weight loss and blood pressure reduction
d. Favorable effects on renal function and albuminuria
e. Not sure

14) In your clinical practice, do you consider patient preferences and lifestyle factors when deciding on the aggressive therapy combination of Sitagliptin +Dapagliflozin?

a. Yes, patient preferences significantly influence my decisions
b. I consider patient preferences along with other clinical factors
c. Patient preferences have minimal impact on my decisions
d. No, patient preferences do not play a role in my decisions

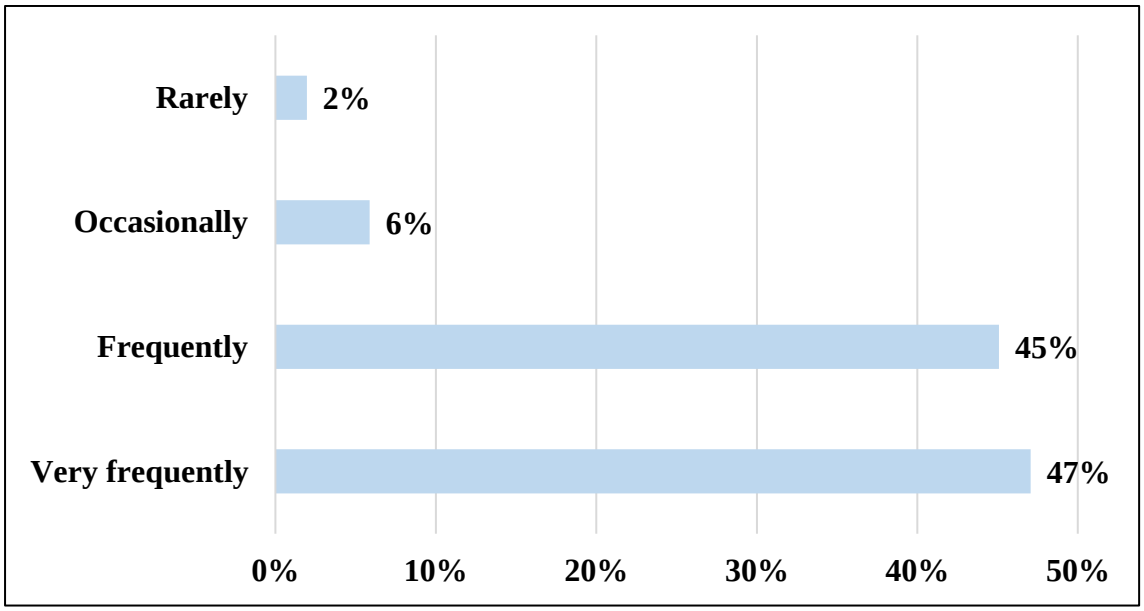
15) How would you rate your level of satisfaction with the overall impact of aggressive therapy using Sitagliptin + Dapagliflozin in your clinical practice?

a. Very satisfied
b. Satisfied
c. Neutral
d. Not very satisfied

Survey Findings

1) How frequently do you prescribe the combination therapy of Sitagliptin + Dapagliflozin for your patients?

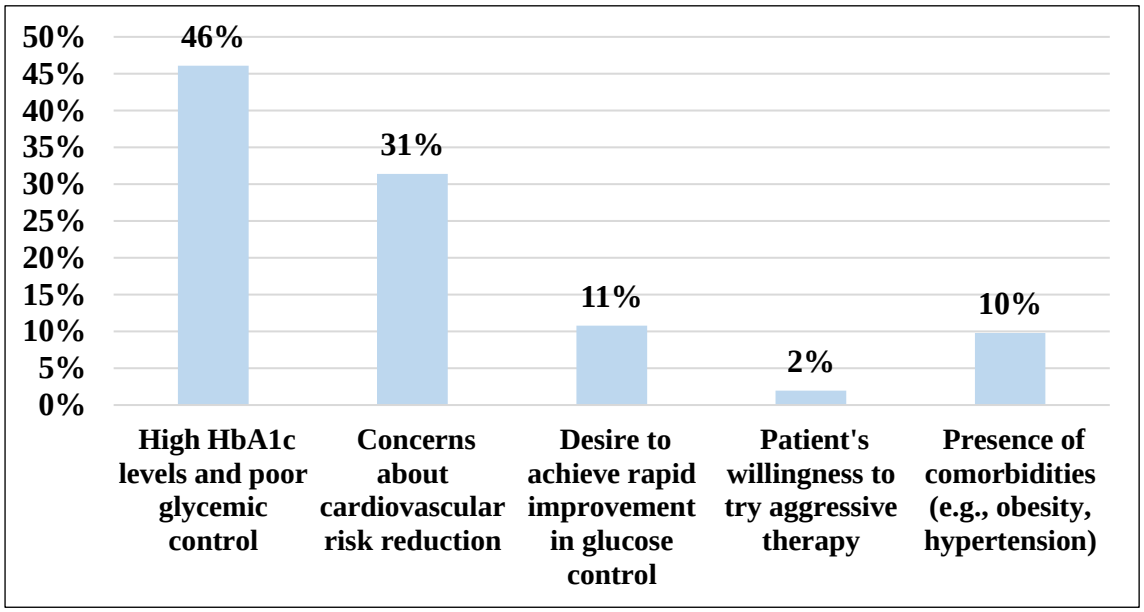
a. Very frequently
b. Frequently
c. Occasionally
d. Rarely



According to 47% of doctors, they prescribe the combination therapy of Sitagliptin + Dapagliflozin for their patients very frequently.

2) What factors influence your decision to opt for the combination therapy of Sitagliptin + Dapagliflozin?

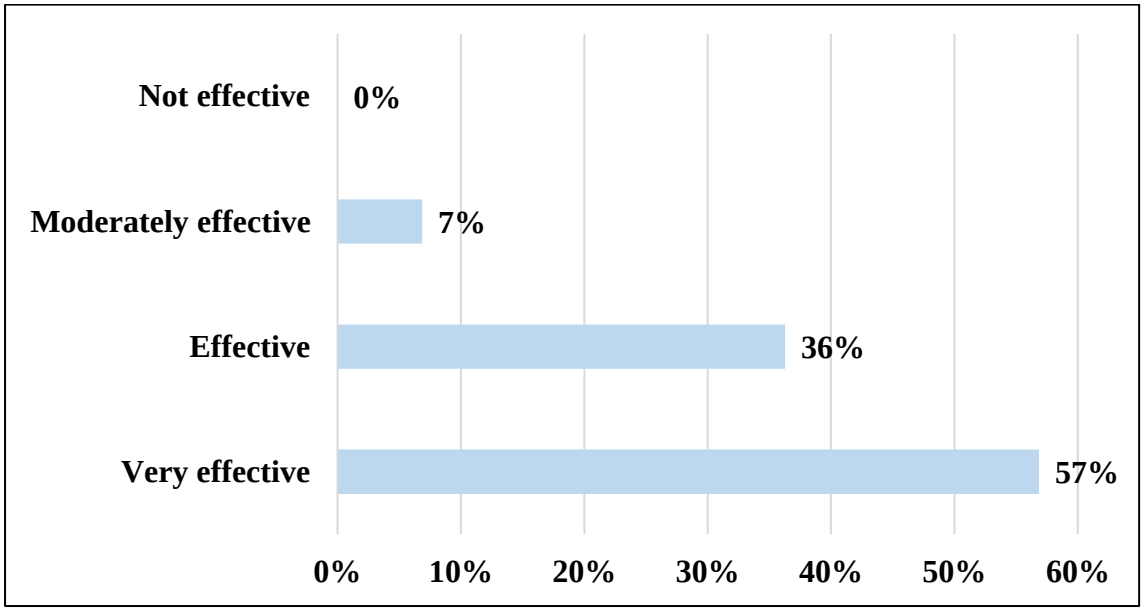
a. High HbA1c levels and poor glycemic control
b. Concerns about cardiovascular risk reduction
c. Desire to achieve rapid improvement in glucose control
d. Patient's willingness to try aggressive therapy
e. Presence of comorbidities (e.g., obesity, hypertension)



According to 46% of doctors, high HbA1c levels and poor glycemic control influence their decision to opt for the combination therapy of Sitagliptin + Dapagliflozin.

3) In your clinical experience, how effective is the combination therapy of Sitagliptin + Dapagliflozin in achieving glycemic control?

a. Very effective
b. Effective
c. Moderately effective
d. Not effective

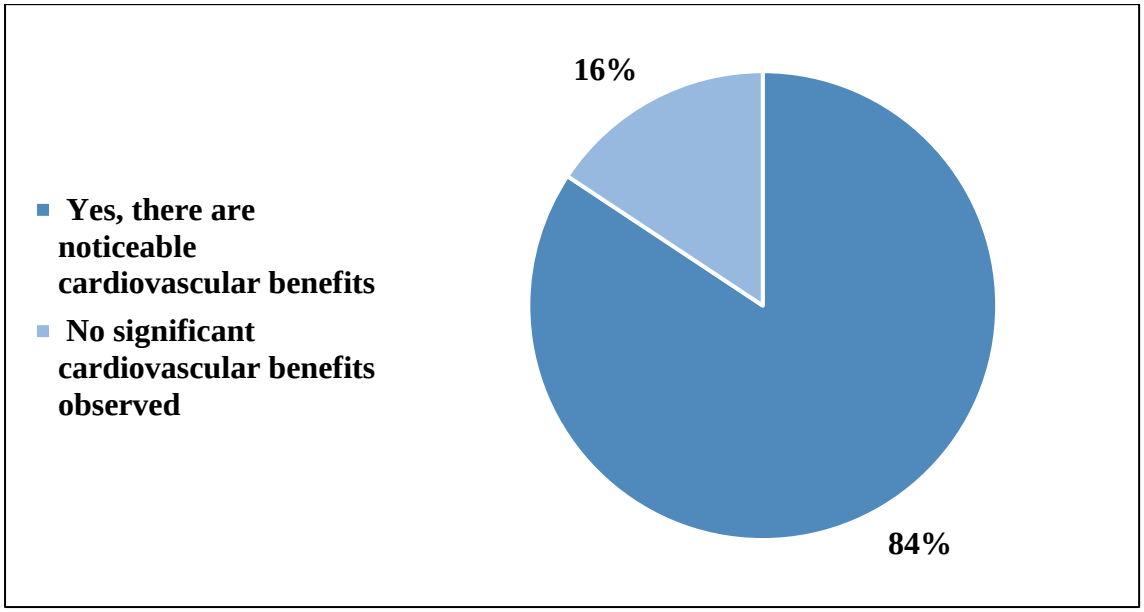


As per 57% of doctors, the combination therapy of Sitagliptin + Dapagliflozin in achieving glycemic control is very effective.

4) Have you observed any significant differences in cardiovascular outcomes or risk reduction among patients using Sitagliptin + Dapagliflozin as Combination therapy?

a. Yes, there are noticeable cardiovascular benefits

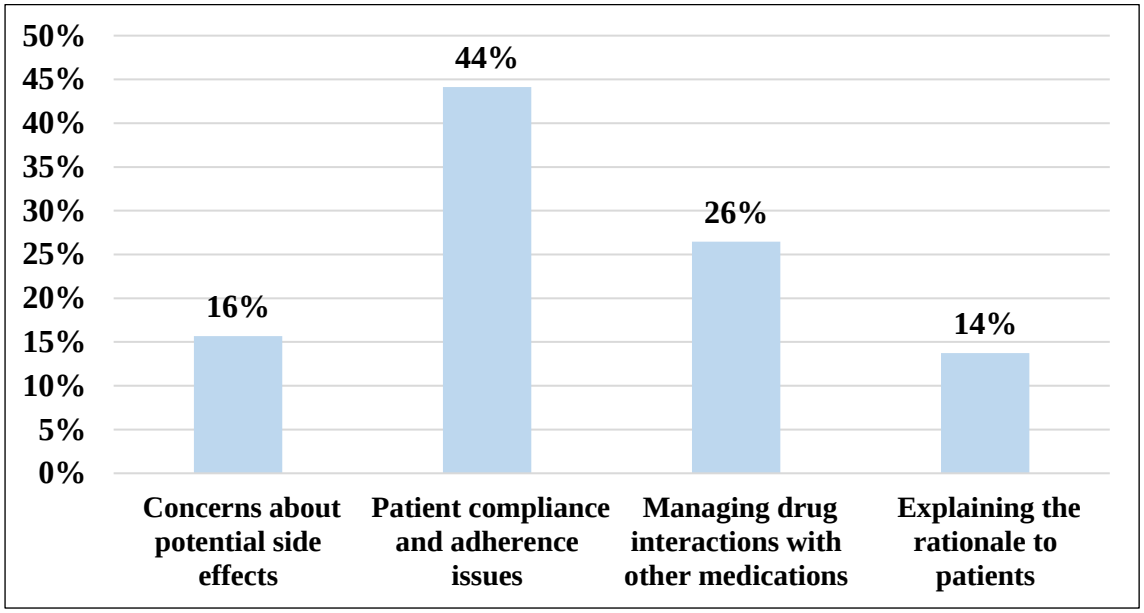
b. No significant cardiovascular benefits observed



As per 84% of doctors, there are noticeable cardiovascular benefits among patients using Sitagliptin + Dapagliflozin as Combination therapy.

5) What are the main challenges, if any, you have encountered when using the combination therapy of Sitagliptin + Dapagliflozin?

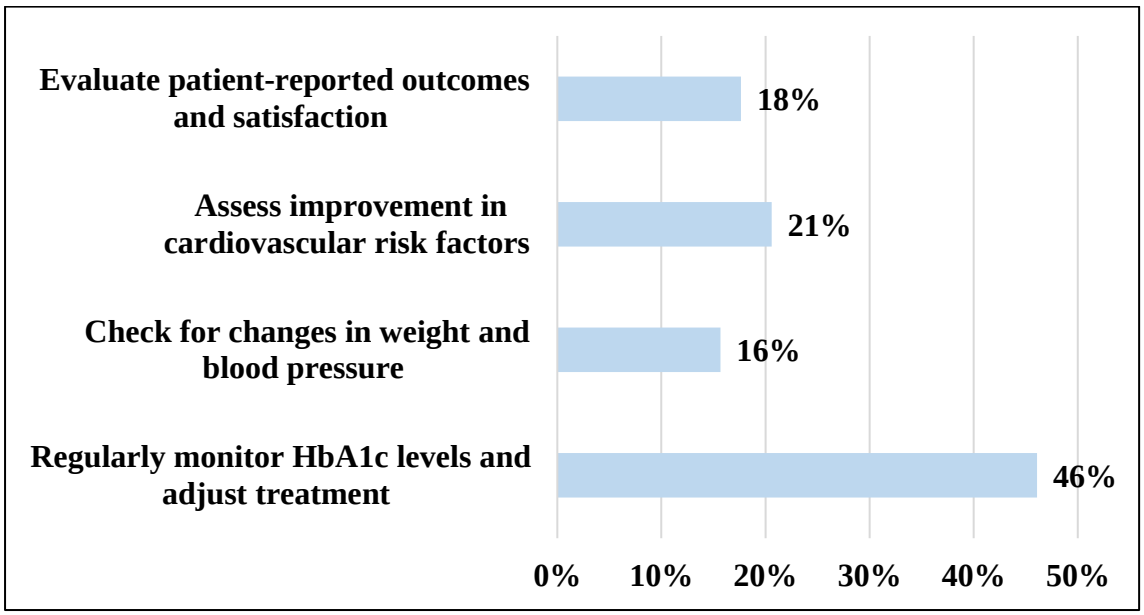
a. Concerns about potential side effects
b. Patient compliance and adherence issues
c. Managing drug interactions with other medications
d. Explaining the rationale to patients



According to 44% of doctors, they have encountered patient compliance and adherence issues when using the combination therapy of Sitagliptin + Dapagliflozin.

6) How do you monitor and assess the response of patients on the combination therapy of Sitagliptin + Dapagliflozin?

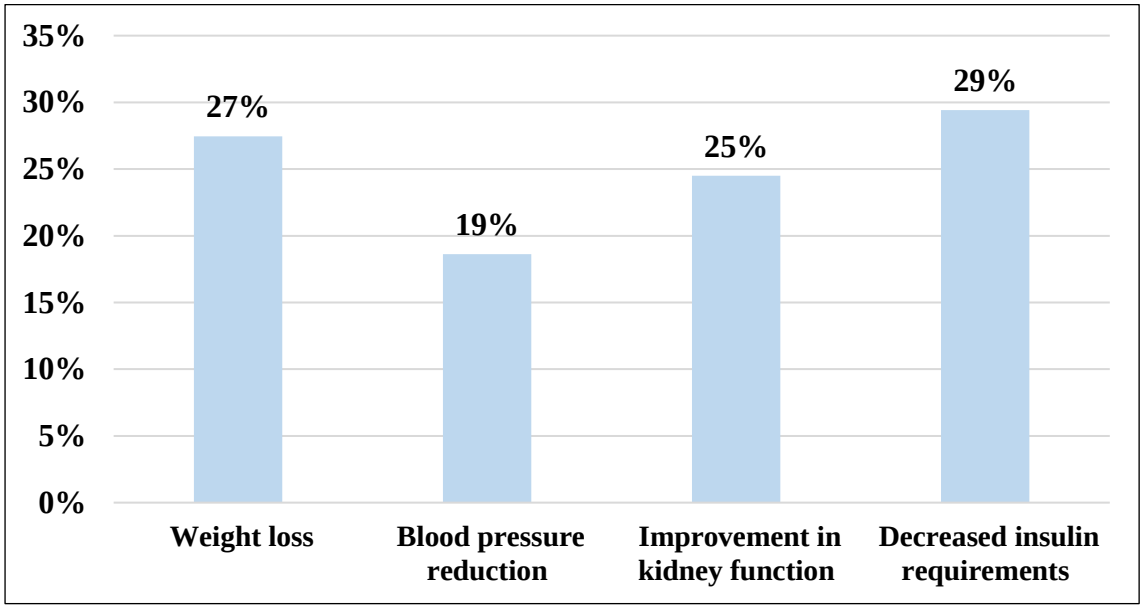
a. Regularly monitor HbA1c levels and adjust treatment
b. Check for changes in weight and blood pressure
c. Assess improvement in cardiovascular risk factors
d. Evaluate patient-reported outcomes and satisfaction



As per 46% of doctors, they monitor and assess the response of patients on the combination therapy of Sitagliptin + Dapagliflozin by regularly monitoring HbA1c levels and adjusting treatment.

7) In your opinion, what additional benefits or improvements have you observed in patients on the combination therapy of Sitagliptin + Dapagliflozin?

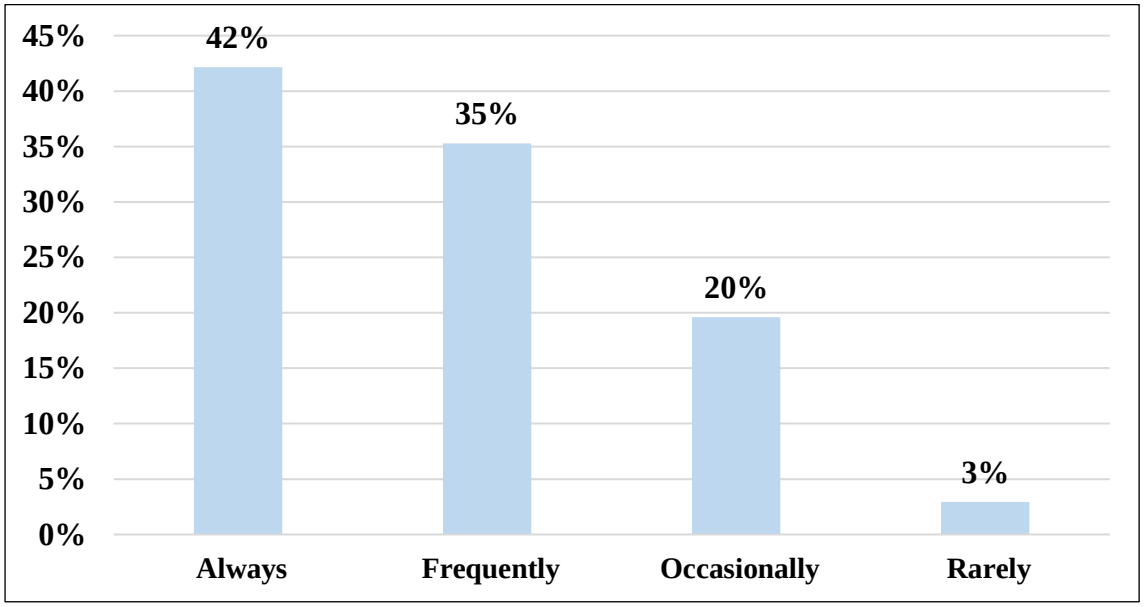
a. Weight loss
b. Blood pressure reduction
c. Improvement in kidney function
d. Decreased insulin requirements



According to 29% of doctors, there is decreased insulin requirement in patients on the combination therapy of Sitagliptin + Dapagliflozin.

8) How frequently do you involve a multidisciplinary healthcare team when initiating and monitoring patients on the combination therapy of Sitagliptin + Dapagliflozin?

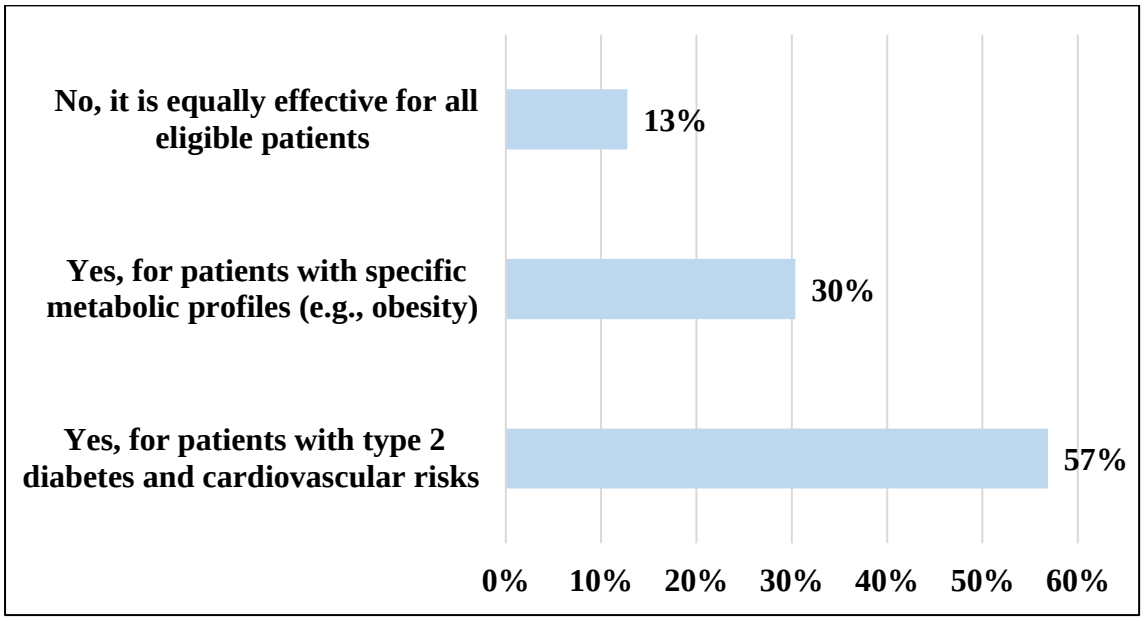
a. Always
b. Frequently
c. Occasionally
d. Rarely



According to 42% of doctors, they always involve a multidisciplinary healthcare team when initiating and monitoring patients on the combination therapy of Sitagliptin + Dapagliflozin.

9) In your experience, do you find that the combination therapy of Sitagliptin + Dapagliflozin is better suited for specific patient populations?

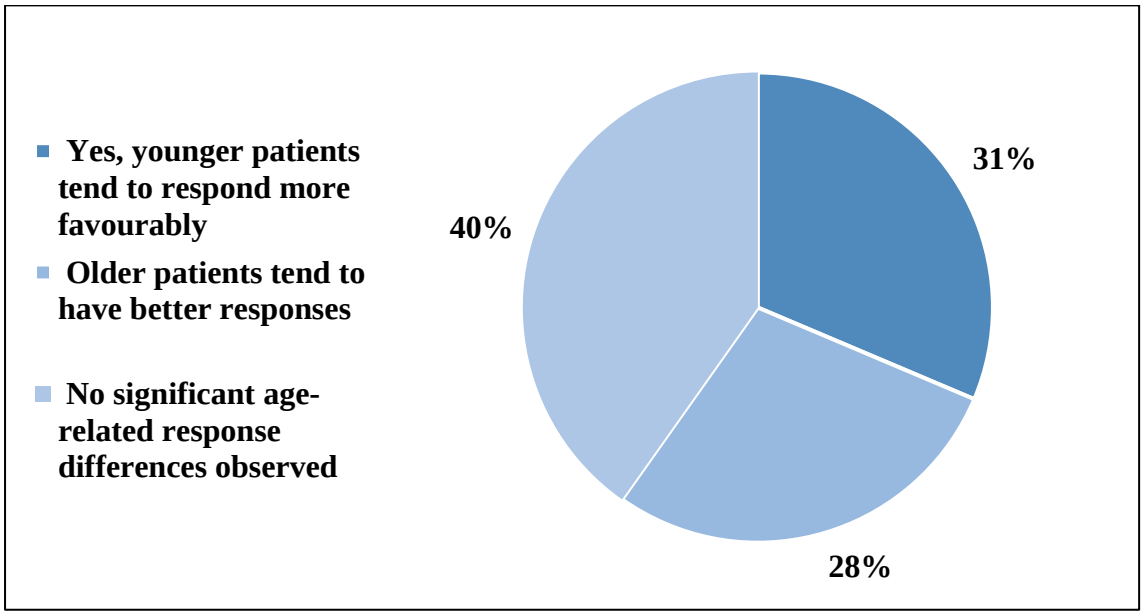
a. Yes, for patients with type 2 diabetes and cardiovascular risks
b. Yes, for patients with specific metabolic profiles (e.g., obesity)
c. No, it is equally effective for all eligible patients



As per 57% of doctors, for patients with type 2 diabetes and cardiovascular risks they find that the combination therapy of Sitagliptin + Dapagliflozin is better suited for specific patient populations.

10) In your clinical experience, have you observed any differences in the response to the combination therapy of Sitagliptin + Dapagliflozin between younger and older patients?

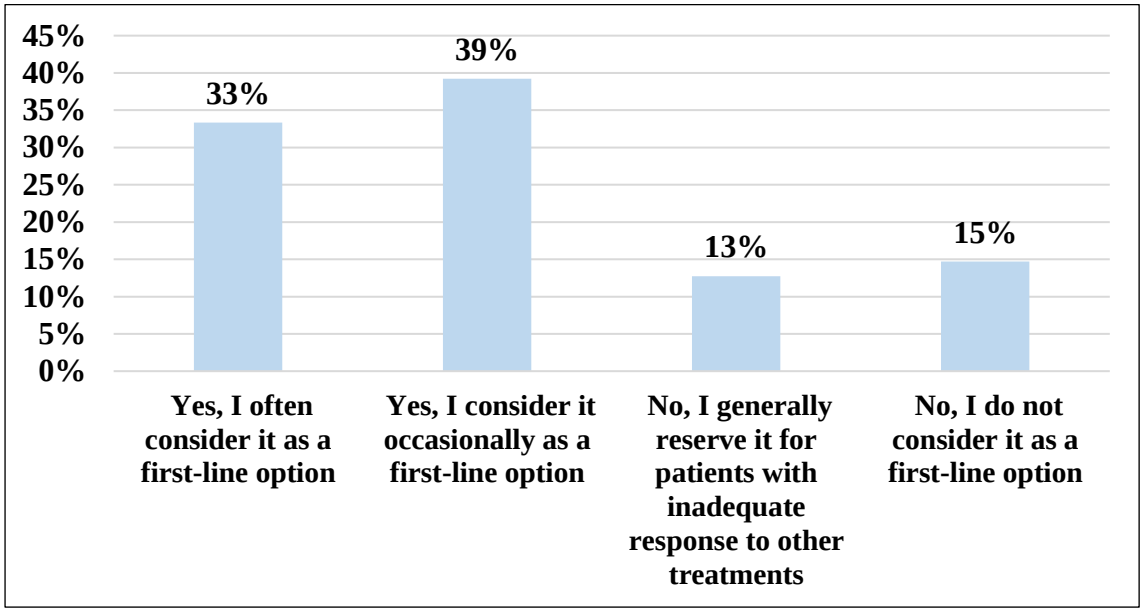
a. Yes, younger patients tend to respond more favourably
b. Older patients tend to have better responses
c. No significant age-related response differences observed



According to 40% of doctors, no significant age-related response differences have been observed to the combination therapy of Sitagliptin + Dapagliflozin between younger and older patients.

11) Do you consider the combination therapy of Sitagliptin + Dapagliflozin as a potential first-line treatment option for patients with newly diagnosed type 2 diabetes?

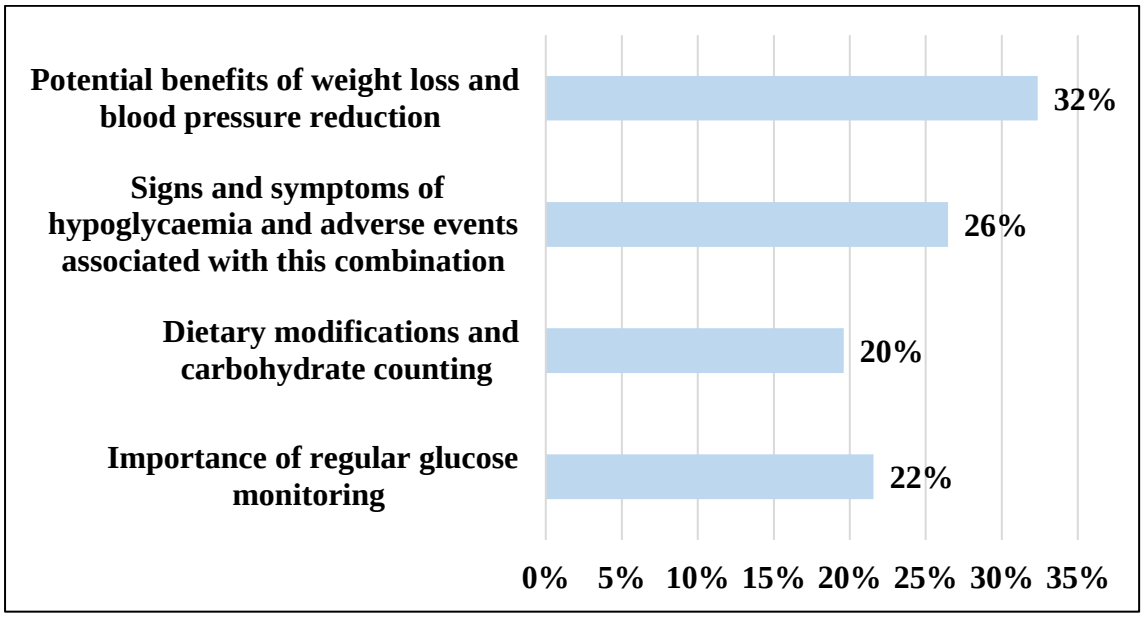
a. Yes, I often consider it as a first-line option
b. Yes, I consider it occasionally as a first-line option
c. No, I generally reserve it for patients with inadequate response to other treatments
d. No, I do not consider it as a first-line option



As per 39% of doctors, they occasionally consider the combination therapy of Sitagliptin + Dapagliflozin as a potential first-line treatment option for patients with newly diagnosed type 2 diabetes.

12) In your experience, what are the key patient education topics that you prioritize when initiating the combination therapy of Sitagliptin + Dapagliflozin?

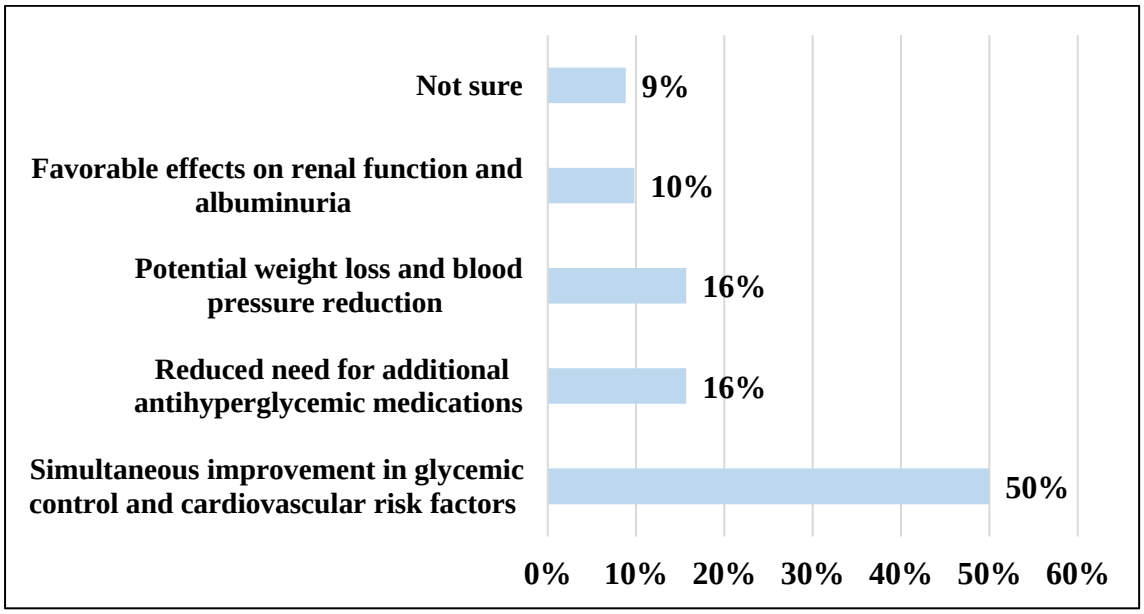
a. Importance of regular glucose monitoring
b. Dietary modifications and carbohydrate counting
c. Signs and symptoms of hypoglycaemia and adverse events associated with this combination
d. Potential benefits of weight loss and blood pressure reduction



As per 32% of doctors, the key patient education topics that they prioritize when initiating the combination therapy of Sitagliptin + Dapagliflozin is potential benefits of weight loss and blood pressure reduction.

13) In your opinion, what are the most significant advantages of the combination therapy of Sitagliptin + Dapagliflozin for patients with type 2 diabetes?

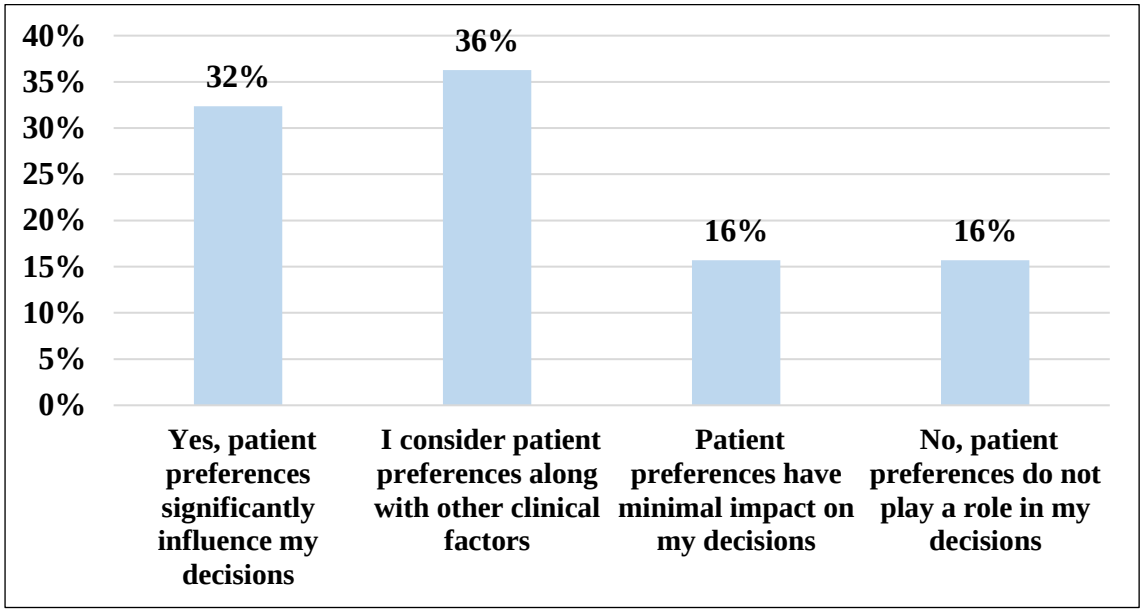
a. Simultaneous improvement in glycemic control and cardiovascular risk factors
b. Reduced need for additional antihyperglycemic medications
c. Potential weight loss and blood pressure reduction
d. Favorable effects on renal function and albuminuria
e. Not sure



As per 50% of doctors, simultaneous improvement in glycemic control and cardiovascular risk factors are the most significant advantages of the combination therapy of Sitagliptin + Dapagliflozin for patients with type 2 diabetes.

14) In your clinical practice, do you consider patient preferences and lifestyle factors when deciding on the aggressive therapy combination of Sitagliptin +Dapagliflozin?

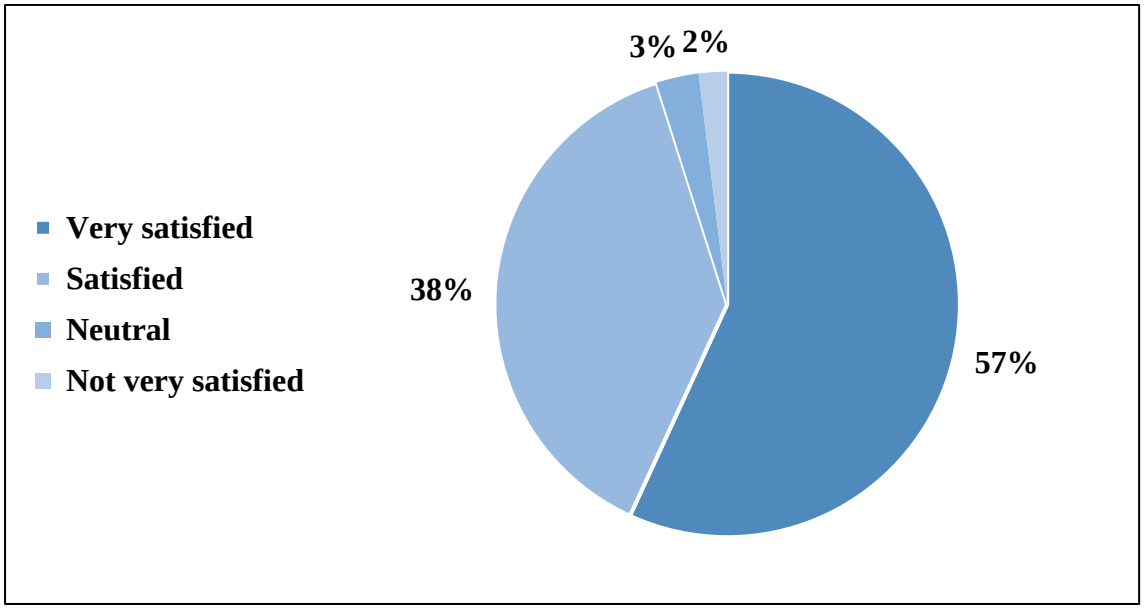
a. Yes, patient preferences significantly influence my decisions
b. I consider patient preferences along with other clinical factors
c. Patient preferences have minimal impact on my decisions
d. No, patient preferences do not play a role in my decisions



According to 36% of doctors, they consider patient preferences along with other clinical factors when deciding on the aggressive therapy combination of Sitagliptin +Dapagliflozin.

15) How would you rate your level of satisfaction with the overall impact of aggressive therapy using Sitagliptin + Dapagliflozin in your clinical practice?

a. Very satisfied
b. Satisfied
c. Neutral
d. Not very satisfied



According to 57% of doctors, they are very satisfied with the overall impact of aggressive therapy using Sitagliptin + Dapagliflozin in their clinical practice.

Summary

- According to 47% of doctors, they prescribe the combination therapy of Sitagliptin + Dapagliflozin for their patients very frequently.
- According to 46% of doctors, high HbA1c levels and poor glycemic control influence their decision to opt for the combination therapy of Sitagliptin + Dapagliflozin.
- As per 57% of doctors, the combination therapy of Sitagliptin + Dapagliflozin in achieving glycemic control is very effective.
- As per 84% of doctors, there are noticeable cardiovascular benefits among patients using Sitagliptin + Dapagliflozin as Combination therapy.
- According to 44% of doctors, they have encountered patient compliance and adherence issues when using the combination therapy of Sitagliptin + Dapagliflozin.
- As per 46% of doctors, they monitor and assess the response of patients on the combination therapy of Sitagliptin + Dapagliflozin by regularly monitoring HbA1c levels and adjusting treatment.
- According to 29% of doctors, there is decreased insulin requirement in patients on the combination therapy of Sitagliptin + Dapagliflozin.
- According to 42% of doctors, they always involve a multidisciplinary healthcare team when initiating and monitoring patients on the combination therapy of Sitagliptin + Dapagliflozin.
- As per 57% of doctors, for patients with type 2 diabetes and cardiovascular risks they find that the combination therapy of Sitagliptin + Dapagliflozin is better suited for specific patient populations.
- According to 40% of doctors, no significant age-related response differences have been observed to the combination therapy of Sitagliptin + Dapagliflozin between younger and older patients.
- As per 39% of doctors, they occasionally consider the combination therapy of Sitagliptin + Dapagliflozin as a potential first-line treatment option for patients with newly diagnosed type 2 diabetes.
- As per 32% of doctors, the key patient education topics that they prioritize when initiating the combination therapy of Sitagliptin + Dapagliflozin is potential benefits of weight loss and blood pressure reduction.

- As per 50% of doctors, simultaneous improvement in glycemic control and cardiovascular risk factors are the most significant advantages of the combination therapy of Sitagliptin + Dapagliflozin for patients with type 2 diabetes.
- According to 36% of doctors, they consider patient preferences along with other clinical factors when deciding on the aggressive therapy combination of Sitagliptin +Dapagliflozin.
- According to 57% of doctors, they are very satisfied with the overall impact of aggressive therapy using Sitagliptin + Dapagliflozin in their clinical practice.

Consultant Opinion

Market Opportunities:

There is a significant market opportunity for pharmaceutical companies to develop and market combination therapies like Sitagliptin + Dapagliflozin, considering the high frequency of prescription by doctors and their perceived effectiveness in achieving glycemic control and cardiovascular benefits.

Value for Healthcare Professionals:

Healthcare professionals highly value the combination therapy of Sitagliptin + Dapagliflozin for its efficacy in achieving glycemic control and providing cardiovascular benefits, indicating its importance in clinical practice.

Adverse Effect Management:

Doctors acknowledge patient compliance and adherence issues with Sitagliptin + Dapagliflozin combination therapy, highlighting the importance of effective adverse effect management strategies.

Withdrawal Management:

Regular monitoring of HbA1c levels and adjustment of treatment are essential for withdrawal management in patients on Sitagliptin + Dapagliflozin combination therapy, ensuring optimal glycemic control.

Market Positioning:

Sitagliptin + Dapagliflozin combination therapy is perceived as suitable for specific patient populations, particularly those with type 2 diabetes and cardiovascular risks, indicating a strong market positioning in these segments.

Personalized Treatment Decisions:

Doctors involve multidisciplinary healthcare teams when initiating and monitoring patients on Sitagliptin + Dapagliflozin combination therapy, reflecting a personalized approach to patient care.

Improving Patient Outcomes:

The combination therapy of Sitagliptin + Dapagliflozin offers simultaneous improvement in glycemic control and cardiovascular risk factors, leading to enhanced patient outcomes, as recognized by healthcare professionals.

NOTES

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Developed by:

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