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SGLT2 Inhibitor: A Cardio-Renal Metabolic Pill

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ABSTRACT

Cardiovascular disease and renal disease continue to be the leading causes of morbidity and mortality among people with type 2 diabetes mellitus, despite decades of research into risk-reduction approaches. sodium-glucose transport protein 2 (SGLT2) inhibitors have been approved by the US Food and Drug Administration (FDA) for improving blood sugar control in adult patients with type 2 diabetes mellitus (T2DM Four types of sodium-glucose transport protein 2 (SGLT2) inhibitors (Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) inhibit SGLT-2 protein expression in renal proximal convoluted tubules, reducing filtration glucose resorption, decreasing Renal Glucose Thresholds (RTG), and increasing urinary glucose excretion. As cardiovascular and renal disease are closely linked to metabolic abnormalities associated with type 2 diabetes mellitus, these conditions can be considered cardiovascular-renal-metabolic disease states. Patients with cardiovascular-renal-metabolic disease states need a holistic approach to managing their disease states. In this article, we discuss the cardiovascular and renal metabolic risks associated with type 2 diabetes mellitus and discuss the mechanism and clinical benefits of SGLT2 inhibitors.

Keywords: sodium-glucose transport protein 2; glycemic control; Type 2 Diabetes Mellitus; Cardiovascular disease; chronic kidney disease.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) affects 463 million people worldwide. Low- and middle-income countries have seen the biggest increase in the prevalence of T2DM, according to reports. There are 77 million people with type 2 diabetics in India, which is second after China (1). T2DM is a risk factor for heart failure (HF) and has a strong link to cardiovascular disease (CVD) (2,3). diabetes is one of the most prevalent risk factors for end-stage renal disease (ESRD) and chronic kidney disease (CKD) is diabetes (4). Furthermore, T2DM medications frequently have harmful side effects. Type 2 diabetes (T2D) management recommendations have evolved over the past ten years from a general recommendation to one that is patient-centered (5-8). Two findings from important diabetes trials have prompted this treatment personalization, which weighs the advantages of glycemic control with its potential risks in the context of lowering cardiovascular risk and includes dietary changes, BP management, and lipid management. First, strict glycemic control may increase the risk of hypoglycemia, which could lead to a lower quality of life and possibly an increase in cardiovascular risk. This highlights the significance of drug classes with low hypoglycemia risk, especially in patients with long-standing T2DM.

Second, the impact of glucose control on cardiovascular-renal complications is much

more modest and does not become apparent for many years, whereas glucose lowering per se slows or stops the onset and development of microvascular complications, highlighting the significance of drug classes with cardiovascular renal benefit. Their action inhibits sodium glucose cotransporter 2 (SGLT2) in the kidney, causing glucosuria. Initially, the therapies were intended to lower blood glucose levels, but they have shown clinical benefits that far surpass expectations in a very short time. This short review describes SGLT2 inhibitors' mechanism and discusses their clinical benefits.

The Action of SGLT2:

In poorly controlled diabetes, glycosuria is one of the main symptoms, along with hyperglycemia and reduced insulin secretion. In order to maintain glucose homeostasis, kidneys participate in all steps of glucose metabolism, including glucose production (gluconeogenesis), utilization, filtration, and reabsorption (9). Most glucose is reabsorbed by SGLT2, a low-affinity, high-capacity glucose transporter. SGLT2 transporters are located within proximal convoluted tubules in the kidney, mainly in S1 and S2 (10). SGLT1, a low-capacity, high-affinity transporter, reabsorbs the remaining glucose in the S3 segment. Approximately 375 mg of glucose can be absorbed by the tubular system per minute, with a plasma glucose level of 200 mg/dL corresponding to that amount of glucose absorbed. In the case of exceeding this threshold, glycosuria occurs. A persistent hyperglycemic state leads to paradoxically higher glucose reabsorption rates in the presence of enhanced SGLT1/2 expression (11).

SGLT2 represents a paradigm shift in the treatment of diabetes, turning a defect into a “mode of action”. As of now, four SGLT2 inhibitors are approved in Europe for use in combination with diet, exercise, and lifestyle changes to treat type 2 diabetes.

SGLT2 Advantages

SGLT2 inhibitors have been shown to improve cardiovascular outcomes in several recent trials. 7020 people with type 2 diabetes and previous cardiovascular disease (CVD) were enrolled in the EMPA-REG OUTCOME study and were randomly assigned to either empagliflozin or placebo additions to standard treatment. There was a 14% relative risk reduction with empagliflozin in three-point MACE, including cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke (P = 0.04 for superiority) (12). In the Canagliflozin Cardiovascular Assessment Study (CANVAS), data were collected from 10142 participants with type 2 diabetes at high risk for cardiovascular events from two trials (CANVAS and CANVAS-R: Canagliflozin Cardiovascular Assessment Study-Renal). Patients were randomly assigned to receive 100-300 mg canagliflozin or placebo and followed up for 3.6 years on average. Canagliflozin significantly reduced the rate of triple MACE compared to placebo (hazard ratio (HR): 0.86; 95% CI: 0.75 - 0.97; P = 0.02 for superiority) (13).

Two observational studies from the CVD-REAL Nordic study corroborated these findings. The first compared SGLT2 inhibitors (94 percent with dapagliflozin) with other antidiabetic medications (HR: 0.78; 95% CI: 0.69-0.87; P 0.001) (14) and the second contrasted newly treated patients with dapagliflozin versus newly treated patients with DPP-4 inhibitors (HR: 0.79; 95% CI:0.67-0.94; P=0.006) (15). The DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events) study, a randomised controlled trial with dapagliflozin, recently published its findings. The significant finding of this study, which set it apart from other SGLT2 inhibitor trials, was that the majority of the patients recruited had never before experienced ASCVD. The researchers enrolled 17160 patients in this study, including 10186 without atherosclerotic cardiovascular disease. Patients were given

dapagliflozin or a placebo at random. Dapagliflozin did not perform worse than a placebo, according to the results of the composite primary endpoints (P 0.001). Dapagliflozin had a MACE rate of 8.8% and placebo had a rate of 9.4% (HR: 0.93; CI: 0.84 - 1.03; P = 0.17). (16).

A meta-analysis of three significant trials, including EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58, was carried out by Zelniker et al. in 2018 and revealed an 11% reduction in MACE by using SGLT2 inhibitors (HR: 0.89; 95% CI: 0.83 - 0.96, P = 0.0014), with this effect only being observed in patients with prior atherosclerotic cardiovascular disease (HR: 0.86; 95% CI: 0.80 - 0.93) (17).

Wu et al. found that patients taking SGLT2 inhibitors experienced a significant decrease in their primary composite cardiovascular endpoints (MACE) when compared to those taking a placebo (relative risk: 0.84; 95% CI: 0.75 - 0.95; P = 0.006). This was based on a meta-analysis of 57 published trials with 33385 patients, six regulatory submissions with 37525 patients, and data for seven different SGLT2 inhibitors (18). SGLT2 inhibitors were associated with a 20% reduction in MACE, according to a recent meta-analysis by Zhang et al. in 2018 that included five randomised controlled trials and 351476 participants (HR: 0.80; 95% CI: 0.69 - 0.92; P = 0.002) (19). Canagliflozin, dapagliflozin, and empagliflozin were compared with placebo and other glucose-lowering medications in a meta-analysis by Tang et al. in 2016 that included 37 trials and 29859 diabetes patients. Only empagliflozin was found to be associated with a significantly lower risk of MACE when compared to placebo (odds ratio (OR): 0.81; 95% CI: 0.70 to 0.93] (20).

Mechanisms of Cardiovascular Impacts

Inhibitors of SGLT2 are associated with lowering blood pressure, reducing blood pressure and vascular resistance, reducing weight, and lowering uric acid and oxidative stress. Several mechanisms have been shown to contribute to the cardiovascular effects of SGLT2 inhibitors. Increases in hematocrit and haemoglobin may also be involved. Hematocrit or haemoglobin levels were strongly correlated with a lower risk of death and heart failure, according to the EMPA REG trial (12, 21-23). Glucagon controls how much glucose is used by the heart and has beneficial inotropic and anti-arrhythmogenic properties (24). Empagliflozin can raise blood glucagon levels, perhaps as a result of increased excretion of glucose or possibly because it directly affects pancreatic alpha cells. Higher levels of glucagon may contribute to the reduction of cardiovascular mortality and heart failure risks (25-27). According to a recent theory, SGLT2 inhibitors may increase the effectiveness of myocardial work by switching the metabolism of fuel from free fatty acids to ketones, which are more effective energetic fuels (28).

Another recent hypothesis proposes that empagliflozin's ability to lower cardiovascular mortality may be attributable to its direct enhancement of myocardial function and suppression of rhythm disturbances in cardiomyocytes. Cardiovascular mortality might be decreased as a result of empagliflozin's weak inhibitory effect on myocardial SGLT1, especially in patients with overexpression of SGLT1 following ischemia (29). Sub-analyses of CVD-REAL found SGLT2 inhibitors to reduce MI risk (30).

Additionally, over 400000 type 2 diabetics across six nations participated in the CVD-REAL2 study, a significant international study with over 400000 participants (31). According to Zhang et al., meta-analysis (19), SGLT2 inhibitors significantly reduced the risk of non-fatal MI. Two meta-analyses by Savarese et al. and Monami et al. reported a significant reduction in MI (32, 33). Additionally, there are mixed results regarding stroke in patients receiving this cutting-edge therapy. The CVD-REAL study found that patients with diabetes who started taking SGLT2 inhibitors had a lower

risk of stroke. Additionally, this finding was supported by the CVD-REAL2 study, a large multinational investigation of people with type 2 diabetes (30, 31).

It is important to note that heart failure is an important comorbidity of type 2 diabetes, especially in older adults (34). A significant decrease in heart failure admissions was observed in the EMPA-REG OUTCOME trial where patients with type 2 diabetes received empagliflozin (12). The effect became evident within six months of starting treatment (35); Zelniker et al. conducted a meta-analysis of this effect. A 23% reduction in cardiovascular mortality or hospitalisation for heart failure was seen in EMPA-REG, CANVAS Program, and DECLARE-TIMI 58 trials of SGLT2 inhibitors. the benefit was similar for patients with and without cardiovascular disease (17).

SGLT2 Inhibitors and Renal Function

Comparing empagliflozin to placebo in the EMPA-REG OUTCOME trial, empagliflozin significantly reduced the relative likelihood of developing macroalbuminuria. The incidence of macroalbuminuria was reduced by 38% with empagliflozin compared to placebo, with 11.2% of patients receiving empagliflozin progressing to the condition (35). According to the results of the CANVAS program, there was a reduction of 27% in albuminuria progression and an increase in albuminuria regression when compared to a placebo (36). The use of SGLT2 inhibitors, in particular canagliflozin and empagliflozin, to patients with or without renal failure improved albuminuria and slowed the rate of progression to macroalbuminuria, according to a recent meta-analysis by Seidu et al. In 2018, there were 40 randomised clinical trials (37).

As shown by the EMPA-REG OUTCOME trial, effagliflozin significantly reduced risk when serum creatinine levels doubled in 1.5% of participants rather than 2.3% of participants receiving a placebo (36). An analysis by Seidu et al. found that SGLT2 inhibitors were associated with an increase in serum creatinine levels at the start of treatment before returning to baseline. Despite this, serum creatinine levels remained unchanged when renal failure was not present (37).

Dialysis or a kidney transplant are necessary for patients with advanced kidney disease (38). A total of 0.3% of empagliflozin-treated patients were initiated on renal replacement therapy versus 0.6% who were treated with placebo in the EMPA-REG OUTCOME trial. By reducing risk by 55%, this difference represents a significant reduction in risk. As a result of the CANVAS programme, composite renal outcomes such as renal replacement therapy, eGFR (estimated glomerular filtration rate) and mortality from renal causes decreased by 40% (13).

The eGFR of the empagliflozin group initially fell during the EMPA-REG OUTCOME trial. In contrast to a modest increase in GFR, the eGFR decreased in empagliflozin users during the first four weeks, with weekly decreases in patients treated with 10 mg and 25 mg of empagliflozin, respectively. In a long-term follow-up, the eGFR was stable in the empagliflozin group but fell in patients who received a placebo; empagliflozin users saw annual drops while those taking the placebo have seen an increase (36).

The eGFR decreased with canagliflozin at three months but remained stable for six years in the CANVAS programme, while the eGFR gradually decreased with placebo (19). In populations with renal impairment, SGLT2 inhibition was associated with an initial decline in the eGFR followed by a return to baseline. Analysis of 17 studies found that in patients with normal renal function, there was no significant difference in eGFR between SGLT2 inhibitors and placebo (37).

The dapagliflozin group outperformed the placebo group in the DECLARE-TIMI trial in terms of the composite renal outcome (16). The meta-analysis of three trials—

EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58 - found that the risk of renal disease progressing by 45% was decreased, and that this benefit was comparable in patients with and without atherosclerotic cardiovascular disease (17).

Mechanisms of SGLT2 Inhibitor Renal Effects

Multiple factors work together to protect the kidneys. A decrease in the kidney's blood flow, a decrease in glomerular hyper filtration, and a decrease in intra-glomerular pressure may result from SGLT2 inhibitors because they decrease sodium reabsorption in the proximal tubule of the kidney and increase sodium delivery to the macula densa (40). Albuminuria and eGFR may decrease abruptly as a result of these effects, but eGFR may then stabilise over time (41). The benefits of SGLT2 inhibitors on a number of renal impairment risk factors, such as high blood pressure, high serum uric acid, high blood sugar, and body weight, have been previously discussed (42).

Weight Loss and SGLT2 Inhibition Mechanisms

Intense lifestyle changes may result in clinically significant weight loss that can be sustained over the long term, and a minimum of 3% weight loss is beneficial for metabolic control (43,44). Due to glucose excretion and osmotic diuresis, calorie loss and water loss are the two main effects of SGLT2 inhibition that contribute to the initial loss of body weight. Both mechanisms appear to start functioning early in the course of therapy, but long-term glycosuria persists with no discernible fluid change. Future studies will be able to conclusively determine whether the remarkable cardiorenal outcomes include the weight loss effect as a primary factor or just as an additional benefit.

The fat loss associated with SGLT2 inhibition is caused by a sophisticated metabolic process that Ferrannini et al. described as a gradual switch to fatty acid utilisation (25, 45). An increase in glucagon concentration in response to lower levels of insulin and blood glucose sets off a chain of metabolic reactions that lead to lipolysis and lipid oxidation. By producing more ketone bodies, which are the heart's preferred source of energy and consume less oxygen during metabolism, it would be possible to enhance the benefits on heart failure. This theory is refuted by the high levels of ketone bodies found in heart failure patients, even when SGLT2 inhibition is not present.

HbA1c Reduction

In trials involving patients with a lower mean age, shorter duration of diabetes, and higher baseline BMI, HbA1c, and fasting glucose, the 24-week reduction of HbA1c with SGLT2 inhibitors was greater. This meta-analysis was published in 2014 (46). Recent clinical trials have shown that the HbA1c reduction is maintained for up to a year after reaching its peak in comparison to placebo at about six months (46). SGLT2 inhibitor therapy has been linked to a similar hypoglycemic risk as metformin and DPP-4 inhibitor therapy.

SGLT2 inhibitors have shown non-inferiority as well as additional metabolic advantages when measured against other oral anti-hyperglycemic medications. For instance, over a 104-week period, HbA1c decreased by 0.65% with canagliflozin 100 mg, 0.74% with canagliflozin 300 mg, and 0.55% with glimepiride 6 or 8 mg in a randomised, double-blind study involving 1,450 patients (47). Additionally, SGLT2 inhibitors have demonstrated additional improvements in glucose control when combined with other anti-hyperglycemic drugs (including insulin and both oral medications). At 24 weeks, dapagliflozin added to patients who were already taking metformin and a sulfonylurea resulted in a decrease in HbA1c of 0.86% as opposed to 0.17% in the placebo group (48). In a 78 week randomised, double-blind, placebo-controlled trial, empagliflozin significantly decreased HbA1c (0.50.1% with 10mg and 0.60.1% with 25mg, both p0.001) in patients with type 2 diabetes who were not

adequately controlled on basal insulin, according to Rosenstock et al. (49).
Furthermore, while the placebo group had to increase their basal insulin dose by 5.5–1.6 units, the empagliflozin 10 mg group decreased their dose by 1.2–1.5 units, and the empagliflozin 25 mg group decreased their dose by 0.5–1.6 units, showing that SGLT2 inhibitors may reduce the amount of insulin needed and prevent weight gain caused by insulin (49). HbA1c decreased by 0.62 percent in the Canagliflozin 100 mg group and by 0.73 percent in the Canagliflozin 300 mg group compared to placebo at 18 weeks in a sub-5study of patients taking 20 units/day of insulin at baseline in the CANagliflozin CardioVascular Assessment Study (CANVAS). At 52 weeks, the HbA1c improvement was essentially unchanged (50).

CONCLUSION

The use of SGLT2 inhibitors has opened up new possibilities for treating T2DM. These medications were initially marketed as effective glycemic control agents, but due to required safety outcome trials, it has become clear that they can also protect the heart and kidneys. As a result, the SGLT2 inhibitors signal a paradigm shift in the treatment of T2DM, where one class of medications can help manage hyperglycemia without raising the risk of hypoglycemia, while also lowering the risk of secondary cardiovascular events and slowing the progression of renal disease. The indications for these drugs may soon increase with the anticipated addition of the SGLT2 inhibitor dapagliflozin to the pharmacological toolbox available for the management of patients with HF who do not have diabetes. Clinicians should make sure they are prepared to fully benefit from the advantages these medications can provide for their patients and should view SGLT2 inhibitors as a preferred class of antihyperglycemic medication for those with T2DM.

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