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SGLT2 INHIBITORS BEYOND GLYCAEMIC CONTROL

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ABSTRACT Globally, Type 2 diabetes (T2DM) is a metabolic disease that is commonly associated with obesity, dyslipidemia, hypertension, heart failure, hyperuricemia, renal failure, and hyperuricemia [1]. Various findings suggest, T2DM is associated with a 2- to 3- fold augmented risk of cardiovascular disease, which is the leading cause of morbidity and mortality in these patients. In addition, up to 40% of T2DM patients can potentially develop diabetic kidney disease. T2DM patients form the major chunk of the population burden that have an end-stage renal disease that may require renal replacement therapy. Remarkably, diabetic kidney disease patients are at markedly higher risk of developing cardiovascular outcomes[2]. Thus, cardiorenal complications in the T2DM population are an area of concern that needs considerable attention. Cardiovascular and renal risk management in T2DM patients requires a comprehensive multipronged approach. This multipronged approach should include, in addition to glycaemic control, the control of blood pressure (BP) and lipids, weight management, smoking cessation, and, when indicated, antiplatelet therapy. Multifaceted pathogenesis of CV disease (CVD) in diabetes makes it imperative to have a specific therapeutic intervention that could diminish the risk for atherosclerosis and renal disorder along with glycaemic control. Unfortunately, the CV safety of the existing antidiabetic medications has become an acute area of concern. Data from various studies and clinical trials show that antidiabetic medications, Rosiglitazone, sulfonylureas, and insulin, have been related to the amplified risk of CV events in T2DM patients[3]. These findings even prompted, the U.S. Food and Drug Administration in 2008, to make it mandatory for all new antidiabetic medications to provide evidence of their CV safety [4]. Though, to date, the potential effects on CV events of several traditionally used glucose-lowering agents viz., sulfonylureas,(in Carolina study Glimepiride is as safe as Linagliptin) glinides, metformin, thiazolidinediones, and insulin, remain uncertain[3]. Amongst all the therapeutic classes of anti-diabetic medications available, Sodium/glucose cotransporter-2 inhibitors (SGLT2i) have emerged to be the magic bullet that can help to therapeutically manage both cardiac as well as renal risks in T2DM patients.

KEYWORDS :

Understanding the physiological role of SGLT2 receptors in glycaemic control and the impact of its inhibition

The kidney plays a vital role in glucose homeostasis, through its role in gluconeogenesis and by reabsorption of glucose from the urine. In normal, non-diabetic individuals, almost 160-180 g of glucose is filtered by the kidneys per day and practically all the filtered glucose is reabsorbed in the proximal tubule of the kidney[5]. The major share of glucose reabsorption (~90%) occurs in the first segment of the proximal tubule by SGLT2 receptors. SGLT2, receptors are the low-affinity, high-capacity transporter present in the early proximal renal tubule[6]. Rest 10% of glucose reabsorption occurs in the distal part of the tubule wherein SGLT1 receptors are present. Contrary to SGLT2, SGLT1 receptors are high-affinity, low-capacity transporter present in the distal renal tubule[7,8]. SGLT2 and T1 are the transporters that are capable of actively transporting glucose along with sodium against a concentration gradient into the cell. During this process of reabsorption, is driven by the active transport of sodium out of the cell by the adenosine triphosphate dependent sodium-potassium pump. Glucosuria occurs, wherein, the blood glucose load exceeds the renal tubular glucose excretion threshold of 180 mg/dL. In diabetic patients, however, this threshold unexpectedly increases to 220 mg/dL. This is attributed to the fact that in diabetic patients upregulation of SGLT2 in the proximal tubule occurs, as a result of which the renal glucose reabsorption capacity is enhanced[6,8]. Additionally, diabetic patients also exhibit increased SGLT2 density in the proximal tubule, which explains the enhanced glucose threshold in diabetic patients.

Inhibitors of the SGLT2 inhibitors drugs inhibit the SGLT2-mediated glucose reabsorption in the proximal tubule of the kidney, thereby increasing the urinary glucose excretion which causes the reduction in plasma glucose levels[9,10]. This mechanism of glucose-lowering is completely independent of insulin. On treatment with SGLT2 inhibitors, the 24-h urinary glucose excretion lies between 60 and 100 g/day, which corresponds to a caloric deficit of 240-400 kcal/day [11,12]. Additionally and mechanistically, SGLT2 inhibitors simultaneously increase the excretion of sodium 26 along with a reduction in plasma volume due to glucose osmotic diuretic effects and natriuresis[13,14].

Currently, three SGLT2 inhibitors are approved are dapagliflozin, canagliflozin, and empagliflozin[15]. Ertugliflozin has also been recently approved in the USA[3]. These SGLT2 inhibitors have been found to lower glycosylated hemoglobin (HbA1c) levels between 0.7 and 0.8% relative to placebo[16]. SGLT2 inhibitor effects are glucose-dependent and insulin-independent, thus reducing the risk of hypoglycemia considerably low. These SGLT2 inhibitors can be co-administered with any other antihyperglycemic medication. Interestingly, studies suggest that SGLT2 inhibitors may improve insulin sensitivity potentially. The net caloric loss along with enhanced insulin sensitivity may facilitate by weight loss. SGLT2 inhibitors have also been found to increase glucagon secretion from α-cells in the pancreatic islet[17]. In addition to these effects on glucose homeostasis, SGLT2 inhibitors exhibit potential beneficial effects on CV and renal risk factors[18,19].

SGLT2 inhibitors beyond glycaemic control

Due to additional mechanisms, SGLT2 inhibitors exhibit a number of different activities, as enlisted and represented in Figure 1.

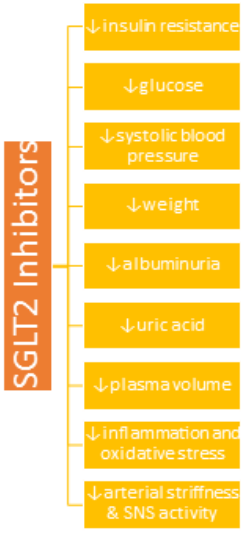

Figure 1: Activities of SGLT2 inhibitors beyond glycaemic control

In diabetic patients, CV complications are one of the most common and serious complications which have a higher probability of mortality as well. SGLT2 inhibitors act by multiple pathways to exert cardiorenal and other multitude benefits. It is proposed that in patients with heart failure, SGLT2 inhibitors prevent myocardial Na^+/H^+ exchange (NHE), thereby increasing the mitochondrial sodium ion concentration and reverses the electrolyte disorder. Further, SGLT2 inhibitors improve myocardial metabolism, increase myocardial oxygen supply, promote ATP energy storage, enhanced oxygen uptake, and transformation at the mitochondrial level, increase in ketone bodies, lowering the insulin-to-glucagon ratio, inhibiting myocardial fibrosis, switch from glucose to ketone utilization during myocardial metabolism and reverse myocardial remodeling. SGLT2 inhibitors also reduce cardiac preload. They can reduce cardiac preload and myocardial oxygen consumption by osmotic diuresis. More importantly, osmotic diuresis induced by SGLT2 inhibitors is distinctly different from that of other diuretic classes and leads to greater electrolyte-free water clearance and subsequently greater fluid clearance from the interstitial fluid space than from the circulation, resulting in congestion relief with minimal impact on blood volume, arterial filling, and organ perfusion. SGLT2 inhibitors also reduce afterload. They can lower blood pressure by osmotic diuresis and increasing urinary sodium excretion, improve cardiovascular function by reducing oxidative stress and endothelial cell inflammation, and then reduce cardiac afterload. SGLT2 inhibitors reduce cardiomyocyte apoptosis and improve myocardial fibrosis. SGLT2 inhibitors lead to progression or inhibition of apoptosis[20]. SGLT2 inhibitors could attenuate cardiac fibrosis by alleviating oxidative stress and TGF-β production and regulating macrophage polarization. SGLT2 inhibitors reduce proteinuria, delaying the progression of renal disease. Proteinuria and renal insufficiency are risk factors for cardiovascular events in patients with diabetes. SGLT2 inhibitors can reduce proteinuria by reducing glomerular hyperfiltration. Besides, SGLT2 inhibitors also have a good renal protective effect, delaying the progressive damage of diabetic nephropathy. Under the hyperglycaemic condition, the reabsorption of SGLT2-mediated sodium and glucose in renal proximal tubules is enhanced and the tubular feedback mechanism is damaged. As a result, renal blood perfusion is increased, vascular wall pressure is increased, the tension of entering glomerular arterioles is abnormal, the basement membrane thickened, and glomeruli are injured. SGLT2 inhibitors block the reabsorption of sodium and glucose in the proximal tubules, regulate renal tubule-glomerular feedback, and reduce glomerular ultrafiltration. SGLT2 inhibitors prevent the active reabsorption of sodium in proximal tubules, thus reducing renal energy consumption and protecting the kidney. SGLT2 inhibitors impede the expression of inflammatory factors and reduce the infiltration of inflammatory factors to reduce renal inflammation and delay changes in structure and function and the progression of fibrosis in the process of diabetic nephropathy. Also, SGLT2 inhibitors restore the mode of cellular energy metabolism. SGLT2 inhibitors improve blood glucose levels. Hyperglycaemia causes glucotoxic damage to the kidney. SGLT2 inhibition is associated with mild negative sodium–water balance due to reabsorption of glucose and sodium which results in an initial decrease in extracellular fluid and plasma volume. The acute natriuretic effect of SGLT2 inhibition is typically manifested by an increase in urine volume of 300 ml per day for the first 2–3 days, returning to baseline levels over several weeks with re-establishment of the sodium–water balance, with an approximately 7% reduction in plasma volume (with a wide range between individuals; interquartile range 5–12%) by 3 months of treatement[21]. Natriuresis and a reduction in plasma volume are likely to be protective against the development of HF and might explain at least part of the rapid-onset reduction in the risk of hospitalization for HF observed in the cardiovascular outcome studies, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial[22] and the DAPA-HF trial[23]. In DAPA-HF, 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less were administered either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary endpoint of the study was, composite worsening of heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. The study was carried over 18 months which revealed that the primary outcome befell in 386 of 2373 patients (16.3%) in the dapagliflozin group while same incidence occurred in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). First worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). While, death from cardiovascular causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Thus, it was concluded that the risk of worsening heart failure or death from cardiovascular causes in patients with HF and reduced ejection fraction, was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes[23]. Further, Canagliflozin has been approved by FDA for CV as well as renal indications. Based on the findings of Canagliflozin Cardiovascular Assessment Study (CANVAS)[27], CANVAS-Renal (CANVAS-R) and CREDENCE[22] trials, FDA has approved Canagliflozin to reduce the risk of MACE in patients with established CVD, to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in patients with diabetic nephropathy with albuminuria. In CANVAS trial, a total of 10,142 participants with type 2 diabetes and high cardiovascular risk, were randomly assigned to receive Canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. In this trial, it was found that, the rate of occurrence of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Further, in the metanalysis, renal parameters were also investigated. It was found that Canagliflozin offered beneficial effect with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite, sustained 40% reduction in the estimated glomerular filtration rate was observed along with reduction in the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77).

Further, CREDENCE trial, was a double-blind, randomized trial, wherein, patients with type 2 diabetes and albuminuric chronic kidney disease were assigned to receive canagliflozin (at a dose of 100 mg daily) or placebo. The patients recruited had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were being administered renin–angiotensin system blockade. The primary outcome of the study was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. It was found that the relative risk of the primary outcome was reduced by 30% in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). While, the relative risk of occurrence of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002)[22].

The outcome of Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial prompted FDA to approve Empagliflozin for reducing the risk of CV death in patients with established CVD, risk of incident or worsening nephropathy, doubling of serum creatinine, progression of kidney disease, progression to macroalbuminuria, initiation of renal replacement therapy[26]. In the EMPA-REG OUTCOME trial, 7020 patients were administered, 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome for the trial was occurrence of the death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, in the pooled empagliflozin group versus the placebo group. While, the key secondary composite outcome was the primary outcome plus hospitalization for unstable angina. It was found that, the primary outcome occurred in 490 of 4687 patients (10.5%) in the pooled empagliflozin group while, 282 of 2333 patients (12.1%) in the placebo group exhibited primary outcome (hazard ratio in the empagliflozin group, 0.86; 95.02% confidence interval, 0.74 to 0.99; P=0.04 for superiority). In the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction). The study

showed that the number of MACE (major adverse cardiovascular events, including cardiovascular-related death, nonfatal cerebral infarction, and nonfatal myocardial infarction) decreased by 14%, the number of cardiovascular-related deaths decreased by 38%, the number of hospitalized cases of heart failure decreased by 35%, and the mortality rate decreased by 32% in the empagliflozin treatment group compared with the placebo group. A follow-up study also found that empagliflozin showed a cardiovascular protective effect from the first month to the third month of treatment, and with the extension of treatment time, the cardiovascular protective effect. Thus, it was concluded that patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care[26].

SGLT2 inhibitors lower blood glucose and reduce renal hypertrophy, injury, and inflammation caused by glucotoxicity. SGLT2 inhibitors improve blood pressure. When the body is in a state of hypertension for a long time, the self-regulating ability of renal vessels decreases, leading to renal dysfunction and proteinuria. SGLT2 inhibitors can slightly lower blood pressure and indirectly affect renal function. The study has proved that dapagliflozin improves morning home systolic BP, independent of albuminuria in patients with diabetic nephropathy [24]. Additionally, SGLT2 inhibitors may reduce body weight and blood pressure in nondiabetic patients [25]. SGLT2 inhibitors decrease uric acid levels. High levels of uric acid can form crystals and deposit in the kidney, reducing the glomerular filtration rate. Also, other studies have confirmed that serum uric acid may promote the occurrence and development of diabetic nephropathy by mediating endothelial dysfunction, RAAS overactivation, and the inflammatory response. SGLT2 inhibitors promote osmotic diuresis and uric acid excretion, thus reducing the burden on the kidney. SGLT2 inhibitors promote weight loss. On the one hand, obesity results in mechanical pressure on the kidney, causing renal hypoxia; on the other hand, obesity affects renal hemodynamics (including increased renal blood flow, glomerular hyperfiltration, and renal tubule sodium retention) and increases glomerular filtration rate and glomerular volume. SGLT2 inhibitors can reduce abdominal and peripheral fat and body weight through glycosuria-related calorie loss and osmotic diuresis, thus improving renal hypoxia and hemodynamics and protecting the kidney. SGLT2 inhibitors increase the level of glucagon. Glucagon can dilate blood vessels and increase renal blood flow, renal filtration, and electrolyte excretion, thereby maintaining renal function. SGLT2 inhibitors can protect the kidney by lowering blood glucose and increasing glucagon. SGLT2 inhibitors reduce the level of insulin. Insulin can promote the proliferation of renal cells and the extracellular matrix and damage renal function. SGLT2 inhibitors can reduce the level of blood glucose, reduce insulin secretion and decrease the burden on the kidney. SGLT2 inhibitors promote diuresis. The synergistic effect of SGLT2i and proximal tubule Na^+/H^+ can produce diuresis and blood pressure reduction, decreasing the burden of the kidney. Additionally, the incidence of ketoacidosis caused by SGLT2 inhibitor is relatively rare, approximately 0.1% [26]. An overview of the therapeutic actions of SGLT2 inhibitors is represented in Figure 2.

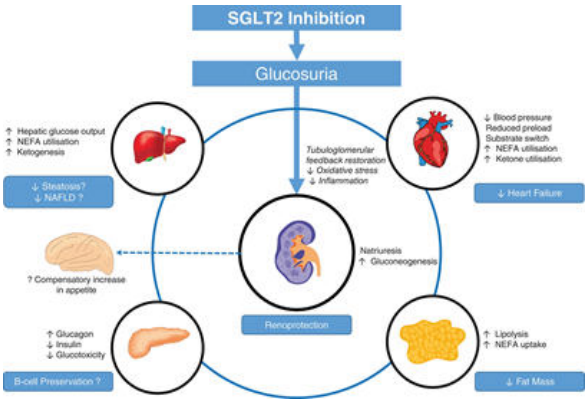

Figure 2: Overview of the SGLT2 inhibitors effect on various organs[29]

Later, the Canagliflozin Cardiovascular Assessment Study (CANVAS) program[27] and the Dapagliflozin effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58) trial[28] showed similar trends (reduction in cardiovascular death and hospitalization for heart failure). Different trials have established the efficacy of the SGLT2 inhibitors in glycaemic as well as non-glycaemic outcomes, enlisted in Table 1. The positive therapeutic efficacy and safety outcome of these trials have established the utility of incorporating SGLT2 inhibitors in the therapy for diabetics, in order to protect them from various CV and renal risk factors.

Table 1: Clinical trial outcomes for SGLT2 Inhibitors with its effect on glycaemic as well as non-glycaemic outcomes

Canagliflozin						Dapagliflozin					
Therapy	**A1C (%)**	**FPG (mmol/L)**	**Weight (kg)**	**SBP (mmHg)**	**Hypo-glycemia (%)**	**Therapy**	**A1C (%)**	**FPG (mmol/L)**	**Weight (kg)**	**SBP (mm Hg)**	**Hypo-glycemia (%)**
Mono-therapy[30] (100 mg and 300 mg, respectively)	-0.77 (p <.001) -1.03 (p <.001)	-1.5 (p <.001) -1.9 (p <.001)	-2.5 (p <.001) -3.4 (p <.001)	-3.3 (p <.001) -5.0 (p <.001)	3.6** 3.0**	**Mono-therapy[31]** (2.5 mg, 5 mg, and 10 mg, respectively)	-0.58‡ -0.77 (p = 0.0005) -0.89 (p <.0001)	-0.84‡ -1.34 (p <.001) -1.60 (p <.0001)	-3.3** -2.8** -3.2**	-4.6** -2.3** -3.6**	1.5** 0** 2.9**
Add-on to MET and PIO[32] (100 mg and 300 mg, respectively)	-0.89 (p<.001) -1.03 (p <.001)	-1.5 (p <.001) -1.8 (p <.001)	-2.6 (p <.001) -3.7 (p <.001)	-5.3 (p <.01) -4.7 (p <.025)	4.4** 6.1**	**Initiated in combo with MET[33]** (5 mg and 10 mg, respectively)	-2.05 (p<0.0001) -1.98 (p<0.0001)	-3.39 (p<0.0001) -3.35 (p <.0001)	-2.66 (p <.0001) -3.33 (p <.0001)	-2.9** -3.3**	2.6** 3.3**
CAN 300 mg Versus SIT (Add-on to MET +SU)[34]	-1.03 (superior to SIT)	-1.7 (p <.001)	-2.3 (p <.001)	-5.1 (p <.001)	43.2 ** (40.7 with SIT)	**Add-on to MET[35]** (2.5 mg, 5 mg, and 10 mg, respectively)	-0.67% (p = 0.0002) -0.7% (p <.0001) -0.84% (p<0.0001)	-0.99 (p = 0.0019) -1.19 (p <.0001) -1.30 (p <.0001)	-2.2 (p <.0001) -3.0 (p <.0001) -2.9 (p<0.0001)	-2.1** -4.3** -5.1**	2** 4** 4**
Versus SIT (Add-on to MET)[35] (100 mg and 300 mg, respectively)	-0.73 (non-inferior to SIT) -0.88 (superior to SIT)	-1.5 (p <.001 vs. SIT) -2.0 (p <.001 vs. SIT)	-3.3 (p <.001 vs. SIT) -3.7 (p <.001 vs. SIT)	-3.5 (p <.001 vs. SIT) -4.7 (p <.001 vs. SIT)	6.8** 6.8** (4.1 with SIT)	**Versus GLIP (Add-on to MET)[36]** (2.5 mg – 10 mg data combined)	-0.52% (non-inferior to glipizide)	-1.24 (from baseline)** -0.20 (vs. glipizide)**	-3.22 (p <.0001 versus glipizide)	-4.3 (from baseline)** -5.0 (vs glipizide)**	3.5 (p <.0001 versus glipizide)

Versus GLIM (Add-on to MET)[37] (100 mg and 300 mg, respectively)	-0.82 (non-inferior to GLIM) -0.93 (superior to GLIM)	-1.35** -1.52**	-3.7 (<.0001 vs GLIM) -4.0 (<.0001 vs GLIM)	-3.3** -4.6**	6 (p <.0001 vs. GLIM) 5 (p <.0001 vs. GLIM) (34 with GLIM	**Add-on to GLIM**[38] (2.5 mg, 5 mg, and 10 mg, respectively)	-0.58 (p <.0001) -0.63 (p <.0001) -0.82 (p<0.0001)	-0.93‡ -1.18 (p <.0001) -1.58 (p <.0001)	-1.18 (p= 0.1410) -1.56 (p = 0.0091) -2.26 (p<0.0001)	-1.1** -1.7** -2.8**	7.1** 6.9** 7.9**

FPG = fasting plasma glucose, SBP = systolic blood pressure, MET = metformin, PIO = pioglitazone, SU=sulfonylurea, CAN = canagliflozin, SIT = sitagliptin, GLIM = glimepiride, GLIP = glipizide, TZD = thiazolidinedione

Outcomes are reported as change from baseline unless otherwise noted.
*P-values are versus placebo unless otherwise indicated.
**P-value not provided
¶Change in kg was -1.9 for 100mg and -2.5 for 300mg but authors only provided p-value for % change in weight
‡No significant difference versus placebo

CONCLUSION

There is an increasing prevalence of T2DM across populations worldwide. However, suboptimal control of glycemia and other CV risk factors achieved with currently available agents necessitates the need for therapies with novel modes of action remains an important clinical priority. SGLT2 inhibitors are novel oral glucose-lowering agents that improve glycemic control with a low risk of hypoglycemia, independent of insulin secretion. Additionally, these agents cause a modest reduction in BP and body weight. The mode of action of SGLT2 is independent of endogenous insulin secretion thus permitting its usage in any stage of T2DM. SGLT2 inhibitors effectively increase glycosuria, improve glycaemic control and reduce body mass owing to calorific loss. In addition, SGLT2 inhibitors promote early natriuresis (with an associated reduction in plasma volume and a rise in hematocrit), a reduction in systemic blood pressure, reduced glomerular hyperfiltration and albuminuria, and a shift towards ketone bodies as the metabolic substrate for the heart and kidney. These mechanisms underline the cardiovascular, renal, and other multitude of benefits of SGLT2 inhibitors, which make them suitable and safe candidates for including them in the anti-diabetic therapy to protect the patient from different risk factors, providing an overall protection form comorbidity.

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