Review Article

Cardiovascular Effects of Sodium Glucose Co-transporter-2 Inhibitors in Patients with Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM), the leading type of diabetes, has a typical association with coronary heart disease. In India, patients with diabetes are at an increased risk of developing coronary disease as compared to people without diabetes and this suggests the requirement of intensive treatment of cardiovascular (CV) risk factors. Consequently, there is a need for an intervention that could target CV risk factors in multiple paths beyond hyperglycemic control alone. Although metformin is the mainstay of treatment in most of the patients with T2DM, a second line of treatment with anti-hyperglycemic agent is warranted in patients with T2DM in the management of CV risk factors beyond glycemic control. Sodium glucose co-transporter-2 (SGLT-2) inhibitors, the oral hypoglycemic drug, that act independent of insulin secretion are associated with a reduced risk of hypoglycemia which is associated with the increased risk of CV events. Moreover, it has been observed that the use of SGLT-2 inhibitors in patients with T2DM is associated with reductions in blood pressure and body weight beyond improved glycemic control. In this article, the clinical efficacy, safety, and tolerability of SGLT-2 inhibitors on glycemic, nonglycemic parameters, and CV outcome including data from the EMPA-REG OUTCOME study are discussed. The EMPA-REG OUTCOME study is the first CV outcome study that demonstrated the association of a glucose lowering agent with the reduced CV mortality and all-cause mortality, and reduced hospitalization for heart failure in patients with T2DM at high risk of CV events. Although the mode of action associated with the CV benefits remains unknown, data from ongoing trials including DECLARE-TIMI (Dapagliflozin Effect on CV Events) and CANVAS (Canagliflozin CV Assessment Study) trials potentially can validate the class-effect for SGLT-2 inhibitors regarding the CV outcomes.

Keywords: Cardiovascular benefits, sodium glucose co-transporter-2 inhibitors, type 2 diabetes mellitus

Type 2 Diabetes and Cardiovascular Disease

In 2014, the World Health Organization estimated that 422 million people had diabetes globally and the prevalence of diabetes among adults >18 years of age was 8.5%. India alone had more than 69 million individuals in 2015 with diabetes and with a predicted 101 million individuals being affected by 2030.[1] Type 2 diabetes mellitus (T2DM), a leading type of diabetes, has a characteristic association with coronary heart disease (CHD). Patients with diabetes have 2- to 4-fold increased risk of developing coronary disease as compared to people without diabetes.[2] Furthermore, 65%–75% of deaths in people with diabetes are considered to be due to the cardiovascular disease (CVD).[3] In addition, it has been observed that patients with T2DM who had no prior myocardial infarction (MI) have comparable risk of MI as patients without diabetes who had prior MI. These data suggest the requirement of intensive treatment of cardiovascular (CV) risk factors in patients with T2DM.[4]

People of Indian Asian origin, who comprise over a fifth of the world's population, are referred as "Asian Indian Phenotype" which denotes the combination of clinical, biochemical, and metabolic abnormalities [Figure 1] that predispose South Asian origin to develop diabetes and CHD.

In India, with the socioeconomic transformation, advanced ageing, rapidly increasing levels of overweight, and individuals and children with prediabetes (impaired glucose regulation),

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increase in T2DM and CHD will result in increased burden in the future.[5]

Despite a normal body mass index by international standards, the increased prevalence of CV risk factors, T2DM, and an earlier onset of CHD among South Asians explains that this population is more susceptible to diabetes and CVD, and that these conditions are interlinked.[5]

Although hyperglycemia remains as the major risk factor for microvascular complications, its association with CV outcomes from the intensive glycemic control intervention still remains debatable.[6] As multiple CV risk factors beyond hyperglycemia are associated with T2DM, a multifactorial approach beyond glucose control including management of blood pressure, lipids and weight, cessation of smoking and anti-platelet therapy, if indicated, are recommended.[7,8] Considering these recommendations, in most patients, it remains challenging to achieve the therapeutic goals owing to the progressive nature of T2DM and the characteristics of the currently available drugs that target only hyperglycemia. Consequently, there is a need for an intervention that could target CV risk factors in multiple paths beyond hyperglycemic control alone.[9,10]

As the clinical efficacy of a particular intervention on CV risk potentially depends upon the mode of action of that specific drug, the safety and clinical efficacy of drugs including sulfonylurea (SU), glinides, metformin, thiazolidinediones, insulin, glucagon-like peptide-1 receptor analogues, or dipeptidyl-peptidase-4 (DPP-4) inhibitors on CV events in patients with T2DM still remain unreliable.[11]

Although metformin is the first-line of drug in most of the patients with T2DM, a second line anti-hyperglycemic agents (AHAs) is required in patients with T2DM in the management of hyperglycemia as well as CV risk factors. SUs, one of the traditional AHAs commonly prescribed in patients with DM, are usually associated with weight gain and hypoglycemia, the major determinants of CV risks. Although it is not well established, SUs potentially can cause all-cause mortality and CV-mortality. In addition, DPP-4 inhibitors, the recent addition to the armamentarium in the management of T2DM, have also failed to show CV benefits; trials including TECOS,[12] SAVOR-TIMI53,[13] and EXAMINE[14] that involved sitagliptin, saxagliptin, and alogliptin showed a neutral effect on CV outcomes among patients with T2DM. Although gliptins are demonstrated to reduce CV risk factors in the preclinical studies and systematic analysis,[15] its neutral effect on the CV outcomes potentially due to the short-term duration of study and involving patients predominantly of high-risk patients. The results of these trials implicate that as the macrovascular complications might be a late complication of the progressive T2DM, an adequate duration of treatment is required. Moreover, in patients with established CV risk, it might be more challenging to reduce the CV risk factors that persist with these treatments.[10]

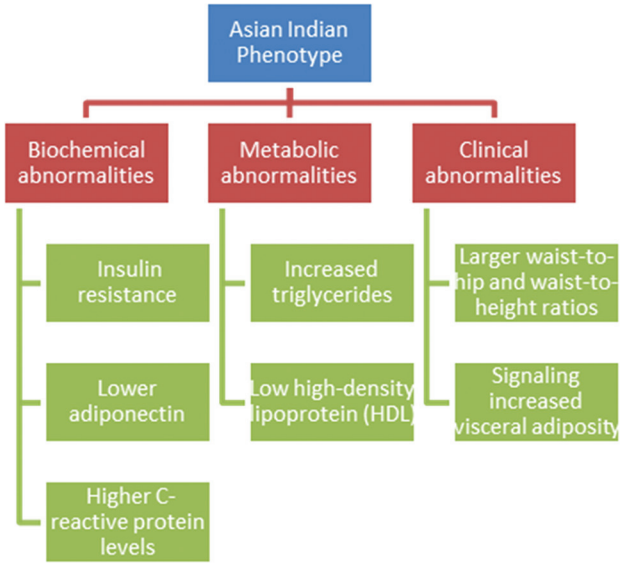

Figure 1: Asian Indian phenotype that predispose to develop diabetes and coronary heart disease

Cardiovascular Markers and Sodium Glucose Co-transporter-2 Inhibitors

With the available evidence that the multiple CV risk factors along with hyperglycemia coexist in most of the patients with T2DM, multifactorial approach is required to address the CV risk factors. As sodium glucose co-transporter-2 (SGLT-2) inhibitors act independent of insulin secretion, these inhibitors are associated with a reduced risk of hypoglycemia that is associated with the increased CV events. Besides improved glycemic control with SGLT-2 inhibitor, it also improves a range of metabolic and hemodynamic factors that increase the risk of CVD with its unique mechanism of action. Moreover, it has been demonstrated that the use of SGLT-2 inhibitors in patients with T2DM are associated with weight loss and reduced visceral fat, reductions in urinary albumin excretion, reductions in blood pressure, increase in high-density lipoprotein and reduced triglycerides, improved endothelial function that reduce arterial stiffness and reductions in uric acid[10] [Figure 2].

Sodium Glucose Co-transporter-2 Inhibitors and Its Mechanism of Action

Kidney plays a vital role in normal glucose homeostasis by balancing the amount of glucose filtered from the plasma into the renal glomerular filtrate and the amount reabsorbed from this filtrate and returned to the blood circulation.[16]

SGLT-2 with a low affinity but high capacity for glucose transport mediates more than 90% of reabsorption of the filtered glucose, while SGLT-1 with a high affinity and low capacity for glucose facilitates only 10% of the renal absorption of the glucose. Owing to the highly efficient reabsorption of

Figure 2: Potential cardiovascular effects of sodium glucose co-transporter-2 inhibitors

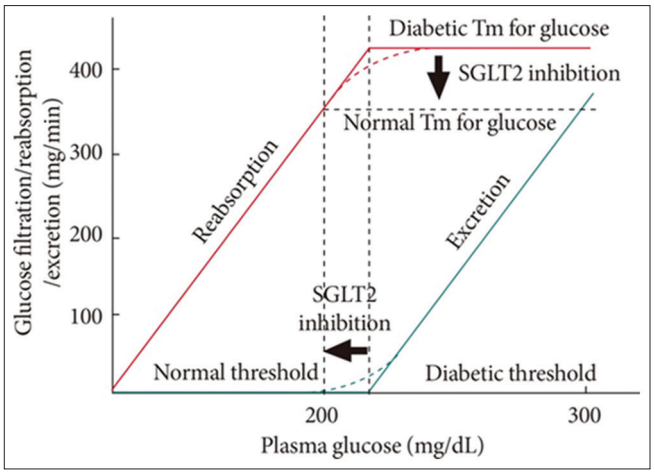

Figure 3: Renal glucose reabsorption before and after sodium glucose co-transporter-2 inhibition

glucose with SGLT-2, drugs that selectively inhibit SGLT-2 have a potentially significant role in the management of diabetes.[17]

The inhibition of SGLT-2, which results in the inhibition of renal glucose reabsorption [Figure 3], is a novel treatment strategy for T2DM owing to the insulin-independent mechanism of action.[17]

As depicted in the schematic representation, with the increase in plasma glucose concentration, the reabsorption of glucose also increases gradually. When the plasma glucose level is <200 mg/100 ml, there is no excretion of glucose in the urine. The maximum ability of the renal tubule to reabsorb glucose or the transport maximum for glucose is exceeded as the plasma glucose level reaches a threshold of around 200–250 mg/100 ml. When it passes this threshold, excretion of glucose in the urine ensues. Owing to the physiological disparity between each nephron, the actual and theoretical threshold for both reabsorption and excretion also varies and this is called "Splay". SGLT-2 inhibitors reduce the renal glucose threshold and thus, resulting in increased urinary glucose excretion (UGE).[17]

With the reduction in the renal threshold for glucose excretion, SGLT-2 inhibitors prevent the renal reabsorption of glucose and thereby, increase the UGE and improve glycemic control. The inhibition of SGLT-2 leads to the hindrance of only ~30%–50% renal reabsorption of the glucose. They act independent of insulin secretion and thus are not associated with any risk of hypoglycemia. They can be used as monotherapy or combination therapy with other drugs. In addition, owing to its osmotic diuretic effect, it potentially may reduce blood pressure and may also be associated with weight loss. Considering these advantages, SGLT-2 inhibitors may have a revolutionary role in the management of diabetes.[16,17]

Several clinical trials have demonstrated that SGLT-2 inhibitors as monotherapy and add-on therapy are efficacious in patients with T2DM inadequately controlled with conventional AHAs.[18-22] Based on the agent and dosage used, SGLT-2 inhibitors reduce glycosylated hemoglobin by 0.5%–1% and fasting plasma glucose (FPG) by 15–35 mg/dL. Moreover, SGLT-2 inhibitors are also associated with modest reductions in weight (−1.5–−3.5 kg) and systolic blood pressure (SBP) (−3–−5 mm Hg). Although increased urination and the genital mycotic infections are the most common adverse effects associated with the use of SGLT-2 inhibitors, it is well tolerated and associated with the reduced risk of hypoglycemia.[18,23-26]

In addition, several studies, which investigated the physiologic response to SGLT-2 inhibitors-induced glycosuria in patients with T2DM, demonstrated that it improved β cell function and insulin sensitivity regardless of the decrease in insulin secretion and tissue glucose disposal and the increase in endogenous glucose production. As a result, SGLT-2 inhibitors-induced glycosuria resulted with the fasting and postprandial glycemia got reduced [Figure 4].[20-22]

Although there have been reports of diabetic ketoacidosis (DKA) associated with the use of SGLT-2 inhibitors in patients with T1DM and T2DM, lesser frequency of DKA was reported in patients with T2DM. Clinical trials which investigated the efficacy and safety of SGLT-2 inhibitors in patients with T2DM demonstrated that canagliflozin associated with 0.07% of DKA in >17,500 patients, dapagliflozin with <0.1% in >18,000 patients and empagliflozin with <0.1% for blinded DKA events in ≈ 7000 patients.[27-29]

With the significantly increased association of T2DM with the CV risk, numerous guidelines highlight the need to prevent and reduce CV complications. Prevailing evidence suggest that the glycemic control plays a vital role in the reduction of the CV complications; however, it still remains debatable

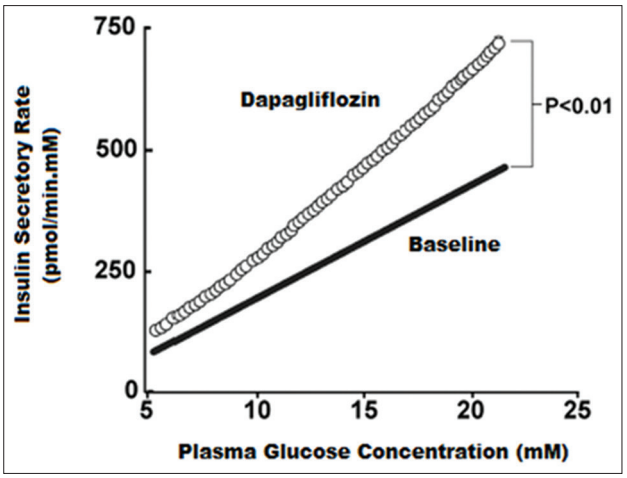

Figure 4: β-cell glucose sensitivity before and after treatment with dapagliflozin

about the effect of glucose control over the CV outcomes from the randomized trials that involves the intensive glycemic control.[30]

As per the American Association of Clinical Endocrinologists' guideline recommendation, SGLT-2 inhibitor is the acceptable alternative to metformin among patients with recent-onset T2DM or mild hyperglycemia (A1c <7.5%). In patients who present with an A1c >7.5%, metformin plus another agent including SGLT-2 inhibitor in addition to lifestyle therapy is recommended.[31] As per the American Diabetes Association guideline, SGLT-2 inhibitors are added to the background of metformin or sulfonylurea plus metformin if glycemic goals are not met.[32]

SGLT-2 inhibitors that are approved for use in the management of T2DM in the United States, European Union, and other countries are canagliflozin,[33] dapagliflozin,[34] and empagliflozin.[35] Ertugliflozin and sotagliflozin (a dual inhibitor of SGLT-2 and SGLT-1) are currently in Phase 3 clinical trials.[36] SGLT-2 inhibitors that have approval in Japan only are ipragliflozin,[37] tofogliflozin,[38] and luseogliflozin.[39]

Effect on Glycemic Parameters

In treatment-naïve T2DM patients, SGLT-2 inhibitors including canagliflozin, dapagliflozin and empagliflozin as monotherapy for 24–26 weeks of study period reduced HbA1c by 0.6%–1.0% as compared with the placebo and also associated with the decreased risk of hypoglycemia ranging from 0% to 3%. In addition, considerable improvements in the FPG levels were also observed.[23,25,40]

A 52-week, double-blind, multicenter, active-controlled, randomized trial, in which the efficacy, safety, and tolerability of dapagliflozin evaluated in patients with T2DM and inadequately controlled with metformin monotherapy as compared with sulfonylurea glipizide, demonstrated that although dapagliflozin showed comparable efficacy, it is associated with the significant weight loss of-3.2 kg versus 1.2 kg with glipizide and decreased risk of hypoglycemia (3.5%) versus glipizide (40.8%; $P < 0.0001$).[26]

A randomized, double-blind, Phase 3 noninferiority trial, which assessed the efficacy and safety of canagliflozin, showed that at 52 weeks canagliflozin 300 mg was superior in reducing HbA1c by 0.93% as compared with glimepiride (0.81%) in patients with T2DM who were inadequately controlled with metformin. The incidence of hypoglycemic risk was significantly lesser with canagliflozin 100 mg (6%) and 300 mg (5%) than with glimepiride (34%) with a $P < 0{\cdot}0001$ for both parameters. It has also been observed that the occurrence of severe hypoglycemia was also lesser with canagliflozin 100 mg (<1%) and 300 mg (<1%) as compared with glimepiride (3%).[41]

Dapagliflozin 10 mg provided statistically significant and clinically relevant improvements in glycemic control compared with placebo (with mean placebo-corrected HbA1c decrease in the different studies ranging from −0.5% to −0.8%), when given as add-on therapy to metformin or sulfonylurea.[40,42]

In addition, in a 52 week, randomized, double-blind, active-controlled, Phase 3 noninferiority trial, compared the efficacy and safety of canagliflozin with glimepiride in patients with T2DM inadequately controlled with metformin, canagliflozin 100 mg was noninferior to glimepiride and canagliflozin 300 mg was superior to glimepiride. Canagliflozin 100 mg and 300 mg also provided sustained reduction in FPG over 52 weeks; however, glimepiride was associated with the increase in FPG after 18 weeks of treatment.[41]

Both empagliflozin doses of 10 and 25 mg as an add-on therapy to metformin also significantly improved of glycemic control (with adjusted mean changes from baseline in HbA1c were −0.70% with empagliflozin 10 mg, and −0.77% with empagliflozin 25 mg and −0.13% with placebo (both $P < 0.001$). Empagliflozin 10 mg and 25 mg as add-on to basal insulin for 78 weeks also improved glycemic control.[43]

A head-to-head trial which evaluated the efficacy and safety of canagliflozin compared with sitagliptin in patients with T2DM and uncontrolled with the dual therapy of metformin and sulfonylurea have demonstrated that canagliflozin 300 mg was superior in reducing the HbA1c (−1.03%) as compared to sitagliptin 100 mg (−0.66%) at 52 weeks. Statistically significant decrease in FPG was also observed in patients treated canagliflozin as compared to sitagliptin-treated patients. The occurrence of hypoglycemia was comparable between both the treatment groups.[44]

Dapagliflozin 10 mg was also shown to have noninferior efficacy versus metformin extended release when both were given as monotherapy for 24 weeks.[45]

Effects on Body Weight

Several clinical trials have shown that the use of SGLT-2 inhibitors is associated with the weight loss ranging from −1.6 to −5 kg versus placebo.[46-48] Furthermore, the reduction in body weight

was maintained over 104 weeks as demonstrated by the clinical trials which evaluated the long-term efficacy of SGLT-2 inhibitors.[49-51] Numerous studies have shown that the weight loss associated with the SGLT-2 inhibitors therapy was owing to the reduced fat mass which accounts for 60%–90% and fluid loss following osmotic diuresis.

Although the urinary energy loss caused by SGLT-2 inhibitor is ~200 kcal/day, chronic glycosuria causes an adaptive increase in energy intake. Therefore, combining SGLT-2 inhibition with dietary restriction potentially can lead to augmented weight loss.[52]

Effect on Blood Pressure

Clinical trials have demonstrated that SGLT-2 inhibitors as monotherapy or as add-on therapy are associated with significant reduction in systolic (–3–−5 mm Hg) blood pressure from the baseline as compared with other oral AHA baseline.[41-43] In addition, SGLT-2 inhibitors are associated with significant reduction in diastolic (–1 to −3 mm Hg) blood pressure from the baseline. Furthermore, 24-h ambulatory BP monitoring was used and the modest reductions in blood pressure were not associated with increased heart rate.[53-56]

A 24-week randomized, double-blind, placebo-controlled study which has been extended to 28-week study evaluated the clinical efficacy and safety of dapagliflozin in T2DM patients who were at high risk for future CVD events. The study demonstrated that dapagliflozin was associated with the sustained reduction in SBP ranging from 2 to 3 mmHg from 24 to 52 weeks.[57]

Although the exact mechanism by which SGLT-2 inhibitors reduces BP is still not known, it has been assumed that it is related to their effects on osmotic diuresis and mild natriuresis. Besides these, the local inhibition of the renin-angiotensin-aldosterone system that occurs following an increased delivery of sodium to the juxtaglomerular apparatus is an additional mechanism by which SGLT-2 inhibitor potentially induced reduction in BP.[10]

SGLT-2 inhibitors provided statistically significant and clinically relevant improvements in SBP control compared with active-comparator (with mean placebo-corrected SBP decrease in the different studies ranging from −3 to −5 SBP), when given as monotherapy.[44,45]

Cardiovascular Safety Outcome Trials for Anti-diabetic Agents

Although the availability of the AHAs for patients with T2DM is enormous, before EMPA-REG trial data was published in 2015, not a single agent is known obviously to reduce CV events. Metformin, the mainstay therapy for patients with T2DM, is observed as associated with CV benefits; however, a large, well-designed, randomized clinical trial needs to confirm this association.[58]

Before the 2008 Food and Drug Administration (FDA) guidance for industry, HbA1c was the efficacy endpoint for approval of antidiabetic therapies. In addition, CV risk assessment was based only through adverse events reported by investigators but no central, blinded adjudication process or planned analyses have been used. However, the CV safety concerns from an excess of serious heart failure events with pioglitazone, the US FDA issued guidance that necessitated drug approval for glucose-lowering agents in T2DM to include a robust assessment of CV safety.[59]

With the FDA recommended rigorous assessment of CV safety, clinical trials which assessed the CV safety of DPP-4 inhibitors (TECOS, SAVOR-TIMI 53, and EXAMINE) demonstrated no CV benefit as compared with placebo plus active comparator.[12-14] Clinical trial, which assessed the CV safety of empagliflozin in patients with T2DM and at the high risk of CV, demonstrated that an anti-hyperglycemia agent reduced CV mortality and all-cause mortality and also, reduced hospitalization for heart failure.[29]

Cardiovascular Outcome Trials with Sodium Glucose co-transporter-2 Inhibitors

In the EMPA-REG OUTCOME trial, the effects of empagliflozin on CV morbidity and mortality in 7020 patients with T2DM at high risk for CV as compared to placebo were studied. The trial demonstrated that empagliflozin (pooled 10 and 25 mg/day doses) significantly reduced the primary major adverse CV event (MACE) outcome (CV death, nonfatal MI, nonfatal stroke) by 14% compared to placebo (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.74–0.99, P = 0.04 for superiority). Although there were no significant between-group differences in the rates of MI or stroke, in the empagliflozin group, there were significantly lower rates of death from CV 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 key secondary outcome that includes the primary outcome plus hospitalization for unstable angina (UA) occurred in 599 of 4687 patients (12.8%) in the empagliflozin group and 333 of 2333 patients (14.3%) in the placebo group (HR = 0.89; 95% CI = 0.78–1.01; $P < 0.001$ for noninferiority and $P = 0.08$ for superiority) ($P = 0.08$ for superiority). Among patients receiving empagliflozin, although there was an increased rate of genital infection, no increase in other adverse events was associated with empagliflozin.[60]

The trial also demonstrated that there was no increase in the incidence of hypoglycemia, renal impairment, urinary tract infections, volume-related side effects, bone fractures, or thromboembolic events. Consequently, the study endorses that safety profile of the SGLT-2-inhibitor could be class effect. Although there are prevailing reports of DKA in T2DM patients treated with SGLT-2 inhibitors, the EMPA-REG OUTCOME trial demonstrated that the incidence of DKA was low (0.035%)

and comparable to the placebo. However, whether the results of EMPA-REG trial are applicable to other patient profiles or represent a class effect remains to be determined.[60]

Owing to their beneficial effects of SGLT-2 inhibitors class of drugs including improved glycemic control, reduced body weight and blood pressure, lesser side effect profile and excellent safety profile, it is expected that it will advance in its placement in the therapeutic algorithm for the management of T2DM.[6]

CV outcomes trials for other agents in SGLT-2 inhibitor drug class are still ongoing and data from these trials can provide a potential class-effect on CV outcomes [Table 1].

DECLARE-TIMI, a multicenter, randomized, double-blind, placebo-controlled, parallel group trial, is the largest SGLT-2 inhibitor CV outcomes trial to date. The trial will investigate the effect of dapagliflozin (10 mg once daily) on the time to first event included in the composite endpoint of CV death, MI or ischemic stroke as primary end point and regarding the secondary outcome is time to first event included in the composite endpoint of CV death or hospitalization due to heart failure.[61]

CANVAS, a multicenter, randomized, double-blind, placebo-controlled, parallel group trial, is designed to assess the efficacy and tolerability of canagliflozin (100 and 300 mg once daily) versus placebo in patients with inadequately controlled T2DM and increased CV risk. The primary outcome is a composite of CV death, nonfatal MI, or nonfatal stroke.[62]

CANVAS-R trial that involves more than ~5800 patients evaluates the effect of canagliflozin on the progression of albuminuria in patients with T2DM and inadequate glycemic control and an increased risk of CV events. The primary endpoint is the number of participants with progression of albuminuria.[63]

CREDENCE trail, which will assess the effect of canagliflozin in reducing the progression of renal impairment (Stages 2 or 3 chronic kidney disease and macroalbuminuria) and CV mortality in patients with T2DM, includes MACE plus as a secondary outcome measure.[64]

Ertugliflozin, the fourth SGLT-2 inhibitor, is currently being assessed in Phase 3 clinical trial, a randomized, double-blind, placebo-controlled, parallel group CV outcomes trial. The primary outcome is a composite of three-point MACE.[65]

Meta-analysis and Pooled Data Analysis

With the beneficial effects of SGLT-2 inhibitors on a number of CVD risk factors, a meta-analysis which involved 25 studies and analyzed the CV safety of SGLT-2 inhibitors including dapagliflozin and canagliflozin in patients at high risk for CV, demonstrated that SGLT-2 inhibitor is not associated with the increased risk of MACEs as compared with the control group with the HR of 0.89 (0.70, 1.14).[66]

A meta-analysis involving nine randomized clinical trials including one Phase 2 trial, seven Phase 3 trial, and one Phase 3 CV outcome trial for canagliflozin as part of the submission to the FDA demonstrated that the MACE plus that includes hospitalization for UA were observed in 18.9% of patients receiving canagliflozin and 20.5% of patients receiving active comparators with a HR of 0.91 (95% CI = 0.68–1.21).[67]

In a pooled data analysis of four placebo-controlled, Phase 3 trials, 24 weeks treatment with empagliflozin resulted in significant glycemic control, weight loss, BP reduction, and positive effect on lipid and uric acid.[68]

In a meta-analysis of CV outcomes from 21 clinical trials, which assessed the efficacy of dapagliflozin among patients at high risk of CV, 128 MACE plus UA events were observed. 67 events occurred in patients receiving dapagliflozin and 61 events in patients receiving control (HR = 0.806; 95% CI = 0.562–1.156). With 95 MACE events observed among patients at high risk of CV, fifty events occurred in patients receiving dapagliflozin and 45 in patients receiving control (HR = 0.802; 95% CI = 0.527–1.221).[69]

In a pooled data analysis of two Phase 2 trials, which evaluated the long-term efficacy, safety and tolerability of dapagliflozin versus placebo in patients with T2DM and CVD, demonstrated that dapagliflozin provided a greater mean reduction in HbA1c versus placebo at 52 weeks (−0.58% [95% CI = −0.68–−0.49])

Table 1: Cardiovascular outcome trials of sodium glucose co-transporter-2 inhibitors

Trials	EMPA-REG outcome	CANVAS	CANVAS-R	CREDENCE	DECLARE	Ertugliflozin CVOT
n	7042	4330	5700	3700	17 150	3900
Interventions (randomization)	EMPA/ PBO (2:1)	CANA/ PBO (2:1)	CANA/ PBO (1:1)	CANA/PBO (1:1)	DAPA/PBO (1:1)	ERTU/PBO (2:1)
Primary endpoint	CV death, non-fatal MI, nonfatal stroke	CV death, nonfatal MI, nonfatal stroke	Progression of albuminuria	ESKD, serum creatinine doubling, renal/CV death	CV death, non-fatal MI, nonfatal ischemic stroke	CV death, nonfatal MI, nonfatal stroke
Target number events	691	≥420	TBD	TBD	1390	TBD
Estimated median follow-up (years)	~3	6-7	3	~4	4-5	5-7
Estimated reporting	2015	2017/2018	2017	2019	2019	2021

CV: Cardiovascular, MI: Myocardial infarction, TBD: To be determined

and 104 weeks (−0.35% [95% CI = −0.59–−0.12]). Mean body weight and SBP reductions versus placebo were maintained at 52 weeks, −2.23 kg and −3.25 mmHg, respectively, and at 104 weeks, −3.16 kg and −2.03 mmHg, respectively. Dapagliflozin was associated with a better three-item composite endpoint of clinical benefit (glycemia, weight and SBP) compared with placebo at week 24 (10.1% vs. 1.1%) and week 104 (LT2, 6.7% vs. 1.4%) [Figure 5].[70]

In a *post hoc* analysis of data pooled from two Phase 3 clinical trials, hypertensive patients with T2DM who were on stable angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy were randomly assigned to dapagliflozin 10 mg or placebo. The study demonstrated that dapagliflozin was associated with increased reductions in albuminuria compared with placebo (−33.2%; 95% CI −45.4–−18.2) over 12 weeks. was also present After adjusting for confounding factors like changes in HbA1c, SBP, body weight and estimated glomerular filtration rate, dapagliflozin was associated with the reduction in albuminuria (−23.5%, 95% CI = −37.6–−6.3). The study concluded that besides its favorable renal effects, dapagliflozin associated with significant improvements in glycemic control and reductions in SBP, may lead to reduced long-term renal and CV risk.[71]

Summary

SGLT-2 inhibitor that is effective in glycemic control in patients with T2DM is also associated with the modest reductions in body weight and BP. Given that less serious adverse events associated with SGLT-2 inhibitors, it is well tolerable among patients with T2DM. Numerous meta-analyses of SGLT-2 inhibitors and CV outcome consistently demonstrated that SGLT-2 inhibitor is not associated with increased risk of CV outcome. The EMPA-REG OUTCOME study demonstrated reduced risk of CV death (38%), risk of hospitalization for heart failure (35%) and improved survival by reducing the risk of death from any cause (32%) with a glucose lowering agent. Although the reductions in the risks of CV death and death from any cause sustained throughout the study, the mode of action associated with the CV benefits remains unknown. Data from ongoing trials including DECLARE-TIMI and CANVAS trials may share some guidance whether CV outcome of SGLT-2 inhibitor is the class-effect or not.

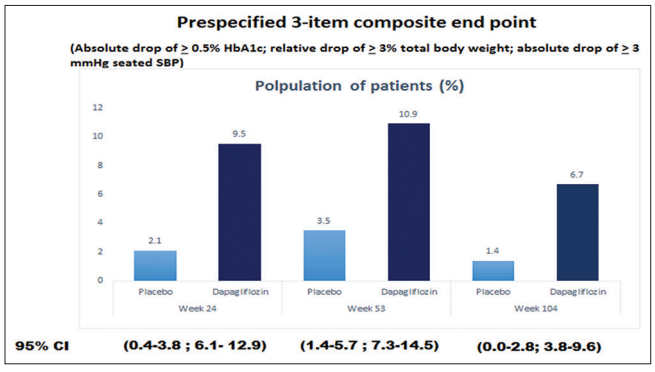

Figure 5: Better three -item composite endpoint of clinical benefit (glycemia, weight and SBP) with Dapagliflozn compared to placebo

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Conflicts of interest

There are no conflicts of interest.

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