# Sodium-glucose Cotransporter-2 Inhibitors: Moving Beyond the Glycemic Treatment Goal

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## Abstract

Revelations of the multifactorial pathogenesis of type 2 diabetes mellitus (T2DM) that extend beyond the role of insulin and glucose utilization have been crucial in redefining the treatment paradigm. The focus of treatment is currently directed towards achieving wide-ranging targets encompassing the management of cardiovascular comorbidities that have been evidenced as indispensable aspects of T2DM. While most currently prescribed antihyperglycemic agents have little or no effect on reducing cardiovascular risks, some have been associated with undesirable effects on common risk factors such as weight gain and cardiovascular sequelae. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are newer additions to the array of therapeutic agents for T2DM that have demonstrated robust glycemic control as mono and add-on therapies. Their unique renal mode of action, independent of insulin modulation, confers complementary metabolic benefits. By virtue of these effects, SGLT2i may have a distinct role in the revised treatment recommendations by established working groups such as the American Diabetes Association and the American Association of Clinical Endocrinologists that advocate a more comprehensive management of T2DM, not restricting to glycemic targets. The current review gives an overview of the changing treatment needs for T2DM and discusses the nonglycemic effects of SGLT2i. It provides an updated summary on the efficacy of canagliflozin, dapagliflozin, and empagliflozin in promoting weight loss, stabilizing blood pressure, and other favorable metabolic effects.

**Keywords:** Blood pressure, glycated hemoglobin, sodium-glucose cotransporter-2 inhibitors, type 2 diabetes mellitus, weight loss

## INTRODUCTION

In 2015, 8.5% individuals had diabetes globally and estimates for 2016 suggest that 7.8% of >1 billion population of India have diabetes.[1] This unprecedented rise in the prevalence of diabetes reflects a parallel increase in the prevalence of contributing risk factors such as obesity and diabetes-related microvascular and macrovascular complications that have detrimental cardiovascular, renal, and ocular manifestations.[1-4] Several epidemiological studies from Asia and India have suggested a strong interplay between rising rates of obesity and the uptrend in diabetes.[5-9] India along with China accounted for 15% of the 671 million obese (body mass index ≥30 kg/mg²) adults worldwide in 2013 highlighting the substantial risk of diabetes in these populations.[1,3,10]

Results from meta-analysis and population-based studies attribute a 2-fold increase in the occurrence of coronary heart disease, multiple types of stroke, and related deaths (relative risk, 1.67–1.75) to diabetes.[4,11] In Asian patients, prediabetes

has been associated with an increased risk of chronic kidney disease (CKD, overall relative risk, 1.12 [95% confidence interval (CI) 1.02–1.21]).[12] A cumulative analysis involving 54 countries indicated that in half of these countries, diabetes was the primary cause of end-stage renal disease (ESRD), accountable for 31% new ESRD.[13] Other complications such as vision impairments because of retinopathy (7%–11% patients with diabetes have vision-threatening retinopathy)[14] and ischemic events (10%–20% higher in patients with diabetes) have also been closely associated with the pathogenesis of diabetes.[1]

Assessments of utility scores for individual complications indicate that ischemic events, stroke, blindness, renal failure, heart failure, and myocardial ischemia result in largest

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reductions in health-related quality of life (QoL).[15] Further, the catastrophic impact of diabetes and related complications on health-related QoL accrues enormous economic burden on the patient, their families, and national health-care networks.[2,16] Thus, prevention of diabetes-related complications is a key component in the management of diabetes that can positively impact the declining QoL and lower the overall disease burden.

## REVIEW METHOD

The MEDLINE/PubMed and Cochrane databases were searched on April 11, 2016. Other data sources included trial registers (http://www.clinicaltrials.gov/) for data on ongoing trials, Google, and Google Scholar for treatment guidelines and prescribing information. Medical Subject Headings and free-text keywords were used and combined using "OR" and "AND" (diabetes mellitus, type 2 diabetes mellitus [T2DM], sodium-glucose cotransporter type 2 inhibitors [SGLT2i], canagliflozin, dapagliflozin, and empagliflozin). Inclusion of articles was based on screening of titles and abstracts. Articles reporting clinical trials, reviews, systematic reviews, and meta-analysis were included and no other filters were used. The search was strengthened by screening reference lists of retrieved articles manually for additional relevant sources.

## CHANGING TREATMENT NEEDS

Raised glycated hemoglobin (HbA1c) has been regarded as a reliable marker of diabetes-related complications, and most accepted guidelines on control of T2DM recommend lowering of HbA1c ($\leq$7.0%) as an obligatory therapeutic goal.[17-20] Among currently prescribed antihyperglycemic agents (AHAs), metformin is the most preferred first-line drug and is generally well tolerated; however, gastrointestinal disturbances and risk of fatal lactic acidosis restrict its use in patients with compromised hepatic functioning.[21-23] Other common AHAs (sulfonylureas, glinides, thiazolidinediones, gliptins, or DPP-IV inhibitors) have been associated with frequent incidences of hypoglycemia, weight gain, cardiovascular sequelae, and other metabolic derailments either as mono or add-on therapies that deter their favorable glycemic effects.[22,24-35] Insulin therapies for T2DM have also been associated with significant weight gain that is nearly proportional to the lowering of glucose.[20,36,37]

Findings from large landmark clinical studies such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[38] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[39] and the Veterans Affairs Diabetes Trial (VADT)[40] underscore the limitations of exclusively glycemia-targeted strategies, emphasizing the need for simultaneous control of multiple metabolic defects [Table 1]. In addition, the benefits of a structured multidrug intervention (combination of glucose-lowering, antihypertensive, lipid-lowering treatments, aspirin, and vitamin supplementation) are supported by results from the Steno-2 study that reported a 50% reduction in cardiovascular risks in patients

with T2DM and microalbuminuria.[41] Durability of favorable cardiovascular outcome following the long-term (mean, 7.8 years) multifactorial approach was observed in a subsequent 5.5-year follow-up study.[42]

## REVISED GUIDELINES FOR DIABETES CARE

Critical observations from the ACCORD, ADVANCE, and VADT studies involving over 23,000 patients have been pivotal in transforming the dogma of diabetes care and refining treatment to attain a more holistic outcome.[38-40,43] Recent amendments of the American Diabetes Association (ADA)[44] and the American Association of Clinical Endocrinologists (AACE)[45] guidelines provide distinct treatment goals for coexisting metabolic conditions along with targets for glycemic control (ADA: HbA1c <7.0%, AACE: HbA1c $\leq$6.5%, if achievable in a safe manner). Both recommendations emphasize on minimizing weight gain and advocate comprehensive assessments of body weight and appropriate and timely adoption of medical or surgical interventions. Targets have also been included for systolic (SBP; ADA:<140 mmHg, AACE: <130 mm Hg) and diastolic blood pressure (DBP; ADA: <90 mm Hg, AACE:<80 mmHg) and both groups endorse monitoring and managing dyslipidemia (AACE: low-density lipoprotein cholesterol [LDL-C], <100 mg/dL or <70 mg/dL; triglyceride, <150 mg/dL). The ADA recommends pharmacological intervention in patients with T2DM having elevated urinary albumin excretion (modest elevation, 30–299 mg/dL; severe elevation, >300 mg/dL) and with eGFR <60 mL/min/1.73 m$^2$.

The ADA and AACE also recommended initiation of combination therapy in patients not achieving desired HbA1c level after 3 months of initial treatment or if the HbA1c is >9.0%, for rapid attainment of target levels.[44] In addition, for patients with multiple comorbidities, adequate treatments with hypolipidemic, antihypertensives, or weight loss medications are regarded imperative for comprehensive management of diabetes and associated complications.[44,45] Thus, taking into account the need for a multifactorial approach, AHAs that provide sustained glycemic control along with additional metabolic benefits would be optimal treatment choices.

## SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS: MOVING BEYOND THE GLYCEMIC TREATMENT GOAL

SGLT2i are a novel class of AHA that lower blood glucose levels by increasing renal glucose excretion. SGLT2 is the active cotransporter of glucose along the proximal renal tubules (S1 and S2 segments) that ensures reabsorption of approximately 90% glucose from the tubular lumen into the cells under normal physiological conditions.[46,47] Under conditions of hyperglycemia, high tubular concentration of glucose triggers an increase in tubular reabsorption until the transport mechanism reaches its maximum capacity.[46,48] SGLT2i lower the threshold for glucose excretion by reducing the affinity of SGLT2 for glucose and increase urinary excretion of glucose, which subsequently results in reduction of blood glucose levels.[46,49,50]

**Table 1: Summary of results from Action to Control Cardiovascular Risk in Diabetes, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation and Veterans Affairs Diabetes Trial studies**

| Name of study | Year | Study population | Intervention | Therapeutic target | Nonglycemic outcomes* |
|---|---|---|---|---|---|
| ACCORD-Glycemia trial | 1999-2008 | 10,251 patients (mean age, 62.2 years) with a median HbA1c level of 8.1% | Combination of oral hypoglycemic agents | Intensive glucose control HbA1c <6.0% | Significant weight gain and fluid retention in intensive therapy vs standard therapy<br><br>No noticeable improvements in LDL-C<br><br>Higher death rates owing to cardiovascular causes in patients receiving intensive therapy |
| ADVANCE trial | 2001-2008 | 11,140 patients (aged ≥55 years) | Intensive treatment arm: gliclazide MR and others<br><br>Standard treatment arm: Any oral hypoglycemic (except gliclazide MR) | Intensive glucose control HbA1c <6.5% | Significant weight gain in patients on intensive treatment<br><br>Significant reduction in microvascular (nephropathy) but not macrovascular events was observed in the intensive treatment arm<br><br>Significant reduction in renal events in intensive treatment arm |
| VADT trial | 2000-2008 | 1791 military veterans (mean age, 60.4 years) with suboptimal response to therapy | Intensive treatment: maximal doses<br><br>Standard treatment: half-maximal doses | Absolute reduction of 1.5% points in intensive-therapy arm versus standard treatment arm | Significant increase in body weight, BMI and number of sudden deaths in the intensive treatment arm<br><br>No significant difference in the time to death from cardiovascular causes, new onset of retinopathy and other renal changes |

*Changes in patients receiving intensive therapy versus those receiving standard therapy. ACCORD: Action to Control Cardiovascular Risk in Diabetes, ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, HbA1c: Glycosylated haemoglobin, LDL-C: Low-density lipoprotein cholesterol, Gliclazide MR: Gliclazide modified release, VADT: Veterans Affairs Diabetes Trial, BMI: Body mass index

The efficacy of SGLT2i in achieving standard glycemic targets either as a single agent or as an add-on to standard ongoing therapies has been evidenced by several clinical studies. A pooled analyses of results for SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, sergliflozin etabonate, remogliflozin etabonate, and tofogliflozin) across multiple doses revealed attainment of glycemic target of HbA1c <7.0% in a significant number of patients that was 2 folds greater than that observed for placebo groups (odds ratio = 2.09, 95% CI, 1.77–2.46).[51] Significant reductions in fasting plasma glucose, mean body weight and blood pressure (SBP and DBP) was also demonstrated following treatment with these SGLT2i.[51] Clinical studies have also revealed persistent glycemic control over long durations of up to 2 years with canagliflozin and empagliflozin and up to 4 years with dapagliflozin.[52-55] These findings are suggestive of sustained clinical efficacy, fundamental for the management of the chronic manifestations of T2DM.[52-55] Thus, SGLT2i may have effects in slowing down the progressive deterioration of beta cell function, a common pathogenic feature of T2DM regarded to be the primary cause of diminishing efficacy of metformin, insulin, and sulfonylurea therapies over time.[56,57]

Unlike most conventional AHAs, SGLT2i do not trigger insulin release while lowering plasma glucose levels owing to their insulin-independent mechanism of action and hence are not associated with the adverse event (AE) of hypoglycemia (except when used in addition to sulfonylurea or insulin where there is an increased risk of hypoglycemia).[49,58] Multiple physiological actions of SGLT2i have been associated with the lower risk of hypoglycemia that include an increase in glucose production possibly via gluconeogenesis, carbohydrate-sparing increase in lipid utilization (ketogenesis) and a compensatory renal effect of SGLT1 mediated glucose reabsorption.[59] Further, the counter regulatory responses triggered by hypoglycemia have been associated with increased risk of cardiovascular events via modulations in sympathetic activity, inflammatory cytokine release and changes in endothelial function, blood coagulation and fibrinolysis.[60] Thus, the absence of clinically significant hypoglycemia may be regarded as a potential cardiovascular benefit of SGLT2i.[59] Other favorable metabolic effects of SGLT2i include lowering of the insulin: glucagon ratio (IGR) by increasing glucagon levels and reducing insulin levels. This effect on IGR is thought to be useful in rectifying the disrupted metabolism (maladaptive anabolism) and associated complications in hyperinsulinemic individuals.[61-63] Further, the 'calorie restriction mimetic' action of SGLT2i by the virtue of increased glycosuria and supplemented by their effects on IGR and ketogenesis has been postulated to have additional metabolic benefits that include body weight reductions.[63,64] Taking into the account the relation of T2DM with cardiovascular risk and the alarming rise in incidences of risk factors, the ADA and Canadian Diabetes Association Clinical Practice Guidelines Expert Committee recommend initiation of SGLT2i therapy in patients not meeting the therapeutic glycemic requirements with conventional treatment strategies for a more comprehensive management of T2DM and its complications.[44,65] The following sections of this review will discuss the nonglycemic benefits of SGLT2 inhibitors currently approved in India (canagliflozin, dapagliflozin and empagliflozin) and highlight their role in the changing treatment strategies for T2DM that focus on achieving targets beyond the standard glycemic goals.

## Effects on body weight

Clinically relevant reductions in body weight associated with SGLT2i have been attributed to the increase in glycosuria resulting in a negative energy balance and calorie loss.[46,48,49,66,67] SGLT2i as monotherapy and add-on to current treatments have shown favorable effects on weight loss [Table 2]. Findings of weight reduction following use of SGLT2i in conjunction with drugs such as sulfonylureas (glipizide, glyburide, glibenclamide) and pioglitazone that are known to trigger weight gain highlight the usefulness of SGLT2i in maximizing the effects of current treatments.[68-72] Reductions in body weight have also been reported with the use of SGLT2i as add-on to insulin therapy thus offering an additional advantage for patients receiving insulin.[73-75] Further, canagliflozin, dapagliflozin and empagliflozin have also demonstrated steady and sustained reductions in body weight similar to observations for glycemic control following treatment for 2–4 years.[52-55] Clinically, modest weight reductions associated with SGLT2i treatment have been accompanied with favorable effects on blood pressure, lipids and inflammatory markers that positively impact the cardiovascular profile of patients at risk.[71,76,77]

SGLT2i have also demonstrated favorable reductions in waist circumference and body fat mass and these effects have been associated with improvements in overall metabolic status. Treatment with canagliflozin has shown reductions in fat mass (in subcutaneous and visceral adipose tissue) that was primarily responsible for the reported weight loss as compared to glimepiride which was associated with an increase in fat mass and body weight.[78,79] Considerable reduction in body weight was observed in canagliflozin treated patients at the end of 104 weeks; nearly two-thirds of which was from reduction in fat mass.[79] Decreases in waist circumference ($-3.1$ to $-3.3$ cm) were also observed following prolonged treatment with canagliflozin for 52–104 weeks in these studies.[78,79] Following treatment with dapagliflozin over 102 weeks, reductions in body weight was accompanied by favorable reductions in fat mass and waist circumference ($-5.0$ cm) versus placebo.[80] Significant reductions in waist circumference ($-1.0$ to $-1.3$ cm) have also been reported with use of empagliflozin over a shorter duration of 12 and 24 weeks versus placebo.[81,82]

## Effects on blood pressure

Stable reductions in blood pressure have been associated with the use of SGLT2i. Although the precise mechanism facilitating this effect remains to be determined, weight loss, osmotic diuresis and mild natriuresis have been linked to reductions in blood pressure.[46,48,49,83] Other secondary mechanisms that are hypothesized to be involved include blockade of the renin-angiotensin-aldosterone system owing to the decreased proximal sodium reabsorption and changes in nitric oxide release due to improved glycemic control.[46,83,84] Cumulatively, all these effects have been associated with a reduction in arterial stiffness and lowering of blood pressure.[84,85]

Clinically significant reductions in blood pressure have been observed with the use of SGLT2i either as single agents or as a combination [Table 2]. Observation of reductions in ambulatory blood pressure, a distinctive measure and a sensitive predictor of cardiovascular endpoint, following short-term treatment (6–12 weeks) with canagliflozin and empagliflozin underscores the effectiveness of these agents in rapid lowering of blood pressure in patients with T2DM and comorbid hypertension.[86,87] Data from pooled analysis of results from phase 2 and 3 clinical studies of SGLT2i involving large patient populations have demonstrated clinically relevant mean reductions in SBP ($-0.27$ to $-4.0$ mm Hg) and DBP ($-0.24$ to $-1.6$ mm Hg).[51,88] Further, analysis of each SGLT2i separately demonstrated significant lowering of SBP and DBP relative to the control.[88] It is important to note that the reduction in blood pressure by SGLT2i is not accompanied by an increase in heart rate.[88,89] Consistent with the findings for glucose control and weight loss, sustained reduction in SBP have also been observed following prolonged use of canagliflozin for 2 years versus sulfonylureas that increased blood pressure marginally.[52]

## Renoprotective effects

Hyperglycemia and hypertension are important mediators of diabetic nephropathy that eventually exacerbates to ESRD. Experimental models of diabetes have regarded glomerular hyperfiltration (125–140 mL/min/1.73 m$^2$) and microalbuminuria as early markers of diabetic renal dysregulation.[90,91]

SGLT2i have shown favorable responses on renal endpoints that are complementary to their glucose control and blood pressure lowering effects, the exact mode of action however is not well-elucidated. Reduction of sodium reabsorption in the proximal nephron by SGLT2i is thought to increase the delivery of sodium to the juxtaglomerular apparatus in the distal nephron thereby activating the tubuloglomerular feedback mechanism. This eventually results in a reduction of glomerular pressure lowering hyperfiltration and inducing a decrease in urinary albumin excretion thus producing ambient physiological changes that may promote renoprotection.[91] Additional postulated mechanisms include reduction in progressive nephron damage through ameliorations in inflammation and restoration of renal microvasculature.[92,93]

Canagliflozin at both doses successfully achieved glycemic targets (reductions in fasting plasma glucose and higher proportion of patients achieving HbA1c <7.0%) versus placebo in patients with stage 3 CKD without negatively impacting the deteriorating renal function in these patients.[94] Pooled data from long-term studies of dapagliflozin involving patients with T2DM having normal or mildly impaired renal function, did not appear to increase the risk of renal toxicity or decline in nephron function.[95] SGLT2 inhibition by empagliflozin has demonstrated attenuation of hyperfiltration ($-33$ mL/min/1.73 m$^2$) during clamped euglycemia in patients with type 1 diabetes mellitus along with significant improvement in eGFR and other renal parameters suggestive of restoration of tubuloglomerular feedback.[84] This along

## Table 2: Summary of results for nonglycemic parameters of sodium-glucose cotransporter-2 inhibitors as monotherapy or add-on to existing treatment

| Study | Study population | Study treatment | Comparator | Body weight (mean change from baseline, kg) | Blood pressure (mean change from baseline, mmHg) | | Lipids (mean change from baseline, mmol/L) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | SBP | DBP | LDL-C | HDL-C | TG |
| Stenlof, 2014 | Patients with type 2 diabetes inadequately controlled with diet and exercise (*n*=587) | Canagliflozin (100, 300 mg) monotherapy for 52 weeks | Placebo | −2.8 to −3.9 | −2.4 to −3.8 | −0.6 to −0.9 | 4.9 to 10.9 | 11.2 to 13.8 | 0.3 to −3.0 |
| Wilding, 2013 | Patients with type 2 diabetes inadequately controlled with metformin + sulfonylurea (*n*=469) | Canagliflozin (100, 300 mg) add-on to metformin + sulphonylurea for 52 weeks | Placebo + metformin and sulfonylurea | −2.0 to −3.1 | −3.0 to −3.70 | −1.7 to −2.2 | 0.01 to 0.2 | 0.07 to 0.09 | −0.14 to 0.04 |
| Lavalle-González, 2013 | Patients with type 2 diabetes inadequately controlled with metformin (*n*=1284) | Canagliflozin (100 or 300 mf) + metformin | Sitagliptin + metformin | −2.1 to −2.5 | −3.50 to −4.7 | −1.8 | 0.11 | 0.12 to 0.14 | −0.12 to −0.19 |
| Neal, 2015 | Patients with type 2 diabetes on insulin therapy | Canagliflozin (100 or 300 mf) + insulin for 52 weeks | Placebo + insulin | −2.8 to −3.5* | −3.1 to −6.2 | −1.2 to −2.4 | 3.5 to 6.8 | 2.3 to 5.0 | −1.6 to −5.6 |
| Ferrannini, 2010 | Treatment naïve patients with T2DM (*n*=559) | Dapagliflozin (2.5, 5 or 10 mg) as monotherapy for 24 weeks | Placebo | −15.2 to −28.8 | −2.3 to −4.6 | −1.7 to −2.8 | NR | 0.02 to 0.17 | NR |
| Bailey, 2013 | Patients with type 2 diabetes inadequately controlled with metformin monotherapy (*n*=546) | Dapagliflozin (2.5, 5, 10mg) as add-on for 102 weeks | Placebo + metformin | −1.10 to −1.74 | 0.70 to −1.1 | −0.10 to −1.50 | NR | NR | NR |
| Wilding, 2012 | Patients with type 2 diabetes inadequately controlled with insulin (*n*=808) | Dapagliflozin (2.5, 5, 10 mg) as add-on to insulin for 48 weeks | Placebo + insulin | −0.96 to −1.61 | −4.09 to −5.30 | −2.64 to −2.96 | NR | NR | NR |
| Nauck, 2011 | Patients with T2DM inadequately controlled on metformin therapy (*n*=814) | Dapagliflozin (2.5 mg) + metformin for 52 weeks | Glipizide + metformin | −3.2 | −4.3 | −1.6 | −0.45 | 5.88 | −1.1 |
| Kadowaki, 2014 | Patients with T2DM (*n*=547) | Empagliflozin (5, 10, 25 or 50 mg) as monotherapy for 12 weeks | Placebo | −2.5 to −3.1 | −2.85 to −5.57 | −2.20 to −3.57 | NR | NR | NR |
| Haring, 2013 | Patients with T2DM inadequately controlled on metformin and sulfonylurea (*n*=669) | Empagliflozin (10 mg or 25 mg) as add-on for 24 weeks | Placebo | −2.16 to −2.39 | −3.5 to −4.1 | −2.1 to −2.2 | 0.04 to 0.10 | 0.05 | 0.03 to 0.17 |
| Ridderstråle, 2014 | Patients with T2DM (*n*=1549) | Empagliflozin (25 mg) + metformin for 104 weeks | Glimepiride + metformin | −4.61 | −6.10 | −3.0 | NR | NR | NR |
| Rosenstock, 2014 | Patients with T2DM inadequately controlled on insulin (*n*=563) | Empagliflozin (10, 25 mg) add-on to multiple daily injections of insulin for 52 weeks | Placebo + multiple daily injections of insulin | −1.95 to −2.04 | | | NR | NR | NR |

*Percentage changes. All data represented as mean changes from baseline (unless otherwise specified). Data presented are for approved doses of the drug only. NR: Not reported, SGLT2i: Sodium-glucose cotransporter-2 inhibitor, T2DM: Type 2 diabetes mellitus, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides

with significant reductions in glomerular hydrostatic pressure suggests meaningful impact on hemodynamic abnormalities that are hallmark pathogenic changes in the progression of nephropathy.[96] Empagliflozin treatment in T2DM patients with

challenged renal functioning has also demonstrated reductions in HbA1c along with improved albumin to creatinine ratio in T2DM patients with stage 2 CKD and a higher number of patients at stage 3 CKD receiving empagliflozin 25 mg improving from macroalbuminuria to microalbuminuria or microalbuminuria to no albuminuria.[97] Thus, in renal-impaired patients with T2DM, long-term treatment with SGLT2i have been successful in attaining therapeutic targets and facilitating improvements in measures of renal function, in this special patient cohort having limited treatment options among the available AHAs.

Because of the large dependence of SGLT2i on renal glucose filtration, assessment of kidney function before initiation of SGLT2i therapy is essential. As per current recommendations, SGLT2i should be used only in patients with eGFR of >60 mL/min/1.73 m$^2$ and not initiated in patients with severely compromised GFR (eGFR, <45 mL/min/1.73 m$^2$).[98-100] Canagliflozin may be used in patients with moderate renal impairment (45–<60 mL/min/1.73 m$^2$) at a recommended once daily dose of 100 mg.[100] Treatment with dapagliflozin is not recommended in patients with eGFR <60 mL/min/1.73 m$^2$.[98] Empagliflozin can be used without dose adjustments in patients with moderate renal impairment (eGFR ≥45 mL/min/1.73 m$^2$).[99]

### Effects on lipid profile

SGLT2i have frequently been associated with mild increase in HDL-C levels and small but undesirable increase in LDL-C levels raising concerns of cardiovascular risk.[89,101] Overall, fewer studies have reported the variable effects of SGLT2i on the lipid profile [Table 2]. Treatments with canagliflozin and dapagliflozin have shown an increase in HDL-C, decrease in triglycerides and an increase in LDL-C.[102,103] Meta-analyses of results from clinical studies of SGLT2i indicated a significant increase in HDL-C levels and no meaningful effects on LDL-C and triglyceride levels.[51,104] In a pooled analysis of four placebo-controlled, phase 3 studies that evaluated the safety and tolerability of canagliflozin, a dose-related increase in total cholesterol and LDL-C from baseline as compared to placebo was reported.[105] Though not significant, comparatively large placebo-subtracted least squares mean percent increase from baseline LDL-C was seen with canagliflozin in the lowest tertile compared with the middle and highest tertiles.[105] Although, an increase in HDL-C and decrease in triglycerides may potentially contribute to the atheroprotective effects of SGLT2i, further studies are needed to illustrate their effects on lipid metabolism.

### Effects on serum levels of uric acid

Another favorable, yet minimally explored effect of SGLT2i includes the reduction of serum uric acid levels. Although not causal, findings from a meta-analysis have linked elevations in serum uric acid levels to metabolic disturbances as well as cardiovascular and all-cause mortality.[106] An increase in glycosuria mediated by SGLT2i leading to an increased exchange of uric acid by the SLC2A9 (GLUT9) transporter, in the apical membrane of tubular cells has been hypothesized

as the possible mechanism for this uricosuric effect.[107,108] Pooled data from 4 studies of canagliflozin (26-week trials) as monotherapy or in combination with AHAs in patients with T2DM and a subset of patients with hyperuricemia (serum uric acid ≥8 mg/dL) showed a reduction of 13% in serum uric acid relative to placebo in the overall population. More patients with hyperuricemia achieved the target serum uric acid levels (<6 mg/dL).[107]

### Completed/ongoing outcome studies

Studies evaluating SGLT2i for focused cardiovascular and renal outcomes such as myocardial infarction, stroke, ESRD, hospitalizations due to cardiovascular events and cardiovascular death in T2DM patients at increased risk for cardiovascular events are important to validate the available findings for surrogate measures. Effects of empagliflozin on cardiovascular morbidity and mortality have been demonstrated by the large clinical study (EMPA-REG OUTCOME) that reported reduction in deaths due to cardiovascular causes in patients receiving empagliflozin as add-on to standard therapy.[109] The effect was accompanied by meaningful changes in risk factors such as lowering of body weight, waist circumference, serum uric acid, blood pressure and marginal rise in HDL levels.[109] Assessment of long-term renal effects from the EMPA-REG OUTCOME study demonstrated delayed progression of kidney disease and lower risk of renal events with empagliflozin treatment versus placebo.[110] Three large outcome studies to evaluate canagliflozin are currently ongoing. Two of these studies are expected to complete in the next 12 months: the CANagliflozin cardiovascular Assessment Study (CANVAS)[111] and the CANVAS – Renal, which comprise the CANVAS Program.[112] The third, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation study that is independent of the CANVAS program, will determine the effects of canagliflozin on CKD and is scheduled for completion by 2020.[113] The DECLARE-TIMI 58 study for dapagliflozin is currently being carried out to assess effectiveness of treatment in reducing cardiovascular events and related mortality.[114]

Results from these large and longer ongoing clinical studies will be pivotal in providing insights and substantial evidence to support findings of beneficial metabolic associations of SGLT2i and establish the benefit-harm balance for these agents.[115] Interestingly, two recent meta-analyses of results from randomized studies (with noncardiovascular endpoints) of multiple SGLT2i support results of the EMPA-REG OUTCOME study and also provide evidence for association of these cardioprotective effects with inhibition of SGLT2 and hence, specific to these agents.[115,116] The results from the first study, majorly driven by results of the EMPA-REG OUTCOME study, were suggestive of an overall favorable effect SGLT2i on cardiovascular outcomes in T2DM patients in contrast to findings from glycemia-centered treatments.[38-40,115] The more recent pooled analysis evaluating effects on specific cardiovascular events, showed significant reduction in myocardial infarction without increased risk of

stroke and included results from two cardiovascular outcome based studies, EMPA-REG OUTCOME and CANVAS studies (interim results).[116]

## Common Adverse Events

The frequently reported AEs of SGLT2i are attributable to their effect of increasing urinary glucose excretion and osmotic diuresis. Most AEs have been regarded as moderate or mild and leading to fewer discontinuations.[117] Common AEs associated with SGLT2i based on pooled data from clinical studies of all approved doses include genital mycotic infections in men (5.4%–11.6%) and women (1.6%–4.2%), urinary tract infections (UTIs) (4.3%–9.3%) and increased frequency of urination (2.9%–5.1%).[117] AEs related to volume depletion (0.3%–3.4%) include hypotension, orthostatic hypotension, dehydration, dizziness and electrolyte imbalances. Other labelled AEs of this drug class include diabetic ketoacidosis, acute kidney injury and impairment in renal function, hypoglycemia (when used with insulin and insulin secretagogues), increased LDL-C, increased risk of bone fracture (canagliflozin) and risk of bladder cancer (dapagliflozin).[98,118,119] The incidences of AEs in Indian patients based on a *post hoc* analysis of pooled data from canagliflozin studies (UTIs, 2.3%–14.3%; female genital mycotic infections, 1.8%–10.2%; male genital mycotic infections, 1.2%–4.5%; volume depletion AEs, 0.9%–2.0%), were analogous to those reported in other Asian populations and generally lower than rates in global populations.[120] Overall, the risk of common AEs is reported to be higher in elderly patients, patients with impaired renal function and hence SGLT2i should be used cautiously in these patient groups.[117,121]

## Conclusions

The existing classes of AHAs have been successful in achieving therapeutic glycemic goals, however, there remains a need for therapies that can reduce long-term risk of vascular complications and contribute to a multidimensional approach for the management of T2DM. In addition to robust glucose control, SGLT2i have demonstrated considerable potency for beneficial metabolic changes that include weight loss and attenuation of major cardiovascular risk factors (high blood pressure, dyslipidemia and deteriorating renal function). These nonglycemic benefits of SGLT2i have placed them at unique position in the changing treatment strategies for T2DM and enabled their inclusion in the revised therapeutic algorithms recommended by key decision making groups. Emerging data from outcome studies are promising and are expected to exemplify the distinct cardiometabolic effects of each SGLT2i, supporting the inclusion of these agents in treatment regimens for T2DM.

### Conflicts of interest

Dr. Nishant Garodia is an employee of Janssen India. Dr. William Canovatchel is an employee of Janssen Research & Development, LLC, USA, and holds company stocks. Dr. Vishal Gupta has received honoraria as a consultant from Janssen India. Dr. B. N. Lokesh was an employee of Janssen India at the time of conception of this review article. Dr. Ravi Santani was an employee of Janssen India until manuscript submission.

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