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ABOUT COVER

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REVIEW

Sodium glucose cotransporter-2 inhibitors and heart disease: Current perspectives

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Abstract

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are antidiabetic medications with remarkable cardiovascular (CV) benefits proven by multiple randomised controlled trials and real-world data. These drugs are also useful in the prevention of CV disease (CVD) in patients with diabetes mellitus (DM). Although DM as such is a huge risk factor for CVD, the CV benefits of SGLT-2i are not just because of antidiabetic effects. These molecules have proven beneficial roles in prevention and management of nondiabetic CVD and renal disease as well. There are various molecular mechanisms for the organ protective effects of SGLT-2i which are still being elucidated. Proper understanding of the role of SGLT-2i in prevention and management of CVD is important not only for the cardiologists but also for other specialists caring for various illnesses which can directly or indirectly impact care of heart diseases. This clinical review compiles the current evidence on the rational use of SGLT-2i in clinical practice.

Key Words: SGLT2 inhibitors; SGLT2i; Cardiovascular disease; Heart failure; Atherosclerotic cardiovascular disease; Diabetic kidney disease

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Core Tip: The new antidiabetic medication class sodium glucose cotransporter-2 inhibitors (SGLT-2i) are found to have remarkable cardiovascular (CV) benefits proven by multiple randomised controlled trials and real-world observational studies. They are also useful in prevention of CV disease (CVD) in patients with diabetes mellitus. The CV benefits of SGLT-2i are not just because of antidiabetic effects. The preventive and management effects of SGLT2i molecules in diabetic and nondiabetic renal disease also translate into CV benefits. This clinical update review compiles the up-to-date evidence on the molecular mechanisms of SGLT-2i in prevention and management of CVD for empowering clinicians to rationalise the use of these molecules in day-to-day medical practice.

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INTRODUCTION

Patients with type 2 diabetes mellitus (T2DM) are predisposed to develop atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), increased cardiovascular (CV) mortality, and renal disease. The cardiac manifestations can include coronary artery disease (CAD), HF, atrial fibrillation (AF), as well as ischemic strokes as and peripheral arterial diseases. Also, diabetes increases the risk of developing albuminuria, and chronic kidney disease (CKD), both of which are independent risk factors for CVD. Thus, the combination of diabetes and cardio-renal comorbidities lead to a cumulative increase in the risk for CV events and mortality.

The first Sodium-linked glucose co-transporter-inhibitor (SGLTi) to be isolated was dihydrochalcone phlorizin, a nonselective SGLTi extracted from apple tree roots. Later, the aromatic O-glycoside sergliflozin and the aromatic C-glycoside dapagliflozin became the first selective SGLTi[1]. Currently several SGLT2i molecules like ipragliflozin, dapagliflozin, canagliflozin, empagliflozin, luseogliflozin, and tofogliflozin are available for treating T2DM, while ipragliflozin and dapagliflozin have also been approved for type 1 diabetes mellitus (T1DM) in some countries[1]. Though the cardio-vascular outcome trials (CVOTs) were conducted to demonstrate CV safety of the anti-diabetic agents, the remarkable results with Empagliflozin and Canagliflozin in the Empagliflozin CV Outcome Event Trial in T2DM Patients (EMPA-REG OUTCOME) and Canagliflozin Cardiovascular Assessment Study (CANVAS) trials demonstrating the beneficial effects of SGLT2i on CV events and HF as well as on renal outcomes revolutionised the management of heart disease in diabetes[2,3]. Soon, the CV and renal benefits of SGLT2i became apparent in patients without diabetes[4,5]. Initially marketed as an anti-diabetic agent, SGLT2i soon became a favourite medicine for cardiologists and nephrologists.

SGLT2I IN PATIENTS WITH ASCVD

Cardiovascular outcome trials of SGLT2i in T2DM

Since 2008 the United States Food and Drug Administration (FDA) required CVOTs to demonstrate CV safety for all new antidiabetic medications. These studies were primarily designed to assess whether new medications are non-inferior with respect to placebo for CV events. Generally, these trials do not assess efficacy for glycemic control, but enroll subjects with high CV risk to gather enough CV events in a short time. SGLT2 inhibitors have been evaluated in dedicated CVOTs and real-world studies for their CV safety and benefit. Given the huge benefits observed in different CV risk factors (hypertension, dyslipidemia, body weight, arterial stiffness, endothelial dysfunction), CVOTs of all 4 agents have been completed and the results are summarized in Table 1. A few meta-analyses and real-world data are also published and discussed below.

The EMPA-REG OUTCOME was designed to test the CV safety of Empagliflozin[6]. In this study, 7020 patients with T2DM and established CVD were randomized to receive either 10 or 25 mg of Empagliflozin or placebo over a median observation period of around 3 years. All the participants received the existing standard of care in terms of CV protection and received antiplatelets, lipid-lowering medications, and blockers of the renin-angiotensin-aldosterone system (RAASi). This study showed a significantly lower percentage (10.5%) of the primary outcome, 3 point - major adverse CV event [(3P-MACE), which was a composite of death from CV causes, non-fatal myocardial infarction (MI) or non-fatal stroke], in the Empagliflozin group compared to the group receiving placebo (12.1%), with a hazard ratio (HR) in the empagliflozin group: 0.86, 95%CI: 0.74-0.99; P = 0.04 for superiority. Regarding the secondary outcomes, empagliflozin treatment resulted in a 32% reduction of mortality from any cause, a 38% reduction in death from CV causes, and 35% lesser rates of hospitalization for HF, although no significant effect was observed in nonfatal MI and stroke rates. Intriguingly, the CV event curves of the empagliflozin and placebo groups started to diverge early after trial initiation.

Table 1 Major cardiovascular outcome trials of sodium glucose cotransporter 2 inhibitors

	EMPA-REG outcome	CANVAS	DECLARE-TIMI 58	VERTIS-CV	SCORED
Intervention	Empagliflozin 10 and 25 mg *vs* placebo	Canagliflozin 100 and 300 mg *vs* placebo	Dapagliflozin 10 mg *vs* placebo	Ertugliflozin 5 and 15 mg *vs* placebo	Sotagliflozin *vs* placebo
Population	*n* = 7020, T2DM with established CV disease	*n* = 10142 patients, T2DM with established CV disease or ≥ 2 CV risk factors	*n* = 17160 patients, T2DM with established CV disease or risk factors for atherosclerotic CV disease	*n* = 8246, T2DM with established CV disease	10584 patients with T2DM and established CV disease or risk factors for athero-sclerotic CV disease
Established CV disease (%)	99	66	41	99	48.6
Follow up period (yr)	3.1	3.6	4.2	3.5	1.3
HbA1c (%) at baseline	7.0% to 10.0% (for those on a stable background therapy); 7.0%-9.0% (for medication-naive patients)	7.0% to 10.5%	6.5% to 12.0%	7.0% to 10.5%	> 7%
Estimated GFR	≥ 30	≥ 30	≥ 60	≥ 30	25-60
Primary outcome, HR (95%CI)	3P-MACE, 0.86 (0.74-0.99)	3P-MACE, 0.86 (0.75-0.97)	3P-MACE, 0.93 (0.84-1.03); CV death or hospitalization for HF, 0.83 (0.73-0.95)	3P-MACE, 0.97 (0.85-1.11)	Total no. of deaths from cardiovascular causes, hospitalizations for HF, and urgent visits for HF 0.74 (0.63-0.88)
Key secondary outcome (s), HR (95%CI)	4P-MACE, 0.89 (0.78-1.01)	All-cause mortality (as below); CV death (as below); progression of albuminuria, 0.73 (0.67-0.79); CV death or hospitalization for HF 0.78 (0.67-0.91)	≥ 40% decline in eGFR to < 60 mL/min/1.73 m^2 or new onset end-stage renal disease or renal/CV mortality, 0.76 (0.67-0.87); all-cause mortality (as below)	CV death or hospitalization for HF, 0.88 (0.75-1.03); CV death (as below); renal death or dialysis/transplant or doubling of serum creatinine from baseline, 0.81 (0.63-1.04)	Total No. or hospitalizations for HF and urgent visits for HF HR: 0.67 (0.55-0.82); deaths from cardiovascular causes (as below)
Other secondary outcomes					
CV death, HR (95%CI)	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.92 (0.77-1.11)	0.90 (0.73-1.12)
All-cause mortality, HR (95%CI)	0.68 (0.57-0.82)	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.93 (0.80-1.08)	0.99 (0.83-1.18)
Fatal or non-fatal myocardial Infarction, HR (95%CI)	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77 − 1.01)	1.04 (0.86-1.26)	0.68 (0.52-0.89)
Fatal or non-fatal stroke, HR (95%CI)	1.18 (0.89-1.56)	0.87 (0.69-1.09)	1.01 (0.84-1.21)	1.06 (0.82-1.37)	0.66 (0.48-0.91)
Hospitalization for HF, HR (95%CI)	0.65 (0.50-0.85)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.70 (0.54-0.90)	0.67 (0.55-0.82)

EMPA-REG outcome: Empagliflozin and canagliflozin in the empagliflozin cardiovascular outcome; event trial in type 2 diabetes mellitus patients; CANVAS: Canagliflozin cardiovascular assessment study; DECLARE-TIMI 58: Dapagliflozin effect on cardiovascular events-thrombolysis in myocardial infarction 58; T2DM: Type 2 diabetes mellitus; CV: Cardiovascular; GFR: Glomerular filtration rate; HR: Hazard ratio; 3P-MACE: 3 point - major adverse CV event; HF: Heart failure; eGFR: Estimated glomerular filtration rate.

The number-needed-to-treat for the empagliflozin group was only 39, indicative of the fact that 39 patients would need treatment with empagliflozin for 3 years to prevent one case of CV mortality.

The CANVAS Program was a composite of two sub-trials: The CANVAS, designed to assess CV safety of Canagliflozin, and the CANVAS-R study (CANVAS-Renal), designed to investigate the effect of canagliflozin on albuminuria[7]. The trial recruited a total of 10142 patients with T2DM, of whom 66% were having established CV disease while 34% had multiple CV risk factors. Patients were randomized to receive Canagliflozin 100 mg, 300 mg, or placebo and the mean follow-up was 3.6 years. Like EMPA-REG OUTCOME, participants were patients treated with routine CV protective regimens using statins, antiplatelets, and RAASi. The primary outcome was significantly lower in the canagliflozin group compared to placebo (26.9 *vs* 31.5 participants per 1000 patient-years; HR: 0.86; 95%CI: 0.75-0.97; P < 0.001 for noninferiority; P = 0.02 for superiority) Additionally, canagliflozin was found to reduce the rate of hospitalization due to HF by 33%. However, there was no significant effect was on all-cause mortality or CV mortality.

The largest CVOT done with dapagliflozin was the 'Dapagliflozin Effect on CV Events-Thrombolysis in MI 58' (DECLARE-TIMI 58) study[8]. A total of 17160 patients with T2DM and established ASCVD (41%) or multiple risk factors for ASCVD (59%) were randomized to receive either dapagliflozin 10 mg or placebo for a median period of 4.2 years. Among two primary outcomes, dapagliflozin was seen to reduce the composite outcome of CV death or hospitalization for HF by 17%, but no beneficial effects were seen in terms of 3P-MACE. Hospitalization due to HF was reduced by 37% and that was the driving factor behind meeting the primary outcome, but no effect was seen in CV death or all-cause mortality. In terms of secondary endpoints, dapagliflozin reduced the composite renal outcome by 24% [≥ 40% decrease in estimated glomerular filtration rate (eGFR) to < 60 mL/min/1.73 m^2, new end-stage renal disease, or death from renal or CV causes], but did not affect the all-cause mortality.

Ertugliflozin was studied in the VERTIS CV Trial, where a total of 8246 patients underwent randomization for ertugliflozin 5 mg, 15 mg, and placebo and were followed for a mean of 3.5 years[9]. Patients treated with Ertugliflozin showed noninferiority for 3P-MACE as compared with placebo (HR: 0.97; 95%CI: 0.85-1.11; $P < 0.001$ for noninferiority). Hospitalization due to heat failure was reduced by 12%, but no benefit was observed in the reduction of CV death, all-cause mortality, or renal outcomes. The basic characteristics of CVOTs are depicted in Table 1.

Sotagliflozin CV outcome trial, SCORED[10], was published recently. It included 10584 patients with established CVD (48.6%) and with multiple risk factors (51.4%) and was randomized between sotagliflozin and placebo and followed up for 1.3 years. Patients treated with sotagliflozin demonstrated a 26% reduction in primary outcome (total number of deaths from CV causes, hospitalizations for HF, and urgent visits for HF) HR: 0.74; 95%CI: 0.63-0.88; $P < 0.001$. There was a 33% reduction in HF, but no benefit was observed for the reduction of CV death. Genital mycotic infections, diarrhea, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than with a placebo.

SGLT2I AND HEART FAILURE

The use of SGLT2i in HF has drastically changed the therapeutic outcomes of these patients. Initially introduced as an agent for glycemic control, SGLT2i gained recognition in the management of HF after the EMPA-REG OUTCOME trial showed a significant reduction in hospitalisation due to HF (HHF) in the empagliflozin group compared to the placebo [2]. This trial and those that were performed in the later years suggested that independent of its glucose-lowering effect, SGLT2i must have a direct effect on HF. The current classification of HF is based on the ejection fraction (EF), with HF with reduced EF (HFrEF) defined as EF ≤ 40%, HF with preserved EF (HFpEF) defined as EF > 50%, and HF with mildly reduced EF (HFmrEF) defined as EF between 40% to 50%[11].

SGLT2i in HFrEF

The DAPA-HF trial recruited patients having HF with an EF ≤ 40% and an eGFR ≥ 30 mL/min per 1.73 m^2. Dapagliflozin was found to reduce the primary composite CV outcomes (which included death from CV causes, hospitalization for HF, or an urgent hospital visit resulting in intravenous therapy for HF) by 24%[4]. The EMPEROR-Reduced trial included patients with HF with a mean EF of 27% and an eGFR ≥ 20 mL/min per 1.73 m^2. There was 22% reduction in the primary composite outcome of CV death or hospitalization for HF in the group receiving empagliflozin[12].

SGLT2i in HFpEF or HFmrEF

In the earlier studies, the beneficial effect of the SGLT2i was demonstrated only in patients with HFrEF, but the EMPEROR-Preserved trial in 2022 showed that empagliflozin improved CV outcomes even in patients with HFpEF[13]. The EMPEROR-Preserved trial was the first trial of SGLT2i which included patients with HFmrEF and HFpEF regardless of whether they had diabetes or not. It was found that with the use of empagliflozin, there was a 19% reduction in the primary composite outcome of CV death and HHF[13]. The recently published DELIVER trial also enrolled patients with HFmrEF and HFpEF. There was an 18% reduction in the primary composite endpoint of worsening HF or CV death[14].

Although the newest addition to the HF therapies, SGLT2i helps in a significant reduction of morbidity and mortality in the entire range of EF. Thus, they form an important pillar in the management of HF. The details of the landmark trials of SGLT2i in HFrEF or HFpEF are outlined in Table 2.

SGLT2i in acute heart failure

In a meta-analysis of RCTs involving 1831 patients with acute HF (AHF), SGLT2i improved the Kansas City Cardiomyopathy Questionnaire scores (mean difference: 4.12; 95%CI: 0.1.89-6.53) and reduced the risk of rehospitalization due to HF (OR: 0.52; 95%CI: 0.42-0.65). However, no significant effect on all-cause mortality was observed. Initiating SGLT2i in patients with AHF did not increase the risk of hypotension or acute kidney injury (AKI)[15].

While SGLT2i use reduces levels of plasma NT-proBNP and improves diastolic function of the heart, improvement in left-ventricular EF was observed only in patients having HFrEF who are in stage C HF. The benefits were not very prominent in patients with HFpEF with HF stages A or B.

SGLT2I AND CV EFFECTS IN T2DM - REAL-WORLD DATA

Real-world data, which possibly better represent everyday clinical practice, do exist in favor of SGLT2i for CV outcome. An observational study from Denmark, Norway, and Sweden by Birkeland *et al*[16] included a total of 91320 patients,

Table 2 Major heart failure trials with sodium glucose cotransporter 2 inhibitors

Trial and medication name	Primary endpoint	Median follow-up	Outcomes
HFrEF			
DAPA-HF (dapagliflozin)	Primary composite outcome: Worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for HF) + cardiovascular death	18 months	Reduction in the primary composite outcome by 24%
EMPEROR-reduced (empagliflozin)	Primary composite outcome: Hospitalisation for heart failure + cardiovascular death	16 months	Reduction in the primary composite outcome by 22%
HFpEF			
EMPEROR-preserved (empagliflozin)	Primary composite outcome: Hospitalisation for heart failure + cardiovascular death	26 months	19% reduction in the primary composite outcome
DELIVER (dapagliflozin)	Primary composite outcome: Worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for HF) + cardiovascular death	28 months	18% reduction in the primary composite endpoint

HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HR: Hazard ratio.

among which 22830 patients with T2DM were on SGLT2i (most commonly Dapagliflozin) and a total of 68490 patients were being treated with other anti-diabetic agents[15,16]. They were observed for a follow-up of around 0.9 years. One-fourth of them already had established CV disease. It was seen that SGLT2i use was associated with a significantly reduced risk of major adverse CV events, CV mortality, and HF-related hospitalisation in comparison to other glucose-lowering drugs. However, the difference in nonfatal MI or stroke was not significant.

SGLT2I IN THE PRIMARY PREVENTION OF CV DISEASES

Though the DECLARE-TIMI 58 and other trials suggested that SGLT2i can reduce the CV composite outcome in patients without established ASCVD, a meta-analysis including data from three major CVOTs with 34322 patients, 39.8% of whom did not have established ASCVD, SGLT2i was found to reduce MACE by 11% (HR: 0.89, 95%CI: 0.83-0.96, $P = 0.001$][17]. However, on subgroup analysis, the benefits were only seen in patients who had established ASCVD [0.86 (0.80-0.93)] but not in those without [1.00 (0.87-1.16), P for interaction = 0.05][16]. The reduction in the composite of CV death or HHF by 23% [0.77 (0.71-0.84), $P < 0.0001$] could, however, be in patients with and without ASCVD and with and without a history of HF. The renal benefits were also seen in both the groups with and without ASCVD. The magnitude of the benefit of SGLT2i differed according to the baseline renal function, with a greater decline in hospitalisations for HF ($P = 0.007$) and a lesser reduction in the progression of CKD ($P = 0.03$) seen in patients with more severe kidney disease at baseline.

CARDIOVASCULAR BENEFIT IN NON-DIABETIC INDIVIDUALS

Some of the SGLT2 trials evaluating kidney and HF outcomes have deliberately enrolled patients without T2DM, but none of these studies were powered to study their effects on atherosclerotic outcomes. Specially, MACE was not included as an outcome in the primary hierarchy of analyses in any of the HF trials like Empagliflozin Outcome Trial in Patients with Chronic HFrEF (EMPEROR Reduced)[17], Empagliflozin Outcome Trial in Patients with Chronic HFpEF (EMPEROR-Preserved)[18], and Dapagliflozin and Prevention of Adverse Outcomes in HF (DAPA HF)[19]. Although in the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA CKD). 3P-MACE (CV death, MI, and stroke) was included as a prespecified, exploratory outcome, but the comparative efficacy of dapagliflozin for this outcome were not presented by baseline T2DM status. Additionally, MACE was seen to occur in only 3% of the trial cohort, meaning that the power was likely insufficient for meaningful MACE analyses classified by T2DM status[20]. Further studies evaluating 3P-MACE in individuals without diabetes may answer this question in the future.

EFFECTS OF SGLT2I ON DIFFERENT CV RISK FACTORS

Trials with various SGLT2i have consistently shown marked benefits in various CV outcomes. This indicates that there might be a class effect of SGLT2i on CV parameters. This benefit cannot be solely attributed to their glucose-lowering effect as significant improvements in different CV outcomes have been found even in patients without diabetes. Instead, the CV benefit is because of the effect of SGLT2i on the various risk factors associated with heart disease most importantly blood pressure control, weight loss, and dyslipidemia. We will now briefly discuss the major CV risk factors and how they are ameliorated by SGLT2i.

Effects on glucose levels

The first indication of SGLT2i after they were designed was to control blood glucose. By inhibiting the SGLT2 co-transporters in the proximal convoluted tubules, they lower the blood glucose and have been found to reduce the HbA1c by around 0.5% in various trials[21]. This would reduce the glucotoxicity and oxidative stress on the cardiac tissues. However, the rapid efficacy observed with the SGLT2i on cardiac endpoints, starting days after the initiation of the drug, suggests other mechanisms playing a role in this cardio-protection.

Effects on body weight

With the use of SGLT2i, there is a loss of glucose in the urine leading to the loss of calories which, in turn, results in the mobilisation of the fatty acids from the adipose tissue stores resulting in weight loss. This has been consistently observed in various trials and metanalyses suggest that the weight reduction is around 2-3 kg[22]. In DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved trials, weight reduction of 0.9 kg, 0.8 kg, and 1.3 kg were observed respectively as compared to the placebo[4,12,13]. Again, this modest weight reduction cannot entirely explain the CV benefit provided by the SGLT2i.

Effects on blood pressure

Hypertension is a very strong adverse risk factor for both HFrEF and HFpEF. Because of the osmotic and diuretic effects of the SGLT2i, there is a modest reduction in blood pressure. In the DAPA-HF trial, there was a mean difference of around -1.4 mmHg in the systolic BP after 8 months which was significant when compared to the placebo. In the EMPEROR-Reduced trial, compared to the placebo, empagliflozin showed a greater reduction (-2.4 *vs* -1.7 mmHg) but it was not significant[4,12]. These modest reductions, although not entirely, will affect the cardiac and vascular remodelling and afterload, leading to improvement in hemodynamics.

Effect on lipid parameters

Although there is a debate regarding the effect of SGLT2i on low-density lipoprotein (LDL) cholesterol, most of the studies showed that there is a minor increase in LDL cholesterol with its use. A study published in 2013 showed an increase in LDL cholesterol by 11.7% with the use of canagliflozin for 52 wk in patients with T2DM[23]. Still SGLT2i has a cardioprotective effect and this paradox can be explained by the fact that SGLT2i might decrease the small dense LDL and increase the large buoyant LDL as was seen with the use of dapagliflozin for 12 wk in T2DM[24]. SGLT2i also resulted in an increase of high-density lipoprotein cholesterol by around 10%-11% with the use of canagliflozin in one study[25]. Moreover, SGLT2i also decreases lipid deposition in the visceral fat, decreases lipid oxidation, and affect the transport of lipid into the cells[26]. All these taken together would provide a cardioprotective benefit with the use of SGLT2i.

Effects on albuminuria and progression of CKD

CV events are the chief cause of mortality in patients with CKD and the risk progressively increases with a decline in eGFR or increasing degrees of albuminuria, making the latter an independent predictor of CV risk[27]. In addition to their glycemic lowering properties and effects on body weight and systemic blood pressure, SGLT2i can reduce intraglomerular pressure, and therefore albuminuria and also slow down GFR decline[28]. Recent data also suggest that SGLT2i can directly reduce oxidative stress, and angiotensinogen levels as well as reduce NLRP3 inflammasome activity in the kidney[29]. The promising results of Canagliflozin in the CREDENCE trial led to it being stopped early and showed a significant reduction in the primary composite end point of ESRD, doubling of serum creatinine, or renal or CV death with up to 32% risk reduction for development of ESRD[28]. It also demonstrated clear benefits on CV outcomes in the advanced CKD group[3]. The DAPA-CKD study with Dapagliflozin was similar except that one-third of the population had other one-third had CKD without T2DM and the endpoints were slightly different. The HR for the renal composite outcome of a sustained decline in eGFR of > 50%, ESRD, or death from renal causes was 0.56 (95%CI: 0.45-0.68; $P < 0.001$) [5].

Effects on uric acid levels in serum

Several studies and meta-analyses have verified the effectiveness of SGLT2i in improving hyperuricemia. The uricosuric effects of dapagliflozin, empagliflozin, and canagliflozin have been seen in patients with or without diabetes[30,31]. The likely mechanism involves the GLUT9 isoform 2. By preventing reabsorption, SGLT2i can increase the concentration of glucose reaching the collecting ducts, which in turn compete with urate for reabsorption *via* the GLUT9 isoform 2 leading to the excretion of more uric acid. Other mechanisms involving activation of the xanthine oxidase by sirtuin activation and alteration of URAT1 transporter have been also proposed[32]. In a nationwide study from Taiwan, that investigated the association, the use of SGLT2i was associated with a lower incidence of gout (HR: 0.89; 95%CI: 0.82-0.96) than DPP4 inhibitors, and this was particularly seen in patients receiving dapagliflozin[33]. Up to 15% reduction in the risk of gout was observed with SGLT2i. Another meta-analysis of 62 studies, including 34941 patients, however, reported that although all the SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, tofogliflozin, luseogliflozin, or ipragliflozin) significantly decreased uric acid levels, empagliflozin resulted in the most superior reduction[30]. No consistent dose-related effects were observed.

Effects on haematocrit

All SGLT2i has been associated with a modest increase in haematocrit between 2%-4%. This effect was seen with empagliflozin in patients with T2DM and stage 2 or 3 CKD, but not stage 4 CKD. Though initially thought to be due to its diuretic effects, the urine volume returns to baseline within 1 wk of SGLT2i, whereas the increase in haematocrit

continues beyond 2 months. In patients with diabetes mellitus, increased glucose uptake by SGLT2 in the proximal tubular epithelial cells results in increased ATP consumption by the Na^+/K^+ pump. There is increased oxygen consumption by the proximal tubular mitochondria to meet the high demand for ATP, resulting in a relative hypoxia within the renal cortical cells[34]. Selective damage to the proximal tubular epithelial cells as seen in diabetic kidney disease induces trans-differentiation of the erythropoietin-producing fibroblasts into myofibroblasts[35], which loses the capacity to produce erythropoietin and starts producing fibrogenic molecules. Low erythropoietin levels have been demonstrated even in patients with T2DM with normal kidney function[36]. This might be due to metabolic stress associated with excessive glucose resorption by the tubular epithelial cells causing a hypoxic microenvironment. SGLT2i can reduce this metabolic stress and reduce ATP consumption by the Na^+/K^+ pump, causing a possible reversion of myofibroblasts to erythropoietin-producing fibroblasts and elevation of the haematocrit. Additionally, the nephroprotective effect of SGLT2i which prevents progression of CKD can also improve erythropoietin levels.

Effects on inflammatory markers

Inflammation is a key component in the development of atherosclerosis and plaque destabilisation/rupture. Indeed, SGLT2 inhibitors have all been shown to reduce inflammation in Apo E -/- mice[37]. Reduced IL-1β, IL-6 and IL-10 levels have been seen with empagliflozin, while dapagliflozin has demonstrated reduced NLRP3, IL-1β and IL-18 levels[38]. Canagliflozin has demonstrated significant reduction in the adhesion molecules, VCAM-1 and MCP-1, while increasing the TIMP-1 inhibitor[37,38]. These anti-inflammatory and vaso-protective effects might explain some of the major mechanisms involved in the CV and nephroprotective benefits of sodium glucose cotransporter-2 inhibitors (SGLT-2i) molecules.

Effects on metabolic syndrome-associated fatty liver disease

The effects of SGLT2i on body weight and their antioxidant and anti-inflammatory effects make them promising candidates for the management of MAFLD. In addition to decreases in in insulin and glucose levels in T2DM, SGLT2i can lead to reduction in the de-novo lipid synthesis in the liver[39]. Also, the glucagon-secreting alpha cells express SGLT2, and inhibition of this reduces intracellular glucose concentration in them thus increasing the secretion of glucagon[40]. The high glucagon levels and elevated glucagon/insulin ratio can stimulate β-oxidation leading to a shift from carbohydrate to fatty acid metabolism and reduction in the hepatic triglyceride content[41]. Thus, SGLT2i can play an important role in reducing hepatic lipid content by reduction in de novo lipid synthesis due to reduced blood glucose and insulin levels along with increased beta-oxidation of fatty acids.

A study comparing ipragliflozin to Pioglitazone found that while pioglitazone demonstrated benefit in terms of reduction in serum ALT and HbA1c; reductions in body weight and visceral fat were seen in those with Ipragliflozin[42]. Canagliflozin has been found to significantly reduce FIB-4 index and ferritin levels in T2DM patients with MAFLD, suggesting improvement in hepatic fibrosis[43]. Dapagliflozin has also been shown to reduce Fibroblast Growth Factor 21 levels and indices of hepatocyte injury[44]. A study using serial liver biopsies showed Canagliflozin use for 24 wk showed remarkable histologic improvement of metabolic-associated steatohepatitis (MASH); with even demonstration from MASH to borderline or non-MASH status[45].

Effects on obstructive sleep apnea

Obstructive sleep apnea (OSA) is related to CVD development and has been identified as a modifiable CV risk factor[46]. SGLT2i have been found to reduce apnea-hypopnea index in patients with T2DM with OSAS in small studies, though their beneficial effects on OSA or sleep-disordered breathing have not been substantiated by other studies or meta-analyses[47-49]. Apart from weight reduction, other postulated beneficial mechanisms could include rostral nasal fluid shift due to diuresis and reduction of circadian sympathetic nerve activity, nocturnal hypertension, and oxidative stress by which SGLT2i might reduce the incidence or the CV effects of OSA[50,51]. Further studies are required to elucidate the benefits of SGLT2i in this regard. The CV benefits of SGLT2i are depicted in Figure 1.

CARDIOVASCULAR BENEFITS WITH SGLT2I - POSSIBLE MECHANISMS

The mechanisms that drive the CV benefits of SGLT2i can be grossly categorised into hemodynamic alterations, metabolic changes, and direct effects on the cardiomyocytes. The CV benefits with Empagliflozin were seen as early as 12 wk after randomization, when the patients treated with empagliflozin were found to have lower rates of HHF (0% *vs* 2.9%), of the composite of HHF/CV deaths (0.2% *vs* 4.1%), and of the composite of HHF or all-cause mortality (0.2% *vs* 4.1%)[52]. A posthoc analysis of the EMPAREG-OUTCOME trial showed that the reduction in risk for empagliflozin *vs* placebo reached a significance at day 17 for HHF, day 27 for the composite of CV death/HHF, and day 59 for CV deaths[53]. The direct effects on the cardiomyocytes have been seen in several in-vitro studies and animal models, but the time taken for these effects to manifest as beneficial effects on the functioning of the human heart is not clear.

Given that the cardioprotective effects of glycemic or weight reduction and other metabolic effects would take more time to manifest, the hemodynamic alterations and effects on the cardiomyocyte actions with SGLT2i may have a more important role behind the early benefits. However, in the long run, the metabolic effects become equally important as the benefits are sustained throughout use[53]. The effects of SGLT2i on different hemodynamic and metabolic risk factors that drive ASCVD or HF are discussed in an earlier section. In the ensuing part, we have discussed the direct effects of SGLT2i on the structure and functioning of the myocardium and blood vessels.

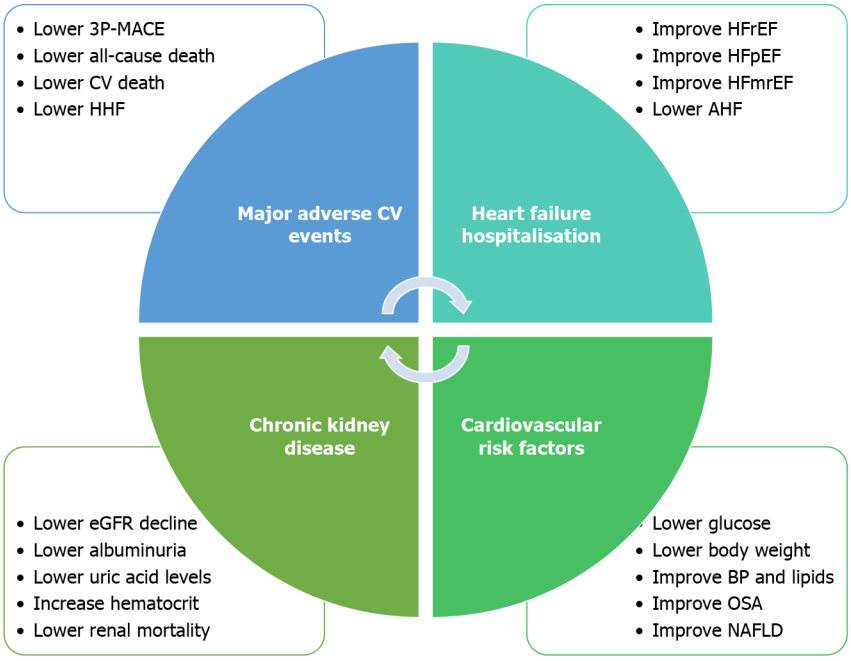

Figure 1 Cardiovascular benefits of sodium glucose cotransporter 2 inhibitors - the evidence from trials. CV: Cardiovascular; HHF: Hospitalisation due to heart failure; 3P-MACE: 3 point - major adverse cardiovascular event; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; HFmrEF: Heart failure with mildly reduced ejection fraction; AHF: Acute heart failure; OSA: Obstructive sleep apnea; NAFLD: Non-alcoholic fatty liver disease; eGFR: Estimated glomerular filtration rate; BP: Blood pressure.

SGLT2I - DIRECT EFFECTS ON MYOCARDIUM AND BLOOD VESSELS

Studies with SGLT2i suggest that the effects of SGLT-2i may not cause significant changes in cardiac stroke volume or output in patients with or without established CV disease. However, diastolic function appears to be directly influenced by SGLT-2i and significant decreases in left ventricular mass have been documented following treatment with SGLT2i [54]. Both of these are associated with endothelial dysfunction, and it is possible that SGLT-2i, by improving endothelial dysfunction, inhibits negative cardiac remodelling and improves diastolic function. The receptors and mediators through which SGLT2i exert their direct effects on the cardiomyocytes remain to be fully elucidated. Cardiomyocytes have been found to express SGLT1, which may be one of the targets for SGLT2i[54]. However, the effects of SGLT2i on HF may not only be mediated by their target receptors. SGLT2i have been found to directly inhibit Na^+/H^+ exchanger-1 (NHE1) in cardiomyocytes. Also, dapagliflozin has been found to directly activate AMP-activated protein kinase (AMPK) leading to reduced lipopolysaccharide-induced myocardial fibrosis[55]. Other cardiac sodium channels like Nav1.5 have also been found to be the targets for SGLT2i and inhibiting these sodium channels can ameliorate dysfunctional calcium overload [56].

Effects on myocardial fuel energetics

Under physiologic circumstances, cardiomyocytes prefer fatty acids as the predominant metabolic fuel for energy generation which account for 70%-90% of ATP synthesis. Although fatty acid metabolism produces more ATP than glucose, complete oxidation of the former also requires more oxygen. In those with diabetes mellitus, due to lesser glucose uptake in cardiomyocytes, they utilise more fatty acids and less glucose as the preferred substrate for oxidative metabolism, leading to greater oxygen consumption and decreased pumping efficiency of the heart[57,58]. SGLT2i has been found to benefit myocardial energy metabolism by increased GLUT1 expression and therefore increased glucose uptake in the human and murine myocardium. Enhanced rates of glycolysis and glucose oxidation have also been demonstrated in the myocardium of db/db mice[59,60]. In mouse models with diabetes, it has been demonstrated that there is increased expression of the O-palmitoyl transferase (CPT) isoform CPT1b on the outer mitochondrial membrane, which facilitates mitochondrial transport and β-oxidation of fatty acids in cardiomyocytes. Empagliflozin was found to reduce mRNA and protein expression of CPT1b[61]. Additionally, empagliflozin has been found to inhibit the mRNA and protein expression of CD36, which serves a downstream mediator of PPAR-γ in cardiomyocytes[62,63]. Following activation of PPAR-α, fatty acid uptake is enhanced compared to glucose. Thus, this effect of SGLT2i might reduce the uptake and accumulation of fatty acids within the myocardium.

One meta-analysis of RCTs showed that SGLT2i can increase adiponectin levels in T2DM[61]. Adiponectin has a negative correlation with serum triglycerides and higher adiponectin levels lead to enhanced utilization of glucose and fatty acids by muscle tissue. SGLT2i increases myocardial utilization of ketone bodies to increase ATP production. Although empagliflozin has not been seen to directly improve the efficiency of myocardial ketone body utilization, empagliflozin can increase levels of ketone bodies in serum, predominantly by promoting expression of the enzyme HMG CoA Synthase which is necessary for ketone body production[64]. The "thrifty" or frugal fuel hypothesis suggests

that ketonemia and ketone body utilisation by cardiomyocytes can increase the efficiency of cardiac mitochondrial oxidation[65].

Effects on myocardial mitochondria

Cardiac mitochondrial dysfunction is a factor behind diabetic cardiomyopathy. Under hyperglycemic conditions, mitochondria within cardiomyocytes undergo dynamin-related protein 1 (Drp1)-mediated fission, ultimately leading to fragmentation, ROS production, and increased oxidative stress. Dapagliflozin significantly reduced myocardial mitochondrial Drp1 level thereby reversing this impairment[66]. Similarly, SGLT2i have been found to normalise the alteration in proteins like MFN1, MFN2 and OPA1 which are responsible for mitochondrial fusion[66]. Additionally, empagliflozin has been seen to reverse the downregulation of *PGC-1α*, *NRF-1*, and *mtTFA* in rat models of T2DM[67]. These allow increased transcription and replication of mitochondrial DNA and activation of mitochondrial electron transport chain (ETC). Hyperglycemia increases O-GlcNAcylation, which in turn leads to decreased activity of ETC complexes I, III, and IV. Dapagliflozin and other SGLT2i can directly reduce O-GlcNAc transferase activity, leading to improvement in the functioning of the mitochondrial respiratory chain[68].

Effects on endothelial cells

Empagliflozin leads to activation of AMPK and inhibition of Drp1 by serine phosphorylation, leading to anti-inflammatory effects on arterial endothelial cells[69]. Dapagliflozin activates voltage-dependent K^+ channels, also known as the Kv channels, which are responsible for maintaining the membrane resting potential and vascular tone. Opening of these channels will lead to hyperpolarization and endothelial-independent vascular smooth muscle relaxation and vasodilation. SGLT2i have been found to inhibit TNFα-induced ROS generation and therefore reduced NO consumption in coronary arterial endothelial cells. Reduced serum uric acid concentrations with SGLT2i can also lead to increased NO synthase activity and improved NO synthesis[55]. Improved flow-mediated dilation has been seen with dapagliflozin, which might be dependent on COX-2 inhibition and reduction in ROS production[70]. SGLT2i have been found to inhibit COX-2 mRNA expression[71].

Effects on ventricular compliance, myocardial fibrosis, and infarct size

Chronic hyperglycaemia increases formation of AGEs by nonenzymatic glycation of proteins. AGEs activate the receptor for AGE (RAGE) leading to proliferation, function, and migration of cardiac fibroblasts, ultimately ending in myocardial fibrosis and cardiac aging. Empagliflozin has been shown to inhibit the AGE/RAGE axis in the kidney, though this action has still now not been demonstrated in the heart[72]. SGLT2i acts directly on cardiomyocyte NHE1 to reduce cytosolic Na^+ and thereafter Ca^{2+} accumulation within the cardiomyocyte[69].

People living with diabetes have larger size of myocardial infarcts than non-diabetics. SGLT2i can promote angiogenesis by reducing the loss of CD31+ micro-vessels, leading to reduction in the size of perfusion defects in diabetes model mice[73]. SGLT2i improves ventricular remodelling and reduces myocardial fibrosis by modulating macrophage polarization in the cardiomyocytes and reducing myocardial expression of collagen I and collagen III proteins as also pro-fibrotic molecules like TGF-β1, p-Smad2, and p-Smad3[71].

Empagliflozin has been found to improve ventricular remodelling in diabetic patients. Empagliflozin increases NO and cGMP concentrations as well as sGC and PKGIα activity leading to a decrease in cardiomyocyte stiffness[74]. Empagliflozin has been shown to reduce left ventricular mass in patients with T2DM and improve left ventricular hypertrophy[75].

Effects on oxidative stress

Canagliflozin and empagliflozin have been found to activate and restore eNOS activity in the myocardium, while the former also reduced iNOS levels, which in turn decreased superoxide and nitrate[76]. In animal T2DM models, SGLT2i has been shown to increase lipid hydroperoxide and MDA levels significantly compared to the control group, while reducing levels of glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD). Empagliflozin has the potential to reverse the imbalance between pro-oxidant molecules like lipid hydroperoxide and MDA levels and anti-oxidant molecules like GSH-Px and SOD in T2DM models, possibly by activation of the Nrf2/HO-1 pathway[77]. SGLT2i also activates Silencing information regulator 2 related enzyme 1 (SIRT1) and corresponding downstream pathways, which might explain how SGLT2i can decrease oxidative stress in diabetic cardiomyopathy *via* the SIRT1/Nrf2 signalling pathway in T1DM or the Sirt1/fork head box[69].

Protective effects against myocardial apoptosis

Diabetes is known to promote programmed cell death of cardiomyocytes. The SGLT2i inhibits caspase-3 activity in the myocardium, as also inhibits the ERK1/2 pathway and promotes the STAT3 pathway, ultimately leading to decreased cardiomyocyte apoptosis[78]. Dapagliflozin has been seen to reverse the increased NLRP3, ASC, IL-1β, or caspase-1 in mice models with T2DM, which reflects increased NLRP3-inflammasome complex formation and risk for pyroptosis (a highly inflammatory type of programmed cell death)[79].

Empagliflozin has been reported to inhibit enhanced crease autophagy of cardiomyocytes by downregulation of *NHE1* and *NHE1*-related genes like *Beclin 1* which induce autophagy[80,81]. ER stress leads to the accumulation of misfolded or unfolded proteins thus initiating an unfolded protein response (UPR) that leads to apoptosis of cells. In ER stress models induced by pressure overload or ischemic injury, SGLT2i, *via* SIRT1 activation and GRP78 reduction can inhibit the increase in p-PERK and its downstream molecules which are associated with ER stress[82,83].

OTHER MECHANISMS OF CARDIOVASCULAR BENEFIT WITH SGLT2I

Effects on the intestinal microbiota

Dapagliflozin has shown favourable alteration in the gut microbiota, including an increased abundance of *Akkermansia muciniphila*[84]. This has been associated with improved glycemic profile and improved generalized vascular functioning in mice with T2DM. Induction of the expression of tight junctions in the gut also reduces endotoxemia-related inflammation and prevents atherosclerosis. Luseogliflozin was found to increase the abundance of other bacteria like *Syntrophothermus lipocalidus*, *Parabacteroidesdistasonis distasonis*, and *Anaerotignum sp*, which produce short-chain fatty acids (SCFAs) which leads to improvement in diabetes and CV function[85]. However, these changes in gut microbiota have not been confirmed in patients with T2DM. The possible mechanisms of CV benefits from SGLT2i are summarised in Figure 2.

Effects on sympathetic nervous system activity

Since sympathetic nervous system hyperactivity is intricately linked with the initiation, progression, and deterioration (poor prognosis) of chronic human HFrEF, in a mechanism akin to β-blockers, SGLT2i, by suppressing sympathetic neural activity can protect the failing myocardium against adrenergic overstimulation. In the EMPA-REG OUTCOME Trial, empagliflozin was found to reduce heart rate somewhat unexpectedly. Consistent with this, Luseogliflozin was also found to cause bradycardia in patients with baseline elevated heart rate. Studies have shown that the FFAR3 (GPR41) receptors are abundant on sympathetic ganglia and nerve endings; and while SCFAs, *via* their stimulation of FFAR3 leads to activation of sympathetic neuronal firing, the ketone body 3-hydroxybutyrate can block it leading to reduced norepinephrine release from sympathetic nerve terminals. The SGLT2i, by their potential to increase production of ketone bodies in humans, could potentially exert sympatholysis by this mechanism[86].

Additionally, treatment of HFD-fed mice with dapagliflozin has demonstrated diminished tyrosine hydroxylase activity in the medulla, primarily by inhibition of G-protein coupled receptor kinase 2 (GRK2) leading to reduced noradrenaline levels. GRK2 has inhibitory effects on the α2-adrenergic receptor (α2-AR) which mediates the feedback mediated reduction in catecholamine release from sympathetic nerve terminals. Downregulated GRK2 by Dapagliflozin can thus lead to increased α2-AR mediated feed-back and an overall reduced catecholamine release from the nerve terminals[87].

Notably, while SGLT2 inhibition can affect sympathoinhibition in some critical target organs, such as the heart and the kidneys, dapagliflozin has been shown to promote sympatho-excitation in white adipose tissue. Increased mRNA levels of the brown adipose tissue-selective gene Ucp1 and its upstream mediator, Pgc-1 has been demonstrated suggestive of "beiging" effect of dapagliflozin[87]. Thus, available evidence suggests SGLT2i can potentially reduce secretion of catecholamines and their effects on the myocardium but promotes sympathetic overactivity of white adipose tissue.

ROLE OF SGLT2I IN ATRIAL FLUTTER/FIBRILLATION

The presence of diabetes mellitus independently predicts the risk for AF[2], and diabetes is part of the CHA_2DS_2-VASc score used to predict stroke risk in patients with AF. HF increases the risk of arrhythmias including atrial flutter and/or fibrillation and the presence of AF is associated with adverse outcomes in patients with HFrEF and HFpEF. In the DECLARE-TIMI 58 trial, dapagliflozin was found to reduce the relative risk of AF by 19% (HR: 0.81, 95%CI: 0.68-0.95)[8]. Also, empagliflozin has demonstrated a greater absolute benefit on renal and HF-related events in individuals with a history of AF (HR: 0.58, 95%CI: 0.36-0.92) and without AF (HR: 0.67, 95%CI: 0.55-0.82, $P_{interaction}$ = 0.56)[88]. The reduction in AF events was seen regardless of the presence of HF, and ASCVD. Other CVOTs of patients with diabetes mellitus also reported lower rates of AF with SGLT2i inhibitor, though the absolute reduction was small ranging between 0.1% to 0.2% per year. However, no consistent reduction in stroke was found. Factors that may contribute to a reduction in atrial tachyarrhythmias could be reduced rates of HF and atrial stretch, reduction in blood pressure and improvements in cardiomyocyte energetics, and arterial compliance. There needs to be additional studies to confirm the reliability and clinical importance of this finding.

ROLE OF SGLT2I IN CARDIAC AUTONOMIC NEUROPATHY

Patients with long-standing diabetes can have cardiac autonomic neuropathy (CAN), in which sympathetic tone predominates over parasympathetic activity. This significantly increases CV morbidity and mortality with a high risk for sudden cardiac death. Unfortunately, to date, there is no definitive treatment for CAN. SGLT2i, by its property to reduce sympathetic nervous system activity, offers hope in the management of CAN. Small studies have demonstrated that SGLT2i can reduce the risk of recurrence of vasovagal syncope, which is related to altered autonomic system function, as evaluated by heart rate variability (HRV), and by ^{123}I-metaiodobenzylguanidine myocardial scintigraphy indexes and also improve HRV and heart rate turbulence parameters while decreasing the frequency of ventricular premature beats[89]. However, in a preliminary analysis of data from the EMPA-HEART CardioLink-6 trial, Holter monitoring analyses and automated algorithms to determine HRV domain measures over 6 months found that the observed cardiac benefits of empagliflozin were not likely associated with modulation of autonomic tone in patients with T2DM and stable CAD[90].

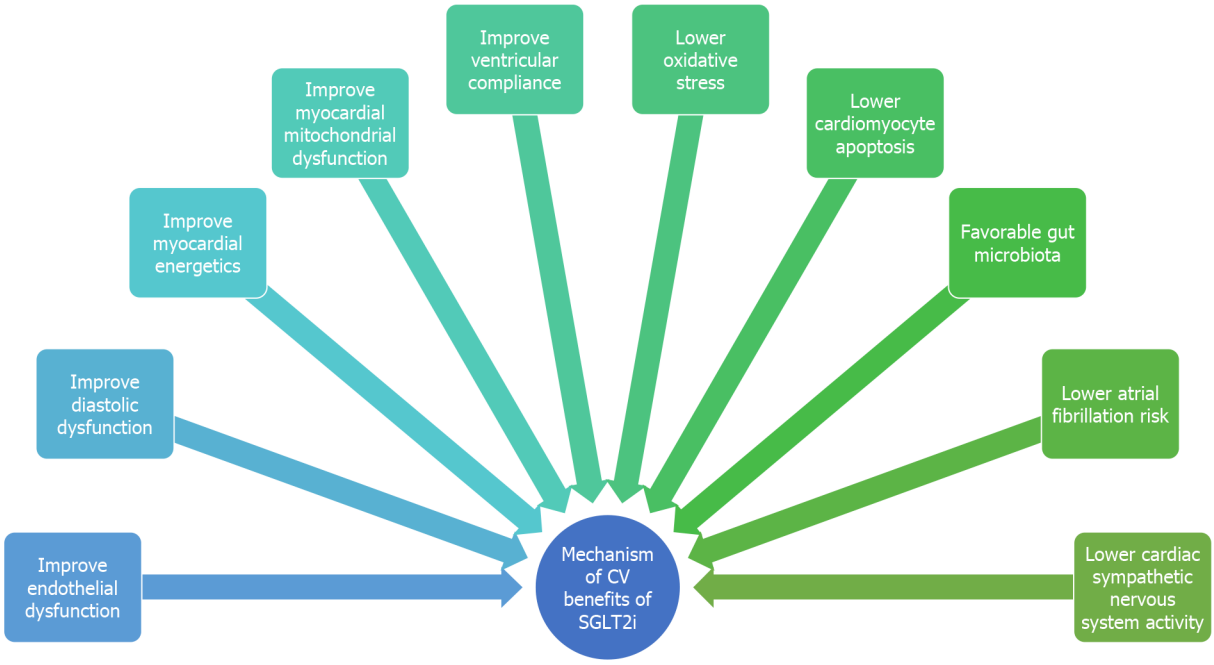

Figure 2 Mechanisms of cardiovascular benefits of sodium glucose cotransporter 2 inhibitors. CV: Cardiovascular; SGLT2i: Sodium glucose cotransporter-2 inhibitors.

CAUTION AND CONTRAINDICATIONS TO THE USE OF SGLT2I IN HEART DISEASE

SGLT2i have been associated with different adverse effects. The glucosuric effect of SGLT2i leads to higher urine glucose levels and thus predisposes patients to urinary tract and genital infections. The data regarding urinary tract infection is conflicting among different studies, but most studies report neutral findings. In the large three CVOT outcome trials, the rates of UTI were not significantly increased when compared with placebo[6-8]. In 2013, one meta-analysis reported a higher incidence of UTI between SGLT2i and either placebo or active competitors[91]. But two subsequent metanalysis refuted this finding[92,93]. Available real-world data highlight the fact that SGLT2i do not increase the frequency of UTIs compared to either DPP 4 inhibitors or GLP1 receptor agonists[94,95]. However, genital mycotic infections have been consistently found to be more frequent in patients on SGLT2i in all three major CVOT outcome trials[6-8] as well as in different meta-analyses[92,93]. Risk factors for genital mycotic infection include female gender and previous history of genital infection. However, the genital infection tends to be non-severe and manageable with systemic or topical antifungal agents without the need for treatment discontinuation[96].

SGLT2i have an osmotic diuretic effect, thus a mild volume depletion state can be observed with them. A slight reduction in blood pressure, orthostatic hypotension, and dizziness can occur with these agents especially when combined with diuretics. A meta-analysis did not find a higher volume depletion with SGLT2i compared to placebo[97]. Still, it is recommended to review the dose of diuretics while initiating a patient with SGLT2i to prevent postural hypotension.

The use of SGLT2i is associated with increased circulating ketone bodies. The incidence of euglycemic diabetic ketoacidosis varies from study to study. CANVAS and EMPAREG trials reported a nonsignificant increase of euglycemic DKA, but DECLARE-TIMI 58 reported a small but significant increase of the same[6-8]. Two meta-analyses reported a nonsignificant increase in the rates of DKA among SGLT2i versus placebo or other anti-diabetic agents[98,99]. Real-world data however suggests slightly higher rates of DKA among SGLT2i users[100,101]. This difference of results might be due to the controlled conditions of RCTs and the cautious selection of participants. Risk factors for euglycemic DKA included T1DM, presence of dehydration, excess alcohol intake, critical illness, post-operative period and intake of very low-carbohydrate diet.

The FDA had issued a warning for AKI with dapagliflozin and canagliflozin in 2016 based on few case reports submitted to the FDA adverse events reporting system (FARES). The possible mechanisms that mediate renal damage by SGLT2i could be related to volume depletion by osmotic diuresis, decreased trans glomerular pressure, and hypoxic injury to the renal medulla[102]. However, none of the CVOTs[6-8] reported a higher incidence of AKI with SGLT2i and the dedicated renal outcome trials reported SGLT2i to be beneficial for renal outcome[20,103,104]. The real-world data also suggest the use of SGLT2i is not associated with an increased risk for AKI[105]. However, a careful selection of patients initiated on an SGLT2i and close monitoring of eGFR would be useful to reduce the likelihood of AKI in the real-world clinical practice settings.

There was a postulation that SGLT2i may affect bone mineral density and bone quality, thereby increasing the risk for fragility fractures. Initial studies with canagliflozin reported a mild increase in serum phosphate, parathyroid hormone, bone resorption markers, and bone formation markers and a slight reduction in total hip bone mineral density without affecting the rest of the skeleton[106,107]. In the CANVAS trial, the risk for fracture was significantly higher with

canagliflozin versus placebo but the same finding was not replicated in other two large CV outcome studies with empagliflozin and dapagliflozin[6-8]. The underlying mechanism for increased incidence of fracture with canagliflozin can be a direct effect on bone metabolism, or it can be due to an increased risk for falls due to orthostatic hypertension associated with SGLT2i. Recently three meta-analyses[108-110] did not find any increased incidence of bone fractures with SGLT2i compared to either placebo or active treatment, thus reassuring about the fracture risk of this class of drugs.

An increased incidence of lower limb amputations was seen with canagliflozin compared to placebo (6.3 *vs* 3.4 participants with amputation per 1000 patient-years) in CANVAS trial[7] as well as in a pharmacovigilance analysis of FARES data[111], but not with other SGLT2i. The difference can be partly explained by the differences in study design and data collection regarding lower limb amputation. A recent meta-analysis[112] of 14 RCTs reported no increase in lower limb amputation with SGLT2 inhibitor as a class. However, upon subgroup analysis there was a higher fracture risk with canagliflozin versus placebo or non-SGLT2i antidiabetic drugs. The fact that there is inter-SGLT2i differences in the risk for fractures and for lower limb amputation remains to be confirmed yet.

A concern regarding an increase in bladder malignancies in male patients receiving dapagliflozin was raised in initial studies but was not clear whether it was due to earlier diagnosis of malignancies in the sub-clinical phase or there indeed was a true increase in rates of bladder cancer[95]. Possible mechanisms for tumor genesis with an SGLT2i could be the enhanced tumor growth from bladder epithelium due to persistent glycosuria in as well as the effects of chronic cystitis or recurrent urinary tract infections. However, one metanalysis[113] did not confirm any significant increase in malignancies with the use of SGLT 2 inhibitors, and further research is needed in this field.

SGLT2 IN THE PREVENTION/MANAGEMENT OF HEART DISEASES: RECOMMENDATIONS

Table 3 summarises the current position of different bodies regarding the use of SGLT2i in patients with heart disease with and without diabetes. While they don't specifically prefer one SGLT2i over another, for a particular indication, all the bodies recommend using SGLT2i that have proven benefits in that aspect.

CHOICE OF SGLT2I - ARE THEY ALL THE SAME?

Although an overall beneficial effect is obvious, there is some heterogeneity in the findings from different SGLT2i CVOTs. Also, although no head-to-head comparison data between the SGLT2i are available, there has been some numerical differences in their results. Whether the differences arise from variation in the pharmacologic properties of the various SGLT2 inhibitors or are the result of disparities in trial design and/or baseline characteristics of the study participants remain unclear. However, the latter limits direct comparability of the CVOTs.

One postulated mechanism has been the differences in specificity of the molecules to the SGLT2 receptor over SGLT1, which is greater than 2500-fold for empagliflozin, 2235-fold for ertugliflozin, 1200-fold for dapagliflozin and 200-fold for canagliflozin[114]. In the EMPA-REG trial, empagliflozin users showed a mean improvement in HbA1c by 0.24% over 206 wk, while canagliflozin over 188 wk resulted in improvement by 0.58% in the CANVAS program.

A network meta-analysis of 38 RCTs including canagliflozin, dapagliflozin or empagliflozin that were published up to November 2015 found that canagliflozin 300 mg reduced HbA1c, FPG and systolic blood pressure and increased LDL cholesterol to a greater extent compared to other SGLT2i or to 100 mg Canagliflozin[115].

However, contrary to the biologic plausibility based on SGLT2 selectivity, the CV superiority for 3P-MACE has been seen with empagliflozin in the EMPA-REG and to some extent with canagliflozin use in the CANVAS and CREDENCE studies, but it has not been seen with dapagliflozin in the DECLARE-TIMI, or with ertugliflozin in the VERTIS-CV trials [6-9].

Although the half-lives, metabolism and elimination of these drugs are quite similar, their oral bioavailability is variable, lowest being for canagliflozin (65%) and the highest for ertugliflozin (100%). There is also some variation in the volume of distribution and plasma protein binding. But to what extent these differences translate into clinically important discrepancies is yet unknown[116].

All the SGLT2i so far have demonstrated non-inferiority for 3P-MACE compared to placebo, and superior outcomes with respect to HHF outcomes, except for ertugliflozin which failed to demonstrate superiority in the VERTIS-CV trial. The studies included population with different co-morbidities and risk factors which can significantly reduce the incidence of CV or renal events during the study period. In the EMPA-REG and VERTIS-CV trials, all the participants had established ASCVD whereas in the CANVAS trial, 66% had ASCVD and in the DECLARE-TIMI, 41% had ASCVD whereas the remaining participants had multiple CV risk factors[6-9]. With regards to HF, the initial CVOTs were inconsistent in their reporting of whether the baseline HF status was HFrEF or HFpEF. A higher proportion of participants in the VERTIS-CV trial had HF (24%) at baseline, compared to the other major CVOTs (approximately 10%-15%), of whom 80% had HFpEF, which might have skewed the results of the trial[9].

The beneficial effects seen in the DECLARE-TIMI trial with respect to the combined outcome of CV death or HHF was driven mainly by gross reduction in HHF. The decrease in all-cause mortality seen in the EMPA-REG and DAPA-HF trials was predominantly due to reduction in CV mortality. Regarding 3P-MACE, it is believed that the differences in the number of participants with HF, specifically HFpEF in the VERTIS-CV trial and also low rates of CV events in the DECLARE-TIMI trial might explain why the superiority of SGLT2i for 3-PMACE couldn't be demonstrated in these trials although this was evident in the EMPA-REG and CANVAS trials.

Table 3 Role of sodium glucose cotransporter 2 inhibitors in the management a prevention of diabetes - position of different guidelines

Organize groups	Position of different guidelines
ADA, 2023	Among people with T2DM who have established ASCVD (a SGLT2i with demonstrated cardiovascular disease benefit is recommended as part of the comprehensive cardiovascular risk reduction and/or glucose-lowering regimens. (LOE: A)
	In people with T2DM who have established ASCVD, multiple atherosclerotic cardiovascular disease risk factors, or DKD, a SGLT2i with demonstrated cardiovascular benefit is recommended to reduce the risk of major adverse cardiovascular events and/or heart failure hospitalization. (LOE: A)
	In people with T2DM and established ASCVD or multiple risk factors for atherosclerotic cardiovascular disease, combined therapy with a SGLT2i and a GLP1-RA may be considered for additive reduction in the risk of adverse cardiovascular and kidney events. (LOE: A)
	In people with T2DM and established heart failure with either preserved or reduced ejection fraction, a SGLT2i with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. (LOE: A)
	In people with T2DM and established heart failure with either preserved or reduced ejection fraction, a SGLT2i with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. (LOE: A)
AACE, 2023	SGLT2i should be started irrespective of glycemic target or other T2DM therapies in patients with T2DM and ASCVD or at high risk for ASCVD (albuminuria/proteinuria, hypertension and left ventricular hypertrophy, LV systolic or diastolic dysfunction, ankle-branchial index < 0.9)
ACC/AHA, 2022	In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalisation for heart failure and CV mortality, irrespective of the presence of type 2 diabetes. (COR: 1, LOE: A)
	In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalisation and CV mortality (COR: 1, LOE: A)
	In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalisation and CV mortality (COR: 1, LOE: A)
ESC, 2022	SGLT2i are recommended in all patients with HFrEF and T2DM to reduce the risk of HF hospitalization and CV death. (COR: 1, LOE: A)
	SGLT2i are recommended in patients with T2DM and LVEF > 40% (HFmrEF and HFpEF) to reduce the risk of HF hospitalization or CV death. (COR: 1, LOE: A)
	SGLT2i are recommended in patients with T2DM with multiple ASCVD risk factors or established ASCVD to reduce the risk of HF hospitalization. (COR: 1, LOE: A)

ADA: American Diabetes Association; AACE: American College of Clinical Endocrinologists; ACC/AHA: American College of Cardiology/American Heart Association; ESC: European Society pf Cardiology; HFrEF: Heart Failure with reduced ejection fraction; HFmrEF: Heart Failure with mildly reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; COR: Class of recommendation; LOE: Level of evidence; T2DM: Type 2 diabetes mellitus; ASCVD: Atherosclerotic cardiovascular disease; SGLT2i: Sodium glucose cotransporter 2 inhibitors; LV: Left ventricle.

Notably, conflicting results have been seen between different trials with the same drug, for example empagliflozin in the EMPA-REG and EMPEROR-preserved) or dapagliflozin in the DECLARE-TIMI and DAPA-HF trials with respect to CV or all-cause mortality[13,19]. Mortality reduction with empagliflozin was seen in the EMPAREG-OUTCOME trial but not in the EMPEROR-reduced trial. Participants in the HF outcome trials (DAPA-HF and EMPEROR-reduced) were different from participants of older CVOTs like EMPAREG or DECLARE-TIMI, as, in the former group, most of the participants had HFrEF, lower BMI, systolic blood pressure and mean eGFR, and a significant proportion was non-diabetic. However, on comparing the HF trials DAPA-HF (dapagliflozin) and EMPEROR-reduced (empagliflozin), significant reduction in the risk of CV deaths was seen in the DAPA-HF trial, but not with empagliflozin in the EMPEROR-reduced trial[35,45] thus raising a question on whether baseline characteristics alone account for the changes or there is a role of individual pharmacologic property of the SGLT2i. Following the results of the DAPA-HF and EMPEROR-reduced trials, it became clear that the beneficial effects on CV death or HHF was observed in participants irrespective of the presence of diabetes.

A recent real-world study involving 25315 patients (empagliflozin: 5302, dapagliflozin: 4681, canagliflozin: 4411, other SGLT2 inhibitors: 10921), the authors reported no significant differences in the risk of developing HF, MI, AP, stroke, and AF among the individual SGLT2 inhibitors. The robustness of the results was also confirmed through a multitude of sensitivity analyses[117].

Overall, till date, there is insufficient evidence to suggest the superiority of any SGLT2i over the other with regards to different CV outcomes and it appears to be a class-effect. Data from available CVOTs may aid in making a choice of one particular SGLT2i over the other depending on the clinical scenario and the purpose of use. Thus, in patients with established ASCVD, empagliflozin appears to have an upper hand when it comes to mortality reduction and empagliflozin and canagliflozin both seem to score over dapagliflozin in reduction of 3P-MACE or the composite of HHF and CV death. However, in those with HFrEF, dapagliflozin seems to score better than empagliflozin in mortality reduction. Ertugliflozin is not a prudent choice in any scenario, whereas for HFpEF, both dapagliflozin and empagliflozin

are equal and can be used irrespective of the presence of diabetes. Talking of those without established ASCVD, a 300 mg dose of Canagliflozin can be a prudent choice based on its effects on the risk factors like the greater degrees of weight loss, BP and HbA1c% reduction. However, this is more of a personalised opinion rather than an evidence based one and the choice must be balanced against the cost in individual countries, availability, and the risk for adverse effects.

SGLT2I FOR CARDIO-PROTECTION IN TYPE 1 DIABETES? - THE CURRENT STATUS

It is a known fact now that children and adults with type 1 diabetes have insulin resistance and display features of metabolic syndrome like obesity, dyslipidemia, hypertension. A significant proportion of T1DM patients go on to develop ASCVD and HF, thus raising the question of the role of SGLT2i as adjuncts to insulin in these patients[118].

The metabolic benefits of SGLT2 inhibition like weight reduction and better Hba1c reduction have been demonstrated in type 1 diabetes in three phase 3 clinical trials- the EASE (empagliflozin), DEPICT (dapagliflozin), and inTandem (sotagliflozin, a dual SGLT1/2 inhibitor)[119].

In 2019, the European Medicines Agency (EMA) had approved dapagliflozin 5 mg as an adjunct pharmacotherapy for overweight-obese individuals with type 1 diabetes with overweight[120]. However, the FDA declined the applications for dapagliflozin and empagliflozin due to risk concerns for DKA[121]. Indeed, SGLT2i-induced glucosuria can lead to negative caloric balance and promote ketone generation. Ketosis can sometimes occur without hyperglycaemia, known as euglycemic DKA, which makes detection more difficult. In most clinical trials, the risk of DKA was dose-dependent and not seen in participants receiving very low doses of SGLT2 inhibitors like dapagliflozin 5 mg or empagliflozin 2.5 mg [118].

But again, it is unclear whether the cardiorenal protection seen with SGLT2i would manifest at such low doses. Also, the risk of DKA could be higher outside the ideal settings of a clinical trial. The EMA approval of dapagliflozin in T1DM was first made subject to a condition of strict risk mitigation strategy and close supervision by prescribers and consequently, was abruptly reversed in October 2021[122]. It is reassuring to note that most real-world data do not show an alarming increase in DKA risk with SGLT2i in T1DM[123].

CONCLUSION

The discovery of the cardioprotective effects of SGLT2i have brought about a paradigm shift in the management of T2DM with a shift of focus towards a holistic approach to target organ protection in T2DM rather than glycemic control alone. While their roles in HF and cardiac risk factors are well established, they have the potential to be used in other heart diseases like diabetic cardiomyopathy and cardiac autonomic neuropathy as well.

FOOTNOTES

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