Review article

Performance of sodium-glucose cotransporter 2 inhibitors in cardiovascular disease

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Aims The use of sodium-glucose cotransporter 2 inhibitors (SGLT2i) as a new class of drug in treating type 2 diabetes has expanded beyond its original framework. Positive results have been achieved in reducing symptoms in patients with cardiovascular disease (CVD). The aim of this article is to present an in-depth review of the basic principles of this class of medications and how it has brought benefits to patients affected particularly by heart failure.

Methods Following a thorough PubMed search, this review includes 62 studies published between 2015 and 2023. Keywords searched included 'sodium-glucose cotransporter 2 inhibitors', 'cardiovascular disease', 'heart failure', 'chronic kidney disease', and 'type 2 diabetes'. The most recent and comprehensive data were used.

Results Positive results have been achieved in reducing symptoms in patients with CVD. SGLT2 inhibitors have also been shown to be useful in other contexts such as nonalcoholic fatty liver disease (NAFLD) by reducing liver fat accumulation, kidney benefits by improving body weight and vascular endothelium, improving eGFR, and reducing progression to end stage kidney disease (ESKD). SGLT2 inhibitors are also effective in reducing the need for heart failure hospitalizations and the risk of serious cardiac adverse events, including cardiovascular and all-cause mortality, in patients with reduced or preserved left ventricular (LV) ejection fraction and in acute or decompensated settings.

Conclusion SGLT2 inhibitors have evolved into metabolic drugs because of their multisystem action and are indicated for the treatment of all spectrums of heart failure, type 2 diabetes, and chronic kidney disease.

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Keywords: all spectrums of heart failure, cardiovascular disease, kidney disease, sodium-glucose cotransporter 2 inhibitors, type 2 diabetes

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Introduction

SGLT2 inhibitors (SGLT2i) are a new class of drugs initially used to treat patients with type 2 diabetes mellitus (T2DM)[1] owing to their efficacy in controlling blood glucose levels. However, their use in clinical practice has expanded beyond their original application. This class of drugs prevents the reabsorption of glucose at the level of the proximal renal tubules, which slightly lowers blood glucose levels and is very effective in treating diabetes.[2] Eventually, this effect results in a reduction in blood pressure because of an increase in natriuresis[3] and weight loss due to calorie loss through glucose excretion, as well as a change in the body's metabolism towards increased fat oxidation and breakdown.[4] SGLT2i showed improvement in diabetic patients by inhibiting the reabsorption of glucose at the level of the renal tubules, thereby inducing a modest reduction in glucose blood levels independently of insulin-release stimulation. This effect on glucose and HbA1c is strongly dependent on the load of glucose filtered and the diuretic effect exerted by the drug. Thus, the ability to lower blood glucose and glycosylated hemoglobin (A1C) is limited by the filtered glucose load and osmotic diuresis caused by this therapy.[2] Numerous studies have been conducted in recent years to determine the potential benefit of SGLT2i in other diseases. In the treatment of cardiovascular diseases such as heart failure with preserved and reduced ejection fraction, positive results have been achieved including a reduction in mortality.[5] SGLT2i have also helped to treat NAFLD by reducing fat accumulation in the liver and addressing the pathophysiological aspects of the disease such as moderate inflammation, oxidative stress, autophagy, and apoptosis.[6] Moreover, SGLT2i have shown beneficial effects on renal function.

SGLT2 inhibitors have glucoretic and natriuretic effects that lower HbA1c, body weight, SBP and triglycerides. The sodium excretion leads to a reversal of tubuloglomerular feedback and a reduction in intraglomerular pressure, which contributes to the nephroprotective effects of SGLT2i. As a result of calorie loss, weight is reduced, insulin sensitivity is increased, lipid metabolism is enhanced and probable lipotoxicity is reduced. This shift to gluconeogenesis and ketogenesis is beneficial for heart

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and kidneys. Moreover, the reduction in tubule cell glucotoxicity reduces mitochondrial dysfunction and inflammation. Through a negative sodium and water balance and potential inhibition of the sympathetic nervous system, SGLT2i probably improve blood pressure and reduce renal hypoxia by reducing tubule energy and oxygen demand. These changes contribute to improved cardiovascular function and are most likely the primary reason for SGLT2i's cardiovascular benefits. SGLT2i also lower hepcidin levels, which improves erythropoiesis and anemia.[7] In diabetic patients with advanced chronic kidney disease (CKD), SGLT2i improve kidney function, glycemic profile, and reduced adverse kidney-related and cardiovascular events.[8] Notably, major vascular complications of T2D are reduced, including major adverse cardiovascular events by 11%, the risk of cardiovascular death or hospitalization for heart failure by 23%, and the risk of renal disease progression by 45%.[9] The benefits of SGLT2i in cardiovascular patients cannot be attributed solely to glucose lowering and weight loss, as other antihyperglycemic drugs do not demonstrate similar cardiovascular benefits. The osmotic diuresis of SGLT2i reduces fluid volume with less neurohormonal activation than traditional diuretics. This diuresis can improve cardiac function, and contribute to early functional improvement in heart failure with preserved ejection fraction (HFpEF) patients. SGLT2 inhibitor-induced natriuresis, achieved through inhibition of NHE3, may explain the reduced diuretic necessity in HFpEF patients. In addition, negative sodium balances induced by natriuresis may reduce aortic stiffness and potentially alleviate the symptoms and progression of HFpEF. The natriuretic and diuretic effects of SGLT2i; contribute to a reduction in hospitalizations and an improvement in symptoms in HFpEF. SGLT2 inhibitors also decrease pro-inflammatory adipokines in epicardial adipose tissue, improve sodium and calcium regulation in cardiomyocytes, and alleviate right ventricular pulmonary hypertension. These direct cardiac actions play an essential role in cardiovascular protection.[10]

In order to discern the pharmacodynamics behind this class of oral antidiabetic agents and their contribution to cardiovascular disease especially in heart failure, this review aims to describe an in-depth analysis of the underlying fundamentals of this class of drugs and how it has improved the management of cardiovascular disease patients.

Pharmacodynamics of sodium-glucose cotransporter 2 inhibitors

The proximal convoluted tubules of the kidneys (PCT) present two types of transporters on their surface: SGLT1 and SGLT2 co-transporters; the latter are responsible for the reabsorption of 90% of the glucose in its first segment (S1) of the PCT, whereas the first reabsorb the remaining quantity present in segments 2 and 3 (S2 and S3). This transfer is actively mediated by a Na+/K+ ATPase pump that transports three Na+ ions into the blood, simultaneously extruding two K+ ions into the lumen. Finally, glucose is transferred back into the blood passively through the GLUT 2 transporter present in the basolateral membrane[11] (Fig. 1).

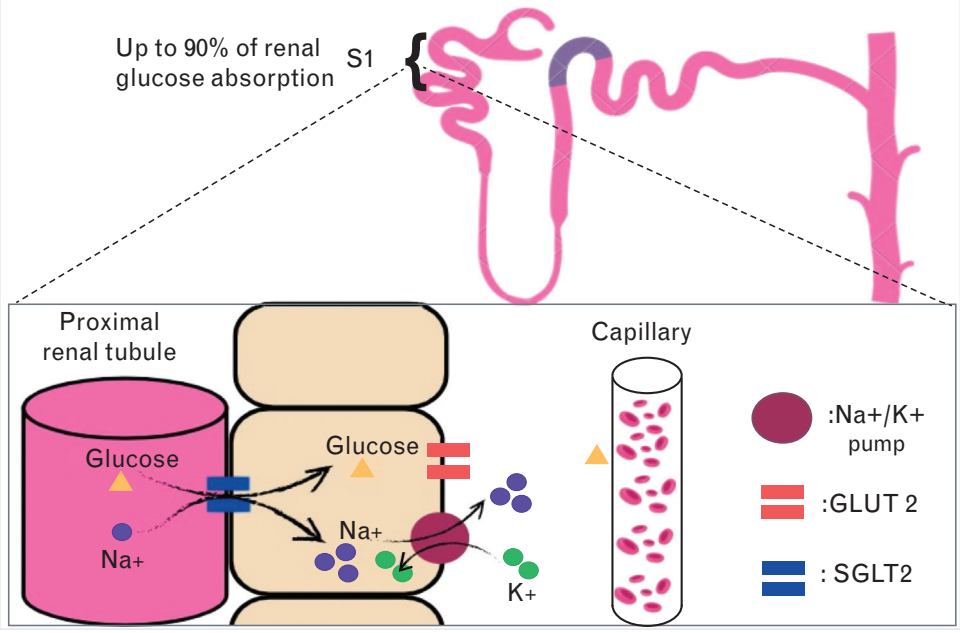
In T2DM patients, on account of hyperglycemia and increased synthesis of angiotensin 2 in the kidney, the PCTs undergo hypertrophy by an upregulation mechanism while simultaneously increasing the SGLT expression because of the fact that in diabetic patients the renal threshold for glucose is higher than in normal patients (200–240 vs. 180 mg/dl) thus leading to a decreased urinary glucose excretion. Not surprisingly, the filtrate production per day will contain an increased level of glucose (a rise from 400–450 to ~500–600 g/day). In the presence of SGLT2i, blockage of the SGLT2 transporters leads to a decreased threshold and increased urinary glucose excretion, ultimately leading to slightly lower blood glucose levels. Interestingly, the activity of this class of drugs is monitored and reduced to prevent hypoglycemia[12] (Fig. 2).

Pharmacokinetics of sodium-glucose cotransporter 2 inhibitors

When tackling their pharmacokinetics, SGLT2i exert similar properties, with minimal differences, in their ADME (absorption, distribution, metabolism, and excretion) characteristics. This class of drugs is administered through the oral route. The daily intake is one dose, because of their long elimination half-life. Moreover, the excretion of this drug is done through metabolite formation via O-glucuronidation by uridine diphosphate glucuronosyl transferases by the liver and the elimination is done primarily by the kidneys.[13,14] There are some drug interactions between SGLT2i and some other drugs. For example, when combined with other insulins or insulin secretagogues, there is a higher risk of hypoglycemia. In patients taking lithium, the simultaneous administration of these drugs may lead to a reduction in their efficacy. Canagliflozin may affect the bioavailability of digoxin by increasing it. Masked symptoms of hypoglycemia may occur in patients taking nonselective beta blockers.[15]

Dapagliflozin shares a very rapid oral absorption (T_{max} is reached 1–1.5 h postadministration), elicits a bioavailability of 78%, and its long half-life (13 h) makes it suitable for a single-dose daily administration. Dapagliflozin is mainly excreted by the kidney (75%) and, to a lesser extent, by the feces (21%).[11]

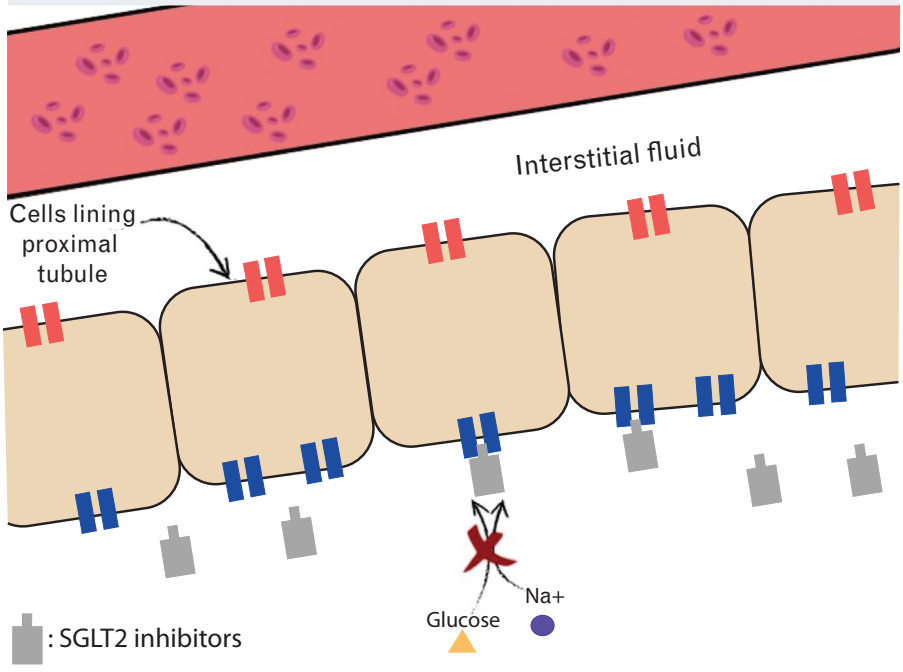
Fig. 1



Glucose reabsorption back into the blood via sodium-glucose cotransporter 2 co-transporters.

Canagliflozin reaches T_{max} 1–2 h postoral administration in the blood, eliciting a bioavailability of 65%. Both the uridine diphosphate-glucuronosyltransferase (UGT) 1A9 and UGT2B4 enzymes metabolize canagliflozin into M7 and M5, respectively. The steady state of canagliflozin is reached on the fourth day. The excretion of this drug is done primarily via the feces (60%) and, to a lesser extent, by the urine (30%). The half-life of this drug is 13.1 h.[13]

Fig. 2



Effect of SGLT2 inhibitors on the sodium-glucose cotransporter 2 co-transporters.

Empagliflozin has the highest selectivity for SGLT2 transporters over SGLT1 (>2500-fold) and is administered once daily in the morning before or after a meal with a recommended dose of 10 mg (which can be titrated to 25 mg once daily). Bioavailability of this drug is attested to be around 75%; similarly to other gliflozins, the T_{max} (peak concentration in the blood) of this drug has rapid onset (1.5 h). Empagliflozin shows no drug–drug interaction in T2DM medications; it is also available in combination with metformin and ligand liptin. The half-life of this drug is 13 h. Moreover, its elimination is done mostly by the renal route (55%), and to a lesser extent by the intestines (40%). This drug is contraindicated in women who are pregnant or breastfeeding; however, it is well tolerated for stage 2–3 CKD patients (hypoglycemia has been shown in stage 4 only).[11]

Effects of sodium-glucose cotransporter 2 inhibitors on atherosclerosis

Atherosclerosis is a cardiovascular disease in which atherosclerotic plaques are deposited in the subendothelial matrix because of the accumulation of oxidized low-density lipoprotein (Ox-LDL). This buildup stimulates the immune system to release pro-inflammatory cytokines, leading to inflammation. The mechanism of SGLT2i is to reduce the inflammatory response and protect the endothelial wall. In addition, SGLT2i contribute to vascular vasodilation by targeting the bioavailability and anabolism of nitric oxide. Preliminary results performed in db/db mice and nondiabetic rats demonstrated the effect of empagliflozin and canagliflozin on improving aortic stiffness and vasodilatation.[16]

SGLT2 inhibitors have been shown to activate AMPK, an enzyme that plays a key role in cellular energy metabolism, which has been linked to beneficial effects on lipid metabolism, including lipolysis, as it induces an insulin-independent decrease in plasma glucose, leading to an increase in lipolysis, subsequent lipid oxidation and reduction in hepatic triglyceride synthesis and total cholesterol, which also affects body weight.[4,17,18] SGLT2 inhibitors can increase HDL levels while improving the expression and function of the LDL receptor in the liver.[19] In addition, SGLT2i can lead to a reduction in uric acid as they reduce uric acid reabsorption by blocking the urate transporter 1 (URAT1) in the renal proximal tubule.[20] All of these effects play an important role in reducing the risk of long-term cardiovascular disease and, theoretically, preventing the development of atherosclerosis or cardiovascular disease.

Action of sodium-glucose cotransporter 2 inhibitors in heart failure

SGLT2 inhibitors have been shown to be significant in the treatment of heart failure across the entire spectrum of left ventricular ejection fraction (LVEF), and in particular the prognostic benefit of SGLT2i has been demonstrated for all phenotypes of heart failure.[21] Recent studies demonstrated the results of a reduction in heart failure hospitalizations and cardiovascular fatalities, suggesting that they may have a direct effect on heart failure regardless of their antihyperglycemic properties. When used to treat T2DM, SGLT2 inhibition only slightly decreases hemoglobin A1c while considerably lowering cardiovascular outcomes, indicating that unfavorable cardiovascular events in T2DM are not entirely mediated by dysglycemia. Furthermore, SGLT2i are the only drugs effective in treating heart failure across the LVEF range based on theoretical mechanisms other than the diuretic or natriuretic effects of the drugs.[22]

Possible mechanism of sodium-glucose cotransporter 2 inhibitors in heart failure patients

A contributor to heart failure is the development of post-inflammatory fibrosis in the heart muscle, and SGLT2i have been shown to reduce inflammatory reactions by inhibiting or attenuating the molecular processes of inflammation leading to fibrosis; for instance, dapagliflozin exerted antifibrotic effects through the inhibition of collagen synthesis in rat hearts postinfarction. Moreover, empagliflozin decreased cell-mediated collagen remodeling in the extracellular matrix. The mechanism behind this anti-inflammatory process is thought to be done by decreasing the anti-inflammatory role of macrophages through glucose-lowering effects of SGLT2i as macrophages use glucose as a fuel source and secondly by inhibiting directly or indirectly the NLRP3 inflammasomes that play a pivotal role in mediating inflammation.[23]

An important factor in the pathophysiology of heart failure is the dysfunction of vascular smooth muscle cells and endothelial dysfunction, both of which are correlated with a poor prognosis with higher mortality and morbidity. SGLT2 inhibitors decrease endothelial cell activation and improve vascular function through direct vasorelaxation by the activation of protein kinase G and voltage-gated potassium channels, ultimately leading to a lower probability of early atherogenesis and arterial wall stiffness. Patients with heart failure present with a decrease in mitochondrial oxidative metabolism and a reliance on glycolysis to yield energy from glycolysis, which ultimately leads to decreased ATP production and a fuel-starved heart. However, SGLT2i have been shown to improve this metabolic function by increasing circulating ketone levels, as they are more efficient at providing an extra source of energy for the failing heart. Although SGLT2i may not directly improve the efficiency of a failing heart, they play an important role in providing the cardiac muscle with a

source of energy, which is considered crucial in an energy-compromised failing heart.[23]

Heart failure with reduced left ventricular ejection fraction

The first study to assess SGLT2i effectiveness in treating patients with heart failure with reduced left ventricular ejection fraction (HFrEF) was the DAPA-HF trial. Four thousand seven hundred and forty-four individuals with stable, chronic heart failure and LVEF 40% or less were included in the study and were monitored for an 18-month period. When compared with placebo, dapagliflozin significantly decreased the key composite outcome of cardiovascular mortality, heart failure hospitalizations, and urgent heart failure visits [16.3 vs. 21.2%; hazard ratio 0.74; 95% confidence interval (CI) 0.65–0.85].[24] In addition, it was discovered that dapagliflozin significantly decreased each component of the primary composite outcome on an individual basis, and the treatment impact persisted regardless of the patient's diabetes condition at the beginning of the study.[25,26]

In a study conducted by Matteo Serenelli *et al.* investigating whether there is a risk of hypotension in patients treated with SGLT2i (dapagliflozin) depending on the baseline SBP in DAPA-HF, the results of this study showed a significantly higher rate for the primary endpoint, which was a composite of heart failure and cardiovascular death (20.6, 95% CI 17.6–24.2) in patients with the lowest SBP category compared with patients with a higher SBP category (13.8, 11.7–16.4). Notably, SBP increased moderately in patients with the lowest baseline SBP at 2 weeks' follow-up (by 1.91 ± 11.12 mmHg with dapagliflozin vs by 3.46 ± 10.21 mmHg with the placebo group) and decreased in patients with a higher baseline SBP ($\geq$130 mmHg) (-8.94 ± 13.26 mmHg with dapagliflozin vs. -4.62 ± 13.01 mmHg with placebo) ($P = 0.012$ for interaction between baseline SBP category and effect of treatment on SBP).[27]

Following the previously mentioned study, the EMPEROR-Reduced assessed the efficacy of empagliflozin in a comparable cohort but with a reduced mean LVEF of up to 27% vs. up to 31% in DAPA-HF. The experiment included 3730 individuals and had a median follow-up of 16 months. Investigators demonstrated that empagliflozin significantly decreased the composite outcome of cardiovascular mortality and heart failure hospitalizations when compared with placebo, with a relative risk reduction of 21% (19.4 vs. 24.7%; hazard ratio 0.75; 95% CI 0.65–0.86).[28]

Both of the trials consisted of the same ratio of participants with and without type 2 diabetes ($\approx$50%). The median NT-proBNP levels were higher ($\approx$at 1900 pg/ml) in EMPEROR-Reduced versus $\approx$1430 pg/ml in DAPA-HF. In contrast, the LVEF was lower (27%) in EMPEROR-Reduced compared with DAPA-HF. Thirty-one percent of patients in the EMPEROR-Reduced trial were hospitalized for heart failure ($\sim$31 vs. 47%) throughout the 12 months; in contrast, a larger number of patients in the EMPEROR-Reduced were in the functional class II of the New York Heart Association. Furthermore, the baseline estimated glomerular filtration rate (eGFR) of DAPA-HF was higher ($\sim$66 ml/min/1.73 m^2) compared with that of EMPEROR-Reduced patients ($\approx$61 ml/min/1.73 m^2). Moreover, prospectively, EMPEROR-Reduced patients had an eGFR of 60 ml/min/1.73 m^2.[29]

Heart failure with preserved left ventricle ejection fraction

Nearly half of all cases of heart failure are caused by HFpEF, which is characterized by diastolic dysfunction and is frequently observed in older people with cardio-renal-metabolic comorbidities. Noteworthily, this disease has fewer therapeutic choices.

The first study to assess the efficacy of the SGLT-2 inhibitor empagliflozin in patients with heart failure with mildly reduced (HFmrEF) and HFpEF, regardless of the patient's diabetic status, was the EMPEROR-Preserved trial. A total of 5988 patients with LVEF greater than 40% participated in the study. Similar to EMPEROR-Reduced, empagliflozin significantly decreased the risk of hospitalizations for heart failure by 27%, which led to a 19% reduction in the key composite outcome of cardiovascular mortality and hospitalizations (13.8 vs. 17.1%; hazard ratio 0.79; 95% CI 0.69–0.90).[30]

The DELIVER trial examined the efficacy of dapagliflozin in people with both HFmrEF and HFpEF. The trial design was comparable to EMPEROR-Preserved, with the exception that patients with improved LVEF (patients with a decreased LVEF who had improved to LVEF $>$40% with medical treatment) were now included. In a population of 6263 patients with a median follow-up of 2.3 years, dapagliflozin significantly decreased the primary composite endpoint (unplanned heart failure hospitalization, heart failure urgent visits and cardiovascular mortality) by 18% when compared with placebo (16.4 vs. 19.5% hazard ratio, 0.82; 95% CI 0.73–0.92; $P < 0.001$), largely because of a 21% decrease in heart failure hospitalizations and urgent heart failure visits (11.8 vs. 14.5%, hazard ratio, 0.79; 95% CI 0.69–0.91). In contrast to what was shown in the EMPEROR-Preserved study, the primary endpoint was reduced across all patients by LVEF 60%.[31]

SGLT2 inhibitors represent the latest addition to medical therapy according to guidelines for the management of

heart failure patients with reduced ejection fraction. The mechanisms underlying these benefits are not fully understood. Recent research suggests that various metabolic and biomolecular targets may play a role in the cause of cardio-renal-metabolic effects in heart failure.

Sodium-glucose cotransporter 2 inhibitors in acute heart failure and congestion

As mentioned above, the diuretic effect of SGLT2i produces a homeostatic sodium environment in the organism, ultimately leading to decreased plasma volume and blood pressure. Improving heart failure symptoms work by targeting both the preload and the after-load; the former will be regulated by the decrease in plasma volume, whereas the latter is decreased by lower blood pressure, ultimately leading to better cardiac flow. On the other hand, SGLT2i work by reducing arterial stiffness via relaxation of the smooth muscle cells.[32] Patients hospitalized for acute heart failure were usually excluded from clinical trials on SGLT2i.

The EMPA-RESPONSE-AHF trial aimed to determine how empagliflozin affected symptoms, diuretic response, NT-pro-BNP levels from baseline to day 4 as well as the combined endpoint of in-hospital worsening of heart failure, all-cause mortality, and heart failure hospitalization at day 60 in acutely decompensated heart failure. Despite the small sample size of this pilot study ($N = 80$), empagliflozin enhanced urine output [difference 3449 (95% CI 578–6321) ml; $P < 0.01$] and decreased the composite clinical outcome when compared with placebo [4 (10%) vs. 13 (33%); $P = 0.014$].[33]

The SOLOIST-WHF study[34] was a multicenter, double-blind study that investigated the effect of starting sotagliflozin early (before or shortly after discharge) after an episode of decompensated heart failure in individuals with T2DM. A total of 1222 patients were randomly assigned and monitored for a median of 9 months; the first dose of sotagliflozin or placebo was given before discharge in 48.8% and 2 days after discharge in 51.2% of the patients. The rate of the primary composite endpoint (cardiovascular death, hospitalization, and emergent visit for heart failure) was lower in the sotagliflozin group than in the placebo group (51.0 vs. 76.3; hazard ratio, 0.67; 95% CI 0.52–0.85; $P < 0.001$). Authors also found a lower incidence of death from cardiovascular causes (10.6 vs. 12.5%; hazard ratio, 0.84; 95% CI 0.58–1.22) and all-cause death (13.5 vs. 16.3%; hazard ratio, 0.82; 95% CI 0.59–1.14) in the sotagliflozin group compared with the placebo group.

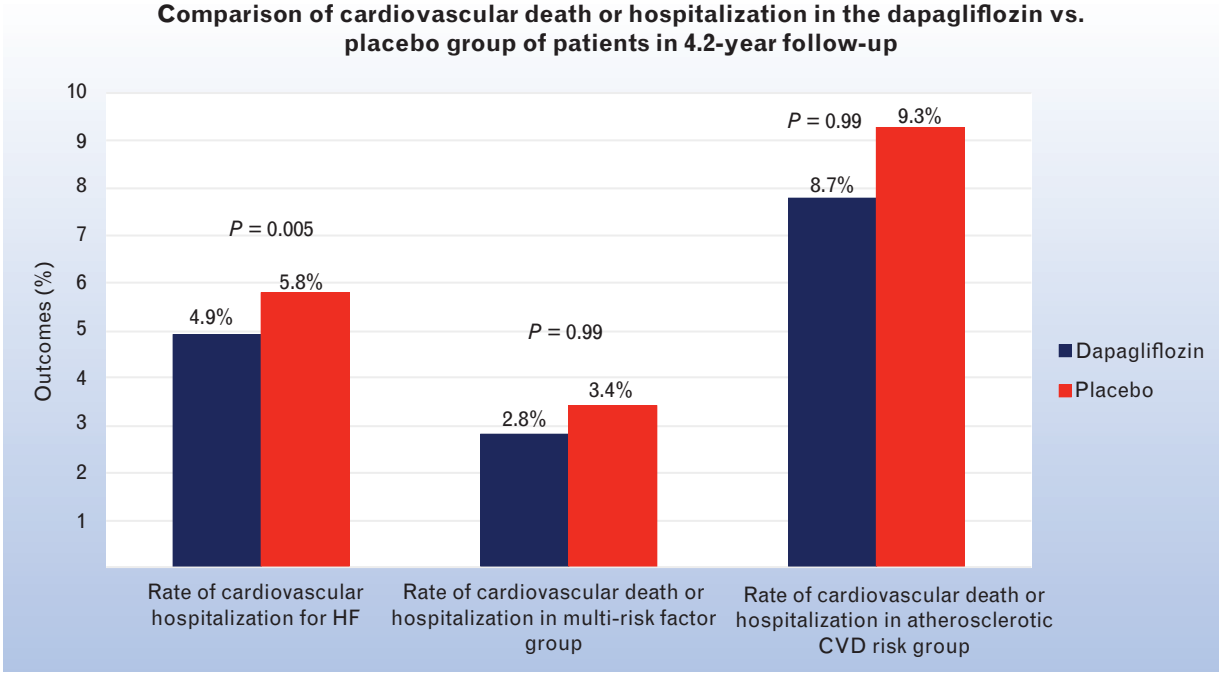
The results of these studies show that SGLT2i can be used safely and effectively in patients with acute decompensated heart failure and that the significant clinical benefit of SGLT2i occurs early, within days to weeks of starting treatment.[35] SOLOIST-WHF showed that initiating treatment with sotagliflozin before or shortly after discharge from heart failure hospitalization significantly reduced the primary endpoint of death from cardiovascular disease, heart failure hospitalization, or urgent heart failure as early as 4 weeks after randomization.[34] In a secondary analysis of DAPA-HF, which aimed to investigate the timing to the onset of clinical benefit of dapagliflozin, a reduction in the risk of cardiovascular death or worsening heart failure was seen early, with statistical significance of the primary endpoint reached 28 days after randomization (hazard ratio 0.51, 95% CI 0.28–0.94; $P = 0.03$).[36] Similarly, empagliflozin reduced the combined risk of death or worsening heart failure compared with placebo as early as 12 days after randomization (hazard ratio 0.76; 95% CI 0.67–0.87; $P < 0.0001$), and the effect was maintained during follow-up in EMPEROR-Reduced trial.[37]

Sodium-glucose cotransporter 2 inhibitors in patients with atherosclerotic disease

The DECLARE-TIMI 58 trial was a multicenter, double-blind randomized trial that inspected the effect of dapagliflozin on cardiovascular events in T2DM participants and established atherosclerotic cardiovascular disease (ASCVD) or multiple cardiovascular risk factors. This pivotal trial on primary and secondary prevention enrolled 17 160 patients at 882 centers in 33 countries with a mean follow-up of 4.2 years. The primary efficacy outcome was of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction, or ischemic stroke. Dapagliflozin significantly reduced cardiovascular death or hospitalization for heart failure compared with placebo (2.8 vs. 3.4%, hazard ratio, 0.84; 95% CI 0.67–1.04; $P = 0.99$ for interaction). It is important to note that the lower rate of the composite primary outcome was mainly driven by a reduction in hospitalizations for heart failure (5.8 vs. 4.9%, hazard ratio, 0.83; 95% CI 0.73–0.95; $P = 0.005$). In addition, the rate of death and hospitalization in the ASCVD risk group of patients was lower in the dapagliflozin group (8.7 vs. 9.3%, hazard ratio, 0.83; 95% CI 0.71–0.98) (Fig. 3). The incidence of the renal composite outcome was also lower in the dapagliflozin group in comparison with the placebo group (4.3 vs. 5.6%, hazard ratio, 0.76; 95% CI 0.67–0.87).[38]

In another randomized, multicenter, double-blind study, the VERTIS CV trial, 8246 patients with type 2 diabetes and established ASCVD were assigned to either the ertugliflozin or placebo group. Among 8238 patients who received at least one dose of ertugliflozin or placebo, the MACE rate was lower in the ertugliflozin group ($n = 653$

Fig. 3



A visual comparison of the findings from DECLARE-TIMI 58 (MOD: DECLARE-TIMI 58). Data from Wiviott *et al.*[38]

of 5493, 11.9%) than in the placebo group ($n = 327$ of 2745, 11.9%) (hazard ratio 0.97; 95.6% CI 0.85–1.11; $P < 0.001$ for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 8.1% of the ertugliflozin group compared with 9.1% of the placebo group (hazard ratio 0.88; 95.8% CI 0.75–1.03; $P = 0.11$ for superiority). No significant effect on cardiovascular death was observed. However, there was a significant reduction in first hospitalizations for heart failure (2.5 vs. 3.6%, hazard ratio 0.70; 95% CI 0.54–0.90.[39]

Braunwald *et al.* demonstrated that SGLT2 inhibition improves cardiovascular outcomes in patients with heart failure across a broad spectrum of ejection fractions, regardless of whether the patients have type 2 diabetes. In addition to their blood glucose-lowering and natriuretic properties, these agents reduce the risk of end-stage kidney disease (ESKD) in patients with type 2 diabetes and CKD. Thus, this major review concluded that SGLT2i are responsible for significant shifts in the treatment of patients with heart failure, a high risk of CKD, or both.[40]

Recently, a meta-analysis was conducted on different patient populations with varying combinations of T2DM, heart failure, and CKD to evaluate the effects of SGLT2i on heart failure outcomes and cardiovascular death. Thirteen studies ($n = 90\,413$) were included in this meta-analysis. Compared with placebo, SGLT2i reduced the risk of first HFH/cardiovascular death by 24% in heart failure (hazard ratio 0.76; 95% CI 0.72–0.81), 23% in T2DM (hazard ratio 0.77; 95% CI 0.73–0.81) and 23% in CKD (hazard ratio 0.77; 95% CI 0.72–0.82). The benefit was consistent in heart failure with or without T2DM, heart failure with or without CKD, and heart failure with reduced or preserved ejection fraction. Similarly, the benefit was consistent in patients with all three comorbidities of T2DM with or without CKD, T2DM without heart failure, and CKD without heart failure. Notably, SGLT2i reduced the number of deaths by 16% in heart failure, 15% in T2DM and 12% in CKD. These results, therefore, support the use of SGLT2i in all three patient groups to improve clinical outcomes.[41]

Effect of sodium-glucose cotransporter 2 inhibitors on kidneys

CKD is a common comorbidity in heart failure patients. In addition, SGLT2i also have direct renal effects including[1] control of intraglomerular arteriolar pressure through active sodium influx causing vasoconstriction[2]; delaying the onset or progression of CKD through improved glycemic control, leading to an improvement in diabetes by a delay in the progression of diabetic nephropathy[3]; CKD prevention by delaying hypertensive nephropathy through an increase in natriuresis.[3,42]

The hypothesis regarding the impact of SGLT2i on cardiovascular outcomes was first raised by the EMPA-REG OUTCOME, a double-blind, randomized study that evaluated the effect of empagliflozin at standard or high dose (respectively, 10 or 25 mg) on 7020 T2DM patients (HbA1c between 7 and 10, eGFR >30 ml/min/1.73 mq, and BMI <45 kg/mq) at high risk for cardiovascular events for a median follow-up of 3.1 years. Regardless of the dose given, empagliflozin significantly reduced the risk of cardiovascular death (3.7 vs. 5.9%, $P<0.001$), death from any cause (5.7 vs. 8.3%, $P<0.001$), and hospitalization for heart failure (2.7 vs. 4.1%, $P=0.002$). Similarly, the trial outcome showed a significantly lower primary endpoint (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) in the empagliflozin group (10.5 vs. 12.1%, $P=0.04$). Moreover, patients treated with empagliflozin had a significantly reduced risk of developing end-stage renal disease or doubling serum creatinine levels while reducing albuminuria.[43] Notably, subsequent sub analysis revealed that, even in nonheart failure patients, empagliflozin reduced the risk of heart failure hospitalization and cardiovascular death independently of the basal heart failure risk category, demonstrating empagliflozin's beneficial effect independently of the presence of heart failure at baseline.[44,45]

In addition to this information, CREDENCE and DAPA-CKD are randomized controlled studies that precisely investigated the efficacy of SGLT2i on a primary kidney endpoint, providing the greatest evidence for treatment in CKD patients.[46,47]

In the DAPA-CKD study, 4304 patients with both diabetic and nondiabetic kidney disease and with eGFRs ranging from 25 to 75 ml/min/1.73 m^2 and ACRs ranging from 200 to 5000 mg/g on maximally tolerated renin–angiotensin–aldosterone system (RAAS) blocking were included. Participants were monitored for a median of 2.4 years. Dapagliflozin reduced the primary combined outcome of sustained greater than 50% decrease in eGFR, ESKD, and renal or cardiovascular death by 39%. Importantly, the effects of dapagliflozin were similar in patients with or without T2DM. All individual components of the renal endpoint demonstrated benefits, with a 36% reduction in ESKD risk and a 47% reduction in 50% eGFR decline. Hospitalization for heart failure or cardiovascular disease was reduced by 29%.[46]

In the CREDENCE study, 4401 patients with T2DM with albuminuria (microalbumin-to-creatinine ratio 300–5000 mg/g), an eGFR of 30–90 ml/min/1.73 m^2, and a HbA1c range of 6.5–12% were enrolled. After a median follow-up of 2.62 years, the study was terminated early because of the interim analysis's finding of benefit. Canagliflozin decreased by 30% the main composite of doubling creatinine, ESKD, and mortality from renal or cardiovascular causes. A decreased risk of doubling serum creatinine and ESKD was seen across all renal endpoints. The rate of eGFR decline was lower in the canagliflozin group (3.19 ml/min per 1.73 m^2 per year) than in the placebo group (4.71 ml/min per 1.73 m^2 per year). Despite just slight changes in blood glucose, weight, and BP, this finding was still found.[47]

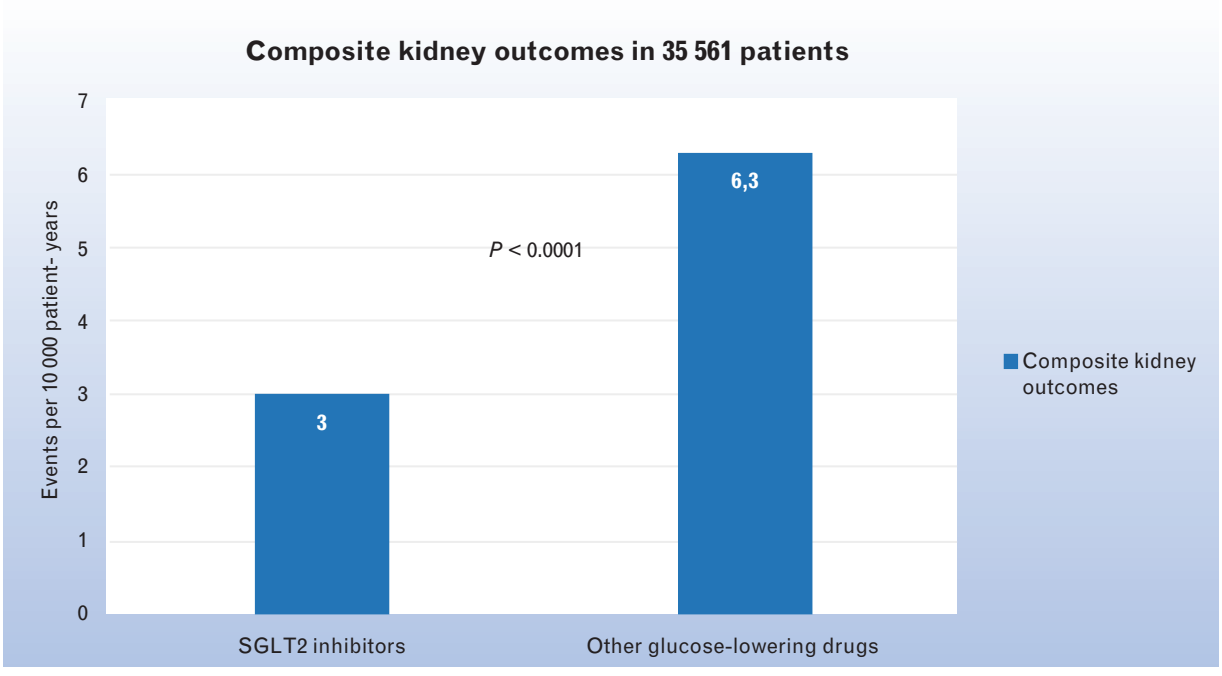
Both CREDENCE and DAPA-CKD represent the significant impact of SGLT2i on the renal endpoints in patients with CKD with albuminuria, independently of diabetes status.

Another study, the EMPA-KIDNEY trial, aimed to evaluate the effects of empagliflozin in patients with CKD who had an eGFR of 20–45 ml/min, or 45–90 ml/min per 1.73 m^2, with a urinary albumin-to-creatinine ratio of at least 200. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (24.8 vs. 29.2 hospitalizations per 100 patient-years: hazard ratio 0.86; 95% CI 0.78–0.95, $P=0.003$), but there were no significant between-group differences in the composite outcome of heart failure hospitalization or death from cardiovascular causes (4.0 vs. 4.6% in the placebo group, $P=0.15$) or death from any cause (in 4.5 and 5.1%, $P=0.21$). The rates of major adverse events were comparable in both groups. Authors showed that empagliflozin therapy resulted in a lower risk of kidney disease progression in a broad spectrum of patients with CKD.[48]

The Canagliflozin Cardiovascular Assessment Study (CANVAS) trial aimed at assessing the renal safety and efficacy of canagliflozin in T2DM patients at high cardiovascular risk. The authors found that albuminuria progression occurred less frequently in the canagliflozin group. Furthermore, the composite outcome of a sustained 40% decline in eGFR, the requirement for renal replacement therapy, or death from renal causes occurred less frequently in patients in the canagliflozin group compared with patients in the placebo group (5.5 vs. 9.0 per 1000 patient-years, hazard ratio 0.60; 95% CI 0.47–0.77).[49]

CVD-REAL 3 is a real-world, observational study aiming at examining renal outcomes in 35 561 patients treated with various glucose-lowering medications and discovered that SGLT2i initiation was associated with reduced eGFR decline (difference in slope for SGLT2i vs. other glucose-lowering drugs 1.53 ml/min per 1.73 m^2 per year, 95% CI 1.34–1.72, $P<0.0001$). During a mean follow-up of 14.9 months, 351 composite kidney outcomes occurred: 114 (30 events per 10 000 patient-years) among initiators of SGLT2i and 237 (63 events per 10 000 patient-years) among initiators of other glucose-lowering drugs (hazard

Fig. 4



A visual comparison of the findings from the CVD-REAL 3 trial. Data from Heerspink *et al.*[50]

ratio 0.49, 95% CI 0.35–0.67; $P < 0.0001$) (Fig. 4). In conclusion, SGLT2i were associated with a slower rate of renal function decline and risk of major kidney events compared with different glucose-lowering drugs.[50]

Another study by McMurray *et al.*[51] examined the effects of dapagliflozin on the relative risk of cardiovascular and renal events in 4304 participants with CKD. Patients were divided into primary and secondary prevention groups, and those in the secondary prevention group ($n = 1610$; 37.4%) were older, more likely to be male individuals, had higher blood pressure and BMI, and were more likely to have diabetes. Dapagliflozin reduced the risk of the primary outcome, which consisted of a sustained decline in eGFR at least 50%, end-stage renal disease, or renal or cardiovascular death, to a similar extent in both the primary (hazard ratio 0.61; 95% CI 0.48–0.78) and secondary prevention groups [0.61 (0.47–0.79)] (P interaction = 0.90). This was also observed for the composite of hospitalization for heart failure or cardiovascular death ($0.67^{0.40-1.13}$ vs. $0.70^{0.52-0.94}$; P interaction = 0.88) and all-cause mortality ($0.63^{0.41-0.98}$ compared with $0.70^{0.52-0.94}$ respectively; P interaction = 0.88), and all-cause mortality ($0.63^{0.41-0.98}$ vs. $0.70^{0.51-0.95}$, respectively; P interaction = 0.71). Therefore, this study showed that dapagliflozin reduces the risk of renal failure, death from cardiovascular causes, or hospitalization for heart failure and independently of the existence of concurrent cardiovascular illness, prolongs survival in patients with CKD, with or without type 2 diabetes.[52]

A meta-analysis of four large clinical trials (EMPA-REG OUTCOME, CANVAS Program, CREDENCE, and DECLARE–TIMI 58) involving 38 723 patients with type 2 diabetes demonstrated that the risk of progression to dialysis, transplantation, or death because of kidney disease was significantly lower with SGLT2i compared with patients receiving placebo (relative risk 0.67; 95% CI 0.52–0.86, $P = 0–0019$). SGLT2 inhibitors also reduced end-stage renal disease (0.65, 0.53–0.81, $P < 0.0001$) and acute kidney injury (0.75, 0.66–0.85, $P < 0.0001$), with benefits consistent across studies. This benefit was observed in all four studies, regardless of baseline eGFR and across a wide range of urinary albumin-to-creatinine ratios, and was independent of glycemic effect. Therefore, SGLT2i reduce the risk of dialysis, transplantation, or death due to kidney disease in people with type 2 diabetes, and provide protection against acute kidney injury.[52]

Adverse effects of sodium-glucose cotransporter 2 inhibitors in clinical trials

SGLT2 inhibitors are safe and well tolerated, which underlines their importance in the treatment of HFrEF.[35] SGLT2 inhibitors produced only modest or no reduction in blood pressure and no increase in acute kidney injury or other

serious adverse events compared with placebo in large clinical trials.[27,39,53] Dapagliflozin lowered SBP only modestly and was well tolerated in the subgroup of patients with the lowest SBP, with a mean SBP reduction of 1 mmHg in DAPA-HF.[27] The benefit of dapagliflozin was consistent across the range of SBP at baseline or even greater in the patients with the lowest SBP, who had a higher rate of the primary endpoint compared with the other subgroups. Between dapagliflozin and placebo, there was no difference in the incidence of adverse events in patients with SBP less than 110 mmHg.[53] Similarly, in the VERTIS CV trial, there was no significant difference in the incidence of hypovolemia, serious acute kidney injury, serious urinary tract infection, or fractures between the ertugliflozin dose group and the placebo group.[39]

Urinary tract infections and pyelonephritis are less common adverse effects. Diabetic ketoacidosis, which is relatively uncommon, can occur, especially in elderly patients with volume depletion. Acute illness or fasting may precipitate the disorder, which is accompanied by severe hypotension.[54] Moreover, patients under SGLT2i are associated with bone disease (particularly fractures). In the CANVAS Program,[49] canagliflozin was associated with a two-fold increase in the incidence of lower limb amputations and a rise in bone fractures. Nevertheless, these side effects have not been documented with other SGLT2i and were not observed in the CREDENCE trial,[47] which also studied canagliflozin. Although there is not enough evidence to draw firm conclusions about the relationship between drug administration and bone fractures, the mechanism behind this adverse effect goes back to one of the main effects of the drug: weight loss, and this event was associated with the identification of a bone resorption biomarker: collagen type 1 β-carboxy-telopeptide.[55]

Sodium-glucose cotransporter 2 inhibitors in current practice guidelines for heart failure

Regardless of diabetes status, the ESC 2021[56] and AHA/ACC/HFSA 2022[57] HF guidelines recommended taking SGLT2i for the treatment of chronic, stable HFrEF with a class 1 recommendation for a decrease in cardiovascular mortality and heart failure hospitalizations. The 2022 AHA/ACC/HFSA HF Guidelines include a I/1A recommendation for heart failure with reduced ejection fraction and a Class 2a recommendation for mildly reduced ejection fraction heart failure (HFmrEF) and HFpEF based on the results of the EMPEROR-Preserved trial, which may be modified in future guidelines following the release of the DELIVER study.[57] The 2023 focused update of the 2021 ESC guideline recommends assumption of SGLT2i (empagliflozin and dapagliflozin) in the management of patients HFmrEF and HFpEF. In addition, a class I recommendation was given for the treatment of symptomatic HFmrEF and HFpEF to reduce the risk of heart failure hospitalization.[58] Similarly, for the prevention of heart failure in patients with T2DM and CKD, SGLT2i (empagliflozin and dapagliflozin) are recommended with a class I recommendation[58] to reduce the risk of heart failure hospitalization or cardiovascular death based on the results of DAPA-CKD,[59] EMPA-KIDNEY,[48] and a recent metanalysis.[60]

In general, there is a high level of agreement between the ESC and ACC/AHA/HFSA guidelines regarding the management of HFrEF. SGLT2 inhibitors are recommended by both guidelines with I/1 A recommendations for heart failure with reduced ejection fraction to reduce the primary endpoint of cardiovascular deaths and heart failure hospitalizations based on RCTs. Notably, ACC/AHA/HFSA recommend SGLT2i as a drug class, which theoretically includes SGLT2i other than empagliflozin and dapagliflozin. The ESC guidelines recommend SGLT2i in T2DM patients at risk of cardiovascular events and for heart failure prevention, whereas the ACC/AHA/HFSA guidelines recommend SGLT2i in a separate section for heart failure prevention.[57,61,62]

Conclusion

On top of their hypoglycemic effect, SGLT2i provide additional cardiovascular and renal benefits, as well as body weight reduction, improving vascular endothelium and myocardial metabolism. Several recent large-scale clinical trials provide strong evidence for the efficacy of SGLT2i in reducing the need for heart failure hospitalizations and the risk of serious cardiac adverse events, including cardiovascular and all-cause mortality, in patients with reduced or preserved LV ejection fraction as well as in acute or decompensated heart failure. Overall, SGLT2i have evolved into metabolic drugs because of their multisystem action and are indicated for the treatment of all spectrums of heart failure, type 2 diabetes, and CKD.

Conflicts of interest

There are no conflicts of interest.

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