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Impact on Cardiovascular Disease of Sodium–Glucose Cotransporter-2 Inhibitors for the Treatment of Type 2 Diabetes: Where are We Now and What can We Expect?

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Abstract

Type 2 diabetes (T2D) has a close link with cardiovascular disease (CVD), which remains the major cause of mortality in the diabetic population worldwide. Sodium–glucose cotransporter-2 inhibitors (SGLT2i) are novel antidiabetic drugs that act by blocking sodium–glucose cotransporter-2 in the renal proximal tubules to inhibit glucose reabsorption and therefore lower blood sugar. SGLT2i have beneficial effects on blood pressure, body weight, albuminuria, uric acid, proinflammatory mediators, and adipokines. Notably, SGLT2i have shown impressive cardioprotection through effects on cardiac fuel energetics, ventricular loading, sodium–hydrogen exchangers, left ventricular remodeling, and cardiomyocyte fibrosis and apoptosis. On the basis of recent large-scale cardiovascular outcome trials (CVOTs) in patients with T2D and established CVD or at high risk of cardiovascular events, SGLT2i protected against cardiovascular mortality and all-cause mortality. Furthermore, SGLT2i lowered the rate of hospitalization for heart failure and progressive kidney disease irrespective of pre-existing CVD or history of heart failure. Dedicated CVOTs have provided a strong evidence of the role of SGLT2i in preventing or slowing the progression of CVD in patients with T2D. This review synthesizes the most cutting-edge insights into the cardioprotective benefits of SGLT2i in individuals with T2D. (J Intern Med Taiwan 2021; 32: 242-256)

Key Words: Sodium–glucose cotransport-2 inhibitor, Type 2 diabetes, Cardiovascular disease, Cardioprotection, Heart failure

Introduction

Individuals with type 2 diabetes (T2D) are estimated to have a 2–3-fold greater risk of cardiovascular events than those without diabetes, and approximately 80% of them die due to cardiovascular causes[1]. Intensive blood glucose control can prevent the development or slow the progression of microvascular complications but has only modest effects on macrovascular complications[2], and it takes up to 10 years for improved glycemic control to have cardiovascular benefits[3]. The control of conventional cardiovascular risk factors can reduce ischemic complications; however, heart failure (HF) risk remains a recalcitrant problem in T2D because it is little affected by intensive glycemic control[4].

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Sodium–glucose cotransporter-2 (SGLT2) inhibitors (SGLT2i) are novel antidiabetic drugs used to inhibit glucose reabsorption through SGLT2 blockade in the renal proximal tubule, thereby reducing circulating plasma glucose levels[5]. This leads to decreases in blood pressure (BP), body weight (BW), and albuminuria[6]. The pleiotropic effects of SGLT2i have been shown to reduce the risk of cardiovascular events and improve renal outcomes in large-scale cardiovascular outcome trials (CVOTs)[7-9]. However, the positive effects of SGLT2i on major adverse cardiovascular events (MACEs) are more prominent in patients with established atherosclerotic cardiovascular disease (CVD) than in those with only multiple cardiovascular risk factors, complicating the interpretation of these data. Thus, better understanding of the precise pharmacophysiology of cardioprotection through SGLT2i and how these are in communication with the body may prevent or improve CVD in patients with T2D.

Established cardioprotective effects

In addition to their established benefits to hyperglycemia, BP, BW, visceral adiposity, and albuminuria[7], SGLT2i can have direct cardiac effects on the translation of cardiac fuel energetics[10-14], cardiac ventricular loading[15-21], sodium–hydrogen exchangers (NHEs)[22-28], cardiac structure[29-34], cardiomyocyte apoptosis[29,32,35,36], oxidative stress (OS) and inflammation[30,33,37-39], adipokine levels[40-42], and uric acid (UA) level[17,43,44]. To date, no antidiabetic agents have demonstrated such cardiovascular benefits as SGLT2i in patients with T2D.

Cardiac fuel energetics

Ketones are a good energy source in the myocardium especially in a failing heart[45]. Patients with T2D have increased cardiac uptake of ketones and decreased cardiac uptake of lactate, glucose, and pyruvate, which might be a compensatory response to the impairment of glucose metabolism in the diabetic heart[46]. In a diabetic mice model of HF, SGLT2i were associated with increased production of cardiac adenosine triphosphate (ATP) through increased rates of cardiac glucose and fatty acid oxidation and increased supply of oxidized ketones by the heart [10]. Furthermore, SGLT2i-boosted ketones in circulation may serve as an additional energy source to sustain myocardial contractile function [47].

Two articles have proposed the "thrifty fuel" hypothesis to explain the cardiorenal benefits of SGLT2i[11,12]. The role of SGLT2i in promoting ketogenesis might account for their favorable effects on the heart and kidneys because enhanced ketone body formation meets the energy needs of organs under stress. However, this mechanism must involve cooperation with other SGLT2 inhibition–induced changes (primarily BP and natriuretic, diuretic, and neurohormonal or vascular effects) to achieve notable cardiac benefits[11,12]. Diabetes represents a state of nutrient overabundance rather than energy deprivation, as evidenced by the activation of molecular pathways that promote both energy retention and storage. The stressed heart preferentially utilizes ketone bodies, and the diabetic kidney is a ketogenic organ. Therefore, it is unclear whether SGLT2i can promote ketone body utilization such that ATP generation increases[13]. Moreover, because this fuel energetics hypothesis was generated in response to the results from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial, and as ketone bodies were not measured during the study, there are no data available to support or refute this hypothesis. Further research is thus required, including relevant clinical studies and investigation of the effect of empagliflozin on muscle ketone oxidation rates[47].

Notably, two opposite hypotheses have been proposed in relation to these inconsistencies[13,14]. The first hypothesis suggests that SGLT2i have the ability to change the trajectory of cellular responses

to a toxic environment by modifying cellular life history programs—either the defense program or the dormancy program[13]. The defense program is characterized by activation of immune responses and anabolic metabolism. The dormancy program is an energy-preserving state with high resistance to environmental stressors, comparable to animal hibernation, where fuel is stored, metabolic rate is suppressed, and insulin secretion is reduced. The choice between these programs is mainly determined by the environment. Hyperglycemia can be regarded as a toxic determinant capable of interfering with the basic programs of cell evolution. The metabolic changes that follow treatment with SGLT2i are similar to the metabolic picture characteristic of the dormancy program. Therefore, the cardioprotective effects of SGLT2i may be related to their ability to switch cellular life programming from a defensive to a dormant state. This hypothesis is largely based on experimental data from animal models. Further dedicated studies, including human studies, are required to test this hypothesis.

The second hypothesis posits that SGLT2i exert effects by activating low-energy sensors that are responsible for mimicking a fasting transcriptional paradigm to produce cardiorenal benefits[14]. SGLT2i induce caloric loss in urine, and glycosuria is accompanied by reduced glucagon synthesis, increased fatty acid oxidation, and shrinkage of adipose tissue depots. From this perspective, the ketonemia observed in relation to these drugs is not the source of an efficient fuel; instead, it is a biomarker of a fasting-like transcriptional state. SGLT2i may not only deceive cells into believing that they are fasting but also that they are hypoxic. Oxygen deprivation stimulates adenosine monophosphate–activated protein kinase (AMPK) and sensors such as sirtuin-1 (SIRT1). SIRT1 activates hypoxia-inducible factor-2 a (HIF-2a) and possibly also hypoxia-inducible factor-1 a (HIF-1a) under certain conditions; these represent the principal stimuli for erythropoietin synthesis. This relationship may explain why, in statistical mediation analysis of large-scale trials, erythrocytosis is the most powerful predictor of the action of SGLT2i in reducing HF events. Enhancement of HIF-1a/HIF-2a signaling by SGLT2i may amplify the autophagic flux already augmented by AMPK/SIRT1, thereby contributing to the remarkable cardiorenal benefits of these drugs.

Taken together, SGLT2i appear to decrease myocardial work through a shift in fuel energetics; however, more studies are required to explore their roles in cardiac fuel energetics.

Cardiac ventricular loading

Through osmotic and sustained natriuretic effects, one of the beneficial actions of SGLT2i is the attenuation of volume loading of ventricles, secondary to reduced preload and overall myocardial strain[15]. This action is particularly favorable in those with T2D and diastolic dysfunction with a steep Frank–Starling curve. A mediation analysis from the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program suggested that the reduction in HF risk was strongly attributable to canagliflozin-induced erythrocyte concentration[16]. Another mediation analysis from the EMPA-REG OUTCOME trial demonstrated that approximately 50% of the cardiovascular beneficial effect was attributable to empagliflozin-induced hemoconcentration[17]. However, hemoconcentration due to the diuretic effect of SGLT2i seems unlikely as the leading cause of the elevated hematocrit[48], which may be due to an effect of SGLT2i on red cell mass, as suggested by transient increases in serum erythropoietin concentrations and reticulocyte count[49]. Two recent studies obtained similar results[18,19]. SGLT2 inhibition with empagliflozin may stimulate erythropoiesis in patients with T2D through an early increase in erythropoietin production[18]. Dapagliflozin, one of the SGLT2i, increases erythropoi-

esis and hematocrit through mechanisms involving the suppression of hepcidin and the modulation of other iron regulatory proteins[19].

SGLT2i reduce interstitial fluid volume and serum sodium without changing the intravascular volume through osmotic diuresis[50]. This selective reduction in the interstitial fluid volume may be a unique feature of SGLT2i, and this may restrict the aberrant reflex neurohumoral stimulation to induce intravascular volume depletion, which is noted with traditional diuretics[51]. Furthermore, SGLT2i are uricosuric, whereas traditional diuretics are related to high levels of serum UA, probably reflecting different effects on cardiovascular outcomes[52].

SGLT2i may improve loading conditions through sustained systolic and diastolic BP reduction, partly through minimal natriuresis and likely sympathetic tone reductions[20]. Through natriuretic and osmotic diuretic effects, SGLT2i could induce volume contraction[21]. SGLT2i can also reduce vascular resistance and arterial stiffness, leading to a decrease in BP[53]. The exact mechanism(s) through which SGLT2i reduce arterial stiffness are not completely understood but may be related to improved glycemic control, BW reduction, volume contraction through osmotic diuresis, or reduced OS[53]. Furthermore, SGLT2i reduce the activities of the renin–angiotensin–aldosterone system and sympathetic nervous system through augmented distal sodium chloride delivery to the macula densa, inducing tubuloglomerular feedback, afferent arteriole narrowing, and attenuated hyperfiltration, all of which are critical determinants of BP[21]. This process may explain the significant long-term renoprotection offered by SGLT2i.

Sodium–hydrogen exchangers

In the renal proximal tubule, NHE3 colocalizes with SGLT2 to reabsorb the majority of filtered sodium[54]. Increased NHE3 activity may be associated with HF and may attenuate the effects of the natriuretic response to these peptides in patients with HF[55]. A study has suggested that pharmacologic inhibition of SGLT activity by phlorizin may be accompanied by marked NHE3 inhibition, indicating that SGLT activity plays a role in sodium bicarbonate reabsorption[22]. Hence, inhibition of NHE3 by SGLT2i may additionally maintain whole-body sodium balance and prevent or treat HF through a common cardiorenal mechanism [23].

The cardioprotective effects of SGLT2i have been hypothesized to be exerted through NHE1 inhibition. In experimental models of HF, increases in cardiac NHE1 activity enhanced cytosolic sodium and calcium levels, leading to cardiomyocyte injury and cardiomyopathy[23]. Thus, NHE1 inhibition has been proposed to attenuate ischemia/reperfusion (I/R) injury. Many animal models of coronary artery occlusion, diabetes, volume overload, and rapid cardiac pacing have suggested that NHE1 inhibition minimized cardiomyocyte injury and decreased cardiac hypertrophy, fibrosis, remodeling, systolic dysfunction, and HF severity[23]. Empagliflozin provided direct cardiac benefits by lowering the cardiac cytoplasmic levels of sodium and calcium and increasing mitochondrial calcium level through myocardial NHE1 inhibition[24]. In an experimental model of rats with heart failure and reduced ejection fraction (HFrEF), empagliflozin interacted with and blocked the NHE1 co-transporter at the cardiomyocyte level, triggering a signaling cascade that halted detrimental cell death[25]. A similar effect was reported in an experimental model of mouse cardiomyocytes and hearts with dapagliflozin and canagliflozin, suggesting a common class effect of SGLT2i[26]. More recently, empagliflozin has been reported to delay ischemic contracture onset through NHE1 inhibition in ex vivo intact hearts, indicating direct cardiac effects, but provided no protection against I/R injury in isolated hearts[27]. A similar result in patients with HFrEF suggests that empagliflozin may not only modulate myocyte mechanical function by affecting

calcium handling or cycling but also offer myocardial protection by maintaining proper myocardial redox balance and mitochondrial energy metabolism [28].

Recognition of the exact mechanisms of NHE1 and NHE3 is necessary to understanding the interplay between diabetes and CVD from both the pathophysiological and pharmacological perspectives. Although clinical studies have investigated the inhibition of NHE1 and NHE3 with SGLT2i, novel drugs selectively inhibiting each NHE isoform should be developed for the optimal management of diabetes in patients with CVD.

Cardiac structure

SGLT2i have been demonstrated to improve cardiac structure in animal models of diabetic cardiomyopathy (DCM), myocardial ischemia, and HF. In streptozotocin-induced DCM rats, empagliflozin protected against DCM in a dose-dependent manner through the attenuation of disordered cell arrays and focal necrosis [29]. In an obese T2D mice model, empagliflozin ameliorated cardiac fibrosis and coronary arterial remodeling [30]. In genetically diabetic mice, empagliflozin attenuated cardiac hypertrophy and remodeling markers, although no significant changes in left ventricular (LV) mass or histologic myocardial fibrosis were observed [31]. In obese insulin-resistant rats with cardiac I/R injury induced by left anterior descending coronary artery (LAD) ligation, dapagliflozin led to myocardial infarct size reduction and LV function preservation [32]. In chronic infarcted rat hearts, dapagliflozin was associated with attenuated myofibroblast infiltration and cardiac fibrosis, but it did not alter the infarct size [33]. Furthermore, canagliflozin attenuated the expression of HF biomarkers, such as N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin I (hsTnI): Compared with placebo, canagliflozin delayed the rise in serum NT-proBNP and hsTnI for >2 years in 666 older adults with T2D [34]. These reports suggest that the improvements in DCM, myocardial ischemia, and HF are potentially class effects of SGLT2i.

Cardiomyocyte apoptosis

Cardiomyocyte apoptosis has been shown to be associated with cardiomyocyte death during myocardial infarction (MI), I/R injury, and end-stage HF [35]. Dapagliflozin attenuated the development of DCM by significantly reducing the number of apoptotic cells in the left ventricle in mice with T2D [36]. In rats with high fat diet–induced obese insulin resistance (prediabetes) and cardiac I/R injury caused by LAD ligation, dapagliflozin attenuated cardiac apoptotic protein expression [32]. In streptozotocin-induced DCM rats, empagliflozin attenuated cardiomyocyte apoptosis by dose-dependently suppressing the endoplasmic reticulum stress pathway [29]. Taken together, these reports suggest that SGLT2i attenuate apoptotic myocardial cells in DCM; however, more studies are required to investigate the precise underlying mechanisms.

OS and inflammation

OS plays a key role in the pathophysiology of cardiac hypertrophic remodeling and dysfunction [37]. In prediabetic rats with metabolic syndrome, empagliflozin reduced cardiac hypertrophy and interstitial fibrosis, which were associated with the attenuation of cardiac OS and inflammation independently of empagliflozin's diuretic or BP-lowering effect [38]. In obese T2D mice, empagliflozin significantly ameliorated cardiac interstitial fibrosis and pericoronary arterial fibrosis by attenuating OS in cardiovascular tissue [30]. In streptozotocin-induced diabetic rats, high-dose (30 mg/kg/day) empagliflozin, but not low-dose (10 mg/kg/day) empagliflozin, significantly decreased the cross-talk between advanced glycation end product (AGE)/AGE-receptor (RAGE) signaling and reactive oxygen species formation [39]. Thus, high-dose empagliflozin treatment appears

to be required for OS reduction. In a postinfarction rat model, dapagliflozin significantly increased the activity of signal transducer and activator of the transcription 3 (STAT3) and regulated the macrophage phenotype through a reactive oxygen and nitrogen species (RONS)/STAT3-dependent pathway[33]. Furthermore, dapagliflozin was associated with attenuated myofibroblast infiltration and cardiac fibrosis at day 28 after infarction. This evidence suggests a novel mechanism of dapagliflozin as an antioxidant and inflammatory modulator through direct RONS-dependent STAT3 signaling during postinfarction remodeling.

Cardiac adipokines

Altered adipokine production leads to a proinflammatory state, contributing to the progression of T2D, CVD, and insulin resistance[56]. Obesity has been speculated to increase the synthesis of adipokine leptin, resulting in volumetric expansion and sodium retention along with renal and cardiac inflammatory and fibrotic changes. Intriguingly, the natriuretic actions of SGLT2i can counter leptin-induced sodium retention. Furthermore, SGLT2i minimize leptin secretion and thus cardiac and renal fibrosis through its paracrine actions by reducing the accumulation of inflammatory perivisceral adipose tissue[40]. Indeed, a post hoc analysis of a clinical trial indicated that compared with glimepiride, canagliflozin reduced leptin levels by 25%, increased adiponectin by 17%, and significantly reduced serum cytokine interleukin-6 by 22%; tumor necrosis-alpha (TNF-α) was increased by 7%[41]. In patients with T2D, dapagliflozin might reduce epicardial adipose tissue and attenuate plasminogen activator inhibitor-1 (PAI-1) and TNF-α levels, which may reduce the risk of cardiovascular events[42].

Cardiac UA

High concentrations of circulating UA increase the risk of CVD, hypertension, and chronic kidney disease (CKD). It has been suggested that SGLT2i increase UA excretion, alleviate circulating UA, and improve cardiac and renal function in patients with T2D[43]. Thus, reduction in circulating UA by SGLT2i in T2D may decrease the risk of cardiovascular events and slow the development of CKD. A univariable mediation analysis suggested a 24.6% reduction in the risk of cardiovascular death following an empagliflozin-induced change in UA in the EMPA-REG OUTCOME trial[17]. However, the cause–effect relationships necessitate further study. A meta-analysis of 62 studies demonstrated that SGLT2i markedly decreased serum UA levels compared with the control in patients with T2D, thus highlighting their beneficial effects in patients with T2D and hyperuricemia[44].

The major cardiovascular outcome trials

As the most novel class of antidiabetic agents, SGLT2i can be a solution for previously unmet clinical needs. Their pleiotropic effects extend beyond glycemic control, as demonstrated in the recent large-scale CVOTs.

Empagliflozin

The EMPA-REG OUTCOME trial is one of the large-scale clinical trials that suggested strong cardioprotection with a significant reduction in cardiovascular mortality and hospitalization for HF (HHF) within the first 3 months of empagliflozin treatment[7]. Empagliflozin reduced composite primary cardiovascular endpoints by 14% (hazard ratio [HR] 0.86; $P = 0.04$) in patients with T2D and either established CVD or angiographically documented diffuse CAD. Furthermore, empagliflozin significantly reduced HHF by 35% (HR 0.65; $P = 0.002$) and any cause mortality by 32% (HR 0.68, $P < 0.001$). Nevertheless, a striking disconnect was found for three cardiovascular outcome measures:

cardiovascular mortality (HR 0.62; P < 0.001), MI (HR 0.87; P = 0.22), and stroke (HR 1.24; P = 0.23). Remarkably, reduced risks of any-cause and cardiovascular mortality were observed shortly after initiating empagliflozin, and these beneficial effects continued throughout the trial.

In the EMPA-REG OUTCOME trial, empagliflozin failed to reduce MI and stroke risks, no improvement of unstable angina was noted, and rapid onset of cardiovascular mortality reduction occurred, suggesting that its cardiovascular benefits are not associated with decelerating the atherosclerotic process and that other factors are involved[57]. This trial provides valuable data indicating the benefits of long-term empagliflozin treatment and providing strong evidence of reduction of risk of cardiovascular events. However, based on the trial results, it is uncertain whether empagliflozin addition to standard care will demonstrate such a striking effect on cardiovascular mortality among patients with earlier nature history of T2D and without well-established CVD[57].

It is more puzzling that the curves of HHF, cardiovascular mortality, and renal outcomes in the EMPA-REG OUTCOME trial separated quickly and widely within 3 months and that this trend continued throughout the study. Such significantly beneficial cardiorenal outcomes unlikely result from reasonable glycaemia control, lipid lowering, or reductions in BP and UA level within 3 months. Other known SGLT2i effects described earlier—such as vascular endothelium, natriuresis, and neurohormonal mechanisms—are also implausible major contributors to cardiovascular and renal benefits. Thus, it was postulated that the cardiorenal benefits of empagliflozin are associated with a metabolic shift of the myocardial/renal fuel away from glucose and fat oxidation, which are energy inefficient in the diabetic heart and kidney, toward an energy-efficient fuel such as ketones, which promote efficiency and function of myocardial and renal work[12].

Canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) program integrates data from the CANVAS and CANVAS-Renal trials in patients with T2D and high cardiovascular risk; it indicated that canagliflozin reduced the composite primary cardiovascular outcome (death from cardiovascular causes, MI, or stroke) by 14% (HR 0.86, P = 0.02) and the risk of HHF by 33% (HR 0.67)[8]. However, the canagliflozin group had a higher risk of lower limb amputation (HR 1.97) than the placebo group, and 71% of the affected patients underwent amputation were at the toe or metatarsal level.

In contrast to the CANVAS program, the risk of lower-limb amputation in the EMPA-REG OUTCOME trial was similar between empagliflozin and placebo groups (HR 1.00) [58]. A similar result was reported in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, suggesting a common class effect of dapagliflozin (HR 1.09)[59]. The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS-CV) trial presented at American Diabetes Association's 80th Scientific Sessions also provided a similar result, suggesting that the amputation rate was consistent with that of other SGLT2i (0.6 per 100 patient years in the ertugliflozin group vs. 0.5 in the placebo group). A meta-analysis of five randomized controlled trials (RCTs) found no significant increase in amputation risk related to treatment with SGLT2i compared with controls (odds ratio [OR] 1.312)[60]. Subgroup analysis revealed that neither canagliflozin, empagliflozin, nor dapagliflozin was associated with increased amputation risk. A recent systematic review and meta-analysis revealed no consistent evidence of a relationship between SGLT2i exposure and increased amputation risk[61].

The potential benefits of canagliflozin regarding cardiovascular outcome in the CANVAS program were comparable to those observed previ-

ously with SGLT2i, yet the degree of influence has varied[7,62]. The benefit to stroke risk in this program was different from a previously reported possible adverse effect on stroke risk[7,62]. The authors suggested that the apparent differences in the effect sizes for other secondary and exploratory outcomes could be attributed to chance due to limited precision in the effect size estimates of the individual trials. Nevertheless, further studies are warranted to clarify the different results.

In a subanalysis of the CANVAS program[63], canagliflozin demonstrated significantly lower risks than placebo for cardiovascular mortality or HHF (HR 0.78), fetal or HHF (HR 0.70), and HHF alone (HR 0.67). Furthermore, the beneficial effect on cardiovascular mortality or HHF may be greater for patients with a history of HF (HR 0.61) compared with those without HF at baseline (HR 0.87; P interaction = 0.021)**,** suggestive of perhaps greater benefits of canagliflozin in those with a history of HF than in those without HF history[63]. The benefits of canagliflozin to cardiovascular outcomes were perceived early in the CANVAS program and continued over approximately 6 years of treatment, even with an increase in hemoglobin A1c (HbA1c) during the study[64]; this implies that canagliflozin exerts HbA1c-independent effects on cardiovascular outcomes.

The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial investigated the renal outcomes in patients with T2D and moderate-to-severe albuminuria[65] and suggested that canagliflozin lowered the risks of cardiovascular mortality, MI, and stroke (HR 0.80, P = 0.01) and HHF (HR 0.61, P < 0.001). However, unlike the CANVAS program, no significant differences in rate of amputation or fracture were discovered comparing canagliflozin with placebo in the CREDENCE trial, which was ascribed to chance or differing trial populations or protocols [65].

Dapagliflozin

The DECLARE-TIMI 58 trial included patients with T2D and a broad range of cardiovascular risks, both those with established CVD and those with multiple cardiovascular risk factors only[9]. Dapagliflozin compared with placebo did not result in a significant reduction in the MACE rate (8.8% vs. 9.4%; HR 0.93; P = 0.17) but did reduce the rate of cardiovascular mortality or HHF (4.9% vs. 5.8%; HR 0.83; P = 0.005); the findings indicated a lower HHF rate (HR 0.73) without difference in cardiovascular mortality (HR 0.98).

The DECLARE-TIMI 58 trial had several key findings. First, dapagliflozin was not inferior to placebo in a wide-ranging population of patients with T2D and carrying multiple cardiovascular risk factors for the MACE composite safety outcome. However, it did not lead to a significantly lower MACE rate than placebo. Second, dapagliflozin was associated with a lower rate of a composite of cardiovascular mortality and HHF, suggesting a lower HHF rate. Third, dapagliflozin compared with placebo demonstrated a consistently lower rate of cardiovascular mortality or HHF across multiple subgroups, which suggested that dapagliflozin defended against cardiovascular events, particularly HHF, in a broadpopulation of patients irrespective of pre-existing atherosclerotic CVD or HF. Finally, the prevention of new-onset HF was remarkable because the majority of patients enrolled were without history of HF[9].

More recently, the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) Trial investigated worsening HF or cardiovascular death in patients with HFrEF (of whom 58% were without diabetes), suggesting that dapagliflozin lowered the risk of first worsening HF events or cardiovascular death by 26% (HR 0.74; P < 0.0001), and that of HHF or cardiovascular death by 25% (HR 0.75; P < 0.0001)[66]. The results for patients with diabetes were similar to those for

patients without diabetes. The trial findings provide additional evidence that the drugs provide benefits unrelated to lowering glucose levels and have as yet undefined mechanisms of action conferring direct cardiovascular benefits to patients with HFrEF, regardless of diabetes history.

Ertugliflozin

The VERTIS-CV trial was one of the larger CVOTs of patients with T2D and established atherosclerotic CVD. The findings presented at American Diabetes Association's 80th Scientific Sessions demonstrated that ertugliflozin did not reduce the risk of cardiovascular events in T2D participants with established CVD. The HR for the composite of cardiovascular death and HHF was 0.88 (P = 0.11 for superiority) and the HR for cardiovascular death alone was 0.92. The HR for MACEs, the primary endpoint, was 0.97 (P < 0.001 for noninferiority). Participants treated with ertugliflozin had similar rates of time to first occurrence of MACEs as those on placebo (both 11.9%; P < 0.001 for noninferiority). Rate of HHF was reduced in participants treated with ertugliflozin compared with those on placebo (HR 0.70). Ertugliflozin falls short of SGLT2s on cardiovascular outcomes, despite its promise for HF treatment. The VERTIS-CV trial cannot be compared with other large-scale CVOTs concerning SGLT2i due to factors such as study design, study population, and study time frame, which may reflect differences in background rates or the use of other medications. Overall, the VERTIS CV trial has helped broaden our understanding of the benefits and risks for this class of drug in patients with T2D.

Meta-analyses data

A meta-analysis was performed for prospective RCTs between Jan 1, 1950 and Sept 30, 2015, to assess the cardiovascular effects of SGLT2i versus control treatments. The Medline, Embase, and Cochrane Library databases and websites of American, European, and Japanese regulatory authorities were searched[62]. Duplicate reports, trials on compound drugs, trials that lasted 7 days or fewer, trials that did not report on outcomes of interest, and articles that presented pooled trial data for which the individual trials could not be identified were excluded. SGLT2i provided protection against the risk of MACEs (relative risk [RR] 0.84; P = 0.006), HF (RR 0.65; P = 0.002), cardiovascular mortality (RR 0.63; P < 0.0001), and all-cause mortality (RR 0.71; P < 0.0001). No statistical significance was observed regarding the effect on MI (RR 0.88; P = 0.18) or angina (RR 0.95; P = 0.70), but a side-effect on stroke was observed (RR 1.30; P = 0.049). No clear evidence has been obtained because each individual drug has had different cardiovascular or mortality effects.

A comprehensive meta-analysis of all RCTs collected up to November 16, 2015 from a Medline database search for SGLT2i was conducted [67]. All trials with a treatment duration of ≥12 weeks, that enrolled patients with T2D, or compared SGLT2i with placebo or other comparators, were included. A total of 71 RCTs assessing cardiovascular events in patients with T2D undergoing treatment with SGLT2i were included. SGLT2i significantly reduced any-cause mortality (Mantel–Haenszel odds ratio 0.70; P < 0.001), cardiovascular mortality (0.43; P < 0.001), and MI (0.77; P < 0.01) except stroke (1.09; P = 0.50) without obvious difference across molecules (after excluding CVOTs). However, this result was greatly influenced by the EMPA-REG OUTCOME trial, which provided 79% of all reported deaths. The reduction of cardiovascular mortality indicated no more significance when the cardiovascular endpoints of the trials were excluded. Thus, the benefits of empagliflozin to cardiovascular and any-cause mortality in the EMPA-REG OUTCOME trial appear to be a class effect. The results also suggested no specific risk of stroke associated with SGLT2i, and the reduction of MI

incidence was apparent, especially in trials enrolling patients with lower cardiovascular risk.

More recently, a meta-analysis of RCTs and CVOTs investigating SGLT2i in patients with T2D involved a search of PubMed and Embase for trials published from database inception to Sept 24, 2018[68]. SGLT2i reduced the number of MACEs by 11% (HR 0.89; P = 0.0014), with a benefit observed only in patients with atherosclerotic CVD (HR 0.86), not in those without (HR 1.00; P = 0.0501). SGLT2i also reduced the risk of cardiovascular mortality or HHF by 23% (HR 0.77; P < 0.0001), with similar benefits in patients with or without pre-existing atherosclerotic CVD and pre-existing HF. The beneficial effects of SGLT2i varied with baseline renal function; greater reduction in HHF (P = 0.0073) and less reduction in the development of renal disease (P = 0.0258) occurred in patients with more severe renal disease at baseline.

Real-world data

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 inhibitors (CVD-REAL) study collected observational data from medical records, medical claims, electronic health and death records, and national registers from the United States, the United Kingdom, Sweden, Norway, and Denmark to assess the effect of SGLT2i compared with other glucose-lowering drugs (GLDs) on the risks of mortality, HF, and HF or mortality in patients with T2D with or without established CVD[69]. In the study, 13% of patients presented with established CVD at baseline. SGLT2i compared with other GLDs result in lower risks of mortality, HF, and the composite of HR and mortality in patients with and without CVD (HR 0.56 vs. 0.56, 0.72 vs. 0.61, and 0.56 vs. 0.63, respectively). Thus, treatment with SGLT2i resulted in lower risks of HF and mortality irrespective of pre-existing CVD. These findings indicate that the cardiovascular benefits of SGLT2i may extend to a broader population of patients with T2D than previously considered.

The Empagliflozin and the risk of HF hospitalization in routine clinical care: A first analysis from the Empagliflozin Comparative Effectiveness And Safety (EMPRISE) study using real-world data suggested that the initiation of empagliflozin decreased the risk of specific HHF (defined as a HF discharge diagnosis in the primary position) by 50% and broad HHF (defined as a HF discharge diagnosis in any position) by 49% compared with dipeptidyl peptidase-4 inhibitors (DPP4i) over a mean follow-up of 5.3 months [70]. This study suggested that the initiation of empagliflozin compared with DPP4i was relevant to a reduced risk of HHF in routine care, supporting the EMPA-REG OUTCOME trial results. The results remained consistent among patients irrespective of pre-existing CVD at baseline.

The CVD-REAL 2 study investigated the associations between SGLT2i treatment versus treatment with other GLDs and a broad range of cardiovascular outcomes in three major world regions: Asia Pacific, the Middle East, and North America[71]. Treatment with SGLT2i compared with other GLDs resulted in lower risks of mortality, HHF, mortality or HHF, MI, and stroke (HR 0.51, P < 0.001; HR 0.64, P = 0.001; HR 0.60, P < 0.001; HR 0.81, P < 0.001; and HR 0.68, P < 0.001, respectively) that were consistent across patient subgroups and countries regardless of pre-existing CVD. The study suggested that the cardiovascular benefits of SGLT2i may extend to a much wider population of patients, as confirmed by the DECLARE-TIMI 58 trial.

More recently, a Swedish cohort study compared dapagliflozin with other glucose-lowering drugs (GLDs) in a real-world population with T2D similar to that of the DECLARE-TIMI 58 trial[72]. Dapagliflozin compared with other GLDs was associated with lower risks of HHF and cardiovascular mortality (HR 0.79) but not significantly associated with a lower risk of MACEs (HR 0.90). Further-

more, risks of HHF and cardiovascular mortality were also lower at HR = 0.79 and 0.79, respectively. No statistical significance was observed for stroke and MI (HR 1.06 vs. 0.91, respectively). Thus, the results of the DECLARE-TIMI 58 trial can be translated to the real world.

Effects of SGLT2i on guideline development

Large RCTs of treatment with SGLT2i for patients with T2D[7,8,9,65] have demonstrated a marked reduction in CVD events among patients with established atherosclerotic CVD[62,67,68]. The development of new therapies is of extreme importance to ensure that optimal care is provided to T2D patients with established atherosclerotic CVD and quality of life outcomes are improved. Metformin is no longer a first-line therapy for patients with T2D. An updated guideline to the guidelines of the European Society of Cardiology/European Association for the Study of Diabetes recommends SGLT2i or glucagon-like peptide-1 receptor agonists as first-line therapies in patients with T2D and high risk of atherosclerotic CVD, regardless of whether they are treatment naïve or already taking metformin[73]. Moreover, empagliflozin is recommended for patients with T2D and CVD to reduce mortality risk. First-line treatments for T2D in patients with HF should include SGLT2i and metformin[73]. The latest update of the Standards of Care of the American Diabetes Association recommends the use of SGLT2i for patients with T2D as an additional agent for lowering glucose, and perhaps more importantly, for lowering cardiovascular and renal risks in patients predisposed to these complications[74]. Similar recommendations have been given by the American College of Endocrinology and American Association of Clinical Endocrinologists[75]. These guideline updates help not only endocrinologists, nephrologists, and cardiologists, but also primary care doctors in daily clinical practice.

Future perspectives

On the basis of this review's explanation of the pleiotropic effects of SGLT2i on cardiac function and analysis of CVOTs, SGLT2i appear to demonstrate potential cardiovascular protection. Several dedicated ongoing CVOTs will further illuminate the role of SGLT2i in cardiovascular endpoints in patients with and without T2D but with CKD. The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease trial (NCT03036150) will investigate the effect of dapagliflozin on cardiovascular mortality and HHF in patients with CKD and with or without T2D[76]. The EMPA-KIDNEY trial (NCT03594110) will investigate the effect of empagliflozin on time to first HHF or cardiovascular death in patients with CKD and with or without T2D[77]. Furthermore, two dedicated ongoing HF trials, EMPEROR-Reduced (NCT03057977)[78] and EMPEROR-Preserved (NCT03057951)[79], are investigating the cardiovascular outcomes. Those ongoing dedicated clinical trials will help clarify the clinical landscape of SGLT2i with respect to cardiovascular endpoints.

Conclusion

The pleiotropic effects of SGLT2i indicate that they have potential cardiovascular benefits beyond mere blood glucose control. Much has been learned because of growing evidence obtained from clinical trials of the meaningful cardiovascular protective effects of SGLT2i, but much more remains to be clarified. Experience from clinical practice with SGLT2i in nondiabetic subjects is currently limited. The results of future and ongoing clinical trials will help elucidate the role of SGLT2i in cardiovascular function in patients with or without T2D.

Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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第2型鈉-葡萄糖共同轉運蛋白抑制劑治療第二型糖尿病對心血管疾病的影響：我們當前如何定位與能期待什麼？

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摘　要

第二型糖尿病和心血管疾病有著密切的關聯，迄今心血管疾病仍然是造成全球糖尿病族群之中主要的死亡原因。第2型鈉-葡萄糖共同轉運蛋白抑制劑是新型抗糖尿病藥物，主要的機轉是透過阻斷腎臟近曲小管中的第2型鈉-葡萄糖共同轉運蛋白來抑制葡萄糖的再吸收，進而達到降血糖的目的。第2型鈉-葡萄糖共同轉運蛋白抑制劑對於血壓、體重、蛋白尿、尿酸、促發炎介質和脂肪激素等方面的改善是有裨益的。特別的是，第2型鈉-葡萄糖共同轉運蛋白抑制劑能透過多種機轉運用在心臟燃料能量學、心室負荷、鈉-氫交換器、左心室重塑和心肌細胞纖維化及凋亡方面呈現多重心臟保護作用。根據最近大規模心血管結果試驗，針對第二型糖尿病已知合併有心血管疾病或有心血管事件高風險的患者，結果顯示第2型鈉-葡萄糖共同轉運蛋白抑制劑能減少心血管死亡率和整體死亡率。此外，無論是事先已有心血管疾病或心臟衰竭的病史，第2型鈉-葡萄糖共同轉運蛋白抑制劑也能降低心臟衰竭住院和腎臟病惡化的比率。針對第二型糖尿病患者，這些心血管結果試驗已提供了第2型鈉-葡萄糖共同轉運蛋白抑制劑在預防或延緩心血管疾病的角色上一強而有力的證據。本篇綜論以嶄新的視野來探討第2型鈉-葡萄糖共同轉運蛋白抑制劑運用在第二型糖尿病患者之心血管保護的益處。