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Cardiorenal Protection of Sodium–Glucose Cotransporter-2 Inhibitors in Patients With Type 2 Diabetes: Clinical Studies to Real-World Evidence

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Abstract

Cardiovascular disease and chronic kidney disease (CKD) are the major causes of mortality in patients with type 2 diabetes (T2D) worldwide. Although intensive glucose control reduces vascular complications in patients with T2D, the increasing prevalence of diabetic cardiorenal disease has persisted globally. Drugs with the potential to halt progressive cardiorenal damage are urgently required. In addition to the glucose-lowering effect, sodium–glucose cotransporter-2 inhibitors (SGLT2is) exert pleotropic effects such as the reduction of blood pressure, weight loss, albuminuria improvement, anti-inflammatory and antifibrotic actions, with potential favorable effects on systemic and intrarenal hemodynamic pathways, thus providing a cardiorenal benefit. In particular, recent trials examining the cardiovascular and renal disease outcomes of SGLT2is treatment have reported that SGLT2is effectively prevented the incidence of worsening heart failure (HF), kidney disease progression, and mortality. These findings were further confirmed by randomized controlled trials conducted in patients with baseline HF and CKD, irrespective of the presence of diabetes, as well as real-world studies. Nevertheless, the effects of SGLT2is in patients with atherosclerotic cardiovascular events remain conflicting. This article reviews the proposed cardiorenal protection provided by this class of drugs by summarizing the evidence generated from clinical trials to real-world studies.

Key Words: Sodium–glucose cotransporter-2 inhibitors; type 2 diabetes; cardiorenal protection; heart failure; cardiovascular disease; chronic kidney disease

Introduction

Diabetes refers to a group of metabolic disorders with multiple etiologies and is characterized by chronic hyperglycemia. Although intensive glycemic control, blood pressure (BP) management, and angiotensin receptor blocker or angiotensin-converting enzyme inhibitor treatment for reducing renal hyperfiltration can prevent the progression of cardiovascular (CV) disease (CVD) and diabetic kidney disease, a substantial proportion of patients still experience disease progression[1].

Type 2 diabetes (T2D) contributes to kidney disease by causing glomerular hyperfiltration, mesangial expansion, and extracellular matrix build-up, ultimately leading to mesangiolysis and glomerular fibrosis[2]. Sodium–glucose cotransporter-2 (SGLT2) inhibitors (SGLT2is) are novel

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glucose-lowering drugs used to inhibit glucose reabsorption in the renal proximal tubule through SGLT2 blockade, thus enhancing urinary glucose excretion and reducing glucose levels[3]. Numerous clinical trials have reported the cardiorenal protective effect of SGLT2is in patients with T2D[4-6]. Moreover, a study indicated that the beneficial effects of SGLT2is may extend to patients with chronic kidney disease (CKD)[7]. However, the mechanisms underlying the cardiorenal protective effect of SGLT2is remain unclear. SGLT2i-induced attenuation of hemodynamic dysfunction, inflammation, oxidative stress (OS), and fibrosis might contribute to their cardiorenal protective effect. A recent trial reported that SGLT2is improved CV and renal outcomes in patients, irrespective of the presence of T2D; the latest American and European clinical practice guidelines recommend SGLT2is as the core component of T2D treatment[8]. Hence, elucidating the precise pharmacophysiology of SGLT2i-induced cardiorenal protection and determining the mechanisms through which SGLT2is prevent or improve CVD and CKD in patients with T2D are essential.

The Heart–Kidney Axis

CVD and kidney disease are closely interrelated. A diseased organ may result in the dysfunction of another organ, ultimately leading to the failure of both organs[9]. Numerous studies have demonstrated that the coexistence of renal dysfunction and macrovascular disease increases CVD risk in patients with T2D[10]. With the deterioration of renal function, excess fluid volume is retained, which, in turn, promotes the progression of heart failure (HF). Volume overload and HF together with increased central venous pressure and low systemic pressure may adversely affect the net renal perfusion pressure and thus result in renal function deterioration. This vicious cycle contributes to the stimulation of many inflammatory markers, cytokines, and neurohumoral factors, which adversely affect cardiac function in part by enhancing endoplasmic reticulum stress[11]. SGLT2is reduce glomerular dysfunction, improve transport systems in renal cortical cells, and enhance or preserve renal function. SGLT2is protect the heart by improving and preserving renal function through both hemodynamic and nonhemodynamic mechanisms[12].

Proposed Mechanisms Underlying the Cardiorenal Protection of SGLT2is

SGLT2is exert beneficial effects through SGLT2 blockade in the renal proximal tubule, inhibiting glucose reabsorption in the kidney and therefore reducing blood sugar levels[3]. Furthermore, these mechanisms improve glycemia and reduce BP, body weight, and albuminuria[13]. Moreover, recent large-scale clinical trials have reported that the pleiotropic effects of SGLT2is reduce the risk of CV events and improve renal outcomes[4-6].

3.1 Established Renoprotective Effects

Many review articles and commentaries have discussed the mechanisms underlying the renoprotective effect of SGLT2is[14-16]. However, the findings of trials examining CV outcomes and real-world evidence should be summarized to better explain the renoprotective effects of SGLT2is.

SGLT2is indirectly exert a renoprotective effect by improving glycemia[13,14]; causing weight loss[13,14]; reducing inflammation, OS, plasma uric acid levels, and BP[14]; and activating angiotensin II receptor type 2[14]; these changes occur regardless of the estimated glomerular filtration rate (eGFR) or reduction in glycated hemoglobin levels[17], possibly through a decline in arterial stiffness[18]. In patients with advanced renal disease, BP reduction may be multifactorial, with hemodynamic and metabolic components contributing to this reduction[19]. In addition, the reduction of sympathetic nervous system activity by SGLT2is through diverse mecha-

nisms may alter glucose metabolism and contribute to renal protection[20,21].

The direct effects of SGLT2is may benefit renal function and are described as follows[22-27]. SGLT2is cause hemodynamic modification possibly through the following mechanisms: (1) by reversing the vasodilation of the afferent arteriole, which, in turn, preserves the eGFR in the long term in diabetic nephropathy[22]; (2) by reducing renal tubular hypoxia by suppressing numerous pathways (including those related to inflammatory activity) and OS[23,24], thus mitigating hemodynamic overload through the reduction of enhanced sympathetic activity[25]; and (3) by increasing the hematocrit level, as suggested by transient increases in the serum erythropoietin concentration and reticulocyte count[26]. Furthermore, SGLT2is exert anti-inflammatory and antifibrotic effects on the kidney, possibly by preventing intrarenal angiotensinogen upregulation and OS[23,24]. SGLT2is alleviate renal ischemia–reperfusion injury through multiple pathways, thus reducing kidney damage[27]. Moreover, SGLT2is induce the formation of ketones, which are a more energy-efficient fuel in renal tubular cells than glucose and may lead to the development of mild ketosis, and ketones reduce renal oxygen consumption and may contribute to the renoprotective effect of SGLT2is; this mechanism is similar to that observed in the myocardium[28,29]. Moreover, ketones ameliorate renal damage by blocking the mechanistic target of rapamycin complex 1 signaling in animal models[30].

3.2 Established Cardioprotective Effects

SGLT2is can considerably improve CV outcomes through their effects on glycemia or glycosuria. Although many mechanisms have been proposed, how SGLT2is exert these effects remains unclear.

The indirect mechanisms underlying the cardioprotective effect of SGLT2is are similar to those underlying their renoprotective effect[13,14,17-21]. SGLT2is directly exert a cardioprotective effect by reducing myocardial work through a shift in fuel energetics[31,32]. The formation of ketones induced by SGLT2i may serve as an additional energy source to sustain myocardial contractile function[31]. Many hypotheses have been proposed to explain the cardiovascular benefits of SGLT2is, including the thrifty fuel hypothesis, modification of cellular life programming as a defense against dormancy, and activation of low-energy sensors for mimicking a fasting transcriptional paradigm to produce cardioprotective effects[32]. However, these mechanisms may only partly explain the CV benefits of SGLT2is. Hence, more studies should be conducted to explore the role of SGLT2is in cardiac fuel energetics. SGLT2is attenuate cardiac ventricular loading, possibly by increasing the hemoconcentration and reducing plasma uric acid levels, the interstitial fluid volume and serum sodium levels through osmotic diuresis, vascular resistance, and arterial stiffness[32]. In addition, SGLT2is inhibit sodium–hydrogen exchangers (NHEs)[33-36]. NHE3 inhibition might prevent or alleviate HF through a common cardiorenal mechanism[33]. NHE1 inhibition can attenuate cardiac ischemic–reperfusion injury[33], suppress cardiac cell apoptosis[34], delay ischemic contracture onset in the ex vivo intact heart[35], and modulate myocyte mechanical function by maintaining an appropriate myocardial redox balance and mitochondrial energy metabolism[36]. Furthermore, SGLT2is can improve the cardiac structure in diabetic cardiomyopathy, myocardial ischemia, and HF, possibly by attenuating disordered cell arrays, focal necrosis, HF biomarker expression, and cardiac hypertrophy and remodeling markers; reducing the myocardial infarct size; and preserving left ventricular (LV) function[32]. SGLT2is can also attenuate cardiomyocyte apoptosis, possibly through the reduction of apoptotic protein expression and the suppression of the endoplasmic retic-

ulum stress pathway[37,38]. Moreover, SGLT2is modulate cardiac antioxidative and inflammatory effects, possibly through direct reactive oxygen and nitrogen species–dependent signal transducer and activator of transcription 3 signaling[39]. SGLT2is exert an antifibrotic effect, possibly by reducing the cardiac extracellular matrix remodeling response and profibrotic markers[40]. SGLT2is promote reverse cardiac remodeling through multiple pathways, thus reducing LV mass regression to provide CV benefits in patients with T2D and CVD[41,42]. In addition, SGLT2is reduce the circulating uric acid level, thus reducing the risk of CV events and delaying the development of CKD[43].

Cardiorenal Outcomes Following SGLT2i Treatment in Clinical Trials

Similar to the majority of antidiabetic agents, SGLT2is can be a solution for previously unmet clinical needs. The benefits of SGLT2is extend beyond glycemic control, as demonstrated in recent large-scale clinical trials examining CV and renal outcomes. The cardiorenal benefits of SGLT2is across the spectrum of CVD and renal diseases are reviewed in this section (Table 1).

Table 1. Summary of the effects of SGLT2is on cardio-renal outcomes in randomized clinical trials

Clinical trials	Intervention (Enrollment)	Main inclusion criteria	Primary outcomes (HR (95% CI); *p* value)	Secondary outcomes (HR [95% CI]; *p* value)
EMPA-REG OUTCOME[44¶]	Empagliflozin (N = 7020)	T2D ASCVD; eGFR ≥ 30 mL/min/1.73 m^2 BMI ≤ 45 kg/m^2 HbA1c: 7.0%-9.0% without GLDs or HbA1c: 7.0%-10.0% with stable GLDs	MACE (CV death, nonfatal MI, or nonfatal stroke): 0.86 (0.74-0.99); $p = 0.04$	CV death or HHF: 0.66 (0.55-0.79); $p < 0.001$ CV death: 0.62 (0.49-0.77); $p < 0.001$ HHF: 0.65 (0.50-0.85); $p = 0.002$ MI: 0.87 (0.70-1.09); $p = 0.220$ Composite renal endpoints (UACR >300 mg/g; sCr doubling and eGFR ≤ 45 mL/min/1.73 m^2; ESRD; renal death): 0.61 (0.53-0.70); $p < 0.001$
CANVAS[5¶]	Canagliflozin (N = 10142)	T2D ASCVD or age ≥ 50 years with 2 or more risk factors for CVD	MACE (CV death, nonfatal MI, or nonfatal stroke): 0.86 (0.75-0.97); $p = 0.02$	CV death or HHF: 0.78 (0.67-0.91) CV death: 0.87 (0.72-1.06) HHF: 0.67 (0.52-0.87) MI: 0.89 (0.73-1.09) Composite renal endpoints (eGFR sustained 40% reduction; ESRD; renal death): 0.60 (0.47-0.77)
DECLARE-TIMI-58[6¶]	Dapagliflozin (N = 17160)	T2D ASCVD or multiple risk factors for ASCVD eGFR ≥ 60 mL/min/1.73 m^2	MACE (CV death, MI, or ischemic stroke): 0.93 (0.84-1.03); $p = 0.17$	CV death or HHF: 0.83 (0.73-0.95); $p = 0.005$ CV death: 0.98 (0.82-1.17) HHF: 0.73 (0.61-0.88) MI: 0.89 (0.77-1.01) Composite renal endpoints (sustained ≥40% reduction in the eGFR to <60 mL/min/1.73 m^2; new ESRD; renal or CV death): 0.53 (0.43-0.66); $p < 0.0001$
VERTIS-CV[56¶]	Ertugliflozin (N = 8246)	T2D CVD Age ≥ 40 years eGFR ≥ 30 mL/min/1.73 m^2	MACE (CV death, nonfatal MI, or nonfatal stroke): 0.97 (0.85-1.11); $p < 0.001$ for noninferiority	CV death or HHF: 0.88 (0.75-1.03); $p = 0.11$ for superiority CV death: 0.92 (0.77-1.11) HHF: 0.70 (0.54-0.90) MI:1.04 (0.86-1.26) Composite renal endpoints (sCr doubling; ESRD; renal death): 0.81 (0.63-1.04)

Clinical trials	Intervention (Enrollment)	Main inclusion criteria	Primary outcomes (HR (95% CI); *p* value)	Secondary outcomes (HR [95% CI]; *p* value)
CREDENCE[51#]	Canagliflozin (N = 4401)	T2D Age ≥ 30 years eGFR 30 to <90 mL/min/1.73 m^2 UACR > 300-5000 mg/g HbA1c: 6.5-12.0% Required stable dose of ACEi or ARB	ESRD (dialysis or transplantation or sustained eGFR <15 ml/min/1.73 m^2), sCr doubling or renal or CV death): 0.70 (0.59-0.82); $p = 0.00001$	MACE (CV death, MI, or stroke): 0.80 (0.67-0.95); $p = 0.01$ CV death or HHF:0.69 (0.57-0.83); $p < 0.001$ HHF: 0.61 (0.47-0.80); $p < 0.001$ CV death, MI, stroke, or HHF or unstable angina: 0.74 (0.63–0.86) Composite renal secondary endpoints (sCr doubling or ESRD or renal death): 0.66 (0.53-0.81); $p < 0.001$
DAPA-CKD[68#]	Dapagliflozin (N = 4304)	eGFR: 25 to 75 mL/min/1.73 m^2 UACR: 200-5000 mg/g Required stable dose of ACEi or ARB	Sustained decline of ≥50% in eGFR (confirmed after ≥28 days), ESRD (dialysis for ≥28 days, transplantation, or eGFR <15 mL/min/1.73 m^2 confirmed after ≥28 days) or renal or CV death: 0.61 (0.51-0.72); $p < 0.001$	MACE: NA CV death or HHF: 0.71 (0.55-0.92); $p = 0.009$ CV death: 0.81 (0.58–1.12) HHF: NA Composite renal secondary endpoints (≥50% decline in the eGFR, ESRD, or renal death): 0.56 (0.45-0.68); $p < 0.001$
SCORED[59#]	Sotagliflozin (N = 10584)	T2D (HbA1c ≥ 7%) eGFR: 25-60 mL/min/1.73 m^2 Risks for CVD	Total number of CV death or HHF or emergency visits for HF: 0.74 (0.63-0.88); $p < 0.001$	MACE (CV death, MI, or stroke): 0.77 (0.65-0.91) CV death or HHF: 0.74 (0.63-0.88); $p < 0.001$ CV death: 0.90 (0.73-1.12); $p = 0.35$ HHF: 0.67 (0.55-0.82); $p < 0.001$ Composite renal secondary endpoints (sustained eGFR decrease of ≥50% for ≥30 days, or long-term dialysis, or renal transplantation, or a sustained eGFR <15 ml/min/1.73 m^2 for ≥30 days): 0.71 (0.46-1.08)
DAKA-HF[55‡]	Dapagliflozin (N = 4744)	EF ≤ 40% NYHA class II, III, or IV NT-proBNP ≥ 600 pg/ml eGFR ≥ 30 mL/min/1.73 m^2	First occurrence of CV death or worsening HF (HHF or emergency visit resulting in intravenous therapy for HF): 0.74 (0.65-0.85); $p < 0.001$	*Primary outcome components and secondary outcomes:* CV death: 0.82 (0.69-0.98) CV death or first HHF: 0.75 (0.65-0.85); $p < 0.001$ CV death or total HHF: 0.75 (0.65-0.88); $p < 0.001$ HHF: 0.70 (0.59-0.83) HHF or an urgent visit for HF: 0.70 (0.59-0.83) Composite renal endpoints (≥50% sustained decline eGFR; ESRD; renal death): 0.71 (0.44-1.16) Least-squares mean change in eGFR (ml/min/1.73 m^2): –1.09 (dapagliflozin) vs −2.85 (placebo)

Clinical trials	Intervention (Enrollment)	Main inclusion criteria	Primary outcomes (HR (95% CI); *p* value)	Secondary outcomes (HR [95% CI]; *p* value)
EMPEROR-Reduced[47]ǂ	Empagliflozin (N = 3730)	EF ≤ 40% NYHA class II, III, or IV	First occurrence of CV death or HHF: 0.75 (0.65-0.86); $p < 0.001$	*Primary outcome components and secondary outcomes:* CV death: 0.92 (0.75-1.12) CV death or first HHF: 0.75 (0.65-0.86); $p < 0.001$ CV death or total HHF: 0.76 (0.65-0.89); $p < 0.001$ HHF: 0.69 (0.59-0.81) HHF or an urgent visit for HF: NA Composite renal endpoints (chronic dialysis or renal transplant ≥40% decrease in eGFR or a sustained eGFR <15 mL/min/1.73 m^2 (if baseline eGFR ≥30) or <10 mL/min/1.73 m^2 (if baseline eGFR <30mL/min/1.73 m^2): 0.50 (0.32-0.77) Least-squares mean change in eGFR (mL/min/1.73 m^2): –0.55 (empagliflozin) vs −2.28 (placebo)
EMPEROR-Preserved[48]ǂ	Empagliflozin (N = 5988)	EF ≥ 40% NYHA class II, III, or IV	First occurrence of CV death or HHF: 0.79 (0.69-0.90); $p < 0.001$	*Primary outcome components and secondary outcomes:* CV death: 0.90 (0.76-1.09) CV death or first HHF: NA CV death or total HHF: NA HHF: 0.71 (0.60-0.83) HHF or emergency visits for HF: 0.69 (0.59-0.80) Composite renal endpoints (chronic dialysis or renal transplant ≥40% decrease in eGFR or a sustained eGFR <15 mL/min/1.73 m^2 (if baseline eGFR ≥30) or <10 mL/min/1.73 m^2 (if baseline eGFR < 30 mL/min/1.73 m^2): 0.95 (0.73-1.24) Least-squares mean change in eGFR (mL/min/1.73 m^2):–1.25 (empagliflozin) vs −2.62 (placebo)
SOLOIST-WHF[58]ǂ	Sotagliflozin (N = 1222)	T2D Previously hospitalized because of the presence of signs and symptoms of HF and received treatment with intravenous diuretic therapy BNP ≥ 150 pg/mL or NT-proBNP > 600 pg/mL eGFR ≥ 30 mL/min/1.73 m^2	Total CV deaths and HHF and emergency visits for HF: 0.67 (0.52-0.85); $p < 0.001$	*Primary outcome components and secondary outcomes* CV death: 0.84 (0.58-1.22); $p = 0.36$ CV death or first HHF: 0.71 (0.56-0.89) CV death or total HHF: 0.68 (0.53-0.88) HHF: NA HHF or an urgent visit for HF: 0.64 (0.49-0.83); $p < 0.001$] Least-squares mean change in eGFR (mL/min/1.73 m^2):–0.34 (sotagliflozin) vs −0.18 (placebo)

Abbreviations: ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CV: cardiovascular; CVD: cardiovascular disease; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; EF: ejection fraction; ESRD: end-stage renal disease; GLDs: glucose-lowering agents; HbA1c: glycated hemoglobin; HF: heart failure; HHF: hospitalization for heart failure; MACE: major adverse cardiovascular event; MI: myocardial infarction; NA: data not available; NYHA: New York Heart Association; NT-proBNP: N-terminal pro B-type natriuretic peptide; BNP: B-type natriuretic peptide; sCr: serum creatinine; SGLT2is: Sodium-glucose co-transporter-2 (SGLT2) inhibitors ;T2D: type 2 diabetes; UACR: urinary albumin/creatinine ratio

¶: ASCVD trial

#: CKD trial

ǂ: HF trial

4.1 CV Benefits

4.1.1 Empagliflozin

The EMPA-REG OUTCOME trial is the first to examine the effects of empagliflozin on CV morbidity and mortality in patients with T2D. The results of the trial indicated that empagliflozin exhibited substantial cardioprotective benefits, with significant reduction in CV mortality and hospitalization for HF (HHF) within the first 3 months of empagliflozin treatment[44]. Empagliflozin markedly reduced primary composite CV endpoints by 14% (hazard ratio [HR] = 0.86, $p = 0.04$)[44]. Moreover, empagliflozin significantly reduced HHF by 35% (HR = 0.65; $p = 0.002$) and any-cause death (ACD) by 32% (HR = 0.68, $p < 0.001$)[44]. Empagliflozin was the most beneficial for HF; however, only 10% of the patients in the cohort developed HF prior to randomization, and no formal confirmation or characterization was presented. Furthermore, the CV benefit of empagliflozin was independent of the CV comorbidity burden[45] and renal function[46]. However, considerable differences were observed among the three CV outcome measures: CV mortality (HR = 0.62, $p < 0.001$), myocardial infarction (MI; HR = 0.87, $p = 0.22$), and stroke (HR = 1.24, $p = 0.23$). Notably, decreased risks of CV mortality and ACD were observed shortly after initiating empagliflozin, and these beneficial effects were noted throughout the trial[44]. Based on these findings, subsequent trials have evaluated the beneficial effects of this class of medication in patients with HF, especially in the absence of T2D.

The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trial focused on patients with HF with reduced ejection fraction (HFrEF) and reported that empagliflozin markedly reduced the risk of CV mortality or HHF, irrespective of the presence of diabetes (HR = 0.75, $p < 0.001$) [47]. Moreover, compared with placebo, empagliflozin was associated with a lower total number of HHF (HR = 0.70, $p < 0.001$)[47]. The Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trial enrolled patients with class II-IV HF and an ejection fraction (EF) of >40% and reported that empagliflozin markedly reduced the combined risk of CV mortality and HHF in patients with HF and a preserved ejection fraction (HFpEF; HR = 0.79, $p < 0.0001$), irrespective of the presence of diabetes [48]. Moreover, empagliflozin reduced the total number of HHF for providing intensive care (HR = 0.71, $p = 0.028$) and the total number of all hospitalizations for providing a vasopressor or a positive inotropic drug (HR = 0.73, $p = 0.033$)[49].

4.1.2 Canagliflozin

The Canagliflozin Cardiovascular Assessment Study (CANVAS) enrolled patients with a high risk of CVD and those with a diagnosis of CVD and reported that canagliflozin reduced the primary composite CV outcome by 14% (HR = 0.86, $p = 0.02$) and the risk of HHF by 33% (HR = 0.67)[5]. In a subanalysis of the CANVAS, compared with placebo, canagliflozin significantly reduced the risks of CV mortality or HHF (HR = 0.78), fetal or HHF (HR = 0.70), and HHF (HR = 0.67)[50]. Moreover, the benefit of canagliflozin for CV mortality or HHF was greater for patients with a history of HF (HR = 0.61) than those without HF at baseline (HR = 0.87, p for interaction = 0.021), suggesting that canagliflozin is more beneficial for patients with a history of HF than those without[50]. Similarly, the Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trial reported that canagliflozin reduced the risks of CV mortality, MI, and stroke (HR = 0.80, $p = 0.01$) and HHF (HR = 0.61, $p < 0.001$)[51].

Although the CANVAS reported that canagliflozin increased the risk of lower limb amputation (HR = 1.97)[50], the subsequent CREDENCE trial[51] and a series of meta-analyses of SGLT2is

indicated no relationship between SGLT2i exposure and increased amputation risk.[52,53] The differences in the findings of these studies might be due to the inclusion of different populations or the adoption of different protocols[51].

4.1.3 Dapagliflozin

The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial included patients with CVD and those with multiple risk factors for CVD and reported that dapagliflozin had no effect on 3-point major adverse cardiovascular events (MACEs; HR = 0.93, $p = 0.17$) but reduced the rate of CV mortality or HHF (HR = 0.83, $p = 0.005$); the findings indicated a lower HHF rate (HR = 0.73) without any difference in CV mortality (HR = 0.98)[6]. The post hoc analysis of the DECLARE-TIMI 58 trial in which patients were stratified by LVEF indicated that dapagliflozin considerably reduced the risk of CV mortality and HHF in patients with reduced EF[54]. However, these findings should be interpreted with caution given the small sample size and the lack of the robust characterization of HF.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial, which is the first trial to investigate the effects of SGLT2is in patients with HFrEF, reported that dapagliflozin reduced the risk of worsening HFrEF or CV mortality in patients with HFrEF by 26% (HR = 0.74, $p < 0.001$)[55]. The results were similar for patients with diabetes and patients without diabetes[55]. The trial findings indicate that SGLT2is provide benefits unrelated to their glucose-lowering effect, and the mechanisms through which SGLT2is provide direct CV benefits to patients with HFrEF, irrespective of the presence of diabetes, remain to be elucidated. The Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (NCT03057951) trial is currently being conducted to evaluate the effects of dapagliflozin in patients HFpEF.

4.1.4 Ertugliflozin

The Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS-CV) trial investigated the effects of ertugliflozin in patients with atherosclerotic CVD and reported that ertugliflozin failed to demonstrate superiority in the primary outcome of 3-point MACEs (HR = 0.97, $p <$ 0.001 for noninferiority) or in any of the key secondary outcomes, including CV mortality (HR = 0.92)[56]. However, the rate of HHF was decreased in participants treated with ertugliflozin compared with those on placebo (HR = 0.70). Despite its potential for HF treatment, ertugliflozin is not as effective as SGLT2is for CV outcomes[56]. This discordant result for CV mortality, especially at the secondary prevention level, is unexpected given the cardiac benefits of ertugliflozin observed in other trials examining CV outcomes. Some plausible explanations for the discordance are pharmacological differences; study time frame; and dissimilarities in study designs, outcome definitions, and enrolled populations, which may reflect differences in background rates or the use of other medications[57]. However, future mechanistic studies and post hoc analyses of the existing trials are necessary to clarify the discordance in the findings of different SGLT2i trials.

4.1.5 Sotagliflozin

The Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF), a dual SGLT2i and gastrointestinal SGLT1i trial, enrolled patients with T2D and recent worsening HF and reported that sotagliflozin treatment initiated before or early after discharge from the hospital significantly reduced CV mortality as well as HHF and emergency visits by 33% (HR = 0.67, $p < 0.0001$)[58]. The Sotagliflozin in Patients with Diabetes and

Chronic Kidney Disease (SCORED) trial enrolled patients with T2D, CKD (eGFR = 20-60 mL/min/1.73 m^2), and CV risk factors and reported that sotagliflozin significantly reduced the modified primary composite cardiac endpoint of mortality from CV causes and HHF and emergency visits for HF by 26% (HR = 0.74, $p < 0.001$)[59]. The effects of sotagliflozin did not significantly differ in terms of the rate of mortality from CV causes and renal endpoints (HR = 0.90, $p = 0.35$)[59]. Longer trials should be conducted to evaluate the effect and safety of sotagliflozin in patients with diabetes and CKD. Neither SCORED nor SOLOIST-WHF exclusively recruited patients with HFrEF.

4.2 Renal Benefits

Although early trials examining CV outcomes following SGLT2i treatment, such as EMPA-REG OUTCOME[44], CANVAS[5], DECLARE-TIMI 58[6], and VERTIS-CV[56], were initially designed to evaluate CV outcomes, they included definite renal endpoints as secondary outcomes, and they demonstrated that SGLT2is prevented the development of CKD and prevented or delayed the worsening of CKD in patients with T2D at any level of renal risk. In the aforementioned trials, few patients with baseline nephropathy were enrolled; however, a recent meta-analysis indicated that SGLT2is were robust and prevented kidney-related adverse outcomes (HR = 0.61)[60].

The significant renal benefit of ertugliflozin observed in the VERTIS-CV trial might be affected by the choice of events comprising prespecified composite renal endpoints; however, by replacing the doubling of serum creatinine with a sustained 40% decrease in the eGFR from baseline, ertugliflozin was noted to be associated with significant preservation of renal function (HR = 0.65), which is consistent with the results of other SGLT2i trials[61].

A similar renal benefit was reported by another trial investigating the effect of SGLT2i in patients with HFrEF with and without diabetes[62]. A meta-analysis of DAPA-HF and EMPEROR-Reduced trials indicated that SGLT2is markedly reduced the risk of the composite renal endpoint (HR = 0.62, $p = 0.013$) in patients with HFrEF, although the number of events accrued was limited[62]. Furthermore, SGLT-2is reduced the rate of decline in the eGFR over time in both the trials, irrespective of the presence of diabetes[63,64]. In the EMPEROR-Preserved trial, empagliflozin markedly reduced the rate of eGFR decline by approximately 50% over time, even though it did not affect the composite renal endpoint defined as time to the first occurrence of chronic dialysis, renal transplantation, a sustained reduction of ≥40% in the eGFR, or a sustained eGFR of <15 mL/min/1.73 m^2 in patients with a baseline eGFR of ≥30 mL/min/1.73 m^2 or of <10 mL/ min/1.73 m^2 in patients with a baseline eGFR of <20 mL/min/1.73 m^2 (HR = 0.95)[62]. A higher proportion of patients with an eGFR of <60 mL/min/1.73 m^2 were enrolled into those trials compared with other trials, suggesting the safety and CV efficacy of SGLT2is in patients with stage 3 CKD[65].

The renoprotective effects of SGLT2is were not influenced by baseline CV risk in these trials, which is generally observed across a wide spectrum of eGFR and albuminuria categories[66]. However, whether these effects are greater in those with preserved or reduced renal function remains unclear. This highlights the need for more dedicated renal outcome trials, of which two are completed: CREDENCE[67] and DAPA-CKD.[68] These trials were both stopped early due to the observation of a marked clinical benefit.

CREDENCE is the first dedicated renal outcome trial that investigated the effect of canagliflozin in patients with T2D with an eGFR of 30-90 mL/min/1.73 m^2 and a urine albumin to creatine ratio (UACR) of 300-5000 mg/g[67]. The reductions in the relative risk (RR) for the canagliflozin group versus the placebo group were −30% (p =

0.00001), −34% ($p < 0.001$), and −32% ($p = 0.002$) for the primary outcome, composite renal-specific outcome, and end-stage renal disease (ESRD), respectively[67]. Moreover, subgroup analyses have reported that canagliflozin was effective and safe, irrespective of the baseline eGFR and albuminuria level, without increasing the risk of acute kidney injury (AKI) in patients with nephropathic diabetes[65,67]. The DAPA-CKD trial included patients with and without T2D with an eGFR of 25-75 mL/min/1.73 m^2 and an UACR of 200-5000 mg/g and indicated that dapagliflozin significantly reduced the composite outcome of a sustained decline of at least 50% in the eGFR, ESRD, or death from renal disease or CVD[68]. Moreover, a prespecified analysis conducted in 624 patients with stage 4 CKD (eGFR of <30 mL/min/1.73 m^2) at baseline indicated that dapagliflozin caused a 29% reduction in the composite renal endpoint (HR = 0.71), with no evidence of an increased risk of adverse events, and dapagliflozin yielded a yearly eGFR slope decline of 2.15 mL/min/1.73 m^2 compared with 3.38 for placebo ($p = 0.005$)[69]. Given that dapagliflozin is effective even in patients with a low eGFR of 25 mL/min/1.73 m^2, physicians should discard the old, obsolete eGFR threshold of 45 or 60 mL/min/1.73 m^2 that is based on glycemic factors, rather than on cardiorenal protection[70].

The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) (NCT03594110) is currently underway and further investigates the cardiorenal benefits of empagliflozin in patients with eGFR as low as 20 mL/min/1.73 m^2 and in patients with a lower eGFR (20-45 mL/min/1.73 m^2) without albuminuria.

Taken together, the findings indicated that SGLT2is produced renal benefits irrespective of baseline eGFR, albuminuria, or renin–angiotensin system inhibitor use[66,71], although post hoc analyses of the trials of SGLT2is have demonstrated that SGLT-2is provided a greater absolute benefit in terms of the eGFR decline in patients with macroalbuminuria at baseline[72,73].

Meta-Analyses of Trials With SGLT2is

5.1 CV Benefits

A meta-analysis investigated the effects of 3 SGLT2is on CV outcomes and mortality and reported that SGLT2is reduced the incidence of MACEs (odds ratio [OR] = 0.86, $p < 0.0001$), MI (OR = 0.86, $p = 0.001$), CV mortality (OR = 0.74, $p < 0.0001$), and ACD (OR = 0.85, $p < 0.0001$)[74]. Similar results were reported in a comprehensive meta-analysis of 71 randomized controlled trials (RCTs)[75]; a meta-analysis of 82 trials, 4 overviews, and 6 regulatory reports[76]; and a meta-analysis of 7 RCTs[77] assessing CV events in patients with T2D. These data indicated that SGLT2is reduce the risks of CV events and mortality.

A meta-analysis of the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 trials reported that SGLT2is reduced the number of MACEs by 11% (HR = 0.89, $p = 0.0014$), with the benefit being observed only in patients with atherosclerotic CVD (HR = 0.86) and not in those without (HR = 1.00, $p = 0.0501$)[78]. In addition, SGLT2is reduced the risk of CV mortality or HHF by 23% (HR = 0.77, $p < 0.0001$), with similar benefits observed in patients with or without preexisting atherosclerotic CVD and preexisting HF[78]. The beneficial effects of SGLT2is varied with baseline renal function; a greater reduction in HHF ($p = 0.0073$) and a lower reduction in renal disease development ($p = 0.0258$) were observed in patients with more severe renal disease at baseline[78]. A meta-analysis of 9 RCTs investigated the effect of SGLT2is in patients with HF and reported that regardless of the LVEF phenotype, SGLT2is had an excellent safety profile and significantly reduced the risk of ACD (HR = 0.86, $p = 0.0008$), CV mortality (HR = 0.86, $p = 0.003$), HHF (HR = 0.68, $p < 0.001$), and CV mor-

tality/HHF (HR = 0.74, $p < 0.001$) compared with placebo[79]. Furthermore, a meta-analysis of EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, CREDENCE, and VERTIS-CV trials including 31116 (66.2%) patients with atherosclerotic CVD reported that SGLT2is reduced the risk of MACEs (HR = 0.90)[60]. Moreover, significant heterogeneity was noted in the association of SGLT2is with CV mortality (HR = 0.85). The largest benefit across this class of drug was observed in terms of an associated reduction in the risk of HHF (HR 0.68) and adverse renal outcomes (HR = 0.62), with the reduction in HHF risk being the most consistent observation across the trials[60].

5.2 Renal Benefits

A meta-analysis of the EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and CREDENCE trials reported that SGLT2is reduced the risks of renal failure by 29% (RR = 0.71, $p = 0.014$), ESRD by 32% (RR = 0.68, $p = 0.001$), and AKI by 25% (RR= 0.75, $p < 0.0001$), with consistent benefits observed across the included studies[71]. Moreover, SGLT2is reduced the risk of substantial renal function loss, ESRD, or renal death by 42% (RR = 0.58, $p < 0.0001$)[71]. An independent meta-analysis of the aforementioned 4 trials reported that SGLT2is reduced the risk of a composite renal outcome by 37% (RR = 0.63); this was true even in patients with an eGFR of <60 mL/min/1.73 m^2 (RR = 0.67)[80]. Moreover, a meta-analysis of 7 RCTs of SGLT2is incorporating trial sequential analysis demonstrated a significant reduced risk of worsening renal function (HR = 0.63)[77].

These findings are consistent with those of a meta-analysis of 9 trials including patients with T2D and CKD treated with SGLT2is, which revealed that SGLT2is significantly reduced the risk of worsening renal function, ESRD, or renal death by 30% in patients with an eGFR of <60 mL/min/1.73 m^2 (HR = 0.70, $I^2 = 0.00\%$) and by 43% in patients with a UACR of >300 mg/g (HR = 0.57, $I^2 = 16.59\%$)[81]. A meta-analysis of 7 trials including 14 113 patients with HF treated with SGLT2is reported a significantly lower renal function decline (RR = 0.673, $p < 0.001$)[82]. A meta-analysis of 14 trials including 3792 Asian patients treated with SGLT2is demonstrated a significantly lower eGFR decline (mean difference [MD] = 0.80, $p < 0.00001$) and reduced serum creatinine levels (standardized MD = − 0.17, $p < 0.00001$) compared with controls.[83] However, no significant difference was found in the UACR reduction between the SGLT2is and control groups (MD = − 8.87, $p = 0.11$)[83]. The finding of the protective effect of SGLT2is for the renal system is inconsistent with the result of a previous meta-analysis that demonstrated that SGLT2is reduced albuminuria and had significant benefits for the composite renal endpoint[84]. The exact underlying mechanisms remain unclear, and more RCTs are warranted to investigate the effect of SGLT2is on Asian patients.

Role of Real-World Observational Data

Because of its low external validity, evidence from RCTs should be complemented by real-world studies (RWSs) to understand the benefits and risks of SGLT2is in clinical practice[85]. RWSs can provide crucial insights into the effectiveness of SGLT2is for cardiorenal protection in T2D over a spectrum of CV and renal risk (Table 2).

6.1 Observational Data: CV Outcomes

The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors (CVD-REAL) is a large RWS that collected observational data from 6 countries to investigate and compare the effect of SGLT2is with those of other glucose -lowering drugs on the risk of death, HF, and HF or death in patients with and without CVD[86]. In this study, only 13% of patients had CVD at baseline in contrast to the population enrolled into the trials examining CV outcomes. This study reported that

Table 2. Summary of the effects of SGLT2is on cardio-renal outcomes in real world data and observational study

Study	Intervention	Patients (Enrollment)	CVD (%)	CKD (%)	Regions	Main CV and renal outcomes (HR [95% CI]; *p* value)
CVD-REAL[86]	SGLT2is vs. oGLDs	N=306156	13.0	2.6	United States, United Kingdom, Sweden, Norway, and Denmark	*With prior CVD:* ACD: 0.56 (0.44-0.70) HHF: 0.72 (0.63-0.82) ACD or HHF: 0.63 (0.57-0.72) *Without prior CVD:* ACD: 0.56 (0.50-0.63) HHF: 0.61 (0.48-0.78) ACD or HHF: 0.56 (0.50-0.62)
Sub-Analysis of CVD-REAL[87]	SGLT2is vs. oGLDs	N=205160	14	N.A	United States, Sweden, Norway and Denmark	MI:0.85 (0.72–1.00); $p = 0.05$ Stroke: 0.83 (0.71–0.97); $p = 0.02$
CVD-REAL Nordic[88]	SGLT2is vs. oGLDs	N=91320	24.9	1.2	Denmark, Norway, and Sweden	MACEs: 0.78 (0.69-0.87); $p < 0.00001$ MI: 0.87 (0.73-1.03); $p = 0.112$ CV death: 0.53 (0.40-0.71); $p < 0.0001$ ACD: 0.51 (0.45-0.53); $p < 0.0001$ HHF: 0.70 (0.61-0.81); $p < 0.00001$ Stroke: 0.86 (0.72-1.04); $p = 0.113$
CVD-REAL Nordic[89]	Dapagliflozin vs DPP4is	N=40908	22.8	2.1	Denmark, Norway, and Sweden	MACEs: 0.79 (0.67-0.94); $p = 0.006$ MI: 0.91 (0.72-1.16); $p = 0.445$ CV death: 0.76 (0.53-1.08); $p = 0.122$ ACD: 0.59 (0.49-0.72); $p < 0.001$ HHF: 0.62 (0.50-0.77); $p < 0.001$
CVD-REAL 2[90]	SGLT2is vs. oGLDs	N=47128	26.2	1.9	South Korea, Japan, Singapore, Israel, Australia, and Canada	MI: 0.81 (0.74-0.88); $p < 0.001$ ACD: 0.51 (0.37-0.70); $p < 0.001$ HHF: 0.64 (0.50-0.82); $p = 0.001$ ACD or HHF:0.60 (0.47-076); $p < 0.001$ Stroke: 0.68 (0.55-0.84); $p < 0.001$
CVD-REAL 3[91]	SGLT2i vs. oGLDs	N=71112	22.6	8.3	Israel, Italy, Japan, Taiwan, and United Kingdom	HHF: 0·60 (0.47-0.76); $p < 0.0001$ ACD: 0·55 (0.48-0.64); $p < 0.0001$ eGFR decline rate: -1.53 mL/min/1.73 m^2 per year (1.34-1.72); $p < 0.0001$ Composite renal outcomes (50% eGFR decline or ESRD): 0.49 (0.35-0.67); $p < 0.0001$
OBSERVE-4D[92]	(a) Canagliflozin vs. oGLDs (b) Empagliflozin, Dapagliflozin vs. oGLDs	N=215633	N.A	7.5	United States (4 databases)	HHF: (a) 0.39 (0.26-0.60) (b) 0.43 (0.30-0.62)
United States cohort[93]	Exposed vs. unexposed dapagliflozin	N=22124	20.0	N.A	United States	ACD: 0.50§ (0.33-0.75); $p = 0.001$ ACD¶: 0.44§ (0.25-0.78); $p = 0.002$
Swedish cohort[94]	Dapagliflozin vs. insulin	N= 37603	33.0	0.0	Sweden	ACD: 0.44 (0.28-0.70); $p < 0.001$ CVD: 0.61 (0.30-0.86); $p < 0.011$

Study	Intervention	Patients (Enrollment)	CVD (%)	CKD (%)	Regions	Main CV and renal outcomes (HR [95% CI]; *p* value)
United States cohort[95]	Canagliflozin vs. (a) DPP4is (b) GLP-1RA (C) SU	N=224999	N.A	6.9	United States	MI: (a) 0.91 (0.64-1.29) (b) 1.03 (0.73-1.44) (c) 0.85 (0.59-1.31) ACD: (a) 0.66 (0.25-1.74) (b) 0.77 (0.32-1.85) (c) 1.34 (0.47-3.) HHF: (a) 0.64 (0.53-0.76) (b) 0.68 (0.58-0.81) (c) 0.47 (0.39-0.56)
Italian cohort[96] (a) Lombardy (b) Apulia	SGLT2is vs. oGLDs	(a)N=30399 (b)N=15836	(a)13.8 (b)14.4	(a)2.5 (b)3.9	Italy	MI: (a) 0.98 (0.83-1.17) (b) 1.07 (0.83-1.39) ACD: (a) 0.47 (0.40-0.54) (b) 0.43 (0.32-0.57) HHF: (a) 0.56 (0.46-0.70) (b) 0.57 (0.42-0.77)
Italian cohort[97]	SGLT2is vs. GLP-1RA	N=8596	17.7	1.6	Italy	MACEs: 0.68 (0.61-0.99); $p = 0.043$ MI: 0.72 (0.53-0.98); $p = 0.035$ ACD: 0.74 (0.43-1.29); $p = 0.0291$ HHF: 0.59 (0.35-0.99); $p = 0.048$ Stroke: 0.91 (0.56-1.48); $p = 0.707$
EASEL[98]	SGLT2is vs. oGLDs	N=111576	100.0	11.7	United States	MACEs: 0.67 (0.60-0.75); $p < 0.0001$ MI: 0.81 (0.64-1.03); $p = 0.0888$ ACD: 0.57 (0.50-0.65); $p < 0.0001$ HHF: 0.57 (0.45-0.73); $p < 0.0001$
EMPRISE[99]	Empagliflozin vs. Sitagliptin	N=16443	25.0	7.2	United States	HHF-specific[ǂ]: 0.50 (0.28-0.91) HHF-broad[ǁ]: 0.51 (0.39-0.68)
EMPRISE East Asia[100]	Empagliflozin vs. DPP4is	N=28712	33.0	4.1	Taiwan, Japan, and South Korea	HHF: 0.82 (0.71-0.94) ACD: 0.64 (0.50-0.81) ESRD: 0.37 (0.24-0.58)
Israel cohort[103]	SGLT2is vs. DPP4is	N=12022	30.5	50.0	Israel	eGFR ≥30% reduction: 0.70[#] (0.49-1.00) AKI: 0.47[#] (0.27-0.80) Hospitalization: 0.66[#] (0.56-0.78) ACD: 0.43[#] (0.20-0.95)
Japan cohort[104]	SGLT2is vs. oGLDs	N=4172	N.A	N.A	Japan	Annual change in eGFR (mL/min/1.73 m^2): -0.86 (0.71-1.01) (SGLT2is) vs. -2.06 (1.93-2.18) (oGLDs) Composite renal endpoints (>40% decline in eGFR, onset of eGFR<30 mL/min/1.73 m^2): 0.70 (0.50-0.98); $p = 0.039$
DARWIN-T2D[105]	Dapagliflozin vs. oGLDs	N=17285	N.A	N.A	Italy	Change in AER: -37% (dapagliflozin) vs. 0% (oGLDs); $p < 0.0001$ eGFR decline (mL/min/1.73 m^2): -1.1±0.5 (dapagliflozin) vs.0.6±9.1 (oGLDs); $p = 0.35$)

Study	Intervention	Patients (Enrollment)	CVD (%)	CKD (%)	Regions	Main CV and renal outcomes (HR [95% CI]; *p* value)
Scandinavian cohort[106]	SGLT2is vs. DPP4is	N=59774	19.0	3.0	Sweden, Denmark, and Norway	Composite renal endpoints (ESRD, renal death, renal-related admission): 0.42 (0.34-0.53) ESRD: 0.32 (0.22-0.47) Renal death: 0.77 (0.26-2.23) Renal-related admission: 0.41(0.32-0.52)
CVD-REAL 3 KOREA[107]	SGLT2is vs. oGLDs	N=90032	48.2	54.7	Korea	ESRD: 0.47 (0.34-0.65) (a) *eGFR < 60 mL/min/1.73 m²* ESRD: 0.39 (0.25-0.63) (b) *eGFR 60–90 mL/min/1.73 m²* ESRD: 0.39 (0.21-0.75) (c) *eGFR ≥ 90 mL/min/1.73 m²* ESRD: 1.45 (0.67-3.11) ACD: 0.82 (0.73-0.93)

Abbreviations: ACD: all-cause mortality; AER: albumin excretion rate; aIRR: adjusted incidence rate ratio; AKI: cute kidney injury; CV: cardiovascular; CVD: cardiovascular disease; CI: confidence interval; CKD: chronic kidney disease; DPP4is: dipeptidyl peptidase 4 inhibitors; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; GLP-1RA: Glucagon-like peptide-1 receptor agonist; HR: hazard ratio; HHF: hospitalization for heart failure; MACEs: major adverse cardiovascular events; MI: myocardial infarction; N.A: data not available; oGLDs: other glucose-lowering drugs; OR: odds ratio; SGLT2is: Sodium-glucose co-transporter-2 inhibitors; SU: Sulfonylureas.
§: aIRR
¶: Low risk for CVD
#: OR
‡: HF discharge diagnosis in the primary position
‖: HF discharge diagnosis in any position

compared with glucose-lowering drugs, SGLT2is resulted in lower risks of mortality, HF, and the composite outcome 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, SGLT2i initiation was associated with lower risks of HF and mortality irrespective of preexisting CVD [86]. A subanalysis conducted in 4 of the 6 countries participating in the CVD-REAL study indicated that SGLT2i initiation was associated with moderately low risks of MI (HR = 0.85, $p = 0.05$) and stroke (HR = 0.83, $p = 0.02$)[87]. Similar results were obtained in the CVD-REAL Nordic study that collected data from the nationwide registries of Denmark, Norway, and Sweden[88,89] and the CVD-REAL 2 study conducted in other 6 countries[90]. The subanalysis demonstrated the wide-ranging CV benefit of SGLT2is in a broader population with diabetes, as also revealed by the DECLARE-TIMI 58 trial. Moreover, the CVD-REAL 3 conducted in 5 countries confirmed that SGLT2is provided protective effects on HHF and ACD compared with glucose-lowering drugs[91].

A real-world meta-analysis of 4 observational databases indicated that new users of canagliflozin had a lower risk of HHF (HR = 0.39) compared with those who did not use SGLT2is, with no significant differences observed between these patients and those treated with other SGLT-2is[92]. Other smaller retrospective cohort studies have shown similar CV benefits, especially in terms of the prevention of ACD[93,94] and HHF[95]. Recently, a RWS conducted in 2 propensity-score-matched Italian cohorts with low baseline CV risk confirmed the favorable effect of SGLT2is on CV outcomes and ACD[96]. A retrospective RWS including 8596 patients with T2D with 82% in primary prevention treated with either SGLT2is or glucagon-like peptide-1 receptor agonists (GLP-1RAs) reported that compared with patients receiving GLP-1RAs, those receiving SGLT2is experienced lower rates of 3-point MACEs

(HR = 0.68, p = 0.043), MI (HR = 0.72, p = 0.035), HHF (HR = 0.59, p = 0. 048), and hospitalization for CV causes (HR = 0.82, p = 0.037)[97].

The Evidence for Cardiovascular Outcomes with Sodium Glucose Cotransporter 2 Inhibitors in the Real World (EASEL) study enrolled 111 576 patients with T2D and CVD and revealed that compared with glucose-lowering drugs, SGLT2is significantly reduced the risks of ACD and HHF (HR = 0.57) and MACEs (HR = 0.67)[98]. However, SGLT2i treatment resulted in an approximately 2-fold higher risk of below-knee lower extremity amputation; 58.1% of these patients received canagliflozin, thus supporting the findings of CANVAS[98]. The Empagliflozin Comparative Effectiveness and Safety (EMPRISE) study investigated the risk of HHF in patients with T2D in the first interim analysis and indicated that compared with sitagliptin, empagliflozin reduced the risk of HHF (HR = 0.51) over a mean follow-up period of 5.3 months, irrespective of the presence of baseline CVD[99]. The results of the EMPRISE East Asia study indicated that compared with dipeptidyl peptidase-4 inhibitors (DPP-4is), empagliflozin significantly reduced the risk of HHF by 18% (HR = 0.82) and ACD by 36% (HR = 0.64), irrespective of the baseline CV risk[100]. Moreover, compared with DPP-4is, empagliflozin markedly reduced the prevalence of ESRD by 63% (HR = 0.37)[100]. Similar results emerged from the CVD-REAL 2 study including a large Israeli database, confirming that SGLT2i initiation was associated with a low risk of HHF or ACD (HR = 0.57, p < 0.001) regardless of baseline LVEF[101].

Taken together, the RWSs strongly indicated the CV benefit of SGLT2is, particularly in terms of the reduction of HHF and ACD. The CV benefit in these studies is greater than that observed in the RCTs, probably due to different designs, settings, and patient characteristics. Although these observational studies can be performed prospectively and propensity score matching can be employed to construct cohorts comparable to those in RCTs, observational studies may be affected by several biases, including confounding, selection, information, time related, and prevalent user biases[102]. As the field continues to grow, academic journals and regulatory agencies should involve peer reviewers with adequate methodological knowledge to ensure the dissemination of the findings of high-quality RWSs and maximize their utility in decision-making[102].

6.2 Observational Data: Renal Outcomes

Although RWSs have investigated the renal effects of SGLT2is, the number of relevant studies are still limited. Early results from a large Israeli cohort study revealed that compared with DPP-4is, SGLT2is were associated with a borderline significant lower risk of ≥30% eGFR reduction (OR = 0.70), particularly in patients with baseline preserved renal function (eGFR > 60 mL/min/1.73 m^2)[103]. Moreover, SGLT2is reduced the risk of AKI (OR = 0.47), hospitalization (OR = 0.66), or ACD (OR = 0.43).[103] Although patients with stage 3 CKD (12.9%) at baseline lacked significant protection from ≥30% eGFR decline, they showed a significant reduction in hospitalization for AKI (adjusted OR = 0.34) or any hospitalization (adjusted OR = 0.57)[103]. Similarly, in a large Japanese cohort study, compared with glucose-lowering drugs, SGLT2is significantly slowed the annualized eGFR decline (− 0.86 vs −2.06 mL/min/1.73 m^2)[104]. Moreover, the SGLT2i group exhibited a lower incidence of composite renal endpoints (HR = 0.70) despite better glycemic control in the glucose-lowering drug group[104].

The Dapagliflozin Real World Evidence in Type 2 Diabetes (DARWIN-T2D) is the first RWS to evaluate changes in renal endpoints in patients with T2D, and the results suggest that dapagliflozin significantly reduced albumin urinary excretion compared with glucose-lowering drugs (−26.4 ± 13.1 mg/g, p = 0.045) over a follow-up of approximately 6 months[105]. However, a mild and marginally

significant decline in eGFR was observed during dapagliflozin treatment. One possible interpretation of this was that short-term follow-up (~6 months) only allows an analysis of acute changes in renal endpoints and a longer observation will be needed to evaluate benefits over time and trends in eGFR[105]. Notably, significantly lower albumin urinary excretion was observed only in patients with microalbuminuria or macroalbuminuria at baseline treated with dapagliflozin[105].

A large Scandinavian cohort study using nationwide data from 3 countries reported that compared with DPP-4is, SGLT2is treatment significantly reduced the risks of ESRD, renal death, and renal-related admission (HR = 0.32, 0.77, and 0.41, respectively)[106]. The CVD-REAL 3 was a multinational observational cohort study that examined the rate of eGFR decline and the composite outcome of 50% eGFR decline or ESRD in patients with T2D receiving SGLT-2is compared with those receiving glucose-lowering drugs. The mean eGFR of the enrolled population was 90 mL/min/1.73 m^2, with only less than 10% of patients reporting baseline eGFR values of ≤60 mL/min/1.73 m^2 [91]. The study reported that SGLT-2is were strongly associated with a decreased eGFR decline (difference in slope = 1.53 mL/min/1.73 m^2, p <0.0001) and a reduction in the composite outcome of 50% eGFR decline or ESRD by 51% (HR = 0.49, p < 0.0001) over a mean follow-up of 14.9 months [91]. Similarly, the CVD-REAL 3 Korea study enrolled patients with a mean eGFR of 89.2 mL/min/1.73 m^2 and reported that compared with glucose-lowering drugs, SGLT2is resulted in lower risks of ESRD (HR = 0.47) and ACD (HR = 0.82)[107]. However, few ESRD events were observed in the subgroup with an eGFR of ≥90 mL/min/1.73 m^2, probably due to a relatively low risk of ESRD considering the clinical natural course of CKD progression[107].

Taken together, the retrospective RWSs conducted thus far have confirmed that SGLT2is resulted in more favorable renal outcomes than did glucose-lowering drugs in patients with T2D. However, these studies included a short follow-up duration, and the analysis of surrogate endpoints was subject to inherent bias. Additional evidence from large observational studies is required to identify patients who would benefit the most from the renal protection offered by SGLT2is.

Conclusions

T2D management has shifted from a glucocentric approach to cardiorenal risk reduction through the treatment of multiple risk factors and the use of new glucose-lowering drugs with pleiotropic effects[108]. Experimental studies and biomarker analyses have demonstrated that SGLT2is have numerous pleiotropic effects, such as those on hematocrit, renal tubular hypoxia, energy substrate use, NHE inhibition, OS and inflammation, which may mediate their cardiorenal protection benefit. RCTs and RWSs have suggested that SGLT2is not only inhibit the progression of albuminuria, reducing overall risk factors for heart and kidney diseases, but also reduce the risks of HHF and CKD progression in different clinical settings, consistently across all the stages of the cardiorenal continuum and irrespective of diabetes status[109]. Although RWSs have reported the most encouraging results, the effect of SGLT2is on specific atherosclerotic CV endpoints remains limited, suggesting that the pleiotropic effects of these drugs are valuable, but SGLT2is alone are insufficient for controlling a multifaceted disease such as diabetes. Additional studies should investigate mechanisms underlying the cardiorenal protective effects of SGLT2is and identify populations that would mostly benefit from treatment.

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在第二型糖尿病患者的心腎保護：臨床研究到真實世界的證據

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摘要

心血管疾病和慢性腎臟病是導致全世界第二型糖尿病患者死亡的主要原因。雖然第二型糖尿病患者積極血糖控制減少了血管併發症的發生，然而全球糖尿病的心腎疾病盛行率依然持續的增加。因此，潛在具有能阻止心腎功能受傷進展的藥物是有其迫切需要的。除了具有降血糖的效果之外，第2型鈉-葡萄糖共同轉運蛋白抑制劑擁有多重性功效，譬如說降血壓、降體重、改善蛋白尿、抗發炎及抗纖維化作用，同時在系統性和腎內血液動力學之路徑上含藏有益的效用，進而提供一個心腎器官保護的益處。特別是在最近探討第2型鈉-葡萄糖共同轉運蛋白抑制劑針對心血管疾病和腎臟疾病的臨床試驗結果，報告顯示第2型鈉-葡萄糖共同轉運蛋白抑制劑可以有效地預防心臟衰竭的惡化和腎臟疾病的進展和死亡。這些發現更進一步被證實在探討在患有心臟衰竭和慢性腎臟病患者的隨機對照試驗以及真實世界的研究上，不管患者本身有無糖尿病。然而，第2型鈉-葡萄糖共同轉運蛋白抑制劑對於患有動脈粥樣硬化心血管事件之病人的效應仍然存有不一致的結果。本篇文章藉由匯整臨床試驗到真實世界之研究，來回顧第2型鈉-葡萄糖共同轉運蛋白抑制劑具有心腎器官保護的證據。