ANNUAL REVIEWS

Annual Review of Medicine

SGLT2 Inhibitors: The Sweet Success for Kidneys

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Annu. Rev. Med. 2023. 74:369–84

The *Annual Review of Medicine* is online at med.annualreviews.org

https://doi.org/10.1146/annurev-med-042921-102135

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Keywords

sodium glucose cotransporter 2 inhibitor, kidney outcomes, diabetic kidney disease, nondiabetic kidney disease, acute kidney injury

Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) were originally developed as antidiabetic agents, with cardiovascular (CV) outcome trials demonstrating improved CV outcomes in patients with type 2 diabetes mellitus (T2D). Secondary analyses of CV outcome trials and later dedicated kidney outcome trials consistently reported improved kidney-related outcomes independent of T2D status and across a range of kidney function and albuminuria. Importantly, SGLT2 inhibitors are generally safe and well tolerated, with clinical trials and real-world analyses demonstrating a decrease in the risk of acute kidney injury. The kidney protective effects of SGLT2 inhibitors generally extend across different members of the class, possibly on the basis of hemodynamic, metabolic, anti-inflammatory, and antifibrotic mechanisms. In this review, we summarize the effects of SGLT2 inhibitors on kidney outcomes in diverse patient populations.

INTRODUCTION

CVOT: cardiovascular outcome trial

ASCVD: atherosclerotic cardiovascular disease

DKD: diabetic kidney disease

RAAS: renin-angiotensin-aldosterone system

KTR: kidney transplant recipient

ESKD: end-stage kidney disease

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the first class of glucose-lowering therapy approved for management of type 2 diabetes mellitus (T2D) after regulatory authorities in the United States and Europe mandated that all new antidiabetic medications undergo trials to prove their cardiovascular (CV) safety (1). These cardiovascular outcome trials (CVOTs) demonstrated the superiority of many SGLT2 inhibitors compared to placebo with respect to CV outcomes in patients with T2D who have or are at risk for atherosclerotic cardiovascular disease (ASCVD) (2–5). Interestingly, post hoc analyses of these CVOTs demonstrated evidence of kidney protection, leading to dedicated kidney outcome trials (2–6). The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial, the first dedicated kidney outcome trial, demonstrated that canagliflozin reduced the rate of the primary kidney outcome in patients with diabetic kidney disease (DKD) and severely increased albuminuria (7). The DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease) trial extended this evidence of kidney protection to patients with chronic kidney disease (CKD) with and without T2D (8). In response, the US Food and Drug Administration designated dapagliflozin a breakthrough therapy for treatment of patients with CKD irrespective of their T2D status, a first for a kidney therapy (9). SGLT2 inhibitors therefore represent one of the significant advances in nephrology in the last 2 decades, since the demonstration of kidney protection with renin-angiotensin-aldosterone system (RAAS) inhibitors in patients with DKD (10, 11).

With robust evidence of kidney protection, there is increased interest in repurposing SGLT2 inhibitors for wider applications in CKD. The EMPA-KIDNEY trial (NCT03594110), which included patients with CKD and estimated glomerular filtration rate (eGFR) as low as 20 mL/min/1.73 m^2, was recently stopped early due to evidence of efficacy (12). Other trials of varying size and scope are currently under way with the aim of exploring the effects of SGLT2 inhibition in novel populations, including kidney transplant recipients (KTRs), patients with type 1 diabetes (T1D) and DKD, and end-stage kidney disease (ESKD) patients. In this review, we briefly discuss hypothesized mechanisms of kidney protection associated with SGLT2 inhibition and summarize their effects on clinical kidney outcomes.

MECHANISMS OF KIDNEY PROTECTION WITH SGLT2 INHIBITORS

The mechanisms by which SGLT2 inhibitors exert their kidney protective effects remain incompletely understood. Systemic and glomerular hemodynamic changes, metabolic benefits, and attenuation of inflammatory and oxidative stress pathways are potential mechanisms through which SGLT2 inhibitors alter the natural disease course of CKD and are summarized in **Figure 1** (13, 14).

SGLT2 Inhibitors and Hemodynamic Effects

In the setting of ambient hyperglycemia, obligate sodium and glucose reabsorption in the proximal tubule by SGLT2 leads to decreased sodium delivery to the distal tubule and macula densa. As originally described in patients with T1D, this reduction in sodium leads to preglomerular afferent arteriolar vasodilatation via aberrant tubulo-glomerular feedback, increased glomerular pressures, and hyperfiltration, which are risk factors for kidney disease progression (15). The proximal tubular natriuresis associated with pharmacological SGLT2 inhibition restores distal sodium delivery and tubulo-glomerular feedback, leading to afferent arteriolar vasoconstriction in patients with T1D and reducing renal hyperfiltration and glomerular pressure (16, 17). This decrease in glomerular pressure is reflected by a transient GFR dip of 2–5 mL/min/1.73 m^2 after initiation

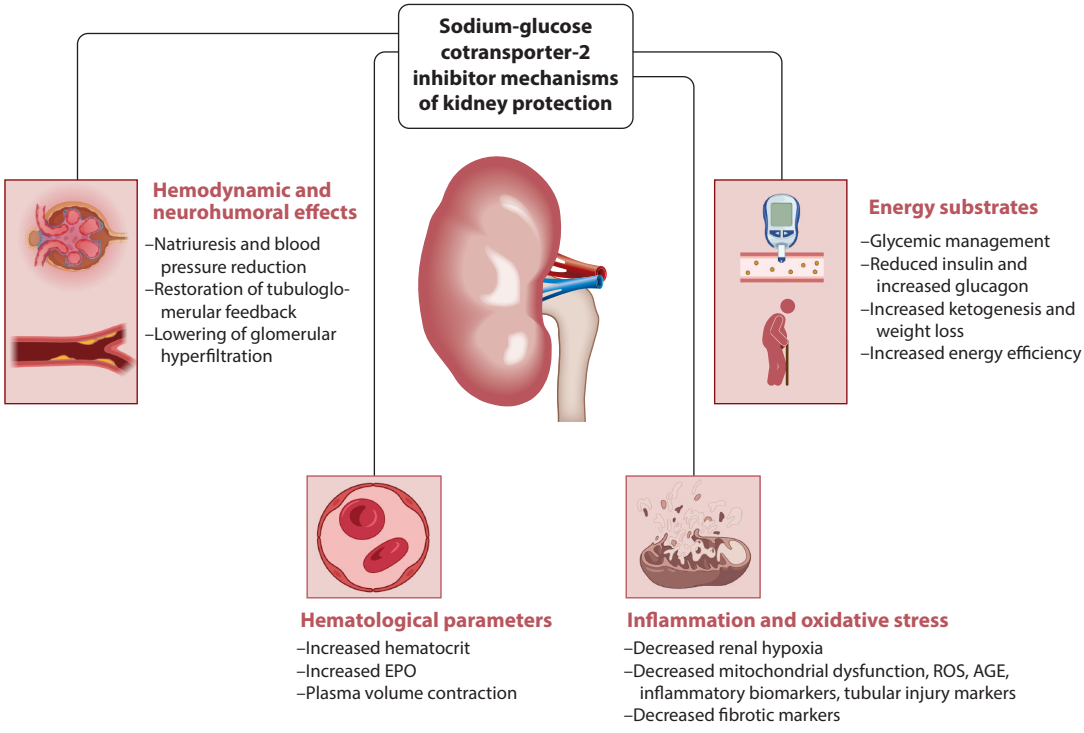

Figure 1

Effects of sodium-glucose cotransporter-2 inhibitors on systemic and renal hemodynamics, energy substrate use, hematologic parameters, and inflammation that potentially mediate observed clinical kidney protection. Abbreviations: AGE, advanced glycolytic end product; EPO, erythropoietin; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species. Figure created with BioRender.com and then adapted for this article.

of an SGLT2 inhibitor (18). Additional mechanistic studies of SGLT2 inhibition in participants with T2D have demonstrated similar reductions in glomerular pressure and GFR (19, 20). Mechanisms linked with kidney protection, including the natriuresis-related eGFR dip, appear to be similar in patients with nondiabetic CKD (8, 18, 21). Improvement in glomerular hypertension is also associated with reduction in albuminuria, which is a known surrogate marker for kidney disease progression (22).

The effects of SGLT2 inhibition on systemic hemodynamics are linked to glomerular hemodynamic changes and are also hypothesized to contribute to kidney protection. SGLT2 inhibition decreases systolic blood pressure by approximately 3–6 mm Hg and diastolic blood pressure by approximately 1–2 mm Hg (23, 24), and is also associated with reduction in arterial stiffness (25). The reduction in blood pressure is observed irrespective of hypertension status (26) and extends to patients with low eGFR (27).

SGLT2 Inhibitors and Metabolic Effect

SGLT2 inhibitors modestly improve glycemic control in patients with T2D and preserved renal function (28, 29). This effect is mediated by promoting glucosuria via inhibition of the SGLT2 transporter predominantly located in the S1 segment of the proximal convoluted tubule and responsible for absorption of 80–90% of the filtered glucose load (30). The associated caloric

loss contributes to a weight loss of approximately 1–3 kg (31). While part of this weight loss is a result of natriuresis, the majority is attributable to reduction in fat mass and is greater in patients with T2D and higher hemoglobin A1c at baseline (32, 33). By promoting glucosuria, SGLT2 inhibitors also induce an overall metabolic shift toward a fasting state, characterized by the increased use of lipids and ketones as energy substrates. This shift in metabolism may increase energy efficiency and upregulate low-energy cellular sensors, leading to decreased hypoxia and improved mitochondrial function at the cellular and organ levels (34, 35). This mechanism is hypothesized to have beneficial CV and kidney protective effects.

Effects of SGLT2 Inhibitors on Inflammatory Pathways, Oxidative Stress, and Hypoxia

Kidney protection with SGLT2 inhibition has also been attributed to anti-inflammatory pathways, with proposed ameliorations in cytokine/chemokine profiles and reductions in oxidative stress and advanced glycolytic end products, as reflected by changes in associated biomarkers (34, 36). Animal and human studies have demonstrated reductions in local reactive oxygen species generation with SGLT2 inhibition, accompanied by improvements in endothelial function (37, 38). As with reactive oxygen species, animal and human studies have consistently noted reductions in tubular injury markers and inflammatory mediators including interleukin-6, nuclear factor-κB, kidney injury molecule-1, and profibrotic factors such as transforming growth factor-β and fibronectin (39, 40). By reducing the energy expenditure involved in tubular sodium and glucose reabsorption, SGLT2 inhibitors may also attenuate renal hypoxia (13, 39). Increases in erythropoietin and hematopoiesis with SGLT2 inhibitors may be related to improvements in renal hypoxia (41). This SGLT2 inhibitor–associated increase in hematocrit is believed to be an important mediator of CV and kidney protection afforded by this class of medications (42, 43).

CLINICAL EVIDENCE OF KIDNEY PROTECTION WITH SGLT2 INHIBITORS

SGLT2 inhibitors represent a major therapeutic advance in the management of patients with CKD irrespective of their T2D status. Evidence of kidney protection has now been demonstrated in randomized controlled trials involving patients with and without T2D, who had varying degrees and types of heart and kidney disease (**Table 1**).

SGLT2 Inhibitors and Kidney Outcomes in Patients with Type 2 Diabetes Mellitus

Prespecified secondary analyses of the initial CVOTs involving SGLT2 inhibitors provided early evidence of kidney protection in patients with T2D. The EMPA-REG OUTCOME trial included 7,020 patients with T2D and established ASCVD; 25.5% of participants had a baseline eGFR <60 mL/min/1.73 m^2, 28.7% had moderately increased albuminuria, and 11.0% had severely increased albuminuria. Secondary analysis found that empagliflozin-treated patients were more likely to experience a sustained improvement from microalbuminuria [urine albumin to creatinine ratio (UACR) 30–300 mg/g] to normoalbuminuria (UACR < 30 mg/g) [hazard ratio (HR) 1.43, 95% confidence interval (CI) 1.22, 1.67] or from macroalbuminuria (UACR ≥ 300 mg/g) toward normoalbuminuria (HR 1.82, 95% CI 1.40, 2.37) (2, 22, 44). A combined analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program subsequently reported that the occurrence of the renal composite outcome of a sustained ≥40% reduction in eGFR, need for renal replacement therapy, or death from renal causes was reduced by 40% in the canagliflozin

Table 1 SGLT2 inhibitors and evidence of composite kidney outcomes from clinical trials

Study (reference)	Inclusion criteria	Renal-specific outcome	Hazard ratio (95% confidence interval)
EMPA-REG Outcome (44)	T2D patients with established CVD and eGFR ≥30 mLl/min/1.73 m^2	Composite renal outcome: dSCr accompanied by eGFR ≤45 mL/min/1.73 m^2, initiation of renal replacement therapy, or death from renal disease	0.54 (0.4, 0.75)
CANVAS Program (45)	T2D patients ≥30 years of age with history of symptomatic ASCVD or ≥50 years of age with ≥2 risk factors for CVD (T2D duration ≥10 years, SBP >140 mm Hg on ≥1 antihypertensive drugs, current smoking, micro/macroalbuminuria, HDL <1 mmol/L) and eGFR >30 mL/min/1.73 m^2	Composite renal outcome: dSCr, ESKD, or death from renal causes	0.53 (0.33–0.84)
DECLARE-TIMI 58 (46)	T2D patients ≥40 years of age having or at risk of having ASCVD and creatinine clearance ≥60 mL/min	Composite renal outcome: sustained decrease in eGFR by ≥40% to <60 mL/min/1.73 m^2, ESKD, or renal death	0.53 (0.43–0.66)
CREDENCE (7)	T2D patients ≥30 years of age and CKD (eGFR 30 to <90 mL/min/1.73 m^2 and UACR >300–5,000); on stable dose of RAAS inhibitors for at least 4 weeks before randomization	Secondary renal specific composite outcome: dSCr, ESKD, or death from renal causes	0.66 (0.53–0.81)
		Exploratory composite renal outcome: dialysis, renal transplantation, or renal death	0.72 (0.54–0.97)
VERTIS-CV (5)	T2D patients ≥40 years of age with established ASCVD	Composite renal outcome: dSCr, renal replacement therapy, or death from renal causes	0.81 (0.63–1.04)
DAPA-CKD (8)	Patients with or without T2D and CKD (eGFR 25–75 mL/min/1.73 m^2 and UACR 200–5,000); on stable dose of RAAS inhibitors for at least 4 weeks before randomization	Renal composite outcome: composite of decline in eGFR of ≥50%, ESKD, or death from renal causes	0.56 (0.45–0.68)
SCORED (53)	Adult patients with T2D and CKD (eGFR 25–60 mL/min/1.73 m^2) and additional cardiovascular risk factors	Composite renal outcome: sustained decrease of ≥50% in eGFR, dialysis, kidney transplantation, or sustained eGFR <15 mL/min/1.73 m^2 for ≥30 days	0.71 (0.46–1.08)
DAPA-HF (62)	Adult patients with or without T2D having established heart failure and a reduced ejection fraction	Composite renal outcome: worsening renal function, i.e., reduction of ≥50% in the eGFR sustained for ≥28 days; ESKD; or death from renal causes	0.71 (0.44–1.16)

(*Continued*)

Table 1 (*Continued*)

Study (reference)	Inclusion criteria	Renal-specific outcome	Hazard ratio (95% confidence interval)
EMPEROR-Reduced (63)	Adult patients having chronic heart failure with LVEF ≤40%	Composite renal outcome: chronic dialysis or renal transplantation or sustained reduction by ≥40% in eGFR or sustained eGFR <15 mL/min/1.73 m^2 in patients with baseline eGFR ≥30 mL/min/1.73 m^2 or more; or sustained eGFR <10 mL/min/1.73 m^2 in those with baseline eGFR <30 mL/min/1.73 m^2	0.50 (0.32–0.77)
EMPEROR-Preserved (64)	Adult patients having chronic heart failure with LVEF >40%	Composite renal outcome: chronic dialysis or renal transplantation or sustained reduction by ≥40% in eGFR or sustained eGFR <15 mL/min/1.73 m^2 in patients with baseline eGFR ≥30 mL/min/1.73 m^2 or more; or sustained eGFR <10 mL/min/1.73 m^2 in those with baseline eGFR <30 mL/min/1.73 m^2	0.95 (0.73–1.24)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; dSCr, doubling of serum creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HDL, high-density lipoprotein; LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin aldosterone system; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus; UACR, urine albumin to creatinine ratio.

group compared to placebo (3, 45). In the DECLARE-TIMI 58 trial, with a participant cohort at the lowest CV risk compared to the previous two CVOTs, use of dapagliflozin was associated with a 24% reduction in the composite outcome of >40% decrease in eGFR, ESKD, or death from renal or CV causes (46). In a secondary analysis of the VERTIS-CV trial, involving a study cohort with T2D and established ASCVD, ertugliflozin had a favorable placebo-adjusted eGFR slope of 0.75 mL/min/1.73 m^2/year (47). While ertugliflozin had a neutral effect on reducing the incidence of the kidney composite outcome that included doubling of serum creatinine, a secondary analysis reported a significant reduction of the kidney composite outcome comprising sustained ≥40% reduction in eGFR, dialysis/transplant, or renal death and also other kidney-related outcomes, which is generally consistent with other members of the drug class (48–50).

Results from CVOTs demonstrated CV and kidney benefits independent of baseline kidney function, CV risk, or glycemic control (51). However, the study cohorts in these CVOTs were not enriched for clinical kidney outcomes, with few participants having advanced CKD or significant albuminuria at baseline. The question of kidney protection with SGLT2 inhibition in those with established proteinuric DKD was first evaluated in CREDENCE, a dedicated kidney outcome trial that included patients with T2D, albuminuria, and baseline eGFR of 30–90 mL/min/1.73 m^2 (7). The mean baseline eGFR was 56.2 mL/min/1.73 m^2 with a median UACR of 927 mg/g; 30% of participants had an eGFR < 45 mL/min/1.73 m^2, and 88% had a UACR > 300 mg/g.

CREDENCE was terminated early after a median follow-up of 2.62 years due to evidence of efficacy, and the primary composite outcome of doubling of serum creatinine, ESKD, or renal

or CV death was reported 30% lower in the canagliflozin-treated group. The rate of decline in eGFR was significantly reduced in those receiving canagliflozin compared to placebo (–1.85 ± 0.13 versus –4.59 ± 0.14 mL/min/1.73 m^2/year). To put this into perspective, compared to placebo-treated participants (including baseline RAAS inhibition), treatment of the average CREDENCE participant with canagliflozin has been theorized in modeling exercises to delay ESKD by more than 15 years (52). Importantly, the CREDENCE findings were independent of baseline eGFR, baseline UACR, glycemic status, type of RAAS blockade, and ASCVD (7).

In addition to CREDENCE, the SCORED trial also examined the impact of sotagliflozin, a dual SGLT1 and -2 inhibitor in patients with T2D and CKD with a median eGFR of 44.5 mL/min/1.73 m^2. While this was not a dedicated kidney outcome trial, it did report a 29% reduction in the secondary kidney composite outcome of a sustained ≥50% decrease in eGFR or ESKD. Although this result was not statistically significant, it is worth noting that the trial was stopped prematurely due to a loss in funding, with a median follow-up duration of 16 months (53). The DAPA-CKD and EMPA-KIDNEY trials, while including patients with and without T2D, had sizable populations with DKD (DAPA-CKD 67%, EMPA-KIDNEY 31%). Both these trials will be discussed in subsequent sections.

Kidney protective effects of SGLT2 inhibitors in patients with DKD have since been mirrored in real-world analyses. In CVD-REAL 3, a real-world study of patients with T2D, the initiation of SGLT2 inhibitor therapy was associated with a slower rate of kidney function decline and lower risk of major kidney events compared with initiation of other glucose-lowering drugs (54). Similarly, a Scandinavian cohort study observed that use of SGLT2 inhibitors was associated with a significantly reduced risk of serious kidney events, when compared with dipeptidyl peptidase-4 inhibitors (55). These data suggest that observed kidney benefits in the rigorous trial setting appear to be generalizable to clinical practice.

SGLT2 Inhibitors and Kidney Outcomes in Patients with Nondiabetic Kidney Disease

Subgroup analyses of CVOTs performed in participants with T2D demonstrated that kidney benefits with SGLT2 inhibitors are independent of glycemic control, leading to significant interest in studying these agents in patients without T2D. In a combined human–rodent pilot study, 8-week treatment with dapagliflozin did not modify renal hemodynamic function or attenuate proteinuria in human or experimental focal segmental glomerulosclerosis (FSGS). This was attributed to downregulation of SGLT2 expression in individuals with FSGS (56). Subsequently, the DIAMOND trial evaluated effects of dapagliflozin in 53 patients without DKD. This was a 6-week crossover trial with a mean measured GFR (mGFR) of 58.3 mL/min/1.73 m^2 and median proteinuria of 1,110 mg/24 h (18). The main finding was that dapagliflozin induced an acute and reversible decline in mGFR, a phenomenon associated with reduced glomerular pressure and with kidney protection (57). Dapagliflozin also resulted in a 17% reduction in UACR, though this was not statistically significant, possibly due to short duration of the study.

DAPA-CKD was the first dedicated kidney outcome trial to assess the efficacy of SGLT2 inhibition in CKD patients with and without T2D (8). DAPA-CKD enrolled 4,304 participants with CKD, with a mean eGFR of 43.1 mL/min/1.73 m^2 and median UACR of 949 mg/g. About one-third of participants did not have T2D. Dapagliflozin was safe and significantly reduced the risk of the primary composite endpoint (≥50% eGFR decline, ESKD, or renal or CV death) by 39% versus placebo, with a number needed to treat of 19 to prevent one primary outcome event. These results were consistent among patients with and without T2D.

When analyzing participants of DAPA-CKD by CKD etiology, the largest subgroup among participants without T2D was the group with chronic glomerulonephritis. Of these 695 (16.1%)

participants, 270 had immunoglobulin A nephropathy (IgAN) (58). This makes DAPA-CKD one of the largest clinical trials involving patients with IgAN (59). In a prespecified analysis of participants with IgAN (mean eGFR 43.8 mL/min/1.73 m^2, median UACR 900 mg/g), a hazard ratio of 0.29 (95% CI 0.12, 0.73) for the primary outcome was observed with dapagliflozin, and UACR was reduced by 26% compared to placebo (60). In another prespecified analysis of the DAPA-CKD trial involving 104 individuals with biopsy-proven FSGS, dapagliflozin reduced the primary composite kidney outcome by 38% (95% CI 0.17, 2.17). While this is not statistically significant, the number of events in this participant subgroup was low. Importantly, the annual mean rate of eGFR decline was lower in those receiving dapagliflozin (–1.9 mL/min/1.73 m^2, 95% CI −3.0, −0.9) compared to placebo (–4.0 mL/min/1.73 m^2, 95% CI −4.9, −3.0) (61).

Heart failure patients with concurrent CKD represent another large population at risk of adverse kidney outcomes. DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) was the first trial to evaluate the efficacy of SGLT2 inhibition in patients with heart failure and reduced ejection fraction (HFrEF) and included patients with eGFRs as low as 30 mL/min/1.73 m^2. Although reduction in rates of the kidney composite outcome was not significant, the rate of eGFR decline was significantly slower with dapagliflozin (mean –1.09 versus –2.85 mL/min/1.73 m^2/year) (62).

The EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) and EMPEROR-Preserved trials assessed the effect of empagliflozin in more than 13,000 subjects with HFrEF and HFpEF (heart failure and preserved ejection fraction). About 50% of participants did not have T2D and had an eGFR < 60 mL/min/1.73 m^2. In both the trials, patients with baseline eGFRs as low as 20 mL/min/1.73 m^2 were enrolled, and empagliflozin significantly attenuated the rate of eGFR decline compared to placebo independent of the baseline kidney function (63, 64).

These studies offer strong and compelling evidence for the use of SGLT2 inhibitors in nondiabetic CKD to complement current standard-of-care therapies. However, the effectiveness of these agents in reducing adverse kidney outcomes remains to be clarified in certain populations, as discussed in the next section.

NEW POTENTIAL AVENUES FOR SGLT2 INHIBITOR USE IN KIDNEY DISEASE

Despite the availability of robust evidence on the use of SGLT2 inhibition in T2D, heart failure, and CKD with albuminuria, there remains a lack of data on multiple subgroups of CKD at high risk of progression to ESKD and adverse CV outcomes.

SGLT2 Inhibitors and Kidney Outcomes in Patients with Type 1 Diabetes Mellitus

Recent advances in therapies for DKD in the setting of T2D have failed to carry over to patients with T1D. Despite optimal blood pressure, RAAS blockade, and glycemic control, a significant proportion of patients with T1D develop DKD. Unfortunately, it is unknown if kidney benefits of SGLT2 inhibitors observed in T2D extend to DKD in the setting of T1D, since these patients were excluded from most cardiorenal outcome trials. Considering that the cardiorenal protective effects of SGLT2 inhibitors are independent of insulin and glycemic control, there is likely overlap between the mechanisms underlying end-organ protection in patients with T2D and the mechanisms in patients with T1D. Accordingly, there is a strong theoretical basis for SGLT2 inhibitors as an option to prevent the progression of DKD in individuals with T1D.

Few studies have investigated the beneficial effects of SGLT2 inhibitors in patients with T1D and DKD. A pooled 52-week analysis of the inTandem1 and inTandem2 trials evaluated the effect of sotagliflozin 200 mg and 400 mg versus placebo in 1,575 adults with T1D (65). Sotagliflozin induced a significant dip in eGFR at 4 weeks—200 mg: –2.5 mL/min/1.73 m^2 [standard error (SE) 0.63], $p < 0.0001$; 400 mg: –2.8 mL/min/1.73 m^2 (SE 0.63), $p < 0.0001$. Effects on eGFR were accompanied by significant reductions in blood pressure and body weight. Although most participants were normoalbuminuric at baseline, in the subgroup with UACR ≥ 30 mg/g, significant reductions in albuminuria were reported with sotagliflozin 400 mg compared to placebo.

A similar analysis was performed in the EASE program, which included two phase III randomized controlled trials of empagliflozin conducted over 52 weeks (EASE-2) and 26 weeks (EASE-3) in patients with T1D (66). As with the inTANDEM analysis, EASE-2 and 3 showed acute and sustained reductions in eGFR with different doses of empagliflozin. In a pooled analysis of EASE-2 and EASE-3, in participants with baseline UACR ≥ 30 mg/g, albuminuria decreased by 16% ($p = 0.27$) and 30% ($p = 0.02$) with empagliflozin 10 mg and 25 mg, respectively (67).

These findings were confirmed in a secondary kidney analysis of the DEPICT-1 and DEPICT-2 (Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes–2) trials, conducted in 251 participants with baseline albuminuria randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo. As with empagliflozin, there were dose-dependent reductions in UACR, as well as reductions in blood pressure and body weight (68). Taken together, these analyses of phase III trials in participants with T1D suggest that mechanisms associated with cardiorenal protection are intact in this population, with the caveat that patients with reduced eGFR or significant albuminuria made up a small proportion of participants in these trials.

SGLT2 Inhibitors in Advanced Chronic Kidney Disease

There is now emerging evidence of kidney protection with SGLT2 inhibition in patients with stage 4 CKD. DAPA-CKD included 624 (14%) participants with eGFR < 30 mL/min/1.73 m^2. In patients randomized to dapagliflozin, a 29% reduction (95% CI 0.49, 1.02) in the renal composite endpoint of 50% sustained decline in eGFR, ESKD, or kidney death was observed. Furthermore, there was no detectable heterogeneity based on diabetes status or degree of albuminuria (69). In the EMPEROR-Reduced trial, 204 patients had stage 4 CKD at baseline, and the effect of empagliflozin on kidney outcomes was similar across eGFR categories (63). In a phase III trial of 277 patients with stage 4 CKD and a mean eGFR of 23.6 mL/min/1.73 m^2, who were treated with sotagliflozin or placebo for 52 weeks, SGLT2 inhibition resulted in an acute eGFR dip and significant reductions in UACR consistent with the activation of kidney protective mechanisms (70).

The EMPA-KIDNEY trial will extend evidence of kidney protection to the lowest eGFR range, having enrolled participants with or without T2D and with eGFR 20–45 mL/min/1.73 m^2 regardless of albuminuria, or eGFR 45–90 mL/min/1.73 m^2 with UACR ≥ 200 mg/g on maximally tolerated RAAS inhibitor. This is the largest SGLT2 inhibitor trial in CKD patients, with 6,609 participants. Their mean eGFR is 37.5 mL/min/1.73 m^2 and median UACR is 412 mg/g. This trial was recently stopped early due to evidence of efficacy, and final results are awaited (12).

SGLT2 Inhibitors in End-Stage Kidney Disease

In observational analyses, residual kidney function (RKF)—defined as the residual clearance of creatinine and urea provided by the remaining functional nephrons in a person with ESKD—is associated with reduced mortality among adults undergoing dialysis. Given that initiation of renal replacement therapy generally occurs at an eGFR of 5–10 mL/min/1.73 m^2 (71, 72), most adults starting dialysis have some RKF. However, with increasing time on dialysis, there is progressive loss of RKF, which also contributes to morbidity and mortality in patients on dialysis (73, 74).

In peritoneal dialysis (PD), RKF also enables less intensive dialysis that may reduce the toxicity induced by glucose and related degradation products on the peritoneal membrane and systemically (75), potentially leading to lower rates of PD treatment failure. Given the importance of RKF in dialysis, strategies that protect RKF may also reduce mortality. To date, RAAS inhibition is the only pharmacological strategy with some evidence for RKF preservation in dialysis patients (76, 77).

There is minimal clinical trial evidence for the use of SGLT2 inhibitors in dialysis in general. For reasons that remain unclear, SGLT2 inhibition has been shown in animal studies to reduce peritoneal fibrosis and improve peritoneal ultrafiltration, potentially allowing for the use of lower glucose concentrations in PD solutions (78, 79). The pharmacokinetics and pharmacodynamics of the SGLT2 inhibitor empagliflozin were studied in eight patients with ESKD, with no observed difference in half-life compared to individuals with normal renal function, and no differences in the area under the curve compared to individuals with mild, moderate, and severe kidney dysfunction (80). The DECODED trial (NCT04764097) aims to study CV benefits of dapagliflozin in hemodialysis patients, though it does not include RKF as an inclusion criterion nor as an outcome measure.

SGLT2 Inhibitors in Kidney Transplant Recipients

The burden of diabetes and CV disease is high in KTRs, making SGLT2 inhibitors an attractive option in this population. However, there are minimal data on their safety and efficacy in KTRs. In the only randomized clinical trial to date, Halden et al. (81) randomized 44 stable KTRs with post-transplant diabetes mellitus to empagliflozin or placebo for 24 weeks. An analysis of kidney function data revealed that eGFR was significantly reduced in the empagliflozin group after 8 weeks of treatment (–4 mL/min/1.73 m^2) compared with the placebo group (–1 mL/min/1.73 m^2), consistent with a reduction in glomerular pressures. Treatment with empagliflozin also resulted in significant reductions in body weight and improvements in glycemic control while being well tolerated (81). The INFINITI trial (NCT04965935) is a mechanistic trial enrolling KTRs with and without diabetes currently underway at our center. The impact of SGLT2 inhibition on longer term kidney outcomes as well as safety in KTRs has generated significant interest in long-term cardiorenal outcome trials in this population (82, 83).

THE SAFETY OF SGLT2 INHIBITORS

The safety profile of SGLT2 inhibitors has been consistent across glycemic control trials, as well as trials examining CV safety, CKD, and heart failure endpoints. In summary, the most common side effect with this class is genital mycotic infections, as described elsewhere (84, 85). Diabetic ketoacidosis (DKA) risk is also increased in those with T2D but it is fortunately extremely rare.

SGLT2 Inhibitors and Diabetic Ketoacidosis

A serious adverse event associated with SGLT2 inhibition therapy is DKA. SGLT2 inhibitors reduce blood glucose through increased glucosuria, thereby inducing a pseudofasting state where the body relies more heavily on fats for energy (24). This, in turn, reduces insulin requirements while also increasing glucagon levels. Additionally, there may be a direct effect of SGLT2 inhibition on alpha cells (86). Together, these changes promote the production of ketones, which serves as an alternative to glucose for energy production and metabolism (15). This increase in ketogenesis is hypothesized to contribute to the cardioprotective effects of SGLT2 inhibitors, but it also increases the risk of DKA (87, 88). The rate of DKA in clinical trials is 0–2.2% in patients with

T2D but 4–6% when used in combination with insulin in patients with T1D (89, 90). While DKA is a major concern in the use of SGLT2 inhibitors in T1D, patient-reported outcome studies have shown that after receiving education about the benefits and risks of SGLT2 inhibitors, patients with T1D preferred the use of SGLT2 inhibitors as an adjunct-to-insulin therapy, even when DKA risk was identified as the most important safety and efficacy attribute for these patients (91).

Appropriate patient selection and DKA mitigation strategies that are beyond the scope of this review will be important aspects of reducing the risk of DKA (92). The EASE trials have shown that lower doses of SGLT2 inhibitors can substantially decrease the risk of DKA and still have glucosuric effects (66).

SGLT2 Inhibitors and Acute Kidney Injury

Due to the initial hemodynamic effect with SGLT2 inhibitors leading to an eGFR dip, there were early concerns that these therapies, like RAAS inhibitors, could promote acute kidney injury (AKI). These concerns were largely based on AKI reports in the US Food and Drug Administration Adverse Event Report System. Clinical trials and real-world analyses have since revealed otherwise and have in fact demonstrated a reduction in the risk of AKI (93, 94). Meta-analyses of clinical trials involving SGLT2 inhibitors have reported that the risk of AKI is reduced by 25–41%, consistent across studies (95, 96). Real-world analyses comparing SGLT2 inhibitors with other antidiabetic agents have also reported that AKI risk was reduced by 21–53% in SGLT2 inhibitor users (97, 98). While these data are reassuring, guidelines continue to recommend that patients follow "sick-day" rules and not receive SGLT2 inhibitor during periods of illness or hospitalization (99).

CONCLUSION

Clinical trials and real-world analyses have consistently shown improved kidney outcomes with SGLT2 inhibitors, irrespective of diabetes status and across a range of levels of kidney function and albuminuria. SGLT2 inhibitors are now part of treatment algorithms for the management of patients with T2D and CKD (100). The clinical and research communities require additional data to understand how these benefits may expand the use of SGLT2 inhibitors into novel applications in patients with CKD. Further work is also required to implement the results of these trials in practice, including the removal of barriers related to cost, access, and education.

DISCLOSURE STATEMENT

D.Z.I.C. has received consulting fees and/or honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, Abbvie, Janssen, Bayer, Prometic, BMS, Maze, Gilead, CSL-Behring, Otsuka, Novartis, Youngene, and Novo-Nordisk and has received operational funding for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen, Sanofi, AstraZeneca, CSL-Behring, and Novo-Nordisk. No potential conflicts of interest relevant to this article were reported by A.D., A.K., or V.S.S.

ACKNOWLEDGMENTS

D.Z.I.C. is supported by a Department of Medicine, University of Toronto Merit Award and receives support from the Canadian Institutes of Health Research (CIHR), Diabetes Canada, and the Heart and Stroke Richard Lewar Centre of Excellence. He is also the recipient of a CIHR–Kidney Foundation of Canada Team Grant. V.S.S. is supported by the Department of Medicine Eliot Phillipson Clinician Scientist Training Program and a Banting and Best Diabetes Centre postdoctoral fellowship at the University of Toronto.

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