

Are SGLT2 Inhibitors Ready for Prime Time for CKD?

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Introduction

Sodium-glucose cotransporter-2 (SGLT2) is a sodium-dependent glucose transport protein, and its inhibitors (SGLT2i - gliflozins) are indicated as an adjunct therapy to diet and exercise for improving glycemic control in type 2 diabetes mellitus (DM2). In fact, SGLT2i usage has been associated with a robust hemoglobin A1c (HbA1c) reduction of 0.5%–0.6%, sustained over 52 weeks of follow-up (1).

Because of their unique mechanism of action, SGLT2i have a range of effects that may translate to potential benefits beyond glycemic control, including BP and weight reduction. A meta-analysis assessing effects on BP, indicated a 2.46 mm Hg reduction in systolic BP following treatment with SGLT2i. The mean difference in diastolic BP was 1.46 mm Hg, and in body weight was 1.88 kg (2). Interestingly, these factors are clearly associated with the risk of not only cardiovascular (CV) disease, but kidney disease also.

This article reviews the current and forthcoming knowledge relating to clinical trials of SGLT2i and its effect on kidney disease.

Main Kidney Findings in the Published Clinical Trials

SGLT2i consistently cause an acute reduction in GFR by approximately 5 ml/min per 1.73 m², as well as a consistent 30%–40% reduction in albuminuria (3). The GFR effect led to initial concern that SGLT2i may increase the risk of AKI. These data support mechanistic studies that suggest proximal tubular natriuresis activates tubule-glomerular feedback through increased macula densa sodium delivery, leading to afferent arteriole vasoconstriction and reduction in intraglomerular pressure (4).

As the glycosuric effects are dependent on glomerular filtration, it is not surprising that these effects are attenuated in patients with a reduced GFR. In contrast, BP lowering, albuminuria lowering effects, and impact on eGFR are preserved in patients with CKD. These data suggest that SGLT2i may have beneficial kidney effects, even in people with reduced kidney function, where glycemic benefits are limited (5). Interestingly, a recent study suggested that canagliflozin slows the progression of kidney function decline independently of effects on glycemia (6).

These observations motivated the development of clinical trials to test the hypothesis that SGLT2i may be a kidney protective treatment. Two major studies describing the impact of the drugs on long-term kidney

outcomes have been reported. In combination with other ongoing clinical trials (Table 1), these studies may shift the therapeutic paradigm in diabetic kidney disease, and perhaps other progressive kidney diseases, expanding the options available to patients.

Firstly, the long-term kidney effects of empagliflozin on kidney outcomes were reported from the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EmpaRegOutcome Trial) (7,8). Participants with DM2 and CV disease, and an eGFR of at least 30 ml/min per 1.73 m², were randomized to receive either empagliflozin or the placebo. Empagliflozin demonstrated a significantly lower risk of major adverse CV events, consisting of myocardial infarction, stroke, or CV death (hazard ratio [HR], 0.86; 95% confidence interval [95% CI], 0.74 to 0.99).

Prespecified kidney outcomes included incident or worsening nephropathy (macroalbuminuria, doubling of creatinine, initiation of RRT, or death from kidney disease) and incident albuminuria. New or worsening kidney disease occurred less frequently (12.7%) in the empagliflozin group compared with placebo (18.8%) (HR, 0.61; 95% CI, 0.53 to 0.70; $P < 0.001$). Doubling of serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 patients (2.6%) in the placebo group (HR, 0.56; 95% CI, 0.40% to 0.75%). RRT was initiated in a lower proportion of the empagliflozin group (13 of 4687 patients [0.3%]) compared with 14 of 2333 patients (0.6%) in the placebo group, (HR, 0.45; 95% CI, 0.21% to 0.97%; $P < 0.05$); however, the small numbers suggest that the results should be interpreted cautiously. Although these kidney outcomes were not confirmed or adjudicated during the trial, *post hoc* assessment of confirmed outcomes showed similar results (9).

More recently, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (9) randomized DM2 patients (in contrast to EMPA-REG, as it also included a primary CV prevention cohort) to receive canagliflozin or placebo. The rate of the primary outcome (composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) was lower with canagliflozin than with placebo (HR, 0.86; 95% CI, 0.75 to 0.97). Kidney outcomes were also prespecified. Patients allocated to canagliflozin had a lower risk of progression of albuminuria (HR, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in eGFR, need for RRT, or death from kidney causes (HR, 0.60; 95% CI, 0.47 to 0.77). In terms of adverse events, CANVAS data

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Table 1. Comparative description of the major SGLT2i studies including a kidney endpoint

Name Of the Study	EMPA-REG OUTCOME	CANVAS/CANVAS R	DECLARE	VERTIS	CREDESCENCE	DAPA-CKD	EMPAGLIFLOZIN RENAL
Clinical trial registration	NCT01131676	NCT01032629 and NCT01989754	NCT01730534	NCT01986881	NCT02065791	NCT03036150	TBA
Intervention	Empagliflozin versus placebo	Canagliflozin versus placebo	Dapagliflozin versus placebo	Ertugliflozin versus placebo	Canagliflozin versus placebo	Dapagliflozin versus placebo	Empagliflozin versus placebo
Patient population	DM2, high CV risk	DM2, high CV risk	DM2, high CV risk	DM2, established vascular disease	DM2, high CV risk	DM2 and nonpatients with diabetes, high CV risk	DM2 and nonpatients with diabetes, high CV risk
Kidney function inclusion criteria	eGFR \geq 30 ml/min per 1.73 m ²	eGFR \geq 30 ml/min per 1.73 m ²	eGFR \geq 30 ml/min per 1.73 m ²	eGFR \geq 30 ml/min per 1.73 m ³	30 \geq eGFR \leq 90 ml/min per 1.73 m ² (CKD 2 and 3)	30 \geq eGFR \leq 90 ml/min per 1.73 m ³ (CKD 2 and 3)	30 \geq eGFR \leq 90 ml/min per 1.73 m ⁴ (CKD 2 and 3)
Number of patients	7021	10,142	17,276	8000 (estimated)	4461	4000 (estimated)	TBA
Prespecified renal endpoints	Incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of RRT, or death from renal disease) and incident albuminuria	Progression to albuminuria, sustained 40% reduction in the eGFR, the need for RRT, or death from renal causes	Time to first event of renal composite endpoint: Confirmed sustained \geq 40% decrease in eGFR to eGFR $<$ 60 ml/min per 1.73 m ² and/or ESRD and/or renal or CV death	Time to composite of renal death, renal dialysis/transplant, or \geq 2 \times increase in baseline serum creatinine	Time to the first occurrence of an event in the primary composite endpoint (primary) ESRD, doubling of serum creatinine, renal or CV death	Time to the first occurrence of any of the components of the composite: \geq 50% sustained decline in eGFR or reaching ESRD or CV death or renal death	TBA
Outcomes	A 44% relative risk reduction of doubling of SCr (1.5% versus 2.6%); 38% relative risk reduction of progression to macroalbuminuria (11.2% versus 16.2%); 55% relative risk reduction of initiation of RRT (0.3% versus 0.6%); slowing GFR decline (annual decrease 0.19 \pm 0.11 versus 1.67 \pm 0.13 ml/min per 1.73 m ² ; P $<$ 0.001).	Reduction in the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the eGFR, the need for RRT, or death from renal causes	In progress, estimated completion in April of 2019	In progress, estimated completion in October of 2019	In progress, estimated completion in June of 2019	In progress, estimated completion in November of 2020	TBA

eGFR is in milliliters per minute per 1.73 m². Urine albumin-to-creatinine ratio is in milligrams per gram. EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; CANVAS/CANVAS R, Canagliflozin Cardiovascular Assessment Study; DECLARE, Dapagliflozin Effect on Cardiovascular Events; VERTIS, Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease; CREDESCENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy; DAPA-CKD, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With CKD; EMPAGLIFLOZIN RENAL, Empagliflozin Trial Kidney Outcome Trial in Chronic Kidney Disease; NCT, ClinicalTrials.gov Identifier, TBA, to be announced; DM2, diabetes mellitus type 2; CV, cardiovascular; SCr, serum creatinine; 95% CI, 95% confidence interval.

suggested a higher incidence of amputations in the treatment arm, which had not been reported from previous studies.

Additional trials assessing the CV safety of SGLT2i with prespecified kidney endpoints will complete over coming years. First, the Dapagliflozin Effect on Cardiovascular Events (DECLARE) study will analyze the effect of dapagliflozin on CV outcomes when added to current background therapy in patients with DM2 (and either established CV disease, or CV risk factors). Kidney outcomes are also going to be compared, since DECLARE captures a predefined secondary kidney composite endpoint (sustained \geq 40% decrease in eGFR to eGFR $<$ 60 ml/min per 1.73 m² and/or ESRD and/or kidney or CV death). Finally, the Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS) trial will assess the CV safety of ertugliflozin and includes a predefined secondary kidney endpoint, namely a composite of kidney death, ESRD, or a doubling of baseline creatinine.

Knowledge Gaps and Future Studies

The results of the EMPA-REG OUTCOME and CANVAS trials are encouraging with regards to a potential impact of SGLT2i on kidney outcomes in people with diabetes.

However, there are knowledge gaps that will need to be addressed before this strategy can be considered routine therapy for this indication and perhaps expanded in kidney diseases not related to diabetes.

First, both above-cited studies considered kidney events as exploratory endpoints and, therefore, were not designed to provide definitive information related to renoprotection. The fact that EMPA-REG OUTCOME and CANVAS provided consistent information regarding effects on albuminuria, a well recognized surrogate marker of risk in diabetic kidney disease, and prespecified but exploratory kidney outcomes is highly encouraging, but requires confirmation in dedicated kidney outcome trials.

Importantly, the number of patients reaching ESRD, the most clinically relevant endpoint for kidney disease progression, is also far smaller than is necessary to draw definitive conclusions (27 events in EMPA-REG OUTCOME and 21 in CANVAS). More data regarding the effects on these outcomes is urgently required.

Another very relevant unanswered question is whether SGLT2i can decrease kidney and CV risk in the population with established CKD. A pooled analysis of 11 phase 3 dapagliflozin clinical trials that assessed changes in HbA1c, body weight, BP, and hematocrit over 24 weeks in patients

with DM2 according to baseline eGFR (eGFR \geq 45 to <60 ml/min per 1.73 m², eGFR \geq 60 to <90 ml/min per 1.73 m², and eGFR \geq 90 ml/min per 1.73 m²) showed that the HbA1c-lowering effects of dapagliflozin decrease as kidney function declines; however, dapagliflozin consistently decreases body weight, BP, and urinary albumin-to-creatinine ratio regardless of eGFR. Similar findings have been reported for other SGLT2 inhibitors, and highlight the possibility that effects on clinically important outcomes might differ in people with reduced kidney function.

Therefore, properly powered studies with a primary aim to assess the effects on important kidney endpoints (especially ESRD) are still crucial to understand the role of SGLT2i in kidney disease. It will also be important that such trials recruit substantial numbers of participants with reduced kidney function, to allow assessment of the consistency or otherwise of effects across the spectrum of kidney function. This information will be available over coming years, when the results of dedicated kidney outcome trials will be reported. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE) trial is a randomized, controlled trial aiming to assess the impact of canagliflozin in reducing the progression of kidney impairment relative to placebo in participants with DM2, stage 2 or 3 CKD, and macroalbuminuria. The primary composite endpoint includes ESRD, doubling of serum creatinine, and kidney or CV death. It has recruited over 4400 participants, including a majority with eGFR<60, and is expected to report its main results in 2019 (Table 1).

Finally, SGLT2i has been shown to slow the progression of kidney function decline independently of glycemic effects (6). Together with the unique mechanism of action of these drugs, which impact the kidney hemodynamics, this observation raises the hypothesis that their impact could also translate into improved kidney outcomes in nonpatients with diabetes. Whether this is true, and the magnitude of any effects, will need to be proven in specifically designed clinical studies. The ongoing trial, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With CKD (DAPA CKD), is recruiting patients with established CKD as an inclusion criterion (half nondiabetic), randomized to dapagliflozin or placebo and will follow them until the time to the first occurrence of the composite of \geq 50% sustained decline in eGFR, ESRD, or CV or kidney death (Table 1). The study is powered to show a kidney benefit also in the subgroup of nonpatients with diabetes. Similarly, a trial of empagliflozin on kidney outcomes in established kidney disease (including those with and without diabetes) has recently been announced (press release), and will shed light on potential kidney benefits of this class of agents outside of the established indication in diabetes.

Conclusions

SGLT2i are an effective glucose lowering therapy for people with DM2, and the first two members of the studied class show overall CV benefit, but also suggest the possibility of dramatic kidney protection in DM2. Future studies will test these hypotheses formally in dedicated kidney outcome trials and may offer the potential to dramatically

reduce the risk of kidney failure in people with diabetes. They will also provide important additional information regarding the safety and efficacy of SGLT2i in people with established CKD, and in people with nondiabetic kidney disease.

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See related article, “Effects of Diabetes Medications Targeting the Incretin System on the Kidney,” on pages 321–323.