CLINICAL FOCUS: DIABETES
REVIEW

SGLT2 inhibitors in patients with type 2 diabetes and renal disease: overview of current evidence

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ABSTRACT
Chronic kidney disease (CKD) is a frequent complication of type 2 diabetes mellitus (T2DM) and is associated with poor clinical outcomes, including an increased risk of all-cause and cardiovascular mortality, as well as adverse economic and social effects. Slowing the development and progression of CKD remains an unmet clinical need in patients with T2DM. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are widely used for the management of T2DM and have effects beyond glucose lowering that include cardiovascular benefits and potential renoprotective effects. Although the glucose-lowering efficacy of these agents is dependent on renal function, the cardiovascular and renal benefits of SGLT2 inhibition appear to be maintained to estimated glomerular filtration levels as low as 30 mL/min/1.73 m². Clinical evidence has indicated that these agents can reduce the risk of development or worsening of albuminuria, a marker of renal damage, through a range of mechanisms. These include blood pressure lowering, reduction of intraglomerular pressure and hyperfiltration, modification of inflammatory processes, reduction of ischemia-related renal injury, and increases in glucagon levels. The blood pressure-lowering effect of SGLT2 inhibitors is maintained in people with CKD and could further contribute to reduced renal burden, as well as potentially offering synergistic effects with antihypertensive therapies in these patients. Several cardiovascular outcomes trials (CVOTs) have included renal endpoints, adding to the growing evidence of the potential renoprotective effects of these agents in patients with T2DM. Several ongoing dedicated renal outcomes trials will provide further guidance on the potential clinical role of SGLT2 inhibitors in slowing the development and progression of renal impairment in individuals with T2DM.

1. Introduction
Individuals with type 2 diabetes (T2DM) frequently have concurrent chronic kidney disease (CKD), characterized by persistent albuminuria, decline in glomerular filtration rate (GFR), rising blood pressure, and increased cardiovascular (CV) risk [1,2]. In the United States, the crude prevalence of CKD (stages 1–4) among adults (aged ≥20 years) with diagnosed diabetes was 36.5% (95% confidence interval [CI], 32.2–40.8) during 2011–2012 [3]. The presence of CKD in patients with T2DM is of particular clinical importance as it is associated with an increased risk of both all-cause and CV mortality [4]. Moreover, increases in mortality and poor clinical outcomes have been observed in patients with early indications of CKD progression, such as reductions in estimated glomerular filtration rate (eGFR) that are below usual thresholds (less than a doubling of serum creatinine concentration) [5], and also in patients with asymptomatic microalbuminuria [6,7]. The occurrence of clinical complications, including CKD and the need for renal dialysis, is expected to rise among older patients with T2DM as the prevalence of T2DM continues to rise in the United States and globally [8,9].

In addition to clinical consequences, CKD has economic and social effects, including increased use of health care resources and the associated costs to individual patients and health care providers [10,11], and a reduction in health-related quality of life (HRQOL) in line with the severity of the renal impairment [12]. Despite the availability of treatments, patients with early-stage diabetic kidney disease may be undertreated and are at risk of progression to more advanced stages of renal impairment [13]. There remains a need for early intervention with treatments that can prevent or delay the progression of micro- or macroalbuminuria in patients with T2DM.

2. SGLT2 inhibitors in the management of T2DM
Sodium-glucose co-transporter 2 (SGLT2) inhibitors are widely used antidiabetes drugs that improve glycemic control, reduce body weight, and lower hypertension, with no associated increase in pulse rate, in patients with T2DM [14–20]. Four SGLT2 inhibitors are currently approved in the United States for use in the improvement of glycemic control in adults with T2DM (dapagliflozin [21], canagliflozin [22], empagliflozin [23],
and ertugliflozin [24]). In addition to the glucose-lowering effects of SGLT2 inhibitors, empagliflozin is also indicated for the reduction of risk of CV death in patients with T2DM and established CV disease (CVD) [23], and similar label expansion has been recently approved for canagliflozin, which is indicated to reduce the risk of major adverse CV events (MACE) in adults with T2DM and established CVD [25]. Furthermore, evidence suggests that SGLT2 inhibitors might confer renoprotective effects, leading to reduction in the rate of progression of diabetic kidney disease [26].

SGLT2 inhibitors have a unique mechanism of action that is independent of insulin or insulin sensitivity, and results from inhibition of SGLT2 in the proximal tubule of the kidney [27]. The mechanism of action of SGLT2 inhibitors has been described in detail previously and is summarized here [28,29]. SGLT2 is a transport protein responsible for the reabsorption of approximately 90% of filtered glucose, the remainder being absorbed by another transporter protein, sodium-glucose co-transporter 1 (SGLT1). Inhibition of SGLT2 results in a reduction in renal capacity for glucose reabsorption by approximately 50%. Preclinical research suggests that glycosuria may not be the only mechanism of glucose-lowering of SGLT2 inhibitors: at least one agent appears to also suppress hepatic glucagon signaling by downregulation of hepatic glucagon receptors [30]. Overall, the glucose-lowering effect of SGLT2 inhibition results from glycosuria [28] and is associated with improvements in glycemic control and reductions in glycated hemoglobin (HbA1c) levels [31]. SGLT2 inhibition also produces a modest natriuretic effect that may contribute to blood pressure lowering; however, these effects are relatively small and transient due to stimulation of homeostatic mechanisms [29]. The blood pressure-lowering effect of SGLT2 inhibitors is likely affected by several other effects of SGLT2 inhibition, including weight loss and diuresis [32].

2.1. Role of SGLT2 inhibitors in patients with T2DM and renal impairment

SGLT2 inhibitors are largely metabolized by the liver via glucuronidation to inactive metabolites, with renal elimination of the unchanged drug [33–36]. There is some variability in the percentage of drug cleared via the liver and kidney between individual SGLT2 inhibitors [33], a feature that influences the tolerability of individual agents in the presence of liver or kidney insufficiency. Overall, the pharmacokinetic parameters of these agents are slightly altered in the presence of CKD, although no dose adjustment is required in the case of mild CKD (defined as eGFR 60–89 mL/min/1.73 m²), using the CKD classification system of the Kidney Disease Outcomes Quality Initiative [KDOQI] and Kidney Disease: Improving Global Outcomes [KDIGO] [37] [33]. For moderate CKD (defined as eGFR 30–59 mL/min/1.73 m²) [37], current prescribing information for these agents states that they may be unsuitable or only used at a reduced daily dose [21–24,33]. The use of SGLT2 inhibitors is contraindicated in patients with severe CKD (eGFR 15–29 mL/min/1.73 m²) [37] including patients with severe renal impairment, end-stage kidney disease (ESRD), or who require dialysis [21–23]. Assessment of renal function is advised before initiating therapy with SGLT2 inhibitors, and these agents should not be initiated if the eGFR is below a certain threshold (specifically, empagliflozin or canagliflozin should not be initiated or should be discontinued if the eGFR is <45 mL/min/1.73 m²; no empagliflozin dose adjustment is needed if the eGFR is ≥45 mL/min/1.73 m²; canagliflozin should be limited to 100 mg/day if the eGFR is between 45 and <60 mL/min/1.73 m²; and dapagliflozin and ertugliflozin should not be initiated or should be discontinued if the eGFR is <60 mL/min/1.73 m²) [21–24]. As the eGFR levels for which SGLT2 inhibitors are indicated/contraindicated can differ between individual agents, the choice of agent must be carefully considered for patients with renal impairment. Since the glucose-lowering effect of SGLT2 inhibitors is dependent on glomerular filtration, urinary glucose excretion declines with increasing severity of renal impairment (as indicated by a reduction in eGFR) [33]. Nonetheless, in patients with mild CKD, glucose-lowering efficacy and safety of SGLT2 inhibitors are similar to these effects in patients with normal kidney function. However, in patients with moderate CKD, the efficacy of SGLT2 inhibitors is reduced and there is a greater risk of adverse effects in general, versus patients with normal renal function [33,38].

In terms of glucose-lowering efficacy, there are conflicting data on the degree of CKD for which SGLT2 inhibition continues to offer clinically relevant reductions in HbA1c. A long-term (104 weeks), phase 2/3, randomized, placebo-controlled trial assessed the efficacy and safety of dapagliflozin in patients with T2DM and moderate renal impairment and showed that glycemic control was not improved versus placebo [39]. However, post hoc analysis by baseline CKD stage revealed a modest reduction in HbA1c (placebo-corrected mean reduction from baseline between −0.33% and −0.37% at Week 24) with dapagliflozin 5 mg and 10 mg among patients with stage 3A CKD (eGFR ≥45 and <60 mL/min/1.73 m²), whereas no change in HbA1c was observed in patients with stage 3B CKD (eGFR ≥30 and <45 mL/min/1.73 m²). Similarly, in a 52-week, phase 3, randomized, placebo-controlled study in which canagliflozin was administered to patients with T2DM and stage 3 CKD (eGFR ≥30 and <50 mL/min/1.73 m²), both 100 mg and 300 mg doses of canagliflozin produced reductions in HbA1c versus placebo (−0.19%, −0.33%, and 0.07%, respectively); placebo-subtracted differences in HbA1c (95% CI) were −0.27% (−0.53, 0.001%) and −0.41% (−0.68, −0.14), respectively [40]. Similar findings were observed in an assessment of empagliflozin as an add-on treatment in patients with T2DM and CKD in a 52-week, phase 3, randomized, placebo-controlled trial [41]. In this trial, the addition of empagliflozin to existing treatment produced reductions in HbA1c in patients with stage 2 and 3 CKD, although no improvements were observed among those with stage 4 CKD [41]. In patients with stage 2 CKD (eGFR ≥60 to <90 mL/min/1.73 m²), adjusted mean treatment differences versus placebo in changes from baseline in HbA1c at Week 24 were −0.52% (95% CI, −0.72, −0.32) for empagliflozin 10 mg and −0.68% (95% CI, −0.88, −0.49) for empagliflozin 25 mg (both p < 0.0001). These HbA1c changes were sustained at Week 52. In patients with stage 3 CKD (eGFR ≥30 to <60 mL/min/1.73 m²), the adjusted mean treatment difference versus placebo in HbA1c change from baseline at Week 24 was −0.42% (95% CI, −0.56, −0.28) with empagliflozin 25 mg (p < 0.0001) and
was sustained at Week 52. For ertugliflozin, a 52-week study of patients with stage 3 CKD (eGFR ≥30 to <60 mL/min/1.73 m²) showed that the addition of this drug to standard T2DM therapy was associated with reductions in HbA1c (although the comparison to the placebo group was not statistically significant, possibly due to an unusually large placebo response linked to surreptitious metformin use) and treatment was generally well tolerated [42].

Because SGLT2 inhibitors can cause contraction of blood volume, physicians are advised to consider factors that might increase the risk of acute kidney injury, including hypovolemia, chronic renal insufficiency, chronic heart failure, and concomitant medications (e.g., diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs) [21–24]. The US Food and Drug Administration (FDA) has previously raised concerns that long-term treatment with SGLT2 inhibition might lead to deterioration in renal function secondary to diuresis, with the development of volume depletion and modest reductions in eGFR [43–45]. However, current evidence suggests that small changes in eGFR after long-term treatment (52 weeks) are reversed within 3 weeks of treatment discontinuation, indicating that the initial changes in renal function in response to SGLT2 inhibitor therapy are a result of hemodynamic changes induced by treatment [41,46].

Overall, the safety of SGLT2 inhibitors does not appear to differ substantially according to the stage of CKD [33]. For example, in a study of empagliflozin in patients with CKD, adverse events (AEs) were reported over 52 weeks [41]. Among patients with stage 2 CKD, AEs were reported in 80% taking empagliflozin 25 mg versus 87% in the placebo group. Corresponding frequencies in patients with stage 3 CKD were 83% for both groups, and were 92% and 84% for empagliflozin 25 mg and placebo groups, respectively, in patients with stage 4 CKD. The incidence of severe and serious AEs was similar in patients treated with empagliflozin and in those receiving placebo.

3. Evidence for potential renal benefits of SGLT2 inhibitors

SGLT2 inhibition is associated with pleiotropic effects, including reductions in blood glucose concentrations, urinary glucose excretion, natriuresis, and decreases in blood pressure and body weight [14–18,47]. These changes might confer protective effects on the kidney by reducing CV and renal risk factors in individuals with T2DM (Figure 1) [29]. Furthermore, there is evidence that SGLT2 inhibitors can reduce the risk of development or worsening of albuminuria, a marker of glomerular damage, in patients with T2DM. In a long-term study of patients with T2DM and moderate renal impairment, participants were more likely to regress to a lower category of albumin excretion when receiving dapagliflozin versus placebo over 104 weeks [39]. In this study, urinary albumin to creatinine ratio (UACR) was divided into three prespecified categories: 0 to <30 mg/g (normoalbuminuria), 30 to <300 mg/g (microalbuminuria), or ≥300 mg/g (macroalbuminuria). For patients who received dapagliflozin (5 mg and 10 mg groups, n = 168 in total), 38 patients shifted from baseline to a lower category at Week 104 compared with 18 patients who shifted to a higher category. For the placebo group (n = 84), a similar number of patients shifted to a lower category (n = 9) of UACR as to a higher category (n = 12). Similarly, a study of patients with T2DM and CKD showed that the addition of empagliflozin to standard care was associated with a reduction in albuminuria over 52 weeks [41]. At the end of treatment, comparison of treatment groups in patients with stage 3 CKD showed that more patients who received empagliflozin 25 mg improved from macroalbuminuria at baseline to microalbuminuria, or from microalbuminuria to no albuminuria, compared with placebo (32.6% [n = 14] with empagliflozin 25 mg vs. 8.6% [n = 3] with placebo, and 27.5% [n = 14] with empagliflozin 25 mg vs. 21.4% [n = 15] with placebo, respectively). The administration of canagliflozin in patients with T2DM and CKD has also been associated with a slowing of the progression of kidney disease versus placebo [48]. In a study of 42 Japanese patients with T2DM, reductions in albuminuria and in markers of tubulointerstitial damage (urinary liver-type fatty acid binding protein, N-acetyl-β-D-glucosaminidase, and β2-microglobulin) were observed over 52 weeks among patients who received canagliflozin 100 mg added to usual care compared with the control group [48].

A mechanistic trial that evaluated the renal hemodynamic effects of SGLT2 inhibition in type 1 diabetes mellitus [49] showed that empagliflozin administration was associated with a reduction in renal hyperfiltration, a potential risk factor for renal disease progression in T2DM [50], probably by affecting tubular-glomerular feedback mechanisms. The findings of this trial indicate that SGLT2 inhibition may produce renoprotective effects due to a reduction in intraglomerular pressure.
Although clinical data supporting the benefits of SGLT2 inhibitors on renal outcomes are currently limited [2], several ongoing trials are expected to provide further evidence of the effects of these agents on renal function. Furthermore, several CV outcomes trials (CVOTs) have included renal endpoints and these provide some insights into the longer-term effects of glucose-lowering therapies on renal outcomes, as described below.

### 3.1. Clinical evidence from CVOTs with SGLT2 inhibitors that included renal endpoints

Two large randomized CVOTs have evaluated the long-term CV safety of empagliflozin (EMPA-REG OUTCOME trial [Empagliflozin Removal of Excess Glucose: Cardiovascular OUTCOME Event Trial in Type 2 Diabetes Mellitus Patients]) [51,52] and canagliflozin (the CANVAS [Canagliflozin Cardiovascular Assessment Study] Program) [53,54]. These studies were primarily designed to evaluate CV outcomes but secondary outcomes also indicated that SGLT2 inhibitors could offer clinically relevant renal benefits to patients with T2DM. A further ongoing CVOT is evaluating ertugliflozin in 8238 patients with established atherosclerotic CVD (ASCVD), and includes a secondary composite outcome of renal death, dialysis/transplant, or doubling of serum creatinine from baseline [55]; the trial is expected to complete in September 2019. In the EMPA-REG OUTCOME trial, a total of 7020 patients with T2DM and at high CV risk were randomized to receive empagliflozin (10 mg or 25 mg once daily) or placebo in addition to standard care, with a median observation time of 3.1 years [51]. Empagliflozin was associated with a reduction in the primary composite endpoint of 3-point MACE (defined as death from CV causes, nonfatal myocardial infarction [MI], or nonfatal stroke) versus placebo (10.5% vs. 12.1%, respectively; hazard ratio [HR], 0.86; 95.02% CI, 0.74–0.99; p < 0.001 for non-inferiority; p = 0.04 for superiority). In the empagliflozin group the rate of CV death was significantly reduced versus placebo (3.7% vs. 5.9%, respectively; 38% relative risk reduction). Empagliflozin was also associated with significant reductions in hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction) and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) compared with placebo. On the basis of these findings, the FDA approved a label change for empagliflozin to include a new indication for the reduction of CV mortality in patients with T2DM and established CVD [56]. The addition of empagliflozin to standard care also was associated with slower progression of kidney disease and lower rates of clinically relevant renal events versus placebo [52]. Incident or worsening nephropathy was observed in 525 of 4124 patients (12.7%) receiving empagliflozin versus 388 of 2061 (18.8%) in the placebo group (HR for empagliflozin group, 0.61; 95% CI, 0.53–0.70; p < 0.001). There was also a significant relative risk reduction of 44% in the occurrence of doubling of serum creatinine levels (70 of 4645 patients [1.5%] in the empagliflozin group vs. 60 of 2323 [2.6%] for placebo). Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group versus in 14 of 2333 (0.6%) in the placebo group, a relative risk reduction of 55% for the empagliflozin group. Although EMPA-REG OUTCOME [51] was not a dedicated renal outcomes trial and renal outcomes were not adjudicated during the study, subsequent analysis has shown similar results using retrospectively confirmed events [57]. In a post hoc analysis of data from the EMPA-REG OUTCOME trial, patients with T2DM and a history of coronary artery bypass graft surgery who were treated with empagliflozin also demonstrated reductions in incident or worsening nephropathy, in addition to reductions in CV mortality, all-cause mortality, and hospitalizations for heart failure, compared with placebo [58]. Similar effects on renal function and CV events were observed in a subanalysis of EMPA-REG OUTCOME data in another high-risk group of patients with T2DM and peripheral artery disease [59]. In a recent slope analysis from the EMPA-REG OUTCOME trial, the decline in eGFR that is observed shortly after initiation of treatment with empagliflozin was shown to be reduced with chronic maintenance treatment, and increased to pretreatment levels after cessation of the drug [60]. This pattern was consistent across patients with a range of eGFR values in the trial, including subgroups at increased risk of CKD progression, and is indicative of the renal hemodynamic effect of empagliflozin. It is possible that the hemodynamic effect of empagliflozin associated with the reduction of intraglomerular pressure may contribute to the long-term preservation of kidney function [61].

In the CANVAS Program, 10,142 patients with T2DM and high CV risk (approximately two-thirds of whom had a history of CVD) were randomized to canagliflozin or placebo in two trials (CANVAS and CANVAS Renal Endpoints [CANVAS-R] trials) and followed for a median of 2.4 years [53]. Canagliflozin therapy was associated with a reduction in the occurrence of the primary composite outcome (death from CV causes, nonfatal MI, or nonfatal stroke) versus placebo (26.9 vs. 31.5 participants per 1000 patient-years, respectively; HR, 0.86; 95% CI, 0.75–0.97; p < 0.001 for noninferiority; p = 0.02 for superiority) [53]. The results also showed a reduction in the progression of albuminuria (89.4 vs. 128.7 participants with an event per 1000 patient-years; HR, 0.73; 95% CI, 0.67–0.79), regression of albuminuria (293.4 vs. 187.5 participants with regression per 1000 patient-years; HR, 1.70; 95% CI, 1.51–1.91), and in the composite outcome of a sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes in patients with T2DM and high CV risk with canagliflozin versus placebo (5.5 vs. 9.0 participants with the outcome per 1000 patient-years, respectively; HR, 0.60; 95% CI, 0.47–0.77) [53]. However, these renal outcomes were not considered statistically significant on the basis of the study’s prespecified hypothesis-testing sequence. These potential benefits of canagliflozin therapy were slightly offset by an increased risk of amputation, and possible increased bone fracture risk [53], although further data are required on the safety of canagliflozin [62]. A recent prespecified exploratory analysis of data from the CANVAS Program showed that...
canagliflozin was associated with renoprotective effects versus placebo, as indicated by a reduced occurrence of albuminuria and a reduced likelihood of developing micro-or macroalbuminuria, in addition to stabilization of renal function (attenuated decline in eGFR over time) [54]. The composite outcome of sustained doubling of serum creatinine, ESRD, and death from renal causes was also observed less frequently among patients receiving canagliflozin versus placebo (1.5 vs. 2.8 per 1000 patient-years, respectively; HR, 0.53; 95% CI, 0.33–0.84). In addition, post hoc analyses of data from the CANVAS Program have shown that the beneficial effects of canagliflozin on CV and renal outcomes were not influenced by baseline renal function in people with T2DM and a history or high risk of CVD down to eGFR levels of 30 mL/min/1.73 m² [63]. This finding has led to the suggestion that the use of canagliflozin might be appropriate for patients with eGFR levels that are below the currently recommended level in view of the potential CV and renal benefits of therapy [63].

A post hoc analysis of a long-term study of dapagliflozin in patients with renal impairment showed that dapagliflozin reduced UACR versus placebo over 2 years in patients with T2DM and stage 3 CKD, without increasing the occurrence of serious renal AEs [64]. Dapagliflozin (5 mg and 10 mg) therapy, compared with placebo, was associated with an increased likelihood of shifting to a lower UACR category (39.6% and 33.9%, respectively, vs. 15.8% with placebo), with fewer patients progressing to a higher UACR category (4.3% and 14.7%, respectively, vs. 27.3% with placebo). Overall, 18.9% and 17.8% of patients in the dapagliflozin 5 mg and 10 mg groups, respectively, improved to normoalbuminuria status versus 7.0% of patients receiving placebo. The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial is the most recent and largest CVOT for the SGLT2 inhibitor class (n = 17,160) [65]. In this trial, dapagliflozin 10 mg was associated with a lower rate of CV death or hospitalization for heart failure versus placebo (HR, 0.83; 95% CI, 0.73–0.95; p = 0.005), primarily due to a 27% reduction in heart failure hospitalizations among patients with T2DM who had or were at risk of ASCVD. Treatment with dapagliflozin was not associated with a reduced rate of 3-point MACE (CV death, MI, or ischemic stroke) versus placebo. Nonetheless, the occurrence of the secondary renal composite outcome (≥40% decrease in eGFR to <60 mL/min/1.73 m², new ESRD, or death from renal or CV cause) was reduced among patients receiving dapagliflozin versus placebo (4.3% and 5.6%, respectively; HR, 0.76; 95% CI, 0.67–0.87), as well as the composite of a sustained ≥40% decrease in eGFR (to eGFR <60 mL/min/1.73 m²), ESRD, or death from renal cause (1.5% and 2.8%, respectively; HR, 0.53; 95% CI, 0.43–0.66) [65]. Renal outcomes will also be included in the DAPA-HF trial (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure) [66]. This study of patients with chronic heart failure with reduced ejection fraction will evaluate the effect of dapagliflozin versus placebo, added to regional standard-of-care therapy, in the prevention of CV death or reduction of heart failure events. A secondary outcome measure will include time to the first occurrence of any of the components of a renal composite (≥50% sustained decline in eGFR, ESRD, or renal death).

### 3.2. Suggested mechanisms for potential renal benefits of SGLT2 inhibitors

The beneficial effects of SGLT2 inhibitors on renal function are thought to arise from several mechanisms as summarized in Figure 2 [29]. These possible mechanisms can be divided into six areas and are described here. 1) Reductions in the renal absorption of glucose and sodium in the proximal tubules are thought to reduce hyperfiltration by increasing sodium delivery to the macula densa, which activates tubuloglomerular feedback, leading to afferent arteriolar vasoconstriction and a reduction in intraglomerular hyperfiltration [29,49,57,67]. 2) Lowering of blood glucose by SGLT2 inhibition results in lowering of potential glucotoxicity in the kidney and other organs, leading to reduced renal growth, inflammation, and injury [29]. 3) Reductions in blood pressure are preserved in patients with CKD receiving SGLT2 inhibitor therapy, and it is possible that a decline in sodium and volume overload, as well as modest decreases in body weight, will lead to a reduced renal and CV burden [29,51,63,68]. 4) SGLT2 is coexpressed with the Na+/H+ exchanger 3 (NHE3) membrane protein in the early proximal tubule, and thus SGLT2 inhibition might produce natriuresis, contributing to blood pressure reduction and associated renal benefits [29]. 5) SGLT2 inhibition is associated with increases in glucagon levels that have a role in maintaining renal function [69]. The renal effects of relatively high doses of glucagon include vasodilation and resultant increases in renal plasma flow, GFR, and electrolyte excretion. In parallel, insulin levels are reduced with SGLT2 inhibition, leading to enhanced lipolysis and hepatic glucoseogenesis [29]. 6) SGLT2 inhibition is possibly associated with a reduced risk of renal injury secondary to ischemia due to increases in the levels of the transcription factor, hypoxia-inducible factor [29]. Other contributory mechanisms for potential renal benefits of SGLT2 inhibitors may include reductions in arterial stiffness [70] and vascular resistance [71], decreases in uric acid levels [51], and modulation of the renal-angiotensin-aldosterone system, both within the kidney and systemically (for summary of potential renoprotective mechanisms, see Supplementary Video) [49,72]. Further research is needed to fully elucidate the potential renal and CV benefits of SGLT2 inhibition and their underlying mechanisms.

### 3.3. Ongoing trials of renal outcomes with SGLT2 inhibitors

Although there is growing evidence to suggest a renoprotective role for SGLT2 inhibitors, several ongoing dedicated renal outcomes trials will provide further insights into the role of SGLT2 inhibitors on renal function in patients with T2DM (Table 1).
The CREDENCE trial (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) has been evaluating the efficacy and safety of adding canagliflozin versus placebo to standard care in patients with CKD and T2DM ([73]). The trial was stopped early due to achievement of prespecified efficacy criteria identified during a planned interim analysis. This decision was based on the demonstration of efficacy of canagliflozin in terms of the primary composite endpoint of ESRD (time to dialysis or kidney transplantation), doubling of serum creatinine, and renal or CV death when used in addition to standard care ([74]). The full report of this trial and the outcomes of other renal outcomes trials of SGLT2 inhibitors are awaited with interest.

A study of dapagliflozin has recently completed (results expected) in which patients with T2DM and CKD were randomized to dapagliflozin (with or without saxagliptin) or placebo ([75]). For renal endpoints, this study evaluated the percentage change in UACR between dapagliflozin 10 mg plus saxagliptin 2.5 mg and placebo, and between dapagliflozin 10 mg and placebo, over 24 weeks, in addition to the proportion of patients who achieve a 30% reduction in UACR over the study period. In a further trial, the effect of dapagliflozin on the progression of kidney disease and CV mortality will be evaluated in patients with CKD, with or without T2DM (DAPA-CKD) ([76]).

For empagliflozin, two trials are underway to investigate the safety and efficacy of empagliflozin versus placebo, added to guideline-directed therapy, in patients with heart failure: two EMPEROR (EMPagliflozin outcome tRial in Patients WithchrOnic heaRt Failure) trials will include patients with either reduced ejection fraction (EMPEROR-Reduced) ([77]) or with preserved ejection fraction (EMPEROR-Preserved) ([78]). Secondary endpoints in both trials will include change in eGFR from baseline, and time to first occurrence of chronic dialysis or renal transplant or sustained reduction of eGFR. Another study, EMPA-KIDNEY, will evaluate patients with established CKD, with and without T2DM, to determine the effect of empagliflozin on time to clinically relevant kidney disease progression or CV death ([79,80]). The findings of this trial will build on results of the EMPA-REG OUTCOME trial ([51]), with important new data on the effects of empagliflozin in a broad range of people, with or without T2DM.

4. Translating clinical trial findings into practice

There is now growing evidence to show that SGLT2 inhibitors have the potential to offer renoprotective effects in patients with T2DM and CKD. On the basis of the findings of the EMPA-REG OUTCOME study, the latest guidelines from the American...
Table 1. Ongoing trials of SGLT2 inhibitors with renal outcomes.

<table>
<thead>
<tr>
<th>Trial acronym/title</th>
<th>ClinicalTrials.gov identifier</th>
<th>Primary study aims</th>
<th>Number of patients enrolled</th>
<th>Estimated completion date</th>
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<tr>
<td>CREDENCE Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy [73]</td>
<td>NCT02065791</td>
<td>To assess whether canagliflozin has a renal and vascular protective effect in reducing the progression of renal impairment relative to placebo in patients with T2DM, stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care (including a maximum tolerated daily dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker).</td>
<td>4401</td>
<td>June 2019</td>
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<tr>
<td>DAPA-HF [66] Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure</td>
<td>NCT03036124</td>
<td>To evaluate the effect of dapagliflozin on the incidence of worsening heart failure or CV death in patients with chronic heart failure with reduced ejection fraction.</td>
<td>4744</td>
<td>December 2019</td>
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<tr>
<td>EMPEROR trials EMPagliflozin outcome Trial in Patients With chronic heart Failure (EMPEROR) With Reduced Ejection Fraction (EMPEROR-Reduced) [77] and With Preserved Ejection Fraction (EMPEROR-Preserved) [78]</td>
<td>NCT03057977 NCT03057951</td>
<td>To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with heart failure with reduced ejection fraction (EMPEROR-Reduced) or preserved ejection fraction (EMPEROR-Preserved).</td>
<td>2850 4126</td>
<td>June 2020 November 2020</td>
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<tr>
<td>DAPA-CKD [76] Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease</td>
<td>NCT03036150</td>
<td>To evaluate the effect of dapagliflozin versus placebo, once daily in addition to standard of care, to prevent the progression of CKD or CV/renal death.</td>
<td>4000</td>
<td>November 2020</td>
</tr>
<tr>
<td>EMPA-KIDNEY [80] The Study of Heart and Kidney Protection With Empagliflozin</td>
<td>NCT03594110</td>
<td>To investigate the effect of empagliflozin on kidney disease progression or CV death versus placebo on top of standard of care in patients with pre-existing CKD.</td>
<td>5000</td>
<td>June 2022</td>
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</tbody>
</table>

Association of Clinical Endocrinologists and American College of Endocrinology refer to a potential benefit of empagliflozin on renal outcomes, in addition to CV benefits [81]. Furthermore, the latest diabetes management guidelines from the American Diabetes Association recommend that SGLT2 inhibitors be considered for patients with T2DM and CKD who require add-on therapy to metformin, on the basis of recent CVOTs indicating that these agents may reduce the risk of CKD progression and CVD events [82]. Although the effect of SGLT2 inhibition on HbA1c reduction declines with progressive reductions in eGFR, the CV and renal benefits of therapy appear to be maintained regardless of eGFR level (down to 30 mL/min/1.73 m$^2$) [63]. The preservation of a blood pressure-lowering effect with SGLT2 inhibitor therapy in patients with T2DM and CKD indicates that this effect could further contribute to a reduced renal burden in these patients [51,63,68]. Furthermore, SGLT2 inhibitors might offer synergistic effects with other blood pressure-lowering agents [83] or diuretics [61] in patients with T2DM and CKD. It is possible, therefore, that SGLT2 inhibitors could have a role in patients with T2DM for uses other than glucose lowering, and may have a future role in patients with eGFR levels below the level at which clinically relevant HbA1c reductions would be expected due to their potential CV and renal benefits [63].

5. Conclusion

SGLT2 inhibitors have an important role in the management of T2DM, adding to the currently available treatment options that can assist with individualization of therapy. The pleiotropic effects of SGLT2 inhibitors have the potential to produce benefits beyond blood glucose control, and there is increasing evidence to indicate that these agents may reduce the risk of progression of renal impairment in patients with T2DM. The findings of ongoing and future clinical trials will help shed further light on the role of SGLT2 inhibitors in the long-term protection of renal and CV function in patients with T2DM.

Funding

This article was supported by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). The author meets criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) and was fully responsible for all content and editorial decisions, was involved at all stages of manuscript development, and approved the final version that reflects the author’s interpretations and conclusions. The author received no direct compensation related to the development of the manuscript. Writing support was provided by Jennifer Garrett, MBBS, of Elevate Scientific Solutions, which was contracted and compensated by BIPI for this service.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial relationships to disclose.

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