Renoprotective effects of sodium-glucose cotransporter-2 inhibitors

Hiddo J.L. Heerspink[1,4], Mikhail Kosiborod[2,4], Silvio E. Inzucchi[3] and David Z.I. Cherney[4]

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [2]Saint Luke's Mid America Heart Institute and University of Missouri, Kansas City, Missouri, USA; [3]Section of Endocrinology, Yale School of Medicine, New Haven, Connecticut, USA; and [4]Department of Medicine, Division of Nephrology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada

Over the past two years, our understanding of anti-hyperglycemic medications used to treat patients with type 2 diabetes (T2D) has fundamentally changed. Before the EMPA-REG OUTCOME trial, agents used to lower blood glucose were felt to prevent or delay the development of microvascular complications, but were not known to definitively reduce cardiovascular risk or mortality. Previous studies with then novel sodium-glucose cotransport-2 (SGLT2) inhibitors demonstrated improvements in several cardiovascular and renal risk factors, including HbA1c, blood pressure, weight, renal hyperfiltration, and albuminuria. However, as with other antihyperglycemic drugs, it could not be known if these salutary effects would translate into improved cardiorenal outcomes. In the EMPA-REG OUTCOME trial, SGLT2 inhibition with empagliflozin reduced the primary outcome of major adverse cardiovascular events (MACE), while also reducing mortality, hospitalization for heart failure, and progression of diabetic kidney disease. In the CANVAS Program trials using canagliflozin, the rates of the 3-point MACE endpoint, the risk of heart failure and the renal composite endpoint were also reduced, albeit with an increased risk of lower extremity amputation and fracture. As a result, clinical practice guidelines recommend the consideration of SGLT2 inhibition in high-risk patient subgroups for cardiovascular risk reduction. Ongoing primary renal endpoint trials will inform the cardio-metabolic-renal community about how to optimally treat patients with chronic kidney disease – including those with and without diabetes. Our aim is to review the rationale for renal protection with SGLT2 inhibitors, and their current place in the clinical management of patients with kidney disease.

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Correspondence: *David Cherney, Toronto General Hospital, 585 University Avenue, 8N-845, Toronto, Ontario, Canada M5G 2N2. E-mail: david.cherney@uhn.ca*

[4]Coprimary authors.

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Trials focused on more intensive glycemic control strategies[1–3] have demonstrated decreases in the risk of micro- or macroalbuminuria and the progression to end-stage renal disease in type 2 diabetes (T2D).[4] However, this strategy is not known to significantly reduce the risk of cardiovascular complications and mortality in this setting.[1–3] The reasons underlying this dichotomy remain the subject of ongoing debate. The variable importance of hyperglycemia on microvascular versus macrovascular complications is a likely explanation. However, the deleterious effects of older anti-hyperglycemic agents including hypoglycemia and weight gain may also play a role. Whatever the reason(s), the perceived cardiovascular risk with certain older glucose-lowering therapies and evidence that HbA1c lowering *per se* is a poor surrogate for cardiovascular benefit led to the regulatory requirement for cardiovascular safety trials for new agents beginning in 2009. In addition, these large studies have also provided investigators with the opportunity to assess the impact of various glucose-lowering compounds on renal outcomes.

In these trials, to date, dipeptidylpeptidase-4 (DPP-4) inhibitors have had largely neutral effects on both cardiovascular and renal outcomes.[5–8] One member of this class, saxaglitpin, however, appeared to increase the risk of heart failure,[9] a signal not found with either alogliptin or sitagliptin.[6,10] Sodium glucose cotransport-2 (SGLT2) inhibitors, however, were subsequently shown to have important benefits on the heart and the kidneys in the EMPA-REG OUTCOME trial with empagliflozin and in the CANVAS Program with canagliflozin.[11–13] The glucagon-like peptide-1 receptor agonists liraglutide and semaglutide also exert beneficial cardiovascular effects and reduce albuminuria progression,[14–16] whereas data from the EXCSEL trial recently demonstrated directionally favorable, but nonsignificant, effects of exenatide once weekly on major adverse cardiovascular events, as well as significant benefit for all-cause mortality (a secondary endpoint).[17] Although not the focus of this review, the thiazolidinedione drug pioglitazone reduced the risk of stroke and myocardial infarction in nondiabetic, insulin-resistant patients with a history of stroke or transient ischemic attack.[18–20] Based on the positive results of these pivotal trials, it is critical for nephrologists to be familiar with recent cardiovascular safety trials of novel glucose-lowering therapies. Accordingly, in this review, we describe the SGLT2 inhibitor class—for both traditional glucose-lowering

and metabolic effects—and summarize available mechanistic and clinical evidence of renal and cardiovascular protection. In addition, we place SGLT2 inhibitors in the context of the current therapeutic portfolio of glucose-lowering drugs for T2D, including newer classes such as DPP4 inhibitors and glucagon-like peptide-1 receptor agonists. Finally, in light of recently announced renal endpoint trials in patients with and without T2D, we outline their rationale and timeline (Table 1).

SGLT2 inhibition and metabolic effects in diabetes

SGLT2 inhibitors reduce blood glucose concentrations by inhibiting the main glucose transporter on the luminal surface of the proximal tubule, thereby lowering the threshold for urinary glucose excretion in the kidney (Tmax),[21] an effect that may be partially offset by compensatory upregulation of SGLT1.[22] Nevertheless, pharmacologic SGLT2 inhibition increases urinary glucose excretion[23] (Figure 1), leading to a net loss of ~70 to 80 g/d of glucose with accompanying daily energy losses of up to ~300 kcal.[24] SGLT2 inhibition also leads to an alteration in fuel substrate consumption, with an increase in fat oxidation and ketogenesis, with a concomitant decrease in carbohydrate utilization.[25]

SGLT2 inhibitors currently available in North America and Europe include canagliflozin, dapagliflozin, and empagliflozin, with others (ipragliflozin, luseogliflozin, and tofogliflozin) available in Japan and several additional agents (e.g., ertugliflozin and sotagliflozin, the latter a combined SGLT2 and SGLT1 inhibitor) currently under investigation.[26,27] Marketed members of this class are approved as glucose-lowering drugs in patients with T2D, typically in combination with metformin once HbA1c levels are no longer adequately controlled. They can also be used in conjunction with other drug categories, such as sulfonylureas, thiazolidinediones, DPP4 inhibitors, glucagon-like peptide-1 receptor agonists, and insulin. This class is somewhat unique in that its efficacy is not dependent on prevailing insulin concentrations. Accordingly, these agents improve glucose control similarly in those with recent as well as long-established disease, even after insulin secretory capacity has faltered.[26] For this reason, and although not approved in this setting, SGLT2 inhibitors have demonstrated efficacy in type 1 diabetes (T1D).[28–33] However, safety concerns surrounding the potential for inducing diabetic ketoacidosis (DKA) are still being examined and will need to be fully understood before being used safely in this patient population.[34]

The HbA1c-lowering potency of SGLT2 inhibitors is on the order of 0.6% to 0.8%,[35] numerically similar to the effects in previous DPP4 inhibitor trials but less than the average results of earlier studies examining metformin, sulfonylureas, thiazolidinediones, and glucagon-like peptide-1 receptor agonists (range, 1%–1.5%). However, when compared head-to-head, SGLT2 inhibitors actually appear more potent than DPP-4 inhibitors[36] and, over time, more durably efficacious than sulfonylureas from an HbA1c standpoint.[37] As with most glucose-lowering medications, more robust effects are seen in those patients with higher baseline HbA1c levels.[26,38]

The SGLT2 inhibitors, due to the induction of calorie loss, are also consistently associated with a mean reduction in body weight of ~2 kg over 3 to 6 months.[35] However, this quickly stabilizes after approximately a year despite the fact that the urinary energy deficits continue. Increased food intake is likely the explanation, resulting in the establishment of a new steady state in chronically treated patients. Weight loss mainly reflects reductions in body fat mass including visceral and subcutaneous fat, with consequent modest reductions in waist circumference and improvements in insulin sensitivity.[39]

A common side effect of the class, directly related to its mechanism of action, is genital mycotic infections, typically candida vaginitis in women and balanitis in men.[23,26] An increased risk of urinary tract infection has also been reported in some studies, although the overall rates of these infections (including pyelonephritis) did not differ between SGLT2 inhibitors recently tested in large outcome trials (empagliflozin and canagliflozin) versus placebo. SGLT2 inhibitors, despite reducing the tubular glucose transport maximum to well below normal ambient glucose concentrations, do not themselves increase the frequency of hypoglycemic events, although the risk of hypoglycemia may be increased when combined with specific other agents such insulin or sulphonylureas.[23,26] Additional considerations regarding potentially serious side effects with SGLT2 inhibitors are presented in a subsequent section of this review.

Table 1 | Summary of primary renal endpoint trials with SGLT2 inhibitors

Study characteristics	CREDENCE	DAPA-CKD
Target enrollment	4200	4000
Agent	100 mg canagliflozin or matching placebo	10 mg dapagliflozin or matching placebo
Primary endpoint composite	ESKD, doubling of serum creatinine, renal or cardiovascular death	ESKD, 50% eGFR decline, renal or cardiovascular death
Main renal clinical endpoint	Composite of ESKD, doubling serum creatinine, renal death	Composite of ESKD, 50% eGFR decline, renal death
Population specifics		
Diabetes status	Type 2 diabetes	Type 2 diabetes and nondiabetic kidney disease
eGFR	≥30 to <90 ml/min per 1.73 m^2	≥25 to <75 ml/min per 1.73 m^2
UACR	>300 to ≤5000 mg/g	>200 to ≤5000 mg/g
ACE inhibition or angiotensin receptor blockade use at enrollment	Mandatory	Mandatory unless contraindicated
Cardiovascular disease history inclusion	No requirement	No requirement

ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SGLT2, sodium glucose cotransport-2; UACR, urine albumin-to-creatinine ratio.

Blood pressure, natriuresis, and SGLT2 inhibition and the influence of chronic kidney disease stage on these parameters

SGLT2 inhibition does not only inhibit proximal glucose reabsorption but also blocks proximal sodium reabsorption, leading to natriuresis (Figure 1). In patients with T2D, urinary sodium excretion increased by ~40 mEq 24 hours after the administration of dapagliflozin.[40] This modest natriuretic effect appears to be transient. A recent study in Japanese T2D patients suggested that the SGLT2 inhibitor canagliflozin increased urinary sodium excretion over 24 hours by ~40 mEq, followed by a return to baseline levels by 48 hours,[41] with other studies showing a return to baseline by 14 days.[40] However, given that this was a small uncontrolled trial, additional studies with multiple consecutively collected 24-hour urine samples are needed to obtain more insight into the time course of the effect.[42]

As a result of the initial increase in sodium excretion, a new steady state is achieved, and SGLT2 inhibition causes a 7% contraction of plasma volume and persistent increase in fractional sodium excretion, which is associated with acute reductions in body weight and blood pressure and modest increases in hematocrit and levels of renin-angiotensin-aldosterone system (RAAS) markers in blood and urine compared with placebo.[29,30,43] The reduction in body weight and increase in hematocrit during the first 2 weeks of treatment persists over time, indicating that the initial acute reduction in body weight with SGLT2 inhibition primarily reflects the volume-mediated diuretic effect, although erythropoietin-mediated effects on hematocrit have also been suggested.[44] However, during prolonged treatment, there appear to be differences between SGLT2 inhibitors and traditional thiazide-type diuretics. The plasma volume contraction with thiazide diuretics dissipates over time so that by 12 weeks, the blood pressure lowering is a result of reductions in systemic vascular resistance.[45]

The rapid effect on plasma volume contraction is a strong candidate mediator for reduced heart failure hospitalization rates in recent clinical trials with SGLT2 inhibitors.[25,46] Dapagliflozin therapy for 6 weeks induces natriuresis, leading to reductions in plasma volume and a decrease in skin sodium concentration measured by ^{23}Na magnetic resonance imaging in patients with T2D,[47] suggesting reductions in tissue total sodium content, thereby possibly protecting against heart failure (HF) risk.[48] Perhaps as a consequence of the natriuresis and osmotic diuresis following SGLT2 inhibition, in patients with preserved renal function, systolic and diastolic blood pressure decrease by ~4 and 2 mm Hg, respectively.[46,49,50] In addition, blood pressure lowering occurs both for daytime and nighttime blood pressure[51] and may restore normal circadian nocturnal "dipping" pattern.[52] Antihypertensive effects of SGLT2 inhibitors are also associated with reductions in arterial stiffness, a marker of cardiovascular and renal risk.[20,28,53]

In patients with T2D and chronic kidney disease (CKD) stage 3A or 3B, dedicated prospective clinical trials and meta-analyses reported that SGLT2 inhibition reduces systolic and diastolic blood pressure by a similar amount compared with patients with normal renal function.[38] Interestingly, in this patient population, SGLT2 inhibition only modestly reduces

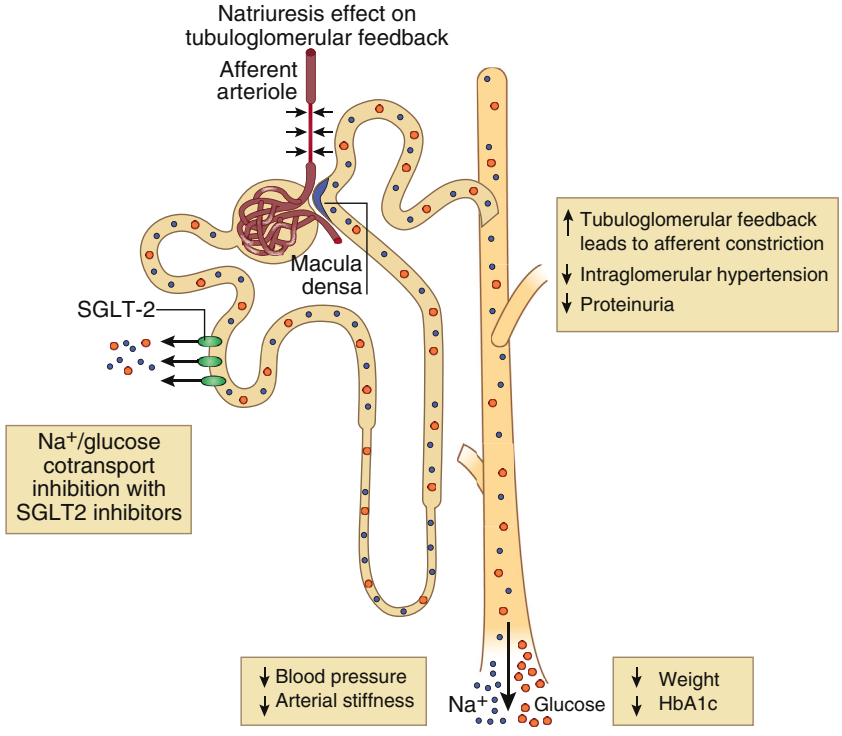

Figure 1 | Mechanism of action of sodium glucose cotransport 2 inhibitors: natriuresis, glucosuria, and impact on clinical parameters. HbA1c, hemoglobin A1c; SGLT2, sodium-glucose cotransport-2.

HbA1c by <0.4%[54–57] due to diminished effects on renal glucose excretion. Other physiological effects associated with natriuresis/diuresis including increases in hematocrit also persist in patients with T2D and CKD.[57] These somewhat surprising observations indicate that effects of SGLT2 inhibitors on sodium excretion and plasma volume may be to some degree uncoupled from their glycemic effects, at least in the context of CKD (Figure 2). Although no clear explanation for this phenomenon exists, the majority of patients with CKD exhibit a sodium-sensitive form of hypertension that leads to marked reductions in blood pressure following administration of diuretic agents. Consequently, the blunted increase in sodium excretion induced by SGLT2 inhibition may have an accentuated effect on blood pressure in CKD.

Description of EMPA-REG OUTCOME and the CANVAS Program trials

The cardio- and nephroprotective effects of SGLT2 inhibition have now been demonstrated in 2 large randomized controlled studies: EMPA-REG OUTOME and CANVAS Program. These studies were both designed primarily to demonstrate the cardiovascular safety of empagliflozin and canagliflozin, respectively, with testing for superiority over placebo performed after noninferiority was demonstrated in a hierarchical sequence of endpoint testing. Consistent with US Food and Drug Administration guidance, the primary endpoint in both studies was traditional 3-point major adverse cardiovascular events (time to first event of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death).

In EMPA-REG OUTCOME, 7020 patients with T2D and established cardiovascular disease were randomly assigned to 1 of the 2 doses of empagliflozin (10 or 25 mg/d) or placebo and followed for a median of 3.1 years. Empagliflozin reduced the primary composite outcome of 3-point major adverse cardiovascular event (hazard ratio [HR]: 0.86; 95% confidence interval [CI] 0.74–0.99; $P < 0.001$ for noninferiority; and $P = 0.04$ for superiority). Importantly, the major adverse cardiovascular event benefit was driven mainly by a reduction in cardiovascular death (HR: 0.62; 95% CI 0.49–0.77; $P < 0.001$), with no significant effect in nonfatal myocardial infarction or stroke. The reduction in cardiovascular death

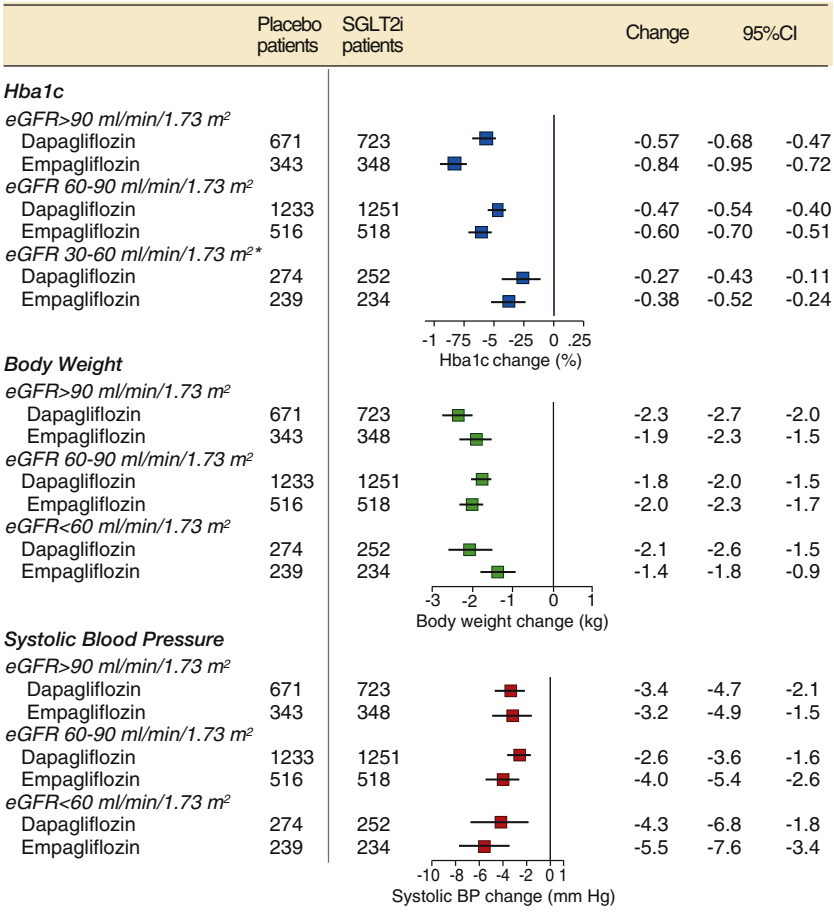

Figure 2 | Glycemic, weight, and systolic blood pressure lowering effects of empagliflozin[38] and dapagliflozin[57] at chronic kidney disease stages 1, 2, and 3. eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; SGLT2, sodium-glucose cotransport-2.

was likely, at least in part, due to a marked reduction in hospitalizations for HF (HR: 0.65; 95% CI 0.50–0.85; $P = 0.002$). These cardiovascular benefits occurred within a very short time period, with event curves diverging within a few months. Although the reduced incidence of hospitalization due to HF was seen in patients both with and without HF at baseline, the majority of patients in the study (~90%) did not have documented HF at baseline, suggesting primarily a HF prevention (rather than a HF treatment) signal. Based on these findings, the US Food and Drug Administration recently allowed a label change for this compound, now including a new indication for the reduction in cardiovascular mortality in patients with T2D and established cardiovascular disease.

In addition to the cardiovascular benefits, patients treated with empagliflozin also experienced a significant reduction in important renal endpoints compared with placebo. Although the study was not specifically designed or powered to evaluate renal outcomes, several prespecified renal endpoints were evaluated. Treatment with empagliflozin significantly reduced incident or worsening nephropathy and progression to macroalbuminuria (39% and 38% relative risk reductions, respectively, both highly significant). Doubling of serum creatinine and initiation of renal replacement therapy were uncommon, but occurred less frequently in patients treated with empagliflozin versus placebo (44% and 55% relative risk reductions, respectively; both highly significant). *Post hoc* analyses demonstrated a long-term stabilization of renal function in empagliflozin-treated patients. Nephroprotective effects were observed despite the fact that the majority of patients in the study (~74%) had a GFR of ≥60 ml/min per 1.73 m^2 at baseline and were already receiving treatment with a RAAS inhibitor.

In the CANVAS Program, 10,142 patients with T2D (approximately two-thirds with established cardiovascular disease) were randomized to either canagliflozin or placebo across 2 trials (CANVAS and CANVAS-R) and followed for a median duration of 2.4 years. Canagliflozin reduced the primary composite outcome of 3-point MACE with a point estimate identical to that seen with empagliflozin in EMPA-REG OUTCOME (HR: 0.86; 95% CI 0.75–0.97; $P < 0.001$ for noninferiority, and $P = 0.02$ for superiority). Although fatal outcomes were numerically lower in canagliflozin-treated patients compared with those receiving placebo, these differences did not reach significance, and similar nonsignificant patterns were observed for the outcomes of nonfatal myocardial infarction and stroke.

Similar to the EMPA-REG OUTCOME, there was a marked reduction in the secondary outcome of hospitalizations for HF in canagliflozin-treated patients versus placebo (HR: 0.67, 95% CI 0.52–0.87). There was also a significant 27% relative risk reduction in prespecified outcomes of progression to albuminuria and a 40% reduction in the composite of sustained 40% reduction in estimated GFR (eGFR), need for renal replacement therapy, or death from renal causes. In contrast to GLP1RA agents that only reduced the incidence of macroalbuminuria in the LEADER and SUSTAIN-6 trials, SGLT2 inhibitors also improve hard clinical renal outcomes (i.e., progressive decline in GFR, as well as the need for renal replacement therapy).[58] These HF and renal benefits were, again, observed despite the fact that the majority of patients in the CANVAS Program had no history of HF failure, significant CKD, or albuminuria at baseline.

It should be emphasized that despite the impressive benefits of both empagliflozin and canagliflozin with regard to hospitalizations for HF and progression of renal disease, neither the EMPA-REG OUTCOME trial nor the CANVAS Program was specifically designed to evaluate these outcomes. Furthermore, the majority of patients did not have HF, CKD, or significant albuminuria at baseline, and the type of HF (i.e., reduced or preserved ejection fraction) was not well characterized in either trial. Therefore, these results should be considered hypothesis generating only. Nevertheless, the consistency and magnitude of the cardiovascular benefits in these trials, along with consistent observations in large, real-world observational studies such as CVD-REAL in >300,000 patients (most without established cardiovascular disease),[59] underscore the likely important role that SGLT2 inhibitors will likely play in the management of T2D patients at high cardiovascular risk.[60,61]

Mechanisms responsible for cardiovascular protection

The mechanisms responsible for improved cardiovascular outcomes with SGLT2 inhibitors remain the subject of ongoing experimental and clinical investigation and have been explored in recent reviews.[46,62–67] Perhaps the most likely and widely cited factor leading to cardiovascular protection with SGLT2 inhibition is the reduction in plasma volume on the basis of natriuretic and osmotic effects.[46,62] The resulting declines in preload (reduced plasma volume) and afterload (blood pressure lowering, decreased arterial stiffness) may be especially beneficial for reducing the risk of hospitalization for heart failure.[25,46,62] SGLT2 inhibition also reduces biomarkers of cardiovascular risk such as high-sensitivity troponin and N-terminal pro-brain natriuretic peptide in certain subgroups such as older adults with T2D.[68] SGLT2 inhibition also reduces epicardial fat volume, which is associated with myocardial inflammation and fibrosis, in obese, nondiabetic patients, an observation that requires additional study to determine whether these changes are ultimately associated with cardiovascular benefits.[69] SGLT2 inhibition is associated with fat loss and "browning" of adipose tissue, which may reflect beneficial energy utilization and weight loss, also leads to anti-inflammatory and antifibrotic effects in animals.[70–73] Based on the expected contraction of plasma volume, it is perhaps not surprising that SGLT2 inhibition activates the RAAS and may also include activation of natriuretic, vasodilatory angiotensin-converting enzyme 2–angiotensin(1-7) pathways.[30,74] It is, however, less clear why the hemodynamic changes induced by SGLT2 inhibition do not appear to stimulate the autonomic nervous system, without any reflex tachycardia, as reported from EMPA-REG OUTCOME. Recent experimental evidence has suggested a suppressive

effect on norepinephrine in the kidney and heart,[13] thereby contributing to blood pressure lowering.[52]

Beyond effects on neurohormones and mediators of inflammation/fibrosis, SGLT2 inhibition influences the intracellular movement of electrolytes into myocardial cells and mitochondria via sodium-hydrogen exchange.[75] These potential advantageous physiological effects may impact energy efficiency, cardiac contractility, or systolic/diastolic function independent of SGLT2 activity because SGLT1 is the only isoform that is expressed in the human heart.[76] In addition, SGLT2 inhibitors may improve myocardial function by increasing the proportion of energy derived from nontraditional sources such as ketones, as hypothesized and reviewed elsewhere.[77,78] Regardless of the mechanism(s) responsible, SGLT2 inhibition improves diastolic dysfunction in animals and small human studies,[79] and, as noted, improved certain cardiovascular outcomes in large clinical trials.

Renal protective pathways, effects on albuminuria, and eGFR slope

The potential mechanisms responsible for renal protection with SGLT2 inhibitors have been reviewed in depth elsewhere[46] and are summarized in Figure 3. Aside from obvious benefits due to blood pressure lowering and weight loss, SGLT2 inhibitors promote anti-inflammatory and antifibrotic pathways and improve renal oxygenation and effects on reduced glomerular hypertension and hyperfiltration.[28,80] Experimental models of T1D and T2D have linked SGLT2 inhibition with reductions in oxidative stress, markers of

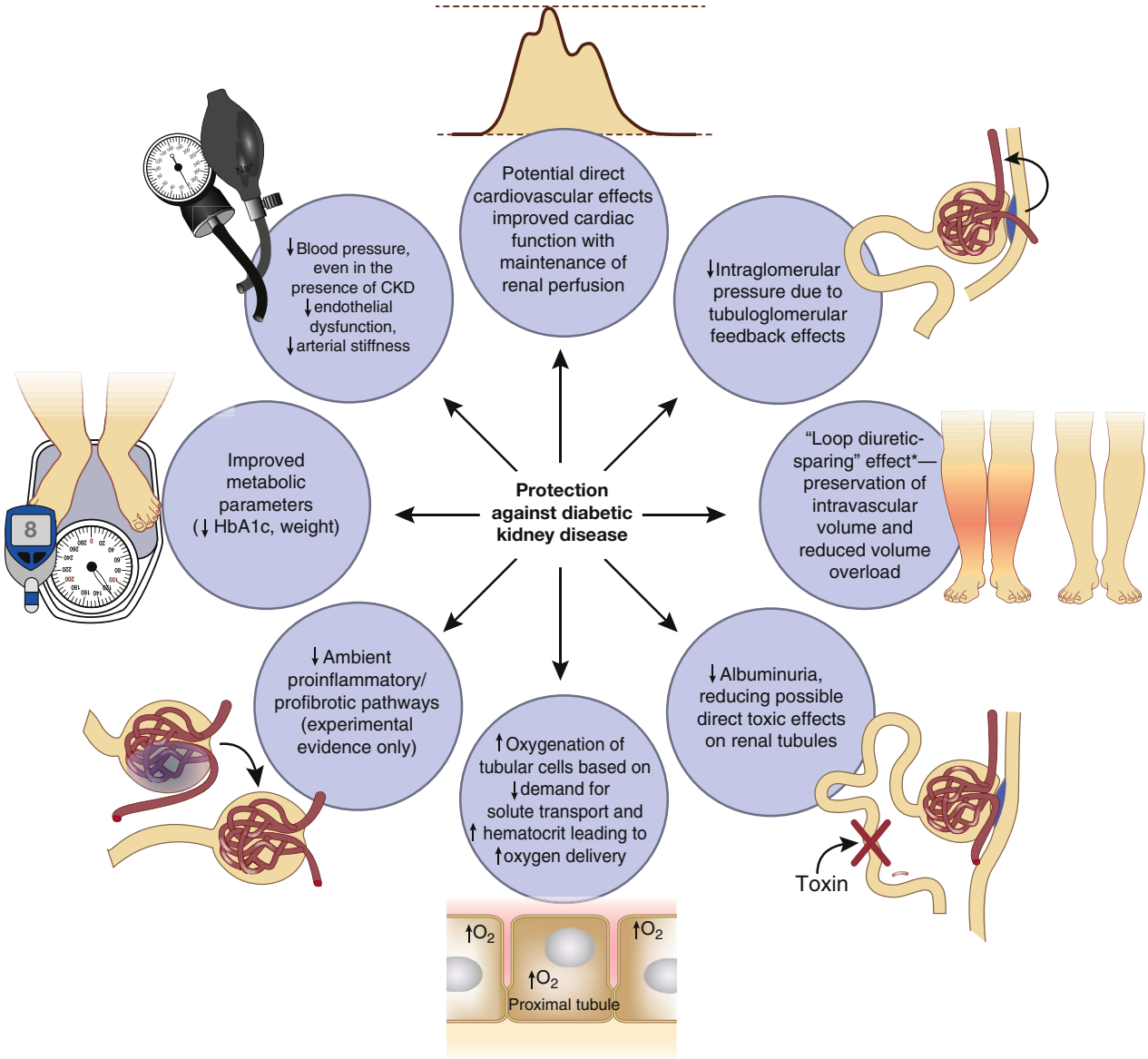

Figure 3 | Summary of potential mechanisms leading to renal protection with sodium glucose cotransport 2 inhibition. *Loop diuretic sparing as defined by a longer time until requiring institution of a loop diuretic in the EMPA-REG OUTCOME trial.[108]

inflammation (nuclear factor κB, interleukin 6, monocyte chemoattractant protein-1, macrophage infiltration) and fibrosis (fibronectin, transforming growth factor-β), and attenuated histologic evidence of nephropathy.[80,81] At the structural level, SGLT2 inhibition reduces glomerular and tubulointerstitial injury in several animal models of diabetes.[81–85] Although levels of cytokines/chemokines can be measured in patients with diabetes across the spectrum of CKD,[86–91] no human data are available to demonstrate responses in these markers in response to SGLT2 inhibition.

In addition to modifying factors that promote inflammation and fibrosis, SGLT2 inhibition may reduce the state of renal hypoxia that is characteristic of diabetes, thereby exerting an effect that is analogous to a β-blocker in the heart. Diabetes is associated with a state of renal hypoxia that is induced by increased delivery of glucose to the proximal tubule. As a consequence, more energy is expended to reabsorb the greater filtered glucose load, causing a reduction in oxygen tension in kidney.[44,92,93] Accordingly, treatment with the SGLT1/2 inhibitor phlorizin improves cortical oxygen tension but at the expense of medullary hypoxia, possibly due to increased distal solute delivery,[94] and selective SGLT2 inhibition may also reduce renal ischemic injury.[92,95] An interesting potential clinical correlate of the amelioration in proximal tubular oxygen delivery relates to changes in hematocrit.[44] Sano *et al.*[44] and others have suggested that the increase in hematocrit with SGLT2 inhibition is due to normalization of renal cortical oxygenation, thereby restoring normal cellular function to erythropoietin-producing cells, which increases hematocrit levels. Improvement or preservation of function of erythropoietin-producing cells in the kidney may partially contribute to the increase in hematocrit observed in clinical trials that persists over time.[44] Further work is required to determine whether the hypoxia hypothesis is relevant in humans.

Although little is known about the molecular mechanisms underlying their renoprotective effects, including hypoxia-related pathways in humans, SGLT2 inhibitor effects on hemodynamic pathways are better understood. Similar to findings in animals, SGLT2 inhibition reduces hyperfiltration in patients with T1D.[29–31,96] In brief, diabetes is associated with intraglomerular hypertension and renal hyperfiltration due to increased proximal tubular sodium and glucose reabsorption on the basis of a possible increase in SGLT2 mRNA upregulation and/or an increase in transporter activity (i.e., lower Tmax).[85,97–99] As a result, the reduction in sodium delivery to the macula densa suppresses tubuloglomerular feedback leading to afferent arteriolar vasodilation, hyperperfusion, and hyperfiltration.[31,33,46] By restoring distal delivery of sodium to the macula densa, tubuloglomerular feedback mechanisms are restored, leading to normalization of afferent tone, a reduction in glomerular hypertension, and, presumably, barotrauma.[46] In clinical trials, due to this putative afferent vasoconstrictive effect, SGLT2 inhibition causes a characteristic eGFR "dip" soon after initiation of therapy by 4 to 6 ml/min per 1.73 m^3, regardless of baseline renal function, even in the absence of changes in glycemic control.[54,56,100] Importantly, eGFR changes are reversible, even after several years of treatment, highlighting the hemodynamic nature of the effect.[11,55]

As a consequence of this reduction in glomerular hypertension, SGLT2 inhibition reduces albuminuria.[101,102] In patients with T2D and micro- or macroalbuminuria, SGLT2 inhibition reduced albuminuria by 30% to 50%, an effect that is largely independent of changes in weight, HbA1c, blood pressure, or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use.[101,102] SGLT2 inhibition also reduces the slope of eGFR decline, especially in patients with baseline micro- or macroalbuminuria.[102,103] Given the association between drug-induced reductions in albuminuria and subsequent renal protection, it seems likely that this may reflect a decrease in glomerular hypertension,[104,105] which is consistently observed even after repeated exposures.[65]

Beyond overall renal protective effects reported in the EMPA-REG OUTCOME and CANVAS Program trials, SGLT2 inhibition modestly attenuates increases in urine albumin excretion in patients with normoalbuminuria at baseline in clinical trials. This is especially relevant given that 20% of patients with diabetic kidney disease develop reduced renal function without ever developing albuminuria.[106,107] In experimental models, SGLT2 inhibition reduces tubulointerstitial disease, levels of inflammatory mediators, and markers of tubular injury, all of which may contribute to "normoalbuminuric" diabetic kidney disease. In EMPA-REG OUTCOME and the CANVAS Program, SGLT2 inhibition reduced albuminuria by 15% and 9% by the end of these trials, respectively, in patients who were initially normoalbuminuric at baseline, suggesting the possibility of a long-term primary prevention effect.[13,102] The risk of progressing from normo- to micro- or macroalbuminuria was not, however, reduced in EMPA-REG OUCOME.[102] In addition, in EMPA-REG OUTCOME, empagliflozin modestly preserved renal function, even in patients who were initially normoalbuminuric at the beginning of the trial. Nevertheless, the impact of SGLT2 inhibition as a primary prevention strategy will remain speculative until data from DECLARE-TIMI 58 (NCT01730534), which contains a large primary prevention component, is reported in 2019.

Use of concomitant blood pressure medications in combination with SGLT2 inhibitors

Because SGLT2 inhibitors lower blood pressure, it is important to determine whether background medications should be modified to avoid potential hypotension or volume depletion. In the CANVAS Program (but not in EMPA-REG OUTCOME), patients taking background diuretic or beta-blocker agents seemed to benefit *more* compared with those not taking these therapies, indirectly suggesting that higher risk individuals derived the most benefit from the addition of canagliflozin.[13] A second important observation about the interaction between diuretics and SGLT2 inhibitors is that the patients allocated to empagliflozin in EMPA-REG

OUTCOME had a loop diuretic added to their regimen less often, suggesting that empagliflozin acted as a "loop diuretic–sparing" agent.[108] This observation is also important in the context of a reduction in acute kidney injury risk in EMPA-REG OUTCOME because loop diuretics induce systemic volume depletion. In conjunction with experimental[109] and administrative data suggesting that there is a minimal additive blood pressure–lowering effect with combined diuretic plus SGLT2 inhibition,[110] available evidence suggests that in the absence of overt hypotension or clinical volume depletion,[66] SGLT2 inhibitors can be safely added to background diuretic therapies and are generally well tolerated from a volume perspective.[111] An important caveat is that patients should be counseled regarding "sick day" management and to seek advice if their body weight decreases, or if they develop signs or symptoms of volume depletion.[112] In addition, there may be specific patients who are very volume sensitive in whom SGLT2 inhibition may carry the risk of volume-related adverse events, including, conceivably, cerebral hypoperfusion and syncope. Accordingly, as with any glucose-lowering agent, proper patient selection is important.

Approaches to the use of novel antihyperglycemic agents in high-risk patients

In light of cardiovascular and renal protective effects with both SGLT2 inhibitors and GLP1RAs, a frequent question in nephrology and other specialty clinics will likely concern which class to start first for end-organ protection. In the absence of head-to-head comparative data, in patients with cardiovascular disease, particularly those at high risk of HF, SGLT2 inhibitors may be emerging as a preferred class based on EMPA-REG OUTCOME and the CANVAS Program trials. In contrast, the LEADER and SUSTAIN-6 trials with liraglutide and semaglutide were neutral around HF outcomes, and the FIGHT and LIVE trials have suggested that GLP1RA may even be harmful in patients with advanced HF with reduced systolic function and recent decompensation,[97,113] possibly due to an increase in heart rate.[114] In patients with atherosclerotic disease but without HF, both SGLT2 inhibition and GLP1RA would also be reasonable choices because liraglutide reduced the risk of MACEs and cardiovascular death in the LEADER trial, and semaglutide reduced the risk of MACEs in SUSTAIN-6. There is therefore potential to use these classes in combination to take advantage of complementary clinical effects with robust protection against atherosclerotic outcomes, HF, and CKD risk.[115] However, there are no currently ongoing long-term outcomes trials testing this hypothesis.

For patients with nephropathy and proteinuria, although both classes reduce the risk of albuminuria progression, both EMPA-REG OUTCOME and the CANVAS Program led to significant reductions in hard renal endpoints, such as renal function decline and need for dialysis, suggesting an advantage for SGLT2 inhibitors.[12,13] In terms of the preferred SGLT2 inhibitor, direct comparative data are unfortunately lacking. The amputation and fracture data from the CANVAS Program are concerning, however, suggesting that empagliflozin may provide the best benefit:risk ratio in this class. Of course, as with any glucose-lowering medication, the advantages, side-effect profiles, and costs should be considered to tailor individualized therapy, as discussed in the following.

For combination therapies and kidney protection, SGLT2 inhibitors and GLP1RA agents may be used together due to their different and unique mechanisms of action for both glycemic and nonglycemic effects.[115] Moreover, it is likely that these 2 classes reduce albuminuria via different mechanisms, with SGLT2 inhibitors acting on predominant hemodynamic pathways and glucagon-like peptide-1 receptors agonists (GLP1RAs) via nonhemodynamic anti-inflammatory and oxidant mechanisms. In addition, as demonstrated in the DURATION-8 trial with dapagliflozin and long-acting exenatide, the combined use of SGLT2 inhibition and GLP1RAs results in greater, albeit modest, HbA1c, weight, and blood pressure–lowering effects compared with either drug alone.[116] Additive effects with other SGLT2 inhibitors such as luseogliflozin to background liraglutide therapy results in similarly augmented effects on these parameters.[117] SGLT2 inhibition combined with DPP4 inhibition and GLP1RA may also have the physiological benefits of natriuresis, albuminuria lowering, and glucose control (Table 2). However, DPP4 inhibitors have not been shown to have the same benefits on either cardiovascular or renal outcomes that have been demonstrated with GLP1RA. Nevertheless, financial costs notwithstanding, we should await long-term trials of combination therapies (such as SGLT2 inhibitors and GLP1RA) before their wide endorsement for purposes other than glucose lowering and their now recognized independent cardiovascular and renal benefits.

The nephrologist's guide to adverse effects with SGLT2 inhibitors

Some of the most important serious adverse effects of SGLT2 inhibitors as a class are likely DKA and volume depletion–related issues. DKA has been reported mostly in patients using the drugs off-label for T1D.[34] In patients with T2D, the risk of DKA is low and has not been captured in clinical trials, but instead in postmarketing data and in observational studies using administrative databases.[118] For example, Fralick *et al.* reported an ~2-fold higher risk of DKA with SGLT2 inhibitor use versus DPP4 inhibitors in >70,000 patients in the United States.[119] As a counterpoint, a recent meta-analysis of previous clinical trials with SGLT2 inhibitors including >10,000 patients reported a reduction in the risk of DKA, a third administrative database analysis in >150,000 patients was neutral, and a final analysis in a Danish cohort also failed to demonstrate a significant DKA risk, highlighting the need for more data to better understand this important potential side effect.[27,120,121] From a clinical perspective, reported DKA episodes were sometimes accompanied by only slightly elevated blood glucose levels, so-called euglycemic DKA, due to ongoing urinary glucose disposal. This important observation provides clinicians a cautionary note because

Table 2 | Possible cardiorenal mechanistic interactions between SGLT2 inhibitors and DPP4 inhibitors

	SGLT2 inhibition	DPP4 inhibition	GLP1-RA	Anticipated impact of combination SGLT2 inhibitor-DPP4 inhibitor therapy	Anticipated impact of Combination SGLT2 inhibitor-GLP1 RA therapy
Renal parameters					
Renal hemodynamics	↓Glomerular hypertension	↔	↔	↓Glomerular hypertension	↓Glomerular hypertension
Albuminuria	↓30%–50%	↓10%–20%	↓20%–30%	↓↓	↓↓
Inflammation	↓MCP-1, IL-6, NF-κB, ROS	↓Inflammation, ROS	↓Inflammation, ROS	↓↓	↓↓
Natriuresis	↑Proximal natriuresis (FENa+)	↑Distal natriuresis (FENa+)	↑Proximal natriuresis (FENa+)	↑↑	↑↑
Blood pressure	↓4–6 mm Hg	↔	↔/↓	↓	↓↓
Cardiovascular events					
Ischemic events	↔/↓	↔/↑	↓	↔/↓	↓/↓↓
Heart failure	↓/↓	↔/↑	↔	↓/↓	↓/↓↓
Metabolic parameters					
HbA1c[a]	↓	↓	↓	↓↓	↓↓
Weight	↓	↔	↓	↓	↓↓

DPP-4, dipeptidyl-peptidase-4; FENa+, fractional excretion of sodium; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor κB; ROS, reactive oxygen species; SGLT2, sodium glucose cotransport-2.
[a]The addition of SGLT2 inhibition to DPP4 inhibition has been shown to reduce HbA1c.[140]

an unexpectedly normal or slightly elevated blood glucose level in this context might delay diagnosis.

The CANVAS Program also reported increased risks of minor and major amputation and fractures.[13] These risks have not yet been reported with other SGLT2 inhibitors and may be unique to canagliflozin.[54,113,122–124] Risk in both randomized groups in the CANVAS Program appeared to mirror known risk factors for amputations, including peripheral arterial disease and previous amputation. Real-world administrative data analyses that have examined the relationship between canagliflozin and amputation have not been consistent.[118,125] Although the mechanisms responsible for this apparent difference in risk between SGLT2 inhibitors is not yet clear, it is perhaps relevant that in pharmacoepidemiologic studies, thiazides have been associated with an increased incidence of lower extremity amputation compared with other antihypertensives in patients with T2D.[126] Therefore, although other mechanisms may be involved,[127] it is tempting to speculate that greater volume depletion associated with canagliflozin suggested in previous analyses may lead to either increased blood viscosity and/or reduced perfusion of ischemic tissue, thereby increasing amputation risk. However, the lack of signal with other SGLT2 inhibitors argues against this mechanism.

In the CANVAS Program, the overall fracture risk was increased.[13] This risk has not been observed in trials with empagliflozin or dapagliflozin and was not significant in a meta-analysis of all 3 agents.[128] Therefore, the fracture risk is likely to be very low and also unlikely to be a class effect. Further research is required to better understand and avoid this potentially serious complication, which may be related to changes in markers of bone turnover or secondary hyperparathyroidism with canagliflozin, or, alternatively, to an increased risk of hypovolemia-related falls.[129,130]

Another important consideration for nephrologists is the impact of SGLT2 inhibitors on volume depletion and electrolyte balance, which can be a substantial problem with other diuretics. Despite the presumed increase in luminal flow at the cortical collecting duct, SGLT2 inhibitors are generally not associated with an increased risk of hypokalemia and do not induce hyponatremia on the basis of volume contraction.[111] Similar neutral effects on calcium, phosphate, and magnesium have also been reported,[131] although small percentage changes in magnesium within the normal reference range have been reported that are unlikely to be of clinical significance.[131,132] SGLT2 inhibition does reduce plasma uric acid by ~15% through induction of uricosuria, an effect that may contribute to cardiorenal protection with these agents.[133–135] Importantly for nephrologists treating patients with impaired renal function, fewer data are available on electrolyte disturbances in patients with an eGFR <30 ml/min per 1.73 m^2. Our understanding of the potential for electrolyte abnormalities, particularly after the characteristic eGFR "dip" shortly after drug initiation in those with an eGFR <30 ml/min per 1.73 m^2, is not yet completely understood due to the lack of published data. For the risk of hypovolemia, in the absence of overt hypotension or effective circulating volume contraction, existing data suggest that SGLT2 inhibitors can be safely combined with other classes of diuretics.[13,66] So although natriuresis and osmotic diuresis may result in the risk of volume contraction, orthostatic symptoms, and, rarely, acute kidney injury, significant imbalance in these side effects related to volume depletion have not been demonstrated in clinical trials in patients treated with this class versus comparators.[23,26,136]

Despite excitement about cardiovascular and renal benefits with SGLT2 inhibitors, these agents should be avoided in certain clinical conditions. First, T2D patients with a history DKA should avoid SGLT2 inhibitors because these previous episodes likely demonstrate either that the patient has severe insulin deficiency or latent autoimmune diabetes of adults and that they may be higher risk of future DKA. Such therapy

should also be approached cautiously in T2D patients who exhibit features of T1D, such as lean body habitus and/or labile glycemic control. Second, patients with severe or recurrent urinary or genital tract infections are also not good candidates for these agents in most circumstances. In men with obstructive voiding symptoms due to benign prostatic hypertrophy or in women with urinary incontinence due to pelvic floor dysfunction, use of these agents often makes matters worse, and quality of life issues should be carefully considered in these populations specifically. Third, because patients with an eGFR ≥30 ml/min per 1.73 m^2 were included in the EMPA-REG OUTCOME and CANVAS Program trials and beneficial effects did not differ according to CKD stage, it is possible that physicians may start to treat high-risk cardiovascular patients with an eGFR between 30 and 60 ml/min per 1.73 m^2 with these agents. However, if this approach is taken based on available data and patients are treated "off-label," it should not be used in patients with an eGFR <30 ml/min per 1.73 m^2 because there are very few data available at this advanced stage of CKD to demonstrate either safety or efficacy. Next, patients with dynamic extracellular volume status such as in patients at risk of volume depletion (gastrointestinal losses, frequent episodes of reduced oral intake) should avoid SGLT2 inhibitors.[62] Similarly, patients undergoing procedures with anticipated reductions in renal perfusion, including elective surgery and i.v. contrast procedures, may need to have their SGLT2 inhibitors held, in a similar way that RAAS inhibitors should be held in these situations.[137] This might also be considered to minimize further volume shifts and the risk of perisurgical DKA. Under appropriate clinical circumstances, as with RAAS inhibitors, SGLT2 inhibitors can be held for 24 to 48 hours before the procedure to avoid changes in renal function. In addition, although patients at high renal or cardiovascular risk should not, as a rule, be treated with nonsteroidal anti-inflammatory drugs, concomitant SGLT2 inhibition plus nonsteroidal anti-inflammatory drug use may pose an additional risk due to reduced renal perfusion and should be avoided in the same way that RAAS inhibitors and nonsteroidal anti-inflammatory drugs should not be coadministered.

As a final comment, the results of the CANVAS Program, which demonstrated an increased risk of lower extremity amputation, have introduced some uncertainty in how to manage high-risk peripheral vascular disease patients with this agent (despite the fact that the other members of this class have not been associated with this complication to date). On the one hand, the presence of peripheral vascular disease made such patients eligible for inclusion in the EMPA-REG OUTCOME and CANVAS Program trials, which ultimately demonstrated remarkable improvements in cardiovascular and renal outcomes, albeit with the greater amputation risk with canagliflozin. Because no safety signal has emerged to suggest any risk of amputation with empagliflozin or dapagliflozin, it may be reasonable to treat patients deemed to be at higher risk of lower extremity amputation with empagliflozin or dapagliflozin, at least until more data are available.[123,124]

Future renal endpoint trials with SGLT2 inhibitors

Based on the promising effects of SGLT2 inhibitors on surrogate markers of kidney function and renal endpoints captured in analyses of cardiovascular outcome trials, it is clear that SGLT2 inhibitors have the potential to delay the progression of kidney function decline. Before these agents can be routinely used in patients with diabetic kidney disease, the results of primary renal outcome trials are needed. Two renal outcome trials are currently ongoing, and additional secondary renal endpoint data are being captured in cardiovascular safety trials.[138] The CREDENCE trial (NCT02065791) will determine the efficacy and safety of canagliflozin 100 mg/d to delay the progression of kidney disease in patients with T2D and kidney disease (Table 1). The DAPA-CKD trial (NCT03036150) will determine the efficacy and safety of dapagliflozin 10 mg/d to delay the progression of kidney disease. In contrast to the CREDENCE trial, DAPA-CKD is enrolling patients with both diabetic and nondiabetic CKD (Table 1), under the hypothesis that the natriuresis associated with SGLT2 inhibition would potentially also affect nonhyperglycemic individuals through effects on tubuloglomerular feedback.[48] A third kidney outcome trial with the empagliflozin has been announced, but details about the design and population are not yet available. The results of the CREDENCE and DAPA-CKD trials are expected in 2019 and 2021, respectively. In addition, the ongoing DECLARE TIMI-58 trial with dapagliflozin consists of both primary and secondary prevention cohorts. Although this might be a risk in terms of being able to demonstrate a significant reduction in cardiovascular risk or death, this trial is by far the largest, with >17,000 participants. It is therefore a unique opportunity to better assess the use of these agents in patients earlier in the disease process, particularly with regard to the primary prevention of CKD.[118] Renal outcomes are also being collected in ongoing, dedicated HF trials, including EMPEROR-Reduced (NCT03057977), EMPEROR-Preserved (NCT03057951), and DAPA-HF (NCT03036124). In addition to data that will emerge from these ongoing trials, the nephrology community also needs to determine whether there is a role for SGLT2 inhibition in patients (including children) with T1D and CKD and whether these agents have primary renal disease prevention effects in this patient group.[102]

CONCLUSION

Meaningful renal protective effects of SGLT2 inhibitors in patients with T2D have been demonstrated in 2 clinical trial programs using different members of this class. The impact of SGLT2 inhibition on the kidney appears to extend beyond reducing albuminuria because they also reduce other ostensibly more important renal outcomes. Notably, the benefits of SGLT2 inhibitors on renal and cardiovascular endpoints do not appear to differ based on background clinical characteristics or baseline eGFR level down to 30 ml/min per 1.73 m^2.

These agents also exert both cardiovascular and antialbuminuric effects regardless of background use of renin-angiotensin system blockade.[139] Accordingly, SGLT2 inhibitors are important emerging therapeutic tools for patients with diabetic kidney disease and in those at high cardiovascular risk. As reflected in recent clinical practice guidelines, antihyperglycemic therapies need to be individualized and prioritized based on background cardiorenal risk factors rather than on glycemic considerations alone.

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