Renoprotective effects of sodium-glucose cotransporter-2 inhibitors

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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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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.