chronic kidney disease

Are SGLT2 inhibitors a targeted treatment for diabetic kidney disease?

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The sodium-dependent glucose cotransporters (SGLT) are a family of transporters on the luminal side of proximal tubular epithelial cells. SGLT2 normally reabsorbs approximately 90% of the filtered glucose load. SGLT2 is more abundantly expressed in proximal tubular epithelial cells in patients with type 2 diabetes mellitus (DM) than in healthy individuals, leading to excessive glucose reabsorption. SGLT2 inhibitors lower blood glucose by increasing urinary glucose excretion. The glucose-lowering effect is independent of insulin (β-cell function and insulin sensitivity) and rarely causes hypoglycemia.

Several clinical trials have demonstrated a renoprotective effect of SGLT2 inhibitors, including the Empagliflozin Cardiovascular Outcome Event Trial in the Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial, the Canagliflozin Cardiovascular Assessment Study (CANVAS) program, and the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58 (DECLARE-TIMI 58) study. Zelniker *et al.*[1] conducted a systematic review including 34,322 participants enrolled in those 3 studies and concluded that SGLT2 inhibitors reduce the risk of the composite of worsening of kidney function, end-stage kidney disease (ESKD), or renal death by 45%. The risk reduction is similar in participants with atherosclerotic cardiovascular disease and in those with multiple risk factors, but the treatment effect is modified by estimated glomerular filtration rate (eGFR).

More recently, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study[2] was stopped early after reaching prespecified efficacy criteria. In contrast to prior studies focused on cardiovascular endpoints, the primary outcome of CREDENCE was a composite of ESKD, doubling of the serum creatinine, or death from renal or cardiovascular causes. In 4401 participants with type 2 diabetes and presumed diabetic kidney disease randomized to the SGLT2 inhibitor canagliflozin or to placebo, canagliflozin reduced the risk of the primary outcome by 30% (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.59–0.82). The effect sizes were similar for a composite outcome excluding cardiovascular death and for ESKD alone.[2] Taken together, the results of these trials support a robust effect of SGLT2 inhibitors on kidney disease outcomes in patients with diabetes (Figure 1).

To explore potential mechanisms underlying the renoprotective effect of SGLT2 inhibitors, Zelniker *et al.*[3] conducted a separate systematic review comparing the effects of SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RAs). In pooled analysis, a composite endpoint (macroalbuminuria, doubling of serum creatinine level or a 40% decline in eGFR, ESKD, or renal death) was significantly reduced by both GLP1-RAs (HR: 0.82; 95% CI: 0.75–0.89; $P < 0.001$) and SGLT2 inhibitors (HR: 0.62; 95% CI: 0.58–0.67; $P < 0.001$). However, only SGLT2 inhibitors reduced the risk of worsening eGFR, ESKD, or

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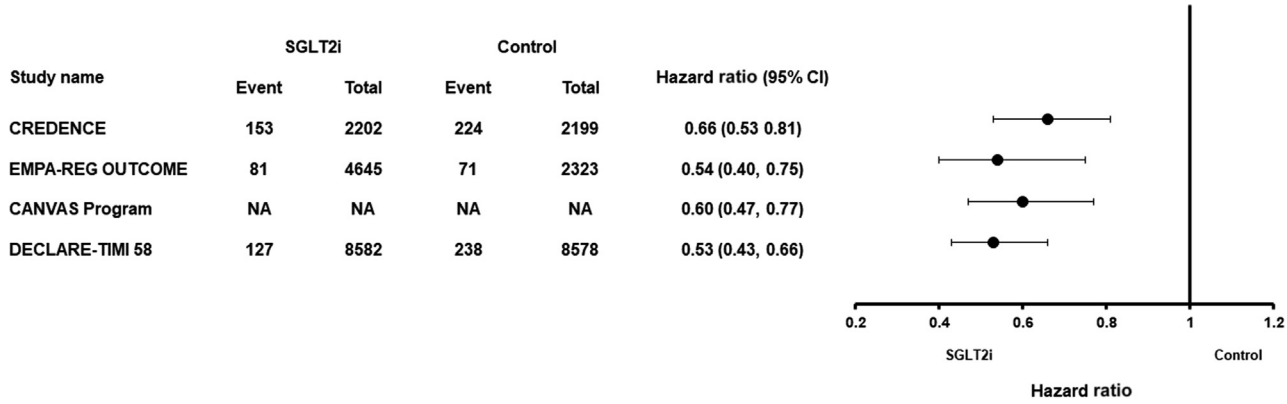

Figure 1 | Effect of sodium-dependent glucose cotransporter-2 (SGLT2) inhibitors on kidney disease endpoints. Unweighted forest plot summarizing the effect of SGLT2 inhibitors on the composite renal endpoint of doubling of serum creatinine, 40% decline in estimated glomerular filtration rate, end-stage kidney disease, or renal death in trials that included primary (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation [CREDENCE]) or secondary kidney disease endpoints (Empagliflozin Cardiovascular Outcome Event Trial in the Type 2 Diabetes Mellitus Patients–Removing Excess Glucose [EMPA-REG OUTCOME] study, Canagliflozin Cardiovascular Assessment Study [CANVAS] program, and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis In Myocardial Infarction 58 [DECLARE-TIMI 58] study). NA, not available.

renal death (HR: 0.55; 95% CI: 0.48–0.64; $P < 0.001$). Moreover, SGLT2 inhibitors also prevented the risk of doubling of serum creatinine (HR: 0.56; 95% CI: 0.44–0.71; $P < 0.001$). Of note, the number of participants treated with SGLT2 inhibitors in the placebo group was significantly higher than the number in the GLP1-RA–treated group, which could result in underestimation of the renoprotective effect of GLP1-RAs in this meta-analysis. However, considering this potential bias, these results suggest that SGLT2 inhibitors may be more effective in preventing the progression of diabetic kidney disease than GLP1-RAs are. The difference in their effects may be due to the mechanism of action of SGLT2 inhibitors.

Several potential mechanisms have been considered. Glomerular hyperfiltration is often observed in DM patients. In the EMPA-REG OUTCOME study, empagliflozin led to an early decrease in eGFR over the first 4 weeks, after which eGFR stabilized. This may suggest that suppression of hyperfiltration by SGLT2 inhibitors contributes to their renoprotective effect. Hyperfiltration is associated with glomerular hypertension and hypertrophy, which promote the progression of diabetic kidney disease. One of the causes of glomerular hyperfiltration is the failure of tubuloglomerular feedback.[4] In DM, reabsorption of glucose and sodium is enhanced through SGLT2 in the proximal tubule, reducing the delivery of sodium chloride to the macula densa. This leads to decreased production of adenosine, which promotes afferent arteriolar vasodilation and leads to glomerular hyperfiltration.[5] SGLT2 inhibitors suppress the reabsorption of glucose and sodium, which may restore tubule-glomerular feedback and prevent hyperfiltration.

The EMPA-REG OUTCOME study also showed sustained improvement of albuminuria after treatment, which suggests that the preservation of kidney function by SGLT2 inhibitors involves not only a reduction in hyperfiltration but also an effect on structural lesions. In patients with type 2 DM, dapagliflozin decreases the levels of the urine kidney injury biomarkers kidney injury molecule-1 and interleukin-6 and may have an anti-inflammatory effect.[6] SGLT2 inhibitors also exert metabolic effects including improvement of insulin sensitivity, reduced glucose toxicity, weight loss, and diuretic and blood pressure–lowering effects.[7] These effects likely contribute to the protective effect on kidney function. Finally, SGLT2 inhibition may also improve mitochondrial dysfunction and reduce oxidative stress.[8] Because GLP1-RAs also induce metabolic improvements and natriuresis,[9] the difference in the renoprotective effects of these agents and the SGLT2 inhibitors may arise from other mechanisms of action of SGLT2 inhibitors, such as inhibition of tubuloglomerular feedback or anti-inflammatory effects.

Clinicians should consider several issues before SGLT2 inhibitors are widely adopted as specific treatment for diabetic kidney disease. First, the clinical trials included in this

systematic review included only patients with eGFR of more than 30 ml/min per 1.73 m^2,[2,3] and the renoprotective effect of SGLT2 inhibitors has not been established in patients with more advanced chronic kidney disease (CKD). Second, SGLT2 inhibitors promote the excretion of a large amount of glucose into urine, which may lead to a lack of energy stores in elderly patients who are under dietary restrictions. Nutritional evaluation of elderly patients is recommended before treatment with SGLT2 inhibitors. Third, the increased risk of diabetic ketoacidosis observed with SGLT2 inhibitors has limited the investigation and use of these agents in patients with type 1 DM. With these caveats, the mechanisms of action of SGLT2 inhibitors suggest that their renoprotective effects may also be applicable to nondiabetic patients with chronic kidney disease. Additional studies are needed to evaluate the use of SGLT2 inhibitors for renoprotection in patients without DM and in those with more advanced chronic kidney disease.

DISCLOSURE

All the authors declared no competing interests.

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hypertension

Functional role of epigenetic regulation in the development of prenatal programmed hypertension

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The hypothesis that prenatal exposure to poor maternal health or nutrition is a risk factor for adult-onset disease was first proposed by the epidemiologist David Barker in 1990, based on observations in a cohort of low birth weight infants followed into adulthood. Fetal programming is now accepted as an important contributor to the development of cardiovascular disease and other adult conditions. Although the mechanisms remain unknown, it is increasingly assumed that epigenetic mechanisms play a key role in fetal programming.[1] Epigenetic regulation refers to stable changes in gene expression that occur