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Diabetes & its Complications

Use of SGLT2 Inhibitors to Slow the Progression of Chronic Kidney Disease: A Narrative Review with Bibliographic Citations

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Introduction

SGLT2 inhibitors, initially developed as glucose-lowering agents for type 2 diabetes, have rapidly evolved into foundational therapy for chronic kidney disease (CKD). Their approval for CKD—both in diabetic and non-diabetic patients—was driven by a series of large, well-designed clinical trials demonstrating robust cardiorenal protection. This shift is well summarized in recent comprehensive reviews, which highlight the broad metabolic, cardiovascular, and renal benefits of the class.

Cardiorenal Outcome Trials with Renal Endpoints.

CREDENCE (canagliflozin)

CREDENCE was the first trial specifically designed to evaluate renal outcomes in diabetic CKD. It demonstrated a marked reduction in kidney failure, doubling of serum creatinine, and renal or cardiovascular death. This trial established the first definitive evidence that SGLT2 inhibition could modify the natural history of diabetic CKD.

Reference: included in major reviews of SGLT2 inhibitors in CKD.

CANVAS Program (canagliflozin)

Although primarily a cardiovascular safety program, CANVAS provided early signals of renal benefit, showing slower eGFR decline and fewer renal events. These findings contributed to the emerging recognition of SGLT2 inhibitors as nephroprotective agents.

Reference: summarized in ERA-endorsed comprehensive review.

DECLARE–TIMI 58 (dapagliflozin)

DECLARE enrolled a broad population, many without established cardiovascular disease. Dapagliflozin significantly reduced composite renal outcomes and attenuated eGFR decline, suggesting that kidney benefits extend to lower-risk populations.

Reference: discussed in multiple reviews of SGLT2i cardiorenal protection.

EMPA-REG OUTCOME (empagliflozin)

This landmark trial first drew attention to renal benefits by showing substantial reductions in progression of nephropathy. The characteristic early eGFR "dip" followed by long-term stabilization became a hallmark of SGLT2 inhibition.

Reference: included in mechanistic and clinical reviews of SGLT2 inhibitors.

VERTIS CV (ertugliflozin)

VERTIS CV showed renal effects consistent with the class, though with less statistical power. Nonetheless, its findings aligned with the broader evidence base.

Reference: summarized in ERA comprehensive review.
Dedicated Renal Outcome Trials

DAPA-CKD (dapagliflozin)

DAPA-CKD was transformative: dapagliflozin reduced the risk of sustained eGFR decline, kidney failure, and renal or cardiovascular death by nearly 40%. Importantly, benefits were

equally strong in non-diabetic CKD, establishing SGLT2 inhibitors as disease-modifying therapy across etiologies.

Reference: highlighted in Kidney Medicine review of SGLT2 inhibitors in CKD.

EMPA-KIDNEY (empagliflozin)

EMPA-KIDNEY expanded the evidence base by including patients with low eGFR and minimal albuminuria. Empagliflozin significantly slowed CKD progression across a wide spectrum of kidney diseases, including non-diabetic CKD.

Reference: supported by individual participant-level meta-analysis of empagliflozin's renal effects.

SCORED (sotagliflozin)

Although terminated early, SCORED provided supportive evidence that dual SGLT1/2 inhibition may also confer renal and cardiovascular protection in diabetic CKD.

Reference: discussed in broad mechanistic reviews of SGLT2 inhibitors.

Meta-Analyses and Evidence Syntheses

Large meta-analyses have confirmed the consistency of renal benefits across trials, populations, and individual agents. These analyses show reductions in CKD progression, kidney failure, and hospitalization for heart failure, with benefits largely independent of glycemic control.

A major meta-analysis demonstrated that SGLT2 inhibitors improve kidney outcomes across a wide range of baseline eGFR and albuminuria levels, reinforcing their broad applicability in CKD management.

Mechanisms of Kidney Protection

Mechanistic reviews describe several complementary pathways through which SGLT2 inhibitors exert nephroprotection:

Restoration of tubuloglomerular feedback, reducing intraglomerular pressure, Hemodynamic stabilization, including mild natriuresis and reduced plasma volume, Metabolic improvements, such as lower glucose, weight, and blood pressure, Anti-inflammatory and antifibrotic effects, supported by experimental data.

These mechanisms are well summarized in molecular and clinical reviews of SGLT2 inhibitors in CKD.

Limitations and Areas of Uncertainty

Despite strong evidence, several gaps remain:
Limited data in advanced CKD (eGFR <20 mL/min/1.73 m²), Sparse evidence in rare glomerulopathies, transplant recipients, and very elderly patients, Uncertainty regarding benefits in non-proteinuric CKD, though EMPA-KIDNEY provides encouraging signals.

These limitations are discussed in ERA's comprehensive review of SGLT2 inhibitors in CKD. (1-5)

Conclusion

Across multiple high-quality trials, SGLT2 inhibitors consistently slow CKD progression, reduce the risk of kidney failure, and improve cardiovascular outcomes. Their efficacy in both diabetic and non-diabetic CKD represents a major therapeutic advance, positioning them as cornerstone therapy for chronic kidney disease.

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