Renoprotective benefits associated with SGLT2 inhibitor use in real-world studies

A systematic review and meta-analysis of observational studies looking at kidney outcomes in people with type 2 diabetes treated with SGLT2 inhibitors supports the findings of randomised controlled trials and suggests that renoprotective benefits extend to a broader adult population, including those with normal renal function and without albuminuria at baseline. Thirty-four studies, including nearly 1.5 million people with type 2 diabetes, were identified. Meta-analysis of 20 of the studies showed that, compared with other glucose-lowering drugs, SGLT2 inhibitor use was associated with a 46% lower risk of kidney failure. The renal benefit associated with SGLT2 inhibitors persisted across a wide range of subgroups, including those with baseline eGFR >90 to <60 mL/min/1.73 m², ACR <3 to >30 mg/mmol, and in people with or without chronic kidney disease. SGLT2 inhibitors were associated with lower risk of kidney failure when compared to DPP-4 inhibitors and to all other glucose-lowering drug classes combined. There was no statistically significant difference between the effects of SGLT2 inhibitors and GLP-1 receptor agonists when directly compared, but the authors warn that other studies have shown greater renal benefits with SGLT2 inhibitors, so this finding should be treated with caution. This review complements randomised clinical trial findings and supports extending SGLT2 inhibitor use to people with type 2 diabetes who may benefit from their renoprotective effects.

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Randomised clinical trials have well-defined inclusion and exclusion criteria and tend to enrol a very limited range of people, often at higher risk of the outcome being studied. "Real-world evidence" from observational studies can complement clinical trial findings and help explore drug effectiveness in broader clinical practice and help us understand whether trial findings are applicable to the people we treat, including those at lower risk.

In this systematic review, Forbes and colleagues from the UK examined 34 studies involving almost 1.5 million people participating in retrospective cohort studies to compare renal outcomes in those treated with SGLT2 inhibitors versus other glucose-lowering drugs. The studies included a broad range of people with type 2 diabetes, including those with and without chronic kidney disease (CKD) or cardiovascular disease, and those using or not using RAAS inhibitors at baseline. People were treated with SGLT2 inhibitors available at the time: canagliflozin, dapagliflozin and empagliflozin.

The primary outcome was a composite of kidney failure events, including renal transplant, dialysis, death from renal failure, sustained eGFR <15 mL/min/1.73 m², or sustained decline in eGFR of ≥40%, ≥50% or ≥57% depending on the study. Twenty-two studies were included in the meta-analysis, including 20 analysed for the kidney failure outcome and six which reported the risk of kidney failure according to baseline albuminuria status.

Results

Compared with other glucose-lowering drugs, SGLT2 inhibitor use was associated with a significant 46% lower risk of kidney failure.

Citation: Brown P (2023) Diabetes Distilled: Real-world evidence supports SGLT2 inhibitor kidney benefits across wider groups. *Diabetes & Primary Care* **25**: 95–6

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Subgroup analysis of this outcome showed that SGLT2 inhibitor use was associated with lower risk of kidney failure across a wide range of characteristics at baseline, including people with or without CKD, those with eGFR >90 to <60 mL/min/1.73 m^2, and those with albuminuria <3 to >30 mg/mmol; however, there was moderate heterogeneity/differences in results identified between individual studies.

Compared to DPP-4 inhibitors and to all other glucose-lowering drug classes combined, SGLT2 inhibitor use was associated with a 50% and 49% risk reduction, respectively, in the composite kidney failure outcome. Although in the subgroup analysis there was no significant difference between SGLT2 inhibitors and GLP-1 receptor agonists in associated kidney failure events, the authors conclude that this should not change practice and needs to be evaluated further. Indeed, a recent network meta-analysis demonstrated greater renal benefits with SGLT2 inhibitors than with GLP-1 RAs (Kawai et al, 2022). On current evidence, clinical guidelines recommend that SGLT2 inhibitors should be prioritised over GLP-1 RAs for renoprotection.

Absolute risk reductions per 100 person-years for kidney failure events in those treated with SGLT2 inhibitors versus other glucose-lowering drugs were calculated from 17 of the 20 studies included in the meta-analysis, and the results pooled. Based on this, to prevent one kidney failure event per year, 156 people with type 2 diabetes would need to be treated with an SGLT2 inhibitor.

Comment

Most observational studies have a moderate risk of bias, particularly due to confounding, and this was a limitation in the present study. The authors concluded that there may also have been a risk of publication bias, as studies with positive findings are more likely to be published, and this could overestimate the benefits of SGLT2 inhibitors.

A recent meta-analysis of placebo-controlled trials demonstrated that SGLT2 inhibitors decreased the risk of kidney disease progression (using similar parameters to those used here, with sustained 50% reduction in eGFR) by 38% in people with diabetes (Baigent et al, 2022). In the DAPA-CKD study, dapagliflozin reduced the risk of kidney disease progression compared to placebo by 51% in those with eGFR ≥45 mL/min/1.73m^2, and by 37% when eGFR was <45 mL/min/1.73 m^2 (Heerspink et al, 2020).

Clinical trials often enrol a very limited range of people who may not fully represent the broader population we treat in primary care. Therefore, it is reassuring to see real-world evidence that, compared with other glucose-lowering drugs, use of SGLT2 inhibitors is associated with renal benefits. ■

Sodium–glucose cotransporter-2 inhibitors and kidney outcomes in real-world type 2 diabetes populations: A systematic review and meta-analysis of observational studies

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Baigent C, Emberson JR, Haynes R et a; Nuffield Department of Population Health Renal Studies Group; SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium (2022) Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: Collaborative meta-analysis of large placebo-controlled trials. *Lancet* **400**: 1788–801

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Kawai Y, Uneda K, Yamada T et al (2022) Comparison of effects of SGLT-2 inhibitors and GLP-1 receptor agonists on cardiovascular and renal outcomes in type 2 diabetes mellitus patients with/without albuminuria: A systematic review and network meta-analysis. *Diabetes Res Clin Pract* **183**: 109146