More evidence that SGLT2 inhibitors slow CKD progression. Are we optimising care?

In the EMPA-KIDNEY randomised controlled trial, published in the *New England Journal of Medicine*, the SGLT2 inhibitor empagliflozin significantly reduced the rate of progression of chronic kidney disease and decreased cardiovascular mortality in people with and without type 2 diabetes. Over 2 years, amongst 6609 participants, the composite primary outcome of progression of renal disease or death from cardiovascular causes was reduced by 28% in those treated with empagliflozin compared with placebo. The benefits were comparable in those with and without type 2 diabetes, and were consistent across a wider range of eGFR values (from 20 to <90 mL/min/1.73 m^2) than those included in the other major renal studies of SGLT2 inhibitors. Rates of hospital admission for any cause were significantly reduced by 14%.

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The EMPA-KIDNEY (Study of Heart and Kidney Protection with Empagliflozin) randomised controlled trial enrolled 6609 people with chronic kidney disease (CKD) who fitted one of two categories: either an eGFR of 20–45 mL/min/1.73 m^2 regardless of urinary ACR level, or an eGFR of 45 to <90 mL/min/1.73 m^2 plus an ACR of ≥200 mg/g (≥22.6 mg/mmol). Participants were randomised to empagliflozin 10 mg or placebo and were followed for a median of 2 years; the study was stopped early due to prespecified efficacy endpoints being met. The composite primary outcome was progression of renal disease (development of end-stage renal disease, sustained eGFR reduction to <10 mL/min/1.73 m^2, sustained eGFR reduction of ≥40% from baseline or death from renal causes) or death from cardiovascular causes.

Results

The primary endpoint occurred in 13.1% of empagliflozin and 16.9% of placebo recipients, a significant relative risk reduction of 28%. Importantly, the reductions were consistent across a wide variety of participants: those with and without diabetes and those in different eGFR ranges at baseline. Rates of hospitalisation for any cause were also reduced by a significant 14% in the empagliflozin group compared with placebo, but there were no between-group differences in two of the other endpoints examined: a composite of hospitalisation for heart failure or cardiovascular death, and all-cause mortality.

At baseline, 48% of participants had a urinary ACR of less than 300 mg/g. There was a limited number of primary composite outcome events in this subgroup, which was to be expected as these people would have had slower progression of their CKD than those with a higher ACR. Because of this, there were comparable rates of the primary outcome between empagliflozin and placebo within this subgroup. However, a pre-specified analysis of the annual rate of change in eGFR, which is an accepted surrogate for CKD progression, demonstrated that empagliflozin did slow the rate of eGFR decline even in these participants. Importantly, rates of serious adverse events were similar between the empagliflozin and placebo groups.

Since treatment with ACE inhibitors or angiotensin receptor blockers is recommended for people with CKD, significant numbers of participants were also receiving one of these drugs. Interestingly, there was less benefit in this study among participants who were not

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"The primary endpoint occurred in 13.1% of empagliflozin and 16.9% of placebo recipients, a significant relative risk reduction of 28%."

also receiving these renin–angiotensin system (RAS) blockers, which raises the question, asked in an accompanying editorial (August, 2023), of whether SGLT2 inhibitors are equally effective without RAS blockade.

Analysis

Beneficial effects of SGLT2 inhibitors on slowing the progression of renal disease in people with type 2 diabetes were initially identified in the cardiovascular outcome trials for agents within the class, resulting in specific studies being undertaken subsequently in people with CKD/diabetic kidney disease. In the case of empagliflozin and dapagliflozin, these studies have included people with and without type 2 diabetes.

Although the results of EMPA-KIDNEY are quantitatively similar to those in the other renal studies of SGLT2 inhibitors, there are differences in the inclusion criteria between the studies, which are important in expanding the range of people who are proven to benefit from SGLT2 inhibitors, and which can help us to understand which of our patients with CKD may benefit from empagliflozin. The CREDENCE trial of canagliflozin (Perkovic et al, 2019) enrolled only people with type 2 diabetes and a urinary ACR of ≥300 mg/g (≥33.9 mg/mmol) and excluded people with an eGFR <30 mL/min/1.73 m^2. This is reflected in the drug's licence (see our recently updated need-to-know guide). The DAPA-CKD trial of dapagliflozin (Heerspink et al, 2020) included significant numbers of people with and without diabetes, and people with an eGFR <30 mL/min/1.73 m^2, as did the present EMPA-KIDNEY study.

This was a large study with good rates of adherence to therapy and follow-up. Despite the lower-than-expected number of cardiovascular events, the reduction in cardiovascular events was similar to that expected and in line with a recent meta-analysis which demonstrated that SGLT2 inhibitors significantly reduce the relative risk of cardiovascular death by 14% and the risk of hospitalisation for heart failure or death from cardiovascular causes by 23% (Baigent et al, 2022).

Even more recently, a pre-specified analysis from the DAPA-CKD study has confirmed that the benefits of dapagliflozin in reducing renal disease progression and cardiovascular events remain consistent irrespective of the types and number of other glucose-lowering treatments being used at baseline (Beernink et al, 2023).

The present study again reminds us we should review people with CKD (either eGFR <60 mL/min/1.73 m^2 or ACR >3 mg/mmol); assess their suitability for ACE inhibitor/ARB treatment; add an appropriate SGLT2 inhibitor if they fit a group likely to benefit; and ensure optimised control of blood pressure, glycaemia and lipids to slow progression of renal disease and reduce the risk of cardiovascular events. We will always find people whose treatment is not yet optimised or where management has lapsed and who would benefit from review. ■

August P (2023) Chronic kidney disease – another step forward. *N Engl J Med* **388**: 179–80

Baigent C, Emberson JR, Haynes R et al; 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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ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND
The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

METHODS
We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m^2 with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

RESULTS
A total of 6609 patients underwent randomization. During a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.

CONCLUSIONS
Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

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117

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