# Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial

*The EMPA-KIDNEY Collaborative Group**

## Summary

**Background** The EMPA-KIDNEY trial showed that empagliflozin reduced the risk of the primary composite outcome of kidney disease progression or cardiovascular death in patients with chronic kidney disease mainly through slowing progression. We aimed to assess how effects of empagliflozin might differ by primary kidney disease across its broad population.

**Methods** EMPA-KIDNEY, a randomised, controlled, phase 3 trial, was conducted at 241 centres in eight countries (Canada, China, Germany, Italy, Japan, Malaysia, the UK, and the USA). Patients were eligible if their estimated glomerular filtration rate (eGFR) was 20 to less than 45 mL/min per 1·73 m², or 45 to less than 90 mL/min per 1·73 m² with a urinary albumin-to-creatinine ratio (uACR) of 200 mg/g or higher at screening. They were randomly assigned (1:1) to 10 mg oral empagliflozin once daily or matching placebo. Effects on kidney disease progression (defined as a sustained ≥40% eGFR decline from randomisation, end-stage kidney disease, a sustained eGFR below 10 mL/min per 1·73 m², or death from kidney failure) were assessed using prespecified Cox models, and eGFR slope analyses used shared parameter models. Subgroup comparisons were performed by including relevant interaction terms in models. EMPA-KIDNEY is registered with ClinicalTrials.gov, NCT03594110.

**Findings** Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and followed up for a median of 2·0 years (IQR 1·5–2·4). Prespecified subgroupings by primary kidney disease included 2057 (31·1%) participants with diabetic kidney disease, 1669 (25·3%) with glomerular disease, 1445 (21·9%) with hypertensive or renovascular disease, and 1438 (21·8%) with other or unknown causes. Kidney disease progression occurred in 384 (11·6%) of 3304 patients in the empagliflozin group and 504 (15·2%) of 3305 patients in the placebo group (hazard ratio 0·71 [95% CI 0·62–0·81]), with no evidence that the relative effect size varied significantly by primary kidney disease ($p_{heterogeneity}$=0·62). The between-group difference in chronic eGFR slopes (ie, from 2 months to final follow-up) was 1·37 mL/min per 1·73 m² per year (95% CI 1·16–1·59), representing a 50% (42–58) reduction in the rate of chronic eGFR decline. This relative effect of empagliflozin on chronic eGFR slope was similar in analyses by different primary kidney diseases, including in explorations by type of glomerular disease and diabetes (p values for heterogeneity all >0·1).

**Interpretation** In a broad range of patients with chronic kidney disease at risk of progression, including a wide range of non-diabetic causes of chronic kidney disease, empagliflozin reduced risk of kidney disease progression. Relative effect sizes were broadly similar irrespective of the cause of primary kidney disease, suggesting that SGLT2 inhibitors should be part of a standard of care to minimise risk of kidney failure in chronic kidney disease.

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## Introduction

Sodium–glucose co-transporter-2 (SGLT2) inhibitors were initially developed for the management of hyperglycaemia in people with type 2 diabetes.[1] In chronic kidney disease, several large-scale placebo-controlled outcome trials have shown that empagliflozin, dapagliflozin, and canagliflozin reduced the risk of primary composite cardiorenal outcomes based on kidney disease progression or cardiovascular death.[2–4] Meta-analysis of these and other large SGLT2 inhibitor trials showed a 37% reduction in risk (relative risk [RR] 0·63 [95% CI 0·58–0·69]) of at least a 50% sustained decline in estimated glomerular filtration rate (eGFR) from randomisation, end-stage kidney disease (ie, commencement of maintenance dialysis or receipt of a kidney transplant), a sustained low eGFR (<15 or <10 mL/min per 1·73 m²), or death from kidney failure.[5] Relative benefits of SGLT2 inhibition seemed to be similar in patients with and without diabetes despite their attenuated effect on glycosuria in the absence of hyperglycaemia.[5] Two trials contributing to this meta-analysis[5] included participants with non-diabetic primary kidney diseases (EMPA-KIDNEY and DAPA-CKD).[2,3] Analyses from these two trials, including 476 kidney disease progression outcomes in participants with

## Research in context

### Evidence before this study

We updated a previous systematic search of the MEDLINE and Embase databases via Ovid (PROSPERO CRD42022351618) to cover the period from database inception to May 30, 2023, to identify large (ie, at least 500 participants per group), double-blind, placebo-controlled, sodium–glucose co-transporter-2 (SGLT2) inhibitor trials with at least 6 months of follow-up. We sought reports that described effects of SGLT2 inhibition on kidney disease progression by primary kidney disease. Other than EMPA-KIDNEY, only one previous large trial of 4304 participants, DAPA-CKD, randomly assigned patients with proteinuric chronic kidney disease with and without diabetes and assessed effects by primary kidney disease. Of the 1398 participants without diabetes in DAPA-CKD, only 128 patients had a primary outcome, including 109 with kidney disease progression, limiting statistical power to explore effects by primary kidney disease. It raised a hypothesis that a primary kidney diagnosis might not modify relative treatment effects.

### Added value of this study

EMPA-KIDNEY recruited 6609 patients with chronic kidney disease, including 1669 (25·3%) with glomerular disease (817 [12·4%] with IgA nephropathy), 1445 (21·9%) with hypertensive or renovascular disease, and 1438 (21·8%) with other or unknown causes. There were 562 kidney disease progression outcomes in these participants with non-diabetic causes of chronic kidney disease. Overall, empagliflozin was generally well tolerated and resulted in a 29% relative risk reduction in kidney disease progression (hazard ratio 0·71 [95% CI 0·62–0·81]). Relative effects across these main categories of primary kidney disease and among the different subtypes of glomerular disease were broadly similar. No important differences in relative effects of empagliflozin were identified in explorations using eGFR slope analyses, which provided increased sensitivity to detect any variation by different types of primary kidney disease.

### Implications of all the available evidence

Subgroup analyses from both the EMPA-KIDNEY and DAPA-CKD trials show that SGLT2 inhibitors substantially slow the progression of chronic kidney disease irrespective of the primary kidney disease. SGLT2 inhibitor use has the potential to reduce the future global burden of kidney failure should it be widely prescribed to patients with chronic kidney disease at risk of progression.

a non-diabetic cause of chronic kidney disease reported that the relative effects of SGLT2 inhibition seemed to be similar across the different primary kidney diagnoses (p value for heterogeneity between groupings of primary kidney disease was 0·67).[5] The meta-analysis did not present any details of effects of SGLT2 inhibition on eGFR slopes, albuminuria, blood pressure, hospitalisation or safety outcomes, or specific baseline characteristics.[5] Such details are often desired by clinicians and guideline committees to inform decisions on when to offer an SGLT2 inhibitor to particular patients.

The EMPA-KIDNEY trial assessed the effects of empagliflozin in 6609 patients with chronic kidney disease, including approximately two-thirds of participants with an investigator-reported non-diabetic primary kidney disease.[2,6] Effects among patients with different primary causes of chronic kidney disease are important to consider because patients with different pathophysiology might respond differently to SGLT2 inhibition. We therefore aimed to assess the effects of empagliflozin on kidney outcomes among participants from the EMPA-KIDNEY trial with different types of kidney disease using sensitive eGFR slope-based outcomes. We also provide information on the observed effects on the range of other collected outcomes, with additional analyses presented in a parallel publication.[7]

## Methods

### Study design and participants

Details of EMPA-KIDNEY's rationale, double-blind placebo-controlled design, protocol, prespecified data analysis plan, completeness of follow-up, and main results have been reported previously.[2,6,8] The trial was conducted at 241 centres in eight countries (Canada, China, Germany, Italy, Japan, Malaysia, the UK, and the USA). Regulatory authorities and ethics committees for each centre approved the trial. Patients aged 18 years or older with a race-adjusted Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation-based[9] eGFR between 20 and less than 45 mL/min per 1·73 m² (irrespective of level of albuminuria), or an eGFR between 45 and less than 90 mL/min per 1·73 m² with a urinary albumin-to-creatinine ratio (uACR) of 200 mg/g or more at the screening visit were eligible, provided they were prescribed a clinically appropriate dose of a single renin–angiotensin system (RAS) inhibitor, where indicated and tolerated. Patients with or without diabetes were eligible, and polycystic kidney disease was the only excluded primary kidney disease. Patients receiving at least 45 mg prednisolone daily (or equivalent) or on intravenous immunosuppression in the past 3 months were excluded.

All eligible and consenting participants entered a pre-randomisation run-in phase and were provided with a 15-week supply of once daily placebo tablets. During this time, local investigators reviewed screening data, assessed current RAS inhibitor use, and approved potential participants for later randomisation. Participant-reported primary kidney disease was confirmed by local lead investigators, and all participants were asked whether they had had a kidney biopsy. Throughout the trial, clinical responsibility for participants remained with their local doctors. After completing the run-in, willing and eligible

participants had central samples of blood and urine collected for central analysis and long-term storage, and were randomly allocated (1:1) to receive empagliflozin (10 mg once daily orally) or matching placebo using a minimisation algorithm.[10] At follow-up visits, participants provided information on renal status (ie, any dialysis treatment or receipt of a kidney transplant), adherence to study treatment (with reasons for stopping) and details of concomitant medication. They were also asked in a structured interview about any serious adverse events (and protocol-specified non-serious adverse events), underwent clinical measurements of blood pressure and weight, and had blood collected for safety assessments of creatinine, liver function, and potassium analysed at local laboratories. Blood samples and, at selected visits, urine samples were also sent to the central laboratory for efficacy analyses (including serum creatinine) and archiving.

### Outcomes

The prespecified primary outcome was time-to-first occurrence of the composite outcome of kidney disease progression or cardiovascular death. Kidney disease progression included end-stage kidney disease, defined as commencing maintenance dialysis or receipt of a kidney transplant; a sustained decline in eGFR to less than 10 mL/min per 1·73 m²; a sustained decline in eGFR of at least 40% from baseline; or death from kidney failure. The term sustained was defined as either measured at two consecutive scheduled study follow-up visits at least 30 days apart, or measured at the last scheduled study follow-up visit or the last scheduled visit before death (or withdrawal of consent or loss to follow-up). Central laboratory serum creatinine measurements were used to calculate CKD-EPI eGFR, with local laboratory creatinine measurement used when central results were missing. Hospitalisation for heart failure or death from cardiovascular causes, all-cause hospitalisations, and all-cause mortality were key secondary outcomes prespecified to be adjusted for multiple testing with the use of the Hochberg step-up procedure. Kidney disease progression was a secondary outcome, and analyses of annual rate of change in eGFR (chronic and total slope) were tertiary outcomes. Further exploratory analyses of these eGFR outcomes were prespecified. Serious acute kidney injury was based on reported adverse events and was subject to confirmation by adjudication.[2] Prespecified subgroups of primary kidney disease were diabetic; glomerular; hypertensive or renovascular; other and unknown combined. To test hypotheses raised by subsidiary reports from the DAPA-CKD trial,[11,12] the glomerular disease subgroup was further split post hoc into IgA nephropathy, focal segmental glomerulosclerosis, and other glomerulonephritides.

### Statistical analysis

Follow-up was planned until at least 1070 participants had a first primary outcome, in order to provide 90% power at two-sided p value of 0·05 to detect an 18% relative reduction in risk,[6] but the trial was recommended to stop early at the single planned formal interim analysis for efficacy in March, 2022. Results based on 990 first primary outcomes (and 888 first kidney disease progression outcomes) have been previously reported.[2] In the present report, we focus on whether effects of SGLT2 inhibition with empagliflozin on kidney disease progression and eGFR slopes varied among participants with different types of primary kidney diseases. Secondarily, we assessed whether effects on albuminuria, blood pressure, cardiovascular, hospitalisation, and safety outcomes varied by primary kidney disease.

All analyses were performed according to the intention-to-treat principle. Time-to-event analyses defined time at risk as originating or starting from randomisation and finishing at final follow-up, or censoring at the earliest of death, loss to follow-up, or withdrawal of consent. A prespecified Cox proportional hazards regression model including adjustment for categorised baseline variables specified in the minimisation algorithm (age, sex, previous diabetes, eGFR, uACR, and region) was used after testing the significance of an interaction between treatment allocation and log(survival time) to confirm no evidence against proportionality for any of the time-to-event outcomes. A treatment by primary kidney disease interaction term was then used to estimate hazard ratios (HRs) and 95% CIs for empagliflozin versus placebo for time-to-event analyses (ie, the primary, kidney disease progression, cardiovascular, and safety categorical outcomes).[13] Tests for heterogeneity between subgroups for time-to-event analyses were performed using the Wald $\chi^2$ statistic for the treatment by primary kidney disease interaction.

Effects of empagliflozin on annual rates of change in eGFR were assessed using prespecified shared parameter models,[14] and emphasised the chronic eGFR slope results (which take account of the reversible acute dip in eGFR when SGLT2 inhibitors are commenced) and relative effects (to enable direct tests of any differences of the effects of empagliflozin between subgroups). These relative effects on eGFR slope were calculated using methods developed for a parallel publication,[7] and required division of the absolute effect (and its 95% CI) by the mean slope in the placebo group. Effects of empagliflozin on continuous outcomes (ie, blood pressure and albuminuria) used a prespecified mixed model for repeated measures (MMRM) approach. Standard tests for heterogeneity between subgroups were performed for annual rate of change in eGFR and continuous outcomes. More complete statistical details are provided in the previously published data analysis plan and in the appendix (p 9).[2] SAS software (version 9.4) and R (version 3.6.2) were used for analyses.

### Role of the funding source

The analyses were performed on the original full database developed and held by the Nuffield Department

| | Diabetic kidney disease (n=2057) | Hypertensive or renovascular disease (n=1445) | Glomerular disease (n=1669) | Other or Unknown (n=1438) |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age at randomisation, years | 68·2 (9·8) | 68·4 (11·9) | 53·5 (13·6) | 65·0 (14·7) |
| Sex | | | | |
| Female | 684 (33·3%) | 430 (29·8%) | 596 (35·7%) | 482 (33·5%) |
| Male | 1373 (66·7%) | 1015 (70·2%) | 1073 (64·3%) | 956 (66·5%) |
| Race (all regions) | | | | |
| White | 1115 (54·2%) | 953 (66·0%) | 765 (45·8%) | 1026 (71·3%) |
| Black | 127 (6·2%) | 85 (5·9%) | 22 (1·3%) | 28 (1·9%) |
| Asian | 780 (37·9%) | 387 (26·8%) | 863 (51·7%) | 363 (25·2%) |
| Mixed | 7 (0·3%) | 3 (0·2%) | 5 (0·3%) | 6 (0·4%) |
| Other | 28 (1·4%) | 17 (1·2%) | 14 (0·8%) | 15 (1·0%) |
| **Previous disease** | | | | |
| Previous diabetes | | | | |
| Yes | 2057 (100·0%) | 402 (27·8%) | 172 (10·3%) | 409 (28·4%) |
| No | 0 | 1043 (72·2%) | 1497 (89·7%) | 1029 (71·6%) |
| Previous diabetes type | | | | |
| Type 1 | 60 (2·9%) | 2 (0·1%) | 0 | 6 (0·4%) |
| Type 2 | 1977 (96·1%) | 397 (27·5%) | 168 (10·1%) | 394 (27·4%) |
| Other or unknown | 20 (1·0%) | 3 (0·2%) | 4 (0·2%) | 9 (0·6%) |
| History of cardiovascular disease* | | | | |
| Yes | 713 (34·7%) | 516 (35·7%) | 144 (8·6%) | 392 (27·3%) |
| No | 1344 (65·3%) | 929 (64·3%) | 1525 (91·4%) | 1046 (72·7%) |
| **Clinical measurements** | | | | |
| Systolic blood pressure, mm Hg | 139·9 (19·2) | 138·0 (18·4) | 132·8 (16·0) | 134·6 (18·3) |
| Diastolic blood pressure, mm Hg | 75·2 (11·6) | 78·0 (12·2) | 82·0 (10·8) | 77·7 (11·7) |
| BMI, kg/m² | 31·7 (7·1) | 30·0 (6·3) | 27·2 (5·8) | 29·6 (6·7) |
| **Laboratory measurements** | | | | |
| eGFR, mL/min per 1·73 m²† | 35·8 (13·9) | 35·1 (11·6) | 42·4 (17·8) | 35·7 (11·9) |
| <30 | 801 (38·9%) | 533 (36·9%) | 452 (27·1%) | 496 (34·5%) |
| 30 to <45 | 901 (43·8%) | 699 (48·4%) | 636 (38·1%) | 692 (48·1%) |
| ≥45 | 355 (17·3%) | 213 (14·7%) | 581 (34·8%) | 250 (17·4%) |
| uACR, mg/g† | | | | |
| Geometric mean (SD) | 251 (7·6) | 110 (7·6) | 577 (3·8) | 126 (7·4) |
| Median (IQR) | 336 (52–1304) | 114 (18–623) | 700 (306–1428) | 149 (23–695) |
| <30 | 376 (18·3%) | 469 (32·5%) | 66 (4·0%) | 417 (29·0%) |
| 30 to 300 | 623 (30·3%) | 444 (30·7%) | 344 (20·6%) | 453 (31·5%) |
| >300 | 1058 (51·4%) | 532 (36·8%) | 1259 (75·4%) | 568 (39·5%) |
| **Concomitant medication use** | | | | |
| RAS inhibitor | 1779 (86·5%) | 1188 (82·2%) | 1535 (92·0%) | 1126 (78·3%) |
| Immunosuppression | 28 (1·4%) | 20 (1·4%) | 139 (8·3%) | 50 (3·5%) |
| **Self-reported investigation** | | | | |
| Kidney biopsy | 136 (6·6%) | 184 (12·7%) | 1312 (78·6%) | 230 (16·0%) |

Data mean (SD), n (%), or median (IQR). eGFR=estimated glomerular filtration rate. RAS=renin–angiotensin system. uACR=urinary albumin-to-creatinine ratio. *Defined as self-reported history of myocardial infarction, heart failure, stroke, transient ischaemic attack, or peripheral arterial disease. †Uses central measurement taken at the randomisation visit, or more recent local laboratory result before randomisation. Previous diabetes defined as participant-reported history of diabetes of any type, use of glucose-lowering medication, or baseline $HbA_{1c}$ of at least 48 mmol/mol (6·5%) at randomisation visit.

***Table 1:*** **Characteristics of participants at recruitment by primary kidney disease**

of Population Health at the University of Oxford (Oxford, UK). Boehringer Ingelheim provided a grant to the University of Oxford and have members on the steering committee, which is responsible for trial design and reviewing all trial publications.

## Results

Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and followed for a median of 2·0 years (IQR 1·5–2·4). Prespecified subgroups of primary kidney disease included 2057 (31·1%) participants with diabetic kidney disease, 1445 (21·9%) with hypertensive or renovascular disease, 1669 (25·3%) with glomerular disease, and 1438 (21·8%) with other or unknown causes (table 1). Of the participants with glomerular disease, 817 (49·0%) had IgA nephropathy, 195 (11·7%) had focal segmental glomerulosclerosis, and 657 (39·4%) had other glomerulonephritides. A more detailed listing of investigator-confirmed primary kidney disease is provided in the appendix (p 11).

Participants with glomerular disease were younger (mean age 53·5 years [SD 13·6]) and were less likely to have diabetes and cardiovascular disease than participants with other causes of kidney disease (table 1; appendix p 12). Patients with glomerular disease also had higher mean eGFR of 42·4 mL/min per 1·73 m² (SD 17·8) and median uACR of 700 mg/g (IQR 306–1428) than the trial overall mean eGFR of 37·3 mL/min per 1·73 m² (14·5) and median uACR of 329 mg/g (49–1069; table 1; appendix pp 12–13). Among 1669 patients with glomerular disease, 1312 (78·6%) reported a previous kidney biopsy compared with 136 (6·6%) of 2057 with diabetic kidney disease, 184 (12·7%) of 1445 with hypertensive or renovascular disease, and 230 (16·0%) of 1438 with other or unknown diagnoses (table 1; appendix pp 11, 14).

The primary composite outcome of kidney disease progression or cardiovascular death occurred in 432 (13·1%) of 3304 patients in the empagliflozin group and 558 (16·9%) of 3305 patients in the placebo group (HR 0·72 [95% CI 0·64–0·82]), with broadly similar effects across the four main categories of cause of kidney disease ($p_{heterogeneity}$=0·56; table 2). Of the 990 primary outcomes, 384 (11·6%) of 3304 patients in the empagliflozin group and 504 (15·2%) of 3305 patients in the placebo group had a kidney disease progression outcome (HR 0·71 [95% CI 0·62–0·81]), and this finding was similar across the kidney disease subgroups ($p_{heterogeneity}$=0·62; table 2; figure 1). Further exploration found no strong evidence of heterogeneity by subtype of glomerular disease ($p_{heterogeneity}$=0·25), but was limited by only 30 outcomes in participants with focal segmental glomerulosclerosis (figure 1). Risk of progression to end-stage kidney disease, sustained eGFR of less than 10 mL/min per 1·73 m², or death from kidney failure was reduced by 31% (HR 0·69 [95% CI 0·56–0·85]), with similar effects across the categories of kidney disease ($p_{heterogeneity}$=0·85; table 2).

Analyses by annual rate of change in eGFR provides a more sensitive approach to assess for any differences in relative effects of study treatment between subgroups. The expected acute decrease in eGFR upon initiation of

empagliflozin was observed (appendix p 20), followed by a slowing of the rate of annual decline. Overall, empagliflozin was associated with a slower decline in eGFR with a between-group difference in the total eGFR slope from randomisation to the final follow-up visit of –0·75 mL/min per 1·73 m² per year (95% CI –0·54 to –0·96). When the early acute dip was excluded, the between-group difference in eGFR from 2 months to final follow-up (chronic slope) was –1·37 mL/min per 1·73 m² per year (95% CI –1·16 to –1·59). This effect

| | Empagliflozin group (n=3304) | | Placebo group (n=3305) | | Hazard ratio (95% CI) | $p_{heterogeneity}$* |
|---|---|---|---|---|---|---|
| | n (%) | Events per 100 person-years | n (%) | Events per 100 person-years | | |
| **Primary outcome and its components** | | | | | | |
| Primary outcome: progression of kidney disease or death from cardiovascular causes | .. | .. | .. | .. | .. | 0·56 |
| Diabetic kidney disease | 161 (15·6%) | 8·10 | 223 (21·8%) | 11·41 | 0·65 (0·53–0·80) | .. |
| Hypertensive or renovascular disease | 82 (11·6%) | 5·95 | 96 (13·0%) | 6·92 | 0·82 (0·61–1·11) | .. |
| Glomerular disease | 117 (13·7%) | 7·48 | 142 (17·4%) | 9·66 | 0·77 (0·60–0·98) | .. |
| Other or unknown | 72 (10·1%) | 5·24 | 97 (13·4%) | 6·84 | 0·73 (0·54–1·00) | .. |
| Overall | 432 (13·1%) | 6·85 | 558 (16·9%) | 8·96 | 0·72 (0·64–0·82) | .. |
| Any kidney disease progression | .. | .. | .. | .. | .. | 0·62 |
| Diabetic kidney disease | 137 (13·3%) | 6·89 | 189 (18·4%) | 9·67 | 0·64 (0·52–0·80) | .. |
| Hypertensive or renovascular disease | 72 (10·2%) | 5·22 | 87 (11·8%) | 6·27 | 0·79 (0·58–1·08) | .. |
| Glomerular disease | 115 (13·5%) | 7·36 | 139 (17·0%) | 9·46 | 0·77 (0·60–0·99) | .. |
| Other or unknown | 60 (8·4%) | 4·37 | 89 (12·3%) | 6·28 | 0·67 (0·48–0·92) | .. |
| Overall | 384 (11·6%) | 6·09 | 504 (15·2%) | 8·09 | 0·71 (0·62–0·81) | .. |
| End-stage kidney disease†, sustained eGFR <10 mL/min per 1·73 m² or death from kidney failure | .. | .. | .. | .. | .. | 0·85 |
| Diabetic kidney disease | 61 (5·9%) | 3·00 | 89 (8·7%) | 4·44 | 0·64 (0·46–0·88) | .. |
| Hypertensive or renovascular disease | 25 (3·5%) | 1·79 | 33 (4·5%) | 2·34 | 0·73 (0·43–1·22) | .. |
| Glomerular disease | 48 (5·6%) | 3·03 | 58 (7·1%) | 3·86 | 0·78 (0·53–1·15) | .. |
| Other or unknown | 24 (3·4%) | 1·73 | 41 (5·7%) | 2·84 | 0·63 (0·38–1·05) | .. |
| Overall | 158 (4·8%) | 2·47 | 221 (6·7%) | 3·47 | 0·69 (0·56–0·85) | .. |
| Sustained ≥40% decline in eGFR from randomisation‡ | .. | .. | .. | .. | .. | 0·49 |
| Diabetic kidney disease | 125 (12·1%) | 6·25 | 174 (17·0%) | 8·88 | 0·63 (0·50–0·79) | .. |
| Hypertensive or renovascular disease | 72 (10·2%) | 5·21 | 82 (11·1%) | 5·88 | 0·86 (0·62–1·18) | .. |
| Glomerular disease | 107 (12·5%) | 6·79 | 136 (16·7%) | 9·20 | 0·72 (0·56–0·92) | .. |
| Other or unknown | 55 (7·7%) | 3·99 | 82 (11·3%) | 5·76 | 0·68 (0·48–0·95) | .. |
| Overall | 359 (10·9%) | 5·67 | 474 (14·3%) | 7·58 | 0·70 (0·61–0·81) | .. |
| **Secondary outcome** | | | | | | |
| End-stage kidney disease† or death from cardiovascular causes | .. | .. | .. | .. | .. | 0·63 |
| Diabetic kidney disease | 67 (6·5%) | 3·28 | 99 (9·7%) | 4·91 | 0·65 (0·48–0·89) | .. |
| Hypertensive or renovascular disease | 25 (3·5%) | 1·79 | 37 (5·0%) | 2·62 | 0·68 (0·41–1·13) | .. |
| Glomerular disease | 39 (4·6%) | 2·45 | 46 (5·6%) | 3·05 | 0·78 (0·51–1·20) | .. |
| Other or unknown | 32 (4·5%) | 2·30 | 35 (4·8%) | 2·42 | 0·93 (0·58–1·51) | .. |
| Overall | 163 (4·9%) | 2·54 | 217 (6·6%) | 3·40 | 0·73 (0·59–0·89) | .. |

A Cox proportional-hazards regression model with adjustment for baseline variables specified in the minimisation algorithm (age, sex, previous diabetes, eGFR, urinary albumin-to-creatinine ratio, and region) and a treatment by primary kidney disease interaction term was used to estimate the hazard ratios and 95% CIs for empagliflozin versus placebo. eGFR=estimated glomerular filtration rate. *p value for heterogeneity between categories of primary kidney diagnosis. †End-stage kidney disease is defined as start of maintenance dialysis or receipt of a kidney transplant. ‡Sustained defined as present on two consecutive scheduled study follow-up visits or last scheduled follow-up visit before death or final follow-up. eGFR measurements were based on central laboratory measurements, wherever available.

***Table 2:*** **Primary and secondary outcomes by primary kidney disease**

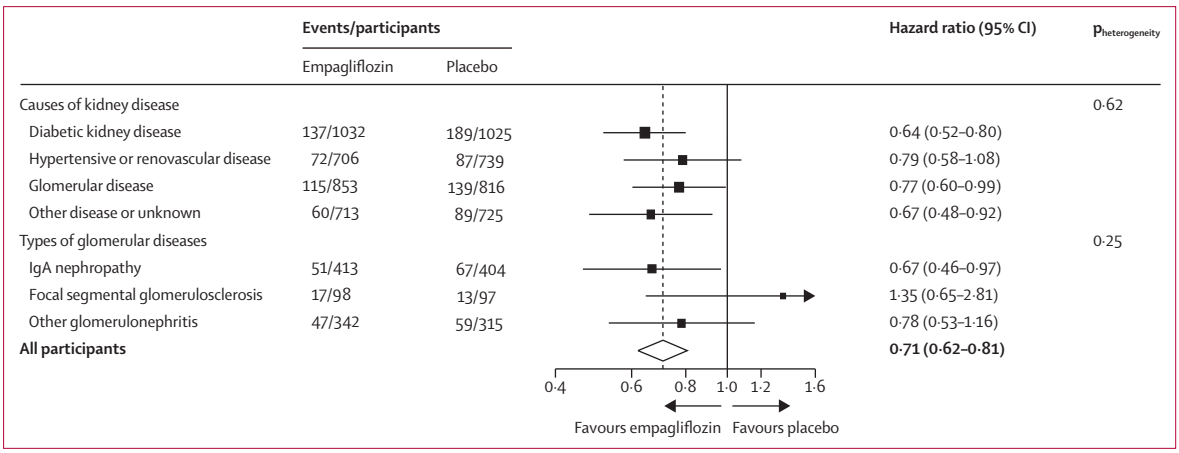


***Figure 1:*** **Kidney disease progression outcome by primary kidney disease**
A Cox proportional-hazards regression model with adjustment for baseline variables specified in the minimisation algorithm (age, sex, diabetes, eGFR, urinary albumin-to-creatinine ratio, and region) and a treatment by primary kidney disease interaction term was used to estimate the hazard ratios and 95% CIs for empagliflozin as compared with placebo. eGFR=estimated glomerular filtration rate.

on chronic slope represented a –50% (95% CI –58 to –42) relative reduction in the rate of eGFR decline. This comprised a relative reduction in the chronic rate of eGFR decline of –59% (95% CI –73 to –45) in patients with diabetic kidney disease, –62% (–83 to –41) in patients with hypertensive or renovascular disease, –40% (–52 to –28) in patients with glomerular disease, and –42% (–63 to –22) in patients with other or unknown causes ($p_{heterogeneity}$=0·11 across the four groups; figure 2). Among patients with different subtypes of glomerular disease, the relative reductions in chronic rate of eGFR decline were –43% (95% CI –59 to –27) in patients with IgA nephropathy, –22% (–60 to 16) in patients with focal segmental glomerulosclerosis, and –41% (–62 to –21) in patients with other causes of glomerular disease ($p_{heterogeneity}$=0·58 across the three groups; figure 2). The effects on annual rate of eGFR decline also appeared similar irrespective of diabetes type (appendix p 21), although only 68 participants had type 1 diabetes.

Compared with placebo, empagliflozin, had no significant effect overall on a key secondary composite outcome of hospitalisation from heart failure or death from cardiovascular causes (131 [4·0%] of 3304 patients *vs* 152 [4·6%] of 3305; HR 0·84 [95% CI 0·67–1·07]), with similar effects regardless of primary kidney disease ($p_{heterogeneity}$=1·00; appendix p 15). Overall, all-cause hospitalisations were less frequent in the empagliflozin group than in the placebo group (24·8 *vs* 29·2 hospitalisations per 100 patient-years; HR 0·86 [95% CI 0·78–0·95]). Effects among patients with diabetic kidney disease, hypertensive or renovascular disease, glomerular disease, and other or unknown causes were similar ($p_{heterogeneity}$=0·23; appendix p 15). There was no significant effect on all-cause mortality between the empagliflozin and placebo groups (2·28 *vs* 2·58 deaths per 100 patient-years; HR 0·87 [95% CI 0·70–1·08]; appendix p 15). Similarly, there was no evidence that empagliflozin modified risk of the tertiary outcome of major cardiovascular events overall or by primary kidney disease ($p_{heterogeneity}$=0·73; appendix p 15).

Geometric mean uACR was 251 mg/g (SD 8) in patients with diabetic kidney disease, 110 mg/g (8) in patients with hypertensive or renovascular disease, 577 mg/g (4) in patients with glomerular disease, and 126 mg/g (7) in patients with other or unknown causes. The difference in geometric mean uACR between randomised groups was –28% (95% CI –34 to –21), –16% (–25 to –7), –15% (–24 to –6), and –14% (–23 to –4) across these subgroups, respectively (table 3), with some weak evidence that empagliflozin lowered albuminuria more in patients with diabetic kidney disease ($p_{heterogeneity}$=0·050). The overall between-group difference in mean systolic blood pressure was –2·6 mm Hg (SE 0·3) and that in diastolic blood pressure was –0·5 mm Hg (0·2; table 3; appendix p 16). Empagliflozin seemed to have larger effects on systolic blood pressure lowering among patients with diabetic kidney disease (reduction 4·1 mm Hg [95% CI –5·3 to –2·9]; $p_{heterogeneity}$=0·023; table 3).

Overall, empagliflozin had no significant effects on risk of serious acute kidney injury (HR 0·78 [95% CI 0·60–1·00]), with similar results across the four main categories of cause of kidney disease ($p_{heterogeneity}$=0·28; appendix p 17). Ketoacidosis occurred in six patients in the empagliflozin group (including five participants on insulin, one of whom had type 1 diabetes, and one participant without diabetes) and one in the placebo group (who was not taking open-label SGLT2 inhibitor). There were 28 lower-limb amputation events in the empagliflozin group and 19 in the placebo group (including 20 *vs* 14 toe amputations). These two safety outcomes mainly occurred in participants with diabetic

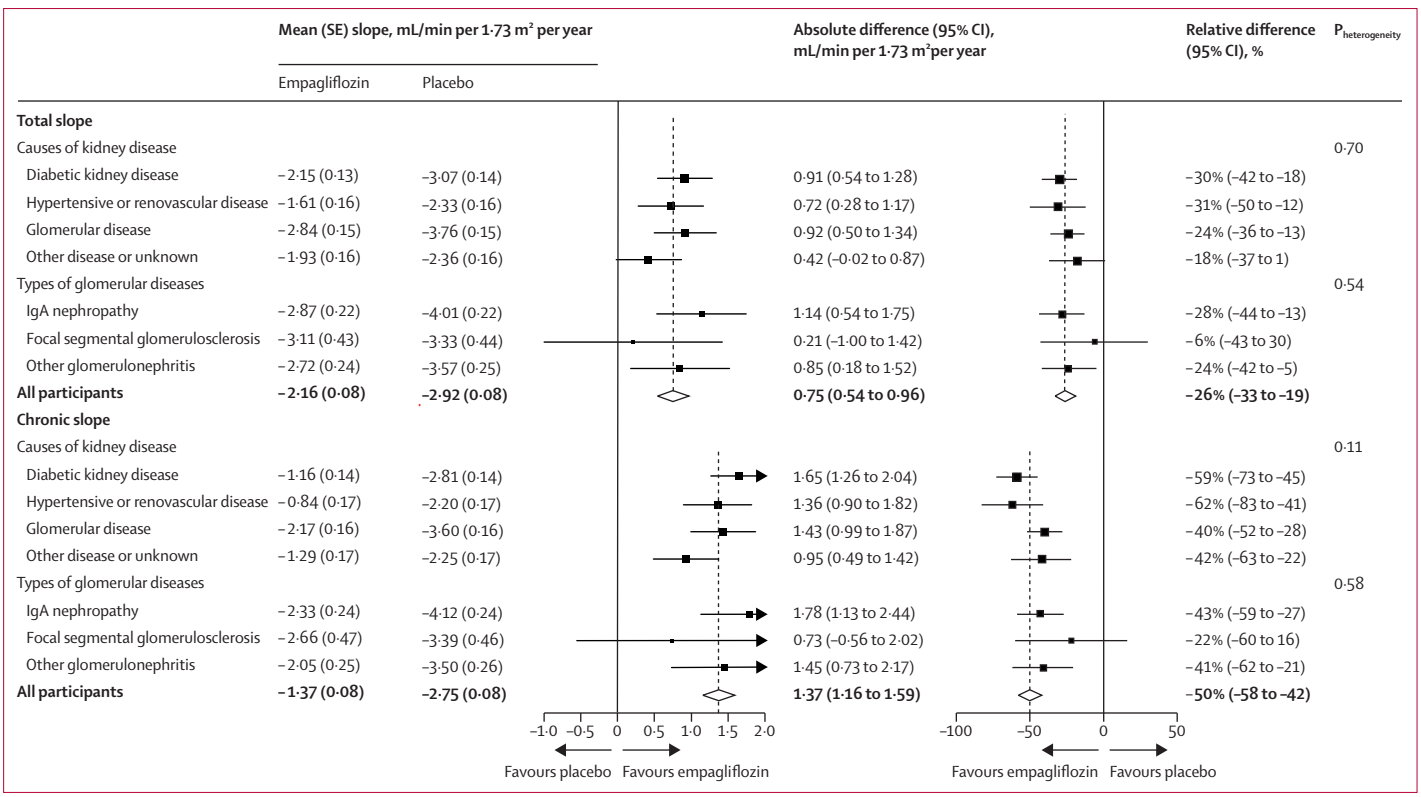


***Figure 2:*** **Effect of empagliflozin on annual rate of change in eGFR by primary kidney disease**
Mean annual rates of change in eGFR from baseline to the final follow-up visit (total slopes), and from 2 months to the final follow-up visit (chronic slopes) by treatment allocation were estimated using shared parameter models adjusted for age, sex, previous diabetes, uACR category, and region. Models estimating chronic slope were additionally adjusted for baseline eGFR (as a continuous variable) and the interaction between baseline eGFR and follow-up time. This approach jointly models the annual rate of change in eGFR and the time to event for end-stage kidney disease or death. Analyses used all available central laboratory eGFR measurements before the development of end-stage kidney disease. Relative difference is the absolute difference as a fraction of the mean slope in the placebo group, expressed as a percentage. The $p_{heterogeneity}$ values shown are calculated from the relative differences. eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio.

kidney disease, with too few events to provide reliable estimates of any effect in participants with non-diabetic causes of kidney disease. The incidence of serious urinary tract infection, hyperkalaemia, serious or symptomatic dehydration, severe hypoglycaemia (mainly in participants with diabetic kidney disease), liver injury, and bone fractures were broadly similar between allocated treatment groups, with findings unmodified by primary kidney disease (appendix pp 17–18).

## Discussion

In these subsidiary analyses of the EMPA-KIDNEY trial, which included a large number of patients with non-diabetic causes of chronic kidney disease at risk of progression, empagliflozin reduced the risk of kidney disease progression, with broadly similar sized effects in patients with different primary kidney diseases. Analyses of annual rate of change of eGFR on a relative scale enabled further detailed exploration of whether the effects of treatment vary. Such analyses suggested empagliflozin slowed decline in eGFR irrespective of these diagnoses. Empagliflozin was also generally safe and well tolerated in the studied population.

The impact of kidney disease on the effect of SGLT2 inhibition on the progression of kidney disease observed in EMPA-KIDNEY is similar to that seen in other large placebo-controlled trials of SGLT2 inhibitors involving patients with chronic kidney disease.[3–5] A previous meta-analysis showed that when standardised to the same definition of kidney disease progression, relative effect sizes are remarkably similar for a given primary cause of kidney disease.[5] The presented analyses add substantially to previous data from DAPA-CKD[12] by including information on eGFR slopes (with novel emphasis on relative effects), cardiovascular outcomes, hospitalisation, blood pressure, albuminuria, and safety in more than double the number of patients with glomerular disease, and about three times more participants with IgA nephropathy (with about half of participants with glomerular disease reporting Asian race). The analyses also include large numbers of patients with other non-diabetic causes of chronic kidney disease, and particularly hypertensive or renovascular disease, and importantly expand the available information among patients with chronic kidney disease with a uACR of less than 200 mg/g, which was previously limited to data from the SCORED trial[15] and analyses from heart failure trials.[16–18]

The observed consistent relative effects of empagliflozin on kidney disease progression across the broad range of different primary kidney diagnoses

| | Diabetic kidney disease (n=2057) | Hypertensive or renovascular disease (n=1445) | Glomerular disease (n=1669) | Other or unknown (n=1438) | $p_{heterogeneity}$ |
|---|---|---|---|---|---|
| uACR, mg/g | | | | | |
| Relative difference in study average uACR compared with placebo | −28% (−34 to −21) | −16% (−25 to −7) | −15% (−24 to −6) | −14% (−23 to −4) | 0·050 |
| Blood pressure, mm Hg | | | | | |
| Study average difference in systolic blood pressure compared with placebo | −4·1 (−5·3 to −2·9) | −1·7 (−3·1 to −0·2) | −2·2 (−3·6 to −0·8) | −1·6 (−3·1 to −0·2) | 0·023 |
| Study average difference in diastolic blood pressure compared with placebo | −1·3 (−2·0 to −0·6) | 0·2 (−0·7 to 1·1) | −0·3 (−1·1 to 0·5) | −0·2 (−1·0 to 0·7) | 0·052 |

Data are study-average differences (95% CI) estimated using an adjusted prespecified mixed model for repeated measures approach. Analysis of effects on uACR uses central laboratory measurements at follow-up timepoints 2, 18, 24, and 30 months, with findings similar in a sensitivity analysis including a baseline quadratic term to assess the effect of the violation of the assumption of linearity for quantitative predictors. Analysis of effects on blood pressure uses measurements obtained at follow-up timepoints: 2, 6, 12, 18, 24, 30, and 36 months. Analyses required participants to have at least one follow-up measurement of the outcome variable and excluded participants with missing baseline measurements (uACR 203 [3·1%] of 6609; no missing baseline blood pressure measurements for analysed participants). uACR=urinary albumin-to-creatinine ratio.

***Table 3:*** **uACR and blood pressure assessments by primary kidney disease**

supports the concept of final common pathways of chronic kidney disease progression. SGLT2 inhibitors restore or enhance tubuloglomerular feedback by increasing afferent arteriolar tone and improve dysregulated glomerular haemodynamics.[7] Clinically, this manifests as an acute dip in eGFR after initiation of an SGLT2 inhibitor (which is reversible on discontinuation),[6,16] followed by a subsequent slowing in loss of eGFR in the longer term.[19] Increased intraglomerular pressure and consequent glomerular hyperfiltration are hypothesised to be common to many forms of chronic kidney disease,[8] including when there is low nephron number.[8,19–22] The presented results might also indicate other common pathways driven by pathophysiology in the kidney tubules. SGLT2 inhibitors decrease tubular workload and oxygen consumption via decreased reabsorption of glucose and sodium, increasing oxygen delivery capacity to the renal tubules. This might explain the larger effects of SGLT2 inhibitors on kidney disease progression than would be predicted from the more modest effects on albuminuria. This mechanism might also explain the beneficial effects on acute kidney injury observed in meta-analyses.[5,23–27] Although there was no significant effect of empagliflozin on the risk of acute kidney injury in the EMPA-KIDNEY trial alone, the point estimate was entirely consistent with the 23% reduction in risk in meta-analyses of about 90 000 participants in 13 large SGLT2 inhibitor trials.[5] These and other proposed mechanisms contributing to long-term kidney protection by SGLT2 inhibitors will be explored in future randomised analyses using the trial's stored blood and urine samples and multiomic assays, and a renal MRI substudy. These explorations are important because, despite moderate-to-large reductions in risk with SGLT2 inhibitors, residual risk remains and identifying and testing new interventions that can safely slow chronic kidney disease progression remains a research priority.

Analyses of cardiovascular outcomes were limited by lower than expected numbers of events, perhaps due to recruitment of low-risk populations or secular trends towards lower cardiovascular risk.[28] This was also a feature of the DAPA-CKD trial, leaving some uncertainty about cardiovascular effects of SGLT2 inhibitors in patients with chronic kidney disease without diabetes. The overall between-group difference in systolic blood pressure in EMPA-KIDNEY of −2·6 mm Hg (95% CI −3·3 to −1·9) was similar to the CREDENCE difference of −3·3 mm Hg (−3·9 to −2·7)[4] and the DAPA-CKD difference of −2·9 mm Hg (−3·6 to −2·3),[29,30] but notably in EMPA-KIDNEY we observed that there might have been larger effects on systolic blood pressure in patients with diabetic kidney disease than in those with other primary diagnoses. Nevertheless, the proven cardiovascular benefits of SGLT2 inhibitors in populations of patients with heart failure (in which about half of the participants had decreased eGFR) did not vary by presence or absence of diabetes.[5]

Empagliflozin was generally well tolerated and reduced the risk of hospitalisation from any cause. The risk of ketoacidosis was low and mainly among patients with diabetes on insulin at baseline. Lower limb amputations mainly occurred among participants with diabetic kidney disease. The effects on serious hyperkalaemia were not significantly different between treatment groups, but the point estimate was entirely aligned with the 17% relative reduction in the risk of hyperkalaemia from a previous meta-analysis.[31]

The results of these analyses from the EMPA-KIDNEY, DAPA-CKD, and other large trials suggest widespread use of SGLT2 inhibitors should substantially reduce the future global burden of kidney failure due to both diabetic and non-diabetic primary causes of kidney disease. The consistency of findings from these and other analyses[7] enables simple clinical practice guidelines for patients with chronic kidney disease.[32,33] These

results are particularly important for patients with chronic kidney disease without diabetes who have been less well studied in the completed RAS inhibitor[34–36] and mineralocorticoid receptor[37] trials, and for whom serious side-effects of SGLT2 inhibitors seem to be uncommon.[5] SGLT2 inhibitors should become part of a standard of care for many patients with chronic kidney disease.

EMPA-KIDNEY was designed to ensure findings would be widely generalisable.[2,6,8] It also provides the largest amount of randomised data on the use of SGLT2 inhibition currently available for patients with chronic kidney disease at risk of progression. A key strength of the presented analyses is the explorations using a range of statistically sensitive approaches (ie, eGFR slope analyses) that used novel analytical approaches developed for a companion publication to assess treatment effects on a relative scale.[7] This approach enabled more reliable subgroup comparisons, as analyses based on absolute effects conflate any between-subgroup differences in baseline absolute risk plus any differences in the relative effect of study treatment.[7] Limitations to the generalisability of the reported findings is the exclusion of patients with a polycystic kidney disease or a kidney transplant. Data among people with a kidney transplant will be available when the Renal Lifecycle trial (NCT05374291) results are reported. Although there were particularly large numbers of participants with IgA nephropathy, there were relatively smaller numbers with other specific causes of glomerular disease, and only 68 participants with type 1 diabetes. This limited power to assess treatment effects on the range of outcomes directly in these less well studied types of patients. The other key limitation is the relatively short median follow-up duration. Consenting EMPA-KIDNEY participants have entered a post-trial follow-up phase in which participants will be observed for the primary outcome over at least a further 2 years following completion of treatment with their randomly allocated study drug.

In summary, in a broad population of patients with chronic kidney disease at risk of progression, empagliflozin safely reduced the risk of kidney disease progression and eGFR decline with broadly similar sized relative effects across patients grouped by different types of primary kidney disease.

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PKJ, NS, RH, and WGH proposed and developed the analyses, had full access to the data, wrote the first draft, and had final responsibility for the decision to submit for publication. NS led analyses of the raw data with KJM and JRE, with replication by DM. AJR performed the systematic review. All authors contributed to data interpretation and manuscript review. PKJ, NS, RH, and WGH assume responsibility for the overall content and integrity of the report.

**Declarations of interests**
The Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford (Oxford, UK), has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. NS, RH, KJM, AJR, SYAN, DZ, PJ, DP, MJL, CB, JRE, and WGH report institutional grant funding from Boehringer Ingelheim and Eli Lilly for the EMPA-KIDNEY trial. NS additionally reports institutional grant funding from Novo Nordisk. RH additionally reports institutional grant funding from Novartis; and trial drug supply from Roche and Regeneron. CB additionally reports grant funding from the UK Medical Research Council (MRC), National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA; 17/140/02), and Health Data Research UK; and advisory roles for Merck, NIHR HTA, the British Heart Foundation, and the European Society of Cardiology. WGH additionally reports advisory roles for the UK Kidney Association, European Renal Association, European Society of Cardiology, and KDIGO.

For the **staff policy** see https://www.ctsu.ox.ac.uk/about/ctsu_honoraria_25june14-1.pdf

**Data sharing**
The complete de-identified patient data set used for presented analyses will be available in due course and the application system to apply to use data will open 6 months after publication. Departmental policy details can be found here: https://www.ndph.ox.ac.uk/data-access. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major Regulatory Authorities. Researchers should use the https://vivli.org/link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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