Effects of empagliflozin on progression of chronic kidney disease: a prespecified secondary analysis from the EMPA-KIDNEY trial

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See Online for appendix

Summary

Background Sodium–glucose co-transporter-2 (SGLT2) inhibitors reduce progression of chronic kidney disease and the risk of cardiovascular morbidity and mortality in a wide range of patients. However, their effects on kidney disease progression in some patients with chronic kidney disease are unclear because few clinical kidney outcomes occurred among such patients in the completed trials. In particular, some guidelines stratify their level of recommendation about who should be treated with SGLT2 inhibitors based on diabetes status and albuminuria. We aimed to assess the effects of empagliflozin on progression of chronic kidney disease both overall and among specific types of participants in the EMPA-KIDNEY trial.

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), and included individuals aged 18 years or older with an estimated glomerular filtration rate (eGFR) of 20 to less than 45 mL/min per 1·73 m², or with an eGFR of 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. We explored the effects of 10 mg oral empagliflozin once daily versus placebo on the annualised rate of change in estimated glomerular filtration rate (eGFR slope), a tertiary outcome. We studied the acute slope (from randomisation to 2 months) and chronic slope (from 2 months onwards) separately, using shared parameter models to estimate the latter. Analyses were done in all randomly assigned participants by intention to treat. EMPA-KIDNEY is registered at ClinicalTrials.gov, NCT03594110.

Findings Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and then followed up for a median of 2·0 years (IQR 1·5–2·4). Prespecified subgroups of eGFR included 2282 (34·5%) participants with an eGFR of less than 30 mL/min per 1·73 m², 2928 (44·3%) with an eGFR of 30 to less than 45 mL/min per 1·73 m², and 1399 (21·2%) with an eGFR 45 mL/min per 1·73 m² or higher. Prespecified subgroups of uACR included 1328 (20·1%) with a uACR of less than 30 mg/g, 1864 (28·2%) with a uACR of 30 to 300 mg/g, and 3417 (51·7%) with a uACR of more than 300 mg/g. Overall, allocation to empagliflozin caused an acute 2·12 mL/min per 1·73 m² (95% CI 1·83–2·41) reduction in eGFR, equivalent to a 6% (5–6) dip in the first 2 months. After this, it halved the chronic slope from –2·75 to –1·37 mL/min per 1·73 m² per year (relative difference 50%, 95% CI 42–58). The absolute and relative benefits of empagliflozin on the magnitude of the chronic slope varied significantly depending on diabetes status and baseline levels of eGFR and uACR. In particular, the absolute difference in chronic slopes was lower in patients with lower baseline uACR, but because this group progressed more slowly than those with higher uACR, this translated to a larger relative difference in chronic slopes in this group (86% [36–136] reduction in the chronic slope among those with baseline uACR <30 mg/g compared with a 29% [19–38] reduction for those with baseline uACR ≥2000 mg/g; p_{trend}<0·0001).

Interpretation Empagliflozin slowed the rate of progression of chronic kidney disease among all types of participant in the EMPA-KIDNEY trial, including those with little albuminuria. Albuminuria alone should not be used to determine whether to treat with an SGLT2 inhibitor.

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Introduction

Chronic kidney disease is common and associated with reduced quality of life and increased risks of kidney failure (which is fatal without costly kidney replacement therapy), cardiovascular disease, and mortality.[1–3] Trials in chronic kidney disease populations have traditionally used dichotomous composite clinical outcomes that combine kidney failure (an infrequent outcome) with a proportional reduction in kidney function (as measured by change in estimated glomerular filtration rate [eGFR]) from baseline in excess of a particular threshold, usually 40–57%.[4] The latter component is now accepted by regulatory authorities as a valid surrogate outcome for kidney failure itself in randomised trials.[4,5] Like all

Research in context

Evidence before this study

We searched MEDLINE and Embase via Ovid for randomised trials published between database inception and Sept 5, 2022, using the search terms "sodium glucose transporter 2 inhibitors", "sglt2", "sglt-2", "sodium-glucose transporter", "sodium-glucose co-transporter", "sodium-glucose cotransporter", " canagliflozin", "dapagliflozin", "ertugliflozin", "ipragliflozin", "luseogliflozin", "remogliflozin", "sergliflozin", "sotagliflozin", or "tofogliflozin". No language restriction was applied. Meta-analysis of the large randomised trials of sodium–glucose co-transporter-2 (SGLT2) inhibitors shows that they reduce the risk of kidney disease progression in patients with chronic kidney disease, as well as acute kidney injury and cardiovascular morbidity and mortality. These analyses were limited by an inability to explore effects in small subgroups or patients whose chronic kidney disease was only progressing slowly. The EMPA-KIDNEY trial recruited a broad range of patients with chronic kidney disease, including patients without significant albuminuria. Relatively few clinical kidney outcomes occurred in this subgroup during 2 years of follow-up, and the results suggested that the proportional benefit of allocation to empagliflozin might be smaller at lower levels of albuminuria. This has led to some uncertainty about the benefits of SGLT2 inhibition in such patients, who constitute the majority of the population of patients with chronic kidney disease globally. The use of estimates of the annualised decline in kidney function (estimated glomerular filtration rate [eGFR] slopes) has recently been proposed as an alternative outcome for trials in chronic kidney disease. It has advantages for exploring the results of large randomised trials because all participants provide information so such analyses are statistically sensitive.

Added value of this study

These analyses show that empagliflozin caused a modest initial drop in kidney function, followed by a substantial slowing of the rate of progression of chronic kidney disease in all patients. These chronic effects varied by baseline diabetes status, eGFR, and urinary albumin-to-creatinine ratio (uACR) in both absolute and relative terms, and these interactions were independent of each other. In particular, the absolute difference in chronic slopes was lower in patients with lower baseline uACR, but because this group progressed more slowly than those with higher uACR, this translated to a larger relative difference in chronic slopes in this group.

Implications of all the available evidence

These results suggest that empagliflozin slows the rate of progression of chronic kidney disease in a broad range of patients. The findings challenge guidelines that have used albuminuria to stratify their level of recommendation about who should be treated with SGLT2 inhibitors. Patients with lower albuminuria (and consequently at lower risk of progression of chronic kidney disease) benefit from treatment with SGLT2 inhibition in terms of preservation of kidney function, in addition to reductions in risk of acute kidney injury and cardiovascular disease.

dichotomous outcomes, the majority of such outcomes during the trial follow-up period occurs in patients at highest risk, unlike in the general population, in which the majority of events occur during the lifetime of patients at moderate risk because of the much larger number of such patients.[6] Analyses based on these outcomes have less statistical sensitivity for determining the effects of treatment among groups of patients who are at lower risk of kidney failure (including those with better preserved kidney function), but ultimately constitute the majority of patients with kidney failure in the general population. There is therefore interest in examining the annualised rate of decline of kidney function (eGFR slope) because this parameter can be calculated for all participants, and so eGFR slopes have improved statistical sensitivity when comparing the effect of an intervention in different types of patients. The eGFR slope might also be considered as a valid surrogate of chronic kidney disease progression per se and be used as a primary outcome in trials.[7,8] Importantly, the effect of a treatment on eGFR slope is not necessarily homogeneous over time; many renoprotective treatments, including renin–angiotensin system (RAS) inhibitors, sodium–glucose co-transporter-2 (SGLT2) inhibitors, and finerenone, cause an early acute negative effect on slope (referred to as an acute dip), followed by a long-term (or chronic) reduction in eGFR slope. It is therefore important to understand the effects of new treatments on these two components of the total slope.

Randomised trials of SGLT2 inhibitors have consistently shown that this class of treatment reduces the risk of progression of kidney disease (measured with dichotomous outcomes) in patients with chronic kidney disease with or without diabetes, largely irrespective of underlying primary kidney disease.[9–12] Secondary analyses of two previous trials of SGLT2 inhibitors in chronic kidney disease populations found some evidence that the effects of SGLT2 inhibitors on the eGFR slope varied in different types of patients, but because the trials only recruited patients with significant albuminuria, they were limited in their ability to explore whether this effect varied according to baseline albuminuria as well as other clinical characteristics.[13,14] Here, we present the effects of empagliflozin versus placebo on eGFR slope from the EMPA-KIDNEY trial, which recruited a uniquely broad range of patients with chronic kidney disease at risk of progression, including those with minimal albuminuria, low eGFR, and with and without diabetes. In a companion paper, we assess the effects of empagliflozin on kidney outcomes in participants with different types of kidney disease.[12]

Methods

Study design and participants

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). Details of EMPA-KIDNEY's rationale, design, protocol, prespecified data analysis plan, and main results have been reported previously.[11,15,16] Regulatory authorities and ethics committees for each centre approved the trial. Individuals aged 18 years or older with a race-adjusted Chronic Kidney Disease-Epidemiology Collaboration equation-based[17] eGFR of 20 to less than 45 mL/min per 1·73 m² (irrespective of level of albuminuria) or with an eGFR of 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 the screening visit were eligible provided they were prescribed a clinically appropriate dose of single-agent RAS inhibitor, where indicated and tolerated. Patients with or without diabetes were eligible, and polycystic kidney disease was the only excluded primary kidney disease. Individuals receiving at least 45 mg prednisolone daily (or equivalent) or had received 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. 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 assigned (1:1) to receive oral empagliflozin (10 mg once daily) or matching placebo.[18] 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 local safety assessment of creatinine, liver function, and potassium. Blood samples and, at selected visits, urine samples were sent to the central laboratory for efficacy analyses and archiving. Surviving participants in the UK were asked to provide a blood sample for local laboratory analysis of creatinine about 4 weeks after their final follow-up visit in order to assess the effect of discontinuing empagliflozin on eGFR.

Outcomes

Annual rate of change in eGFR calculated separately for the period from baseline to the final follow-up visit (ie, total slope) and for the period from 2 months to the final follow-up visit (ie, chronic slope) were tertiary outcomes in the original protocol, with exploratory analyses of these outcomes prespecified. Acute dips in eGFR were calculated as the difference in eGFR between baseline and the 2-month follow-up visit.

Statistical analysis

Unless stated otherwise, all analyses were performed according to the intention-to-treat principle, including all randomly assigned participants. Effects of empagliflozin on annual rate of change in eGFR were assessed using prespecified shared parameter models,[19,20] which were used to calculate the chronic eGFR slope. For subgroup analyses, absolute differences in chronic slopes were calculated, and, from these chronic slope, relative differences were calculated by dividing the absolute effect and its 95% CI by the mean slope in the placebo group. Prespecified subgroup categories for eGFR were less than 30 mL/min per 1·73 m², 30 to less than 45 mL/min per 1·73 m², and 45 mL/min per 1·73 m² or higher and those for uACR were less than 30 mg/g, 30–300 mg/g, and 300 mg/g or higher. The lowest eGFR and highest uACR categories were further subdivided to give post-hoc expanded subgroups (eGFR <20 mL/min per 1·73 m², 20 to <30 mL/min per 1·73 m², 30 to <45 mL/min per 1·73 m², ≥45 mL/min per 1·73 m² and less than 30 mg/g, 30 to 300 mg/g, >300 to <1000 mg/g, 1000 to <2000 mg/g, and 2000 mg/g or higher), and the prespecified uACR subgroup was also divided by diabetes status. In keeping with the prespecified analyses of the chronic slopes, effects of empagliflozin on acute dips were estimated using linear regression models adjusted for baseline variables specified in the minimisation algorithm (age, sex, previous diabetes, eGFR, uACR, and region). Subgroup-specific effects were estimated through the inclusion of treatment by subgroup interaction terms. Relative differences in acute dips as a percentage of mean baseline eGFR were also calculated. Standard tests for heterogeneity or trend across subgroups were performed for relative differences in eGFR slopes and acute dips.

Sensitivity analyses for annual rate of change in eGFR included the addition of interactions with other key subgroups (to standardise the distribution of other characteristics across subgroups; post hoc), as well as restricting analyses to on-treatment eGFR measurements (post hoc) and using eGFR measurements based on local creatinine values (prespecified). In the surviving UK participants with a 4-week post-final follow-up blood sample, the effect of stopping study treatment on mean eGFR (after taking account of any differences in eGFR at final follow-up) was estimated using linear regression models adjusted for age, sex, previous diabetes, and uACR, as specified in the minimisation algorithm and eGFR at the final follow-up visit. Effects of empagliflozin on albuminuria used a prespecified mixed model for repeated measures (MMRM) approach.[11] The normality of residuals assumption was examined for each linear

regression model and MMRM through the inspection of histograms and Q–Q plots. The assumption of homoscedasticity was assessed through visual inspection of a plot of fitted values against the residuals. No violations of the assumptions underlying the linear regression models or MMRM were identified.

	eGFR (mL/min per 1·73 m²)			uACR (mg/g)		
	<30 (n=2282)	≥30 to <45 (n=2928)	≥45 (n=1399)	<30 (n=1328)	30–300 (n=1864)	>300 (n=3417)
Demographics						
Age at randomisation, years	65 (13)	64 (13)	58 (15)	71 (9)	66 (13)	59 (14)
Sex						
Male	1533 (67·2%)	1937 (66·2%)	947 (67·7%)	725 (54·6%)	1268 (68·0%)	2424 (70·9%)
Female	749 (32·8%)	991 (33·8%)	452 (32·3%)	603 (45·4%)	596 (32·0%)	993 (29·1%)
Race						
White	1440 (63·1%)	1833 (62·6%)	586 (41·9%)	1069 (80·5%)	1189 (63·8%)	1601 (46·9%)
Black	98 (4·3%)	119 (4·1%)	45 (3·2%)	71 (5·3%)	89 (4·8%)	102 (3·0%)
Asian	707 (31·0%)	930 (31·8%)	756 (54·0%)	173 (13·0%)	562 (30·2%)	1658 (48·5%)
Mixed	6 (0·3%)	13 (0·4%)	2 (0·1%)	2 (0·2%)	6 (0·3%)	13 (0·4%)
Other	31 (1·4%)	33 (1·1%)	10 (0·7%)	13 (1·0%)	18 (1·0%)	43 (1·3%)
Previous disease						
Previous diabetes*	1151 (50·4%)	1371 (46·8%)	518 (37·0%)	647 (48·7%)	943 (50·6%)	1450 (42·4%)
Previous diabetes type						
Type 1	31 (1·4%)	28 (1·0%)	9 (0·6%)	11 (0·8%)	20 (1·1%)	37 (1·1%)
Type 2	1106 (48·5%)	1333 (45·5%)	497 (35·5%)	633 (47·7%)	916 (49·1%)	1387 (40·6%)
Other or unknown	14 (0·6%)	10 (0·3%)	12 (0·9%)	3 (0·2%)	7 (0·4%)	26 (0·8%)
History of cardiovascular disease†	718 (31·5%)	828 (28·3%)	219 (15·7%)	484 (36·4%)	579 (31·1%)	702 (20·5%)
Clinical measurements						
Systolic blood pressure, mm Hg	137·6 (18·6)	136·0 (18·2)	135·9 (17·8)	130·8 (18·0)	134·3 (17·7)	139·9 (18·0)
Diastolic blood pressure, mm Hg	76·5 (11·8)	77·9 (11·7)	80·9 (11·6)	73·5 (10·7)	75·8 (11·6)	81·0 (11·5)
BMI, kg/m²	30·1 (6·7)	30·1 (6·9)	28·5 (6·5)	31·5 (7·1)	29·9 (6·6)	29·0 (6·6)
Laboratory measurements						
eGFR, mL/min per 1·73 m²‡	24·6 (3·6)	36·8 (4·2)	59·3 (13·5)	35·1 (8·2)	36·3 (12·8)	38·7 (16·8)
<30	2282 (100%)	0	0	386 (29·1%)	639 (34·3%)	1257 (36·8%)
30 to <45	0	2928 (100%)	0	789 (59·4%)	896 (48·1%)	1243 (36·4%)
≥45	0	0	1399 (100%)	153 (11·5%)	329 (17·7%)	917 (26·8%)
uACR, mg/g‡	410 (59–1373)	187 (26–781)	515 (214–1199)	7 (6–18)	117 (59–202)	1033 (575–1910)
<30	386 (16·9%)	789 (26·9%)	153 (10·9%)	1328 (100%)	0	0
30 to 300	639 (28·0%)	896 (30·6%)	329 (23·5%)	0	1864 (100%)	
>300	1257 (55·1%)	1243 (42·5%)	917 (65·5%)	0	0	3417 (100%)
NT-proBNP, ng/L	713 (1681)	470 (1091)	211 (476)	506 (930)	535 (1220)	477 (1384)
HbA_{1c}, mmol/mol	45·5 (13·7)	45·5 (13·7)	43·1 (13·1)	45·5 (12·1)	45·8 (13·4)	44·3 (14·2)
HbA_{1c}, %	4·2% (1·3)	4·2% (1·3)	3·9% (1·2)	4·2% (1·1)	4·2% (1·2)	4·1% (1·3)
Concomitant medication use						
RAS inhibitor	1872 (82·0%)	2487 (84·9%)	1269 (90·7%)	1073 (80·8%)	1545 (82·9%)	3010 (88·1%)
Any diuretic	1151 (50·4%)	1271 (43·4%)	393 (28·1%)	777 (58·5%)	868 (46·6%)	1170 (34·2%)
Any lipid-lowering medication	1657 (72·6%)	1955 (66·8%)	766 (54·8%)	992 (74·7%)	1274 (68·3%)	2112 (61·8%)
Cause of kidney disease						
Diabetic kidney disease	801 (35·1%)	901 (30·8%)	355 (25·4%)	376 (28·3%)	623 (33·4%)	1058 (31·0%)
Hypertensive or renovascular disease	533 (23·4%)	699 (23·9%)	213 (15·2%)	469 (35·3%)	444 (23·8%)	532 (15·6%)
Glomerular disease	452 (19·8%)	636 (21·7%)	581 (41·5%)	66 (5·0%)	344 (18·5%)	1259 (36·8%)
Other or unknown	496 (21·7%)	692 (23·6%)	250 (17·9%)	417 (31·4%)	453 (24·3%)	568 (16·6%)

Data are mean (SD), n (%), or median (IQR). eGFR=estimated glomerular filtration rate. RAS=renin–angiotensin system. uACR=urinary albumin-to-creatinine ratio. *Previous diabetes defined as diabetes at randomisation is defined as participant-reported history of diabetes of any type, use of glucose-lowering medication or baseline HbA_{1c} ≥48 mmol/mol (6·5%) at randomisation visit. †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.

Table 1: **Baseline characteristics by eGFR and uACR**

The proportion of treatment effect for the primary composite outcome of kidney disease progression or cardiovascular death explained by on-study uACR, systolic blood pressure, diastolic blood pressure, and HbA_{1c} was estimated using the landmark method,[21,22] adjusting the prespecified Cox regression model for 2-month values of the biomarkers. Bias-corrected and accelerated bootstrap intervals with 10 000 replications were used to construct the 95% CIs. Time-to-event analyses defined time at risk starting from randomisation, and finishing at the date of event of interest, final follow-up, or censoring at the earliest of death, loss to follow-up, or withdrawal of consent. Assessment of the proportional hazards assumption (by testing the significance of an interaction between treatment allocation and log[survival time]) found no evidence against proportionality for any of the time to event outcomes. The landmark method was also used to estimate the proportion of the treatment effect on chronic slope explained by the same on-study biomarkers. Changes in Wald χ^2 statistics are also presented to quantify the reduction in the strength of the association between treatment allocation and outcomes after adjustment for 2-month biomarkers.

Further statistical details are provided in the previously published data analysis plan, appendix (pp 12–13), and primary report.[11] Analyses used SAS software (version 9.4) and R (version 4.3.0).

An independent data and safety monitoring committee oversaw safety and the formal interim analysis for efficacy. EMPA-KIDNEY is registered at ClinicalTrials.gov, NCT03594110.

Role of the funding source

The main trial funder (Boehringer Ingelheim) has minority representation on the trial Steering Committee, which provided oversight of trial design, data collection, and data interpretation. NS, RH, CB, and WH are responsible for the analyses performed by the University of Oxford (Oxford, UK), where the original full database is held.

Results

Between May 15, 2019, and April 16, 2021, 6609 participants were randomly assigned and then followed up for a median of 2·0 years (IQR 1·5–2·4). Prespecified subgroups of eGFR included 2282 (34·5%) participants with an eGFR of less than 30 mL/min per 1·73 m², 2928 (44·3%) with an eGFR of 30 to less than 45 mL/min per 1·73 m², and 1399 (21·2%) with an eGFR 45 mL/min per 1·73 m² or higher. Prespecified subgroups of uACR included 1328 (20·1%) with a uACR of less than 30 mg/g, 1864 (28·2%) with a uACR of 30 to 300 mg/g, and 3417 (51·7%) with a uACR or more than 300 mg/g (table 1). Participants with lower eGFR were older and more likely to have diabetes. uACR was highest among participants with an eGFR 45 mL/min per 1·73 m² or higher, due to the requirement for them to have a uACR 200 mg/g or higher at screening to be eligible. Participants with a higher uACR were younger, were less likely to have diabetes, and had a higher mean eGFR (table 1). Baseline characteristics for the expanded eGFR and uACR categories are given in the appendix (p 15).

Between randomisation and the 2-month follow-up visit, the placebo-adjusted acute dip in eGFR with empagliflozin was 2·12 mL/min per 1·73 m² (95% CI 1·83–2·41), or, in relative terms, 6% (5–6). The relative effects varied significantly across the key subgroups (figure 1) but were generally similar across other prespecified subgroups with statistical evidence for some effect modification by age, BMI, HbA_{1c}, and use of lipid-lowering medication

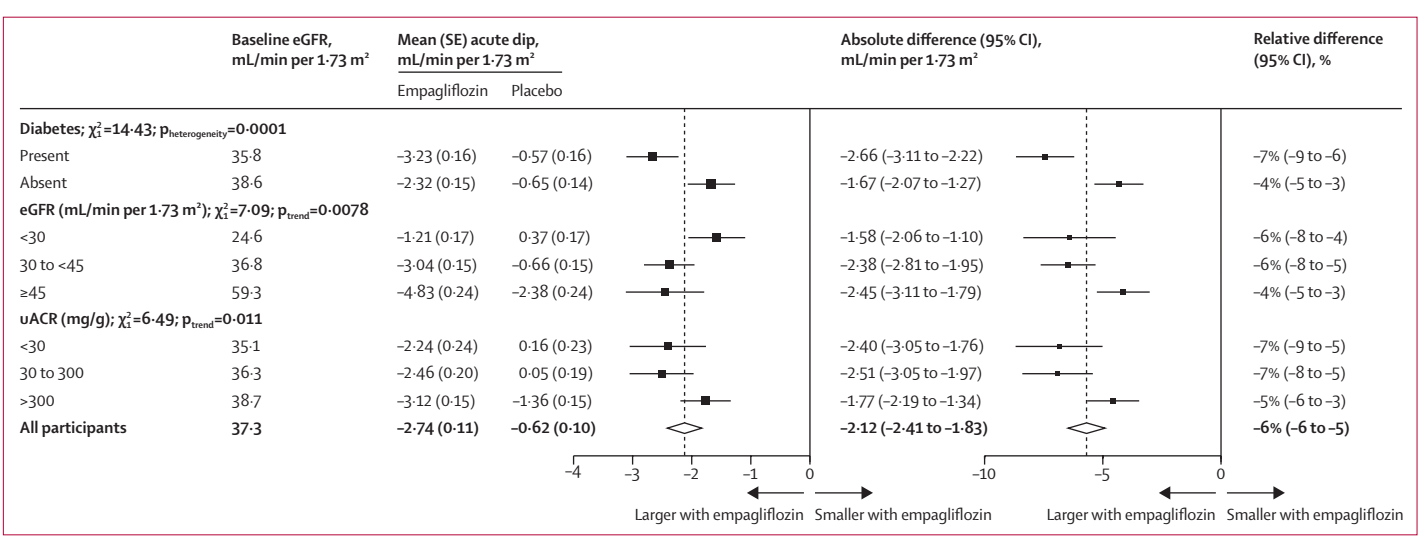


Figure 1: **Effect of allocation to empagliflozin on acute changes in estimated glomerular filtration rate, by key subgroups**
The p value for test of heterogeneity between absolute differences for patients with and without diabetes is 0·0010, the p value for test for trend in absolute differences across eGFR categories is 0·016 and that across uACR categories is 0·050. eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio.

(appendix p 21). In the surviving UK participants with a 4-week post-final follow-up blood sample, this acute dip reversed when study treatment was discontinued, with the mean eGFR at 4 weeks post-final follow-up being 29·89 mL/min per 1·73 m² (SE 0·23) in the empagliflozin group and 27·98 mL/min per 1·73 m² (0·24) in the placebo group (difference 1·91 mL/min per 1·73 m² [95% CI 1·26–2·56]), after accounting for any differences at final follow-up; appendix p 16), with similar differences observed in subgroup analyses by baseline eGFR and uACR categories (appendix p 17).

The geometric mean study average uACR was 202 mg/g (SE 4) in the empagliflozin group and 250 mg/g (5) in the placebo group, a relative reduction in the empagliflozin group of 19% (95% CI 15 to 23). The relative reduction in study average uACR varied substantially between different types of participant, in particular by baseline uACR (appendix p 18). The relative reduction was 5% (95% CI –6 to 15) among patients with a baseline uACR of less than 30 mg/g compared with 26% (20 to 31) among patients with a baseline uACR of higher than 300 mg/g.

Overall, allocation to empagliflozin slowed the rate of decline in eGFR from 2 months to final follow-up (the chronic slope) by 1·37 mL/min per 1·73 m² per year (95% CI 1·16–1·59), which represented a 50% (42–58) relative reduction in the mean chronic slope (figure 2). Larger relative effects were observed among partici-

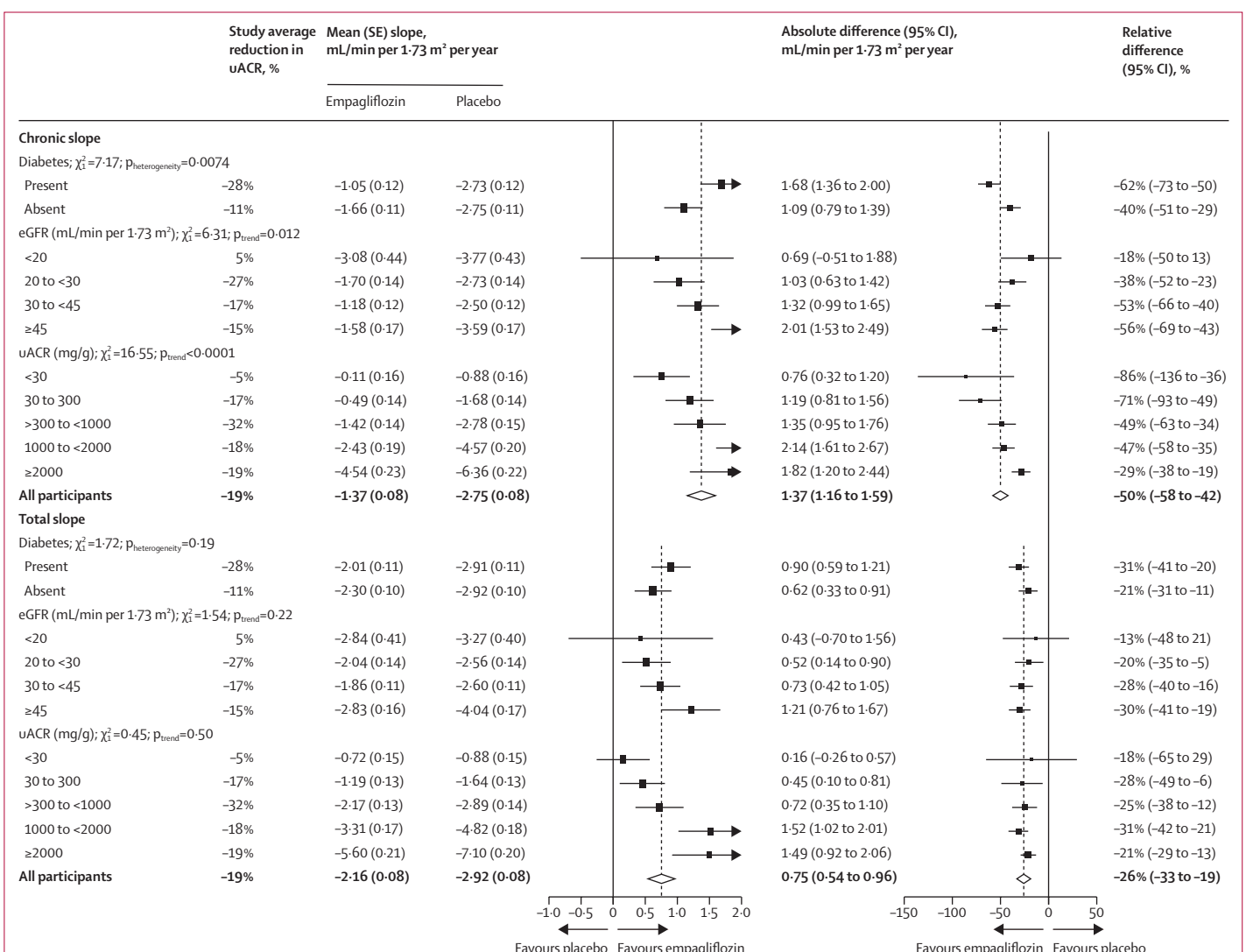
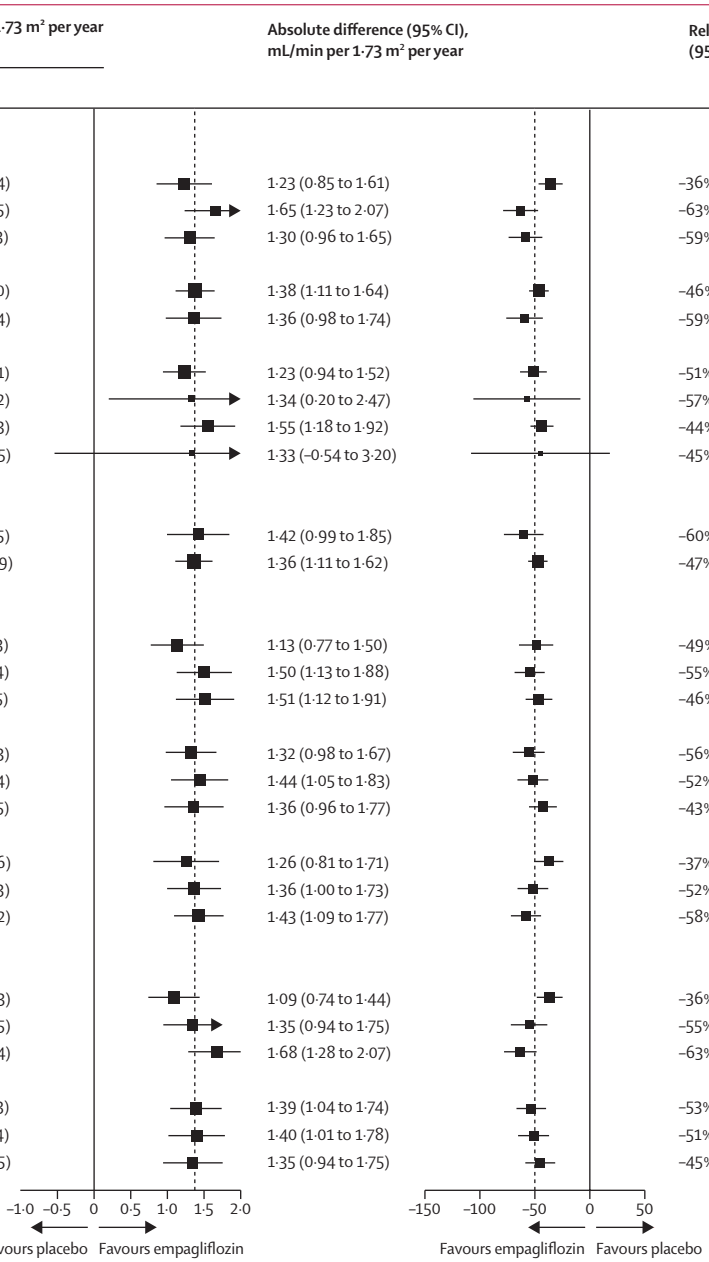


Figure 2: **Absolute and relative effects of allocation to empagliflozin on total slopes and chronic slopes, by prespecified diabetes subgroup, and post-hoc expanded eGFR and uACR subgroups**
The p value for test of heterogeneity between absolute difference in chronic slopes for patients with and without diabetes is 0·0085, the p value for test for trend in absolute differences in chronic slope across eGFR categories is 0·0013 and that across uACR categories is less than 0·0001. The p value for heterogeneity between absolute differences in total slopes for patients with and without diabetes is 0·19, and the p value for test for trend in absolute differences in total slope across eGFR categories is 0·023 and that across uACR categories is less than 0·0001. eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio.

pants with diabetes than those without diabetes (62% [50–73] *vs* 40% [29–51], $p_{heterogeneity}$=0·0074; figure 2). The effect in participants with type 1 diabetes was consistent with that seen in those with type 2 diabetes, although the power to detect a difference was low due to the low number of patients with type 1 diabetes (appendix p 22). There was some evidence that the relative effects differed across eGFR categories in exploratory analyses splitting out the lowest eGFR category into less than 20 mL/min per 1·73 m² and 20 to less than 30 mL/min per 1·73 m² (p_{trend}=0·012; figure 2). The treatment effects on the primary composite of kidney disease progression or cardiovascular death across these expanded eGFR categories showed no evidence of effect modification by eGFR (p_{trend}=0·81; appendix p 23).

Smaller absolute differences between empagliflozin and placebo in chronic slopes were observed in the lowest uACR categories, but the mean rate of decline was also substantially lower in these groups. As a result, when comparing the relative differences in chronic slope, this trend was reversed, with participants in the

	Mean (SE) slope, mL/min per 1·73 m² per year		Absolute difference (95% CI), mL/min per 1·73 m² per year	Relative difference (95% CI), %
	Empagliflozin	Placebo		
Demographics				
Age at randomisation (years); χ^2_1=7·23; p_{trend}=0·0072				
<60	−2·22 (0·14)	−3·45 (0·14)	1·23 (0·85 to 1·61)	−36% (−47 to −25)
60 to <70	−0·97 (0·15)	−2·63 (0·15)	1·65 (1·23 to 2·07)	−63% (−79 to −47)
≥70	−0·92 (0·12)	−2·23 (0·13)	1·30 (0·96 to 1·65)	−59% (−74 to −43)
Sex; χ^2_1=1·84; $p_{heterogeneity}$=0·18				
Male	−1·60 (0·10)	−2·97 (0·10)	1·38 (1·11 to 1·64)	−46% (−55 to −37)
Female	−0·93 (0·14)	−2·29 (0·14)	1·36 (0·98 to 1·74)	−59% (−76 to −43)
Race; χ^2_3=1·08; $p_{heterogeneity}$=0·78				
White	−1·17 (0·11)	−2·40 (0·11)	1·23 (0·94 to 1·52)	−51% (−63 to −39)
Black	−1·00 (0·40)	−2·33 (0·42)	1·34 (0·20 to 2·47)	−57% (−106 to −9)
Asian	−2·01 (0·14)	−3·56 (0·13)	1·55 (1·18 to 1·92)	−44% (−54 to −33)
Other	−1·63 (0·70)	−2·97 (0·65)	1·33 (−0·54 to 3·20)	−45% (−108 to 18)
Previous disease				
History of cardiovascular disease; χ^2_1=1·58; $p_{heterogeneity}$=0·21				
Yes	−0·94 (0·16)	−2·36 (0·15)	1·42 (0·99 to 1·85)	−60% (−78 to −42)
No	−1·52 (0·09)	−2·88 (0·09)	1·36 (1·11 to 1·62)	−47% (−56 to −38)
Clinical measurements				
Systolic blood pressure (mm Hg); χ^2_1=0·15; p_{trend}=0·70				
<130	−1·19 (0·13)	−2·32 (0·13)	1·13 (0·77 to 1·50)	−49% (−64 to −33)
130 to <145	−1·24 (0·14)	−2·75 (0·14)	1·50 (1·13 to 1·88)	−55% (−68 to −41)
≥145	−1·76 (0·15)	−3·27 (0·15)	1·51 (1·12 to 1·91)	−46% (−58 to −34)
Diastolic blood pressure (mm Hg); χ^2_1=1·80; p_{trend}=0·18				
<75	−1·06 (0·13)	−2·38 (0·13)	1·32 (0·98 to 1·67)	−56% (−70 to −41)
75 to <85	−1·34 (0·14)	−2·78 (0·14)	1·44 (1·05 to 1·83)	−52% (−66 to −38)
≥85	−1·83 (0·15)	−3·19 (0·15)	1·36 (0·96 to 1·77)	−43% (−55 to −30)
BMI (kg/m²); χ^2_1=4·49; p_{trend}=0·034				
<25	−2·10 (0·16)	−3·36 (0·16)	1·26 (0·81 to 1·71)	−37% (−51 to −24)
25 to <30	−1·27 (0·13)	−2·63 (0·13)	1·36 (1·00 to 1·73)	−52% (−66 to −38)
≥30	−1·03 (0·12)	−2·46 (0·12)	1·43 (1·09 to 1·77)	−58% (−72 to −44)
Laboratory measurements				
HbA_{1c} (mmol/mol); χ^2_1=8·18; p_{trend}=0·0042				
<39	−1·90 (0·13)	−2·99 (0·13)	1·09 (0·74 to 1·44)	−36% (−48 to −25)
39 to <48	−1·09 (0·14)	−2·44 (0·15)	1·35 (0·94 to 1·75)	−55% (−72 to −39)
≥48	−0·97 (0·14)	−2·65 (0·14)	1·68 (1·28 to 2·07)	−63% (−78 to −48)
NT-proBNP (ng/L); χ^2_1=0·70; p_{trend}=0·40				
<110	−1·22 (0·13)	−2·61 (0·13)	1·39 (1·04 to 1·74)	−53% (−67 to −40)
110 to <330	−1·33 (0·14)	−2·73 (0·14)	1·40 (1·01 to 1·78)	−51% (−65 to −37)
≥330	−1·64 (0·15)	−2·99 (0·15)	1·35 (0·94 to 1·75)	−45% (−59 to −31)



(Figure 3 continues on next page)

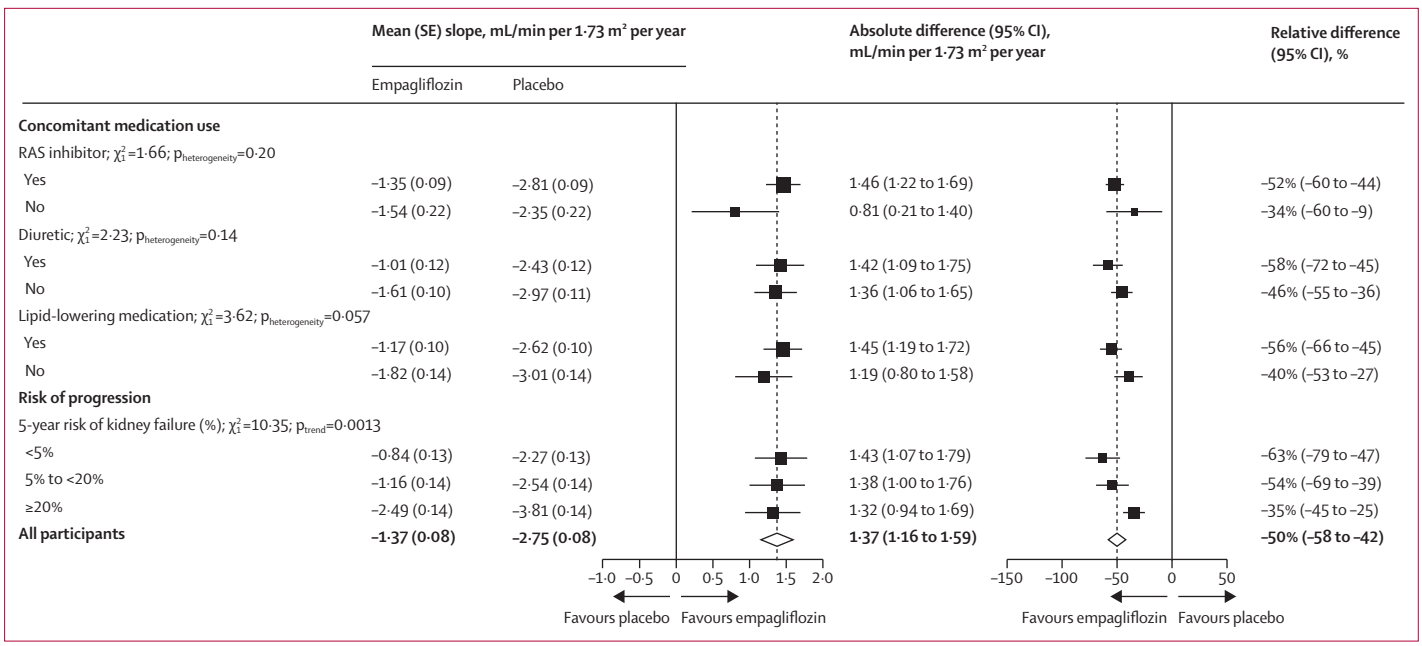


Figure 3: **Effect of allocation to empagliflozin on chronic slopes, by other subgroups**
eGFR=estimated glomerular filtration rate. uACR=urinary albumin-to-creatinine ratio.

	HR (95% CI) for empagliflozin *vs* placebo*	Wald χ^2	Percentage reduction in χ^2	Proportion of treatment effect explained (95% CI)
None	0·73 (0·63 to 0·83)	20·5	0	..
uACR	0·83 (0·72 to 0·95)	7·2	65	40% (24 to 73)
Systolic blood pressure	0·75 (0·65 to 0·86)	16·3	21	10% (3 to 23)
Diastolic blood pressure	0·73 (0·64 to 0·84)	18·9	8	4% (0 to 11)
HbA_{1c}	0·72 (0·63 to 0·83)	20·7	−1	0% (−5 to 4)
uACR, systolic and diastolic blood pressure, and HbA_{1c}	0·83 (0·72 to 0·95)	6·8	67	41% (23 to 77)

Analyses were restricted to 5465 participants with measurements of uACR, systolic and diastolic blood pressure, and HbA_{1c} at 2 months. Participants with an event in the first 2 months of follow-up were excluded. HR=hazard ratio. uACR=urinary albumin-to-creatinine ratio. *After adjustment for biomarkers at 2 months. All analyses were additionally adjusted for baseline variables specified in the minimisation algorithm (age, sex, previous diabetes, estimated glomerular filtration rate, uACR, and region).

Table 2: **Proportion of treatment effect for primary composite outcome explained by 2-month biomarkers**

lowest uACR categories having the largest relative reduction in the chronic slope (relative reduction 86% [95% CI 36–136] in those with uACR <30 mg/g compared with 29% [19–38] in those with uACR ≥2000 mg/g, p_{trend}<0·0001; figure 2). The trend seen in the relative difference in the chronic slope depending on uACR was similar among participants with and without diabetes (appendix p 24).

Relative differences in the chronic slope were generally similar across other subgroups, with statistical evidence for some effect modification by age, HbA_{1c}, and 5-year risk of kidney failure, although clear benefits remained in all subgroups (figure 3). Differences in the relative effects on the chronic slope for the diabetes and uACR subgroups were not explained by their correlation with other key characteristics (as results were essentially unchanged after including interactions with other key subgroups; appendix p 25). Results were also similar in sensitivity analyses restricted to on-treatment eGFR measurements and using eGFR measurements based on local laboratory creatinine values (appendix pp 26, 27).

Overall, allocation to empagliflozin slowed the rate of decline in eGFR from baseline to final follow-up by 0·75 mL/min per 1·73 m² per year (95% CI 0·54–0·96), which represents a 26% (19–33) relative reduction in the mean total slope (figure 2). These differences reflect the combinations of the effects on the acute dips in eGFR and the chronic slopes. Relative differences in total slope were similar across all the expanded key subgroups and other subgroups (appendix p 28).

In exploratory analyses, on-study levels of uACR, systolic blood pressure, diastolic blood pressure, and HbA_{1c} explained 41% (95% CI 23–77) of the treatment effect on the primary composite of kidney disease progression or cardiovascular death (an attenuation of the hazard ratio from 0·73 [0·63 to 0·83] to 0·83 [0·72 to 0·95], and 67% reduction in χ^2 from 20·5 to 6·8; table 2). uACR alone explained 40% (24 to 73) of the treatment effect, whereas systolic blood pressure and diastolic blood pressure explained fairly modest proportions (10% [3 to 23] and 4% [0 to 11], respectively) and HbA_{1c} did not explain any of the treatment effect (0% [−5 to 4]; table 2). Similar patterns were observed for chronic slope, although the proportion of the treatment effect explained by the biomarkers was somewhat lower (26% [19 to 35]; appendix p 19).

Discussion

Our analyses showed that, in this cohort of patients with chronic kidney disease at risk of progression, allocation to empagliflozin caused a small dip in kidney function of approximately 2 mL/min per 1·73 m² (or 6%) and then halved the subsequent rate of long-term loss of kidney function. This overall result complements the 29% (95% CI 19–38) reduction in risk of kidney disease progression when assessed with the categorical composite outcome of end-stage kidney disease, a sustained decrease from baseline in eGFR of at least 40% or to less than 10 mL/min per 1·73 m², or death from kidney failure. The beneficial effects of empagliflozin on the progression of chronic kidney disease varied by diabetes status and eGFR, but most prominently by albuminuria, where relative benefits might in fact be larger among participants with lower albuminuria. These findings are consistent with observations in other trials of SGLT2 inhibitors in chronic kidney disease, although these trials focused on patients with diabetes, significant levels of albuminuria, or both.[13,14] The broad range of patients included in the large EMPA-KIDNEY trial has allowed this to be explored in a more diverse population than those included in other large trials of SGLT2 inhibition in chronic kidney disease; in particular, EMPA-KIDNEY included participants with an eGFR of less than 25 mL/min per 1·73 m² and with a uACR of less than 200 mg/g who were excluded from these previous trials.

The acute dip in eGFR when empagliflozin was initiated in EMPA-KIDNEY was modest (in all participant subgroups; it was on average <3 mL/min per 1·73 m² or <10% of baseline eGFR) and was largely reversible when treatment was discontinued. The acute effect was larger among participants with diabetes than in those without (on both absolute and relative scales), which might reflect the greater prevalence and degree of hyperfiltration in this group. The acute effect of SGLT2 inhibition on kidney function was recognised early in the development of this drug class (although not in all studies[23]) and is believed to be due to the acute reduction in intraglomerular pressure caused by afferent arteriolar vasoconstriction stimulated by increased sodium delivery to the macula densa.[24,25] The associated rapid reduction in albuminuria supports this hypothesis,[26] and this reduction in intraglomerular pressure is one of the postulated mechanisms of the beneficial effects of SGLT2 inhibition on kidney function.[25] Our exploratory analyses suggest that the reduction in albuminuria might be the most important measured determinant of the benefits observed in EMPA-KIDNEY, explaining a fifth of the effect on chronic slopes and two-fifths of the effect on the primary composite outcome of kidney disease progression, consistent with analyses from other trials in chronic kidney disease.[27] These analyses need to be interpreted with some caution because they could have been subject to bias due to measurement error and residual mediator–outcome confounding. Whether this association is due to avoidance of direct toxic effects of albumin on tubular function, a reduction in intraglomerular pressure, or another unmeasured correlate of urinary albumin is not clear. However, these analyses also suggest that other mechanisms unrelated to albuminuria, blood pressure, or glycaemic control contribute to the benefit of SGTL2 inhibition on kidney function.

Our analyses focused on chronic slopes. Although effects on total slope correlate strongly with effects on clinical outcomes over short (2–3-year) follow-up periods,[8] the chronic slope is likely to be more informative for longer time periods. When the magnitude of the acute dip correlates with the relative reduction in the chronic slope (which is plausible because they share causal mechanisms, such as reduced intraglomerular pressure), this reduces variation between subgroups in total slope when measured over 2–3 years. However, this would not be the case with longer follow-up (see appendix p 29 for an explanatory example). Clinicians seeking to delay or avoid kidney failure would usually consider such longer time periods for which the chronic slope is most relevant. Furthermore, the limited variation in total slopes between patient subgroups reduces the ability to explore any such differences in treatment effect that might exist between those subgroups. This is shown by the apparent consistency of treatment effect on total slope in EMPA-KIDNEY versus the evidence of effect modification when using chronic slopes.

When comparing chronic slopes, we have reported both the absolute and relative differences but have emphasised the latter. Absolute differences are determined by both the background annual rate of change in eGFR and the relative effect of treatment, so any heterogeneity observed could be due to either of these components. This is demonstrated in the analysis by baseline uACR: the absolute difference in the chronic slope among participants with a uACR of 2000 mg/g or higher was 1·82 mL/min per 1·73 m² per year, whereas the background chronic slope among participants with a uACR of less than 30 mg/g was 0·88 mL/min per 1·73 m² per year, so it was impossible for the absolute difference in the latter subgroup to be similar to that observed in the highest uACR subgroup. Indeed, the absolute difference in the chronic slope was positively associated with baseline uACR; however, the relative difference was inversely associated such that participants with the lowest baseline uACR had the largest relative reduction (86% [95% CI 36–136] in those with uACR <30 mg/g *vs* 29% [19–38] in those with uACR ≥2000 mg/g). There was no strong evidence that this association was importantly modified by the presence or absence of diabetes. Contrary to some international guidelines that only suggest (rather than recommend) using SGLT2 inhibitors in patients without diabetes and without significant albuminuria (uACR <200 mg/g),[28] these analyses suggest that patients with low albuminuria (with or without diabetes) are likely to gain substantial

benefit in terms of preservation of kidney function from SGLT2 inhibition, in addition to the other benefits of reductions in risk of acute kidney injury and cardiovascular disease.[29] Given the short follow-up in EMPA-KIDNEY (median 2 years) it would be expected that a treatment that causes a 2 mL/min per 1·73 m² acute dip in eGFR in the subgroup of patients with uACR <30 mg/g (progressing at only 1 mL/min per 1·73 m² per year) would not demonstrate definitive benefits on the categorical outcome (by contrast with subgroups with higher uACR progressing faster than 2 mL/min per 1·73 m² per year). These analyses of the chronic slope suggest that important benefits would likely emerge with longer treatment (see appendix p 29 for an example).

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These analyses are limited by the characteristics of patients included in EMPA-KIDNEY.[11] Few patients with type 1 diabetes were included, and patients with autosomal dominant polycystic kidney disease or with a kidney transplant were not eligible for the trial. In a companion paper, we assess whether the effects of allocation empagliflozin vary in different types of kidney disease.[12] The trial deliberately excluded patients at low risk of chronic kidney disease progression (ie, those with an eGFR of ≥45 mL/min per 1·73 m² and uACR <200 mg/g), but demonstrated that the relative benefit on the chronic slope was inversely proportional to predicted risk of kidney failure. Participants only received study treatment for 2 years on average because the trial was stopped earlier than planned owing to clear evidence of benefit. A further 2 years of off-treatment follow-up is underway to assess the longer-term effects of an average of 2 years of treatment.

In summary, in EMPA-KIDNEY, allocation to empagliflozin compared with placebo caused a modest acute dip in eGFR, and then substantially slowed the longer-term progression of chronic kidney disease. The longer-term benefits varied by diabetes status, eGFR, and most prominently uACR (and related characteristics such as predicted risk of kidney failure). Although the trial stopped early because of clear benefits emerging based on results in patients at highest risk, these analyses show that patients at lower risk such as those with lower levels of albuminuria—many of whom in their lifetime would otherwise develop kidney failure—could benefit in terms of preservation of kidney function, in addition to other proven cardiovascular and mortality benefits.[29] If widely implemented, use of SGLT2 inhibitors could have a substantial effect on the public health impacts of chronic kidney disease.

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NS, RH, CB, and WGH proposed and developed the analyses, had full access to and verified the data, wrote the first draft, and have final responsibility for the decision to submit for publication. NS led analyses with JRE, and replication by SS. All authors contributed to data interpretation and manuscript review. NS, RH, CB, and WH had final responsibility for the decision to submit for publication.

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Data sharing

The EMPA-KIDNEY Steering Committee has developed a comprehensive analysis plan for subsidiary analyses which will be presented in future scientific presentations and publications. Data will be made available to other researchers in 2024. Application is by email to data.access@ndph.ox.ac.uk: https://www.ndph.ox.ac.uk/files/about/data_access_enquiry_form_13_6_2019.docx. 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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