# SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

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## Summary

**Background** The effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on kidney failure, particularly the need for dialysis or transplantation or death due to kidney disease, is uncertain. Additionally, previous studies have been underpowered to robustly assess heterogeneity of effects on kidney outcomes by different levels of estimated glomerular filtration rate (eGFR) and albuminuria. We aimed to do a systematic review and meta-analysis to assess the effects of SGLT2 inhibitors on major kidney outcomes in patients with type 2 diabetes and to determine the consistency of effect size across trials and different levels of eGFR and albuminuria.

**Methods** We did a systematic review and meta-analysis of randomised, controlled, cardiovascular or kidney outcome trials of SGLT2 inhibitors that reported effects on major kidney outcomes in people with type 2 diabetes. We searched MEDLINE and Embase from database inception to June 14, 2019, to identify eligible trials. The primary outcome was a composite of dialysis, transplantation, or death due to kidney disease. We used random-effects models to obtain summary relative risks (RRs) with 95% CIs and random-effects meta-regression to explore effect modification by subgroups of baseline eGFR, albuminuria, and use of renin–angiotensin system (RAS) blockade. This review is registered with PROSPERO (CRD42019131774).

**Findings** From 2085 records identified, four studies met our inclusion criteria, assessing three SGLT2 inhibitors: empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program and CREDENCE), and dapagliflozin (DECLARE–TIMI 58). From a total of 38 723 participants, 252 required dialysis or transplantation or died of kidney disease, 335 developed end-stage kidney disease, and 943 had acute kidney injury. SGLT2 inhibitors substantially reduced the risk of dialysis, transplantation, or death due to kidney disease (RR 0·67, 95% CI 0·52–0·86, p=0·0019), an effect consistent across studies ($I^2$=0%, $p_{heterogeneity}$=0·53). SGLT2 inhibitors also reduced end-stage kidney disease (0·65, 0·53–0·81, p<0·0001), and acute kidney injury (0·75, 0·66–0·85, p<0·0001), with consistent benefits across studies. Although we identified some evidence that the proportional effect of SGLT2 inhibitors might attenuate with declining kidney function ($p_{trend}$=0·073), there was clear, separate evidence of benefit for all eGFR subgroups, including for participants with a baseline eGFR 30–45 mL/min per 1·73 m² (RR 0·70, 95% CI 0·54–0·91, p=0·0080). Renoprotection was also consistent across studies irrespective of baseline albuminuria ($p_{trend}$=0·66) and use of RAS blockade ($p_{heterogeneity}$=0·31).

**Interpretation** SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney disease in individuals with type 2 diabetes and provided protection against acute kidney injury. These data provide substantive evidence supporting the use of SGLT2 inhibitors to prevent major kidney outcomes in people with type 2 diabetes.

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## Introduction

About 2·6 million people are estimated to have received dialysis or undergone kidney transplantation for kidney failure in 2010, and this number is projected to more than double by 2030.[1] In many countries, more than half of all patients entering dialysis programmes have type 2 diabetes, making this disease a leading cause of kidney failure worldwide.[2] Kidney failure due to type 2 diabetes is a large and growing challenge, not only for patients, their families, and caregivers, but also for health systems and governments.[3]

Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been shown to prevent major adverse kidney outcomes in people with diabetes, and these drugs are recommended by clinical practice guidelines for the treatment of people with type 2 diabetes who have, or are at high risk of, kidney disease.[4–8] However, the residual risk remains high, and new treatments are urgently needed to reduce the growing burden of kidney failure.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are glucose-lowering drugs that also lower blood

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## Research in context

### Evidence before this study

Large-scale randomised cardiovascular outcome trials of sodium-glucose co-transporter-2 (SGLT2) inhibitors in people with type 2 diabetes have suggested promising effects of these drugs on albuminuria and creatinine-based kidney outcomes. However, these trials included few participants at high risk of clinically important kidney outcomes and, as a result, the effect of SGLT2 inhibitors on kidney outcomes that are of greatest concern to patients—namely, the need for long-term dialysis or transplantation, or death due to kidney disease—is unclear. Additionally, SGLT2 inhibitors are not approved for use in patients with estimated glomerular filtration rate (eGFR) lower than 45 mL/min per 1·73 m² in most countries, mainly because their glucose-lowering effect is substantially dependent on kidney function. In a 2018 meta-analysis of these trials, the renoprotective effect of SGLT2 inhibitors was reported to be attenuated with declining kidney function. However, fewer than a sixth of participants studied had a baseline eGFR lower than 60 mL/min per 1·73 m², and even fewer had baseline eGFR lower than 45 mL/min per 1·73 m². Therefore, the ability to robustly assess effects in people with reduced kidney function was limited, especially because few patient-level kidney outcomes occurred. Although, collectively, these trials have suggested that SGLT2 inhibitors might protect against acute kidney injury, the safety of these drugs in patients at high risk of adverse kidney outcomes has remained a concern. In 2019, the primary results of the CREDENCE trial were reported—this trial was designed specifically to examine the effect of SGLT2 inhibition (with canagliflozin) in patients with type 2 diabetes at high risk of kidney disease progression. Therefore, we did a systematic review and meta-analysis of randomised, controlled, event-driven trials in patients with type 2 diabetes that reported effects of SGLT2 inhibition on major kidney outcomes. We searched MEDLINE and Embase from database inception to June 14, 2019, to identify potentially relevant studies.

### Added value of this study

Our systematic review and meta-analysis summarises and pools data from four studies including a total of 38 723 participants across six continents. We identified clear evidence that SGLT2 inhibitors reduce the risk of dialysis, transplantation, or death due to kidney disease, as well as a range of other major kidney outcomes, and that these drugs also provide protection against acute kidney injury. Additionally, we identified benefit at all levels of kidney function, including a proportional risk reduction of about 30% in the composite kidney outcome in participants with baseline eGFR lower than 45 mL/min per 1·73 m², in whom these drugs are mostly not approved for use.

### Implications of all the available evidence

To the best of our knowledge, these results provide the strongest evidence yet that SGLT2 inhibitors should be routinely offered to individuals with type 2 diabetes at risk of progressive kidney disease. The clear evidence of renoprotection across the spectrum of kidney function studied to date calls into question the existing restrictions on the use of SGLT2 inhibitors in people with reduced kidney function and suggests that many more individuals with type 2 diabetes at high risk of kidney failure are likely to benefit from treatment with these drugs.

pressure, bodyweight, and albuminuria and might have direct haemodynamic effects on the kidney.[9] Large-scale cardiovascular outcome trials[10–15] of SGLT2 inhibitors, which were originally designed to meet regulatory requirements and ensure cardiovascular safety, have shown promising effects on a range of albuminuria and serum creatinine-based kidney outcomes in patients with, or at high risk of, atherosclerotic cardiovascular disease. Most participants in these trials were at low risk of clinically important kidney outcomes and, as a result, event rates for kidney failure were low, with few participants requiring dialysis or kidney transplantation, or dying from kidney disease, in each trial. Because these trials were also not explicitly designed to provide definitive information on renoprotective effects, kidney endpoints were not always prespecified or adjudicated and the distinction between acute and chronic reductions in estimated glomerular filtration rate (eGFR) was not possible in all studies.

The results of a 2018 meta-analysis[14] of cardiovascular outcome trials suggested that the effect of SGLT2 inhibitors on kidney outcomes attenuates with declining eGFR. However, less than a sixth of participants in the analysis had baseline eGFR lower than 60 mL/min per 1·73 m² and thus, the ability to robustly assess effect modification by kidney function was limited. Additionally, because very few participants with baseline eGFR lower than 45 mL/min per 1·73 m² were assessed in the cardiovascular outcome trials of SGLT2 inhibitors, whether these patients derive protection against kidney failure outcomes has also been unclear, given that the glycaemic efficacy of SGLT2 inhibitors is substantially attenuated in this population. Similarly, most participants in cardiovascular outcome trials of SGTL2 inhibitors had normal albuminuria and, therefore, the consistency of treatment effect across different levels of albuminuria is unclear. Although these trials have collectively suggested protection against acute kidney injury,[16] the safety of SGLT2 inhibitors in patients at high risk of adverse kidney outcomes has not been well established. In 2019, the results of the CREDENCE trial[17]—the first study designed to specifically assess the effect of an SGLT2 inhibitor (canagliflozin) on a primary kidney outcome in people with established diabetic kidney disease—were reported.

Therefore, we did a systematic review and meta-analysis to assess the consistency of effect size across

trials of SGLT2 inhibitors and different levels of kidney function and albuminuria, summarise results, and integrate available data for the effects of SGLT2 inhibition on the risk of clinically important kidney outcomes in people with type 2 diabetes.

## Methods

### Search strategy and selection criteria

For this systematic review and meta-analysis, we searched MEDLINE and Embase from database inception to June 14, 2019, for English-language publications using search terms including "sodium-glucose transporter" and related phrases, the names of individual SGLT2 inhibitor drugs, and terms related to randomised clinical trials. Details of the search strategy, including text words and medical subject headings, are provided in the appendix (p 2). We included all randomised, controlled, event-driven, cardiovascular or kidney outcome trials of SGLT2 inhibitors versus active or placebo control in patients with type 2 diabetes, to capture those with meaningful numbers of clinical kidney outcomes. Trials with extension periods and those including participants with type 1 diabetes or those younger than 18 years were excluded. Two authors (BLN and TY) independently screened the titles and abstracts of all identified articles and, when required, reviewed full-text reports to identify potentially relevant studies. Any disagreements related to the identification or eligibility of studies were resolved through discussion with a third author (MJJ). Study sponsors and investigators were contacted to obtain additional trial-level data and clarify outcome definitions when required.

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement to guide the conduct and reporting of this systematic review and meta-analysis. The protocol for this review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) for registration before the analyses were initiated (on April 10, 2019), and the study was registered before the analyses were completed (PROSPERO registration number CRD42019131774).

### Data analysis

Two authors (BLN and TY) independently extracted all data using a standardised data form and assessed risk of bias at the study level using the Cochrane risk-of-bias tool.[18] We used image extraction software to extract data presented only in figures without corresponding numerical data (WebPlotDigitizer, version 4.1). These data were summarised descriptively and not used for quantitative synthesis. Any discrepancies in data extraction or risk-of-bias assessment were resolved in consultation with a third author (MJJ). Because of the small number of eligible trials, we did not assess publication bias.

The primary outcome of interest was a composite of chronic dialysis, kidney transplantation, or death due to kidney disease. Other kidney outcomes assessed were end-stage kidney disease (defined as chronic dialysis, kidney transplantation, or sustained eGFR lower than 15 mL/min per 1·73 m²); substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease; substantial loss of kidney function, end-stage kidney disease, or death due to cardiovascular or kidney disease; long-term eGFR slope; and acute kidney injury. Substantial loss of kidney function was preferentially defined as a sustained doubling of serum creatinine (representing a roughly 57% decline in kidney function).[19] Where sustained doubling of serum creatinine was not reported, we included sustained 40% decline in eGFR or non-sustained doubling of serum creatinine, as defined by study authors. We preferentially used data on sustained kidney outcomes confirmed with repeat assessment where these were reported, to exclude acute changes in kidney function and initiation of dialysis for acute kidney injury, but we accepted non-sustained outcomes where these were the only ones reported. The definitions of long-term eGFR slope (annualised difference in eGFR between treatment and control) and acute kidney injury varied across studies, and we used these outcomes as defined and reported in each study.

See Online for appendix

We prespecified that results for dichotomous outcomes were to be quantitatively synthesised by individual studies with use of a random-effects model with inverse variance weighting to obtain summary effect estimates represented as relative risk with associated 95% CIs. We also decided a priori to pool, in order of preference, hazard ratios, incidence rate ratios (events per patient-years), and risk ratios (events per number of participants) to maximise the use of trial-level data from included studies, particularly for canagliflozin, where the integrated analysis and reporting of two parallel companion trials with different randomisation ratios and different follow-up durations precluded the use of risk ratios.[20] When the preferred outcome definition for substantial loss of kidney function was not reported in certain studies, we did sensitivity tests excluding those studies to assess the effect of endpoint definition on the results. We prospectively decided to summarise the effect of SGLT2 inhibitors on long-term eGFR slope descriptively because of variations in the definition of this outcome and because it measured the absolute rather than proportional effect of treatment. Therefore, any heterogeneity between studies for this outcome could not be meaningfully assessed, because differences in absolute effect reflected differences in baseline kidney risk. For all other outcomes, we assessed heterogeneity between studies using the $I^2$ statistic and p values for heterogeneity obtained from a random-effects model. $I^2$ values lower than 25% were considered to represent a low likelihood of differences between studies, with values of 25–75% representing a moderate likelihood, and those from higher than 75% to 100% representing a high likelihood.

For the **WebPlotDigitizer** see https://automeris.io/WebPlotDigitizer/

| | EMPA-REG OUTCOME | CANVAS Program | DECLARE–TIMI 58 | CREDENCE |
|---|---|---|---|---|
| Drug | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin |
| Dose (mg) | 10 and 25 | 100 and 300 | 10 | 100 |
| Number of participants | 7020 | 10 142 | 17 160 | 4401 |
| Mean age (years) | 63·1 | 63·3 | 63·9 | 63·0 |
| Sex | | | | |
| Men | 5016 (71·5%) | 6509 (64·2%) | 10 738 (62·6%) | 2907 (66·1%) |
| Women | 2004 (28·5%) | 3633 (35·8%) | 6422 (37·4%) | 1494 (33·9%) |
| Median follow-up (years) | 3·1 | 2·4 | 4·2 | 2·6* |
| eGFR inclusion criteria | ≥30 (MDRD) | ≥30 (MDRD) | CrCl ≥60 mL/min (Cockcroft-Gault) | 30 to <90 (CKD-EPI) |
| Baseline eGFR subgroup (mL/min per 1·73 m²)†‡ | | | | |
| ≥90 | 1538 (21·9%) | 2476 (24·4%) | 8162 (47·6%) | 0 |
| 60 to <90 | 3661 (52·2%) | 5625 (55·5%) | 7732 (45·1%) | 1809 (41·1%) |
| 45 to <60 | 1249 (17·8%) | 1485 (14·6%) | 1265 (7·4%)§ | 1279 (29·1%) |
| <45 | 570 (8·1%) | 554 (5·5%) | NA | 1313 (29·8%) |
| Missing baseline eGFR | 2 (<0·1%) | 2 (<0·1%) | 1 (<0·1%) | 0 |
| UACR criteria (mg/g) | None | None | None | >300 to 5000 |
| Baseline UACR subgroup (mg/g)‡ | | | | |
| <30 | 4171 (59·4%) | 7007 (69·1%) | 11 644 (67·9%) | 0 |
| 30–300 | 2013 (28·7%) | 2266 (22·3%) | 4030 (23·5%) | 0 |
| >300 | 769 (11·0%) | 760 (7·5%) | 1169 (6·8%) | 4401 (100·0%) |
| Missing baseline UACR | 67 (1·0%) | 109 (1·1%) | 317 (1·8%) | 0 |
| Baseline use of RAS blockade | 5666 (80·7%) | 8116 (80·0%) | 13 950 (81·3%) | 4395 (99·9%) |

Data are n (%), unless otherwise specified. eGFR=estimate glomerular filtration rate. MDRD=Modification of Diet in Renal Disease equation. CrCl=creatinine clearance. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation. UACR=urine albumin-to-creatinine ratio. RAS=renin–angiotensin system. NA=not available. *Stopped early after a planned interim analysis on the recommendation of the independent data monitoring committee. †Based on the MDRD equation in EMPA-REG OUTCOME and the CANVAS Program and on the CKD-EPI equation in DECLARE–TIMI 58 and CREDENCE. ‡Based on screening (rather than baseline) eGFR and UACR measurements in the CREDENCE trial. §Includes all DECLARE–TIMI 58 participants with eGFR lower than 60 mL/min per 1·73m².

***Table:*** **Characteristics of included studies**

Because of the kidney-based mechanism of action and albuminuria-lowering effect of SGLT2 inhibitors, we prospectively decided to do subgroup analyses for efficacy outcomes to assess effect modification by three kidney-related subgroups. The effects of SGLT2 inhibitors on the composite kidney outcome of substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease were assessed across different levels of baseline kidney function and urinary albumin excretion. Additionally, because ACE inhibitors and ARBs are recommended for the treatment of diabetic kidney disease, we also analysed whether the effects of SGLT2 inhibition differed by baseline use of renin–angiotensin system (RAS) blockade. Because the results are from few individual studies, we did multiple sensitivity analyses to assess the vulnerability of the eGFR subgroup analysis outcomes to definitional and methodological decisions. We assessed the effect of SGLT2 inhibitors by eGFR categories (eGFR <45, 45 to <60, 60 to <90, and ≥90 mL/min per 1·73 m²) and levels of albuminuria (urine albumin-to-creatinine ratio [UACR] <30, 30–300, and >300 mg/g) as the main analysis. In studies in which data for the subgroup with eGFR lower than 60 mL/min per 1·73 m² were reported without more granular categories, we excluded these data from the main analysis. However, we did a sensitivity analysis in which the outcomes for the baseline subgroup of eGFR lower than 60 mL/min per 1·73 m² were included with the eGFR 45 to less than 60 mL/min per 1·73 m² category, on the assumption that most of these participants were likely to have an eGFR within this range (on the basis of trial exclusion criteria). We did an additional sensitivity analysis to assess the effects of treatment in participants with eGFR lower than 60 mL/min per 1·73 m² and those with an eGFR of 60 mL/min per 1·73 m² or higher. When required, effect estimates for subgroups within the same study (eg, eGFR 30 to <45 mL/min per 1·73 m² and 45 to <60 mL/min per 1·73 m²) were merged by use of a fixed-effects model. For the eGFR slope outcome, data were stratified by kidney function (eGFR <60 mL/min per 1·73 m² and ≥60 mL/min per 1·73 m²) and albuminuria (UACR <30, 30–300, and >300 mg/g) and summarised descriptively.

We decided a priori to use random-effects meta-regression to assess trends in treatment effects across eGFR and albuminuria subgroups as the primary analysis. In sensitivity analyses, we repeated the meta-regression analyses treating subgroups as categories without assumptions of linearity. $p_{trend}$ and $p_{heterogeneity}$ values lower than 0·1 were considered to reflect a high likelihood of difference beyond that expected by chance. All analyses were done with Stata, version 15.1.

### Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and agreed on the decision to submit for publication.

## Results

We identified 2085 records through database searching and screened their summaries for eligibility, after removal of duplicates. Of 58 full-text articles assessed, we identified four separate studies, comprising five individual trials, after applying the study selection criteria (appendix pp 3,13). We used data from several secondary analyses of these studies in this meta-analysis.[10,11–13,15,21–24] Sustained kidney outcomes in the EMPA-REG OUTCOME trial were reported in a separate correspondence[21] to the main trial publication,[11] and these were preferentially used where possible. One secondary analysis[15] of the DECLARE–TIMI 58 trial, which was published shortly before the systematic literature search was done (and had not yet been added to the databases), was identified independently.

All four studies compared an SGLT2 inhibitor with matching placebo. The CANVAS Program comprised two companion trials (CANVAS and CANVAS-R) that were done in parallel and analysed and reported as a single programme.[25] Three studies[25–27] were

designed as cardiovascular outcome trials testing the effect of empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program), and dapagliflozin (DECLARE–TIMI 58) on a primary composite cardiovascular outcome of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death, with a range of prespecified exploratory and post-hoc kidney outcomes also reported. One study (CREDENCE)[17] was an event-driven kidney outcome trial for canagliflozin, with a primary composite outcome of sustained doubling of serum creatinine, end-stage kidney disease, or death due to cardiovascular or kidney disease. The risk of bias was low for all indicators; all participants and investigators were masked to treatment allocation, with complete reporting of outcomes (appendix p 3).

Our meta-analysis included data for a total of 38 723 randomly assigned participants from six continents. The mean age across the studies ranged from 63·0 to 63·9 years, and 13 553 (35·0%) participants overall were women (table). The proportion of participants with an eGFR less than 60 mL/min per 1·73m² ranged from 7·4% in DECLARE–TIMI 58 to 58·9% in CREDENCE. Most of the participants in the three trials assessing cardiovascular outcomes had a UACR lower than 30 mg/g at baseline (ranging from 59·4% to 69·1% of participants), whereas UACR higher than 300 mg/g was an entry criterion for the CREDENCE trial (table). An eGFR of 30 mL/min per 1·73 m² or higher was an inclusion criterion in all studies apart from DECLARE–TIMI 58, in which a creatinine clearance of 60 mL/min or higher (based on the Cockroft-Gault equation) was required. Treatment with RAS blockade was required for entry in the CREDENCE trial. Accordingly, almost all (99·9%) participants in CREDENCE were treated with ACE inhibitors or ARBs at baseline, compared with about 80% of participants in the other trials (table).

Across all included studies, 252 participants required dialysis or transplantation or died because of kidney disease. Overall, there were 335 end-stage kidney disease events; 967 occurrences of substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease; 2323 cases of substantial loss of kidney function, end-stage kidney disease, or death due to cardiovascular or kidney disease; and 943 participants having an episode of acute kidney injury. The prespecification of outcomes, requirements for changes in kidney function to be confirmed on repeated measurement, and adjudication procedures differed across the studies (appendix pp 4–5). Kidney endpoints were also defined and reported differently across the studies (appendix pp 6–9).

SGLT2 inhibitor treatment reduced the risk of dialysis, transplantation, or death due to kidney disease by 33% (figure 1) compared with placebo. The effect of SGLT2 inhibitors on this outcome was consistent across studies ($I^2$=0%, $p_{heterogeneity}$=0·53). SGLT2 inhibitor treatment reduced the risk of end-stage kidney disease by 35%

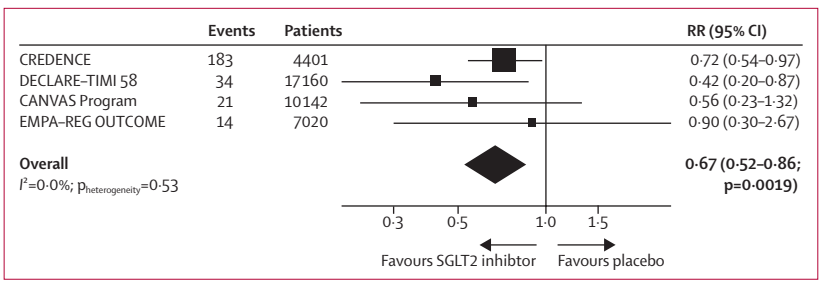


***Figure 1:*** **Effect of SGLT2 inhibitors on dialysis, transplantation, or death due to kidney disease**
Weights were from random-effects meta-analysis. Data from DECLARE-TIMI 58 have not been previously reported. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

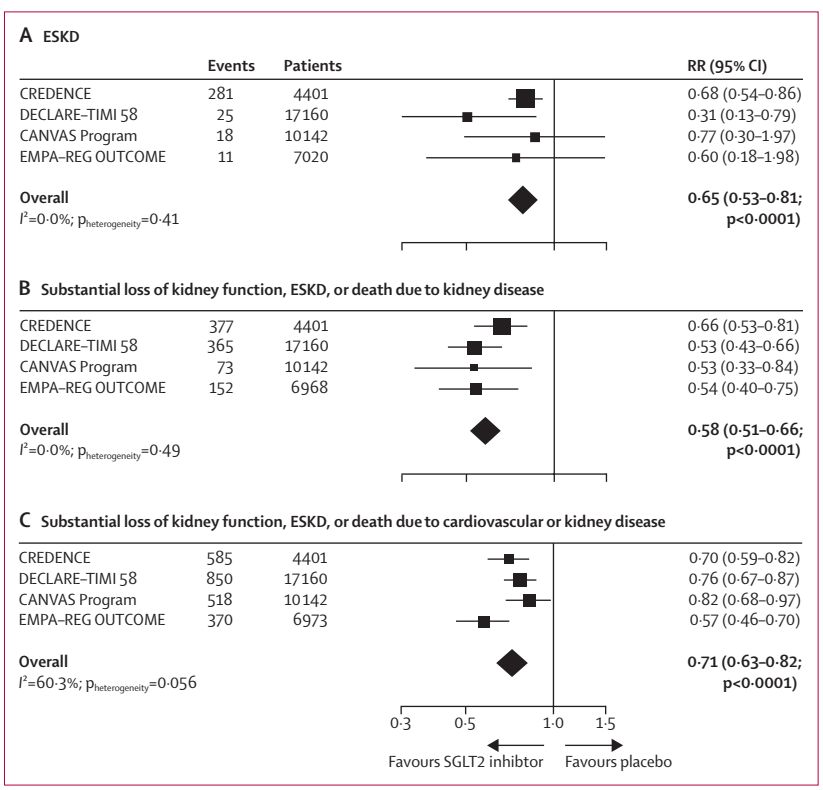


***Figure 2:*** **Effect of SGLT2 inhibitors on ESKD (A), substantial loss of kidney function, ESKD, or death due to kidney disease (B), and substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease (C)**
Weights were from random effects meta-analysis. ESKD was defined as chronic dialysis, transplantation, or sustained estimated glomerular filtration rate (eGFR) lower than 15 mL/min per 1·73 m², apart from in the EMPA-REG OUTCOME trial, in which it was defined as chronic dialysis or transplantation. Substantial loss of kidney function was defined as doubling of serum creatinine, apart from in the DECLARE–TIMI 58 trial, in which it was defined as sustained 40% decline in eGFR. Data on substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease (C) in EMPA-REG OUTCOME have not been previously published. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

(figure 2), with no differences in treatment effect across studies ($I^2$=0·0%, $p_{heterogeneity}$=0·41). The use of SGLT2 inhibitors also reduced the risk of substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease by 42% (figure 2), with no evidence of differences between studies ($I^2$=0·0%, $p_{heterogeneity}$=0·49). The results from sensitivity testing, which excluded studies that did not report our preferred event definition

of substantial loss of kidney function, were mostly unchanged (appendix p 10). The overall effect of SGLT2 inhibitors on substantial loss of kidney function, end-stage kidney disease, death due to cardiovascular or kidney disease (overall 29% reduction; figure 2) varied across studies, primarily because of the EMPA-REG OUTCOME trial, in which a greater magnitude of effect on death due to cardiovascular disease was observed ($I^2$=60·3%, $p_{heterogeneity}$=0·056).

Treatment with SGLT2 inhibitors also lowered the risk of acute kidney injury by 25% (figure 3), with no evidence of differences between studies ($I^2$=0%, $p_{heterogeneity}$=0·68). Acute kidney injury events, both serious and non-serious, were reported variably across individual trials and were not adjudicated (appendix p 9). The overall effects of SGLT2 inhibition on major kidney outcomes are summarised in figure 4.

The effect on the outcome of substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease was reported according to eGFR and UACR subgroups and according to baseline use of RAS blockade in all four studies. We identified some evidence that the magnitude of benefit might be attenuated across progressively lower eGFR subgroups ($p_{trend}$=0·073; figure 5A). However, clear, separately significant evidence of benefit was apparent for all eGFR subgroups, including for participants with a baseline eGFR lower than 45 mL/min per 1·73 m², in whom a 30% relative risk reduction was identified (figure 5A). Clear and consistent benefits were also apparent when participants were subdivided into those with an eGFR below 60 mL/min per 1·73 m² and those with an eGFR of 60 mL/min per 1·73 m² or higher ($p_{heterogeneity}$=0·33; appendix p 14). The results for tests of heterogeneity altered slightly in the different sensitivity analyses (appendix p 11), but the evidence of clear separate benefit for all eGFR subgroups remained constant. We identified no evidence of differences in treatment effect for the composite outcome across UACR subgroups ($p_{trend}$=0·66; figure 5B). The effect of SGLT2 inhibitors was also consistent between users and non-users of RAS blockade-based treatments at baseline ($p_{heterogeneity}$=0·31; figure 5C).

The absolute effect of SGLT2 inhibitors on annualised long-term eGFR slope is summarised in the appendix (p 12). In DECLARE–TIMI 58, mean eGFR over time was reported as a prespecified outcome, instead of annualised eGFR slope. The rate of eGFR decline in participants treated with placebo varied between trials, from –0·85 mL/min per 1·73 m² per year in the CANVAS Program to –4·59 mL/min per 1·73 m² per year in the CREDENCE trial. As a result, annual placebo-subtracted differences in eGFR also differed, with the greatest absolute benefit in terms of eGFR decline seen in the CREDENCE trial (2·74 mL/min per 1·73 m² per year, 95% CI 2·37–3·11).

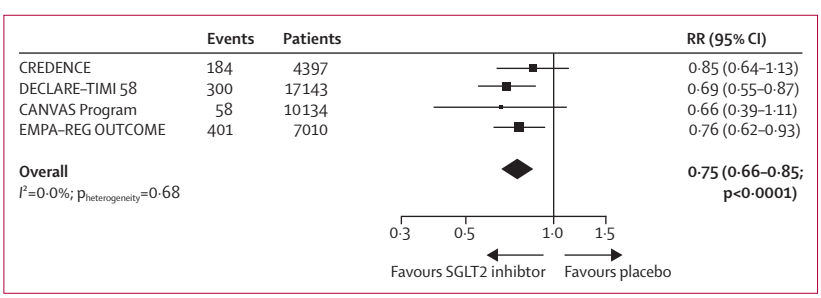


*Figure 3:* **Effect of SGLT2 inhibitors on acute kidney injury**
Weights were from random-effects meta-analysis. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

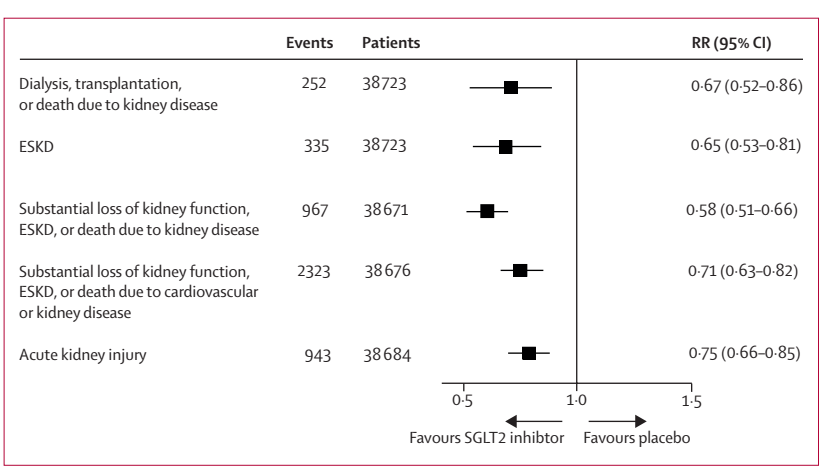


*Figure 4:* **Summary of the effects of SGLT2 inhibition on major kidney outcomes**
ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

## Discussion

The development of kidney failure is among the most important consequences of diabetic kidney disease and is of great concern to patients. The evidence from completed trials summarised in this systematic review and meta-analysis shows that SGLT2 inhibitors can reduce the risk of dialysis, transplantation, or death due to kidney disease, with compelling evidence of benefits on a broad range of other clinically important kidney outcomes. Importantly, renoprotection was achieved across all levels of baseline kidney function, down to an eGFR of 30 mL/min per 1·73 m², with clear benefits seen even for the subgroup with baseline eGFR between 30 and 45 mL/min per 1·73 m², for whom these drugs are not currently approved for use in most countries. Additionally, the protective effect of SGLT2 inhibitors against acute kidney injury allays early concerns about the risk of adverse effects resulting from the haemodynamic mechanism of action of this class of drugs. Furthermore, the inclusion of CREDENCE, a trial that mandated the use of RAS blockade, further supported that the benefits of SGLT2 inhibitors are cumulative with those of RAS blockade. Our findings provide the strongest evidence yet that SGLT2 inhibition should be routinely offered to individuals with type 2 diabetes at risk of progressive kidney disease.

The glycaemic efficacy of SGLT2 inhibitors is directly proportional to glomerular filtration rate,[9,28] but whether

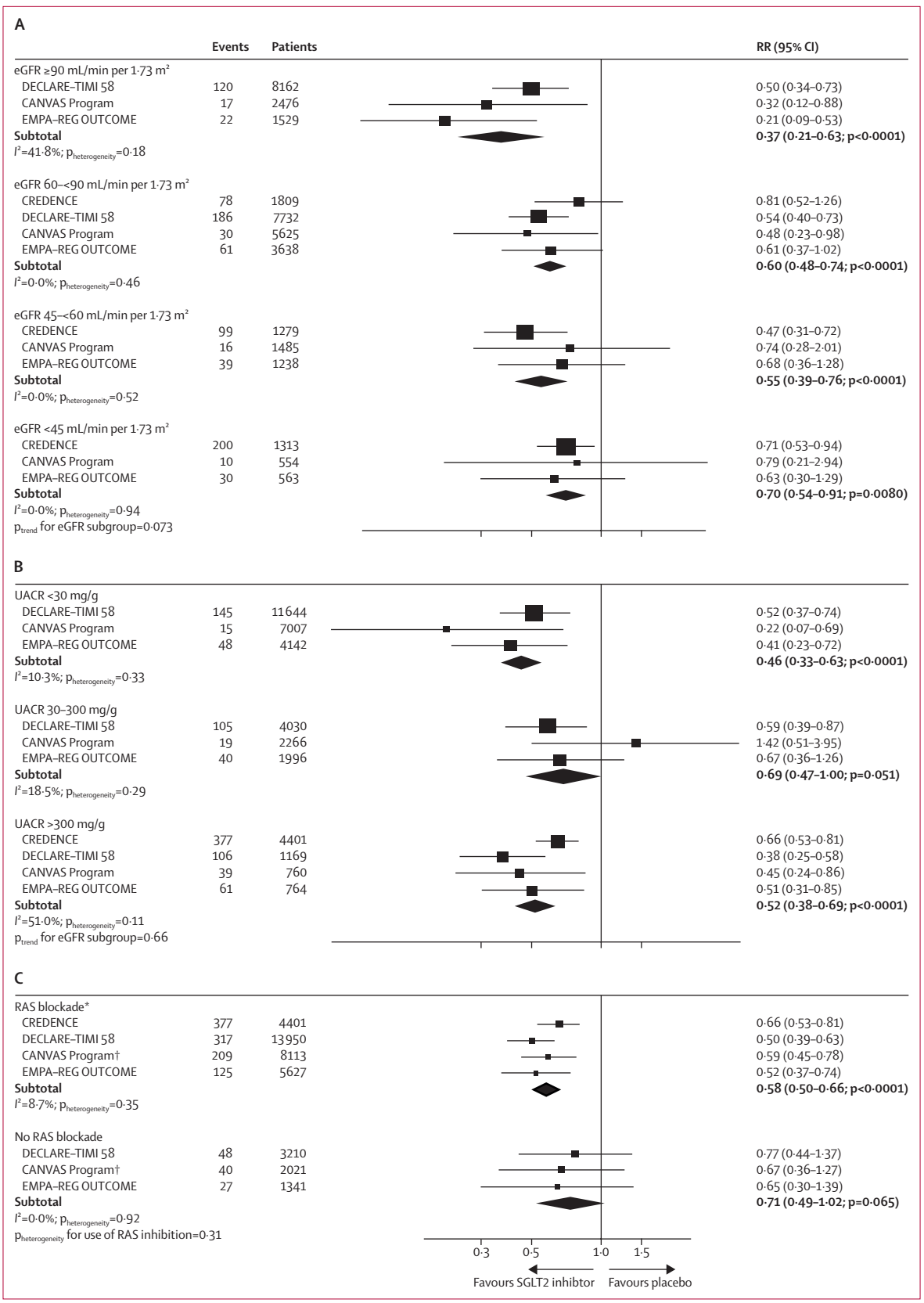


***Figure 5:*** **Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease, stratified by baseline eGFR (A), UACR (B), and use of RAS blockade (C)**

Weights were from random-effects meta-analysis. $p_{trend}$ values across eGFR and UACR subgroups were calculated against a t-distribution in random-effects meta-regression with use of restricted maximum likelihood with Hartung Knapp modification. $p_{heterogeneity}$ for between subgroup differences based on use of RAS inhibition was obtained from a random-effects model. Substantial loss of kidney function was defined as doubling of serum creatinine, apart from in the DECLARE–TIMI 58 trial, in which it was defined as sustained 40% decline in eGFR. Results from the CREDENCE trial are based on screening eGFR and UACR measurements. eGFR and UACR subgroup data from the CANVAS Program have not been previously published. ESKD=end-stage kidney disease. eGFR=estimated glomerular filtration rate. UACR=urine albumin-to-creatinine ratio. RAS=renin-angiotensin system. SGLT2=sodium-glucose co-transporter-2. RR=relative risk. *Use of RAS blockade was mandated as part of entry into the CREDENCE trial. †For analysis by baseline use of RAS blockade in the CANVAS Program, substantial loss of kidney function was defined as 40% decline in eGFR because no doubling of serum creatinine events occurred in participants not receiving RAS blockade.

the renoprotective effects are modified by declining kidney function has been less clear. A 2018 meta-analysis[14] of SGLT2 inhibitor cardiovascular outcome trials suggested that the renoprotective effect of these agents attenuates with declining kidney function. However, too few participants with baseline eGFR lower than 60 mL/min per 1·73 m² were included in that meta-analysis to adequately assess trend by eGFR. Additionally, whether participants with starting eGFR lower than 45 mL/min per 1·73 m² had benefits on kidney outcomes, despite substantially attenuated glycaemic efficacy, was also unclear. The accumulated trial evidence, including the CREDENCE trial in which about 60% of participants had a baseline eGFR lower than 60 mL/min per 1·73 m², has allowed the robust exploration of possible modifying effects. Although our findings suggest that the magnitude of relative (but not absolute) benefit might attenuate somewhat across progressively lower eGFR subgroups, these results clearly show that renoprotection was achieved across the entire spectrum of eGFR levels studied to date, down to an eGFR of 30 mL/min per 1·73 m². SGLT2 inhibitors are not currently indicated for people with an eGFR lower than 45 ml/min per 1·73 m² in most countries, largely because of insufficient glycaemic efficacy.[29] Because these individuals are at much greater risk of kidney failure than those with higher eGFRs, the absolute benefits of SGLT2 inhibition are likely to be at least as large as those for people with higher eGFRs.[30] With evidence of renoprotection now available from the accumulated trials, these restrictions are called into question, suggesting that many more individuals at high risk of major kidney outcomes are likely to benefit from treatment, and that trials in people with even more advanced kidney disease are warranted. The absence of effect modification by baseline albuminuria contrasts with the findings from trials of RAS blockade.[31–33] These data suggest that mechanisms other than those associated with albuminuria reduction might also be important. Furthermore, renoprotection with SGLT2 inhibitors seems consistent, irrespective of baseline use of RAS blockade. Taken together, these findings suggest that SGLT2 inhibition should provide benefit for a broader patient population.

A plausible mechanistic explanation for the renoprotective effect of SGLT2 inhibitors is correction of aberrant glomerular haemodynamics induced by hyperglycaemia, which drive progressive nephron loss.[34,35] Blocking sodium reuptake in the proximal tubule has been suggested to restore delivery of sodium to the macula densa, leading to afferent arteriolar constriction and a reduction in intraglomerular pressure.[36] This haemodynamic effect results in an early fall in eGFR, but is followed by protection against decline in kidney function, with reversal of the haemodynamic effect achieved on drug cessation.[12,37] The effect parallels that seen with RAS blockade, the only other treatment effective in slowing the progression of diabetic kidney disease, and suggests some similarities in mechanisms of action based on reducing intraglomerular pressure—SGLT2 inhibitors by enhancing afferent arteriolar vasoconstriction and RAS blockers by increasing efferent arteriolar vasodilatation.[38] Although this might be the most plausible mechanistic explanation for the renoprotective effect of these drugs, the mechanism for the effect on kidney haemodynamics has only been studied in patients with type 1 diabetes with whole-kidney hyperfiltration and at an individual nephron level in animal models;[39] whether these effects are also apparent in patients with type 2 diabetes is currently unknown.[36] Other pathways by which SGLT2 inhibitors might protect the kidney include (but are not limited to) enhancement of oxygenation of the kidney (through a reduction in tubular energy requirements), metabolic and anti-inflammatory effects, albuminuria-lowering effects, and direct effects on glomerular endothelial function.[28,40]

Protection against acute kidney injury is a welcome finding, in view of early concerns that SGLT2 inhibitor treatment could potentially increase risk. These findings strengthen those of a previous meta-analysis[16] of SGLT2 inhibitor cardiovascular outcome trials. Although serious and non-serious acute kidney injury events were investigator reported, collected variably, and not adjudicated, the large number of events and consistency of effect across the trials is striking and gives confidence to the finding that SGLT2 inhibitors provide protection against acute kidney injury. The mechanism for this protection is still unknown, but could involve reduced energy expenditure in the proximal tubule, reducing the susceptibility of tubular cells to acute ischaemic or volume-related insults.[28,41,42] Clearly, any reduction in the risk of acute kidney injury with SGLT2 inhibition should be considered in the context of other adverse effects that might also occur during an acute intercurrent illness (such as ketoacidosis), and further work is needed to better understand the mechanism, or mechanisms, by which SGLT2 inhibitors reduce the risk of acute kidney injury and how this evidence might be applied in practice.

The validity of these overview results is reinforced by the high quality of the included studies, but several limitations should be considered when interpreting our findings. We included only event-driven cardiovascular or kidney outcome trials, which had accrued substantial follow-up time. This selection was necessary because our main interest was in assessing the outcomes of need for dialysis or transplantation, or death due to kidney disease, which were unlikely to be identified or to be responsive to therapy in trials of short duration. A substantial proportion of the data were derived from a single study of canagliflozin (CREDENCE) that was stopped early, which might increase the risk of overestimating treatment effects.[43] However, the consistency with the results from the other trials reduces that risk and is an important finding of this analysis. Because the CREDENCE trial alone was specifically powered for kidney outcomes, the consistency of effects among other SGLT2 inhibitors remains somewhat

uncertain, although no evidence of substantive heterogeneity exists. The broader generalisability of these results might also be somewhat affected by the characteristics of participants in the included studies, and thus future work to assess the use of these drugs in routine clinical practice will be important. Data for acute kidney injury might be less robust than those for other endpoints, because of variances in the collection and reporting of this outcome. The effects of SGLT2 inhibition on kidney (and cardiovascular and safety) outcomes in patients with eGFR lower than 30 mL/min per 1·73 m² also remains an important and unanswered question, as does the comparative effectiveness of SGLT2 inhibitors against other glucose-lowering drugs, such as glucagon-like peptide-1 (GLP-1) receptor agonists, that have also shown promising effects on kidney outcomes.[44]

Other kidney outcome trials for dapagliflozin (DAPA-CKD, NCT03036150) and empagliflozin (EMPA-KIDNEY, NCT03594110) are underway and are expected to further enrich our understanding of the role of SGLT2 inhibitors for the prevention of kidney failure.[24,45] Both of these trials are recruiting participants with and without type 2 diabetes on the basis of the hypothesised non-glycaemic mechanisms of renoprotection. Additionally, the SCORED trial (NCT03315143) is testing the effects of sotagliflozin, a combined SGLT1 and SGLT2 inhibitor, on a primary cardiovascular endpoint (with other secondary kidney outcomes prespecified) in participants with type 2 diabetes and reduced kidney function. These trials will include participants with starting eGFR as low as 20 mL/min per 1·73 m² and thus, will provide some important information on the effects of SGLT2 inhibition in patients with more advanced kidney disease. Future studies assessing the combination of SGLT2 inhibitors with other glucose-lowering agents that have shown beneficial effects on kidney function, such as GLP-1 receptor agonists, are another potential area of interest, particularly in patients with established diabetic kidney disease.[46]

In conclusion, SGLT2 inhibition can reduce the risk of dialysis, transplantation, or death due to kidney disease in people with type 2 diabetes and a broad range of risk for kidney outcomes. These data provide substantive evidence supporting the use of SGLT2 inhibitors to prevent clinically important kidney outcomes in individuals with type 2 diabetes.

#### Contributors

BLN, VP, and MJJ contributed to the concept and design of this study. BLN contributed to the literature search, data extraction, risk-of-bias assessment, data analysis, interpretation, and writing of the report. TY contributed to the literature search, data extraction, risk-of-bias assessment, interpretation, and writing of the report. LB contributed to the statistical analysis, interpretation, and critical review of the report. HJLH, BN, VP, KWM, DMC, DCW, CA, SB, and AL contributed to the interpretation, writing, and critical review of the report.

#### Declaration of interests

BLN has received travel support from Janssen. TY has received sponsorship to attend meetings from Eli Lily and Novo Nordisk. HJLH has served as a consultant for Abbvie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Janssen, and Merck, and has received grant support from AstraZeneca and Boehringer Ingelheim, with all honoraria paid to his institution. BN has received research support from Janssen, Roche, Servier, and Merck Schering Plough, and is serving on advisory boards or is involved in continuing medical education programmes for Abbott, Janssen, Novartis, Pfizer, Roche, and Servier, with any consultancy, honoraria, or travel support paid to his institution. VP is serving on steering committees for AbbVie, Boehringer Ingelheim, GlaxoSmithKline, Janssen, and Pfizer, and is serving on advisory boards or speaking at scientific meetings for AbbVie, Astellas, AstraZeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier, and Vitae. KWM reports receiving grants from Afferent, Amgen, Apple, AstraZeneca, Cardiva Medical, Daiichi, Ferring, Verily, Johnson & Johnson, Luitpold, Medtronic, Merck, Novartis, Sanofi, St Jude, and Tenax; receiving personal fees from Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Cardiometabolic Health Congress, Elsevier, GlaxoSmithKline, Johnson & Johnson, Medscape, Merck, Mitsubishi, Myokardia, Novartis, Oculeve, Portola, Radiometer, Springer Publishing, Theravance, University of California San Francisco, and WebMD; and having equity in BioPrint Fitness. DMC has served on clinical events committees or data safety and monitoring boards for PLC Medical, AstraZeneca, Allena Pharmaceuticals, and Merck; served on steering committees for Zoll Medical and Janssen Pharmaceuticals; and reported consulting fees or travel fees from Daichi Sankyo, Fresenius, and Medtronic/Coviden. DCW reports having received consultancy fees from Akebia Therapeutics, Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Ono, Napp, Mundipharma, and Vifor Fresenius; speaker honoraria from Amgen and Vifor Fresenius; and research support from AstraZeneca. MJJ is responsible for research projects that have received unrestricted funding from Gambro, Baxter, CSL, Amgen, Eli Lilly, and Merck; has served on advisory boards sponsored by Akebia, Baxter, and Boehringer Ingelheim; and has spoken at scientific meetings sponsored by Janssen, Amgen, and Roche, with any consultancy, honoraria, or travel support paid to her institution. LB and SB are full-time employees of The George Institute for Global Health, the parent organisation of George Clinical, a contract research organisation that provides research services to Janssen for trials of sodium-glucose co-transporter-2 (SGLT2) inhibitors. VP, KWM, HLJH, MJJ, BN, DCW, AL, and DMC were on the steering committee for a kidney outcome trial of an SGLT2 inhibitor (canagliflozin; CREDENCE, NCT02065791), with VP and KWM serving as chair and co-chair. CA declares no competing interests.

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