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

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Abstract: Background
The impact of sodium-glucose cotransporter 2 (SGLT2) inhibitors on kidney failure, particularly the need for dialysis and transplantation, or death due to kidney disease, has been uncertain.
Methods
We conducted a systematic review and meta-analysis of randomized, controlled, cardiovascular or kidney outcome trials of SGLT2 inhibitors reporting effects on kidney failure and other major kidney outcomes in people with type 2 diabetes (PROSPERO registration number CRD42019131774). MEDLINE and EMBASE were searched from inception to 1 March 2019 to identify eligible trials. The primary outcome was kidney failure, defined as dialysis, transplantation, or death due to kidney disease. We used random effects models to obtain summary relative risks (RR) with 95% confidence intervals (CI) and random effects meta-regression to explore effect modification by baseline estimated glomerular filtration rate (eGFR).
Findings
Data were obtained from four studies including 38,723 participants of whom 218 reached kidney failure, 310 developed end-stage kidney disease (ESKD), and 943 experienced acute kidney injury (AKI). SGLT2 inhibitors reduced the risk of kidney failure by 29% (RR 0 71, 95% CI 0 54-0 93, p=0 014), ESKD by 32% (RR 0 68, 95% CI 0 55-0 85, p=0 001), and AKI by 25% (RR 0 75, 95% CI 0 66-0 85, p<0 0001), with consistent benefits across studies. While there was some evidence that the proportional effect of SGLT2 inhibitors might attenuate with declining kidney function (P-trend=0 07), there was clear, separate evidence of benefit for all eGFR subgroups, including for participants with baseline eGFR <45 mL/min/1 73m2 (RR 0 70, 95% CI 0 54-0 91, p=0 008).
Interpretation
SGLT2 inhibitors reduce the risk of kidney failure and provide 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.

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

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RESEARCH IN CONEXT

Evidence before this study

Large-scale randomized cardiovascular outcome trials of sodium glucose cotransporter-2 (SGLT2) inhibitors have suggested promising effects 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 the outcomes of greatest concern to patients – namely, the need for long-term dialysis, transplantation or death due to kidney disease – has been uncertain. More recently the CREDENCE trial (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation) has been published, which was designed specifically to examine the impact of SGLT2 inhibition in people at high risk of kidney disease progression. These agents are also not currently approved for use in patients with estimated glomerular filtration rate (eGFR) less than 45 or 60 mL/min/1·73m^2 in most countries, primarily because their glucose lowering effect is dependent on kidney function. We therefore conducted a systematic review and meta-analysis of randomized, controlled, event-driven, cardiovascular and kidney outcome trials reporting effects of major kidney outcomes in patients with type 2 diabetes. MEDLINE and EMBASE were searched from inception until March 1 2019 to identify potentially relevant studies. The protocol for this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42019131774).

Added value of this study

This review summarises data from four studies including 38,723 participants across six continents. There was clear evidence that SGLT2 inhibitors reduce the risk dialysis, transplantation or death due to kidney disease, as well as a range of other major kidney outcomes, and that these agents also provide protection against acute kidney injury. Additionally, there were definitive, separate benefits at all levels of kidney function, including an approximate 30% proportional risk reduction in the

composite kidney outcome in participants with baseline eGFR less than 45 mL/min/1·73m^2 in whom these drugs are mostly not permitted for use.

Implications of all the available evidence

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 call into question current restrictions on the use of SGLT2 inhibitors in people with reduced kidney function, and suggest that many more individuals with type 2 diabetes at high risk of kidney failure are likely to benefit from treatment.

SUMMARY

Background

The impact of sodium-glucose cotransporter 2 (SGLT2) inhibitors on kidney failure, particularly the need for dialysis and transplantation, or death due to kidney disease, has been uncertain.

Methods

We conducted a systematic review and meta-analysis of randomized, controlled, cardiovascular or kidney outcome trials of SGLT2 inhibitors reporting effects on kidney failure and other major kidney outcomes in people with type 2 diabetes (PROSPERO registration number CRD42019131774). MEDLINE and EMBASE were searched from inception to 1 March 2019 to identify eligible trials. The primary outcome was kidney failure, defined as dialysis, transplantation, or death due to kidney disease. We used random effects models to obtain summary relative risks (RR) with 95% confidence intervals (CI) and random effects meta-regression to explore effect modification by baseline estimated glomerular filtration rate (eGFR).

Findings

Data were obtained from four studies including 38,723 participants of whom 218 reached kidney failure, 310 developed end-stage kidney disease (ESKD), and 943 experienced acute kidney injury (AKI). SGLT2 inhibitors reduced the risk of kidney failure by 29% (RR 0·71, 95% CI 0·54-0·93, p=0·014), ESKD by 32% (RR 0·68, 95% CI 0·55-0·85, p=0·001), and AKI by 25% (RR 0·75, 95% CI 0·66-0·85, p<0·0001), with consistent benefits across studies. While there was some evidence that the proportional effect of SGLT2 inhibitors might attenuate with declining kidney function (P-trend=0·07), there was clear, separate evidence of benefit for all eGFR subgroups, including for participants with baseline eGFR <45 mL/min/1·73m^2 (RR 0·70, 95% CI 0·54-0·91, p=0·008).

Interpretation

SGLT2 inhibitors reduce the risk of kidney failure and provide 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.

Funding

INTRODUCTION

It is estimated that approximately 2·6 million people received dialysis or underwent 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 mellitus (T2DM), making it a leading cause of kidney failure worldwide.[2] Kidney failure due to T2DM is a large and growing challenge, not only for patients and 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 kidney outcomes in people with diabetes, and these agents are currently recommended by clinical practice guidelines for the treatment of people with T2DM who have, or are at high risk of, kidney disease.[4-8] However, the residual risk remains high with new treatments urgently needed to reduce the growing burden of kidney failure.

SGLT2 inhibitors are a newer class of glucose-lowering agent that also lower blood pressure, body weight and albuminuria, and may have direct haemodynamic effects on the kidney.[9] These multiple effects have translated into a reduction in cardiovascular events in people with T2DM in large cardiovascular outcome trials.[10-12] The trials also demonstrated promising effects on a range of albuminuria and serum creatinine based kidney outcomes.[13-16] The majority of 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 due to kidney disease, in each trial. As they were also not explicitly designed to provide definitive information on renoprotective effects, kidney endpoints were not always pre-specified, were not always adjudicated, and the distinction between acute and chronic reductions in estimated glomerular filtration rate (eGFR) was not possible in all studies. Furthermore, since each trial included only modest numbers of patients at any given level of kidney function or albuminuria, the

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ability to robustly examine the consistency of treatment effect across different levels of kidney function or albuminuria has been limited. Most recently, the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial has been reported, which is the first study designed to specifically evaluate the impact of an SGLT2 inhibitor on a primary kidney outcome in people with established diabetic kidney disease.[17]

We therefore undertook a systematic review and meta-analysis to determine the consistency of effect size across SGLT2 trials and different levels of kidney function and albuminuria, summarize results, and integrate available data on the effects of SGLT2 inhibition on the risk of clinically important kidney outcomes in people with T2DM.

METHODS

This systematic review and meta-analysis was conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The protocol for this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42019131774) and can be accessed at: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019131774.

Search strategy and selection criteria

We searched MEDLINE and EMBASE from inception to 1 March 2019 to identify potentially eligible studies. Details of the search strategy, including text words and medical subject headings are provided in Table S1. We included all randomized, controlled, event-driven, cardiovascular or kidney outcome trials of SGLT2 inhibitors versus active or placebo control, in order to capture those with meaningful numbers of clinical kidney outcomes. Trials with extension periods and those including participants with type 1 diabetes or individuals less than 18 years of age were excluded. Two authors (B.L.N and T.Y) independently screened the titles and abstracts of all

identified articles and, when required, reviewed full-text manuscripts to identify potentially relevant studies. Any disagreements related to the identification or eligibility of studies was resolved through discussion with a third author (M.J.J).

Data synthesis and analysis

Two authors (B.L.N and T.Y) independently extracted all data using a standardized data form and assessed risk of bias 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, Ankit Rohatgi, Austin, TX, https://automeris.io/WebPlotDigitizer/). These data were summarized 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 (M.J.J). Due to the small number of eligible trials, publication bias was not assessed.

The primary outcome of interest was kidney failure, defined as the need for chronic dialysis or kidney transplantation, or death due to kidney disease. Other kidney outcomes included: (1) ESKD, defined as chronic dialysis, kidney transplantation, or sustained eGFR less than 15 mL/min/1·73m^2, (2) substantial loss of kidney function, ESKD, or death due to kidney disease, (3) substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease, (4) long-term eGFR slope, and (5) acute kidney injury (AKI). Substantial loss of kidney function was preferentially defined as a sustained doubling of serum creatinine (representing an approximate 57% decline in kidney function). Where sustained doubling of serum creatinine was not reported, we included sustained 40% decline in eGFR or unsustained 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 AKI, but accepted unsustained outcomes where these were the only ones reported. The definitions of long-term eGFR slope (reported as the annualized difference in eGFR between

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treatment and control) and AKI varied across studies and we used these outcomes as defined and reported in each study.

We quantitatively synthesized results for dichotomous outcomes by individual studies using a random effects model with inverse variance weighting to obtain summary effect estimates represented as relative risk (RR) with associated 95% confidence intervals (CI). We pooled, in order of preference, hazard ratios, incidence rate ratios (events/patient-years), and risk ratios (events/number of participants) to maximize 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 randomization ratios and different follow-up durations precluded the use of risk ratios.[19] When studies did not report the preferred outcome definition for substantial loss of kidney function, we performed sensitivity tests excluding those studies to assess the impact of endpoint definition on the results. Because the eGFR slope outcome measured the absolute rather than proportional effect of treatment, heterogeneity between studies could not be meaningfully assessed, as differences in absolute effect reflected differences in baseline kidney risk. These data were therefore summarized descriptively. For all other outcomes we assessed heterogeneity between studies using the I^2 test and P-heterogeneity values obtained from a random effects model. I^2 values of <25%, 25-75%, and >75-100% were considered to reflect low, moderate, and high likelihood of differences between studies, respectively.

Because of the kidney-based mechanism of action and albuminuria lowering effect of SGLT2 inhibitors, we performed additional analyses to assess whether treatment effects varied 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. We prospectively decided to conduct these analyses for efficacy outcomes

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(i.e. all outcomes except AKI) where subgroup data were reported in two or more studies. Because the results come from relatively few individual studies, we performed multiple sensitivity analyses to assess the vulnerability of the subgroup analysis outcomes to definitional and methodological decisions. For the outcome substantial loss of kidney function, ESKD or death due to kidney disease, we assessed the impact of SGLT2 inhibitors by eGFR categories (eGFR <45, 45-<60, 60-<90 and ≥90 mL/min/1·73m^2) and levels of albuminuria (urinary albumin:creatinine ratio [UACR] <30, 30-300, and >300 mg/g) as the main analysis. Where studies reported the eGFR <60mL/min/1·73m^2 subgroup without more granular categories, as occurred in the DECLARE-TIMI 58 trial, we excluded these data from the main analysis. However we performed a sensitivity analysis in which the outcomes for the baseline eGFR <60mL/min/1·73m^2 subgroup were included with the eGFR 45-<60 mL/min/1·73m^2 category, on the assumption that a large majority of these participants were likely to have an eGFR 45-60 mL/min/1·73m^2 based on the trial exclusion criteria. We conducted a sensitivity analysis to assess the effects of treatment in participants with eGFR <60 and ≥60 mL/min/1·73m^2. When required, effect estimates for subgroups within the same study (e.g. eGFR 30-<45 and 45-<60 mL/min/1·73m^2) were merged using a fixed effects model. For the eGFR slope outcome, data were stratified by kidney function (eGFR <60 and ≥60 mL/min/1·73m^2) and albuminuria (UACR <30, 30-300, and >300 mg/g) and summarized descriptively.

We used random effects meta-regression with restricted maximum likelihood and Hartung Knapp adjustment to assess trend in treatment effects across eGFR and albuminuria subgroups. In sensitivity analyses we repeated the meta-regression analyses treating subgroups as categories without assumptions of linearity. A *P*-trend and *P*-heterogeneity of <0·10 were considered to reflect a high likelihood of differences beyond chance.

All analyses were performed using Stata 15·1 (StataCorp 2017. Stata Statistical Software: Release 15. College Station, TX; StataCorp LLC).

Role of the funding source

This study was not specifically funded. All authors had full access to the data and agreed on the final decision to submit for publication.

RESULTS

We identified four separate studies comprising five individual trials after applying the search strategy and study selection criteria (Table S1 and Figure S1). The CANVAS Program comprised two companion trials (CANVAS and CANVAS-R) that were conducted in parallel and analysed and reported as a single program. All studies compared an SGLT2 inhibitor with matching placebo. Three studies were designed as cardiovascular outcome trials testing the impact of empagliflozin, canagliflozin, and dapagliflozin on a primary composite cardiovascular outcome of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death, with a range of pre-specified exploratory and post-hoc kidney outcomes also reported. One study was an event-driven kidney outcome trial for canagliflozin with a primary composite outcome of sustained doubling of serum creatinine, ESKD, or death due to cardiovascular or kidney disease. The risk of bias was low for all indicators; all participants and investigators were blinded to treatment allocation with complete reporting of outcomes (Figure S2).

In total, this meta-analysis included data on 38,723 randomised participants from six continents. The mean age across the studies ranged from 61·3 to 63·9 years, while 35·0% of participants overall were female (Table 1). The proportion of participants with eGFR <60 mL/min/1·73m^2 ranged from 7·4% in DECLARE-TIMI 58 to 58·8% in CREDENCE. The majority of participants in the three cardiovascular outcome trials had a UACR <30 mg/g at baseline (range 59·4% to

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69·8%), while 88·0% in CREDENCE had a baseline UACR >300 mg/g (Table 1). An eGFR of ≥30 mL/min/1·73m^2 was an inclusion criterion in all studies with the exception of the DECLARE-TIMI 58 trial where Cockroft Gault creatinine clearance of ≥60 mL/min was required. Treatment with RAS blockade was required for entry by the CREDENCE trial only. Accordingly, virtually all (99·9%) CREDENCE participants were treated with ACE inhibitors or ARBs at baseline compared with approximately 80% of participants in the other trials (Table 1).

Overall, there were 218 occurrences of kidney failure. There were 310 ESKD events; 967 incidences of substantial loss of kidney function, ESKD or death due to kidney disease; 2,323 cases of substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease; and 943 episodes of AKI. Pre-specification of outcomes, requirements for changes in kidney function to be confirmed on repeated measurement, and adjudication procedures differed across the studies (Table S3). Kidney endpoints were also defined and reported variably across the studies (Table S4-S5).

Primary outcome
SGLT2 inhibitors reduced the risk of kidney failure by 29% (RR 0·71, 95% CI 0·54-0·93, p=0·014). The effect of SGLT2 inhibitors on this outcome was consistent across studies ($I^2 = 0\%$, *P*-heterogeneity=0·79; Figure 1).

Other kidney outcomes
SGLT2 inhibitors reduced the risk of ESKD by 32% (RR 0·68, 95% CI 0·55-0·85, p=0·001), with no differences in treatment effect across studies (I^2=0·0%, *P*-heterogeneity=0·95). SGLT2 inhibition also reduced the risk of substantial loss of kidney function, ESKD, or death due to kidney disease by 42% (0·58, 95% CI 0·51-0·66, p<0·0001; Figure 2) with no evidence of differences between studies (I^2=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 essentially unchanged (Table S6). The overall effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, death due to cardiovascular or kidney disease (RR 0·71, 95% CI 0·0.63-0·82, $p<0·0001$; Figure 2) varied across studies, primarily due to the EMPA-REG OUTCOME trial (I^2 =60·3%, P-heterogeneity=0·06).

SGLT2 inhibitors also lowered the risk of AKI by 25% (RR 0·75, 95% CI 0·66-0·85, $p<0·0001$; Figure 4), with no evidence of differences between studies (I^2=0%, P-heterogeneity=0·68). AKI events, both serious and non-serious, were reported variably across individual trials and were not adjudicated (Table S5). Overall effects of SGLT2 inhibition on major kidney outcomes are summarised in Figure 5.

Subgroup analyses

The effect on the outcome of substantial loss of kidney function, ESKD or death due to kidney disease was reported according to eGFR subgroups in four studies, while effects according to baseline albuminuria were reported in two studies. There was some evidence that the magnitude of relative benefit might be attenuated across progressively lower eGFR subgroups (P-trend=0·07; Figure 3). However, there was still clear, separately significant evidence of benefit for all eGFR subgroups, including for participants with a baseline eGFR <45 mL/min/1·73m^2, where a 30% relative risk reduction was observed (RR 0·70, 95% CI 0·54-0·91, $p=0·008$). There were also clear and consistent benefits in participants with eGFR above and below 60 mL/min/1·73m^2 (P-heterogeneity=0·28; Figure S2). Results for tests of heterogeneity altered slightly in the different sensitivity analyses (Table S7) but the evidence of clear separate benefit for all eGFR subgroups remained constant. There was no evidence of differences in treatment effect for the composite outcome across UACR subgroups (P-trend=0·31; Figure 3). The effect of SGLT2 inhibitors was

also consistent irrespective of the use of renin-angiotensin system blockade at baseline (*P*-heterogeneity=0·77; Figure S3).

Absolute effects on eGFR slope

The absolute effect of SGLT2 inhibitors on long-term eGFR slope was reported in three studies (Table S8). The rate of eGFR decline in placebo treated participants varied between trials from -0·85 mL/min/1·73m^2/year in the CANVAS Program to -4·59 mL/min/1·73m^2/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 observed in CREDENCE trial (2·74 mL/min/1·73m^2/year, 95% CI 2·37-3·11, *p*<0·0001). Data by eGFR and UACR subgroups were reported in the CANVAS Program and EMPA-REG OUTCOME trial, and are displayed in Table S8.

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 review clearly shows that SGLT2 inhibitors definitively reduce the risk of kidney failure, with compelling evidence of benefits on a broad range of other clinically important kidney outcomes. Importantly, renoprotection is achieved across all levels of kidney function down to eGFR 30 mL/min/1·73m^2, with clear benefits even for the subgroup with baseline eGFR between 30 to 45 mL/min/1·73m^2 in whom these drugs are currently not approved for use in most countries. The clear protective effect against AKI allays early concerns about the risk of adverse effects consequent upon the haemodynamic mechanism of action of this class of agent. Furthermore, the inclusion of CREDENCE, a trial that mandated the use of RAS blockade, shows that the benefits of SGLT2 inhibitors are cumulative with those of RAS blockade. These results provide the strongest

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evidence yet that SGLT2 inhibition should be routinely offered to individuals with T2DM at risk of progressive kidney disease.

The glycaemic efficacy of SGLT2 inhibitors is directly proportional to glomerular filtration rate,[9,20] but whether the renoprotective effects are modified by declining kidney function has been less clear. Most individual trials included few participants with eGFR <45 mL/min/1·73m^2 at baseline and were inadequately powered to test for effect modification by eGFR or albuminuria. The accumulated trial evidence, including the CREDENCE trial in which approximately 60% of participants had a baseline eGFR <60 mL/min/1·73m^2, has made it possible to robustly explore possible modifying effects. While our findings raise the possibility that the magnitude of relative (but not absolute) benefit might attenuate across progressively lower eGFR subgroups, these results clearly demonstrate that renoprotection is achieved across the entire spectrum of eGFR levels studied to date, down to an eGFR of 30 mL/min/1·73m^2. SGLT2 inhibitors are currently not indicated in people with eGFR <45 ml/min/1·73m^2 in most countries, largely due to limited glycaemic efficacy.[21] As these individuals are at much greater risk of kidney failure, the absolute benefits of SGLT2 inhibition are likely to be at least as large as for people with higher eGFR.[22] With evidence of renoprotection now available from the cumulated 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.[23-26] These data suggest that mechanisms other than those associated with albuminuria reduction might also be important, and 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.[27,28] Blocking sodium re-uptake 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.[29] This haemodynamic effect results in an early fall in eGFR, but is followed by marked protection against decline in kidney function, with reversal of the haemodynamic effect achieved upon drug cessation.[15,30] The effect parallels that observed with RAS blockade, the only other treatment effective in slowing the progression of diabetic kidney disease, and suggests some commonality in a mechanism of action based upon reducing intraglomerular pressure – SGLT2 inhibitors by enhancing afferent arteriolar vasoconstriction and RAS blockers by increasing efferent arteriolar vasodilatation.[31] Other pathways by which SGLT2 inhibitors may protect the kidney include metabolic and anti-inflammatory effects, albuminuria lowering, and direct effects on glomerular endothelial function, and are an area of active study.[20,32]

Protection against AKI is a welcome finding given early concerns about a potential increase in risk. While serious and non-serious AKI 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 observation that SGLT2 inhibitors provide protection against AKI. The mechanism is unknown, but could involve reduced energy expenditure in the proximal tubule, thus improving oxygenation and reducing the susceptibility of tubular cells to acute ischemic or volume-related insults.[20,33,34] Clearly any reduction in the risk of AKI with SGLT2 inhibition must 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(s) by which SGLT2 inhibitors reduce the risk of AKI 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 there are a number of limitations that should be considered when interpreting our findings. We included only event-driven cardiovascular or kidney outcome trials with substantial accrued follow-

up time. This was necessary as our main interest was in assessing kidney failure events, which are unlikely to be observed or responsive to therapy in trials of short duration. A single trial contributed a substantial proportion of the data using a single agent, conducted in the population at highest risk of kidney failure. The consistency of effects among other members of the class remains somewhat uncertain although there is currently no evidence of substantive heterogeneity. Data for several outcomes were not available for all studies and the data on AKI might be less robust than for other endpoints, due to 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 <30 mL/min/1·73m^2 also remains an important and unanswered question.

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.[35,36] Both trials are recruiting participants with and without T2DM on the basis of the hypothesized non-glycaemic mechanism(s) of renoprotection. Additionally the SCORED trial (NCT03315143) is testing the effects of sotagliflozin on a primary cardiovascular endpoint (with other secondary kidney outcomes prespecified) in participants with T2DM and reduced kidney function. These trials will include participants with starting eGFR as low as 20 mL/min/1·73m^2 and will thus provide some important information on the effects of SGLT2 inhibition in patients with more advanced kidney disease.

In conclusion, SGLT2 inhibition reduces the risk of dialysis, transplantation or death due to kidney disease, in people with T2DM and a broad range of kidney risk. These data provide substantive evidence supporting the use of SGLT2 inhibitors to prevent clinically important, patient-level kidney outcomes in individuals with T2DM.

Contributions

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 manuscript. TY contributed to the literature search, data extraction, risk of bias assessment, interpretation, and drafting of the manuscript. LB contributed to the statistical analysis, interpretation, and critical review of the manuscript. HJLH, BN, VP, KWM, DMC, DCW, CA, SB, and AL contributed to the interpretation, writing, and critical review of the manuscript. BLN and MJJ drafted the first version of the manuscript and all authors contributed to revisions. All authors had full access to the data and take responsibility for the integrity of the data and accuracy of the data analysis.

Declarations of interest

BLN has received travel support from Janssen. TY has received sponsorship to attend meeting by 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

steering committee for a kidney outcome trial of an SGLT2 inhibitor (canagliflozin), with VP and KWM serving as Chair and Co-Chair.

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FIGURE LEGENDS

Figure 1. Effect of SGLT2 inhibitors on kidney failure (dialysis, transplantation or death due to kidney disease).

SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval; N/A: not available.

Figure 2. Effect of SGLT2 inhibitors on (A) ESKD, (B) substantial loss of kidney function, ESKD, or death due to kidney disease and (C) substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease .

ESKD: end-stage kidney disease; SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval; N/A: not available.

Figure 3. Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD or death due to kidney disease, stratified by (A) baseline eGFR and (B) UACR subgroups

ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval; N/A: not available.

Figure 4. Effect of SGLT2 inhibitors on acute kidney injury.

SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval.

Figure 5. Summary of the effects of SGLT2 inhibition on major kidney outcomes

SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval

Table 1

Table 1. Characteristics of included studies

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: urinary albumin:creatinine ratio; RAS: renin-angiotensin system blockade; N/A: not

available

Study	EMPA-REG OUTCOME (n=7020)	CANVAS Program (n=10142)	DECLARE-TIMI 58 (n=17160)	CREDENCE (n=4401)
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Dose	10mg and 25mg	100mg and 300mg	10mg	100mg
Number of participants	7020	10142	17160	4401
Mean age (years)	61·3	63·3	63·9	63·0
Female, n (%)	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-<90 (CKD-EPI)
eGFR*, mL/min/1·73m^2, n (%)				
?90	1538 (21·9)	2476 (24·4)	8162 (47·6)	211 (4·8)
60-<90	3661 (52·2)	5625 (55·5)	7732 (45·1)	1558 (35·4)
45-<60	1249 (17·8)	1485 (14·6)	1265[¶] (7·4)	1266 (28·8)
<45	570 (8·1)	554 (5·5)	N/A	1365 (31·0)
UACR criteria, mg/g	None	None	None	?300 to ≤5000
UACR mg/g, n (%)				
<30	4142 (59·0)	7007 (69·1)	11 652 (67·9)	31 (0·7)
30-300	1996 (28·4)	2266 (22·3)	4023 (23·4)	496 (11·3)
>300	764 (10·9)	760 (7·5)	1169 (6·8)	3874 (88·0)
Baseline use of RAS blockade, n (%)	5666 (80·7)	8116 (80·0)	13950 (81·3)	4395 (99·9)

*Based on the MDRD equation in EMPA-REG OUTCOME and the CANVAS Program and the CKD-EPI equation in DECLARE-TIMI 58 and CREDENCE.

¶Includes all DECLARE-TIMI58 participants with eGFR <60 mL/min/1·73m2

Figure 1

Figure 1. Effect of SGLT2 inhibitors on kidney failure (chronic dialysis, transplantation or death due to kidney disease)

SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval; N/A: not available.

Study	Events	Patients	Events per 1000 patient-years			RR (95% CI)
			SGLT2	Placebo		
CREDENCE	183	4401	13 6	18 6		0 72 (0 54, 0 97)
CANVAS Program	21	10142	0 4	0 8		0 56 (0 23, 1 32)
EMPA-REG OUTCOME	14	7020	N/A	N/A		0 90 (0 30, 2 67)
Overall (p=0 014, I^2=0 0%, P-heterogeneity=0 79)						0 71 (0 54, 0 93)

0 3   0 5   1   1 5

Favours SGLT2 inhibitor   Favours placebo
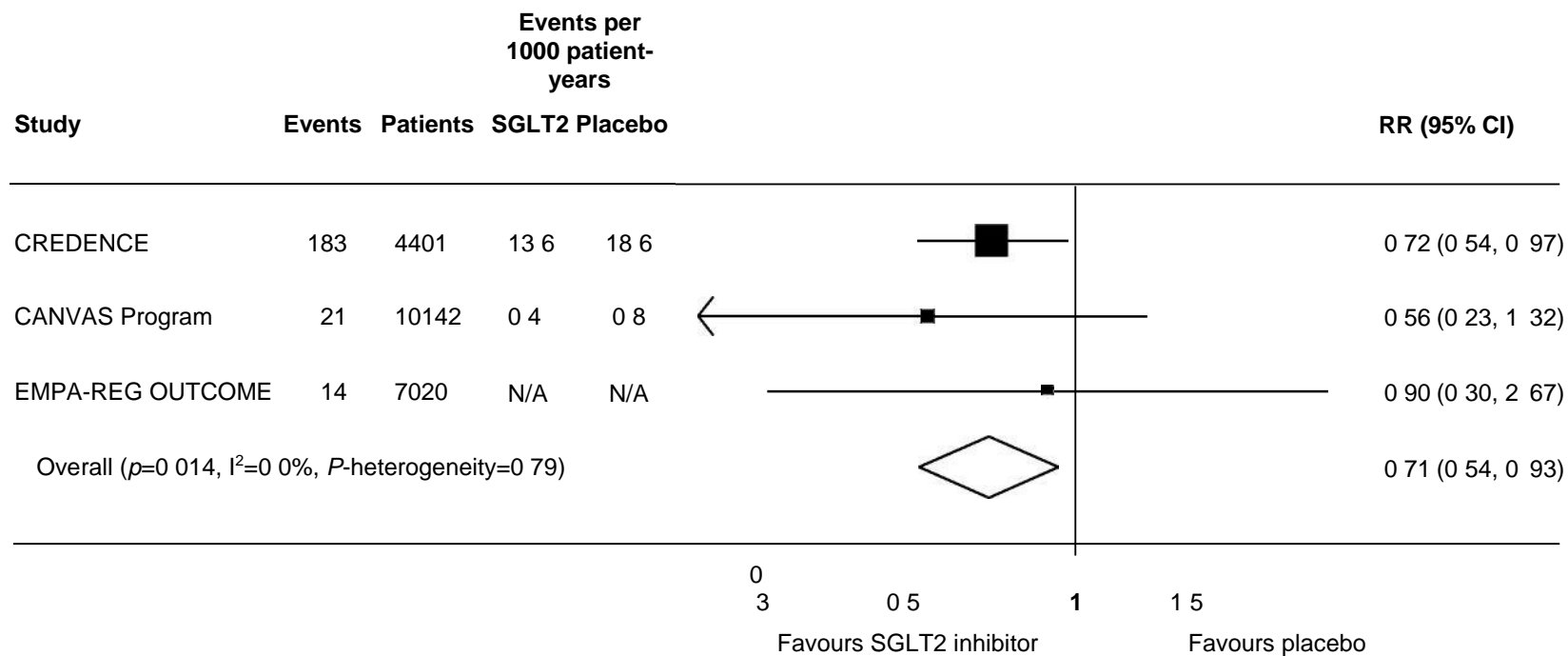
Figure 2

**Figure 2. Effects of SGLT2 inhibitors on (A) ESKD*, (B) substantial loss of kidney function[¶],
ESKD, or death due to kidney disease and (C) substantial loss on kidney function, ESKD, or
death due to cardiovascular or kidney disease**

ESKD: end-stage kidney disease; SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative
risk; CI: confidence interval; N/A: not available.

Study	Events	Patients	SGLT2	Placebo		RR (95% CI)
(A) ESKD						
CREDENCE	281	4401	20·4	29·4		0·68 (0·54, 0·86)
CANVAS Program	18	10142	0·4	0·6		0·77 (0·30, 1·97)
EMPA-REG	11	7020	0·4	0·7		0·60 (0·18, 1·98)
Overall (p=0·001, I²=0·0%, P-heterogeneity=0·95)						0·68 (0·55, 0·85)
(B) Substantial loss of kidney function, ESKD or death due to kidney disease						
CREDENCE	377	4401	27·0	40·4		0·66 (0·53, 0·81)
DECLARE-TIMI 58	365	17160	3·7	7·0		0·53 (0·43, 0·66)
CANVAS Program	73	10142	1·5	2·8		0·53 (0·33, 0·84)
EMPA-REG	152	6968	6·3	11·5		0·54 (0·40, 0·75)
Overall (p<0·0001, I²=0·0%, P-heterogeneity=0·49)						0·58 (0·51, 0·66)
(C) Substantial loss of kidney function, ESKD or death due to cardiovascular or kidney disease						
CREDENCE	585	4401	43·2	61·2		0·70 (0·59, 0·82)
DECLARE-TIMI 58	850	17160	10·8	14·1		0·76 (0·67, 0·87)
CANVAS Program	518	10142	13·2	15·8		0·82 (0·68, 0·97)
EMPA-REG	370	6973	N/A	N/A		0·57 (0·46, 0·70)
Overall (p<0·0001, I²=60·3%, P-heterogeneity=0·06)						0·71 (0·63, 0·82)

0·3   0·5   1   1·5

Favours SGLT2 inhibitor   Favours placebo

*ESKD was defined as chronic dialysis, transplantation, or sustained eGFR <15 mL/min/1.73m²,
except in the EMPA-REG OUTCOME trial where it was defined as chronic dialysis or
transplantation.

¶Substantial loss of kidney function was defined as doubling of serum creatinine, except in the DECLARE-TIMI 58 trial, where it was defined as sustained 40% decline in eGFR

Figure 3

Figure 3. Effect of SGLT2 inhibitors on substantial loss of kidney function*, ESKD, or death due to kidney disease, stratified by (A) baseline eGFR¶ and (B) UACR subgroups¶

ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval; N/A: not available.

Study	Events	Patients	Events per 1000 patient-years		RR (95% CI)	P-trend
			SGLT2	Placebo		
eGFR≥90						0·07
DECLARE-TIMI 58	120	8162	2·5	4·9	0·50 (0·34, 0·73)	0·32
CANVAS Program	17	2476	1·1	3·3	(0·12, 0·88)	0·21
EMPA-REG OUTCOME	22	1529	N/A	N/A	(0·09, 0·53)	0·37
Subtotal (p<0·0001, I²=41·8%, P-heterogeneity=0·18)					(0·21, 0·63)	
eGFR 60-<90						
CREDENCE	78	1809	14·9	18·5	0·81 (0·52, 1·26)	
DECLARE-TIMI 58	186	7732	4·2	7·8	0·54 (0·40, 0·73)	
CANVAS Program	30	5625	1·1	2·0	0·48 (0·23, 0·98)	
EMPA-REG OUTCOME	61	3638	N/A	N/A	0·61 (0·37, 1·02)	
Subtotal (p<0·0001, I²=0·0%, P-heterogeneity=0·46)					0·60 (0·48, 0·74)	
eGFR 45-<60						
CREDENCE	99	1279	19·7	40·8	0·47 (0·31, 0·72)	
CANVAS Program	16	1485	2·8	3·9	0·74 (0·28, 2·01)	
EMPA-REG OUTCOME	39	1238	N/A	N/A	0·68 (0·36, 1·28)	
Subtotal (p<0·0001, I²=0·0%, P-heterogeneity=0·52)					0·55 (0·39, 0·76)	
eGFR<45						
CREDENCE	200	1313	51·6	71·7	0·71 (0·53, 0·94)	
CANVAS Program	10	554	6·2	6·0	0·79 (0·21, 2·94)	
EMPA-REG OUTCOME	30	563	N/A	N/A	0·63 (0·30, 1·29)	
Subtotal (p=0·008, I²=0·0%, P-heterogeneity=0·94)					0·70 (0·54, 0·91)	

0·3 0·5 1 1·5

Favours SGLT2 inhibitor Favours placebo

(A)

Events per 1000 patient-years

Study	Events	Patients	SGLT2	Placebo		RR (95% CI)	P-trend
UACR <30							0·31
CANVAS Program	15	7007	0·2	1·1		0·22 (0·07, 0·69)	
EMPA-REG OUTCOME	48	4142	N/A	N/A		0·41 (0·23, 0·72)	
Subtotal (*p*<0·0001, I² =0·0%, *P*-heterogeneity=0·34)						0·36 (0·22, 0·60)	
UACR 30-300							
CANVAS Program	19	2266	2.8	1.7		1·42 (0·51, 3·95)	
EMPA-REG OUTCOME	40	1996	N/A	N/A		0·67 (0·36, 1·26)	
Subtotal (*p*=0·70, I²=33·6%, *P*-heterogeneity=0·22)						0·87 (0·43, 1·76)	
UACR >300							
CREDENCE	377	4401	27.0	40·4		0·66 (0·53, 0·81)	
CANVAS Program	39	760	12·4	24·5		0·45 (0·24, 0·86)	
EMPA-REG OUTCOME	61	764	N/A	N/A		0·51 (0·31, 0·85)	
Subtotal (*p*<0·0001, I²= 0·0%, *P*-heterogeneity=0·39)						0·62 (0·51, 0·74)	

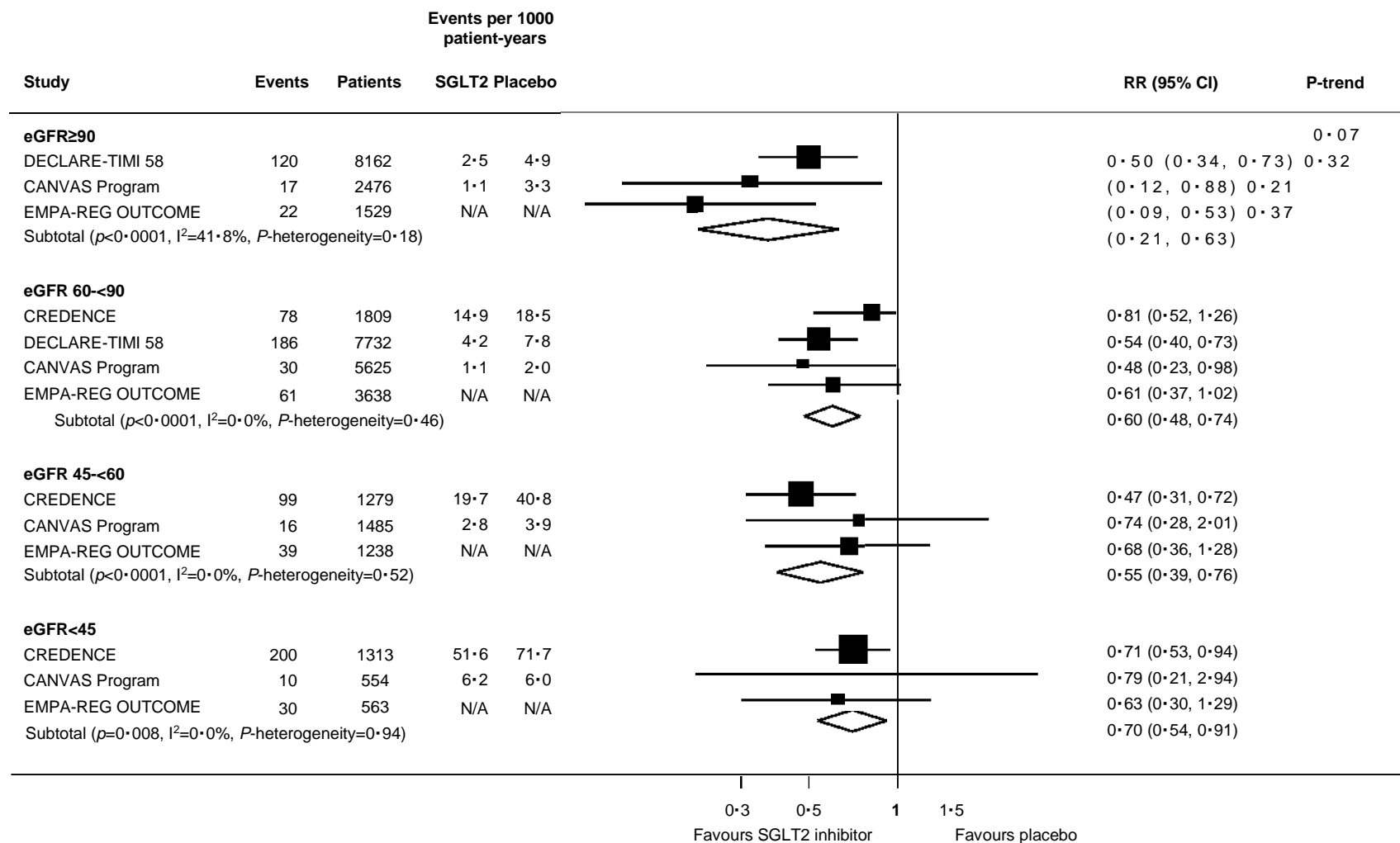0·3 0·5 1 1·5

Favours SGLT2 inhibitor   Favours placebo

(B)

*Substantial loss of kidney function was defined as doubling of serum creatinine, except in the DECLARE-TIMI 58 trial, where it was defined as sustained 40% decline in eGFR.
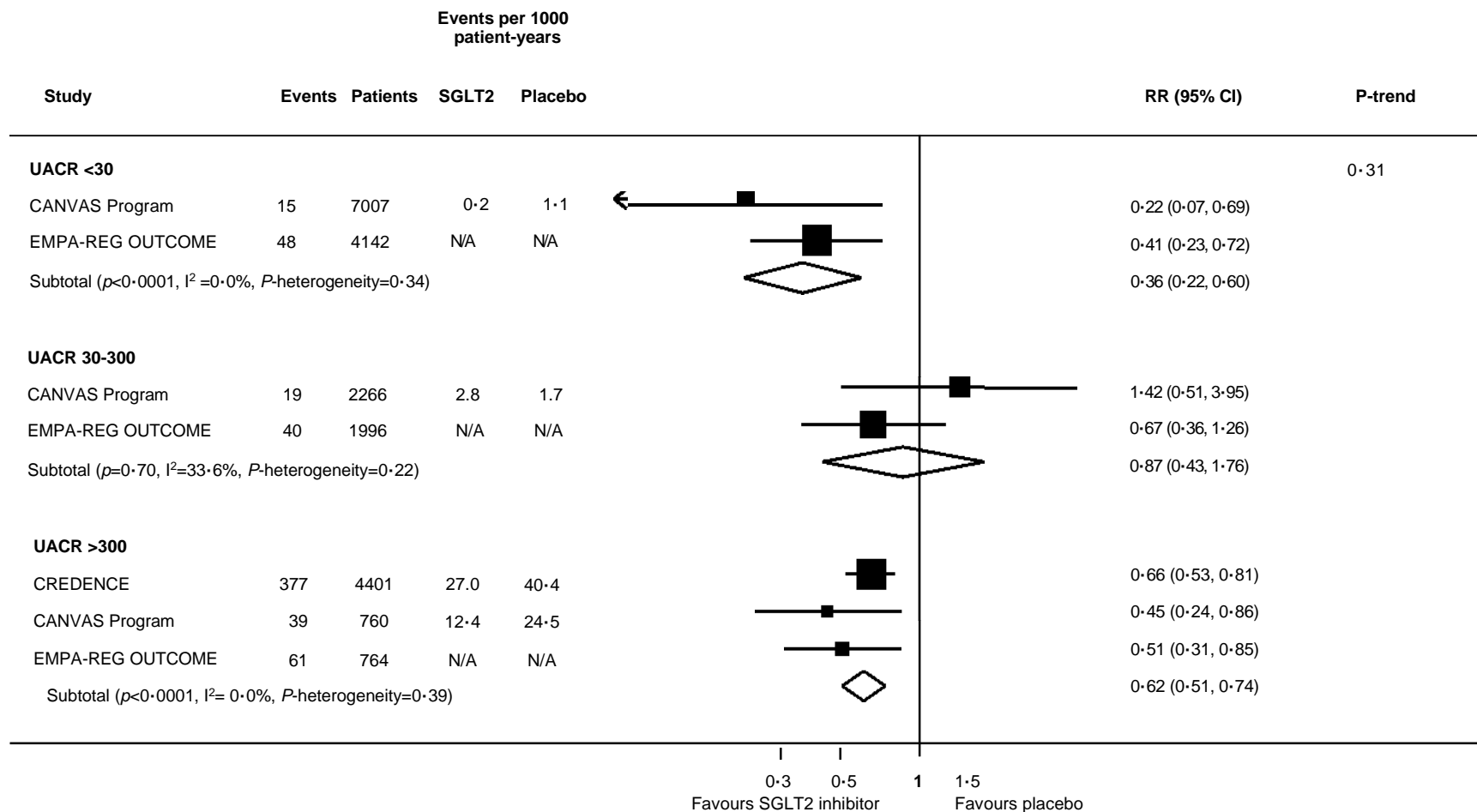
¶Results from the CREDENCE trial based on screening eGFR and UACR measurements.

Figure 4

Figure 4. Effect of SGLT2 inhibitors on acute kidney injury

SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval.

Study	Events	Patients	Events per 1000 patient-years SGLT2	Placebo		RR (95% CI)
CREDENCE	184	4397	16·9	20·0		0·85 (0·64, 1·13)
DECLARE-TIMI 58	300	17160	3·6	5·0		0·69 (0·55, 0·87)
CANVAS Program	58	10142	1·6	2·5		0·66 (0·39, 1·11)
EMPA-REG OUTCOME	401	7010	16·9	21·4		0·76 (0·62, 0·93)
Overall ($p<0·0001$, $I^2=0·0\%$, P-heterogeneity=0·68)						0·75 (0·66. 0·85)

0.3

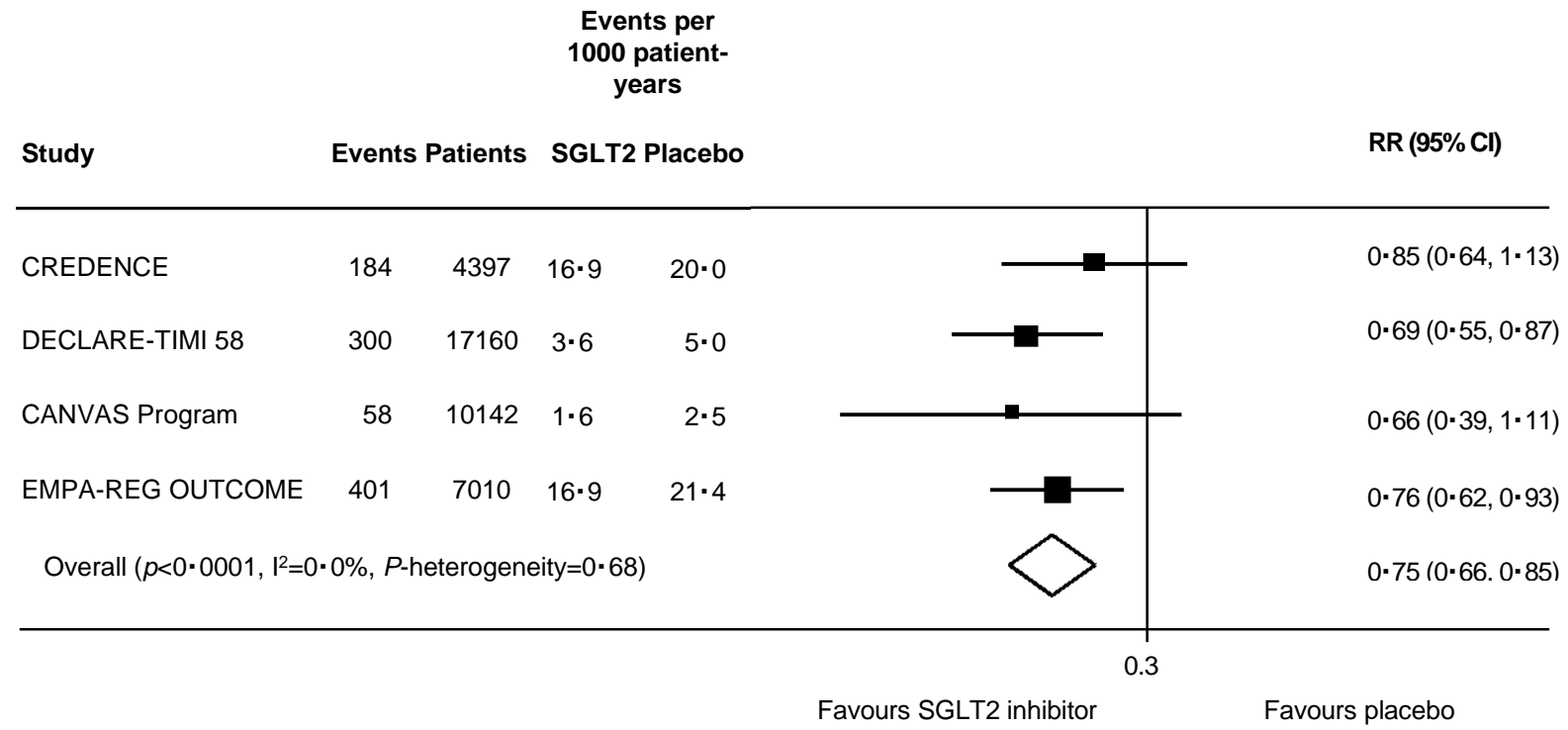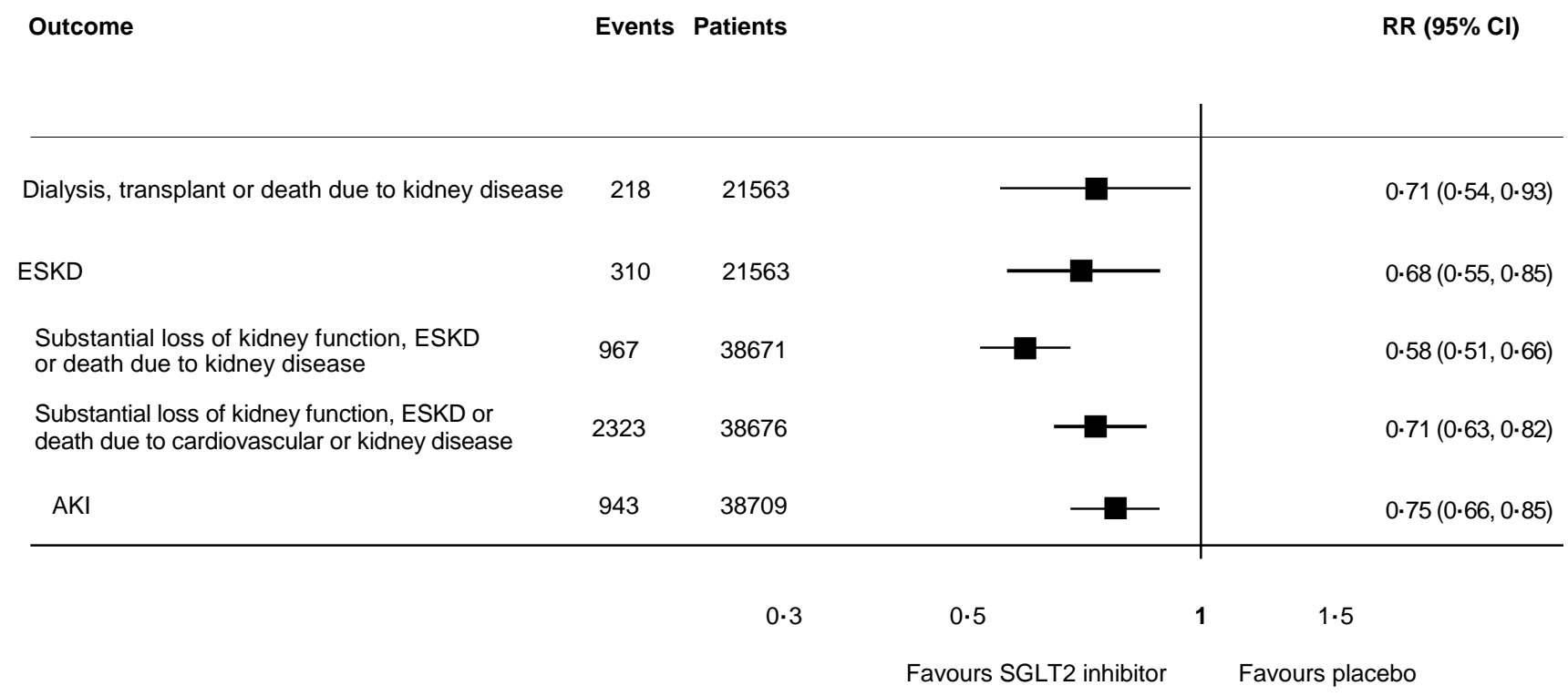Favours SGLT2 inhibitor   Favours placebo

Figure 5

Figure 5. Summary of the effects of SGLT2 inhibition on major kidney outcomes

ESKD: end-stage kidney disease; AKI: acute kidney injury; SGLT2: sodium-glucose cotransporter 2 inhibitor; RR: relative risk; CI: confidence interval.

Outcome	Events	Patients		RR (95% CI)
Dialysis, transplant or death due to kidney disease	218	21563		0·71 (0·54, 0·93)
ESKD	310	21563		0·68 (0·55, 0·85)
Substantial loss of kidney function, ESKD or death due to kidney disease	967	38671		0·58 (0·51, 0·66)
Substantial loss of kidney function, ESKD or death due to cardiovascular or kidney disease	2323	38676		0·71 (0·63, 0·82)
AKI	943	38709		0·75 (0·66, 0·85)

0·3　　0·5　　1　　1·5

Favours SGLT2 inhibitor　　Favours placebo

Supplementary appendix

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