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ORIGINAL ARTICLE

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# Sodium-glucose co-transporter-2 inhibitors with and without metformin: A meta-analysis of cardiovascular, kidney and mortality outcomes

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## Abstract

**Aim:** To assess whether the effects of sodium-glucose co-transporter-2 (SGLT2) inhibitors on cardiovascular, kidney and mortality outcomes are consistent with and without concomitant metformin use.

**Material and methods:** We conducted a meta-analysis of event-driven, randomized, placebo-controlled SGLT2 inhibitor trials that reported cardiovascular, kidney or mortality outcomes by baseline metformin use. Treatment effects, reported as hazards ratios (HRs) and 95% confidence intervals (CIs), were pooled using random-effects meta-analysis. The main outcomes in this analysis were (i) major adverse cardiovascular events (MACE) and (ii) hospitalization for heart failure (HHF) or cardiovascular death.

**Results:** We included six trials of four SGLT2 inhibitors that enrolled a total of 51 743 participants. Baseline metformin use varied from 21% in DAPA-HF to 82% in DECLARE-TIMI 58. SGLT2 inhibitors reduced the risk of MACE, with and without concomitant metformin use (HR 0.93, 95% CI 0.87–1.00 and HR 0.82, 95% CI 0.71–0.86, respectively; *P*-heterogeneity = 0.14). There were also clear and separate

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reductions in HHF or cardiovascular death with SGLT2 inhibitors, irrespective of metformin use (HR 0.79, 95% CI 0.73–0.86 and HR 0.74, 95% CI 0.63–0.87, respectively; *P*-heterogeneity = 0.48), as well as for major kidney outcomes and all-cause mortality (all *P*-heterogeneity > 0.40).

**Conclusion:** Treatment with SGLT2 inhibitors results in clear and consistent reductions in cardiovascular, kidney and mortality outcomes regardless of whether patients are receiving or not receiving metformin.

**KEYWORDS**

cardiovascular disease, clinical trial, diabetic nephropathy, heart failure, meta-analysis, SGLT2 inhibitor

## 1 | INTRODUCTION

Almost all clinical practice guidelines recommend metformin as first-line pharmacotherapy for people with type 2 diabetes mellitus (T2DM). In light of clear evidence of benefit for cardiovascular and kidney outcomes in large-scale randomized trials of sodium-glucose co-transporter-2 (SGLT2) inhibitors,[1,2] these agents are now recommended as the preferred second-line therapy in people who do not achieve sufficient glucose control on metformin alone, particularly for those with heart failure or chronic kidney disease.[3]

The central role of metformin in clinical practice recommendations is based largely on its tolerability, effects on body weight and low cost, as well as the beneficial effects on myocardial infarction and mortality outcomes demonstrated in the UK Prospective Diabetes Study (UKPDS).[4] However, that study was conducted over two decades ago, prior to the widespread use of renin-angiotensin system blockade, statins, and other cardioprotective therapies, therefore, direct comparisons with treatment effects observed in contemporary cardiovascular outcome trials of newer glucose-lowering agents are challenging. Nevertheless, meta-analyses of randomized trials have not demonstrated clear benefits with metformin for cardiovascular outcomes in people with T2DM, with very limited data on effects on kidney outcomes.[5–7] In the context of robust evidence of benefit with SGLT2 inhibitors (and glucagon-like-peptide-1 receptor agonists), there have been some calls for a reappraisal of the role of metformin as the first-line oral pharmacotherapy for all patients with T2DM.[8]

New guidelines from the European Society of Cardiology, developed in collaboration with the European Association for the Study of Diabetes, suggest that SGLT2 inhibitors be used in patients with T2DM who are at high or very high cardiovascular risk, *irrespective of whether they are treatment-naïve or already receiving metformin*.[9] Whether the effects of SGLT2 inhibitors on cardiovascular, kidney and mortality outcomes are consistent when used with versus without metformin is uncertain.

We therefore conducted a meta-analysis of the effects of SGLT2 inhibitors on cardiovascular, kidney and mortality outcomes by baseline metformin use, hypothesizing that the benefits of treatment for clinical outcomes would be similar regardless of metformin use.

## 2 | METHODS

This meta-analysis included event-driven, randomized, placebo-controlled SGLT2 inhibitor cardiovascular or kidney outcome trials that reported at least one cardiovascular, kidney or mortality outcome by baseline metformin use. Treatment effects by baseline metformin use were obtained from published reports.[10–13] For eligible trials of SGLT2 inhibitors that recruited participants with and without T2DM, we included data only from participants with T2DM. Data from the CANVAS Program[14] and the CREDENCE trial[15] were analysed by the authors, who had full access to individual participant data for these trials.

The main outcomes for this analysis were major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke, and hospitalization for heart failure (HHF) or cardiovascular death. We also assessed effects on the following outcomes by baseline metformin use: cardiovascular death; HHF; worsening kidney function, end-stage kidney disease or kidney death (as defined in the published trials); and all-cause mortality.

We pooled treatment effect estimates, expressed as hazards ratios (HRs) and 95% confidence intervals (CIs), by baseline metformin use from each individual study using random-effects meta-analysis. Potential heterogeneity in treatment effect estimates across baseline metformin use was assessed using the $I^2$ and *P*-heterogeneity statistics.

To assess the impact of differences in characteristics between participants receiving and not receiving metformin, we performed additional analyses of the CANVAS Program and CREDENCE trial for which we had access to individual participant data to compare unadjusted and adjusted treatment effects. We adjusted treatment effects estimates obtained from Cox models for baseline age, sex, race, glycated haemoglobin, diabetes duration, history of cardiovascular disease, microvascular complications, heart failure, systolic blood

pressure, body mass index, estimated glomerular filtration rate (eGFR), urinary albumin: creatinine ratio, total cholesterol, triglycerides, and insulin use. This approach was similar to that used in a subgroup analysis from the DECLARE-TIMI 58 trial.[11] In these analyses, interaction *P* values were obtained using likelihood ratio tests comparing models with and without treatment by subgroup interaction terms, with no adjustment for multiplicity.

All analyses were performed using STATA version 15.1 and SAS version 9.4.

## 3 | RESULTS

We included six event-driven, randomized, placebo-controlled trials of four SGLT2 inhibitors enrolling 51 743 participants, with median follow-up of between 1.5 and 4.2 years. The characteristics of included studies are summarized in Table 1. Four trials were cardiovascular outcome trials conducted in people with T2DM at high cardiovascular risk: EMPA-REG OUTCOME (n = 7020), the CANVAS program (n = 10142), DECLARE-TIMI 58 (17160), and VERTIS-CV (8246);[10,11,14,16] one (CREDENCE, n = 4401) was a kidney outcome trial in people with T2DM and chronic kidney disease[15] and one was a heart failure trial in people with heart failure with reduced ejection fraction, irrespective of diabetes status (DAPA-HF, n = 4744).[12]

The proportion of participants receiving metformin varied across the trials. Because approximately half of the participants in DAPA-HF did not have diabetes, this trial had the lowest proportion of participants receiving metformin at baseline (21%). CREDENCE included fewer participants on metformin at baseline (58%) compared to other trials that enrolled people with T2DM, in view of the much higher proportion of participants with reduced kidney function. In the cardiovascular outcome trials for empagliflozin, canagliflozin, dapagliflozin and ertugliflozin, baseline use of metformin was high in each trial and overall (74%–82%). Participants in these trials who were not receiving metformin at baseline were more likely to be older and using insulin, and to have a longer diabetes duration, lower eGFR and a history of heart failure. Detailed baseline characteristics of participants by metformin use in the CANVAS Program and CREDENCE trial are shown in Tables S1 and S2.

Sodium-glucose co-transporter-2 inhibitors reduced the risk of MACE regardless of baseline metformin use (HR 0.93, 95% CI 0.87–1.00 and HR 0.82, 95% CI 0.71–0.96, respectively; *P*-heterogeneity = 0.14 [Figure 1]). For the outcome of HHF or cardiovascular death, there were clear and separately statistically significant relative risk reductions in people receiving and not receiving metformin at baseline (HR 0.79, 95% CI 0.73–0.86 and HR 0.74, 95% CI 0.63–0.87; *P*-heterogeneity = 0.48; [Figure 1]). For HHF alone and for cardiovascular death, separately significant reductions were also observed, irrespective of metformin use at baseline (*P*-heterogeneity = 0.42 and 0.43; Figures 2 and 3).

Sodium-glucose co-transporter-2 inhibitors reduced the risk of worsening kidney function, end-stage kidney disease or kidney death similarly in people receiving and not receiving metformin at baseline

**TABLE 1** Characteristics of included studies

| | EMPA-REG OUTCOME | CANVAS Program | DECLARE-TIMI 58 | CREDENCE | DAPA-HF | VERTIS-CV |
|---|---|---|---|---|---|---|
| SGLT2 inhibitor | Empagliflozin | Canagliflozin | Dapagliflozin | Canagliflozin | Dapagliflozin | Ertugliflozin |
| Population | T2DM and high CV risk | T2DM and high CV risk | T2DM and high CV risk | Diabetic kidney disease | Heart failure with reduced ejection fraction | T2DM and high CV risk |
| Participants, n | 7020 | 10 142 | 17 160 | 4401 | 4774 | 8246 |
| Median follow-up, years | 3.1 | 2.4 | 4.2 | 2.6 | 1.5 | 3.0 |
| Atherosclerotic cardiovascular disease, n (%) | 7020 (100) | 6656 (65.6) | 6974 (40.6) | 2223 (50.3) | N/A | 8246 (100) |
| Heart failure, n (%) | 706 (10.1) | 1461 (14.4) | 1724 (10.0) | 652 (14.8) | 4774 (100.0) | 1958 (23.7) |
| eGFR < 60 mL/min/1.73m$^2$, n (%) | 1818 (25.9) | 2039 (20.1) | 1270 (7.4) | 2631 (59.8) | 1926 (40.3) | 1807 (21.9) |
| Proportion of participants with T2DM (%) | 100 | 100 | 100 | 100 | 44.8 | 100 |
| Baseline use of metformin, n (%) | 5193 (74.0) | 7825 (77.2) | 14 068 (82.0) | 2543 (57.8) | 1020 (21.4) | 6292 (76.3) |

Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; SGLT2, sodium glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

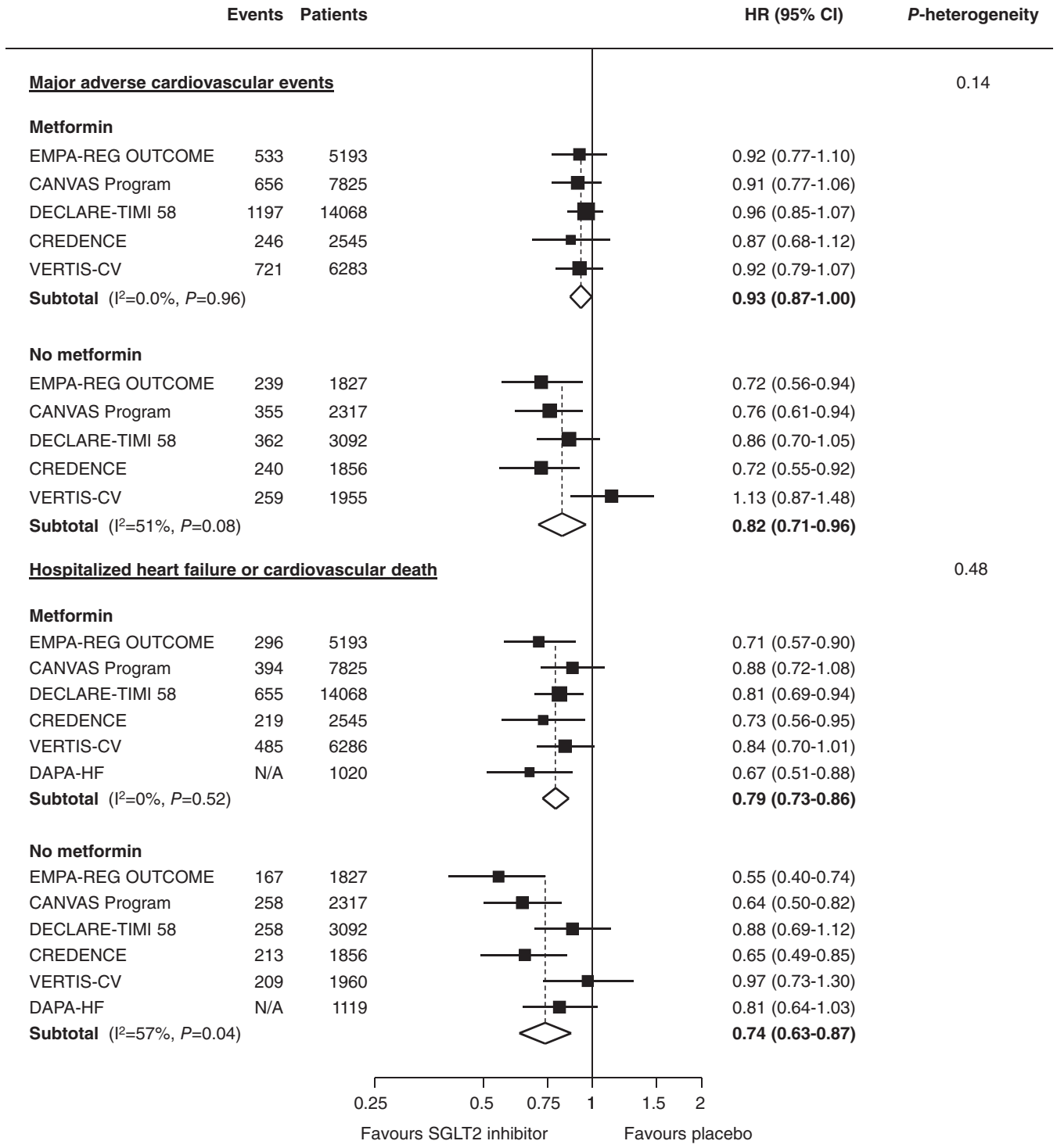



**FIGURE 1** Effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on major adverse cardiovascular events (MACE) and hospitalization for heart failure (HHF) or cardiovascular death by baseline metformin use. MACE were defined as nonfatal myocardial infarction, non-fatal stroke or cardiovascular death. In DAPA-HF, HHF was defined as hospitalization or urgent visit requiring intravenous therapy for heart failure. N/A, not available; CI, confidence interval

(HR 0.58, 95% CI 0.48–0.69 and HR 0.63, 95% CI 0.48–0.83; *P*-heterogeneity = 0.62 [Figure 4]). The risk of all-cause mortality was also lower in people treated with SGLT2 inhibitors, with consistent benefit regardless of baseline metformin use (*P*-heterogeneity = 0.57; Figure 4).

In exploratory analyses using individual participant data from the CANVAS Program and CREDENCE trial, the effects of SGLT2 inhibition on cardiovascular, kidney and mortality outcomes by baseline metformin use were similar after adjusting for differences between participants receiving and not receiving metformin (Table S3 and S4).

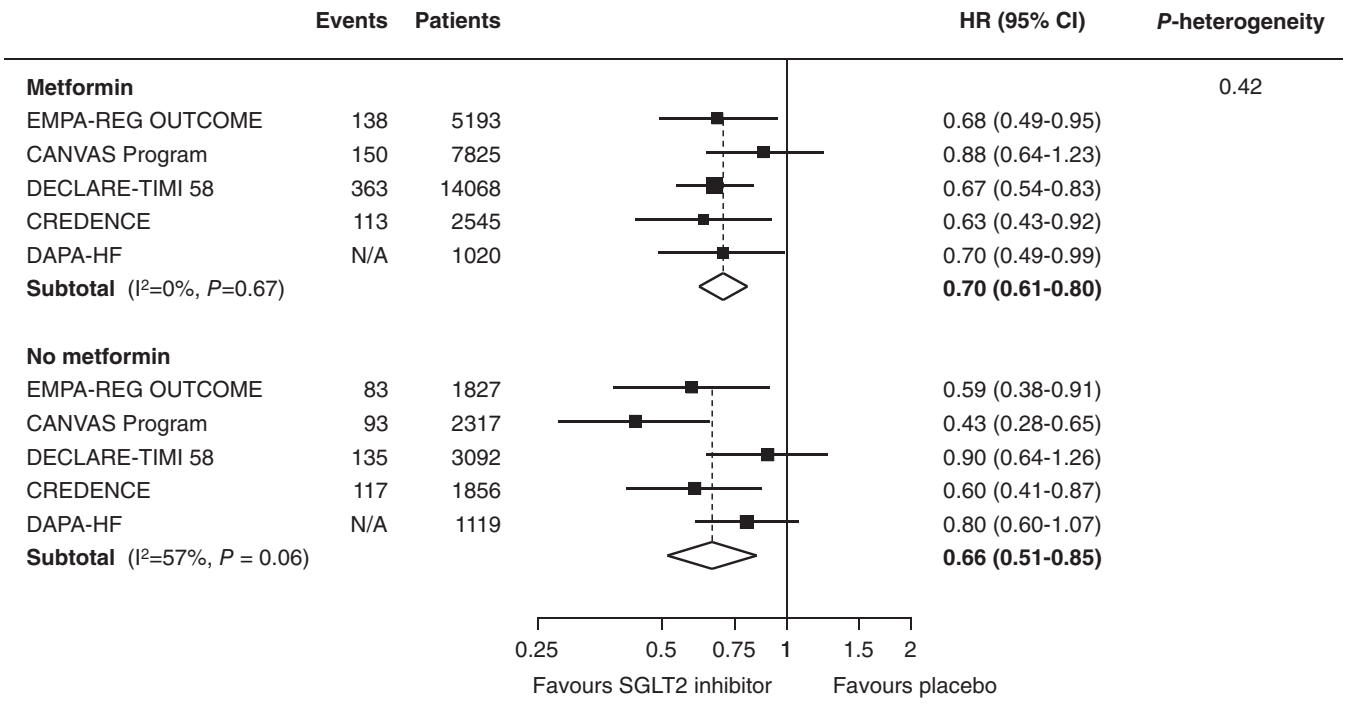



**FIGURE 2** Effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on hospitalization for heart failure by baseline metformin use. N/A, not available; CI, confidence interval

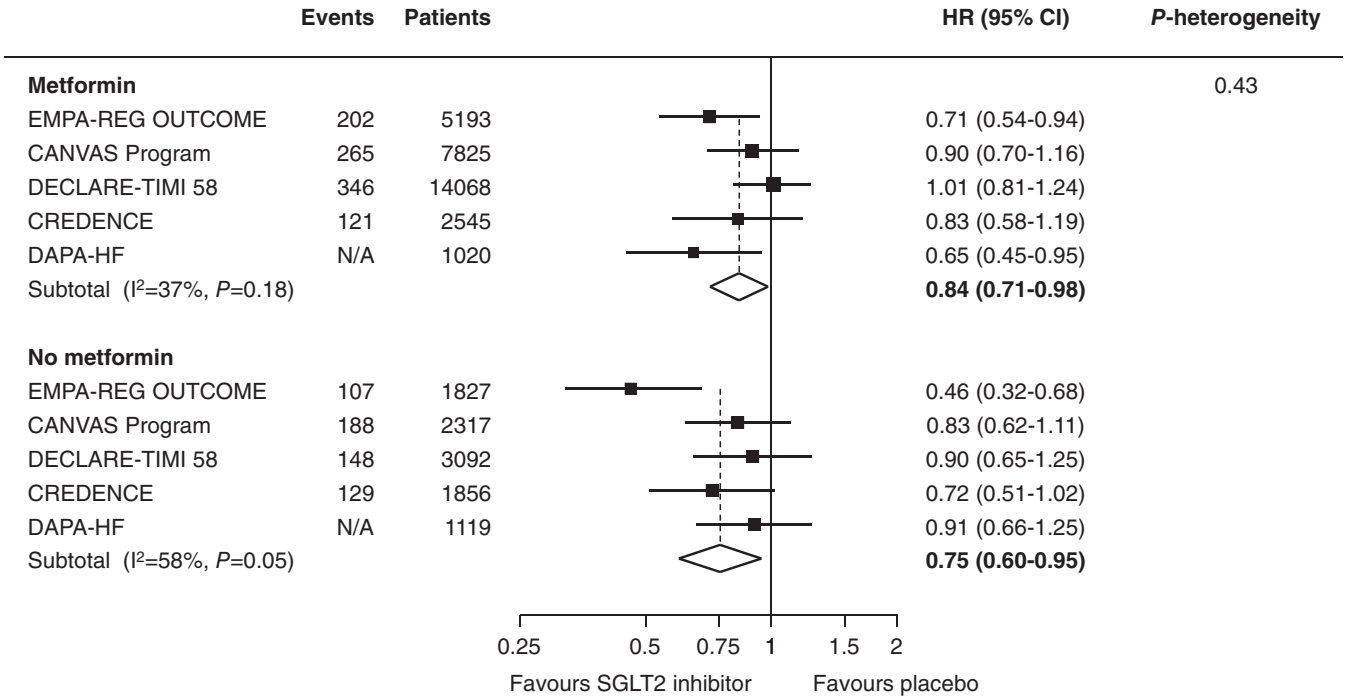



**FIGURE 3** Effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on cardiovascular death by baseline metformin use. CI, confidence interval; NA, not available

## 4 | DISCUSSION

In this meta-analysis of the effect of SGLT2 inhibitors on cardiovascular, kidney and mortality outcomes, we observed consistent and separately statistically significant relative risk reductions for all outcomes, including all-cause death, irrespective of metformin use at baseline. These data were derived from large, event-driven, randomized controlled trials conducted to a high standard that enrolled

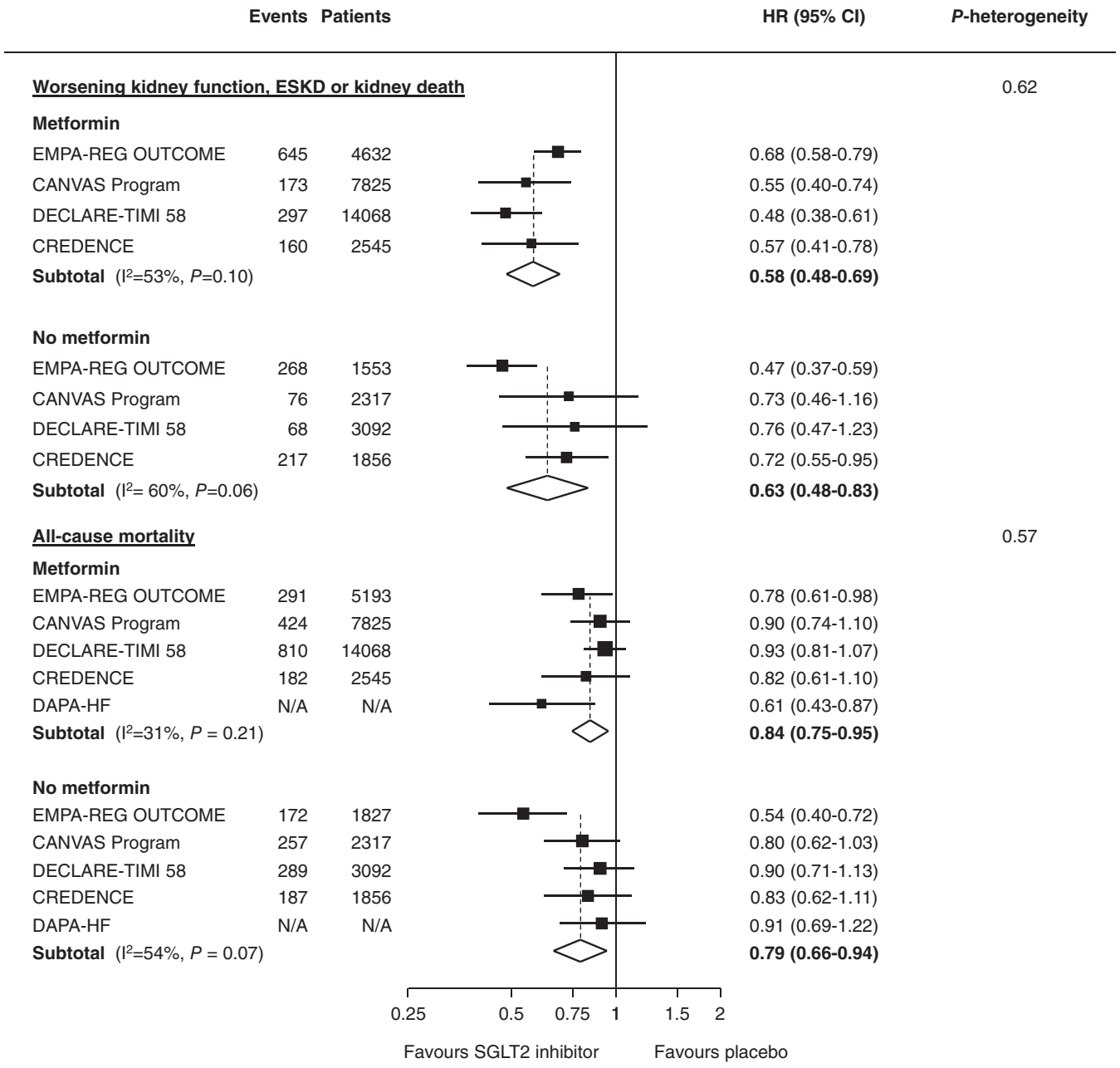



**FIGURE 4** Effect of sodium-glucose co-transporter-2 (SGLT2) inhibitors on (A) worsening kidney function,* end-stage kidney disease or kidney death and (B) all-cause mortality by baseline metformin use. *Worsening kidney function was defined as doubling of serum creatinine or progression to macroalbuminuria in EMPA-REG OUTCOME, sustained 40% decline in eGFR in the CANVAS Program and DECLARE-TIMI 58, and sustained doubling of serum creatinine in CREDENCE. CI, confidence interval; ESKD, end-stage kidney disease

diverse populations including participants with T2DM and established atherosclerotic cardiovascular disease,[14,16–18] T2DM and chronic kidney disease,[15] as well as heart failure with reduced ejection fraction, irrespective of the presence of diabetes.[19]

For decades, metformin has been recommended as the first-line pharmacological treatment for T2DM based on its tolerability, weight benefits and low cost. The main randomized evidence supporting the effect of metformin on patient-level outcomes comes from the UKPDS, which demonstrated that metformin reduces the risk of diabetes-related complications, myocardial infarction and all-cause mortality compared to other early glucose-lowering therapies and diet alone, both after a decade of randomized treatment and in long-term post-trial follow-up.[4,20] The UKPDS was conducted over two decades ago, prior to the widespread use of renin-angiotensin system blockade, statins and other widely used cardioprotective therapies, with substantially fewer events observed in comparison to contemporary cardiovascular outcome trials of glucose-lowering agents that have been mandated by regulatory agencies.[8] While the benefits of metformin on cardiovascular outcomes have largely not been corroborated since the UKPDS was conducted,[5,6] almost all clinical practice

guidelines continue to recommend that metformin be used as first-line pharmacotherapy for people with T2DM.[21] In light of evidence of the clinical benefits of SGLT2 inhibitors, these guidelines now recommend these agents as the preferred second-line therapy in people with concomitant chronic kidney disease or heart failure who do not achieve adequate glucose control on metformin alone.[3]

The results of this meta-analysis support new recommendations from the European Society of Cardiology that suggest SGLT2 inhibitors be used in patients with T2DM at high or very high cardiovascular risk, irrespective of whether they are treatment-naïve or already receiving metformin.[22] The results of DAPA-HF, EMPEROR-Reduced and DAPA-CKD, which demonstrated clear treatment benefits on cardiovascular, kidney and mortality outcomes regardless of the presence of diabetes,[19,23–25] further indicate that these agents should be considered primarily as cardiovascular and kidney protective therapies, rather than glucose-lowering agents. Taken together, the data call into question current clinical practice recommendations that recommend SGLT2 inhibitors be used as second-line treatment only in people who do not achieve satisfactory glucose control with metformin alone.

There are several important factors that need to be considered when interpreting these results. Because the T2DM cardiovascular outcome trials recruited participants largely at high cardiovascular risk, almost all of these individuals had a long duration of diabetes (mean duration of greater than a decade). As a result, the data do not directly address the question of whether SGLT2 inhibitors should be used preferentially in patients with early T2DM, which requires a dedicated randomized trial. An ongoing registry-based randomized trial (SMARTEST, NCT03982381) aims to assess directly the effect of dapagliflozin versus metformin on a primary composite endpoint of macro- or microvascular events in approximately 4300 participants with early T2DM, which may provide additional evidence in due course. We had limited capacity to explore the impact of differences between metformin and non-metformin users on treatment effects in this meta-analysis because we used study-level data. In the CANVAS and CREDENCE trials, where individual participant data were available, adjustment for differences in baseline characteristics did not substantially affect the observed treatment effects. However, it is important to recognize that it is not possible to fully account for differences between patients receiving and not receiving metformin and it is likely that residual confounding remains. Nevertheless, our results were consistent with a similar analysis from the DECLARE-TIMI 58 trial.[11] While we are unable to determine why specific individuals with T2DM were not receiving metformin, the available data suggest that most people not receiving metformin were those with longer disease duration and therefore greater need for insulin, as well as being strongly influenced by baseline kidney function. Other factors, such as gastrointestinal intolerance, could have also contributed. Finally, data on kidney outcomes, which were variably defined, were not available across all the trials. However, the consistency of the effect across the available studies suggests that inclusion of additional data yet to be reported is unlikely to materially alter our findings.

In conclusion, treatment with SGLT2 inhibitors results in clear and consistent reductions in cardiovascular, kidney and mortality outcomes regardless of whether patients are receiving or not receiving metformin.

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## CONFLICTS OF INTEREST

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## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

Data from the CANVAS Program and CREDENCE trial will be made available in the public domain via the Yale University Open Data Access Project (YODA; http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in Europe and the United States and the study has been completed for 18 months.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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