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ORIGINAL RESEARCH

Sodium-Glucose Cotransporter-2 Inhibitors and Primary Prevention of Atherosclerotic Cardiovascular Disease: A Meta-Analysis of Randomized Trials and Systematic Review

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BACKGROUND: Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce atherosclerotic cardiovascular disease (ASCVD) events in patients with prior ASCVD and type 2 diabetes; however, this benefit is uncertain in patients without established ASCVD.

METHODS AND RESULTS: Large-scale cardiovascular outcome randomized controlled trials or their prespecified subgroup analyses were selected, evaluating SGLT2 inhibitors versus placebo for primary prevention of ASCVD (inception, March 2023). The primary outcome was atherosclerotic major adverse cardiovascular events (MACEs), which was a composite of cardiovascular mortality, myocardial infarction, and stroke. The secondary outcomes were individual components of MACEs and all-cause mortality. The outcomes were reported as random-effect relative risk (RR) with a 95% CI. This analysis, comprising 23 987 patients enrolled in 5 randomized controlled trials with a mean follow-up duration of ≈135 weeks, found no significant reduction in atherosclerotic MACEs with SGLT2 inhibitors in comparison to placebo (RR, 0.85 [95% CI, 0.71–1.01]; P=0.07; I^2=44). There were no significant differences in cardiovascular mortality (RR, 0.93 [95% CI, 0.77–1.14]; P=0.50; I^2=0), myocardial infarction (RR, 0.88 [95% CI, 0.69–1.11]; P=0.28; I^2=23), and stroke (RR, 0.84 [95% CI, 0.62–1.16]; P=0.29; I^2=46). SGLT2 inhibitors significantly improved all-cause mortality (RR, 0.85 [95% CI, 0.72–1.0]; P=0.04; I^2=23). On subgroup analyses, the use of SGLT2 inhibitors led to significant reductions in MACEs (RR, 0.74 [95% CI, 0.61–0.89]; P=0.001), myocardial infarction (RR, 0.67 [95% CI, 0.47–0.97]; P=0.03), and stroke (RR, 0.61 [95% CI, 0.41–0.91]; P=0.01) primarily in patients with chronic kidney disease along with type 2 diabetes, whereas these benefits were not observed in patients with type 2 diabetes without chronic kidney disease.

CONCLUSIONS: SGLT2 inhibitors significantly reduced atherosclerotic MACEs in subjects having both chronic kidney disease and type 2 diabetes without established ASCVD.

Key Words: atherosclerotic major adverse cardiovascular events ■ primary prevention ■ sodium-glucose cotransporter-2 inhibitors

See Editorial by xxx.

Contemporary large-scale trials have proven robust clinical benefits of sodium-glucose cotransporter-2 (SGLT2) inhibitors in patients with heart failure and renal disease regardless of presence or absence of diabetes.[1,2] The SGLT2 inhibitors have been shown to reduce atherosclerotic cardiovascular disease

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CLINICAL PERSPECTIVE

What Is New?

- In patients with both chronic kidney disease and type 2 diabetes without established atherosclerotic cardiovascular disease, sodium-glucose cotransporter-2 inhibitors reduce atherosclerotic major adverse cardiovascular events, myocardial infarction, and stroke.
- A similar benefit was not observed in patients having type 2 diabetes without chronic kidney disease.

What Are the Clinical Implications?

- The study provides rationale for use of sodium-glucose cotransporter-2 inhibitors for primary prevention of atherosclerotic cardiovascular disease in patients having both chronic kidney disease and type 2 diabetes besides the already established effectiveness in secondary prevention of atherosclerotic cardiovascular disease, heart failure, and renal dysfunction.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiovascular event
MRF	multiple risk factors
SGLT2	sodium-glucose cotransporter-2
T2D	type 2 diabetes

(ASCVD) events in patients with type 2 diabetes (T2D) and existing ASCVD.[3–6] A previous meta-analysis (Zelniker et al [2019]), comprising 3 cardiovascular outcome randomized controlled trials (RCTs) evaluating SGLT2 inhibitors in patients with T2D, demonstrated that the atherosclerotic major adverse cardiovascular event (MACE) reduction was restricted to subjects with prior ASCVD.[3] This benefit was not observed in subjects with T2D and multiple risk factors (MRF) for ASCVD based on data from subgroup analysis of 2 RCTs.

In contrast, prespecified subgroup analyses of CREDENCE (Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation) trial (2019) and SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) trial (2022) demonstrated atherosclerotic MACE reductions in subjects with underlying reduced estimated glomerular filtration rate (eGFR) and albuminuria along with T2D in the absence of prior clinical ASCVD.[7,8] To this date, there has been no dedicated high-quality randomized study to evaluate the role of SGLT2 inhibitors in primary prevention of ASVCD in high-risk subjects. We conducted this meta-analysis to combine available data from all large-scale clinical outcome RCTs to investigate the potential benefits of SGLT2 inhibitors in preventing atherosclerotic events in patients without established ASCVD.

METHODS

This meta-analysis was conducted following the Cochrane Collaboration guidelines,[9] the Journal of the American Heart Association (*JAHA*) Transparency and Openness Promotion guidelines,[10] and Systematic Reviews and Meta-Analyses report.[11] Authors declare that all supporting data are available within the article and in the Data Supplement. The Institutional Review Board approval and informed consent were waived because the meta-analysis used information from previously published trials. Two authors (H.R. and P.G.) used online databases (PubMed, Google Scholar, and Cochrane Central Register of Controlled Trials) to search required articles. We reviewed citations as well as bibliographies of relevant trials, review articles, and meta-analyses to extract needed studies. The keywords and search strategy are mentioned in Data S1. The EndNote X9 (Clarivate, Philadelphia, PA) was used to upload references and remove any duplicates.

The inclusion criteria are as follows: (1) large-scale clinical outcome RCTs (≥500 participants in each arm) or their prespecified subgroup analyses, (2) evaluating SGLT2 inhibitors versus placebo, (3) in patients aged ≥18 years without established ASCVD and eGFR ≥25 mL/min per 1.73 m^2, (4) reporting atherosclerotic MACEs, and (5) with a median follow-up duration of ≥52 weeks. We excluded trials or subgroup analyses that reported MACEs merely composed of heart failure or renal outcomes because the beneficial effects of SGLT2 inhibitors on heart failure morbidity and renal function decline are well established even in patients without established ASCVD. The primary outcome of this study was atherosclerotic MACE, which was a composite of cardiovascular mortality, myocardial infarction (MI), and stroke. The secondary outcomes were cardiovascular mortality, all-cause mortality, MI, and stroke. We included the events in the analysis as reported by each study.

The studies were evaluated at the title and abstract level, followed by full-text inspection based on the selection criteria by 2 authors (H.R. and A.N.L.), which was supervised by a third party (S.U.K., S.S., and E.K.), and disagreements were resolved by consensus. The data gathering was performed using 3 data collection forms consisting of study and baseline participant characteristics (study design, type of

SGLT2 inhibitor, sample size, and follow-up duration), outcomes (events, sample size, event rate, and crude point estimates), and adverse events. Quality assessment of RCTs was performed using the Cochrane bias risk assessment (H.R.), as provided in Table S1.[12] Data extraction and quality assessment of qualifying studies were performed by 2 investigators (H.R. and M.K.) under the supervision of a third investigator (S.S.).

Statistical Analysis

This meta-analysis was performed using the random-effect model[13] by (H.R. and S.U.K.) augmented with a fixed-effect model provided in the supplementary file. We reported the estimates as risk ratio (RR) with a 95% CI and depicted as forest plots. $P \leq 0.05$ was considered statistically significant. We supplemented the results with a heterogeneity measure using the Q statistics and gauged with the I^2 index.[14] We used the event rates provided by the studies to calculate the RR. The studies that provided only hazard ratios with CIs were incorporated to calculate the pooled outcome measure. We conducted sensitivity analyses of outcomes to assess robustness of data. In addition to pooled analysis, subgroup analysis was performed on the basis of trials enrolling subjects with T2D with MRF for atherosclerosis and patients with chronic kidney disease (CKD) with or without T2D. CKD was defined as eGFR <90 mL/min per 1.73 m^2 with or without albuminuria. Meta-regression analysis could not be performed because of unavailability of baseline demographics of all the included subgroup analyses.[15] Comprehensive meta-analysis software, version 4.0 (Biostat, Englewood, NJ), was used for all analyses.

RESULTS

The search strategy yielded 2749 articles, and 2496 articles were screened after removal by automation tools and duplicates. A total of 195 records were eliminated at the title and abstract level. In addition, 49 articles were removed after the full-text review based on the predetermined selection criteria (Figure S1). Overall, this analysis was composed of subgroup analyses of prespecified outcomes from 5 clinical outcome RCTs, which included 23 987 subjects without established ASCVD.[7,8,16–22] The outcome data were extracted from either the index RCT[16,18–20,22] or separately published subgroup analyses.[7,8,17,21] All the RCTs were placebo controlled and were conducted internationally. The baseline demographics of participants in the included RCTs are summarized in the Table 1.[16,18–20,22] The characteristics of participants without ASCVD were separately reported only by 3 studies (Table S2).[7,17,21] Among the participants, 93% had T2D and <15% had a history of heart failure. Two studies were conducted

Table 1. Baseline Characteristics of Included RCTs

RCTs	Design	Total participants/ without established CVD	Intervention	Diabetes, %	eGFR <60 mL/min per 1.73 m^2, %	Urine albumin/ creatinine ratio ≥30 mg/g, %	CHF, %	Statins, %	RAAS inhibitors, %	Follow-up duration, median, wk
CANVAS (2017)[16]	Multinational, placebo-controlled, subgroup analysis	10 142/3486	Canagliflozin, 100 or 300 mg, once daily	100	19.8	30.2	14.4	74.9	80.0	126
DECLARE-TIMI 58 (2019)[18]	Multinational, placebo-controlled, subgroup analysis	17 160/10 186	Dapagliflozin, 10 mg, once daily	100	7.4	30.3	10.0	74.9	81.3	218
CREDENCE (2019)[19]	Multinational, placebo-controlled, subgroup analysis	4401/2181	Canagliflozin, 100 mg, once daily	100	58.9	100	14.8	69.0	99.9	137
DAPA-CKD (2020)[20]	Multinational, placebo-controlled, subgroup analysis	4304/2694	Dapagliflozin, 10 mg, once daily	67.5	89.5	100	10.9	64.9	98.0	125
SCORED (2021)[22]	Multinational, placebo-controlled, subgroup analysis	10 584/5440	Sotagliflozin, 400 mg, once daily	100	100	65	31	-	88.5	69

CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CHF, congestive heart failure; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation; CVD, cardiovascular disease; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; and SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk.

in subjects with T2D with MRF for ASCVD.[6,16,18] The inclusion criteria used for MRF in these studies are reported in Table S3. The CREDENCE trial enrolled subjects with T2D with reduced eGFR (≥30 to <90 mL/min per 1.73 m^2) and albuminuria (urine albumin/creatinine ratio ≥300 mg/g).[19] Likewise, the SCORED trial included patients with T2D with reduced eGFR (≥25 to 60 mL/min per 1.73 m^2).[22] The DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial recruited subjects with reduced eGFR (25–75 mL/min per 1.73 m^2) and albuminuria (urine albumin/creatinine ratio ≥200 mg/g) with or without T2D (67%).[20] All studies excluded patients with eGFR <25 mL/min per 1.73 m^2. Among patients in the latter 3 CKD studies, >90% were taking 1 of the renin-angiotensin-aldosterone system inhibitors at baseline.[19,20,22] The studies conducted primarily in subjects with heart failure did not meet the inclusion criteria because atherosclerotic MACE outcomes were not reported. The included RCTs evaluated dapagliflozin, canagliflozin, and sotagliflozin. We reported the number of events per total population in each arm along with event rate per 1000 patient-year in each study (Table S4). The serious adverse events reported in each trial are summarized in Table S5. The mean follow-up duration of the included studies was ≈135 weeks.

In an analysis of 23 987 subjects, there was no significant relative risk reduction of atherosclerotic MACE events with SGLT2 inhibitors compared with placebo in patients without established ASCVD (RR, 0.85 [95% CI, 0.71–1.01]; P=0.07; I^2=44), as shown in Figure 1. The sensitivity analysis, by removing 1 study each time, revealed a significant reduction in MACEs after excluding data of DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58). On study-level subgroup analysis, there was significant improvement in MACEs limited to studies enrolling patients with CKD along with T2D (RR, 0.74 [95% CI, 0.61–0.89]; P=0.001; I^2=0), whereas this benefit was not observed in patients with T2D and MRF (RR, 1.01 [95% CI, 0.86–1.18]; P=0.91; I^2=0) (Figure 2). The heterogeneity of effect within studies improved on subgroup analysis. The cardiovascular mortality was not significantly reduced by SGLT2 inhibitors (RR, 0.93 [95% CI, 0.77–1.14]; P=0.50; I^2 = 0) (Figure 1). The results did not change in the subgroup analysis (Figure 2).

Use of SGLT2 inhibitors led to a significant reduction in all-cause mortality (RR, 0.85 [95% CI, 0.72–1.0]; P=0.04; I^2=23), as shown in the forest plot (Figure 1). Among the included studies, dapagliflozin independently reduced all-cause mortality in analysis of 2694 subjects with CKD and albuminuria. There was no significant difference found between the 2 arms with regard to MI (RR, 0.88 [95% CI, 0.69–1.11]; P=0.28; I^2=23) and stroke (RR, 0.84 [95% CI, 0.62–1.16]; P=0.29; I^2=46) (Figure 1). Subgroup analyses revealed significant reduction in MI (RR, 0.67 [95% CI, 0.47–0.97]; P=0.03; I^2=0) and stroke (RR, 0.61 [95% CI, 0.41–0.91]; P=0.01; I^2=0) in subjects with both CKD and T2D, whereas no difference was established for MI (RR, 0.99 [95% CI, 0.79–1.25]; P=0.95; I^2=0) and stroke (RR, 1.06 [95% CI, 0.83–1.37]; P=0.62; I^2=0) in patients with T2D and MRF (Figure 2). The outcomes using fixed-effect model, illustrated in Figures S2 and S3, led to similar overall observations compared with random-effect analyses, except there was a significant reduction in all-cause mortality in patients on SGLT2 inhibitors having CKD along with T2D in contrast to those with T2D without CKD.

DISCUSSION

This meta-analysis comprising of 23 987 patients without established ASCVD enrolled in 5 clinical outcome RCTs evaluated SGLT2 inhibitors versus placebo and provided insights on role of SGLT2 inhibitors in primary prevention of ASCVD. The study found a reduction in MACEs with SGLT2 inhibitors primarily in patients with both CKD (eGFR ≥25 to <90 mL/min per 1.73 m^2 with or without albuminuria) and T2D, whereas this benefit was not noticed in patients with T2D and MRF in the absence of CKD. The intervention arm contributed 15% relative risk reduction in all-cause mortality in patients without established ASCVD; however, no statistically significant reduction in cardiovascular mortality was noted. Similarly, SGLT2 inhibitors provided 33% and 39% relative risk reduction in MI and stroke, respectively, in patients with both CKD and T2D. In contrast, there was no significant reduction in MI and stroke in patients with T2D and MRF.

The results of the present study pointed toward the additional benefits of SGLT2 inhibitors in primary prevention of ASCVD, along with the already established favorable effects on heart failure and renal outcomes regardless of existing T2D and ASCVD, as well as secondary prevention of ASCVD in T2D.[1,2] Like our study, a previous meta-analysis (Zelniker et al [2019]) demonstrated lack of significant reduction in atherosclerotic MACEs in patients with T2D with MRF for ASCVD.[3] However, Zelniker et al did not include data from 3 RCTs conducted in patients with renal dysfunction.[19,20,22] Similarly, a meta-analysis of 6 RCTs (McGuire et al [2021]) revealed MACE reduction with SGLT2 inhibitors in patients with existing ASCVD, but not among patients without prior ASCVD.[5] The study also did not contain results of DAPA-CKD and SCORED trials.[8,20] Our study incorporated data from these 2 studies and demonstrated a reduction in atherosclerotic MACEs in patients with both CKD and T2D.

The benefit of atherosclerotic MACEs found in patients having reduced eGFR or albuminuria along with T2D could be related to clinically silent or inapparent

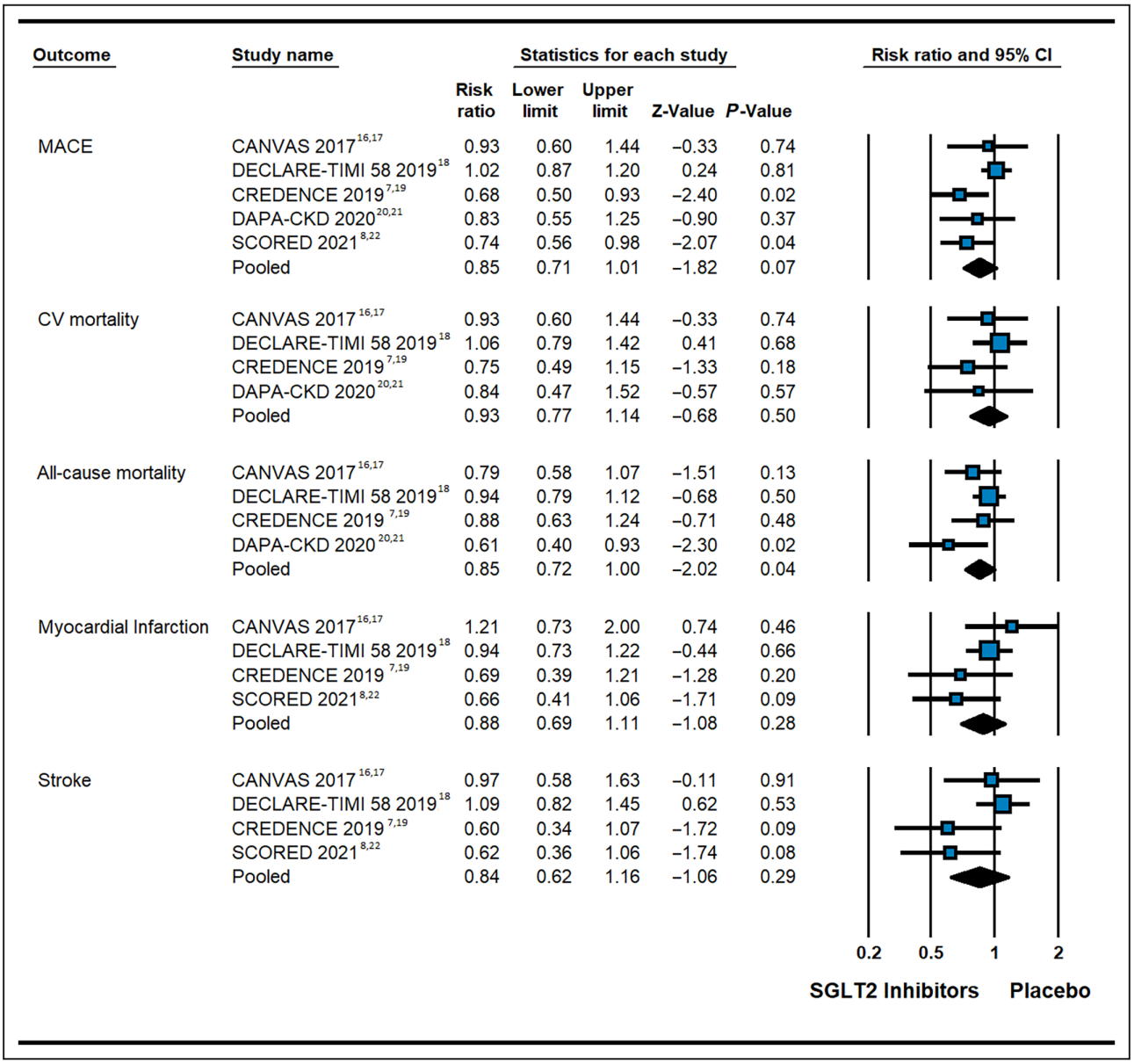

Figure 1. Forest plot comparing sodium-glucose cotransporter-2 (SGLT2) inhibitors vs placebo for major adverse cardiovascular (CV) events (MACEs), CV mortality, all-cause mortality, myocardial infarction, and stroke.
CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; and SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk.

ASCVD. The incidence of cardiovascular disease in patients having CKD is higher than becoming dialysis dependent, indicating CKD is 1 of the strongest predictors for ASCVD.[23] There have been data to suggest that the risk of ASCVD events, including stroke, increases incrementally with increasing albuminuria with or without decrease in eGFR in patients with diabetes.[24,25] There was a higher MACE rate per 1000 patient-year among the trials enrolling patients with CKD along with T2D compared with those with T2D with MRF (Table S4). In the subgroup analysis of CANVAS (Canagliflozin Cardiovascular Assessment Study), there was a trend toward improvement in atherosclerotic MACEs by SGLT2 inhibitors with decreasing eGFR and increasing albuminuria.[6,16] The impact of SGLT2 inhibitors with or without background statins is unclear; however, SGLT2 inhibitors led to significant reduction in MACEs even with background statins in CANVAS. This compelling benefit of primary prevention of ASCVD in patients having both CKD and T2D furnishes another rationale

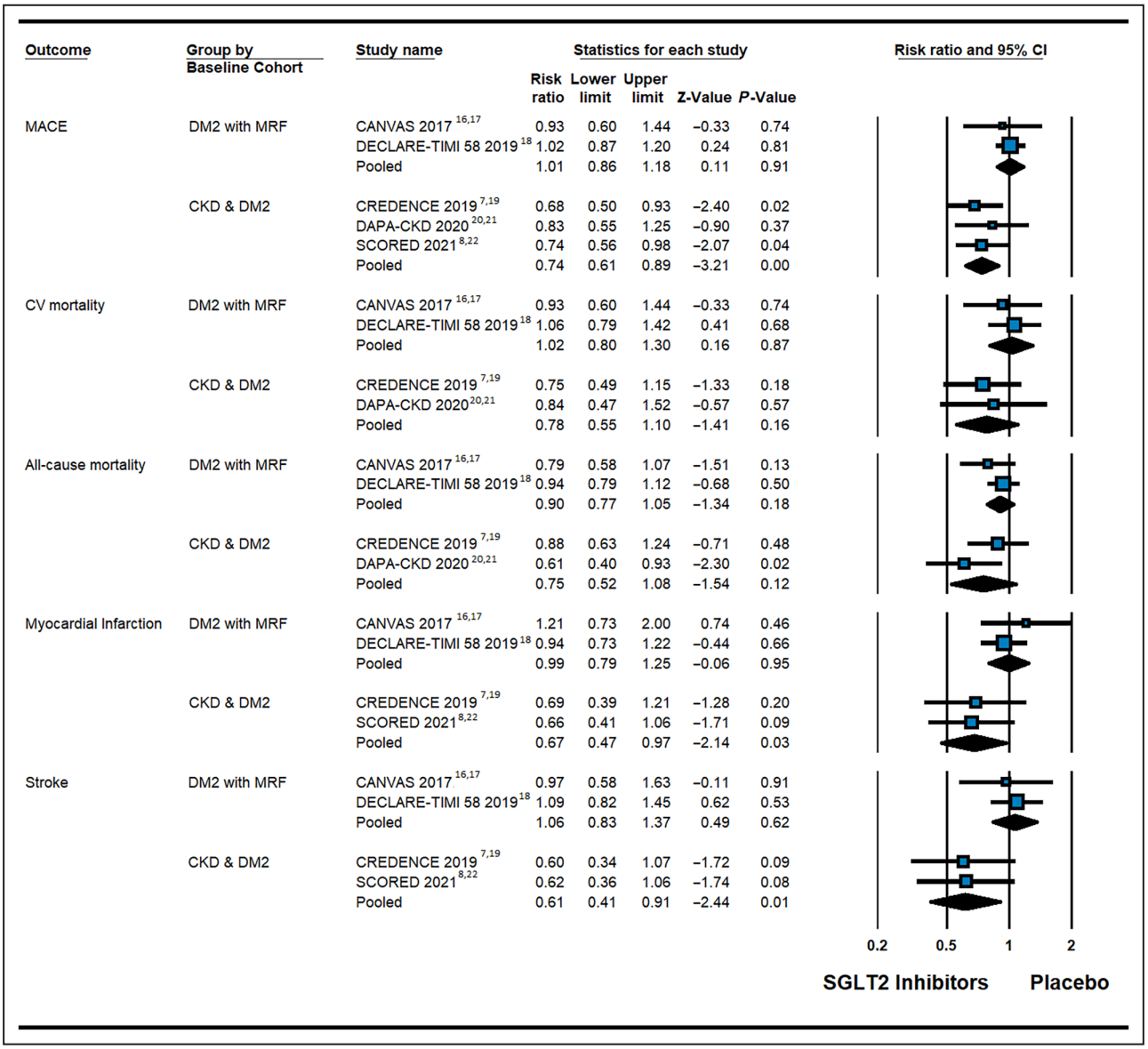

Figure 2. Forest plot comparing sodium-glucose cotransporter-2 (SGLT2) inhibitors vs placebo for subgroup analyses of major adverse cardiovascular (CV) events (MACEs), CV mortality, all-cause mortality, myocardial infarction, and stroke. CANVAS indicates Canagliflozin Cardiovascular Assessment Study; CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DECLARE TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; DM2, type 2 diabetes; MRF, multiple risk factors; and SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk.

for SGLT2 inhibitor use besides its effectiveness in improving heart failure and renal outcomes. Furthermore, the survival benefit found in this study is likely related to composite benefits of SGLT2 inhibitors in improving the heart failure, ASCVD, and renal outcomes regardless of ASCVD.

There are several proposed mechanisms by which SGLT2 inhibitors exert their beneficial effects. These include (but are not limited to) the following: positive effects on natriuresis, eliminating glucose in urine, glycemic control, blood pressure reduction, weight loss, intraglomerular pressure, and reducing inflammation.[26] Literature suggested a plaque-stabilizing effect of SGLT2 inhibitors in the animal models.[27] The exact mechanism by which SGLT2 inhibitors reduce atherosclerotic events is debatable and indicates need for further research. In our study, 3 SGLT2 inhibitors were studied, including dapagliflozin, canagliflozin, and sotagliflozin. The former 2 agents are pure SGLT2 inhibitors and are US Food and Drug Administration approved. The sotagliflozin is a dual SGLT2 and SGLT1 inhibitor, and its US Food and Drug Administration approval status is

under review. The benefit in atherosclerotic MACEs was driven mainly by the CREDENCE and SCORED trials, whereas reduction in all-cause mortality was driven by the DAPA-CKD trial. This potential difference could be explained by the 100% prevalence of T2D in SCORED and CREDENCE trials compared with 60% in DAPA-CKD trial. In addition, further research is required to evaluate anti-inflammatory and antiatherosclerotic effects of individual SGLT2-inhibitors. The overall safety of all 3 SGLT2 inhibitors is found to be acceptable. All these agents increase the risk of mycotic urogenital infections, which can be simply treated in most cases. The overall incidence of euglycemic ketoacidosis is low, ≈0.1%.[28] There was increased risk of lower limb amputation with canagliflozin found in CANVAS[16]; however, this finding was not observed in the CREDENCE trial, indicating the need for proper selection of patients.[19] In addition, the target dose of canagliflozin used in CANVAS was 300 mg once daily, whereas 100 mg once daily dose was studied in the CREDENCE trial.

The present study has several limitations. First, this study is based on subgroup analyses of large-scale clinical outcome RCTs, although only prespecified subgroup analyses were included in the analysis. There is lack of a dedicated large-scale cardiovascular outcome trial to investigate SGLT2 inhibitors for primary prevention of ASCVD. The current study is based on study-level meta-analysis rather than patient-level meta-analysis because of inaccessibility of data. The patients were screened for ASCVD by investigators of RCTs; however, subclinical ASCVD was not evaluated, which could have misclassified primary prevention group. The subgroup analyses of our study for MACEs in patients with both CKD and T2D also included data from DAPA-CKD trial, which included patients with CKD with ≈60% T2D.[21] Even with exclusion of DAPA-CKD trial, results did not change the MACE outcome in subgroup analysis. The present study did not include the contemporary EMPA-KIDNEY (Study of Heart and Kidney Protection With Empagliflozin) published in 2023 because of unavailability of subgroup analyses of atherosclerotic MACEs.[29] In addition, the results of our study are based on 3 different SGLT2 inhibitors, with 1 agent being both an SGLT2 and an SGLT1 inhibitor. The background distribution of statins was uniform among patients on SGLT2 inhibitors and placebo; however, the detail about statins is not provided in the SCORED trial.

In conclusion, among patients with diabetes and CKD (reduced eGFR or albuminuria) without clinically established ASCVD, SGLT2 inhibitors significantly reduced atherosclerotic MACEs, MI, and stroke. These benefits were not observed in similar subjects in the absence of CKD. We advocate for a large-scale cardiovascular outcome RCT to further validate the role of SGLT2 inhibitors in primary prevention of ASCVD in those with diabetes and CKD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Key words for search strategy:

"SGLT2 inhibitors"[All Fields] OR "canagliflozin"[All Fields] OR "dapagliflozin"[All Fields] OR "empagliflozin"[All Fields] OR "sotagliflozin"[All Fields] OR "albuminuria"[All Fields] OR "cardiovascular outcomes"[All Fields] OR "diabetes mellitus"[All Fields] OR "chronic kidney disease"[All Fields] OR "heart failure"[All Fields] OR "randomized controlled trials"[All Fields]

Table S1. Cochrane quality assessment tool for assessment of risk of bias for the randomized trials.

Studies	Randomization	Allocation concealment	Blinding	Deviation from intended intervention	Outcome assessment bias	Free of other biases
CANVAS (2017)[16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DECLARE-TIMI 58 (2019)[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CREDENCE (2019)[19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DAPA-CKD (2020)[20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
SCORED (2021)[22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S2. Detailed baseline characteristics of included subgroup studies. DECLARE-TIMI 58 and SCORED trial detailed subgroup demographics are not available.

Studies	**CANVAS (2017)**[16,17]		**CREDENCE (2019)**[7,19]		**DAPA-CKD (2020)**[20,21]	
Study arms	Canagliflozin	Placebo	Canagliflozin	Placebo	Dapagliflozin	Placebo
No. of participants	2039	1447	1089	1092	1339	1355
Age (years)	62.7±7.3	62.8±7.3	61.1±9.7	61.7±9.4	59±12.5	59.4±12.9
Female (%)	44.9	45.7	37.2	36.1	36.1	34.5
Hypertension (%)	91.0	91.6	96.1	96.0	94.2	93.6
Current Smoker (%)	24.3	25.5	15.8	13.1	13.9	13.6
Hx of CHF (%)	7.1	9.8	5.8	5.3	-	-
Insulin (%)	47.2	49.6	63.5	62.4	32.3	30.8
DPP4 inhibitors (%)	13.9	14.8	19.4	19.3	17.3	17.2
GLP-1 agonists (%)	4.2	5.2	3.7	4.5	2.5	2.7
Statins	63.0	63.4	65.0	62.4	57.7	58.3
RAAS inhibitors (%)	80.8	80.1	100.0	99.6	96.8	97.3

CHF, congestive heart failure; DPP4, Dipeptidyl peptidase-4; GLP-1, Glucagon like peptide; Hx, history; RAAS inhibitors, renin angiotensin aldosterone system inhibitors.

Table S3. Inclusion criteria of multiple risk factors for atherosclerotic cardiovascular disease among patients with type 2 diabetes mellitus.

Studies	Inclusion criteria of multiple risk factors for atherosclerotic cardiovascular disease
CANVAS (2017)[16]	≥50 years old with two or more of the following risk factors for cardiovascular disease, - ≥10 years of diabetes duration - Hypertension with systolic blood pressure (SBP)>140 while on one or more antihypertensives - Current smoking - Microalbuminuria or macroalbuminuria - High-density lipoprotein (HDL) cholesterol level of less than 1 mmol per liter (38.7 mg per deciliter)
DECLARE-TIMI 58 (2019)[18]	Age≥55 years in men and ≥60 in women with at least one of the following - Dyslipidemia which is LDL-C>130 mg/dl or on lipid lowering medications for LDL-C>130 mg/dl for >1 year. - Hypertension with SBP>140 or diastolic BP>90 or on antihypertensives - Current smoking

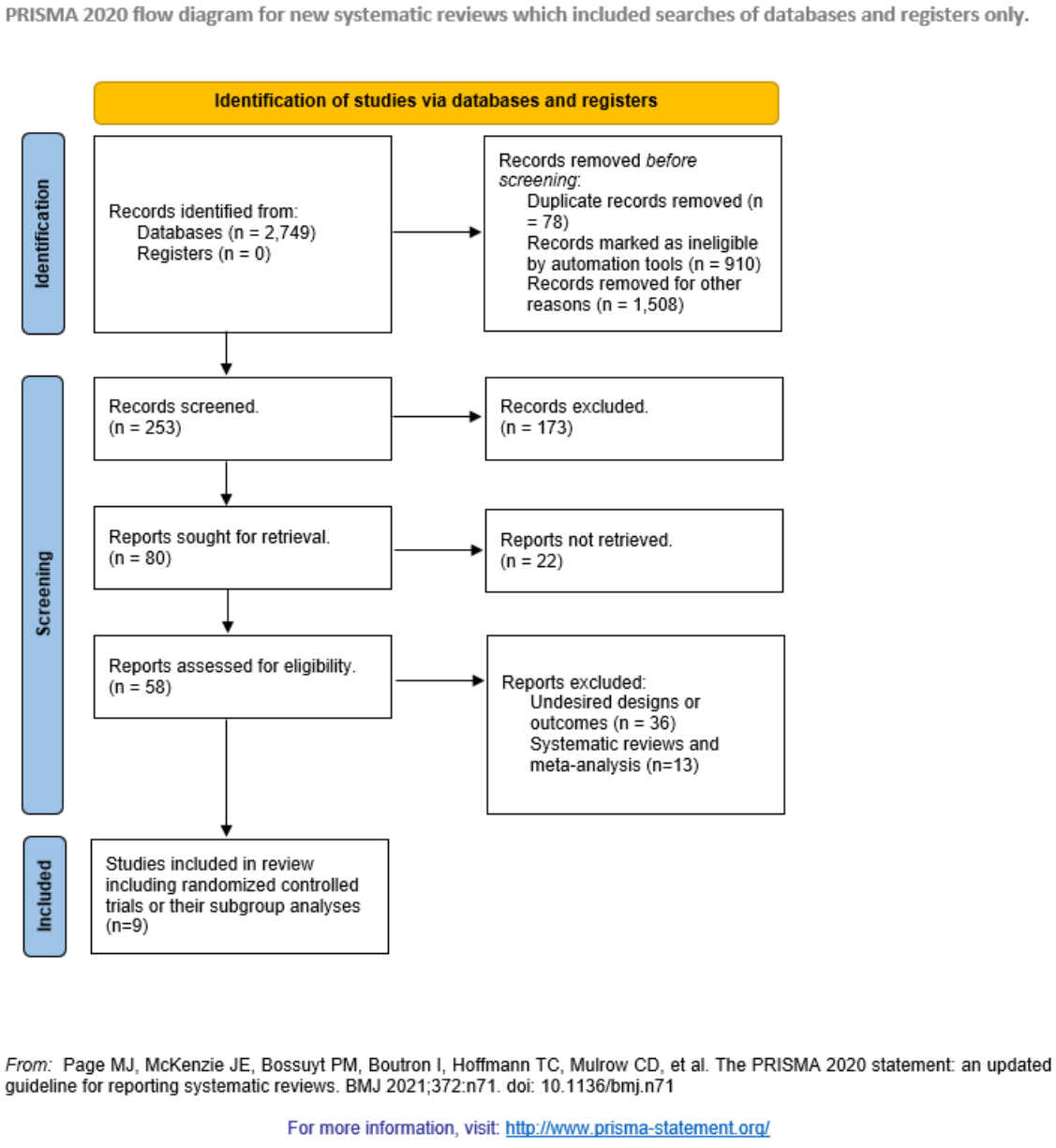
Table S4. Number of events per total population along with event rate per 1000 patient-year in the included studies.

Studies	**Agents**	**Major adverse cardiovascular events** Events/total No. of patients (Events/1000 patient-year)	**Cardiovascular mortality** Events/total No. of patients (Events/1000 patient-year)	**All-cause mortality** Events/total No. of patients (Events/1000 patient-year)	**Myocardial infarction** Events/total No. of patients (Events/1000 patient-year)	**Stroke** Events/total No. of patients (Events/1000 patient-year)
CANVAS[16,17]	Canagliflozin	NA/2039 (15.8)	NA/2039 (6.5)	NA/2039 (11.2)	NA/2039 (5.5)	NA/2039 (4.5)
	Placebo	NA/1447 (15.5)	NA/1447 (6.2)	NA/1447 (13.4)	NA/1447 (4.4)	NA/1447 (5.0)
DECLARE-TIMI 58[18]	Dapagliflozin	273/5108 (13.4)	92/5108 (4.4)	230/5108 (11.0))	114/5108 (5.6)	98/5108 (5.2)
	Placebo	266/5078 (13.3)	86/5078 (4.1)	243/5078 (11.7)	120/5078 (5.9)	89/5078 (5.1)
CREDENCE[7, 19]	Canagliflozin	62/1089 (22.0)	35/1089 (12.2)	60/1089 (20.9)	20/1089 (7.0)	18/1089 (6.3)
	Placebo	91/1092 (32.7)	47/1092 (16.4)	68/1092 (23.7)	29/1092 (10.3)	30/1092 (10.7)
DAPA-CKD[20,21]	Dapagliflozin	41/1339 (15.0)	20/1339 (7.0)	33/1339 (11.0)	NA	NA
	Placebo	50/1355 (21.0)	24/1355 (8.0)	55/1355 (18.0)	NA	NA
SCORED[8,22]	Sotagliflozin	6.7% (34.1)	NA	NA	2.5% (12.7)	1.4% (7.0)
	Placebo	7.6% (38.7)	NA	NA	3.0% (15.2)	2.6% (13.2)

Table S5. Serious adverse events reported by randomized controlled trials.

Studies	Agents	No. of participants		Amputations	Ketoacidosis	Mycotic genital infections	Fractures	Urinary tract infections
CANVAS[16]	Canagliflozin 100 or 300 mg OD	5795	Events/1000 patient year	6.3	0.6	34.9 (males) 68.8 (females)	15.4	40.0
	Placebo	4347	Events/1000 patient year	3.4	0.3	10.8 (males) 17.5 (females)	11.9	37.0
DECLARE-TIMI 58[18]	Dapagliflozin 10 mg OD	8574	No. (%)	123 (1.4)	27 (0.3)	76 (0.9)	457 (5.3)	127 (1.5)
	Placebo	8569	No. (%)	113 (1.3)	12 (0.1)	9 (0.1)	440 (5.1)	133 (1.6)
CREDENCE[19]	Canagliflozin 100 mg OD	2200	No. (%)	70 (3.1)	11 (0.5)	50 (2.3)	67 (3.0)	245 (11.1)
	Placebo	2197	No. (%)	63 (2.9)	1 (0.05)	13 (0.6)	68 (3.1)	221 (10.1)
DAPA-CKD[20]	Dapagliflozin 10 mg OD	2149	No. (%)	35 (1.6)	0 (0.0)	-	85 (4.0)	20 (0.9)
	Placebo	2149	No. (%)	39 (1.8)	2 (0.09)	-	69 (3.2)	15 (0.7)
SCORED[22]	Sotagliflozin 400 mg OD	5291	No. (%)	32 (0.6)	30 (0.6)	125 (2.4)	111 (2.1)	610 (11.5)
	Placebo	5286	No. (%)	33 (0.6)	14 (0.3)	45 (0.9)	117 (2.2)	585 (11.1)

Figure S1. PRISMA flow diagram.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Figure S2. Forest plot comparing SGLT2 inhibitors vs. placebo using fixed-effect for major adverse cardiovascular events (MACE), cardiovascular (CV) mortality, all-cause mortality, myocardial infarction, and stroke.

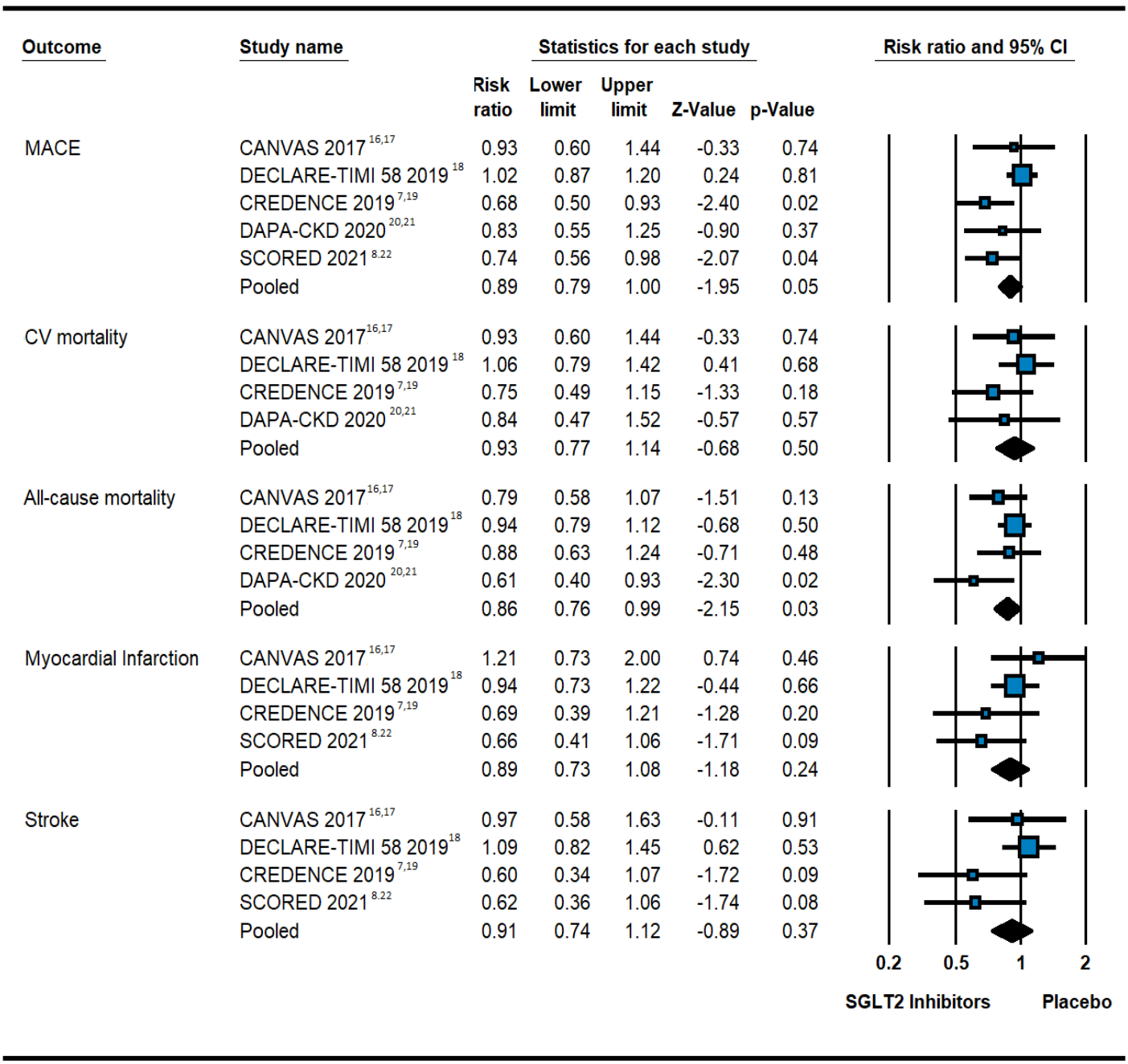


Figure S3. Forest plot comparing SGLT2 inhibitors vs placebo using fixed-effect for subgroup analyses.

Outcome	Group by Baseline Cohort	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
MACE	DM2 with MRF	CANVAS 2017 [16,17]	0.93	0.60	1.44	-0.33	0.74
		DECLARE-TIMI 58 2019 [18]	1.02	0.87	1.20	0.24	0.81
			1.01	0.86	1.18	0.11	0.91
	CKD & DM2	CREDENCE 2019 [7,19]	0.68	0.50	0.93	-2.40	0.02
		DAPA-CKD 2020 [20,21]	0.83	0.55	1.25	-0.90	0.37
		SCORED 2021 [8,22]	0.74	0.56	0.98	-2.07	0.04
			0.74	0.61	0.89	-3.21	0.00
CV mortality	DM2 with MRF	CANVAS 2017 [16,17]	0.93	0.60	1.44	-0.33	0.74
		DECLARE-TIMI 58 2019 [18]	1.06	0.79	1.42	0.41	0.68
			1.02	0.80	1.30	0.16	0.87
	CKD & DM2	CREDENCE 2019 [7,19]	0.75	0.49	1.15	-1.33	0.18
		DAPA-CKD 2020 [20,21]	0.84	0.47	1.52	-0.57	0.57
			0.78	0.55	1.10	-1.41	0.16
All-cause mortality	DM2 with MRF	CANVAS 2017 [16,17]	0.79	0.58	1.07	-1.51	0.13
		DECLARE-TIMI 58 2019 [18]	0.94	0.79	1.12	-0.68	0.50
			0.90	0.77	1.05	-1.34	0.18
	CKD & DM2	CREDENCE 2019 [7,19]	0.88	0.63	1.24	-0.71	0.48
		DAPA-CKD 2020 [20,21]	0.61	0.40	0.93	-2.30	0.02
			0.77	0.59	1.00	-1.99	0.05
Myocardial Infarction	DM2 with MRF	CANVAS 2017 [16,17]	1.21	0.73	2.00	0.74	0.46
		DECLARE-TIMI 58 2019 [18]	0.94	0.73	1.22	-0.44	0.66
			0.99	0.79	1.25	-0.06	0.95
	CKD & DM2	CREDENCE 2019 [7,19]	0.69	0.39	1.21	-1.28	0.20
		SCORED 2021 [8,22]	0.66	0.41	1.06	-1.71	0.09
			0.67	0.47	0.97	-2.14	0.03
Stroke	DM2 with MRF	CANVAS 2017 [16,17]	0.97	0.58	1.63	-0.11	0.91
		DECLARE-TIMI 58 2019 [18]	1.09	0.82	1.45	0.62	0.53
			1.06	0.83	1.37	0.49	0.62
	CKD & DM2	CREDENCE 2019 [7,19]	0.60	0.34	1.07	-1.72	0.09
		SCORED 2021 [8,22]	0.62	0.36	1.06	-1.74	0.08
			0.61	0.41	0.91	-2.44	0.01