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ORIGINAL RESEARCH ARTICLE

Sodium-Glucose Cotransporter-2 Inhibitors and Major Adverse Cardiovascular Outcomes: A SMART-C Collaborative Meta-Analysis

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BACKGROUND: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) consistently improve heart failure and kidney-related outcomes; however, effects on major adverse cardiovascular events (MACE) across different patient populations are less clear.

METHODS: This was a collaborative trial-level meta-analysis from the SGLT2i Meta-analysis Cardio-Renal Trialists Consortium, which includes all phase 3, placebo-controlled, outcomes trials of SGLT2i across 3 patient populations (patients with diabetes at high risk for atherosclerotic cardiovascular disease, heart failure [HF], or chronic kidney disease). The outcomes of interest were MACE (composite of cardiovascular death, myocardial infarction , or stroke), individual components of MACE (inclusive of fatal and nonfatal events), all-cause mortality, and death subtypes. Effect estimates for SGLT2i versus placebo were meta-analyzed across trials and examined across key subgroups (established atherosclerotic cardiovascular disease, previous myocardial infarction, diabetes, previous HF, albuminuria, chronic kidney disease stages, and risk groups).

RESULTS: A total of 78 607 patients across 11 trials were included: 42 568 (54.2%), 20 725 (26.4%), and 15 314 (19.5%) were included from trials of patients with diabetes at high risk for atherosclerotic cardiovascular disease, HF, or chronic kidney disease, respectively. SGLT2i reduced the rate of MACE by 9% (hazard ration [HR], 0.91 [95% CI, 0.87–0.96], $P<0.0001$) with a consistent effect across all 3 patient populations ($I^2=0\%$) and across all key subgroups. This effect was primarily driven by a reduction in cardiovascular death (HR, 0.86 [95% CI, 0.81–0.92], $P<0.0001$), with no significant effect for myocardial infarction in the overall population (HR, 0.95 [95% CI, 0.87–1.04], $P=0.29$), and no effect on stroke (HR, 0.99 [95% CI, 0.91–1.07], $P=0.77$). The benefit for cardiovascular death was driven primarily by reductions in HF death and sudden cardiac death (HR, 0.68 [95% CI, 0.46–1.02] and HR, 0.86 [95% CI, 0.78–0.95], respectively) and was generally consistent across subgroups, with the possible exception of being more apparent in those with albuminuria ($P_{interaction}=0.02$).

CONCLUSIONS: SGLT2i reduce the risk of MACE across a broad range of patients irrespective of atherosclerotic cardiovascular disease, diabetes, kidney function, or other major clinical characteristics at baseline. This effect is driven primarily by a reduction of cardiovascular death, particularly HF death and sudden cardiac death, without a significant effect on myocardial infarction in the overall population, and no effect on stroke. These data may help inform selection for SGLT2i therapies across the spectrum of cardiovascular-kidney-metabolic disease.

Key Words: diabetes mellitus ■ heart failure ■ meta-analysis ■ metabolic syndrome ■ renal insufficiency, chronic ■ sodium-glucose cotransporter-2 inhibitors

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Clinical Perspective

What Is New?

- Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce the risk of major adverse cardiovascular events (composite of cardiovascular death, myocardial infarction, or stroke) across a broad range of patient populations and key subgroups.
- The primary benefit of SGLT2i for major adverse cardiovascular events is driven by a reduction in cardiovascular death, without a clear effect on myocardial infarction or stroke.
- The treatment benefit of SGLT2i for cardiovascular death is mediated primarily by a reduction in the risk of heart failure death and sudden cardiac death.

What Are the Clinical Implications?

- These data suggest that SGLT2i have beneficial effects on major adverse cardiovascular events that are consistent irrespective of established atherosclerotic cardiovascular disease or diabetes status at baseline, and across a wide range of kidney function, including in the subset of patients with advanced stage chronic kidney disease.
- These data may collectively help to inform the selection of SGLT2i therapy across a broad range of patients encountered in clinical practice.

Nonstandard Abbreviations and Acronyms

ASCVD	atherosclerotic cardiovascular disease
eGFR	estimated glomerular filtration rate
KDIGO	Kidney Disease Improving Global Outcomes
MACE	major adverse cardiovascular events
MI	myocardial infarction
SGLT2i	sodium-glucose cotransporter-2 inhibitors
SMART-C	SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been rigorously examined in several large, randomized, placebo-controlled, clinical outcomes trials that have enrolled a broad range of patient populations, including those with type 2 diabetes and established atherosclerotic cardiovascular disease (ASCVD) or with multiple ASCVD risk factors,[1–4] heart failure across the ejection fraction spectrum,[5–9] and chronic kidney disease across a spectrum of severity.[10–13] Although initially developed as glucose-lowering agents for use in patients with diabetes, data from these trials have demonstrated that SGLT2i provide consistent reductions in adverse heart failure and kidney outcomes across the class, irrespective of diabetes status at baseline.[14,15] However, the effects of SGLT2i on major adverse cardiovascular events (MACE) have been more modest, with differences observed between trials. Prior meta-analyses have been relatively underpowered to definitively examine the effects of SGLT2i on individual components of MACE or on subtypes of these components.[16,17] Moreover, ongoing uncertainty exists regarding the effects of SGLT2i on MACE across several important subgroups of patients, including those without ASCVD or diabetes at baseline, and those with more advanced stages of chronic kidney disease.

Accordingly, leveraging data from all large-scale, placebo-controlled, outcomes trials of SGLT2i to date, we conducted a collaborative meta-analysis to examine the effect of SGLT2i on the risk of MACE and its individual components, overall and within clinically relevant subgroups of patients. We also assessed the effect of SGLT2i on death subtypes.

METHODS

Search Strategy and Selection Criteria

This study was a collaborative trial-level meta-analysis of SMART-C (SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists Consortium). In brief, SMART-C includes investigators of all large, placebo-controlled, phase 3 outcomes trials of SGLT2i, allowing for sharing of trial data across the consortium as previously described.[15] Each of the included trials was approved by the governing institutional review board or ethics committee at each site and written informed consent was obtained from all participants. We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Reviewers and Meta-analyses (PRISMA) reporting guideline. A systematic literature search of randomized, placebo-controlled cardiovascular outcomes trials of SGLT2i between January 1, 2012, and December 28, 2023, was conducted in PubMed (Figure S1). To restrict to studies of sufficient size and follow-up time to support a rigorous examination of the treatment effect of SGLT2i on cardiovascular events, eligible studies included phase 3 placebo-controlled, double-blind, randomized trials of SGLT2i therapy that enrolled at least 1000 participants in each arm, with median follow-up of at least 6 months. Studies with combination SGLT1/2i were excluded from the present analysis. All eligible studies were reviewed independently by 2 authors (S.M.P., Y.M.K.). Risk of bias assessments were also completed independently by 2 authors (S.M.P., Y.M.K.) using the Cochrane risk-of-bias assessment tool (Table S1). All conflicts were resolved by consensus discussion.

Outcomes

The primary outcome of interest for this meta-analysis was the 3-point MACE composite of cardiovascular death, myocardial infarction (MI), or stroke (inclusive of all types). The individual components, inclusive of fatal and nonfatal events for MI and stroke, were also assessed. All-cause mortality and subtypes

of death (fatal MI, fatal stroke, heart failure death, sudden cardiac death, other cardiovascular death, and non-cardiovascular death), were also examined. All outcomes were reported at the trial level per standard definitions as described within the trial-specific clinical events committee charters.[1–8,10–12] Each outcome was analyzed as time-to-event, and the trial-specific effect estimates used in the meta-analysis were intention-to-treat.

Data Analysis

The SMART-C investigators provided the requisite trial-level summary data (hazard ratio and corresponding 95% CI) for each included study in this collaborative meta-analysis. Owing to the possibility that treatment effects for some outcomes may vary across the studied populations, trial effect estimates were first meta-analyzed using a fixed-effects model within each of the 3 primary patient populations (type 2 diabetes at high risk for ASCVD, heart failure, and chronic kidney disease), and then pooled as random effects for calculation of the overall effect estimates. A sensitivity analysis was also performed using fixed effects to calculate overall estimates for the main effects. Heterogeneity of estimated treatment effects across the 3 primary trial populations was assessed using the Cochrane Q statistic and Higgins and Thompson I^2 and was considered to be low if I^2 was <25%, moderate if I^2 was 25 to <75%, and high if I^2 was ≥75%.

Effect modification was examined by random-effects meta regression models, including an intercept and the subgroup of interest as a moderator using the method of residual maximum likelihood and Hartung-Knapp adjustment. Predefined subgroups of interest in this study included established ASCVD or not (protocol-defined in some trials, derived post hoc in others; Table S2), diabetes status at baseline, previous MI, history of heart failure (specific predefined criteria in the heart failure trials, simple medical history question in the non–heart failure trials), chronic kidney disease (assessed dichotomously as estimated glomerular filtration rate [eGFR] <60 versus ≥60 mL·min^{-1}·1.73 m^{-2} and categorically by the Kidney Disease Improving Global Outcomes [KDIGO] stages),[18] albuminuria at baseline (<30 versus ≥30 mg/g), and KDIGO risk groups defined by a combination of eGFR and albuminuria.[18] Specifically for the ordered KDIGO stages and risk groups, a linear test-for-trend was used to examine increases or decreases in treatment effect across groups, whereas effect modification for the nonordinal subgroups was assessed using a Hartung-Knapp test as mentioned earlier. Data availability for subgroups across trials is presented in Table S3.

All reported *P* values were 2-sided, and values <0.05 were considered statistically significant. However, heterogeneity and *P* values were interpreted carefully in the context of multiple hypothesis testing. All analyses were performed using the Metafor package[19] and R Statistical Software (v4.0.4; R Core Team 2021).

RESULTS

Analysis Population Characteristics

A total of 78 607 patients were included across 11 randomized trials of SGLT2i versus placebo, with 42 568 (54.2%), 20 725 (26.4%), and 15 314 (19.5%) included from trials that focused on enrolling patients with diabetes at high risk for ASCVD, patients with established heart failure, or patients with chronic kidney disease, respectively (Table). The mean age ranged from 62 to 72 years across trials, with 27 702 (34.4%) patients of female sex and 58 571 (74.5%) of White race; older age and female sex tended to be more prevalent in the heart failure trial populations. Overall, 62 654 (79.7%) patients had diabetes, 28 352 (36.0%) had heart failure, and 29 237 (37.2%) had an eGFR <60 mL·min^{-1}·1.73 m^{-2} at baseline. A total of 46 305 (58.9%) patients had established ASCVD, and 22 414 (28.5%) had previous MI at baseline; both established ASCVD and previous MI were least prevalent among patients enrolled in the chronic kidney disease trials, with otherwise similar prevalence among the patients with diabetes at high risk for ASCVD and heart failure trial populations (Table).

Treatment Effect in Overall Population

The median follow-up ranged from 2.4 to 4.2 years, 1.3 to 2.2 years, and 2.0 to 2.6 years for the patients with diabetes at high risk for ASCVD, heart failure, and chronic kidney disease trials, respectively (Table). A total of 7976 (10.1%) patients experienced MACE, with 4148 (5.3%), 2819 (3.6%), and 2220 (2.8%) experiencing cardiovascular death, MI, and stroke, respectively, during follow-up. Stratifying by trial population, incidence rates of MACE and cardiovascular death were highest in the heart failure trials, whereas rates of MI and stroke were highest in the trials of patients with diabetes at high risk for ASCVD (Figures 1 and 2).

SGLT2i reduced the rate of MACE by 9% overall (hazard ratio [HR], 0.91 [95% CI, 0.87–0.96], *P*<0.0001), with a consistent effect observed across all 3 trial populations ($I^2 = 0$; Figure 1). In terms of the individual components, SGLT2i had the clearest effect on cardiovascular death (HR, 0.86 [95% CI, 0.81–0.92], *P*<0.0001; Figure 2). There was no clear effect on MI in the overall population (HR, 0.95 [95% CI, 0.87–1.04], *P*=0.29), and no effect on stroke (HR, 0.99 [95% CI, 0.91–1.07], *P*=0.77; Figure 2).

The distribution of cardiovascular death subtypes in the placebo arm across trial types is shown in Figure 3. In the trials of patients with diabetes at high risk for ASCVD, sudden cardiac death accounted for about half of cardiovascular deaths, with fatal MI/stroke accounting for ≈25% and heart failure deaths just >10%. In the heart failure trials, sudden cardiac deaths and heart failure deaths together accounted for >70% of cardiovascular deaths, with fatal MI/stroke accounting for ≈10%. In the chronic kidney disease trials, sudden cardiac deaths accounted for ≈40% of the cardiovascular deaths, with heart failure deaths and fatal MI/stroke each accounting for 20% to 25% of cardiovascular deaths.

Table. Baseline Characteristics Across SGLT2 Inhibitor Trials

Characteristics by trial	Diabetes at high risk for ASCVD				Heart failure				Chronic kidney disease		
	EMPA-REG Outcome	CANVAS Program	DECLARE-TIMI 58	VERTIS CV	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	DELIVER	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Participants	7020	10142	17160	8246	4744	3730	5988	6263	4401	4304	6609
Median follow-up, y	3.1	2.4	4.2	3.0	1.5	1.3	2.2	2.3	2.6	2.4	2.0
Age, y	63.1±8.7	63.3±8.3	63.9±6.8	64.4±8.1	66.3±10.9	66.9±11.0	71.9±9.5	71.7±9.6	63.0±9.2	61.8±12.1	63.8±13.9
Female sex	2004 (28.5)	3633 (35.8)	6422 (37.4)	2477 (30.0)	1109 (23.4)	893 (23.9)	2676 (44.7)	2747 (43.9)	1494 (33.9)	1425 (33.1)	2192 (33.2)
Race, n (%)											
White	5081 (72.4)	7944 (78.3)	13653 (79.6)	7240 (87.8)	3333 (70.3)	2629 (70.4)	4542 (75.9)	4439 (70.9)	2931 (66.6)	2920 (67.8)	3859 (58.4)
Asian	1517 (21.6)	1284 (12.7)	2303 (13.4)	498 (6.0)	1116 (23.5)	672 (18.0)	824 (13.8)	1274 (20.3)	877 (19.9)	1467 (34.1)	2393 (36.2)
Black	357 (5.1)	336 (3.3)	603 (3.5)	235 (2.8)	226 (4.7)	257 (6.9)	258 (4.3)	159 (2.5)	224 (5.1)	191 (4.4)	262 (4.0)
Other or missing*	65 (0.9)	578 (5.7)	601 (3.5)	273 (3.3)	69 (1.5)	172 (4.6)	364 (6.1)	391 (6.2)	369 (8.4)	356 (8.2)	95 (1.4)
Medical history											
Established ASCVD, n (%)	7020 (100.0)	6656 (65.6)	6974 (40.6)	8246 (100.0)	3042 (64.1)	2406 (64.5)	3320 (55.4)	3598 (57.4)	2220 (50.4)	1329 (30.9)	1494 (22.6)
Diabetes, n (%)	7020 (100.0)	10142 (100.0)	17160 (100.0)	8246 (100.0)	2139 (45.1)	1856 (49.8)	2938 (49.1)	2806 (44.8)	4401 (100.0)	2906 (67.5)	3040 (46.0)
Previous MI, n (%)	3273 (46.6)	2956 (29.1)	3584 (20.9)	3931 (47.7)	2092 (44.1)	1623 (43.5)	1780 (29.7)	1639 (26.2)	442 (10.0)	392 (9.1)	702 (10.6)
Previous HF, n (%)	706 (10.1)	1461 (14.4)	1724 (10.0)	1958 (23.7)	4744 (100.0)	3730 (100.0)	5988 (100.0)	6263 (100.0)	652 (15.0)	468 (11.0)	658 (10.0)
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	74±21	77±21	85±16	76±21	66±19	62±22	61±20	61±19	56±18	43±12	37±14
eGFR groups, n (%)											
>90	1538 (21.9)	2476 (24.4)	8162 (47.6)	2048 (24.8)	621 (13.1)	449 (12.0)	468 (7.8)	503 (8.0)	211 (4.8)	0 (0.0)	46 (0.7)
60 to <90	3661 (52.2)	5625 (55.5)	7732 (45.1)	4390 (53.2)	2195 (46.3)	1480 (39.7)	2530 (42.3)	2689 (42.9)	1558 (35.4)	454 (10.5)	465 (7.0)
45 to <60	1249 (17.8)	1485 (14.6)	1076 (6.3)	1319 (16.0)	1207 (25.4)	900 (24.1)	1565 (26.1)	1657 (26.5)	1266 (28.8)	1328 (30.9)	888 (13.4)
30 to <45	543 (7.7)	526 (5.2)	169 (1.0)	457 (5.5)	695 (14.7)	694 (18.6)	1114 (18.6)	1221 (19.5)	1191 (27.1)	1898 (44.1)	2928 (44.3)
<30	27 (0.4)	28 (0.3)	20 (0.1)	0 (0.0)	24 (0.5)	205 (5.5)	309 (5.2)	192 (3.1)	174 (4.0)	624 (14.5)	2282 (34.5)
UACR											
UACR, mg/g	17.7 (7.1–72.5)	12.3 (6.7–42.1)	13.1 (6.0–43.6)	19.0 (6.0–68.0)	NA	22.1 (8.0–81.3)	21.0 (8.0–71.6)	NA	927 (463–1833)	949 (477–1885)	329 (49–1069)
UACR groups, n (%)											
<30	4171 (60.0)	7007 (69.8)	11644 (69.1)	4783 (58.0)	NA	2078 (56.0)	3474 (58.0)	NA	31 (0.7)	0 (0.0)	1328 (20.1)
30 to <300	2013 (29.0)	2266 (22.6)	4030 (23.9)	2492 (30.2)	NA	1236 (33.3)	1860 (31.1)	NA	495 (11.2)	444 (10.3)	1864 (28.2)
≥300	769 (11.0)	760 (7.6)	1169 (6.9)	755 (9.2)	NA	396 (10.7)	629 (10.5)	NA	3875 (88.0)	3859 (89.7)	3417 (51.7)

All values represent n (%) for categorical variables and mean±SD for continuous variables with the exception of UACR, which is reported as median (25th–75th percentile). ASCVD indicates atherosclerotic cardiovascular disease; CANVAS Program, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; EMPA-REG Outcome; 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; HF, heart failure; MI, myocardial infarction; NA, not available; UACR, urine albumin-to-creatinine ratio; and VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

*Other indicates a race category not listed or combination races.

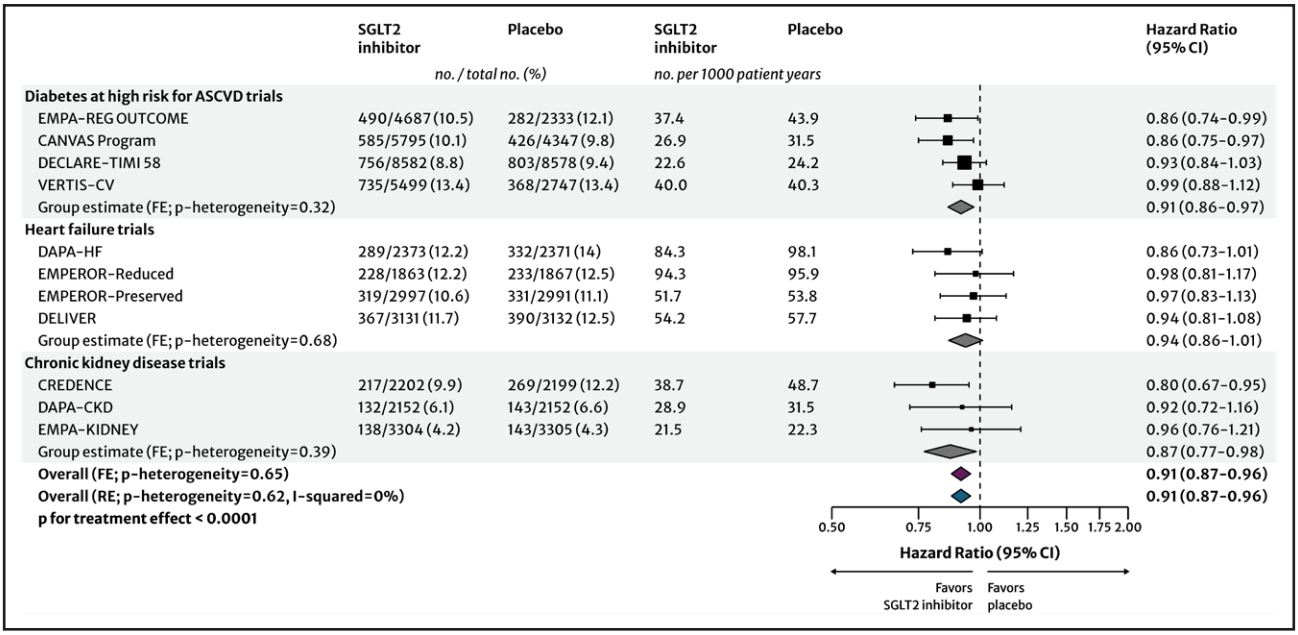

Figure 1. Overall effect of sodium-glucose cotransporter-2 inhibition on the major adverse cardiovascular events composite. The forest plot depicts the treatment effect of SGLT2 inhibitors on major adverse cardiovascular events composite at the level of the individual trials, by trial type, and in the overall study population. ASCVD indicates atherosclerotic cardiovascular disease; CANVAS Program, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; EMPA-REG Outcome; 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; FE, ,fixed effects; RE, random effects; SGLT2, sodium-glucose cotransporter-2; and VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

The reduction in cardiovascular death was driven primarily by a reduction in heart failure death (HR, 0.68 [95% CI, 0.46–1.02]) and sudden cardiac death (HR, 0.86 [95% CI, 0.78–0.95]), with no effect on fatal MI or fatal stroke (Figure 4). SGLT2i also reduced all-cause mortality (HR, 0.88 [95% CI, 0.82–0.94], $P<0.001$; Figure S2), with directional consistency for non-cardiovascular death (HR, 0.91 [95% CI, 0.79–1.05]; Figure S3), and with moderate heterogeneity for both across trial types (I^2= 46% and 65%, respectively). The numerically largest effect on all-cause and non-cardiovascular mortality was observed for patients enrolled in the chronic kidney disease trials (HR, 0.80 [95% CI, 0.71–0.91] and HR, 0.81 [95% CI, 0.66–0.98], respectively).

Treatment Effect Across Subgroups

The treatment effect of SGLT2i on MACE and cardiovascular death by subgroups is presented in Figure 5A and 5B. Incidence rates for MACE were higher among patients with established ASCVD across all 3 trial types (Figure S4). SGLT2i consistently reduced the risk of MACE in those with versus without established ASCVD at baseline (HR, 0.92 [95% CI, 0.88–0.97] versus 0.90 [95% CI, 0.82–0.99], $P_{interaction}$=0.60; Figure 5A; Figures S4 and S5). SGLT2i also reduced cardiovascular death irrespective of established ASCVD at baseline (HR, 0.86 [95% CI, 0.80–0.93] versus 0.86 [0.76–0.97], $P_{interaction}$=0.94; Figure 5B; Figure S5). For MI, the effect estimates were similar in those with or without established ASCVD (HR, 0.96 [95% CI, 0.85–1.07] versus 0.98 [95% CI, 0.82–1.18], respectively; $P_{interaction}$=0.72; Figure S5). Of note, in the dedicated trials of patients with diabetes at high risk for ASCVD (which had the most rigorous definitions for established ASCVD), in the subset with established ASCVD, the HR for the effect of SGLT2i on MI was 0.91 (95% CI, 0.82–0.998, P=0.046; Figure S5). These results were consistent when stratifying by history of MI (Figure 5; Figure S6).

The effects of SGLT2i on MACE and cardiovascular death were consistent when further stratified by diabetes status, previous heart failure, and eGFR at baseline assessed dichotomously (<60 versus ≥60 mL·min^{-1}·1.73 m^{-2}; Figure 5; Figures S7 through S9). Moreover, the effects of SGLT2i on MACE and cardiovascular death were consistent across a wide range of kidney function, including in participants with eGFR <30 mL·min^{-1}·1.73 m^{-2} (HR, 0.83 [95% CI, 0.67–1.03]

ORIGINAL RESEARCH ARTICLE

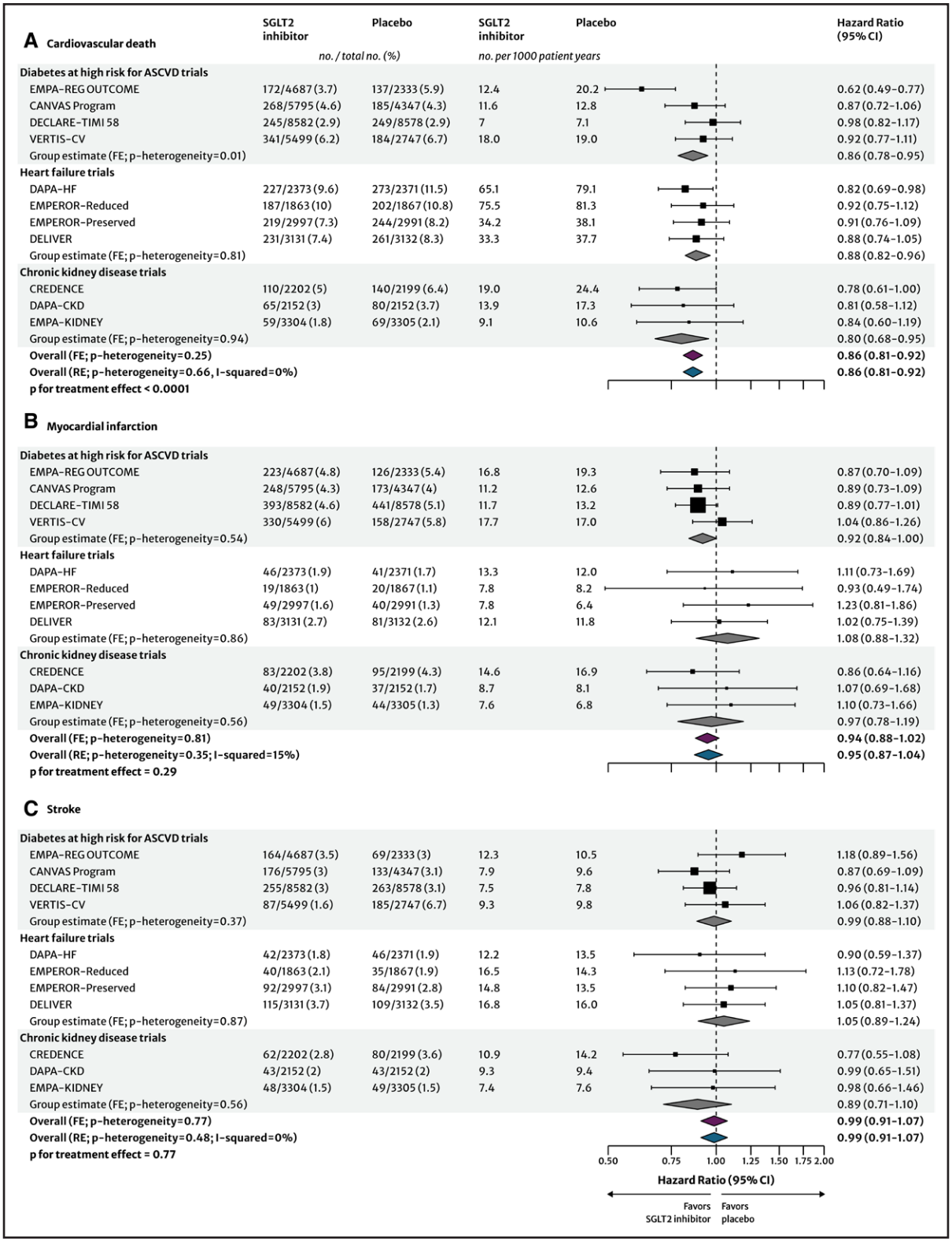

Figure 2. Overall effect of sodium-glucose cotransporter-2 inhibition on individual components.
These forest plots depict the treatment effect of SGLT2 inhibitors on the individual components of the major adverse cardiovascular events composite, at the level of the individual trials, by trial type, and in the overall study population. **A**, The treatment effect on cardiovascular death. **B**, The effect on myocardial infarction. **C**, The effect on stroke. ASCVD indicates atherosclerotic cardiovascular disease; CANVAS Program, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure), DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58; DELIVER, Dapagliflozin Evaluation to (*Continued*)

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Figure 2 Continued. Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; EMPA-REG Outcome; 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Preserved, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; FE – fixed effects; RE, random effects; SGLT2, sodium-glucose cotransporter-2; and VERTIS CV, Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial.

and 0.83 [95% CI, 0.63–1.09], respectively; Figures S10 and S11). Stratifying by albuminuria, the effect of SGLT2i on MACE appeared consistent ($P_{interaction}$=0.31), whereas for cardiovascular death, there was some evidence that the benefit appeared to be primarily among those with at least some (ie, ≥30 mg/g) albuminuria ($P_{interaction}$=0.02; Figure 5; Figures S12 and S13). Assessed across KDIGO risk groups, the benefit for MACE and cardiovascular death was consistent across groups (P_{trend}=0.35 and 0.31, respectively; Figures S14 and S15).

DISCUSSION

In this collaborative meta-analysis of ≈78 000 patients across 11 randomized trials, we examined the treatment effect of SGLT2i on MACE, the individual MACE components, and subtypes of death. Moreover, by leveraging the large sample size and number of events across a broad range of patient populations afforded by this dataset, we further explored the heterogeneity of treatment effect across several clinically relevant subgroups. Overall, we observed a 9% reduction in the rate of MACE, an effect that was generally consistent across patient populations, including those with or without established ASCVD, diabetes, or heart failure at baseline, and across a wide range of kidney function. With regard to the latter, it is notable that there was no attenuation of the benefit of SGLT2i on MACE even in individuals with an eGFR <30 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$, a subgroup in whom there was initial doubt regarding the efficacy of this class of medications due to the lesser effect on urinary glucose excretion and thus glycemic control.[20] These data collectively provide a comprehensive overview of the anticipated treatment effects of SGLT2i across a wide range of patient populations and may help inform selection of SGLT2i therapies in patients encountered in clinical practice.

Treatment Effect on Individual MACE Components

In terms of the individual MACE components, the benefit of SGLT2i was driven primarily by a reduction in cardiovascular death, specifically heart failure death and sudden cardiac death. There was a nonsignificant 5% lower rate of MI in the overall study populations, suggesting that any benefit of SGLT2i on MI is likely to be small. There was no effect of SGLT2i on the risk of stroke. In addition to helping refine the expected benefit of SGLT2i, these findings also speak to some limitations of a traditional 3-point MACE composite as a clinical trial end point, which is commonly used with the intent of capturing ASCVD-related events. Our findings highlight the heterogeneity in event type that may be captured by such a composite, which becomes particularly relevant when applied across different patient populations where the risk for non–ASCVD-related cardiovascular deaths may be greater (eg, heart failure–related death versus coronary heart disease death). With respect to clinical implications, these data speak to the specific types of MACE events that may be reduced with SGLT2i and may be useful to clinicians to guide decision-making regarding the selection of glucose-lowering therapies in patients with diabetes.

Treatment Effect on Cardiovascular Death Subtypes

With respect to subtypes of death, the benefit on cardiovascular death appeared driven largely by heart failure and sudden cardiac deaths. It is notable that sudden death is not synonymous with arrhythmia and is often a default adjudication when an unwitnessed out-of-hospital death occurs.[21] Such deaths may encompass both heart failure–related death (including arrhythmia) or fatal ASCVD-related deaths (including fatal MI) that occurred outside of a medical setting. As such, these findings raise the possibility that the salutary effects of SGLT2i on cardiovascular death, and thus MACE, could be driven primarily by modification of heart failure–related events. The benefit for cardiovascular death appeared to be primarily in those with some degree of albuminuria at baseline, who had approximately double the event rate compared with those without albuminuria. It remains unclear whether this is driven by the fact that albuminuria is an independent risk predictor for adverse outcomes or alternatively indicates that the mechanism of benefit may be related to the nephroprotective effects of SGLT2i. Moreover, given the large number of subgroups tested, it is also conceivable that this finding may represent a play of chance. We further found a consistent reduction in all-cause mortality with directional consistency also for noncardiovascular death. However, the mechanism of benefit of SGLT2i on noncardiovascular death remains unclear. Although other potential salutary effects of SGLT2i on outcomes beyond conventional cardiovascular and kidney end points have been reported,[22,23] it is important to note that some of the SGLT2i trials, namely all of the

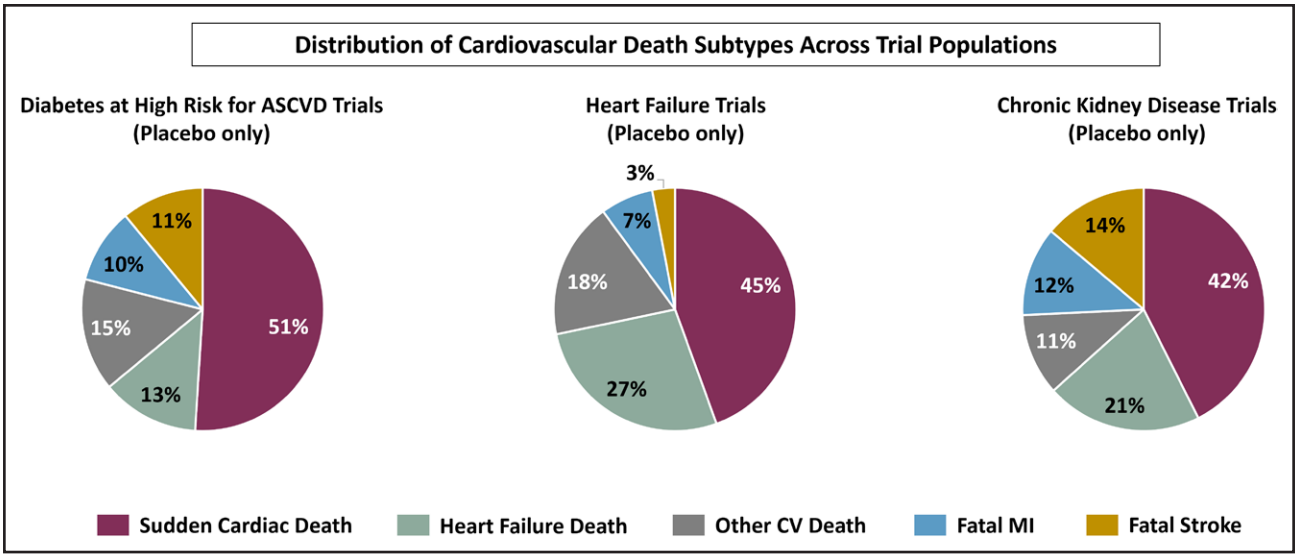

Figure 3. Cardiovascular death subtypes across trial populations (placebo arms only).
The pie charts show the distribution of subtypes of cardiovascular death in the placebo arms of each trial grouped by trial type. ASCVD indicates atherosclerotic cardiovascular disease; CV, cardiovascular; and MI, myocardial infarction.

chronic kidney disease trials, were prematurely terminated, which may result in an overestimate of the treatment effect in this regard.

Potential Differences by Patient Populations and Mechanisms of Benefit

Although the effect of SGLT2i on MI was not significant in the overall population, these data raise the possibility that there could be a potential benefit among patients clinically felt to be at a high risk of future ASCVD events, particularly the subset with definitively established ASCVD at baseline. These observations may be attributable to differences in the baseline risk of the patient populations or perhaps reflect the heterogeneity of the established ASCVD definition across trial types. For example, in the dedicated trials enrolling patients with diabetes at high risk for ASCVD, rigorous definitions for established ASCVD were prospectively applied to ensure selection of a secondary prevention population as necessary to maintain the targeted event rate. In contrast, in the heart failure or chronic kidney disease trials, a retrospective definition was applied to delineate the established ASCVD group, where patients with any indication of coronary, peripheral, or cerebrovascular disease in the medical history (eg, incidentally noted coronary calcification) may have been included. In the case of the latter, these patients would be expected to be lower risk than a traditional secondary prevention population (eg, those with a previous MI), and thus could be expected to derive lower absolute benefit from such therapies. To that end, there was a 9% reduction in the rate of MI in patients with established ASCVD from the dedicated trials that required a rigorous prespecified definition for this group, and this effect was similar in the subset with previous MI from these trials.

The mechanistic underpinnings underlying the cardiovascular benefits of SGLT2i remain unclear. For MI specifically, it is uncertain whether a treatment benefit would be mediated primarily by direct atheroprotective effects, with a resultant reduction in the risk of acute plaque rupture or erosion (ie, type 1 MI), or alternatively, by a reduction in the risk of heart failure or progression in kidney disease from various pleiotropic effects that collectively may have beneficial effects for type 2 MI. We also observed no effect on stroke, which, although acknowledged as a heterogeneous entity reflective of a multitude of possible causes (both ischemic and hemorrhagic, with the former inclusive of atherosclerosis-related, cardioembolic, and small vessel/lacunar subtypes), typically has been shown to benefit from other ASCVD-modifying therapies.[24–27] In addition, in DAPA-MI (Dapagliflozin Effects on Cardiometabolic Outcomes in Patients With an Acute Heart Attack), which enrolled patients presenting with acute MI but excluded those with preexisting heart failure or diabetes (ie, excluding a subset potentially at higher risk for recurrent type 2 MI), there was no effect on the risk of MI.[28]

Contextualizing Findings With Previous Data

Results from previous meta-analyses have demonstrated a robust reduction in the risk of heart failure and kidney outcomes with SGLT2i, with consistency of treatment effect across a multitude of subgroups.[15,29] However, the effects of SGLT2i on MACE have remained less certain. Among the trials specifically designed to enroll patients

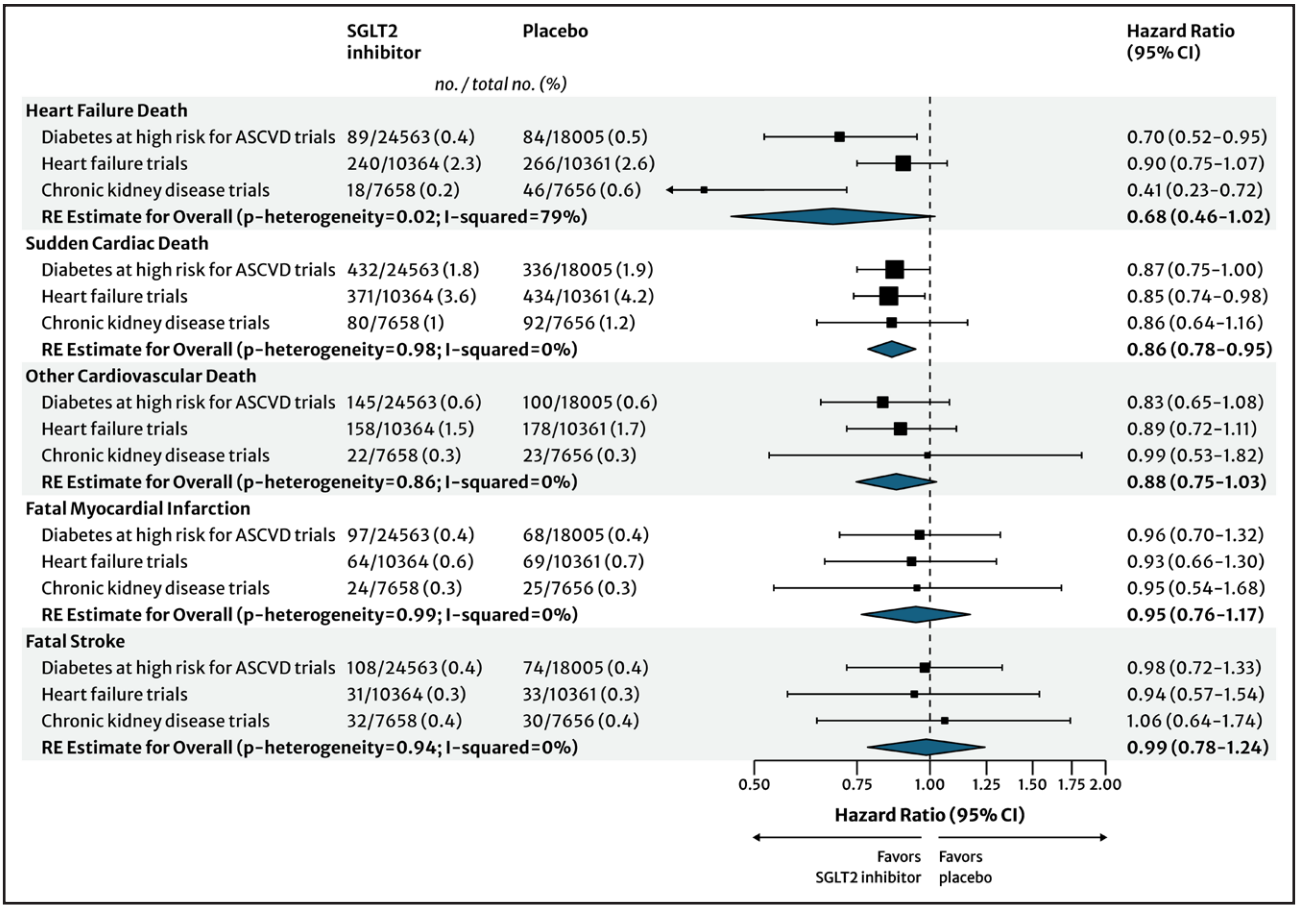

Figure 4. Overall effect of sodium-glucose cotransporter-2 inhibition on subtypes of cardiovascular death.
These forest plots depict the treatment effect of SGLT2 inhibitors on subtypes of cardiovascular death. ASCVD indicates atherosclerotic cardiovascular disease; RE, random effects; and SGLT2, sodium-glucose cotransporter-2.

with diabetes at high risk for ASCVD, a within-trial effect on MACE was seen in 2 of the trials,[1,2] but not in 2 other trials.[3,4] Pooling data from these 4 trials, previous meta-analyses demonstrated a reduction in MACE with SGLT2i versus placebo restricted to the subset of patients with established ASCVD, with an otherwise neutral effect in the subgroup without ASCVD.[16,17] Our study expands on these previous findings, leveraging the totality of randomized data for SGLT2i across a broader range of patient populations with the more nuanced findings noted above.

Limitations

Several limitations of our study should be acknowledged. Our results should be interpreted in the context of the differences in eligibility criteria, follow-up duration, and subgroup definitions (in particular, the definition of established ASCVD) across studies. With only 1 or 2 trials of each drug in each disease state, the data do not permit rigorous comparisons of different members of the class. Because all included patients are reflective of those enrolled on the basis of diabetes with high risk for ASCVD, heart failure, or chronic kidney disease at baseline, the absence of 1 characteristic (eg, no diabetes) may select for another (eg, either heart failure or chronic kidney disease), and thus, these findings may not be generalizable to all patients (eg, a patient without diabetes, heart failure, and chronic kidney disease) encountered in clinical practice. Observations regarding possible heterogeneity of treatment effect in subgroups should be interpreted as hypothesis-generating given the multiple outcomes and subgroups tested.

Conclusions

SGLT2i consistently reduce the risk of MACE across a broad range of patient populations irrespective of ASCVD, diabetes, or kidney function at baseline. This benefit appears to be driven primarily by a reduction in cardiovascular death, particularly heart failure death and sudden cardiac death, without a significant effect on MI in the overall population and no effect on stroke. These data may help inform the selection of SGLT2i therapies across the spectrum of cardiovascular-kidney-metabolic disease.

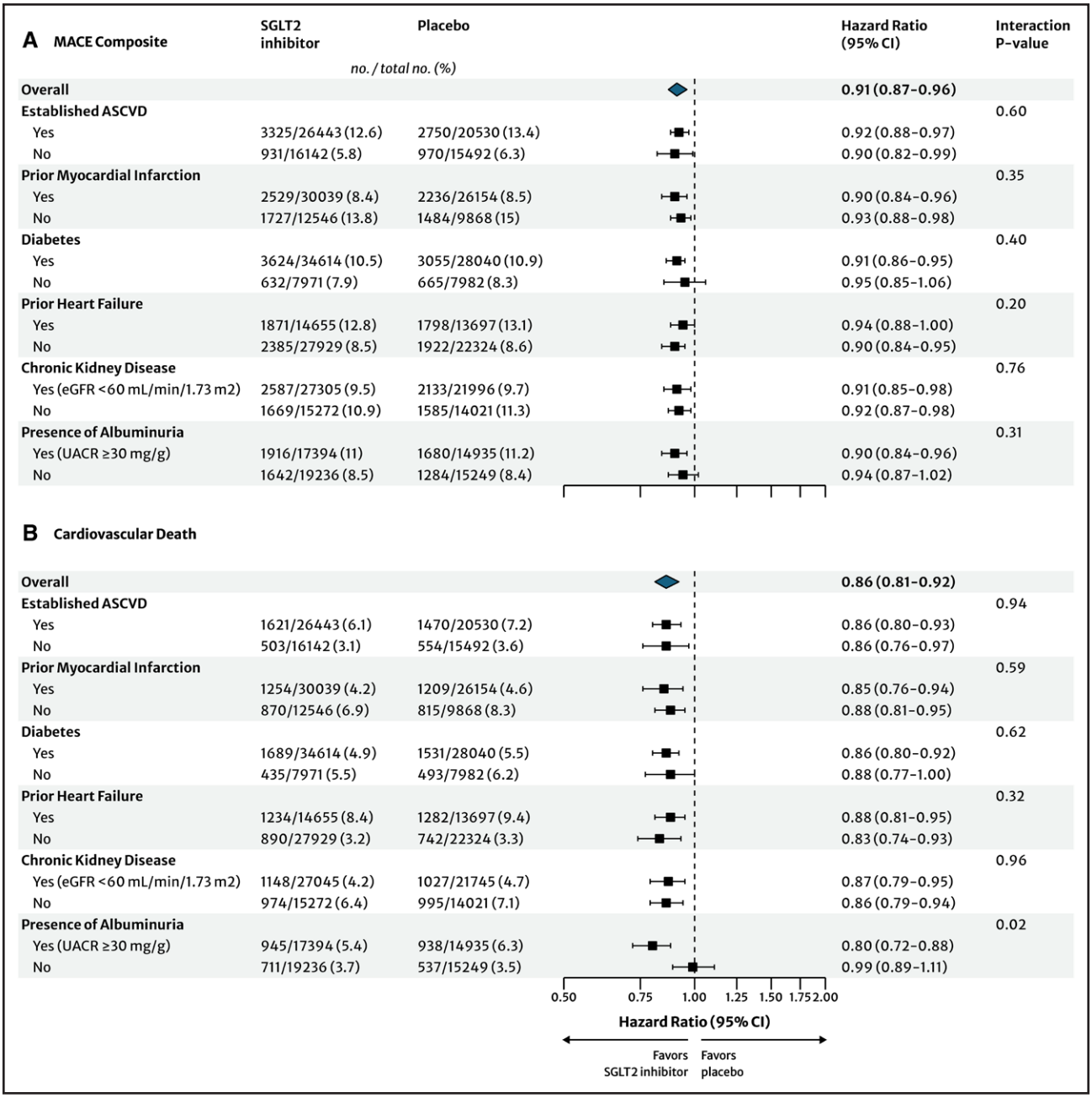

Figure 5. Overall effect of sodium-glucose cotransporter-2 inhibition by subgroups for the major adverse cardiovascular events composite and cardiovascular death.

A, The treatment effect of SGLT2 inhibitors on the MACE composite across subgroups. **B**, The treatment effect on cardiovascular death across subgroups. ASCVD indicates atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; SGLT2i, sodium-glucose cotransporter-2; and UACR, urine albumin-to-creatinine ratio.

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Supplemental Material

Tables S1–S3

Figures S1–S15

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