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ORIGINAL RESEARCH ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in People With Type 2 Diabetes, According to SGLT2i Use: Prespecified Analyses of the SOUL Randomized Trial

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BACKGROUND: Both GLP-1 (glucagon-like peptide-1) receptor agonists and SGLT2 (sodium-glucose cotransporter-2) inhibitors (SGLT2i) improve cardiovascular outcomes in people with type 2 diabetes and cardiovascular or chronic kidney disease. However, there are limited data about the effect of combining these agents on cardiovascular and safety outcomes.

METHODS: The SOUL trial (Semaglutide Cardiovascular Outcomes Trial; NCT03914326) randomized 9650 participants with type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease to oral semaglutide or placebo. As prespecified, participants were analyzed according to baseline use of SGLT2i (yes, n=2596; no, n=7054), and subsequently for any use of SGLT2i during the trial (yes, n=4718; no, n=4932). The primary outcome was time to first major adverse cardiovascular event, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Safety was evaluated by comparing the incidence of serious adverse events.

RESULTS: Over a mean follow-up of 47.5±10.9 months, the risk of the primary outcome in the overall trial population was 14% lower for oral semaglutide versus placebo (hazard ratio, 0.86; 95% CI, 0.77–0.96). In those taking SGLT2i at baseline, there were 143 of 1296 (semaglutide) versus 158 of 1300 (placebo) primary outcome events (hazard ratio, 0.89; 95% CI, 0.71–1.11); and 436 of 3529 versus 510 of 3525, respectively, in participants not taking SGLT2i at baseline (hazard ratio, 0.84; 95% CI, 0.74–0.95; *P*-interaction, 0.66). An analysis of major adverse cardiovascular events by any in-trial SGLT2i use versus no use also showed no evidence of heterogeneity in the effects of oral semaglutide. The adverse event profiles of oral semaglutide with or without concomitant SGLT2i were similar.

CONCLUSIONS: Oral semaglutide reduced major adverse cardiovascular event outcomes independently of concomitant SGLT2i treatment, and this combination appeared to be safe.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03914326.

Key Words: cardiovascular diseases ■ cardiovascular system ■ diabetes mellitus, type 2 ■ glucagon-like peptide-1 receptor agonists ■ renal insufficiency, chronic ■ semaglutide ■ sodium-glucose transporter 2 inhibitors

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Clinical Perspective

What Is New?

- Several studies have independently demonstrated cardiovascular benefit with GLP-1 (glucagon-like peptide-1) receptor agonists or SGLT2 (sodium-glucose cotransporter-2) inhibitors (SGLT2i) in patients with type 2 diabetes at high cardiovascular risk; however, evidence supporting combination treatment is lacking.
- The SOUL trial included 9650 participants (randomized 1:1 to oral semaglutide or placebo), of whom 2596 (26.9%) were using SGLT2i at baseline and 4718 (48.9%) had any SGLT2i use during the trial.
- This prespecified analysis of the largest data set of combined use of GLP-1 receptor agonists and SGLT2i in a cardiovascular outcomes trial to date explored the effects of oral semaglutide use on top of SGLT2i on the trial primary outcome of major adverse cardiovascular events and safety.

What Are the Clinical Implications?

- The findings from this prespecified analysis of the SOUL trial suggest that oral semaglutide reduces major adverse cardiovascular event outcomes in type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease consistently in participants with and without concomitant SGLT2i use, and the combination appears to be safe.
- These findings therefore provide clinicians further confidence to combine GLP-1 receptor agonists and SGLT2i with the aim of reducing cardiovascular events in people with type 2 diabetes at high cardiovascular risk and underscore current guideline recommendations for the additive use of both agents in people with type 2 diabetes and atherosclerotic cardiovascular disease.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
CKD	chronic kidney disease
CRP	C-reactive protein
CVOT	cardiovascular outcomes trial
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	glycated hemoglobin
HR	hazard ratio
LDL	low-density lipoprotein
MACE	major adverse cardiovascular event
SGLT2i	sodium-glucose cotransporter-2 inhibitor
SOUL	Semaglutide Cardiovascular Outcomes Trial
T2D	type 2 diabetes

Individuals with type 2 diabetes (T2D) have an increased risk of developing cardiovascular and chronic kidney disease (CKD), and the presence of these comorbidities has a major impact on prognosis.

Results from several outcome trials have independently demonstrated benefits on cardiovascular outcomes of GLP-1 (glucagon-like peptide-1) receptor agonists (RA)[1–6] and of sodium-glucose cotransporter-2 inhibitors (SGLT2i)[7–11] in people with T2D and high cardiovascular risk and/or CKD. Based on these trial results, as well as on data from meta-analyses for both drug classes,[12,13] current guidelines recommend treatment with GLP-1 RA and SGLT2i in people with T2D and atherosclerotic cardiovascular disease (ASCVD) to reduce cardiovascular risk, independent of glucose control and concomitant glucose-lowering medications.[14,15] Although both classes are recommended in guidelines, there is little evidence about the efficacy of combination therapy with both drug classes. The trials that examined GLP-1 RA and SGLT2i were conducted concurrently, and therefore relatively few participants in each of the trials were receiving the other class of drug. As the biological mechanisms contributing to the beneficial effects of both drug classes are likely to be different, they are potentially complementary and therefore additive. Several short-term trials investigating the combination of GLP-1 RA and SGLT2i have shown further improvement of metabolic parameters[16] versus their monotherapies, but as yet, no randomized study has been published to evaluate cardiovascular outcomes of combination treatment. Data on the cardiovascular effects of the combination therapy with GLP-1 RA and SGLT2i are therefore only available from subgroup analyses of cardiovascular outcomes trials (CVOTs) involving GLP-1 RA, such as AMPLITUDE-O, HARMONY OUTCOMES, and FLOW, all suggesting consistent benefits of GLP-1 RA in participants with and without baseline SGLT2i use.[17–19] A recent meta-analysis including these 3 trials confirmed the consistent cardiovascular benefits of GLP-1 RAs, regardless of SGLT2i use, but overall, only 10.2% of all participants were receiving an SGLT2 inhibitor at baseline.[20]

In SOUL, a randomized, placebo-controlled trial examining the effects of the oral GLP-1 RA semaglutide on the risk of cardiovascular events in 9650 individuals with T2D and established ASCVD and/or CKD, use of SGLT2i at baseline was 26.9%, providing the largest data set from a single CVOT on the combined use of GLP-1 RA and SGLT2i.[21,22] We hypothesized that the benefit of oral semaglutide on cardiovascular outcomes in SOUL is independent of SGLT2i use and that the combination of both agents is safe. Therefore, in prespecified analyses, we examined the effect of oral

semaglutide on cardiovascular outcomes, stratified by baseline use of SGLT2i, and in addition analyzed the impact of overall SGLT2i therapy during the trial, including incident use after randomization.

METHODS

De-identified participant-level data will be made available on a specialized data platform after completion of the research and approval of the product and product use in both the European Union and the United States. The clinical study report will be made available after completion of the research and approval of the product and product use in both the European Union and the United States. Data will be shared with bona fide researchers submitting a research proposal requesting access to data for research use, as approved by the institutional review board. The access request proposal form and full details of access criteria can be found at http://www.novonordisk-trials.com.

Study Design and Participants

The SOUL trial was a double-blind, randomized, placebo-controlled, event-driven phase 3b trial in 33 countries (444 sites) evaluating once-daily oral semaglutide (up to 14 mg) given as an adjunct to standard-of-care treatment in participants with T2D and established ASCVD and/or CKD. The primary efficacy outcome was time to first occurrence of major adverse cardiovascular events (MACE). The protocol for SOUL was approved by the institutional review board and ethics committee at each participating center. All participants provided written informed consent before any trial-specific activity. Study design, participant baseline characteristics, and overall study outcomes have been published previously.[21,22] The study is registered with http://www.clinicaltrials.gov (Unique identifier: NCT03914326).

Men or women ≥50 years of age with T2D (American Diabetes Association criteria)[23] and glycated hemoglobin (HbA1c) of 6.5% to 10.0% (47–86 mmol/mol) were eligible and were included if they had established ASCVD (≥1 coronary artery disease, cerebrovascular disease, or symptomatic peripheral arterial disease) and/or CKD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. Exclusion criteria included myocardial infarction; stroke; hospitalization for unstable angina or transient ischemic attack within 60 days before screening; planned coronary, carotid, or peripheral artery revascularization; New York Heart Association class IV heart failure; end-stage kidney disease requiring dialysis; and GLP-1 RA treatment within 30 days before screening.

The present prespecified analyses investigated the associations between SGLT2i use at baseline and any SGLT2i use during the trial on primary and secondary efficacy outcomes in participants randomized to receive oral semaglutide versus placebo.

Randomization and Masking

Participants were randomly assigned (1:1) to receive oral semaglutide or placebo using a central interactive web response system on the same day as screening or up to 3 weeks afterward.[21] Participants received 3 mg of oral semaglutide or matching placebo once daily for 4 weeks, followed by 7 mg once daily for 4 weeks and then 14 mg once daily until the end of the trial. Masking was achieved through use of visually identical oral semaglutide and placebo tablets, in identical packaging.[21] Investigators were permitted to extend these dose escalation intervals, reduce the dose of the study product, or pause treatment if tolerability issues occurred. Investigators were instructed to manage hyperglycemia and cardiovascular risk factors according to local guidelines with the limitation that addition of a GLP-1 RA was not allowed.

Outcomes

The primary outcome of the SOUL trial was time from randomization to first occurrence of MACE (a composite outcome comprising time to cardiovascular death, time to nonfatal myocardial infarction, or time to nonfatal stroke) in participants receiving oral semaglutide or placebo. Secondary outcomes included time to all-cause death, single components of the combined primary outcome, and changes in HbA1c, blood pressure, body weight, LDL (low-density lipoprotein) cholesterol, estimated glomerular filtration rate, and high-sensitivity CRP (C-reactive protein). Cardiovascular events, as well as selected adverse events, were adjudicated by a central adjudication committee blinded to treatment assignment. Outcomes were also analyzed to explore the associations between use of SGLT2i at any time during the study (including use at baseline and initiation at any time during the study) and efficacy outcomes of interest. Safety is reported as the incidence of serious adverse events among participants receiving oral semaglutide and placebo who were, and were not, using SGLT2i at baseline.

Statistical Analysis

Details on the overall statistical analysis plan are reported in the primary article.[22] The current analysis was prespecified in the statistical analysis plan. The estimand for all study objectives including safety objectives was based on the intention-to-treat principle, evaluating the effect of the randomized treatment irrespective of adherence to treatment and changes to background medication (including SGLT2i), and conducted in the full analysis set, which included all randomized participants across the in-trial observation period. All analyses used the time to first event from time of randomization. Composite outcomes were defined by the first incident component of the composite. For reporting of individual components of composites, the earliest event of the specific component of the composite is reported.

Baseline characteristics and participant demographics are summarized according to use of SGLT2i or not at baseline, overall, and according to randomization to receive oral semaglutide or placebo.

Time-to-event outcomes were analyzed using a Cox proportional hazards model, with randomized treatment group (oral semaglutide or placebo) as a fixed factor. Subgroup analyses were performed adding the interaction term between SGLT2i use at baseline or SGLT2i during the trial and treatment group. Data from participants who withdrew from the trial, died from causes not included in the outcome, or were lost to follow-up were censored at the time of these events. Time-to-event outcomes were plotted by randomized treatment group and SGLT2i use at baseline using the Aalen-Johansen estimator and are presented as cumulative incidences considering non-cardiovascular death or all-cause death as a competing event

dependent of the outcome. Furthermore, 2 time-dependent Cox proportional hazards models were performed, one with SGLT2i use as time-dependent variable (yes or no) during trial and randomized treatment as a fixed factor, and another with SGLT2i use during trial as time-dependent variable interacting with randomized treatment. These nonrandomized comparisons do not account for possible differential indications for modifying SGLT2i use across treatment groups.

Additional models explored estimation of treatment effects if first initiation and first discontinuation of SGLT2i use were similar in both treatment groups under the acceptance of strict assumptions of no unmeasured confounding and no informative censoring. An inverse probability weighting analysis of time to first MACE was performed using a marginal structural Cox proportional hazards model.[24] The weights in these analyses were calculated in 2 time-dependent Cox proportional hazards models by each treatment group and then combined, one for time to first initiation of SGLT2i use or censoring among those participants who did not use SGLT2i at baseline and one for time to first discontinuation of SGLT2i or censoring among those who used SGLT2i at baseline. The stabilized weights were calculated for each participant by each day from randomization until either first MACE or censoring.[25] The denominator was calculated as the predicted probability (1 minus the survival probability) of either initiating or discontinuing SGLT2i use, using baseline covariables and time-dependent covariables (the numerator was calculated using an empty model). These weights for each participant and each day were then truncated, such that the 1% of most extreme weights in each tail were set to the 1% and 99% percentiles, respectively.[25] The stabilized weights were then applied in a weighted time-dependent robust Cox proportional hazards model using a sandwich estimator with treatment group and (time-dependent) SGLT2i use defined as above as fixed factors when evaluating the occurrence of first MACE.[26] Furthermore, a model with the interaction term between treatment arm and SGLT2i use during the trial was performed. The estimates from these models should be cautiously interpreted as the assumptions of no unmeasured confounding and no informative censoring cannot be verified in the observed data.

Continuous outcomes from baseline to week 104 and week 156 were analyzed using a linear regression with treatment group, SGLT2i use at baseline, and the interaction term between treatment group and SGLT2i use at baseline adjusted for baseline values of the outcome. Multiple imputations (n=500) were used for missing values under a missing-at-random assumption. An imputation model (linear regression) is estimated separately for each treatment group including baseline value as a covariate and fitted to participants having an observed data point at year 2 and year 3, respectively. Results were combined using the Rubin rule. Missing data were defined as data planned to be collected according to protocol but are not present in the database. Hence, data that are absent in the database because of death or administrative censoring were not considered missing and hence not imputed. Interaction *P* values were derived from an F test of equality between the treatment differences across the SGLT2i use. Log transformation was applied before analysis for parameters specified in the statistical analysis plan, and treatment differences were expressed as a treatment mean ratio.

No adjustment for multiplicity or alpha protection was performed for these prespecified SGLT2i-related analyses. Two-sided *P* values <0.05 were considered significant. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC). Novo Nordisk A/S (Copenhagen, Denmark) maintained the clinical database and performed the statistical analyses.

RESULTS

Baseline Characteristics

Between June 2019 and March 2021, a total of 9650 individuals were randomized (4825 per arm), of whom 2596 (26.9%) participants were receiving SGLT2i at baseline (1296 in the oral semaglutide and 1300 in the placebo group). The mean follow-up was 47.5±10.9 months, and 9495 (98.4%) participants completed the trial (attended the follow-up visit or died). Vital status was available for 99.5% of participants. Baseline characteristics according to SGLT2i use at study entry are shown in Table 1 and for participants receiving oral semaglutide versus placebo according to SGLT2i use at baseline in Table S1. Participants receiving SGLT2i at baseline were younger, were less frequently women, and had a lower systolic and diastolic blood pressure, a higher estimated glomerular filtration rate, and lower high-sensitivity CRP. In addition, they more often had a history of coronary artery disease, but less often previous stroke, heart failure, or peripheral artery disease. Concomitant use of beta-blockers (68.9% versus 62.6%), statins (91.2% versus 84.3%), and platelet aggregation inhibitors (81.2% versus 75.7%) was slightly higher in those using SGLT2i at baseline, whereas the use of diuretics (38.8% versus 43.3%) was less in this group. ACE (angiotensin-converting enzyme) inhibitor/angiotensin receptor blocker use (80.8% versus 78.3%) and insulin use (49.3% versus 51.1%) were comparable between participants with or without SGLT2i use at baseline. The flowchart in Figure S1 depicts the disposition of SGLT2i at baseline and during the trial. The time pattern of discontinuation of SGLT2i at any time during the trial among participants who were receiving SGLT2i at baseline is shown in Figure S2A from randomization to month 54. The time pattern of initiation of SGLT2i from randomization to month 54 after randomization among participants who were not using SGLT2i at baseline is depicted in Figure S2B. Any SGLT2i use, at baseline or initiation during the trial, is shown in Figure S2C. During the trial, SGLT2i use (either at baseline or initiated during the trial) was 44.9% of participants randomized to oral semaglutide and 52.8% of participants randomized to placebo.

Among those not using SGLT2i at baseline, the proportions of participants who initiated SGLT2i during the trial were 24.7% and 35.5% of those randomized to oral semaglutide and placebo, respectively, with a hazard ratio (HR) of 0.63 (95% CI, 0.58–0.68; Figure S3). Among those on SGLT2i at baseline, 24.5% in the oral semaglutide and 20.5% in the placebo groups discontinued

Table 1. Baseline Characteristics According to SGLT2i Use at Baseline

	SGLT2i use (n=2596)	No SGLT2i use (n=7054)
Sex, female	577 (22.2)	2213 (31.4)
Age, y	65.0 (59.0–70.0)	67.0 (61.0–72.0)
Race or ethnic group		
White	1820 (70.1)	4828 (68.4)
Black or African American	37 (1.4)	215 (3.0)
Asian	655 (25.2)	1600 (22.7)
Other or not reported	84 (3.2)	411 (5.8)
Body weight, kg	86.3 (74.7–99.8)	85.9 (74.0–99.1)
BMI, kg/m^2	29.8 (26.6–34.0)	30.5 (27.0–34.6)
Diabetes duration, y	15.1 (9.8–20.8)	14.3 (8.7–20.8)
Current smoking	329 (12.7)	800 (11.3)
Systolic blood pressure, mm Hg	131.0 (120.0–142.0)	136.0 (125.0–145.0)
Diastolic blood pressure, mm Hg	76.0 (70.0–83.0)	78.0 (70.0–83.0)
HbA1c, %	7.7 (7.2–8.5)	7.8 (7.1–8.7)
Total cholesterol, mmol/L	3.7 (3.2–4.4)	3.9 (3.3–4.7)
LDL cholesterol, mmol/L	1.7 (1.3–2.2)	1.9 (1.5–2.5)
HDL cholesterol, mmol/L	1.1 (0.9–1.3)	1.1 (0.9–1.3)
eGFR, mL/min/1.73 m^2	82.0 (62.0–94.0)	74.0 (54.0–92.0)
hsCRP, mg/L	1.8 (0.9–3.9)	2.1 (0.9–4.6)
Previous CAD		
Previous MI	1154 (45.0)	2707 (39.0)
Previous coronary revascularization	1663 (64.1)	3535 (50.1)
Previous stroke	330 (12.7)	1158 (16.5)
Previous heart failure	562 (21.6)	1667 (23.6)
Previous PAD	358 (13.8)	1157 (16.4)
Concomitant cardiovascular medications		
Beta-blockers	1788 (68.9)	4413 (62.6)
Diuretics	1008 (38.8)	3056 (43.3)
ACE inhibitors/ARBs	2097 (80.8)	5521 (78.3)
Statins	2367 (91.2)	5948 (84.3)
Platelet aggregation inhibitors	2108 (81.2)	5337 (75.7)
Concomitant T2D medications		
Metformin	2195 (84.6)	5131 (72.7)
DPP4i	758 (29.2)	1477 (20.9)
Insulins	1281 (49.3)	3608 (51.1)
Sulfonylureas	698 (26.9)	2122 (30.1)
SGLT2i, n (%)		
Dapagliflozin	708 (27.3)	0 (0.0)
Canagliflozin	233 (9.0)	0 (0.0)
Empagliflozin	1581 (60.9)	0 (0.0)
Ertugliflozin	10 (0.4)	0 (0.0)

Values are n (%) and median (IQR). Two-sided *P* values were derived from a χ^2 test for categorial variables or a Mann-Whitney *U* test for continuous variables. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; DPP-4i, dipeptidyl-4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral artery disease; SGLT2i, sodium-glucose cotransporter-2 inhibitor; and T2D, type 2 diabetes.

SGLT2i during the trial with an HR of 1.23 (95% CI, 1.04–1.45; Figure S4).

Outcomes of Oral Semaglutide Versus Placebo by Baseline SGLT2i Use

Primary Outcome and All-Cause Death

MACE outcomes by randomized treatment for subgroups with or without SGLT2i use at baseline are shown in Figure 1. In the subgroup of participants with SGLT2i at baseline, there were 143 of 1296 (11.0%) MACE events in the oral semaglutide group versus 158 of 1300 (12.2%) in the placebo group (HR, 0.89; 95% CI, 0.71–1.11). In the subgroup without SGLT2i at baseline, there were 436 of 3529 (12.4%) primary outcomes with semaglutide versus 510 of 3525 (14.5%) in participants with placebo (HR, 0.84; 95% CI, 0.74–0.95; *P*-interaction, 0.66; Figure 1A). The incidence rates for first MACE were 2.84 versus 3.20 per 100 patient-years of observation for oral semaglutide versus placebo with SGLT2i use at baseline. The corresponding incidence rates without SGLT2i at baseline were 3.22 versus 3.84 per 100 patient-years. Similarly, no significant interaction between the subgroups with or without baseline SGLT2i use was observed for the single components of the composite primary outcome or on all-cause death (Figure 1B through 1E).

The effect of oral semaglutide versus placebo for the components of the primary outcomes and all-cause death by SGLT2i use at baseline is shown in Figure 2. Forest plots showing HRs for the primary outcome and components for subgroups with previous ASCVD, CKD, and ASCVD and CKD according to SGLT2i use at baseline are shown in Figure 3.

Secondary Efficacy Outcomes and Safety

The reduction in HbA1c from baseline to week 104 was significantly greater with oral semaglutide versus placebo, with a decrease of −0.66% versus −0.13% for participants using SGLT2 inhibitors at baseline, and −0.73% versus −0.16% for those not using SGLT2i (*P*-interaction, 0.44). Body mass index also decreased more with semaglutide compared with placebo, with reductions of −1.5 kg/m^2 versus −0.4 kg/m^2 that were similar regardless of SGLT2i use at baseline (*P*-interaction, 0.86). Data on changes from baseline in clinical and laboratory parameters at 104 weeks, including high-sensitivity CRP, according to baseline SGLT2i use are shown in Table 2. Data on changes in these parameters at 156 weeks are shown in Table S2.

Serious adverse events in the subgroup with SGLT2i use at baseline were reported in 48.3% versus 48.6% participants receiving oral semaglutide versus placebo, and 47.8% versus 50.9%, respectively, in the subgroup without SGLT2i use at baseline, suggesting that the adverse event profiles of oral semaglutide with or without an SGLT2i were similar. In particular, there were no

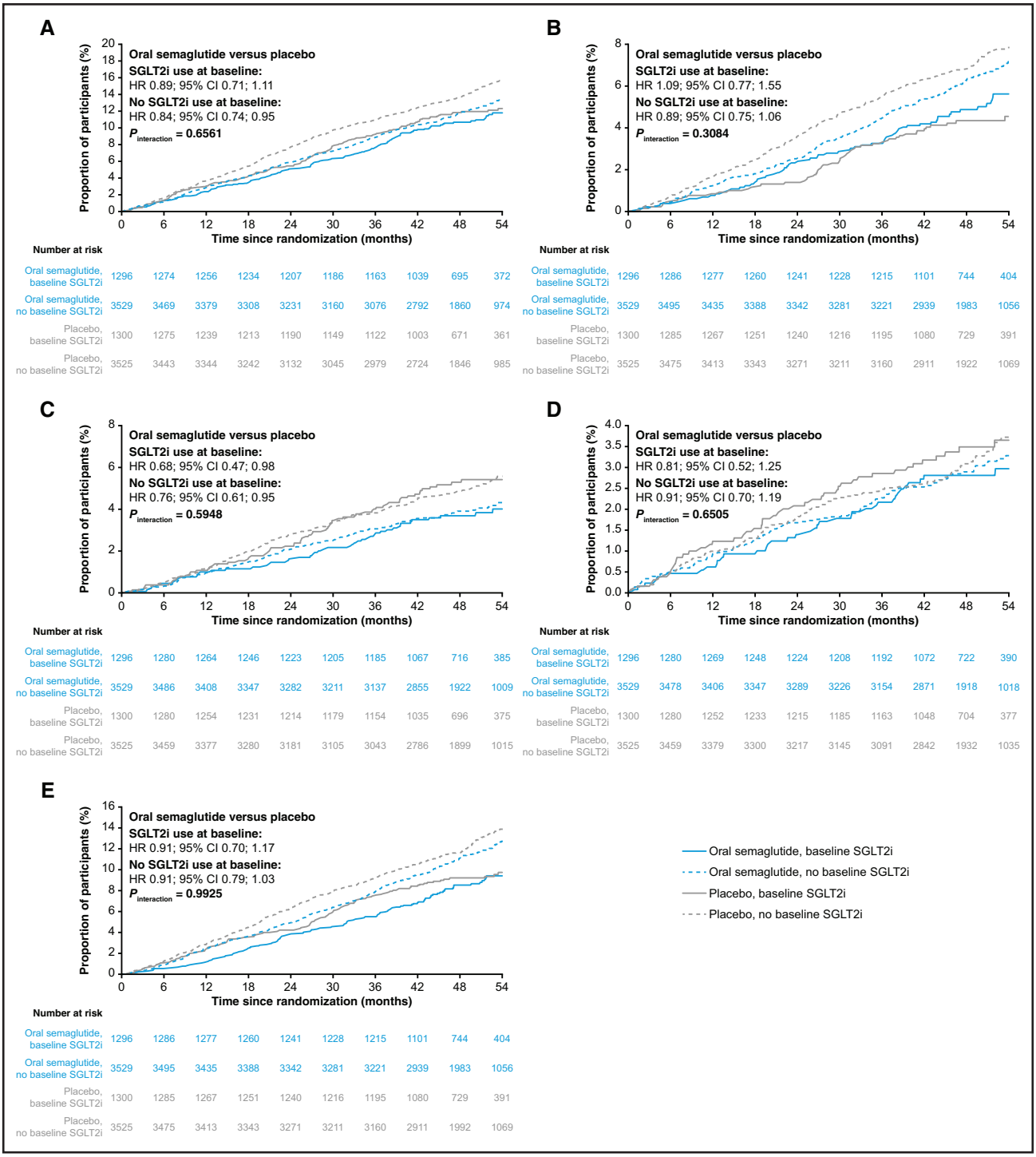

Figure 1. Cumulative incidence plots of outcomes for oral semaglutide vs placebo in subgroups with or without SGLT2i use at baseline.

A, Time to first occurrence of MACE. **B**, Time to cardiovascular death. **C**, Time to first nonfatal myocardial infarction event. **D**, Time to first nonfatal stroke event. **E**, Time to all-cause death. The cumulative incidence rate is calculated using the Aalen-Johansen method with noncardiovascular death (**A** and **B**)/all-cause death (**C** and **D**) as a competing risk. CV indicates cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; and SGLT2i, sodium-glucose cotransporter-2 inhibitor

differences in the incidence of severe hypoglycemia (with SGLT2i at baseline, 5.9% versus 6.5%; no SGLT2i at baseline, 2.2% versus 2.4%) or ketoacidosis (with SGLT2i at baseline, 0.6% versus 0.5%; no SGLT2i at baseline, 0.2% versus 0.2%) in participants treated with oral semaglutide versus placebo. Overviews of safety findings by system organ classes and preferred terms are shown in Table S3.

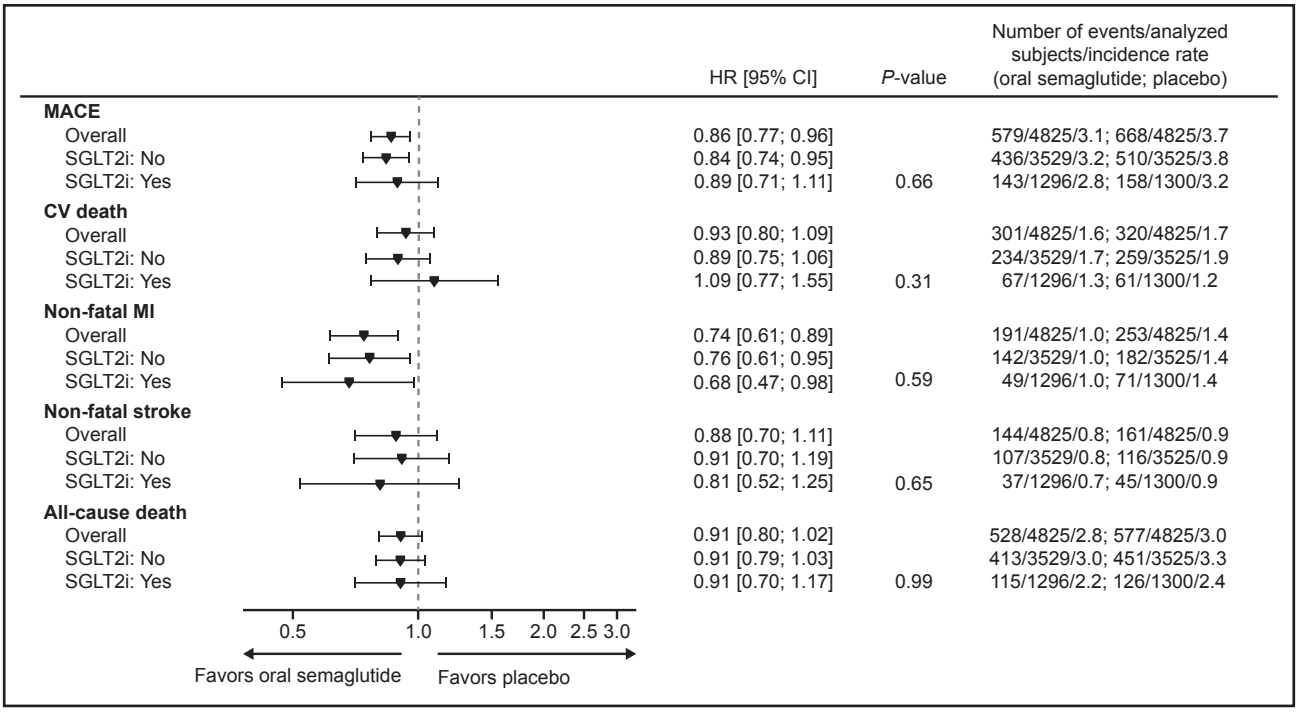

Figure 2. Forest plot: primary outcomes, components and all-cause death according to SGLT2i use at baseline.
Data from the in-trial period. Time from randomization to relevant end point was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor. Participants without events of interest were censored at the end of their in-trial period. For the subgroup analyses, estimated HRs and corresponding CIs are calculated in a Cox proportional hazards model with interaction between treatment group and subgroup as fixed factor. *P*-value, *P* value for the test of no interaction effect. CV indicates cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Initiation of SGLT2i During the Trial

In analyses of the primary outcome among participants who reported SGLT2i use at baseline or initiated SGLT2i during the study (n=2168 for oral semaglutide and n=2550 for placebo), there were 250 MACE events (11.5%) in the semaglutide group and 326 MACE events (12.8%) in the placebo group, generating an HR of 0.89 (95% CI, 0.76–1.05; Table S4A). For participants who did not use SGLT2i at baseline or during the study (n=2657 for semaglutide and n=2275 for placebo), the corresponding numbers were 329 (12.4%) for semaglutide and 342 (15.0%) for placebo with an HR of 0.79 (95% CI, 0.68–0.92; *P*-interaction, 0.31; Table S4B). Cumulative incidence rate data on time to first MACE by any SGLT2i use are shown in Figure S5.

When SGLT2i use during the study was treated as a time-dependent covariable in a Cox regression analysis, the HR for the primary outcome was 0.84 (95% CI, 0.75–0.94) (Table S5). In addition, using a time-dependent Cox regression analysis with SGLT2i use categorized by randomized treatment as a fixed factor yielded HRs for the primary outcome of 0.87 (95% CI, 0.71–1.06) for those using SGLT2i during the study (either from baseline or initiated during the study) and 0.83 (95% CI, 0.73–0.95) for those who never used SGLT2i throughout the study (Table S6).

Results from the weighted time-dependent Cox regression analyses of data for the in-trial period for time from randomization to the first MACE are shown in Table S7. The HR for the primary outcome was 0.82 (95% CI, 0.73–0.93). Using a weighted time-dependent Cox regression with randomized treatment, SGLT2i use during the study, and the interaction of randomized treatment by SGLT2i use during the study as categorical fixed factors, the HR for the primary outcome was 0.86 (95% CI, 0.70–1.06) for those with any SGLT2i use during the study and 0.81 (95% CI, 0.70–0.93) for those with no SGLT2i use. The interaction *P* value was 0.64 (Table S8).

DISCUSSION

In these prespecified analyses of the SOUL trial, the beneficial effects of oral semaglutide on cardiovascular outcomes in people with T2D and ASCVD and/or CKD were independent of concomitant SGLT2i use. SOUL, involving nearly 10 000 participants over a mean of 4 years, demonstrated a significant 14% reduction in MACE in the semaglutide group versus placebo with each of the 3 components of the primary outcome contributing to the risk reduction.[22] The benefits of oral semaglutide on MACE events did not differ between those treated with or without an SGLT2i at baseline.

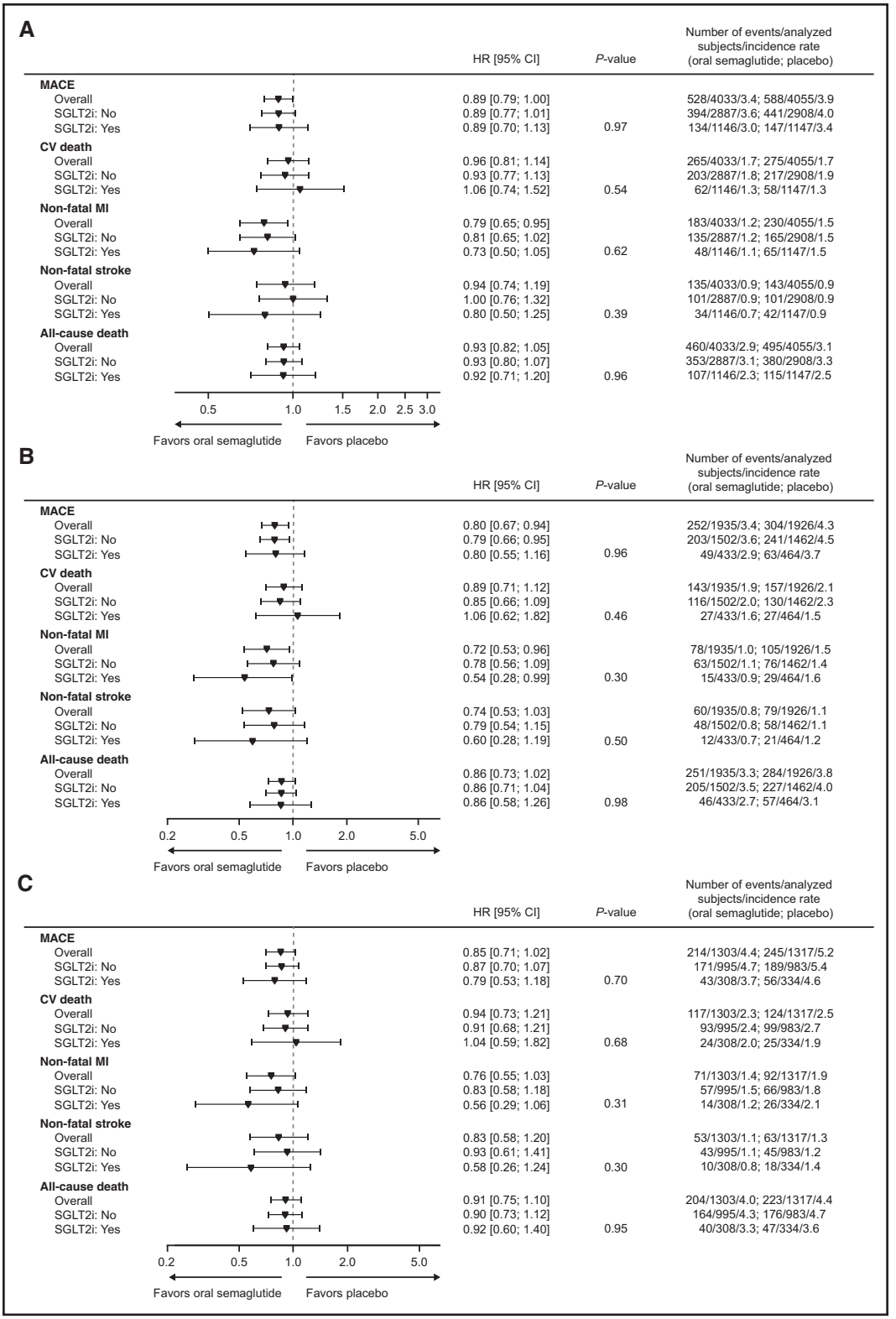

Figure 3. Forest plot: cardiovascular outcomes according to SGLT2i use at baseline, by cardiovascular and kidney subgroups. **A**, ASCVD. **B**, CKD. **C**, ASCVD and CKD. Each plot shows data from the in-trial period. Time from randomization to relevant end point was analyzed using a Cox proportional hazards model with treatment as a fixed factor. Participants without events of interest were censored at the end of their in-trial period. For the subgroup analyses, estimated HRs and corresponding CIs are calculated in a Cox proportional hazards model with interaction between treatment group and subgroup as fixed factor. *P*-value, *P* value for the test of no interaction effect. ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Table 2. Changes From Baseline to Week 104 in Clinical and Laboratory Parameters, According to SGLT2i Use at Baseline

	No baseline SGLT2i (n=7054)				Baseline SGLT2i (n=2596)				
	Oral semaglutide (n=3529)	Placebo (n=3525)	Adj LMS difference	*P* value	Oral semaglutide (n=1296)	Placebo (n=1300)	Adj LMS difference	*P* value	*P* interaction
HbA1c, %	−0.73 (−0.77 to −0.69)	−0.16 (−0.20 to −0.12)	−0.57 (−0.63 to −0.52)	<0.0001	−0.66 (−0.73 to −0.60)	−0.13 (−0.19 to −0.067)	−0.53 (−0.62 to −0.45)	<0.0001	0.44
SBP, mm Hg	−2.7 (−3.2 to −2.1)	−0.87 (−1.4 to −0.35)	−1.8 (−2.5 to −1.1)	<0.0001	−3.8 (−4.6 to −3.0)	−2.3 (−3.1 to −1.4)	−1.5 (−2.7 to −0.34)	0.012	0.72
DBP, mm Hg	−0.73 (−1.0 to −0.42)	−1.2 (−1.5 to −0.85)	0.44 (0.002 to 0.88)	0.049	−1.2 (−1.7 to −0.68)	−1.2 (−1.7 to −0.71)	0.031 (−0.69 to 0.75)	0.93	0.34
Body weight, %	−4.8 (−5.0 to −4.5)	−1.4 (−1.6 to −1.1)	−3.4 (−3.7 to −3.1)	<0.0001	−4.7 (−5.1 to −4.4)	−1.2 (−1.6 to −0.88)	−3.5 (−4.0 to −3.0)	<0.0001	0.77
BMI, kg/m^2	−1.5 (−1.6 to −1.4)	−0.44 (−0.51 to −0.37)	−1.1 (−1.2 to −1.0)	<0.0001	−1.5 (−1.6 to −1.4)	−0.43 (−0.54 to −0.32)	−1.1 (−1.2 to −0.93)	<0.0001	0.86
LDL*	0.99 (0.97 to 1.00)	0.98 (0.97 to 0.99)	1.01 (0.99 to 1.03)	0.47	0.94 (0.92 to 0.97)	0.94 (0.92 to 0.96)	1.01 (0.97 to 1.04)	0.72	0.95
eGFR, mL/min/ 1.73 m^2	−3.6 (−4.0 to −3.3)	−4.4 (−4.8 to −4.0)	0.78 (0.24 to 1.3)	0.0045	−1.6 (−2.3 to −1.0)	−2.5 (−3.1 to −1.8)	0.82 (−0.049 to 1.69)	0.064	0.93
hsCRP*	0.81 (0.78 to 0.84)	1.03 (1.00 to 1.07)	0.79 (0.75 to 0.83)	<0.0001	0.73 (0.69 to 0.77)	0.98 (0.93 to 1.04)	0.74 (0.69 to 0.81)	<0.0001	0.25

All data are mean (95% CI) change from baseline other than

*(ratio to baseline). Data are estimated mean changes or geometric mean ratios to baseline analyzed using an analysis of covariance with treatment group, SGLT2i use at baseline, and treatment group–by–SGLT2i use interaction as fixed factors, and baseline value as a covariable, using data from the in-trial observation period. Multiple imputation through linear regression was used to impute missing week 104 data separately for each treatment group. The model included the baseline value as a covariable and was fitted to all participants with a measurement regardless of treatment status at week 104. Mean estimates were adjusted according to observed baseline distribution. hsCRP and LDL observations were log-transformed before analysis and the estimates back-transformed afterwards. *P* value interactions were derived from an F-test. LDL was measured in mmol/L, and hsCRP was measured in mg/L, but changes were calculated as ratios from baseline. Body weight was measured in kilograms, but changes were calculated as percentage change from baseline. Adj indicates adjusted; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LMS, least mean squares; SBP, systolic blood pressure; and SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Furthermore, no significant difference was observed in the individual components of the primary outcome, and the effects of semaglutide on HbA1c, blood pressure, body mass index, estimated glomerular filtration rate, and high-sensitivity CRP were independent of concurrent SGLT2i use. With the highest proportion of SGLT2i use at baseline (26.9%) in any GLP-1 RA CVOT, and concomitant use of both drugs rising to almost 50% by the end of the trial, our results provide important information on the independence of semaglutide cardiovascular efficacy and safety with or without concomitant SGLT2i use in a high-risk population with T2D.

Even with imbalanced drop-in rates of SGLT2i use during the trial (24.7% in those on oral semaglutide versus 35.5% of those on placebo), the overall benefit of oral semaglutide on MACE was confirmed. In addition, analyses aiming to adjust for the SGLT2i imbalance between groups during the trial suggest no evidence of heterogeneity in the effects of oral semaglutide on MACE. Numerous trials have consistently shown that GLP-1 RA and SGLT2i, individually, provide significant benefits for cardiovascular outcomes in participants with T2D and high cardiovascular risk and/or CKD.[1–11] While the 2 classes of medications exert complementary and independent effects in the management of hyperglycemia in T2D, there is currently limited evidence from clinical trials on the combined use of GLP-1 RA and SGLT2i on cardiovascular outcomes. So far, data of combination therapy with SGLT2i and GLP-1 RA on cardiovascular outcomes primarily stem from subgroup analyses of CVOTs involving GLP-1 RA, as well as results from meta-analyses of these data, each suggesting consistent benefits regardless of the concomitant use of SGLT2i.[17–20] However, it is important to note that the proportion of participants taking SGLT2i at baseline in previously completed GLP-1 RA trials ranged from only 6.1% to 15.6%.[17–19] In contrast, in SOUL, 26.9% of participants reported SGLT2i treatment at baseline, providing data on a total of 2596 participants. Moreover, results from analyses of the larger subgroup of participants with any (n=4718; 49%) versus never (n=4932; 51%) use of SGLT2i during the trial also suggest no evidence of heterogeneity in the effects of oral semaglutide on MACE. Beyond the outcome data, the large number of participants on concomitant treatment with GLP-1 RA and SGLT2i provides important safety data with no significant differences in serious adverse events in participants with and without SGLT2i use.

The present analysis has certain limitations. First, although these analyses were prespecified in the statistical analysis plan, the SOUL trial was not powered to assess treatment effects for cardiovascular outcomes

related to SGLT2i use. Dedicated studies are warranted to assess and quantify in detail the incremental benefit of the combined use of GLP-1 RA and SGLT2i in T2D and cardiovascular disease/CKD. Second, baseline SGLT2i use was not stratified and may reflect differences in participant characteristics, as denoted in Table 1. Indeed, participants taking SGLT2i at baseline tended to be younger with a higher proportion of previous coronary artery disease and a more extensive concomitant cardiovascular medication use with agents such as β blockers and statins. Unsurprisingly, the new initiation of SGLT2i use also differed between participants in the 2 randomized groups, with a higher proportion of participants who were receiving placebo initiating SGLT2i during the trial compared with those on oral semaglutide. Moreover, more participants on baseline SGLT2i in the oral semaglutide group stopped SGLT2i treatment during the trial compared with the placebo group. It is important to note that SGLT2i initiation (or discontinuation) during the trial was neither stratified nor controlled and may point to differences in on-trial glycemic control or other aspects of disease progression, or potential protopathic bias.[27] Therefore, the findings of time-dependent regression analyses of the associations between SGLT2i use and the primary cardiovascular efficacy outcome during the trial must be interpreted with great caution, as the clinical decision to initiate on SGLT2i in-trial is very likely to be influenced by many evolving participant factors. Despite these limitations, the findings that the effects of oral semaglutide on cardiovascular outcomes were comparable in those with or without baseline or incident SGLT2i are noteworthy, because SOUL is now the GLP-1 RA trial with the highest penetrance of overall concurrent SGLT2i use, and this question remains an important one in clinical practice.

The demonstration of consistent effects of semaglutide on cardiovascular outcomes independent of its formulation (injectable or oral) provides important guidance for practicing clinicians treating people with T2D and ASCVD and/or CKD.[2,6,22] First, people with T2D and ASCVD and/or CKD may expect equivalent cardiovascular benefits from oral semaglutide regardless of background SGLT2i therapy. Results from various clinical trials have shown that SGLT2i provide pronounced cardiovascular benefits in people with T2D and preexisting ASCVD and/or CKD,[8,9,13] a population at very high risk for MACE. Results from the present analyses suggest that the addition of oral semaglutide for people in these subgroups already on an SGLT2i leads to a further reduction of MACE, thus underscoring current guideline recommendation for the concurrent use of both agents in people with T2D and ASCVD.[14,28] Second, the present results from a cohort with a mean follow-up of nearly 4 years suggest that GLP-1 RA and SGLT2i can safely be used together. Last, the SOUL trial explored the oral administration of semaglutide, which may be particularly appealing to many people compared with subcutaneous injections. Overall, our data may provide clinicians further confidence to combine an oral regimen of GLP-1 RA and SGLT2i with the aim of reducing cardiovascular events in patients at high cardiovascular risk.

In conclusion, results from these prespecified analyses on the largest data set of combined use of GLP-1 RA and SGLT2i in a single CVOT to date suggest that oral semaglutide reduces MACE outcomes in T2D and ASCVD and/or CKD consistently in participants with and without concomitant SGLT2i use and that the combination of both agents appears to be safe.

ARTICLE INFORMATION

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Supplemental Material

Figures S1–S5

Tables S1–S8

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