

# Oral Semaglutide and Change in Cardiovascular Risk Factors in High-Risk Type 2 Diabetes

## A Post Hoc Secondary Analysis of the SOUL Randomized Clinical Trial

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**IMPORTANCE** Individuals with type 2 diabetes (T2D) are at high risk of atherosclerotic cardiovascular disease (ASCVD). In the SOUL randomized clinical trial, once-daily oral semaglutide reduced risk of major adverse cardiovascular (CV) events by 14% vs placebo in people with T2D and ASCVD and/or chronic kidney disease (CKD) receiving standard of care (SoC); however, whether oral semaglutide modifies recognized CV risk factors in the long term is unclear.

**OBJECTIVE** To investigate whether treatment with oral semaglutide was associated with changes in ASCVD risk factors vs placebo.

**DESIGN, SETTING, AND PARTICIPANTS** This secondary analysis comprises post hoc intention-to-treat analyses of the SOUL (A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes) double-blind multicenter randomized clinical trial (randomization 1:1 to oral semaglutide or placebo) among adults with T2D and ASCVD and/or CKD receiving SoC. Participants underwent randomization from June 2019 to March 2021, with a mean (SD) of 47.5 (10.9) months of follow-up, and data were analyzed from February to December 2025.

**INTERVENTIONS(S)** Participants were treated with either once-daily oral semaglutide (maximum dose, 14 mg) or placebo, in addition to standard care.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the association of oral semaglutide vs placebo with glycated hemoglobin (HbA<sub>1c</sub>), body weight, and blood pressure (BP) using estimated treatment differences (ETDs) and with high-sensitivity C-reactive protein (hsCRP) and lipid plasma levels using estimated treatment ratios (ETRs).

**RESULTS** Of 9650 randomized participants (mean [SD] age, 66.1 (7.6) years; 2790 female participants [28.9%]), 9495 participants (98.4%) completed the trial. Early (13 weeks) improvements in HbA<sub>1c</sub> (−0.87 percentage points), body weight (−2.54%), systolic BP (SBP, −3.84 mm Hg), pulse pressure (−3.81 mm Hg), hsCRP (−18.08%), total cholesterol (TC, −7.00%), non-high-density lipoprotein cholesterol (non-HDL-C, −8.02%), HDL-C (−4.49%), and triglycerides (−8.15%) were observed with oral semaglutide vs placebo and sustained over the trial duration. Body weight reductions were gradual across both groups. At week 156, in favor of oral semaglutide were ETDs for HbA<sub>1c</sub> (−0.47 percentage points; 95% CI, −0.52 to −0.42), body weight (−3.26 percentage points; 95% CI, −3.55 to −2.98), SBP (−1.83 mm Hg; 95% CI, −2.47 to −1.18), and pulse pressure (−2.17 mm Hg; 95% CI, −2.72 to −1.61) and ETRs for hsCRP (0.77; 95% CI, 0.74-0.81), TC (0.99; 95% CI, 0.98-1.00), non-HDL-C (0.98; 95% CI, 0.97-0.99), HDL-C (1.01; 95% CI, 1.01-1.02), and triglycerides (0.94; 95% CI, 0.93-0.96). No significant treatment differences were observed for low-density lipoprotein cholesterol or diastolic BP.

**CONCLUSIONS AND RELEVANCE** In this post hoc secondary analysis of the SOUL randomized clinical trial, oral semaglutide was associated with early and sustained improvements vs placebo in multiple ASCVD risk factors in high-risk participants with T2D and ASCVD and/or CKD, incremental to SoC.

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 [Supplemental content](#)

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**D**iabetes is a global health concern with an estimated prevalence among people aged 20 to 79 years of 11.1% (589 million) in 2025, and this figure is expected to increase to 13.0% (852.5 million) by 2050, with the overwhelming majority having type 2 diabetes (T2D).<sup>1</sup> Cardiovascular disease (CVD) and chronic kidney disease (CKD) are common and inter-related complications of diabetes, with around one-third of people with T2D having some type of CVD.<sup>2,3</sup> Atherosclerotic CVD (ASCVD) continues to be the predominant cause of morbidity and mortality in this population,<sup>4,5</sup> and preventing CVD events is therefore a central goal in diabetes management.

The treatment paradigm for individuals with T2D has shifted from a glucose-centric approach toward a personalized approach focusing on risk mitigation for prevalent cardiovascular (CV) and kidney comorbidities, recommending newer drug classes after several CV outcome trials with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) demonstrated a reduction in CV events through mechanisms at least in part independent of their glycemic effects.<sup>4,6-9</sup> GLP-1 RAs may mediate these reductions through direct effects on the CV system, reducing progression of and stabilizing atherosclerotic plaques, and indirectly by improving endothelial function, reducing inflammation, blood pressure (BP), glycemia, and body weight, and improving postprandial glucose metabolism.<sup>10-13</sup>

Semaglutide is a long-acting GLP-1 RA available in both an injectable and an oral formulation.<sup>14,15</sup> The injectable formulation has been shown to reduce the risk of CV events vs placebo in people with T2D and ASCVD or at high risk of ASCVD and in those with T2D and CKD.<sup>16,17</sup> The semaglutide cardiovascular outcomes trial (SOUL [A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes]; NCT03914326)<sup>18</sup> investigated the cardiovascular efficacy of oral semaglutide, the first oral GLP-1 RA, in individuals with T2D and ASCVD and/or CKD. Treatment with oral semaglutide led to a statistically significant 14% reduction in the risk of major adverse cardiovascular events (MACE) compared with placebo.<sup>19</sup> Oral semaglutide was also associated with significantly reducing glycated hemoglobin (HbA<sub>1c</sub>) levels, body weight, and levels of high-sensitivity C-reactive protein (hsCRP), a marker of inflammation, compared with placebo at week 104 of SOUL.<sup>19</sup> However, the extent to which oral semaglutide improved other metabolic and inflammatory ASCVD risk factors in SOUL is unknown.

The aim of these secondary post hoc analyses of the SOUL trial was to investigate the short-term and long-term treatment association of oral semaglutide vs placebo with traditional CV risk factors (HbA<sub>1c</sub>, body weight, BP, pulse, hsCRP, and lipids) among all SOUL participants and subanalyses among those categorized according to trial entry criteria (ASCVD only, ASCVD + CKD, or CKD only).

## Methods

### Trial Design and Participant Population

A detailed description of the phase 3b international, double-blind, placebo-controlled SOUL randomized clinical trial has

## Key Points

**Question** What is the association between oral semaglutide and recognized cardiovascular risk factors vs placebo in the SOUL randomized clinical trial?

**Findings** In this post hoc secondary analysis of the SOUL randomized clinical trial, oral semaglutide was associated with sustained improvements in multiple cardiovascular risk factors in high-risk participants with type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease receiving standard of care.

**Meaning** These risk factor benefits may contribute to the overall benefit of oral semaglutide on outcomes for major adverse cardiovascular events, providing supporting evidence for the use of oral semaglutide in cardiovascular risk reduction.

been published.<sup>19</sup> Eligible participants were men or women, aged 50 years or older, diagnosed with T2D, and with HbA<sub>1c</sub> between 6.5% and 10.0%. Participants were also required to have at least 1 of the following conditions: coronary heart disease, cerebrovascular disease, symptomatic peripheral artery disease, and/or CKD. Key exclusion criteria included any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischemic attack within the past 60 days prior to the day of screening, planned coronary, carotid or peripheral artery revascularization known on the day of screening, heart failure presently classified as being in New York Heart Association class IV, and/or treatment with any GLP-1 RA within 30 days before screening.

Participants, all receiving standard of care (SoC) for CV risk mitigation and for glucose management, were randomized in a 1:1 ratio to once-daily treatment with either oral semaglutide or matching placebo. Healthy lifestyle advice was not protocolized in SOUL, but recommendations for such advice in accord with regional standards were included in the SOUL SoC guidance document for application throughout the trial period and independent of randomized treatment assignment. Full details on the trial treatments have been reported previously.<sup>19</sup>

The SOUL protocol (available with the statistical analysis plan in [Supplement 1](#)) was approved by the institutional review board and ethics committee for each participating center, which included 444 sites globally and 88 sites in the US. The trial was conducted in compliance with the International Conference for Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in accordance with the Declaration of Helsinki. All the participants provided written informed consent. The trial results are reported in accordance with the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guidelines.

## Outcomes

These secondary post hoc analyses of the SOUL trial evaluated the treatment association of oral semaglutide vs placebo on traditional CV risk factors. Supportive secondary end points included change in HbA<sub>1c</sub> and change in body weight. Post hoc analyses included BP (systolic BP [SBP],

diastolic BP [DBP], pulse pressure), pulse, plasma levels of hsCRP and lipids (total cholesterol [TC], non-high-density lipoprotein cholesterol [non-HDL-C], HDL-C, low-density lipoprotein cholesterol [LDL-C], and triglycerides; all measured in a nonfasting state). All protocol-required blood tests, including HbA<sub>1c</sub> and plasma levels of lipids and hsCRP, were collected at study sites and analyzed in a central laboratory to ensure consistency and accuracy of the measurements.

Assessments were taken at baseline and at weeks 13, 52, 104, 156, and 208 for all CV risk factors except hsCRP plasma level (done at baseline and at weeks 13 and 104). Estimated treatment differences (ETDs) and/or estimated treatment ratios (ETRs) were calculated at weeks 13 and 156, except for hsCRP plasma level (ETR/odds ratio [OR] calculated at week 104).

### Subgroup Analyses

The previously mentioned CV risk factors were also assessed in subgroups by baseline presence of ASCVD, CKD, or both.

### Statistical Analysis

The analyses of CV risk factors in the overall trial population were intention-to-treat (ITT) analyses using in-trial data and therefore included all randomized participants (full analysis set) regardless of treatment adherence. The main ITT analysis was supplemented with analyses of the ASCVD-only, CKD-only, and ASCVD + CKD subgroups based on the first period receiving treatment (ie, observation period until the first time not receiving treatment for >35 days [5 times the half-life of semaglutide]).<sup>20</sup>

ETDs and ETRs were determined using analysis of covariance (ANCOVA) models with treatment as a fixed factor and baseline value as a covariate. Before analyses, missing data were imputed as follows: the imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all participants with a measurement regardless of treatment status at week 156 (week 104 for hsCRP plasma level). The fitted models were used to impute values for participants with missing data at week 156 (week 104 for hsCRP plasma level). ORs were determined using logistic regression models with treatment and baseline category as fixed factors. Standard errors were calculated on the logarithmic scale and backtransformed to original scale using the delta method. The complete datasets were analyzed and the results combined using the Rubin rule.<sup>21</sup> Mean estimates were adjusted according to observed baseline distribution. For subgroup analyses, the interaction between treatment group and subgroup was added to the models.

## Results

### Patient Characteristics

Full details of the trial population are published.<sup>19</sup> In brief, 9650 individuals (eFigure 1 in Supplement 2) were randomized (4825 in each arm), and 9495 participants (98.4%) com-

pleted the trial (attended end-of-trial visit or had died), with a mean (SD) follow-up of 47.5 (10.9) months.

A total of 2790 participants (28.9%) were female, and the mean (SD) age was 66.1 (7.6) years. Participant demographics and clinical characteristics, including CV risk factor profile, were well balanced at baseline. The numbers of participants with ASCVD only were 2730 (56.6%) and 2748 (56.7%) in the oral semaglutide and placebo groups, respectively, while the numbers of participants with both ASCVD and CKD were 1303 (27%) and 1317 (27.3%), and 632 (13.1%) and 609 (12.6%) had CKD only. For the glucose-lowering and CV-related medications, the percentages of each class used at baseline were similar in both treatment groups (Table 1 and Table 2; eTable in Supplement 2).<sup>19,27</sup>

Data were collected from most patients for most end points at most time points, although during the COVID-19 pandemic, some site visits were converted to telephone visits or missed, accounting for the majority of the missing data. As an example, 10.1% of data for body weight at week 156 were missing for the oral semaglutide arm, with 11.5% missing for the placebo arm. Similar proportions of data were missing for the other risk factors at either week 156 or week 104.

### Association of Oral Semaglutide With Changes in CV Risk Factors

Blood pressure decreased over time in all participants (Figure 1 depicts ITT mean values over time, while eFigure 2 in Supplement 2 shows ITT and first receiving-treatment changes over time). A substantial reduction in SBP was observed by week 13 in the oral semaglutide group (−3.84 mm Hg), and this was sustained throughout the trial (−3.63 mm Hg at week 156) compared with a smaller and more gradual reduction in SBP with placebo. Pulse pressure also reduced substantially in the oral semaglutide group by week 13 (−3.81 mm Hg), with gradual attenuation thereafter (−2.04 mm Hg at week 156) and no change observed at any time point in the placebo group (Figure 1; eFigure 2 in Supplement 2). At week 13, there were reductions in favor of semaglutide for SBP (ETD: −3.19 mm Hg; 95% CI, −3.76 to −2.62;  $P < .001$ ) and pulse pressure (ETD: −3.70 mm Hg; 95% CI, −4.19 to −3.21;  $P < .001$ ). Similar reductions in favor of semaglutide were observed at week 156 for both SBP (ETD: −1.83 mm Hg; 95% CI, −2.47 to −1.18;  $P < .001$ ) and pulse pressure (ETD: −2.17 mm Hg; 95% CI, −2.72 to −1.61;  $P < .001$ ), but not for DBP (ETD: 0.33 mm Hg; 95% CI, −0.06 to 0.73;  $P = .10$ ) (Figure 1; eFigure 2 in Supplement 2). Similar reductions over time in pulse were observed in all participants (eFigure 3 in Supplement 2 [ITT mean values over time, ITT and first receiving-treatment changes over time]).

For plasma levels of lipids at week 13, reductions in TC, non-HDL-C, and HDL-C were observed in all participants but were of greater magnitude in semaglutide-treated participants (Figure 2 [ITT mean values over time]; eFigure 4 in Supplement 2 [ITT and first receiving-treatment changes over time]). TC and non-HDL-C were reduced substantially by week 13 in semaglutide-treated participants (−7.00% and

Table 1. Participant Demographics and Medical History at Baseline

Demographic characteristic	No. (%)							
	Oral semaglutide				Placebo			
	FAS (n = 4825)	ASCVD only (n = 2730)	CKD only (n = 632)	ASCVD + CKD (n = 1303)	FAS (n = 4825)	ASCVD only (n = 2739)	CKD only (n = 609)	ASCVD + CKD (n = 1317)
Age, median (IQR), y	66 (61-72)	64 (59-70)	69 (63-74)	69 (63-73)	66 (61-72)	65 (59-70)	69 (63-74)	68 (63-73)
Sex								
Female	1376 (28.5)	623 (22.8)	292 (46.2)	392 (30.1)	1414 (29.3)	680 (24.8)	303 (49.8)	360 (27.3)
Male	3449 (71.5)	2107 (77.2)	340 (53.8)	911 (69.9)	3411 (70.7)	2059 (75.2)	306 (50.2)	957 (72.7)
Race <sup>a</sup>								
African American or Black	124 (2.6)	53 (1.9)	32 (5.1)	33 (2.5)	128 (2.7)	53 (1.9)	40 (6.6)	34 (2.6)
American Indian or Alaska Native	7 (0.1)	5 (0.2)	2 (0.3)	0	12 (0.2)	4 (0.1)	3 (0.5)	4 (0.3)
Asian	1134 (23.5)	659 (24.1)	183 (29.0)	260 (20.0)	1121 (23.2)	642 (23.4)	173 (28.4)	266 (20.2)
Native Hawaiian or Pacific Islander	4 (<0.1)	2 (<0.1)	0	1 (<0.1)	5 (0.1)	1 (<0.1)	2 (0.3)	1 (<0.1)
White	3327 (69.0)	1886 (69.1)	376 (59.5)	955 (73.3)	3321 (68.8)	1908 (69.7)	350 (57.5)	965 (73.3)
Other <sup>b</sup>	185 (3.8)	102 (3.7)	29 (4.6)	43 (3.3)	192 (4.0)	99 (3.6)	35 (5.7)	40 (3.0)
Not reported	44 (0.9)	23 (0.8)	10 (1.6)	11 (0.8)	46 (1.0)	32 (1.2)	6 (1.0)	7 (0.5)
Ethnicity								
Hispanic or Latino	674 (14.0)	347 (12.7)	109 (17.2)	171 (13.1)	706 (14.6)	364 (13.3)	117 (19.2)	186 (14.1)
Not Hispanic or Latino	4106 (85.1)	2359 (86.4)	513 (81.2)	1121 (86.0)	4071 (84.4)	2342 (85.5)	486 (79.8)	1123 (85.3)
Not reported	45 (0.9)	24 (0.9)	10 (1.6)	11 (0.8)	47 (1.0)	32 (1.2)	6 (1.0)	8 (0.6)
History of CVD								
Coronary artery disease	3406 (70.6)	2288 (83.8)	NA	1074 (82.4)	3415 (70.8)	2304 (84.1)	NA	1085 (82.4)
Cerebrovascular disease	1026 (21.3)	649 (23.8)	NA	363 (27.9)	1016 (21.1)	664 (24.2)	NA	342 (26.0)
Prior MI or stroke	2522 (52.3)	1707 (62.5)	NA	780 (59.9)	2474 (51.3)	1714 (62.6)	NA	738 (56.0)
Peripheral arterial disease	771 (16.0)	438 (16.0)	NA	326 (25.0)	744 (15.4)	394 (14.4)	NA	346 (26.3)
Heart failure	1105 (22.9)	568 (20.8)	41 (6.5)	475 (36.5)	1124 (23.3)	581 (21.2)	56 (9.2)	470 (35.7)
CKD <sup>c</sup>	2041 (42.3)	NA	632 (100)	1303 (100)	2051 (42.5)	NA	609 (100)	1317 (100)
Hypertension	4378 (90.7)	NA	NA	NA	4381 (90.8)	NA	NA	NA
Duration of diabetes, median (IQR), y	14.7 (9.0-20.8)	13.1 (7.9-19.8)	16.0 (10.7-21.8)	16.0 (10.9-22.5)	14.6 (8.9-20.8)	13.1 (7.7-19.8)	16.6 (10.9-22.8)	15.9 (10.8-22.0)
Current smoking	545 (11.3)	373 (13.7)	58 (9.2)	100 (7.7)	584 (12.1)	369 (13.5)	52 (8.5)	147 (11.2)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; FAS, full analysis; MI, myocardial infarction; NA, not applicable.

<sup>a</sup> Race and ethnicity were reported by participants.

<sup>b</sup> Reflects participants in France, where collecting data on race and ethnicity is prohibited by law.

<sup>c</sup> Reported by the investigators at screening. CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>.

–8.02%, respectively). Thereafter, placebo-adjusted differences were attenuated, whereas HDL-C only increased after week 13 in semaglutide-treated patients only and differences were sustained thereafter. Compared with placebo, differences were apparent at week 13 in LDL-C (oral semaglutide: –7.53%; placebo: –1.66%) and triglycerides (oral semaglutide: –8.15%; placebo: –1.20%). However, while these differences in triglycerides were maintained throughout follow-up, no differences were apparent in LDL-C from week 104 onwards (Figure 2; eFigure 4 in Supplement 2).

Statistically significant improvements were observed at week 13 in TC (ETR: 0.94; 95% CI, 0.94-0.95;  $P < .001$ ), non-HDL-C (ETR: 0.93; 95% CI, 0.92-0.94;  $P < .001$ ), HDL-C (ETR: 0.97; 95% CI, 0.96-0.98;  $P < .001$ ), and triglycerides (ETR: 0.93; 95% CI, 0.92-0.94;  $P < .001$ ). Similarly, at week

156, semaglutide was associated with statistically significant relative improvements in TC (–4.21% from baseline; ETR: 0.99; 95% CI, 0.98-1.00;  $P = .03$ ), non-HDL-C (–6.70% from baseline; ETR: 0.98; 95% CI, 0.97-0.99;  $P = .002$ ), HDL-C (0.94% from baseline; ETR: 1.01; 95% CI, 1.01-1.02;  $P < .001$ ), and triglycerides (–11.70% from baseline; ETR: 0.94; 95% CI, 0.93-0.96;  $P < .001$ ) (Figure 2; eFigure 4 in Supplement 2). At week 13, there was a significant difference between treatment groups in LDL-C (ETR: 0.94; 95% CI, 0.93-0.95;  $P < .001$ ), but no difference at week 156 (ETR: 1.00; 95% CI, 0.98-1.02;  $P = .87$ ) (–7.53% and –4.22% from baseline for semaglutide at weeks 13 and 156, respectively) (Figure 2; eFigure 4 in Supplement 2).

Mean values for HbA<sub>1c</sub>, hsCRP, and body weight over time have been published previously.<sup>19</sup> Reductions from

Table 2. Participant Vital Signs and Laboratory History at Baseline

	Median (IQR)		Placebo					
	Oral semaglutide		ASCVd only (n = 2730)	CKD only (n = 632)	ASCVd + CKD (n = 1303)	FAS (n = 4825)	ASCVd only (n = 2739)	CKD only (n = 609)
Body weight, kg	85.7 (74.0-98.9)	85.5 (74.2-98.5)	82.8 (71.2-96.5)	88.1 (75.2-100.0)	86.3 (74.4-100.0)	86.4 (74.5-99.3)	83.9 (73.5-97.9)	87.0 (75.2-102.4)
BMI <sup>a</sup>	30.3 (26.9-34.2)	29.8 (26.7-33.7)	30.4 (26.8-35.1)	31.3 (27.3-35.3)	30.4 (27.0-34.5)	30.0 (26.8-34.0)	31.2 (27.5-35.5)	30.9 (27.3-35.4)
HbA <sub>1c</sub> , mmol/mol	61.8 (54.1-71.6)	60.7 (54.1-71.6)	60.7 (54.1-69.4)	61.8 (55.2-71.6)	61.8 (54.1-70.5)	60.7 (54.1-71.6)	61.8 (54.1-69.4)	61.8 (55.2-70.5)
HbA <sub>1c</sub> , %	7.8 (7.1-8.7)	7.7 (7.1-8.7)	7.7 (7.1-8.5)	7.8 (7.2-8.7)	7.8 (7.1-8.6)	7.7 (7.1-8.7)	7.8 (7.1-8.5)	7.8 (7.2-8.6)
Systolic blood pressure, mm Hg	134 (124-144)	134 (123-143)	136 (125-147)	135 (124-145)	135 (124-144)	133 (123-143)	137 (126-147)	136 (125-146)
Diastolic blood pressure, mm Hg	77 (70-83)	78 (70-84)	76 (70-82)	76 (68-82)	78 (70-83)	78 (70-83)	77 (70-83)	76 (69-83)
Pulse, beats/min	72 (65-80)	72 (65-80)	75 (66-83)	72 (64-78)	72 (65-80)	72 (65-80)	74 (66-82)	72 (64-79)
Lipids, mg/dL								
Total cholesterol	149.0 (127.0-178.0)	145.8 (124.3-173.0)	159.3 (136.5-187.5)	150.6 (127.4-178.6)	147.9 (126.3-176.8)	145.9 (124.7-172.6)	155.6 (134.4-184.9)	147.3 (127.0-177.6)
Non-HDL-C	105.8 (85.7-133.6)	103.1 (83.4-130.1)	113.1 (92.7-140.2)	108.5 (86.9-135.5)	104.6 (84.9-133.2)	102.3 (83.0-129.3)	111.4 (91.5-139.8)	105.8 (86.5-137.3)
HDL-C	40.9 (34.7-48.6)	40.5 (34.7-48.3)	42.5 (36.3-51.0)	40.5 (34.0-47.9)	40.9 (34.7-48.3)	40.9 (35.1-47.9)	43.2 (35.9-51.0)	39.8 (33.6-47.1)
LDL-C	72.6 (55.2-95.0)	70.7 (53.3-92.3)	78.2 (61.0-98.8)	73.4 (55.6-96.9)	70.7 (54.1-93.8)	69.5 (52.9-91.1)	77.6 (57.5-98.1)	70.3 (53.7-95.0)
Triglycerides	156.6 (112.1-220.7)	152.2 (108.6-214.5)	170.9 (124.6-235.9)	161.1 (114.8-226.1)	157.1 (112.1-224.3)	151.3 (108.1-216.3)	165.5 (117.5-235.0)	167.3 (118.4-238.5)
hsCRP, mg/dL	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.5)	0.2 (0.1-0.5)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.3 (0.1-0.5)	0.2 (0.1-0.5)
eGFR, mL/min/1.73 m <sup>2</sup> (CKD-EPI method <sup>27</sup> ) <sup>b</sup>	77.0 (56.0-93.0)	90.0 (77.0-98.0)	52.0 (42.0-61.0)	57.5 (44.0-73.5)	76.0 (56.0-92.0)	89.0 (76.0-97.0)	51.0 (41.0-62.0)	57.0 (44.0-73.0)
eGFR, mL/min/1.73 m <sup>2</sup> , No. (%) <sup>c</sup>								
End-stage kidney disease (<15)	7 (0.1)	0	3 (0.5)	4 (0.3)	4 (<0.1)	0	1 (0.2)	3 (0.2)
≥15 to <30	113 (2.3)	6 (0.2)	39 (6.2)	54 (4.1)	114 (2.4)	6 (0.2)	38 (6.2)	63 (4.8)
≥30 to <45	474 (9.8)	21 (0.8)	151 (23.9)	269 (20.6)	475 (9.8)	17 (0.6)	154 (25.3)	265 (20.1)
≥45 to <60	811 (16.8)	132 (4.8)	256 (40.5)	380 (29.2)	818 (17.0)	138 (5.0)	243 (39.9)	381 (28.9)
≥60 to <90	1845 (38.2)	1190 (43.6)	163 (25.8)	446 (34.2)	1903 (39.4)	1246 (45.5)	157 (25.8)	459 (34.9)
≥90	1531 (31.7)	1357 (49.7)	12 (1.9)	139 (10.7)	1472 (30.5)	1310 (47.8)	12 (2.0)	134 (10.2)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; multiply by 0.0259; triglycerides, from mg/dL to mmol/L, multiply by 0.0113.

<sup>a</sup> Calculated as eGFR <60 mL/min/1.73 m<sup>2</sup>; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR,

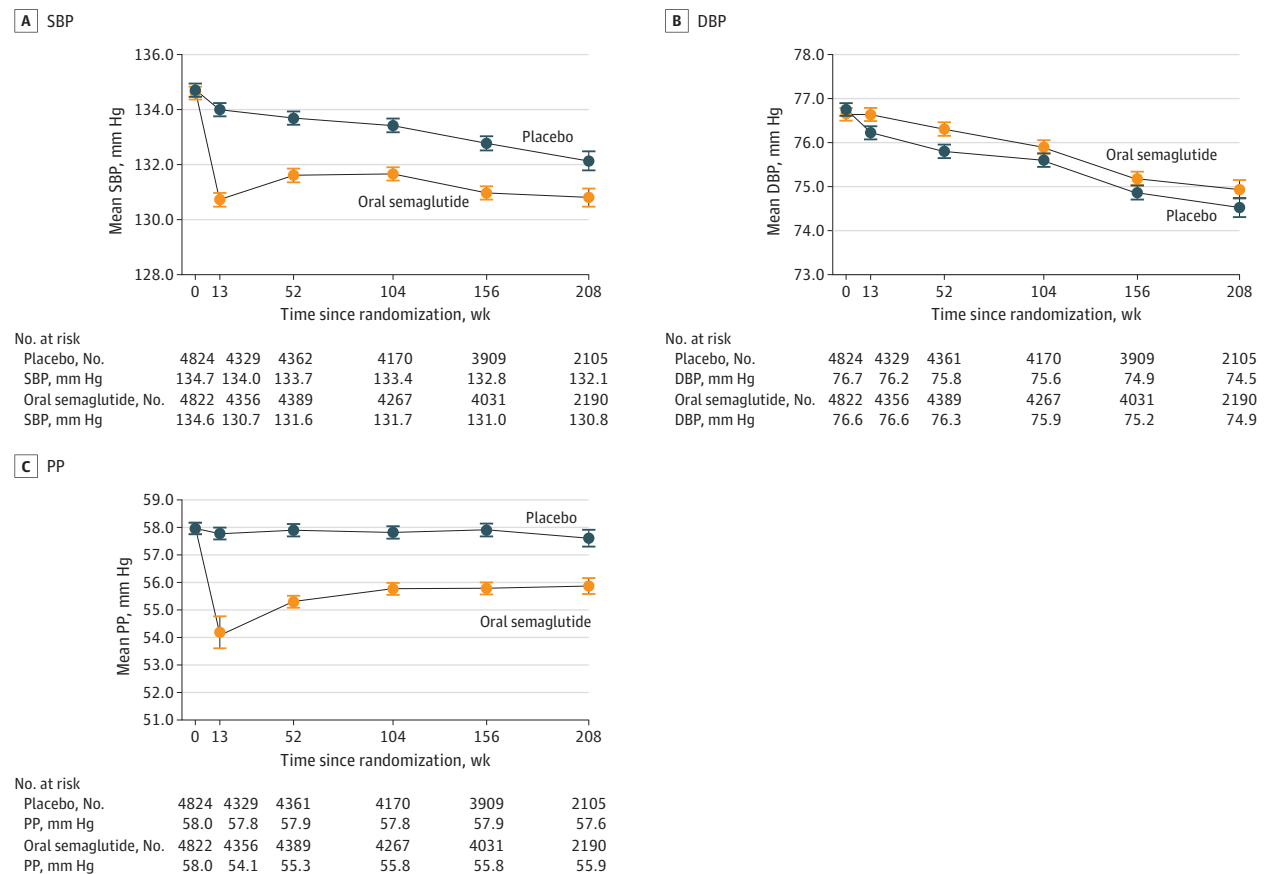
estimated glomerular filtration rate; FAS, full analysis set; HbA<sub>1c</sub>, glycated hemoglobin; HDL-C, high-density

lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

<sup>b</sup> Reported by the investigators at screening.

<sup>c</sup> Measured at randomization.

Figure 1. Line Graph Showing Mean Blood Pressure Values Over Time (Full Analysis Set)



Blood pressure values include systolic blood pressure (SBP) (A), diastolic BP (DBP) (B), and pulse pressure (PP) (C). Data were analyzed according to the intention-to-treat principle. Error bars are standard error of the mean. The responses were analyzed using an analysis of covariance with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done

separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete datasets were analyzed and the results combined using the Rubin rule. Mean estimates were adjusted according to observed baseline distribution.

baseline in HbA<sub>1c</sub> and hsCRP were observed in semaglutide-treated participants only (eFigure 5A and B in Supplement 2 [ITT and first receiving treatment]). For both variables, a notable reduction was observed by week 13 (−0.87 percentage points for HbA<sub>1c</sub> and −18.08% for hsCRP), and these improvements were sustained throughout the trial (−0.61 percentage points for HbA<sub>1c</sub> at week 156 and −21.03% for hsCRP at week 104). Body weight decreased over time in both treatment arms, with a greater reduction (−2.54% at week 13 and −5.26% at week 156) in the semaglutide arm (eFigure 5C in Supplement 2 [ITT and first receiving treatment]). The reduction in body weight was more gradual than that of HbA<sub>1c</sub> and hsCRP. At week 13, the ETD in HbA<sub>1c</sub> was −0.82 percentage points (95% CI, −0.85 to −0.79; *P* < .001); for body weight, ETD was −2.28 percentage points (95% CI, −2.41 to −2.15; *P* < .001) with oral semaglutide vs placebo. At week 156, the ETD in HbA<sub>1c</sub> was −0.47 percentage points (95% CI, −0.52 to −0.42; *P* < .001); for body weight, ETD was −3.26 percentage points (95% CI, −3.55 to −2.98; *P* < .001). The ETR for hsCRP at week 13 was 0.81 (95% CI, 0.78-0.84;

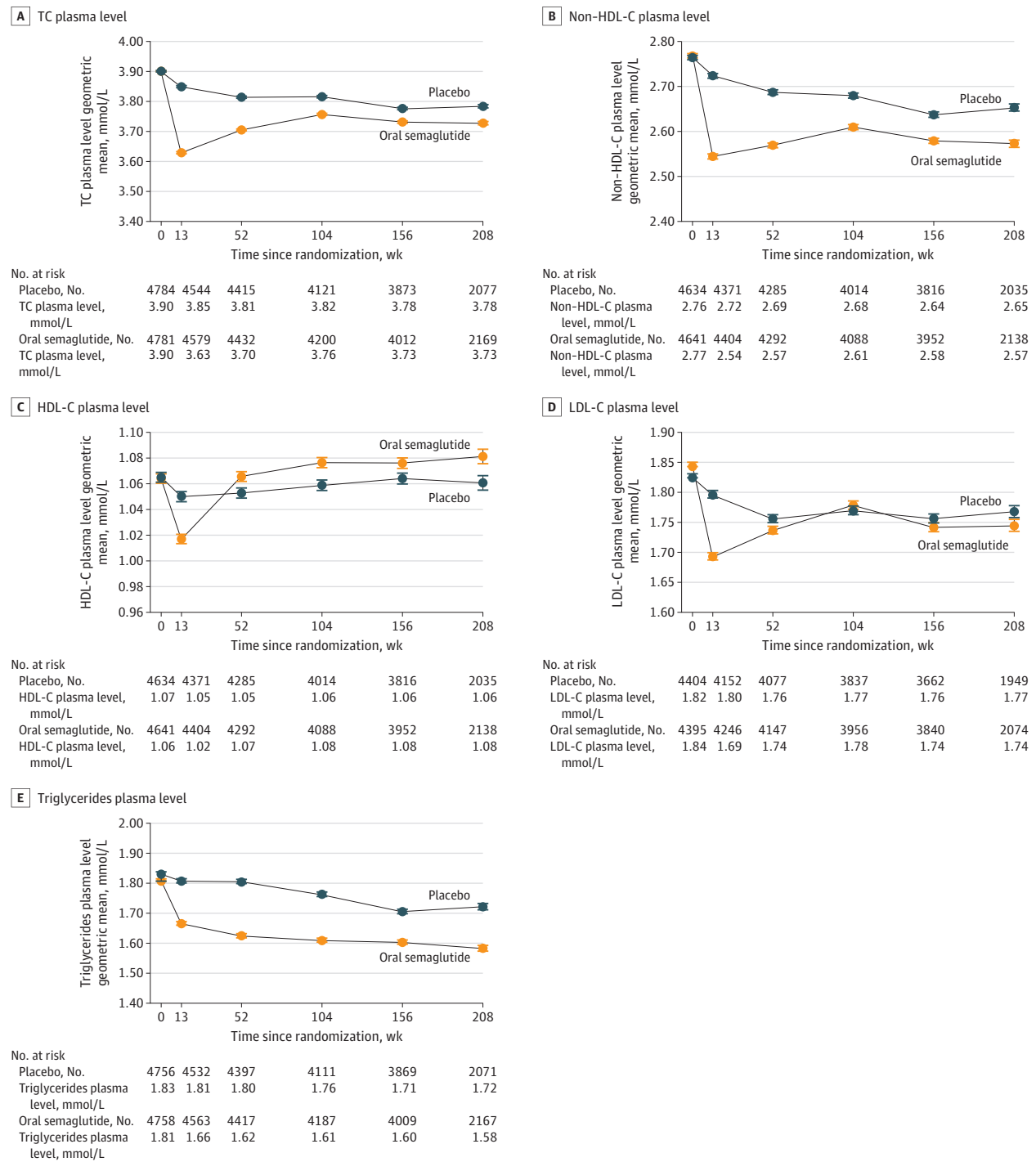
*P* < .001), and at week 104 ETR was 0.77 (95% CI, 0.74-0.81; *P* < .001) with oral semaglutide vs placebo (eFigure 5A-C in Supplement 2).

**Subgroup Analyses by CV Risk History Subgroups**

For BP, there was no significant interaction between treatment and CV risk history (*P* values for interaction = .53 for SBP, .79 for DBP, and .70 for pulse pressure) (Figure 3A). Findings on pulse (eFigure 6 in Supplement 2) and lipids (Figure 3B) were broadly similar across the subgroups.

Among the ASCVD-only, CKD-only, and ASCVD + CKD subgroups, the ETDs for HbA<sub>1c</sub> at week 156 with oral semaglutide vs placebo were −0.54 percentage points (95% CI, −0.60 to −0.47), −0.68 percentage points (95% CI, −0.82 to −0.53), and −0.54 percentage points (95% CI, −0.64 to −0.44), respectively (eFigure 7 in Supplement 2). There was no significant interaction between treatment and change in HbA<sub>1c</sub> (*P* for interaction = .20). For hsCRP at week 104, the ETRs with oral semaglutide vs placebo were 0.38 (95% CI, 0.23-0.61), 0.75 (95% CI, 0.28-2.05), and 0.71

Figure 2. Line Graph Showing Geometric Mean Plasma Levels of Lipids Over Time (Full Analysis Set)

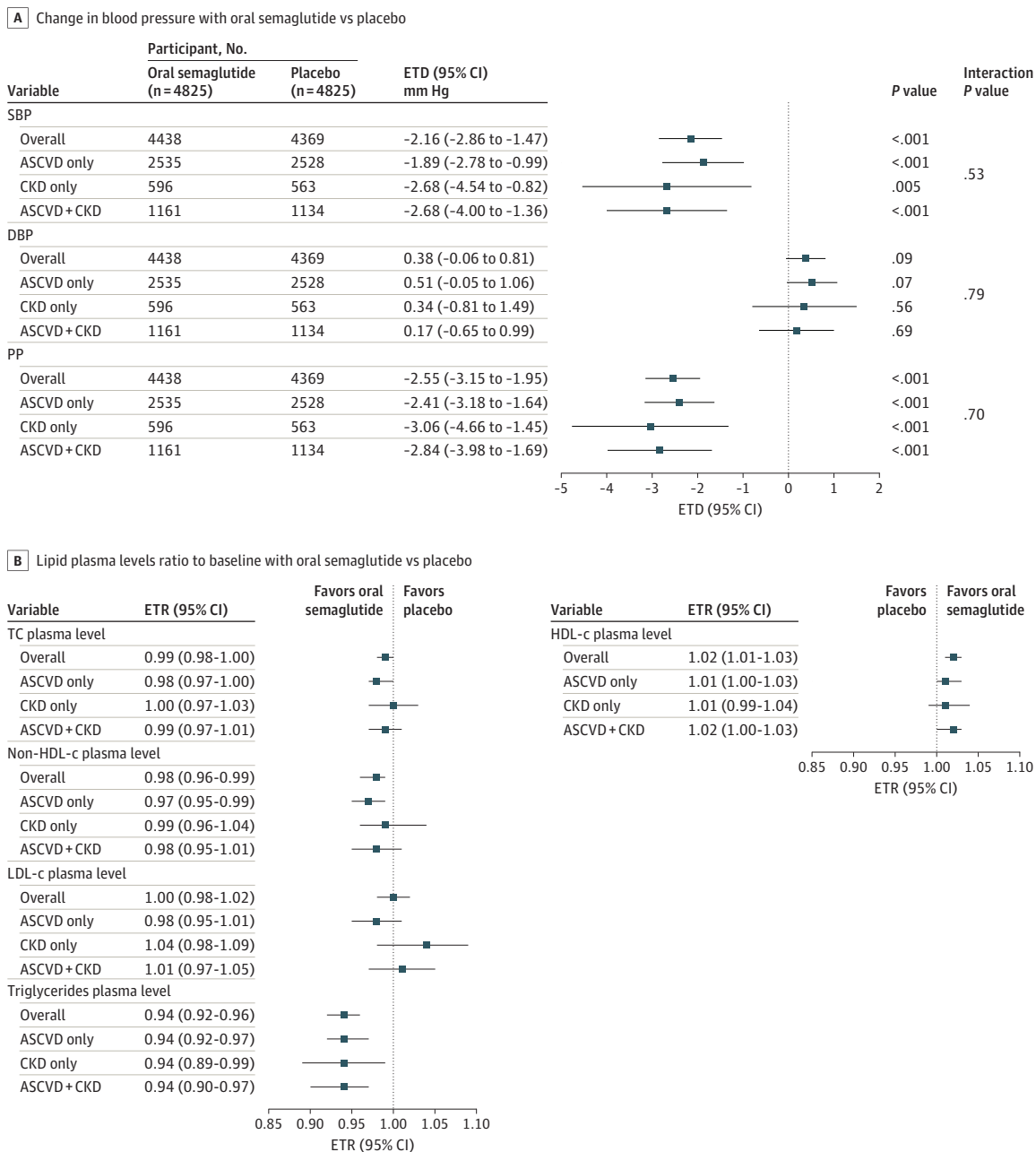


Plasma lipid levels measured include total cholesterol (TC) (A), non-high-density lipoprotein cholesterol (non-HDL-C) (B), HDL-C (C), low-density lipoprotein cholesterol (LDL-C) (D), and triglycerides (E). Observed data from the in-trial period. Error bars are standard error of the mean. The effects were analyzed using analysis of covariance with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiply imputed 500 times. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of

treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete datasets were analyzed and the results combined using the Rubin rule. Mean estimates were adjusted according to observed baseline distribution.

SI conversion factors: To convert TC, non-HDL-C, HDL-C, and LDL-C from mg/dL to mmol/L, multiply by 0.0259; triglycerides, from mg/dL to mmol/L, multiply by 0.0113.

Figure 3. Forest Plots Showing Treatment Difference in Change in Blood Pressure and Lipid Plasma Level Ratio (First Period Receiving Treatment)



Panels show change in blood pressure (A) and lipid plasma levels ratio to baseline (B) with oral semaglutide vs placebo. The responses were analyzed using analysis of covariance with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiply imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete

datasets were analyzed and the results combined using the Rubin rule. Decreases in plasma levels of total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides and increases in plasma levels of HDL-C favored oral semaglutide. ASCVD indicates atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; ETD, estimated treatment difference; ETR, estimated treatment ratio; PP, pulse pressure; SBP, systolic blood pressure.

(95% CI, 0.35-1.43), respectively (eFigure 7 in Supplement 2). There was no significant interaction between treatment and hsCRP (*P* for interaction = .49). For body weight at week 156, the ETDs with oral semaglutide vs placebo were -3.17 percentage points (95% CI, -3.57 to -2.77), -4.76

percentage points (95% CI, -5.58 to -3.93), and -4.26 percentage points (95% CI, -4.85 to -3.67), respectively (eFigure 7 in Supplement 2). There was a significant interaction between treatment and body weight (*P* for interaction < .001).

## Discussion

The results from these post hoc secondary analyses of the SOUL randomized clinical trial demonstrate that treatment with oral semaglutide compared with placebo in participants already receiving SoC for CV risk and glucose control was associated with sustained improvements in recognized CV risk factors, including HbA<sub>1c</sub>, body weight, hsCRP, SBP, and plasma levels of TC, non-HDL-C, HDL-C, and triglycerides. Importantly, site investigators were instructed to ensure that all participants' CV risk factors were managed according to local guidelines in collaboration with the participants' usual care clinicians. Such associations were observed soon after initiation (except for HDL-C), sustained for at least 2 and up to 4 years (median trial duration), and were consistent across all entry criteria subgroups.

Improvements in HbA<sub>1c</sub>, SBP, hsCRP, non-HDL-C, and triglycerides with oral semaglutide were greatest at week 13 and sustained thereafter, whereas the decline in body weight was maximized at 52 weeks and maintained thereafter. The overall effect associated with oral semaglutide on lipid plasma levels was favorable. TC, non-HDL-C, and triglyceride levels fell significantly more in the oral semaglutide group vs placebo, while HDL-C levels rose and LDL-C levels were not significantly changed. A potential concern might be that differences between the treatment groups in these risk factors could be confounded by between-group differences in the use of concomitant CV or glucose-lowering therapies—ie, any greater associations of oral semaglutide with glucose, BP, or lipid levels might be offset by a relatively greater use of anti-hyperglycemic, antihypertensive, or lipid-lowering therapies, respectively, in the placebo group. However, this does not appear to be the case, as the baseline and incident use of such drugs were remarkably consistent between the treatment groups (eTable in Supplement 2). For example, statins were used in more than 80% of enrolled participants, and renin-angiotensin system inhibitors in almost all. Thus, the observed differences in risk factors between groups likely represent the true treatment association of oral semaglutide in the context of SoC. It is known that a sustained reduction of 10 mm Hg in SBP is associated with an approximately 30% reduction in the 4-year risk of stroke<sup>22</sup> and a 20% reduction in the 4-year risk of MACE.<sup>23</sup> Similarly, in a meta-analysis of randomized clinical trials to determine whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with T2D, a reduction of 0.9 percentage points in HbA<sub>1c</sub> was associated with a 17% reduction in non-fatal myocardial infarction, with no significant associations observed on events of stroke.<sup>24</sup> These observations are broadly consistent with those concerning MACE in the semaglutide

cardiovascular outcome trials<sup>16,19,25</sup> and suggest that the observed CV outcome benefits of GLP-1 RAs may be associated with the changes on multiple risk factors beyond glycemia.

## Limitations

This study has several limitations. First, the analyses were post hoc, not adjusted for multiplicity, and thus should be used as a prompt for further validation studies. Second, the demographic characteristics of this trial population are not representative of the global population, since only 28.9% of enrolled participants were women and 2.6% were African American or Black.<sup>26</sup> Third, the impact of improved individual CV risk factors (as part of SoC) over the course of the study on MACE remains unclear. For example, if patients with higher baseline HbA<sub>1c</sub> also had a higher overall baseline CV risk (such as higher LDL-C, higher BP), then the differences reported herein may not be due to baseline glycemic control or glycemic improvement over the trial, but rather to a potential improvement of suboptimally controlled baseline CV risk factors. Further analyses are warranted to determine the influence of glycemic control and other individual baseline CV risk factors on MACE. Furthermore, postbaseline incident background CV medications were not systematically captured (other than SGLT2is); therefore, the present findings should be interpreted in the context that changes may have occurred in background cardiometabolic therapies. Additionally, owing to the trial design, there is limited insight into treatment associations prior to week 13, and there were no measurements of waist circumference or postbaseline liver parameters. Lastly, due to the eligibility criteria, all participants had ASCVD and/or CKD, whereas in the real world, around a third of people with T2D are estimated to have ASCVD, and CKD is reported to affect approximately 40% of people with diabetes. Further investigation is needed to confirm the impact on people with T2D with less advanced disease.<sup>2,3</sup>

## Conclusions

In conclusion, in this secondary analysis of the SOUL randomized clinical trial, oral semaglutide showed early and sustained improvements up to 4 years (median trial duration) in multiple CV risk factors (HbA<sub>1c</sub>, body weight, SBP, pulse, hsCRP, TC, non-HDL-C, HDL-C, and triglycerides) in a large sample of high-risk patients with T2D and ASCVD and/or CKD receiving SoC. Although the observed beneficial changes were relatively small in magnitude when assessed individually, these risk factor benefits may collectively contribute to the overall benefit of oral semaglutide on MACE outcomes. These findings thus substantiate the evolving evidence for the use of oral semaglutide in CV risk reduction.<sup>19</sup>

### ARTICLE INFORMATION

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