ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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ABSTRACT

BACKGROUND

Semaglutide, a glucagon-like peptide-1 receptor agonist, has been shown to reduce the risk of adverse cardiovascular events in patients with diabetes. Whether semaglutide can reduce cardiovascular risk associated with overweight and obesity in the absence of diabetes is unknown.

METHODS

In a multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial, we enrolled patients 45 years of age or older who had preexisting cardiovascular disease and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27 or greater but no history of diabetes. Patients were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis. Safety was also assessed.

RESULTS

A total of 17,604 patients were enrolled; 8803 were assigned to receive semaglutide and 8801 to receive placebo. The mean (±SD) duration of exposure to semaglutide or placebo was 34.2±13.7 months, and the mean duration of follow-up was 39.8±9.4 months. A primary cardiovascular end-point event occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and in 701 of the 8801 patients (8.0%) in the placebo group (hazard ratio, 0.80; 95% confidence interval, 0.72 to 0.90; P<0.001). Adverse events leading to permanent discontinuation of the trial product occurred in 1461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group (P<0.001).

CONCLUSIONS

In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months. (Funded by Novo Nordisk; SELECT ClinicalTrials.gov number, NCT03574597.)

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More than half the world population is projected to have overweight or obesity by the year 2035.[1] High body-mass index (BMI) is estimated to have accounted for 4 million deaths globally in 2015, more than two thirds of which were caused by cardiovascular diseases.[2] Overweight and obesity are independently associated with an increased risk of cardiovascular events, even after the influence of metabolic cardiovascular risk factors linked to excess weight has been accounted for.[3-6] Although reducing the risk of cardiovascular disease by treating dyslipidemia,[7] hypertension,[8] and diabetes[9,10] is standard evidence-based practice, the concept of treating obesity to reduce the risk of cardiovascular complications has been hampered by the lack of evidence from trials indicating that lifestyle or pharmacologic interventions for overweight or obesity improve cardiovascular outcomes.[11-15]

Agonists of the glucagon-like peptide-1 (GLP-1) receptor are used in the management of type 2 diabetes and overweight or obesity and have been shown to reduce the risk of major adverse cardiovascular events in patients with type 2 diabetes who are at high cardiovascular risk.[10] Although these agents affect a broad range of metabolic pathways associated with glucose metabolism, energy homeostasis, and inflammation that might be hypothesized to also improve cardiovascular outcomes among people who do not have diabetes,[16,17] it is unknown whether GLP-1 receptor agonists can reduce the cardiovascular risk associated with overweight and obesity. Semaglutide, a long-acting analogue of GLP-1, administered at a dose of 2.4 mg subcutaneously once weekly for 104 weeks, was found to reduce body weight by a mean of 15.2% among patients with overweight or obesity who did not have diabetes.[18] In the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial, we tested the hypothesis that the addition of semaglutide to standard care would be superior to placebo in reducing the risk of major adverse cardiovascular events among patients with overweight or obesity and preexisting cardiovascular disease who did not have diabetes.

Methods

Trial Design

We conducted this multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial at 804 clinical sites in 41 countries (details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial design has been published previously.[19] The trial protocol (available at NEJM.org) was designed by the sponsor, Novo Nordisk, and the academic steering committee. Details of the organization of the trial are provided in the Supplementary Appendix. National and institutional regulatory and ethical authorities approved the protocol, and all the patients provided written informed consent. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Population

Patients were eligible for enrollment if they were 45 years of age or older, had a BMI (the weight in kilograms divided by the square of the height in meters) of 27 or greater, and had established cardiovascular disease. Cardiovascular disease was defined as previous myocardial infarction, previous stroke, or symptomatic peripheral arterial disease. Key exclusion criteria were a previous diagnosis of diabetes, a glycated hemoglobin level of 6.5% (48 mmol per mole) or higher measured at screening, treatment with any glucose-lowering medication or GLP-1 receptor agonist within the previous 90 days, New York Heart Association class IV heart failure, or end-stage kidney disease or dialysis. Patients could not be enrolled within 60 days after a cardiovascular or neurologic event or if they planned to undergo coronary, carotid, or peripheral revascularization. A detailed list of the eligibility criteria is provided in the Supplementary Appendix.

Intervention and Management

Patients were randomly assigned, with the use of a centralized system in a double-blind manner and in a 1:1 ratio without stratification, to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The starting dose of semaglutide was 0.24 mg once weekly, and the dose was increased every 4 weeks (to once-weekly doses of 0.5, 1.0, 1.7, and 2.4 mg) until the target dose of 2.4 mg was reached after 16 weeks. If dose escalation led to unacceptable adverse effects, the dose-escalation intervals could be extended, treatment could be paused, or maintenance doses below the 2.4 mg per week target dose could be used. Semaglutide or pla-

cebo was to be discontinued if patients became or planned to become pregnant, if pancreatitis developed, or if the patient had a calcitonin level equal to or greater than 100 ng per liter (see the Supplementary Appendix for the calcitonin-monitoring protocol). Investigators were encouraged to follow evidence-based recommendations in their choice of medical management of underlying cardiovascular disease. If diabetes developed during the trial, the patient continued to take the assigned trial product. The use of glucose-lowering medications was at the discretion of the investigator, although initiation of open-label treatment with a GLP-1 receptor agonist was prohibited.

END POINTS

The primary cardiovascular efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, assessed in a time-to-first-event analysis. Confirmatory secondary end points, assessed in time-to-first-event analyses and tested in hierarchical order, were death from cardiovascular causes, a composite heart failure end point (death from cardiovascular causes or hospitalization or an urgent medical visit for heart failure), and death from any cause. Supportive secondary end points and adjudicated end-point definitions are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

This event-driven trial was designed to provide 90% power to detect a relative risk reduction of 17% for a primary end-point event in the semaglutide group as compared with the placebo group (hazard ratio, 0.83) at an overall one-sided significance level of 0.025. This design required that a minimum of 1225 primary end-point events be accrued. Assuming an event rate for the primary end point of 2.2% per year in the placebo group, a trial duration of 59 months, and a withdrawal or loss-to-follow-up rate of 1% per year in both groups, we estimated that 17,500 patients would need to be enrolled. One interim analysis for superiority with respect to the primary end point was prespecified to occur when two thirds of the total planned number of primary end-point events had accrued (additional details are provided in the Supplementary Appendix).

Efficacy analyses were based on the intention-to-treat principle and included all unique patients who underwent randomization irrespective of adherence to semaglutide or placebo or changes to background medications. Data from patients who withdrew from the trial, died from causes not included in the end point, or were lost to follow-up were censored at the time of withdrawal, death, or last contact with the investigator. Cause-specific hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional hazards model with randomization assignment (semaglutide or placebo) as a fixed factor. One-sided P values were obtained from a score test. For the primary end point, the hazard ratio, 95% confidence interval, and P value were adjusted for the group sequential design with the use of likelihood-ratio ordering.[20]

If primary end-point events occurred in a smaller percentage of patients treated with semaglutide than with placebo, confirmatory secondary end points were to be evaluated in the following hierarchical order: death from cardiovascular causes, the heart failure composite end point, and death from any cause. A gatekeeping testing strategy was used, with statistical significance at each step required in order to test the next hypothesis, with the use of a separate alpha-spending function as described by Glimm and colleagues[21] to preserve the studywise one-sided type 1 error at 2.5%. Although the statistical analysis plan specified that one-sided P values would be used for hypothesis testing, results are reported here with two-sided P values. Continuous supportive secondary end points (changes from baseline to week 104) were assessed by analysis of covariance, with multiple imputation used for missing values under a missing-at-random assumption; because these supportive end points were not adjusted for multiplicity, confidence intervals should not be used in place of a hypothesis test. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute).

RESULTS

RANDOMIZATION, PATIENT CHARACTERISTICS, AND FOLLOW-UP

From October 2018 through March 2021, a total of 17,604 patients underwent randomization; 8803 were assigned to receive semaglutide and 8801 to receive placebo. The baseline demographic and clinical characteristics of the patients are

summarized in Table 1 and Table S1 in the Supplementary Appendix, and the representativeness of patients enrolled in the trial is shown in Table S2; detailed characteristics of the pooled patient population (before the randomization assignments were revealed) have been reported previously.[23] The mean (±SD) age of the patients was 61.6±8.9 years, and 12,732 patients (72.3%) were male. The mean BMI was 33.3±5.0, and 12,580 patients (71.5%) met the BMI criterion for obesity (≥30). The mean glycated hemoglobin level was 5.8±0.3%, and 11,696 patients (66.4%) met the glycated hemoglobin criterion for prediabetes (defined as a mean level of 5.7 to 6.4%). More than three quarters of the patients had had a previous myocardial infarction, and nearly one quarter had chronic heart failure. The use of guideline-based medical therapies for cardiovascular disease appeared to be well balanced between the groups. Most of the patients were receiving lipid-lowering medications (90.1%) and platelet-aggregation inhibitors (86.2%), 70.2% of the patients were taking beta-blockers, 45.0% were taking angiotensin-converting–enzyme inhibitors, and 29.5% were taking angiotensin-receptor blockers.

Patient flow through the trial is shown in Figure S1. Patients were followed up for a mean of 39.8±9.4 months. Permanent premature discontinuation of semaglutide or placebo occurred in 2351 patients (26.7%) in the semaglutide group and 2078 (23.6%) in the placebo group (Fig. S2). The mean duration of exposure to semaglutide or placebo in the overall trial population was 34.2±13.7 months (33.3±14.4 months for semaglutide and 35.1±13.0 months for placebo); patients received the assigned trial product for 82.5% and 87.7% of the potential treatment time in the semaglutide group and the placebo group, respectively. Administration of semaglutide over time is summarized in Figure S3; by 104 weeks, approximately 77% of the patients receiving semaglutide were taking the target 2.4-mg weekly dose. Treatment with an open-label GLP-1 receptor agonist was initiated during the trial (a violation of the trial protocol) in 36 patients (semaglutide in 28 patients) in the semaglutide group and in 121 patients (semaglutide in 92 patients) in the placebo group. No patient was taking a sodium–glucose transport protein 2 inhibitor at the time of randomization, but treatment with a medication of that class was initiated in 213 patients in the semaglutide group and 332 patients in the placebo group. A total of 17,061 patients (96.9%) completed the trial (defined as having died or attended the final trial visit), and vital status was available for 17,495 (99.4%).

EFFICACY END POINTS

A primary cardiovascular end-point event (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and 701 of the 8801 patients (8.0%) in the placebo group (hazard ratio, 0.80; 95% confidence interval [CI], 0.72 to 0.90; P<0.001 [nominal significance level for superiority after adjustment for the interim analysis, 0.046]) (Fig. 1A and Table 2). Death from cardiovascular causes, the first confirmatory secondary end point, occurred in 223 patients (2.5%) in the semaglutide group and in 262 patients (3.0%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.71 to 1.01; P=0.07 [nominal significance level for superiority, 0.023]) (Fig. 1B). Because the between-group difference with respect to death from cardiovascular causes did not meet the required P value for hierarchical testing, superiority testing was not performed for the remaining confirmatory secondary end points (Fig. 1C and 1D). The hazard ratio for the heart failure composite end point was 0.82 (95% CI, 0.71 to 0.96), and the hazard ratio for death from any cause was 0.81 (95% CI, 0.71 to 0.93). Directionally consistent effects were observed for all time-to-first-event supportive secondary end points (Fig. S4). The effects of semaglutide on the primary end point appeared to be similar across all prespecified subgroups (Fig. S5).

BODY WEIGHT AND OTHER END POINTS

Table 3 provides a summary of the continuous and binary supportive secondary end points. Changes in body weight and waist circumference over the course of the trial are shown in Figure S6. The mean change in body weight over the 104 weeks after randomization was −9.39% with semaglutide and −0.88% with placebo (estimated treatment difference, −8.51 percentage points; 95% CI, −8.75 to −8.27).

ADVERSE EVENTS

Adverse events are reported in Table 4 and Table S3. Serious adverse events were reported in 2941

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N=8803)	Placebo (N=8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)
Median high-sensitivity CRP level (IQR) — mg/liter	1.87 (0.89–4.18)	1.80 (0.86–4.06)
Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
eGFR — ml/min/1.73 m^2	82.4±17.5	82.5±17.3
Median lipid level (IQR) — mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)
Systolic blood pressure — mm Hg	131.0±15.6	130.9±15.3
Diastolic blood pressure — mm Hg	79.4±10.0	79.2±9.9
Pulse — beats/min	68.9±10.6	68.6±10.7
EQ-5D-5L index score¶	0.88±0.15	0.88±0.15
EQ-5D-VAS score¶	77.15±15.63	77.15±15.73

* Plus–minus values are means ±SD. To convert the values for high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glycated hemoglobin to millimoles per mole, multiply by 10.929 and subtract 2.15. CRP denotes C-reactive protein, eGFR estimated glomerular filtration rate, and IQR interquartile range.

† Race and ethnic group were reported by the patients. Race was not reported for 95 patients (1.1%) in the semaglutide group and 74 patients (0.8%) in the placebo group. The category "Other" includes patients who reported their race as American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or other. Information on whether patients identified as Hispanic or Latino was not reported for 95 patients (1.1%) in the semaglutide group and 76 patients (0.9%) in the placebo group.

‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

§ This category includes patients for whom it was not known whether only one or several criteria were fulfilled and patients who underwent randomization in error and did not fulfill any criteria.

¶ The EuroQol 5-Dimension 5-Level (EQ-5D-5L) index score[22] ranges from 0 to 1, with higher scores indicating better patient-reported health status. The index score is calculated only if responses are available from all five questions. The EuroQol 5-Dimension Visual Analogue Scale (EQ-5D-VAS) score ranges from 0 to 100, with higher scores indicating better patient-reported health status.

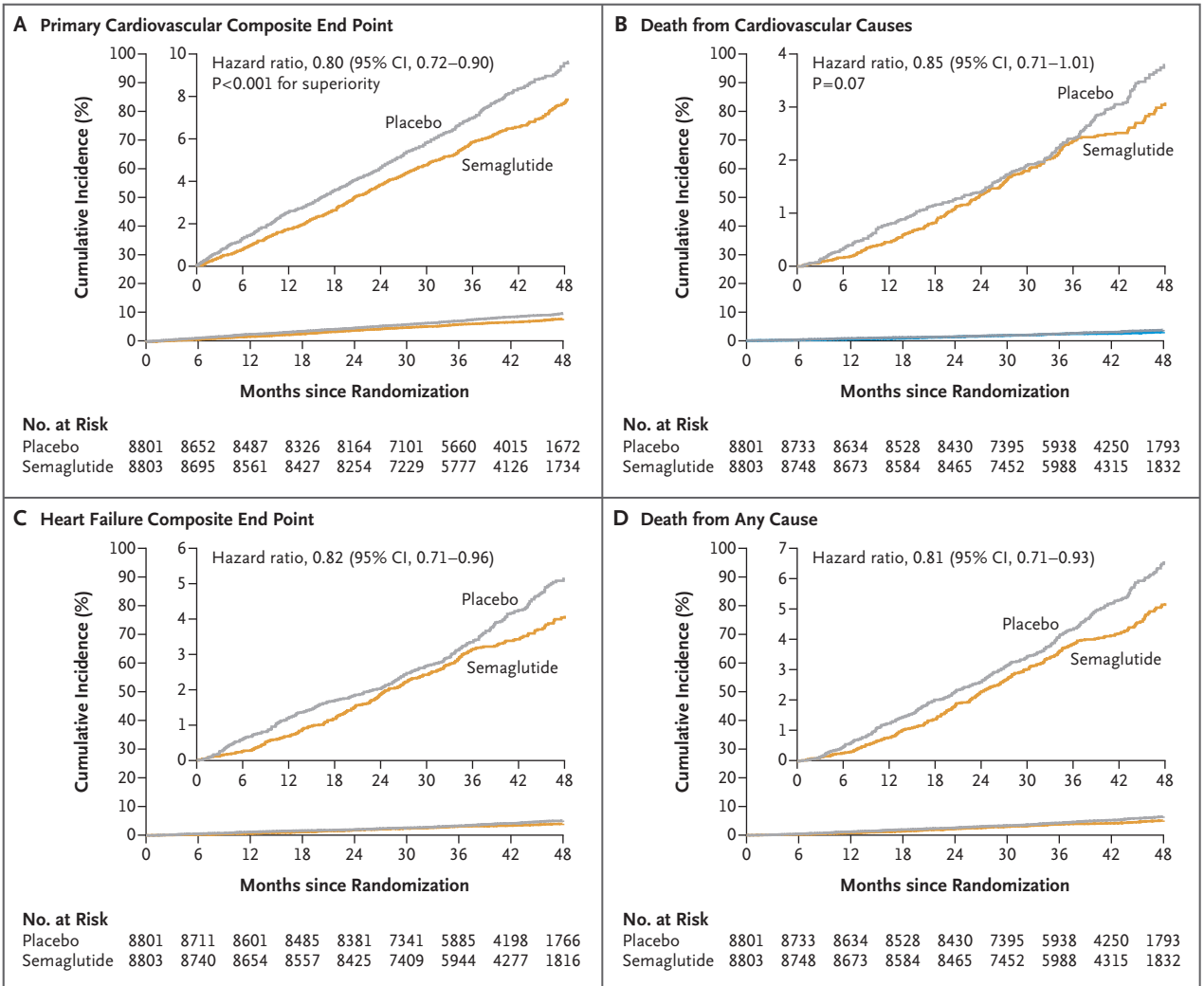

Figure 1. Time-to-First-Event Analysis for Primary and Confirmatory Secondary Efficacy End Points.

Panel A shows the cumulative incidence of the primary cardiovascular composite end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). Panel B shows the cumulative incidence of the first confirmatory secondary end point (death from cardiovascular causes). Panel C shows the cumulative incidence of the second confirmatory secondary end point (heart failure composite end point: death from cardiovascular causes or hospitalization or an urgent medical visit for heart failure). Panel D shows the cumulative incidence of the third confirmatory secondary end point (death from any cause). The definitions of all end points are provided in the Supplementary Appendix. Cumulative incidence was estimated with the use of the Aalen–Johansen method with accounting for competing risk,[24] and hazard ratios were estimated with the Cox proportional hazards regression model. Because the between-group difference in death from cardiovascular causes did not meet the required P value for hierarchical testing, results for the two subsequent end points in the testing hierarchy are reported as point estimates and 95% confidence intervals. The widths of these confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for these secondary end points. The insets show the same data on an enlarged y axis. The x axis is truncated at 48 months because of the limited number of patients in the trial after 48 months.

patients (33.4%) in the semaglutide group and 3204 patients (36.4%) in the placebo group (P<0.001). Adverse events leading to permanent discontinuation of semaglutide or placebo occurred in 1461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group (P<0.001); these events included gastrointestinal disorders in 880 patients (10.0%) in the semaglutide group and 172 patients (2.0%) in the placebo group (P<0.001) and gallbladder-related disorders in 246 patients (2.8%) and 203 patients (2.3%), respectively (P=0.04).

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA
Unstable angina leading to hospitalization	109 (1.2)	124 (1.4)	0.87 (0.67 to 1.13)	NA
Glycated hemoglobin level ≥6.5%††	306 (3.5)	1059 (12.0)	0.27 (0.24 to 0.31)	NA
Nephropathy composite end point‡‡	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)	NA
Glycated hemoglobin level ≥5.7% among patients with baseline glycated hemoglobin <5.7%§§	623 (21.3)	1501 (50.4)	0.33 (0.30 to 0.36)	NA

* Data are for the full analysis population during the in-trial observation period (from randomization to the final follow-up visit). All end points were analyzed with the use of a Cox proportional hazards model with treatment as a categorical fixed factor. Data from patients without events of interest were censored at the end of their in-trial period. NA denotes not applicable.

† The primary efficacy end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratio, 95% confidence interval, and P value were adjusted for the group sequential design with the use of likelihood-ratio ordering, and the nominal two-sided significance level was 0.046.

‡ Confirmatory secondary end points were analyzed under multiplicity control through a stagewise hierarchical testing scheme in which all P values after the first nonsignificant P value are not reported. The P values (unadjusted) for the primary and confirmatory secondary end points were to be compared with the nominal significance level derived from the relevant alpha spending function for the end point; if the P value was below the nominal limit, superiority would be shown. The nominal two-sided significance level was 0.023 for death from cardiovascular causes.

§ The heart failure composite end point was the first occurrence of death from cardiovascular causes or hospitalization or an urgent medical visit for heart failure.

¶ Because supportive secondary end points were not corrected for multiplicity, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for supportive secondary end points.

‖ The cardiovascular expanded end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina leading to hospitalization.

** The cardiovascular end point with death from any cause was a composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke.

†† Patients who underwent randomization in error and had a baseline glycated hemoglobin level higher than 6.5% (48 mmol per mole) were excluded from this analysis; 8800 patients in the semaglutide group and 8797 patients in the placebo group were included.

‡‡ The nephropathy end point was a five-component composite of death from renal causes, initiation of long-term renal replacement therapy (dialysis or transplantation), onset of a persistent eGFR lower than 15 ml per minute per 1.73 m^2, persistent 50% reduction in eGFR relative to baseline, or onset of persistent macroalbuminuria (urinary albumin-to-creatine ratio, >300 mg per gram).

§§ A glycated hemoglobin level of 5.7% or higher was assessed in a time-to-first-event analysis only among patients whose glycated hemoglobin was lower than 5.7% at baseline screening; 2925 patients in the semaglutide group and 2980 patients in the placebo group were included.

DISCUSSION

GLP-1 receptor agonists are recognized to have cardioprotective effects in patients with type 2 diabetes. We conducted this trial to determine whether semaglutide, a potent long-acting medication in this class,[25] would diminish excess cardiovascular risk associated with overweight

Table 3. Supportive Binary and Continuous Secondary End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

* Plus–minus values are means ±SE. Data are from the full analysis population. The binary end points were analyzed by logistic regression with treatment as factor and the baseline glycated hemoglobin level as a covariate. The continuous end points assessing changes from randomization to week 104 were analyzed with the use of analysis of covariance with treatment as factor and the baseline value as a covariate, with multiple imputation for missing values under a missing-at-random assumption. High-sensitivity CRP, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were log-transformed before analysis, and the results are thus reported as relative changes (i.e., percentage changes). Because supportive secondary end points were not corrected for multiplicity, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for supportive secondary end points. To convert values for glycated hemoglobin to millimoles per mole, multiply by 10.929 and subtract 2.15.

† Differences are given as the odds ratio for the binary glycated hemoglobin end points and as the between-group difference for the changes in continuous end points from baseline to 104 weeks.

‡ This end point was assessed among patients whose glycated hemoglobin level was 5.7% or higher at baseline screening and who had an assessment or imputed data at the time point of interest.

§ The EQ-5D-5L index score ranges from 0 to 1, with higher scores indicating better patient-reported health status. The index score is calculated only if responses are available from all five questions. The EQ-5D-VAS score ranges from 0 to 100, with higher scores indicating better patient-reported health status.

or obesity in patients with no history of diabetes. Among 17,604 patients with a BMI of 27 or greater and preexisting cardiovascular disease but without diabetes, treatment with once-weekly subcutaneous semaglutide at a dose of 2.4 mg for a mean duration of 33 months reduced the risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90). The effects of semaglutide occurred early after the initiation of treatment and were directionally similar across cardiovascular end points and among prespecified patient subgroups. Semaglutide was associated with decreases in body weight and waist circumference, findings consistent with the known metabolic effects of this class of medications.

The incidence of serious adverse events was lower among patients assigned to receive semaglutide than among those assigned to receive placebo. A higher percentage of patients discontinued semaglutide than placebo because of adverse events, a difference that appeared to be due to the greater incidence of gastrointestinal symptoms with semaglutide. Nausea, vomiting, and diarrhea are not uncommon during treat-

Table 4. Investigator-Reported Adverse Events.*

Event	Semaglutide (N=8803)	Placebo (N=8801)	P Value†
	no. of patients (%)		
Serious adverse events‡	2941 (33.4)	3204 (36.4)	<0.001
Cardiac disorders	1008 (11.5)	1184 (13.5)	<0.001
Infections and infestations	624 (7.1)	738 (8.4)	0.001
Nervous system disorders	444 (5.0)	496 (5.6)	0.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<0.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	0.94
Gastrointestinal disorders	342 (3.9)	323 (3.7)	0.48
Adverse events leading to permanent discontinuation of trial product, irrespective of seriousness‡	1461 (16.6)	718 (8.2)	<0.001
Gastrointestinal disorders	880 (10.0)	172 (2.0)	<0.001
Nervous system disorders	124 (1.4)	92 (1.0)	0.03
Metabolism and nutrition disorders	108 (1.2)	27 (0.3)	<0.001
General disorders and administration-site conditions	105 (1.2)	47 (0.5)	<0.001
Neoplasms benign, malignant, and unspecified	80 (0.9)	105 (1.2)	0.07
Infections and infestations	75 (0.9)	84 (1.0)	0.47
Prespecified adverse events of special interest, irrespective of seriousness§			
Covid-19–related events	2108 (23.9)	2150 (24.4)	0.46
Malignant neoplasms	422 (4.8)	418 (4.7)	0.92
Gallbladder-related disorders	246 (2.8)	203 (2.3)	0.04
Acute kidney failure	171 (1.9)	200 (2.3)	0.13
Acute pancreatitis¶	17 (0.2)	24 (0.3)	0.28

* This trial involved targeted collection of safety data, in which the only adverse events systematically recorded and reported were serious adverse events, adverse events leading to discontinuation of the trial product irrespective of seriousness, and adverse events of prespecified special interest irrespective of seriousness. Details of the adverse-event reporting are provided in the Supplementary Appendix. Events are classified according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 26.0, preferred terms. An expanded list of investigator-reported adverse events is provided in Table S3.

† P values are two-sided and were calculated with a Fisher's exact test for the test of no difference.

‡ Events are listed according to system organ class.

§ The adverse events of special interest were based on prespecified MedDRA queries.

¶ Acute pancreatitis events recorded here are those that were confirmed by the events adjudication committee. Investigators reported pancreatitis (acute or other type) events in 29 patients (0.3%) in the semaglutide group and 30 patients (0.3%) in the placebo group.

ment with GLP-1 receptor agonists, particularly at initiation and dose escalation.[26] The incidence of gallbladder-related disorders was higher with semaglutide than with placebo, an association that has also been reported previously.[27] Nonetheless, serious adverse events related to gastrointestinal disease, acute kidney failure, pancreatitis, cancers, or psychiatric disorders were not more frequent with semaglutide than with placebo.

Mechanisms of cardiovascular risk reduction with semaglutide may include those related to physiological benefits from the reduction of excess abnormal body fat and actions of semaglutide other than weight loss. Weight loss across a spectrum of elevated BMIs produces not only improvements in glucose levels and the traditional cardiovascular intermediate risk factors[28] but also reductions in ectopic adipose tissue depots that may contribute to atherosclerosis and myocardial dysfunction.[29] Perivascular and epicardial adipose tissue impose direct adverse effects on the vascular endothelium and myocar-

dium.[30] In addition, reductions in excess abnormal body fat ameliorate the systemic proinflammatory and prothrombotic milieu associated with obesity.[31]

Semaglutide improved cardiovascular outcomes in this trial, whereas lifestyle and pharmacologic interventions for overweight or obesity tested in previous trials have uniformly failed to do so.[11,14] The reductions in body weight achieved with other nonsurgical approaches have been substantially lower than the mean 9.4% decrease observed with semaglutide in this trial, and a post hoc analysis of data from a previous trial has suggested that cardiovascular risk might be decreased among patients who lose at least 10% of their body weight.[32] Similarly, bariatric surgery, in which reductions in body weight of more than 20% can be achieved, has been associated with fewer cardiovascular events than usual care.[33,34] However, the data are consistent with the between-group difference in the incidence of cardiovascular disease emerging early in this trial, which suggests that more rapid treatment-induced physiological changes beyond the magnitude of body-weight loss may have mediated at least part of the cardiovascular benefit.

Medications in the GLP-1 receptor agonist class have been shown in animals with or without diabetes to reduce inflammation, improve endothelial and left ventricular function, promote plaque stability, and decrease platelet aggregation.[16] In this trial, semaglutide was associated with changes in multiple biomarkers of cardiovascular risk, including blood pressure, waist circumference, glycemic control, nephropathy, and levels of lipids and C-reactive protein. For perspective, the observed decrease of 3.3 mm Hg in systolic blood pressure in this trial is greater than the decrease of 2 mm Hg predicted by a meta-analysis to yield a 7% reduction in vascular mortality,[35] and the 37.8-percentage-point decrease in the high-sensitivity C-reactive protein level with semaglutide in this trial is similar to that reported with statins.[36] These changes in cardiovascular biomarkers are notable for having been achieved on a background of high rates of use of statins, antihypertensive agents, and other evidence-based medications for atherosclerotic disease. Although our understanding of the mechanisms of cardiovascular protection with semaglutide remains speculative, the consistent effects on cardiometabolic risk factors support the hypothesis that clinical benefit is achieved through multiple interrelated pathways.

An important limitation of this trial is that we included only patients with preexisting cardiovascular disease. The effects of semaglutide on primary prevention of cardiovascular events in persons with overweight or obesity but without previous atherosclerotic disease were not studied. Moreover, the diversity of the patient group does not duplicate a globally representative population, particularly because only 27.7% and 3.8% of the enrolled patients were women or Black persons, respectively. With regard to the latter group, however, 12.5% of the patients enrolled in the United States identified as Black.

Recommendations for the treatment of type 2 diabetes have long targeted cardiovascular risk reduction,[37] and current guidelines recommend the use of GLP-1 receptor agonists in patients with diabetes who need cardiovascular risk reduction, weight management, or both.[38,39] Major adverse cardiovascular events were reduced by approximately 14% in a meta-analysis of GLP-1 receptor agonists (hazard ratio, 0.86; 95% CI, 0.80 to 0.93) among patients with type 2 diabetes and preexisting cardiovascular disease or cardiovascular risk factors,[10] with similar benefits observed in these patient groups in trials of subcutaneous or oral semaglutide (hazard ratios of 0.74 and 0.79, respectively).[40,41] The estimated global prevalence of diabetes is approximately 30% among patients with chronic coronary syndromes, and thus most people with cardiovascular disease do not have diabetes.[42] The magnitude of the effect of semaglutide in the current trial was similar to that among patients with diabetes in previous studies (within the constraints of between-trial comparisons), which suggests that treatment with semaglutide could be applied more broadly for secondary prevention of cardiovascular events in the expanding population of patients with overweight and obesity and atherosclerotic vascular disease. Moreover, because two thirds of the patients in this trial had dysglycemia (glycated hemoglobin levels of 5.7 to 6.4%), our findings support a more attentive therapeutic approach to prediabetes,[43] not only because of the association between prediabetes and cardiovascular risk but also because of the opportunity to improve cardiovascular outcomes through appropriate weight management.

In this randomized, placebo-controlled trial involving patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months.

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APPENDIX

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