ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

METHODS

We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

RESULTS

At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority). Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04). Rates of death from cardiovascular causes were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.

CONCLUSIONS

In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide. (Funded by Novo Nordisk; SUSTAIN-6 ClinicalTrials.gov number, NCT01720446.)

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Cardiovascular disease is the leading cause of death and complications in patients with type 2 diabetes.[1] Recently, trials evaluating a sodium–glucose cotransporter 2 inhibitor (empagliflozin) and a glucagon-like peptide 1 (GLP-1) analogue (liraglutide) have shown improved cardiovascular outcomes in patients with type 2 diabetes who were at high risk for cardiovascular events.[2,3]

Semaglutide, a GLP-1 analogue with an extended half-life of approximately 1 week (which permits once-weekly subcutaneous administration),[4] is currently in development but not yet approved for the treatment of type 2 diabetes. Regulatory guidance specifies the need to establish the cardiovascular safety of new therapies for type 2 diabetes in order to rule out excess cardiovascular risk.[5] The preapproval Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) was designed to assess the noninferiority of semaglutide as compared with placebo in terms of cardiovascular safety in patients with type 2 diabetes.

Methods

Trial Design and Oversight

We performed a randomized, double-blind, placebo-controlled, parallel-group trial at 230 sites in 20 countries. The trial protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board and ethics committee at each participating center. All patients provided written informed consent.

Patients were randomized in a 1:1:1:1 ratio to receive either 0.5 mg or 1.0 mg of once-weekly subcutaneous semaglutide or volume-matched placebo, which maintained blinding within dose. The trial consisted of a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period) in which patients who had prematurely discontinued a study treatment were also included.

The sponsor, Novo Nordisk, designed the study. Data were gathered by the site investigators, and the sponsor performed site monitoring, data collection, and data analysis. An independent data and safety monitoring committee performed ongoing surveillance and had access to all the data in an unblinded fashion.

All the authors had confidential access to the final trial results and actively contributed to manuscript preparation. A working group that included the first and last authors wrote the first draft of the manuscript, which was revised and approved by all the authors, who made the decision to submit the manuscript for publication. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol. Editorial support was funded by the sponsor and provided by independent medical writers under the guidance of the authors.

Patients

Patients with type 2 diabetes and a glycated hemoglobin level of 7% or more were eligible if they had not been treated with an antihyperglycemic drug or had been treated with no more than two oral antihyperglycemic agents, with or without basal or premixed insulin. Key inclusion criteria were an age of 50 years or more with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III), or chronic kidney disease of stage 3 or higher or an age of 60 years or more with at least one cardiovascular risk factor (as defined in Table S1 in the Supplementary Appendix, available at NEJM.org).

Key exclusion criteria included treatment with a dipeptidyl-peptidase 4 inhibitor within 30 days before screening or with a GLP-1–receptor agonist or insulin other than basal or premixed within 90 days before screening; a history of an acute coronary or cerebrovascular event within 90 days before randomization; planned revascularization of a coronary, carotid, or peripheral artery; or long-term dialysis. (A complete list of exclusion criteria is provided in Table S2 in the Supplementary Appendix.)

Procedures

The randomization of patients was stratified according to cardiovascular disease status (established cardiovascular or chronic kidney disease or cardiovascular risk factors only), insulin treatment (none, basal insulin only, or premixed insulin), and estimated glomerular filtration rate (≤30 ml or >30 ml per minute per 1.73 m^2 of body-surface area) at screening. A fixed dose-escalation procedure was used, with a starting dose of 0.25 mg for 4 weeks that escalated to 0.5 mg for 4 weeks until the maintenance dose (0.5 mg or 1.0 mg)

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was reached. No change in the maintenance dose of either semaglutide or placebo was permitted during the treatment period.

Patients were scheduled for quarterly site visits during the trial. All investigators were encouraged to treat all the patients according to local guidelines to achieve the most effective glycemic control (Table S3 in the Supplementary Appendix), and additional noninvestigational antihyperglycemic medication (nonincretin-based therapy) could be added or adjusted.

OUTCOMES

The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction (including silent), or nonfatal stroke. Prespecified secondary outcomes included the first occurrence of an expanded composite cardiovascular outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization [coronary or peripheral], and hospitalization for unstable angina or heart failure), an additional composite outcome (death from all causes, nonfatal myocardial infarction, or nonfatal stroke), the individual components of the composite outcomes, retinopathy complications, and new or worsening nephropathy. Each outcome, except for peripheral revascularization, was adjudicated in a blinded fashion by an external, independent event-adjudication committee.

Continuous efficacy and safety outcomes were assessed as the change from baseline to week 104. From baseline to week 109, we assessed serious and nonserious adverse events and hypoglycemic episodes, which were defined as severe (according to American Diabetes Association criteria[6]) or as confirmed on analysis of plasma glucose (with symptomatic hypoglycemia defined as <56 mg per deciliter [3.1 mmol per liter]). Neoplasm and pancreatitis events were adjudicated. (All definitions of adjudicated events are provided in Table S4 in the Supplementary Appendix.)

STATISTICAL ANALYSIS

The prespecified statistical analysis plan is available with the protocol at NEJM.org. We based the sample size for the trial on an assumed annual primary-event rate of 1.98% in each group, a dropout rate of less than 10.0%, a mean in-trial observation time of 2.1 years, and a true hazard ratio of 1.00. We determined that the enrollment of 3260 patients would be required to determine the primary outcome in at least 122 patients and provide a power of 90% to reject a hazard ratio of at least 1.80 at the 0.05 level of significance.

The prespecified analysis for the primary outcome was a Cox proportional-hazards model, with pooled treatment (semaglutide vs. placebo) as a fixed factor, and categorized according to all possible combinations of stratification factors used for randomization. The primary hypothesis was for noninferiority for the primary outcome. Such noninferiority was confirmed if the upper boundary of the two-sided 95% confidence interval of the hazard ratio was below the noninferiority margin of 1.80.[5] Testing for superiority for the primary outcome was not prespecified or adjusted for multiplicity. We conducted prespecified sensitivity analyses of the primary outcome, using alternative patient selection and data-censoring strategies for exposure to treatment, and per-protocol sensitivity analyses were performed post hoc. (Details regarding analysis sets are provided in the Supplementary Appendix.)

The primary outcome was evaluated in subgroups according to demographic and disease measures at baseline. We evaluated the effect of dose on the primary outcome by repeating the primary analysis with the four treatment groups (semaglutide doses of 0.5 mg and 1.0 mg and corresponding placebo doses) using volume-matched treatment comparisons. Efficacy and safety outcome analyses were prespecified to include the four treatment groups.

All P values are two-sided, with a level of 0.05 considered to indicate statistical significance. P values other than that for the primary hypothesis have not been adjusted for multiplicity and have been calculated to test for null hypotheses of no difference. All results were analyzed on an intention-to-treat basis that included the full analysis set (i.e., all patients who underwent randomization according to the planned treatment), with the exception of adverse events leading to premature discontinuation, which were included in the as-treated safety analysis.

RESULTS

PATIENTS

From February 2013 through December 2013, a total of 4346 patients were screened, and 3297 underwent randomization; of these patients, 3232

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Semaglutide (N=1648)		Placebo (N=1649)		Total (N=3297)
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)	
Age — yr	64.6±7.3	64.7±7.1	64.8±7.6	64.4±7.5	64.6±7.4
Male sex — no. (%)	495 (59.9)	518 (63.0)	482 (58.5)	507 (61.5)	2002 (60.7)
Body weight — kg	91.8±20.3	92.9±21.1	91.8±20.3	91.9±20.8	92.1±20.6
Type 2 diabetes					
Duration — yr	14.3±8.2	14.1±8.2	14.0±8.5	13.2±7.4	13.9±8.1
Glycated hemoglobin — %	8.7±1.4	8.7±1.5	8.7±1.5	8.7±1.5	8.7±1.5
Cardiovascular risk factors					
Systolic blood pressure — mm Hg	136.1±18.0	135.8±17.0	135.8±16.2	134.8±17.5	135.6±17.2
Diastolic blood pressure — mm Hg	77.1±9.8	76.9±10.2	77.5±9.9	76.7±10.2	77.0±10.0
Low-density lipoprotein cholesterol — mg/dl†	81.6±47.1	83.3±41.2	80.9±48.1	83.6±45.9	82.3±45.6
Never smoked — no. (%)	390 (47.2)	364 (44.3)	391 (47.5)	348 (42.2)	1493 (45.3)
History of cardiovascular disease — no. (%)					
Ischemic heart disease	493 (59.7)	495 (60.2)	510 (61.9)	496 (60.1)	1994 (60.5)
Myocardial infarction	266 (32.2)	264 (32.1)	267 (32.4)	275 (33.3)	1072 (32.5)
Heart failure	201 (24.3)	180 (21.9)	190 (23.1)	206 (25.0)	777 (23.6)
Ischemic stroke	89 (10.8)	89 (10.8)	96 (11.7)	109 (13.2)	383 (11.6)
Hemorrhagic stroke	28 (3.4)	24 (2.9)	27 (3.3)	29 (3.5)	108 (3.3)
Hypertension	772 (93.5)	771 (93.8)	756 (91.7)	760 (92.1)	3059 (92.8)

* Plus–minus values are means ±SD unless otherwise indicated. Differences in baseline characteristics were assessed with the use of analysis of covariance for continuous characteristics and logistic regression for categorical characteristics. There were no significant differences between the groups except for the duration of type 2 diabetes (P=0.048). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

† Values are geometric means and coefficients of variation.

(98.0%) attended the last follow-up visit at an investigator site, were contacted by telephone, or died during the trial. The date of the last patient visit was March 15, 2016. Vital status was known for 99.6% of the patients by the end of the trial (Figs. S1A and S1B in the Supplementary Appendix).

The median observation time was 2.1 years. Rates of premature treatment discontinuation were similar across groups (20% overall) (Table S5 in the Supplementary Appendix). The mean percentage of time during which patients received semaglutide was 86.5% (87.7% among those receiving 0.5 mg and 85.3% among those receiving 1.0 mg), and the mean percentage during which patients received placebo was 89.5% (89.4% among those receiving 0.5 mg and 89.6% among those receiving 1.0 mg).

Demographic and clinical characteristics of the patients at baseline were similar across treatment groups (Table 1, and Table S6 in the Supplementary Appendix). Of the 3297 patients, 2735 (83.0%) had established cardiovascular disease (including chronic kidney disease of stage 3 or higher), 1940 patients (58.8%) had established cardiovascular disease without chronic kidney disease, 353 (10.7%) had chronic kidney disease only, and 442 (13.4%) had both cardiovascular disease and kidney disease; 17% of the patients had cardiovascular risk factors and were 60 years of age or older. The overall mean duration of type 2 diabetes was 13.9 years, and the mean glycated hemoglobin level was 8.7%. The use of antihyperglycemic and cardiovascular medications was well balanced between the groups (Tables S7A and S8A in the Supplementary Appendix). Most patients (93.5%) were taking antihypertensive medication, including angiotensin-converting–enzyme inhibitors (49.8%) and angiotensin-receptor blockers (33.7%); 76.5%

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were receiving lipid-lowering medications; and 76.3% were receiving antithrombotic medications, including acetylsalicylic acid (63.9%) and adenosine diphosphate receptor inhibitors (21.1%) (Table S8A in the Supplementary Appendix).

CARDIOVASCULAR OUTCOMES

The composite primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and 146 of 1649 (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority; P=0.02 for superiority) (Fig. 1A). Sensitivity analyses supported the findings from the primary analysis (Fig. S2 in the Supplementary Appendix). Nonfatal myocardial infarction occurred in 47 patients (2.9%) in the semaglutide group and 64 (3.9%) in the placebo group, a difference that was not significant (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12) (Fig. 1B). Nonfatal stroke occurred in 27 patients (1.6%) in the semaglutide group and 44 (2.7%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04) (Fig. 1C). The risk of cardiovascular death was similar in the two groups, with deaths reported in 44 patients (2.7%) in the semaglutide group and 46 (2.8%) in the placebo group (hazard ratio, 0.98; 95% CI, 0.65 to 1.48; P=0.92) (Fig. 1D).

No significant treatment interactions were identified for any subgroups (Fig. S3 in the Supplementary Appendix). Similar risk reductions for the primary outcome and its components were observed for both doses of semaglutide (Fig. S4 in the Supplementary Appendix). Cardiovascular outcomes are provided in Table 2, and in Table S9 in the Supplementary Appendix. Throughout the trial, a greater proportion of patients in the placebo group than in the semaglutide group received additional cardiovascular medications, including antihypertensive agents, diuretics, and lipid-lowering medications (Table S8B in the Supplementary Appendix).

GLYCEMIC CONTROL

At week 104, among patients receiving semaglutide, the mean glycated hemoglobin level decreased from 8.7% at baseline to 7.6% in the group receiving 0.5 mg and to 7.3% in the group receiving 1.0 mg, for changes of –1.1% and –1.4%, respectively; in the placebo group, the mean level decreased to 8.3% in the two dose groups, for a reduction of 0.4% in each group. Thus, the mean glycated hemoglobin level in the semaglutide group, as compared with the placebo group, was 0.7 percentage points lower in the group receiving 0.5 mg and 1.0 percentage point lower in the group receiving 1.0 mg (estimated treatment difference) (P<0.001 for both comparisons) (Fig. 2A, and Table S10 in the Supplementary Appendix). During the trial, significantly more patients in the placebo group than in the semaglutide group received additional antihyperglycemic agents, including insulin, which was initiated more than twice as frequently in the placebo group (Table S7B in the Supplementary Appendix).

BODY WEIGHT

At week 104, among patients receiving semaglutide, the mean body weight decreased from 92.1 kg at baseline to 88.5 kg in the group receiving 0.5 mg and to 87.2 kg in the group receiving 1.0 mg, for changes of −3.6 kg and −4.9 kg, respectively; in the placebo group, the mean body weight decreased to 91.4 kg and 91.6 kg, for changes of −0.7 kg and −0.5 kg, respectively. Thus, the mean body weight in the semaglutide group, as compared with the placebo group, was 2.9 kg lower in the group receiving 0.5 mg and 4.3 kg lower in the group receiving 1.0 mg (P<0.001 for both comparisons) (Fig. 2B, and Table S10 in the Supplementary Appendix).

MICROVASCULAR OUTCOMES

Diabetic retinopathy complications occurred in 50 patients (3.0%) in the semaglutide group and 29 (1.8%) in the placebo group (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02) (Table 2, and Table S9 and Fig. S5 in the Supplementary Appendix). The treatment difference between groups was first seen very early in the trial. The numbers of patients who required retinal photocoagulation were 38 (2.3%) in the semaglutide group versus 20 (1.2%) in the placebo group, the numbers of those who required the use of an intravitreal agent were 16 (1.0%) versus 13 (0.8%), the numbers of those who had a vitreous hemorrhage were 16 (1.0%) versus 7 (0.4%), and the numbers of those who had an onset of diabetes-related blindness were 5 (0.3%) versus 1 (0.1%) (Table S9 in the Supplementary Appendix). Of the 79 patients with retinopathy complications, 66 (83.5%) had preexisting retinopathy at baseline (42 of 50 [84.0%] in the semaglutide group and 24 of 29 [82.8%] in the placebo group). New or worsening nephrop-

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Figure 1. Cardiovascular Outcomes.

Shown are Kaplan–Meier plots of the primary outcome (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), nonfatal myocardial infarction (Panel B), nonfatal stroke (Panel C), and death from cardiovascular causes (Panel D). The trial included a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period). In Panel C, there were no events in the semaglutide group after week 104. Insets show the same data on an expanded y axis.

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Table 2. Primary and Secondary Cardiovascular and Microvascular Outcomes.

Outcome	Semaglutide (N=1648)		Placebo (N=1649)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no./100 person-yr*	*no. (%)*	*no./100 person-yr*		
Primary composite outcome†	108 (6.6)	3.24	146 (8.9)	4.44	0.74 (0.58–0.95)	<0.001 for noninferiority; 0.02 for superiority
Expanded composite outcome‡	199 (12.1)	6.17	264 (16.0)	8.36	0.74 (0.62–0.89)	0.002
All-cause death, nonfatal myocardial infarction, or nonfatal stroke	122 (7.4)	3.66	158 (9.6)	4.81	0.77 (0.61–0.97)	0.03
Death						
From any cause	62 (3.8)	1.82	60 (3.6)	1.76	1.05 (0.74–1.50)	0.79
From cardiovascular cause	44 (2.7)	1.29	46 (2.8)	1.35	0.98 (0.65–1.48)	0.92
Nonfatal myocardial infarction	47 (2.9)	1.40	64 (3.9)	1.92	0.74 (0.51–1.08)	0.12
Nonfatal stroke	27 (1.6)	0.80	44 (2.7)	1.31	0.61 (0.38–0.99)	0.04
Hospitalization for unstable angina pectoris	22 (1.3)	0.65	27 (1.6)	0.80	0.82 (0.47–1.44)	0.49
Revascularization	83 (5.0)	2.50	126 (7.6)	3.85	0.65 (0.50–0.86)	0.003
Hospitalization for heart failure	59 (3.6)	1.76	54 (3.3)	1.61	1.11 (0.77–1.61)	0.57
Retinopathy complications§	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11–2.78)	0.02
New or worsening nephropathy¶	62 (3.8)	1.86	100 (6.1)	3.06	0.64 (0.46–0.88)	0.005

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with the study treatments as fixed factors and stratified according to all combinations of stratification factors used in the randomization.
† The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure.
§ Retinopathy complications include vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation.
¶ New or worsening nephropathy includes persistent macroalbuminuria, persistent doubling of the serum creatinine level and a creatinine clearance of less than 45 ml per minute per 1.73 m^2 of body-surface area (according to the Modification of Diet in Renal Disease criteria), or the need for continuous renal-replacement therapy.

athy occurred in 62 patients (3.8%) in the semaglutide group and 100 (6.1%) in the placebo group (hazard ratio, 0.64; 95% CI, 0.46 to 0.88; P=0.005) (Table 2, and Table S9 and Fig. S5 in the Supplementary Appendix).

OTHER OUTCOMES

At week 104, among patients receiving semaglutide, the mean systolic blood pressure decreased from 135.6 mm Hg at baseline to 132.2 mm Hg among those receiving 0.5 mg and to 130.3 mm Hg among those receiving 1.0 mg, for reductions of 3.4 mm Hg and 5.4 mm Hg, respectively; in the placebo group, the mean systolic blood pressure decreased to 133.5 mm Hg and 132.8 mm Hg, for reductions of 2.2 mm Hg and 2.8 mm Hg, respectively. Thus, the mean systolic blood pressure in the semaglutide group, as compared with the placebo group, was 1.3 mm Hg lower in the group receiving 0.5 mg (P=0.10) and 2.6 mm Hg lower in the group receiving 1.0 mg (P<0.001) (Table S10 and Fig. S6 in the Supplementary Appendix).

At week 104, among patients in the semaglutide group, the mean pulse rate increased from a baseline value of 72.0 bpm by 2.1 bpm among those receiving 0.5 mg and by 2.4 bpm among those receiving 1.0 mg; in the placebo group, the corresponding changes were an increase of 0.1 bpm and a decrease of 0.1 bpm. Thus, the mean pulse rate in the semaglutide group, as compared with the placebo group, was 2.0 bpm higher in the group receiving 0.5 mg and 2.5 bpm higher in the group

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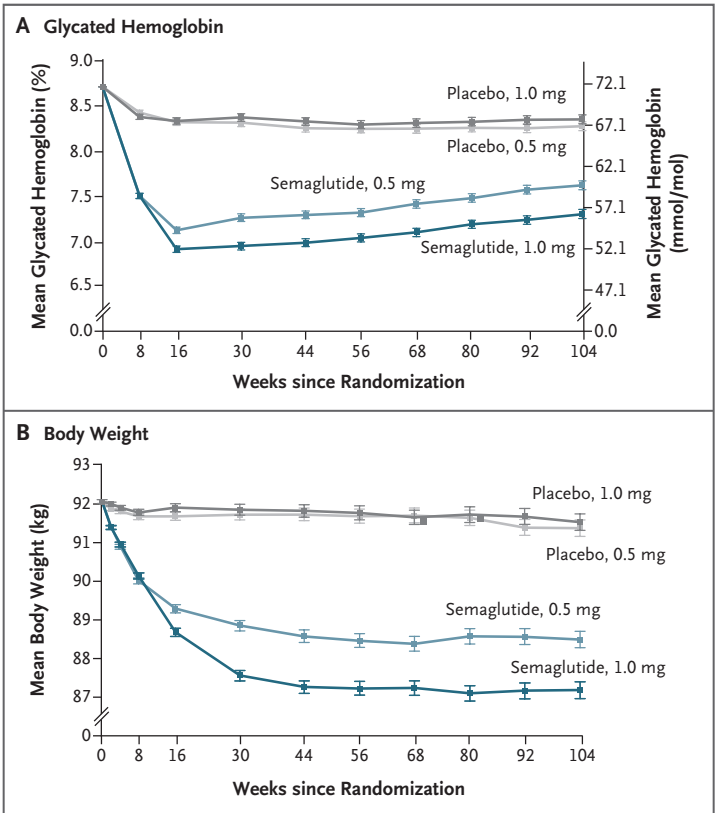

Figure 2. Glycated Hemoglobin and Body Weight.

Shown are the mean values for glycated hemoglobin (Panel A) and body weight (Panel B) during the trial period. The I bars represent standard errors. Data were estimated on the basis of scheduled visits in the full analysis set with the use of a mixed model for repeated measures with treatment group (semaglutide doses of 0.5 mg and 1.0 mg and corresponding placebo doses) and all possible combinations of stratification factors used for randomization as fixed factors.

receiving 1.0 mg (P<0.001 for both comparisons). Changes in diastolic blood pressure were similar in the treatment groups. Lipid measurements are provided in Table S10 in the Supplementary Appendix.

SAFETY

Gastrointestinal disorders were more frequent in the semaglutide group than in the placebo group (Table 3, and Table S11 in the Supplementary Appendix). The majority of gastrointestinal events were mild or moderate in severity and occurred during the first 30 weeks. Treatment discontinuation because of adverse events (mainly gastrointestinal) was more frequent in the semaglutide group than in the placebo group. The frequency and rate of serious adverse events, including serious cardiac disorders, were lower in the semaglutide group than in the placebo group (Table S11 in the Supplementary Appendix).

Acute pancreatitis occurred in 9 patients in the semaglutide group and in 12 in the placebo group; all events were mild, according to the revised Atlanta criteria.[7] Lipase and amylase levels were significantly higher in the semaglutide group than in the placebo group (Fig. S7 in the Supplementary Appendix). Gallbladder disorders occurred in 58 patients in the semaglutide group and 61 in the placebo group. The rates of malignant neoplasms, which were similar in the two groups, were higher in the semaglutide group receiving 1.0 mg and lower in the group receiving 0.5 mg than in the placebo groups (Table 3, and Fig. S8 in the Supplementary Appendix). Pancreatic cancer occurred in 1 patient receiving 1.0 mg of semaglutide and in 4 patients receiving placebo. No medullary thyroid carcinomas were confirmed by the event-adjudication committee in either treatment group. Antibodies against semaglutide were detected in 30 patients treated with semaglutide, with the greatest number of patients (14) testing positive at week 44. In the majority of patients, antibody formation was transient — only 4 patients tested positive during follow-up — and antibody titers were generally low.

Similar numbers and occurrence rates of severe hypoglycemic episodes or hypoglycemia as confirmed on plasma glucose testing were seen with semaglutide doses of 0.5 mg and 1.0 mg (191 [23.1%] and 178 [21.7%], respectively), as compared with placebo doses of 0.5 and 1.0 mg (177 [21.5%] and 173 [21.0%]).

DISCUSSION

In this cardiovascular outcomes trial, we confirmed our primary hypothesis that semaglutide would be noninferior to placebo. Semaglutide-treated patients had a significant 26% lower risk of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than did those receiving placebo. This lower risk was principally driven by a significant (39%) decrease in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal myocardial infarction, with no significant difference in the rate of cardiovascular death. Similar risk reductions were observed with both doses of semaglutide. The number of

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Table 3. Selected Adverse Events.*

Event	Semaglutide		Placebo	
	0.5 mg (N=826)	1.0 mg (N=822)	0.5 mg (N=824)	1.0 mg (N=825)
	number of patients (percent)			
Adverse event	740 (89.6)	732 (89.1)	748 (90.8)	736 (89.2)
Serious adverse event†	289 (35.0)	276 (33.6)	329 (39.9)	298 (36.1)
Severe adverse event‡	200 (24.2)	207 (25.2)	216 (26.2)	194 (23.5)
Adverse event leading to treatment discontinuation	95 (11.5)	119 (14.5)	47 (5.7)	63 (7.6)
Nausea	18 (2.2)	38 (4.6)	2 (0.2)	2 (0.2)
Vomiting	14 (1.7)	23 (2.8)	3 (0.4)	2 (0.2)
Diarrhea	15 (1.8)	19 (2.3)	5 (0.6)	2 (0.2)
Gastrointestinal disorder§	419 (50.7)	430 (52.3)	294 (35.7)	290 (35.2)
Diarrhea	148 (17.9)	151 (18.4)	98 (11.9)	87 (10.5)
Nausea	143 (17.3)	180 (21.9)	62 (7.5)	67 (8.1)
Vomiting	87 (10.5)	122 (14.8)	43 (5.2)	34 (4.1)
Cardiac disorder§	173 (20.9)	150 (18.2)	189 (22.9)	173 (21.0)
Atrial fibrillation	27 (3.3)	23 (2.8)	32 (3.9)	26 (3.2)
Acute pancreatitis¶	6 (0.7)	3 (0.4)	3 (0.4)	9 (1.1)
Gallbladder disorder‖	32 (3.9)	26 (3.2)	38 (4.6)	23 (2.8)
Cholelithiasis	21 (2.5)	17 (2.1)	19 (2.3)	12 (1.5)
Acute cholecystitis	4 (0.5)	0	6 (0.7)	2 (0.2)
Severe or symptomatic hypoglycemic event**	191 (23.1)	178 (21.7)	177 (21.5)	173 (21.0)
Acute renal failure‖	42 (5.1)	23 (2.8)	34 (4.1)	35 (4.2)
Allergic reaction‖	49 (5.9)	49 (6.0)	46 (5.6)	57 (6.9)
Injection-site reaction‖	8 (1.0)	9 (1.1)	9 (1.1)	12 (1.5)
Neoplasm¶	66 (8.0)	89 (10.8)	70 (8.5)	69 (8.4)
Benign	40 (4.8)	54 (6.6)	36 (4.4)	34 (4.1)
Premalignant	4 (0.5)	6 (0.7)	3 (0.4)	2 (0.2)
Malignant				
Any	26 (3.1)	40 (4.9)	35 (4.2)	35 (4.2)
Pancreatic	0	1 (0.1)	2 (0.2)	2 (0.2)

* Adverse events were selected on the basis of the safety areas of interest for GLP-1–receptor agonists. All data are based on investigator-reported adverse events unless otherwise specified. All data were reported during the trial, except for adverse events leading to treatment discontinuation, which are reported on an as-treated basis. A complete list of serious adverse events according to system organ class is provided in Table S10 in the Supplementary Appendix.

† A serious adverse event was defined as death, a life-threatening episode, hospitalization or prolongation of existing hospitalization, a persistent or substantial disability or incapacity, or an event otherwise considered to be an important medical event.

‡ A severe adverse event was defined as an event that considerably interferes with the patient's daily activities and is unacceptable.

§ This category was defined according to the system organ class in the *Medical Dictionary for Regulatory Activities* (MedDRA).

¶ This event was confirmed by the event-adjudication committee.

‖ This category was based on the group of preferred terms in MedDRA.

** This category of hypoglycemic event includes episodes of severe hypoglycemia (defined according to the American Diabetes Association criteria) or symptomatic hypoglycemia as confirmed on plasma glucose testing (<56 mg per deciliter [3.1 mmol per liter]).

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patients who would need to be treated to prevent one event of the primary outcome over a period of 24 months was 45 on the basis of Kaplan–Meier estimates.[8] Most study patients were receiving cardiovascular risk management at baseline, as shown by a high proportion of patients receiving antihypertensive, lipid-lowering, and anti-platelet medications. The risk reduction for the primary outcome was seen despite an increase in pulse rate, a class effect for GLP-1–receptor agonists.

Semaglutide-treated patients had a lower risk of new or worsening nephropathy, according to differences in macroalbuminuria, but a higher risk of diabetic retinopathy complications than did those receiving placebo. Although the overall number of retinopathy events was low, there was an unexpected higher rate of retinopathy complications (vitreous hemorrhage, blindness, or the need for treatment with an intravitreal agent or photocoagulation) in the semaglutide group. An association between rapid glucose lowering and worsening of retinopathy has been reported in patients with type 1 diabetes.[9,10] The applicability of such an association to our finding is unclear, and a direct effect of semaglutide cannot be ruled out.

Semaglutide was associated with significant and sustained reductions in glycated hemoglobin levels, as compared with placebo, with similar rates of hypoglycemia. During the trial, more patients in the placebo group than in the semaglutide group intensified their antihyperglycemic treatment. However, the between-group difference in glycated hemoglobin levels remained after 2 years. Clinically meaningful and sustained weight loss and a reduction in systolic blood pressure occurred in the semaglutide group versus the placebo group over 2 years. The reductions in glycated hemoglobin, body weight, and systolic blood pressure may all have contributed to the observed reduction in cardiovascular risk with semaglutide.

With the exception of complications of retinopathy, semaglutide had a safety profile similar to that of other GLP-1–receptor agonists. The rate of malignant neoplasms was similar in the pooled semaglutide group and the pooled placebo group, although the highest rate was observed with the semaglutide dose of 1.0 mg. The rate of pancreatic cancer — an event of interest for this drug class — was lower with semaglutide, and no medullary thyroid carcinomas were reported in this trial. Pancreatitis occurred in low yet similar numbers of patients in the two pooled groups.

To date, two antihyperglycemic agents have been shown to reduce the rate of cardiovascular events in patients with type 2 diabetes at high cardiovascular risk.[2,3] In this trial, the risk reduction of the primary outcome was driven by a significant decrease in the rate of nonfatal stroke and a nonsignificant decrease in the rate of nonfatal myocardial infarction, with no difference in cardiovascular death. The beneficial effect of semaglutide on cardiovascular outcomes may relate to modification of the progression of atherosclerosis.

This trial was powered as a noninferiority study to exclude a preapproval safety margin of 1.8 set by the Food and Drug Administration. It was not powered to show superiority, so such testing was not prespecified. However, the treatment effect of semaglutide and the accrual of more events than estimated resulted in a significantly lower risk of the primary outcome among patients in the semaglutide group. Patients were followed for a relatively short duration (2.1 years) and were at high cardiovascular risk. The generalizability of these findings to other populations and a longer duration of treatment is unknown. It is also unknown to what extent the greater glycated hemoglobin reductions in the semaglutide group contributed to the results.

In conclusion, among patients with type 2 diabetes at high cardiovascular risk, the rate of first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was significantly lower in those receiving semaglutide than in those receiving placebo, which confirmed noninferiority.

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