The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2023 VOL. 389 NO. 12

Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

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ABSTRACT

BACKGROUND

Heart failure with preserved ejection fraction is increasing in prevalence and is associated with a high symptom burden and functional impairment, especially in persons with obesity. No therapies have been approved to target obesity-related heart failure with preserved ejection fraction.

METHODS

We randomly assigned 529 patients who had heart failure with preserved ejection fraction and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The dual primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight. Confirmatory secondary end points included the change in the 6-minute walk distance; a hierarchical composite end point that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6-minute walk distance; and the change in the C-reactive protein (CRP) level.

RESULTS

The mean change in the KCCQ-CSS was 16.6 points with semaglutide and 8.7 points with placebo (estimated difference, 7.8 points; 95% confidence interval [CI], 4.8 to 10.9; P<0.001), and the mean percentage change in body weight was –13.3% with semaglutide and –2.6% with placebo (estimated difference, –10.7 percentage points; 95% CI, –11.9 to –9.4; P<0.001). The mean change in the 6-minute walk distance was 21.5 m with semaglutide and 1.2 m with placebo (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1; P<0.001). In the analysis of the hierarchical composite end point, semaglutide produced more wins than placebo (win ratio, 1.72; 95% CI, 1.37 to 2.15; P<0.001). The mean percentage change in the CRP level was –43.5% with semaglutide and –7.3% with placebo (estimated treatment ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). Serious adverse events were reported in 35 participants (13.3%) in the semaglutide group and 71 (26.7%) in the placebo group.

CONCLUSIONS

In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo. (Funded by Novo Nordisk; STEP-HFpEF ClinicalTrials.gov number, NCT04788511.)

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*A list of the STEP HFpEF trial committees and investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 25, 2023, at NEJM.org.

N Engl J Med 2023;389:1069-84.
DOI: 10.1056/NEJMoa2306963

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Heart failure with preserved ejection fraction accounts for more than half of all cases of heart failure in the United States and is increasing in prevalence.[1-3] The majority of persons with the condition have overweight or obesity, and growing evidence suggests that obesity and excess adiposity are not simply coexisting conditions but may play a role in the development and progression of heart failure with preserved ejection fraction.[4-8] Patients with this condition and obesity have more adverse hemodynamic and clinical features and a greater symptom burden, worse functional capacity, and more severely impaired quality of life than those with heart failure with preserved ejection fraction but no obesity.[9-12]

Whether the use of pharmacotherapies that specifically target obesity can reduce symptoms and physical limitations and improve exercise function in this distinct group of patients is unknown. Once weekly semaglutide at a dose of 2.4 mg administered subcutaneously is a potent glucagon-like peptide 1 receptor agonist that is approved for long-term weight management and has previously been shown to produce major weight loss in persons with overweight or obesity and to have favorable effects on cardiometabolic risk factors.[13,14] We asked whether once weekly semaglutide at a dose of 2.4 mg might lead to reductions in symptoms and physical limitations and to improved exercise function, in addition to weight loss, in patients with heart failure with preserved ejection fraction and obesity.

Methods

Trial Design and Oversight

We conducted the Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction (STEP-HFpEF) trial, a randomized, double-blind, placebo-controlled trial, at 96 sites in 13 countries in Asia, Europe, and North and South America. The steering committee, which included both academic researchers and representatives of the sponsor (Novo Nordisk), designed the trial in collaboration with the sponsor and was primarily responsible for trial-related academic publications. A global expert panel provided academic, medical, and operational input in each country. The design of the trial and the baseline characteristics of the trial participants have been published previously.[15] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol, available with the full text of this article at NEJM.org, was approved by the independent ethics committee or institutional review board at each site. The results for the dual primary end points and confirmatory secondary efficacy end points used in the testing hierarchy were validated by a sponsor-independent statistician who had access to all relevant data sets.

The sponsor assumes responsibility for activities related to trial conduct, data collection, and statistical analysis. The first draft of the manuscript was prepared by the first author, who had full access to all the trial data. The authors interpreted the data, contributed to the writing of the submitted manuscript, approved the final version of the manuscript, had final responsibility for the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Participants

Persons 18 years of age or older were eligible to participate if they had a left ventricular ejection fraction of at least 45%; a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of at least 30; New York Heart Association functional class II, III, or IV symptoms; a Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of less than 90 points (scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations); a 6-minute walk distance of at least 100 m; and at least one of the following findings: elevated left ventricular filling pressures (on the basis of direct invasive measurements), elevated natriuretic peptide levels (with thresholds stratified according to the BMI at baseline) plus echocardiographic abnormalities, or hospitalization for heart failure in the 12 months before screening plus ongoing treatment with diuretics or echocardiographic abnormalities.

Key exclusion criteria were a patient-reported change in body weight of more than 5 kg within 90 days before screening and a history of diabetes (glycated hemoglobin level of ≥6.5% based on medical record data within 3 months before

screening or on a local laboratory value at the time of screening; patients were also excluded if they had a known medical history of diabetes). The full list of eligibility criteria is provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

TRIAL PROCEDURES AND OUTCOMES

Participants were randomly assigned in a 1:1 ratio with the use of an interactive Web-based response system to receive once weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 52 weeks, followed by a 5-week follow-up period. Randomization was stratified according to baseline BMI (<35 vs. ≥35). Semaglutide treatment was initiated at a dose of 0.25 mg once weekly for the first 4 weeks, and the dose was escalated every 4 weeks with the aim of reaching the maintenance dose of 2.4 mg by week 16 (Fig. S1). Participants who discontinued treatment prematurely remained in the trial.

The dual primary end points were the change in the KCCQ-CSS and the percentage change in body weight from baseline to week 52. The KCCQ is a standardized, 23-item, participant-administered instrument that quantifies heart failure–related symptoms (frequency, severity, and recent changes), physical function, quality of life, and social function.[16-18] For each domain, the validity, reproducibility, responsiveness, and interpretability have been independently established.[16-18] Scores are transformed to a range of 0 to 100, with higher scores reflecting better health status; the KCCQ-CSS includes the symptom and physical function domains.

The confirmatory secondary end points were the change in the 6-minute walk distance from baseline to week 52, a hierarchical composite end point (described in detail below) for which the number of wins was compared between the semaglutide and placebo groups, and the change in the log-transformed C-reactive protein (CRP) level from screening (week –2) to week 52. The hierarchical composite end point included death from any cause from baseline to week 57; the number and timing of heart failure events (defined as adjudicated events of hospitalization for heart failure or urgent visits in which intravenous therapy was administered, baseline to week 57); differences of at least 15, at least 10, and at least 5 points in the change in the KCCQ-CSS from baseline to week 52; and a difference of at least 30 m in the change in the 6-minute walk distance from baseline to week 52. Supportive secondary and exploratory end points are described in the Supplemental Methods section and in Table S2.

Safety assessments included serious adverse events and adverse events of special interest (baseline to week 57). An independent external committee, the members of which were unaware of the trial-group assignments, adjudicated hospitalizations for heart failure, urgent visits in which intravenous therapy was administered, and all deaths. All laboratory assays were performed in a central laboratory.

STATISTICAL ANALYSIS

Details of the statistical methods are provided in the statistical analysis plan (available with the protocol at NEJM.org) and have been reported previously.[15] A sample size of 516 participants provided a marginal power of 90% to detect a between-group difference of 4.1 points in the change in the KCCQ-CSS and 99% to detect a between-group difference of 9.9 percentage points in the percentage change in body weight at an alpha level of 4% and 1%, respectively.[15] Efficacy end points were analyzed in the full analysis population (all participants who underwent randomization, included in the analysis according to the intention-to-treat principle); safety end points were analyzed in the safety analysis population (an as-treated population that included all participants who underwent randomization and received at least one dose of semaglutide or placebo). Observation periods included the in-trial period (i.e., during participation in the trial, regardless of treatment discontinuation or rescue intervention) and the treatment period (i.e., the period from the first date of administration of semaglutide or placebo to the date of the last administration, excluding potential intervals during which treatment was not being received [i.e., two or more consecutive missed doses]). All results of statistical analyses are provided with two-sided 95% confidence intervals; two-sided P values are reported only for the confirmatory end points that involved the treatment policy estimand.

Two estimands (a treatment policy estimand consistent with the intention-to-treat principle and a hypothetical trial product estimand [if treatment was taken as intended]) were used to evaluate

efficacy and therefore accounted for intercurrent events (which included discontinuation of treatment [including discontinuation due to death], initiation of treatment with other weight-management agents, or bariatric surgery). All analyses in the statistical testing hierarchy were based on the primary treatment policy estimand. The Supplementary Appendix and statistical analysis plan provide further details on the estimands, statistical analyses, and imputation methods used to account for missing data.

The dual primary end points were evaluated with the use of analysis of covariance, with the change in the corresponding end point at week 52 used as the dependent variable, randomly assigned group and BMI stratum used as fixed factors, and adjustment for the baseline value of the corresponding end point used as a continuous variable for each imputation data set. Treatment effects and standard errors were combined with the use of Rubin's rule.

Strong control for type I error was used in analyses of the dual primary and confirmatory secondary end points that involved the treatment policy estimand, as reported previously (see the testing hierarchy in the statistical analysis plan, the Supplemental Methods section, and Fig. S2).[15] Supportive secondary and exploratory end-point analyses were not controlled for multiple comparisons, and the confidence intervals should not be used to infer definitive treatment effects. Comparisons of serious adverse events between the groups were performed with Fisher's exact test and are reported with unadjusted two-sided P values.

RESULTS

RANDOMIZATION AND PARTICIPANT CHARACTERISTICS

Between March 2021 and March 2022, a total of 529 participants underwent randomization at 83 of the 96 trial sites; 263 participants were assigned to the semaglutide group and 266 to the placebo group. Every participant received at least one dose of semaglutide or placebo. Premature discontinuation of treatment occurred in 42 participants (16.0%) in the semaglutide group and 42 (15.8%) in the placebo group, and 256 participants (97.3%) in the semaglutide group and 254 (95.5%) in the placebo group completed the trial. Among the participants who were still receiving treatment at week 52 (221 in the semaglutide group and 224 in the placebo group), 185 (83.7%) were receiving the intended 2.4-mg dose of semaglutide, whereas 219 (97.8%) were receiving the intended dose of placebo. The number of participants who withdrew consent or were lost to follow-up was 4 in the semaglutide group and 8 in the placebo group. Vital status was known for all but 3 participants at the end of the trial (Fig. S3). Two participants in the semaglutide group and 4 in the placebo group received postrandomization weight-loss interventions (i.e., other antiobesity medication). No participants underwent bariatric surgery.

Overall, 14.6% of the participants qualified for participation in the trial on the basis of elevated filling pressures, 13.4% on the basis of hospitalization for heart failure within 12 months in combination with ongoing diuretic treatment or echocardiographic abnormalities (or both), and 72.0% on the basis of N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in combination with echocardiographic abnormalities. The demographic and baseline clinical characteristics of the participants were balanced between the groups (Table 1 and Table S3). Most of the participants were women (56.1%) and were White (95.8%), and the median age was 69 years. The median body weight and BMI were 105.1 kg and 37.0, respectively, and 349 participants (66.0%) had a BMI of 35 or higher. The median KCCQ-CSS was 58.9 points, and the median 6-minute walk distance was 320.0 m. The median CRP level was 3.8 mg per liter, the median left ventricular ejection fraction was 57.0%, and the median NT-proBNP level was 450.8 pg per milliliter. Overall, 275 participants (52.0%) had a history of atrial fibrillation, and 81 (15.3%) had been hospitalized for heart failure within the previous 12 months; the NYHA class was II in 66.2% and III or IV in 33.8%. Most participants received beta-blockers, diuretics, and renin–angiotensin system blockers; 34.8% received mineralocorticoid receptor antagonists, and 3.6% received sodium–glucose cotransporter 2 (SGLT2) inhibitors.

DUAL PRIMARY END POINTS

Results for the dual primary, confirmatory secondary, supportive secondary, and selected exploratory end points for the treatment policy estimand are summarized in Table 2. The corresponding results for the trial product estimand (dual primary

Table 1. Baseline Demographic and Clinical Characteristics of the Participants.*

Characteristic	Semaglutide (N=263)	Placebo (N=266)	Total (N=529)
Female sex — no. (%)	149 (56.7)	148 (55.6)	297 (56.1)
Median age (IQR) — yr	70 (62–75)	69 (62–75)	69 (62–75)
Ethnic group — no. (%)†			
Hispanic or Latino	15 (5.7)	21 (7.9)	36 (6.8)
Not Hispanic or Latino	248 (94.3)	245 (92.1)	493 (93.2)
Race — no. (%)†			
Black	8 (3.0)	13 (4.9)	21 (4.0)
White	255 (97.0)	252 (94.7)	507 (95.8)
Other	0	1 (0.4)	1 (0.2)
Median body weight (IQR) — kg	104.7 (92.4–120.1)	105.3 (92.4–122.0)	105.1 (92.4–120.8)
Median BMI (IQR)	37.2 (33.9–41.1)	36.9 (33.3–41.6)	37.0 (33.7–41.4)
BMI stratum — no. (%)			
30 to <35	89 (33.8)	91 (34.2)	180 (34.0)
≥35	174 (66.2)	175 (65.8)	349 (66.0)
Median waist circumference (IQR) — cm	119.0 (110.5–127.1)	120.0 (110.5–129.0)	119.4 (110.5–128.0)
Median systolic blood pressure (IQR) — mm Hg	133 (122–145)	132 (120–142)	133 (121–144)
Median NT-proBNP level (IQR) — pg/ml	414.4 (229.2–1014.0)	499.8 (204.7–1025.0)	450.8 (218.2–1015.0)
Median CRP level (IQR) — mg/liter	3.8 (1.9–7.0)	3.9 (2.0–8.4)	3.8 (1.9–7.7)
Median LVEF (IQR) — %	57.0 (50.0–60.0)	57.0 (50.0–60.0)	57.0 (50.0–60.0)
LVEF stratum — no. (%)			
45 to <50%‡	37 (14.1)	48 (18.0)	85 (16.1)
50 to 59%	113 (43.0)	102 (38.3)	215 (40.6)
≥60%	113 (43.0)	116 (43.6)	229 (43.3)
Median KCCQ-CSS (IQR) — points§	59.4 (42.7–72.9)	58.3 (40.5–72.9)	58.9 (41.7–72.9)
Median 6-minute walk distance (IQR) — m	316.0 (251.0–386.0)	325.8 (232.4–392.0)	320.0 (240.0–389.0)
Hospitalization for heart failure within 1 year — no. (%)	42 (16.0)	39 (14.7)	81 (15.3)
Coexisting conditions at screening — no. (%)			
Atrial fibrillation	135 (51.3)	140 (52.6)	275 (52.0)
Hypertension	216 (82.1)	217 (81.6)	433 (81.9)
Coronary artery disease	53 (20.2)	45 (16.9)	98 (18.5)
NYHA functional class — no. (%)			
II	183 (69.6)	167 (62.8)	350 (66.2)
III or IV	80 (30.4)	99 (37.2)	179 (33.8)
Concomitant medication — no. (%)			
Diuretic	207 (78.7)	220 (82.7)	427 (80.7)
Loop diuretic	158 (60.1)	171 (64.3)	329 (62.2)
Thiazide	40 (15.2)	50 (18.8)	90 (17.0)
MRA	89 (33.8)	95 (35.7)	184 (34.8)
ACEI, ARB, or ARNI	210 (79.8)	214 (80.5)	424 (80.2)
Beta-blocker	201 (76.4)	217 (81.6)	418 (79.0)
SGLT2 inhibitor	8 (3.0)	11 (4.1)	19 (3.6)

* Data are from the full analysis population. Percentages may not total 100 because of rounding. ACEI denotes angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, BMI body-mass index, CRP C-reactive protein, IQR interquartile range, MRA mineralocorticoid receptor antagonist, NT-proBNP N-terminal pro–B-type natriuretic peptide, NYHA New York Heart Association, and SGLT2 sodium–glucose cotransporter 2.

† Race and ethnic group were reported by the investigator.

‡ This category includes one participant with a left ventricular ejection fraction (LVEF) of 33%.

§ The Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) ranges from 0 to 100, with higher scores reflecting better health status.

Table 2. Efficacy End Points.*

End Point	Semaglutide (N=263)	Placebo (N=266)	Estimated Difference or Ratio (95% CI)	P Value
Dual primary end points				
Change in KCCQ-CSS from baseline to week 52 — points	16.6	8.7	7.8 (4.8 to 10.9)†	<0.001
Percentage change in body weight from baseline to week 52	–13.3	–2.6	–10.7 (–11.9 to –9.4)†	<0.001
Confirmatory secondary end points				
Change from baseline to week 52 in 6-minute walk distance — m	21.5	1.2	20.3 (8.6 to 32.1)†	<0.001
Change from baseline to week 52 in CRP level — %	–43.5	–7.3	0.61 (0.51 to 0.72) ‡§	<0.001
Hierarchical composite end point — crude percentage of wins¶	60.1	34.9	1.72 (1.37 to 2.15)‖	<0.001
Supportive secondary end points				
Change from baseline to week 52 in systolic blood pressure — mm Hg	–4.9	–2.0	–2.9 (–5.8 to 0.1)†	—
Change from baseline to week 52 in waist circumference — cm	–11.7	–2.7	–9.1 (–10.6 to –7.5)†	—
Change from baseline to week 52 in KCCQ-OSS — points**	16.6	9.1	7.5 (4.4 to 10.6)†	—
Percentage reduction in body weight at week 52 — % of participants				
≥10% reduction	65.9	9.5	15.5 (9.4 to 25.4)‖	—
≥15% reduction	43.9	2.1	30.6 (12.2 to 76.6)‖	—
≥20% reduction	23.6	0.4	56.0 (7.8 to 400.8)‖	—
Increase in KCCQ-CSS at week 52 — % of participants				
≥5-point increase	75.3	63.7	1.9 (1.3 to 2.8)‖	—
≥10-point increase	63.4	48.5	2.1 (1.4 to 3.1)‖	—
Attainment of anchor-based threshold for change in KCCQ-CSS — % of participants††	43.2	32.5	1.9 (1.3 to 2.9)‖	—
Attainment of anchor-based threshold for change in 6-minute walk distance — % of participants‡‡	42.5	28.0	2.0 (1.4 to 3.0)‖	—
Exploratory end points assessed in the overall population				
Percentage reduction from baseline to week 52 in NT-proBNP level	–20.9	–5.3	0.84 (0.71 to 0.98)‡§§	—
≥15-point improvement in KCCQ-CSS at week 52 — no. of participants (%)	123 (50.6)	85 (35.9)	2.2 (1.5 to 3.2)‖	—
Adjudicated heart failure event (hospitalization or urgent visit for heart failure), time-to-event analysis — no. of events	1	12	0.08 (0.00 to 0.42)¶¶	—

* Analyses are based on the treatment policy estimand, which assessed the treatment effect regardless of whether treatment was discontinued or a rescue intervention was received. Analyses of continuous end points at week 52 were conducted with the use of analysis of covariance models with data from the in-trial observation period, with treatment and BMI stratum used as fixed factors, baseline end-point value used as a covariate, and an imputation approach used for missing values. For binary end points, odds ratios comparing semaglutide and placebo were estimated from a logistic regression model with data from the in-trial period, with randomly assigned group and BMI stratum used as fixed factors, baseline end-point value used as a covariate, and an imputation approach used for missing data. Data expressed as percentages of participants are observed data from the in-trial period, defined as the time from randomization to last contact with a trial site, regardless of whether treatment was discontinued or a rescue intervention was received.

† The value is the estimated between-group difference.

‡ The value is the estimated treatment ratio (i.e., the ratio [semaglutide:placebo] between the geometric mean ratios of the week 52 value to the baseline value). The ratio to baseline and the corresponding baseline value were log-transformed before analysis. The approximate relative changes were derived from estimated ratios by subtracting 1 and multiplying by 100.

§ The geometric mean ratio of the week 52 value to the baseline value was 0.56 in the semaglutide group and 0.93 in the placebo group. The estimated treatment ratio is calculated as 0.56/0.93=0.61.

¶ The hierarchical end point (in-trial period) was a composite that included death from any cause from baseline to week 57; the number and timing of heart failure events; a difference of at least 15, at least 10, and at least 5 points in the change in the KCCQ-CSS from baseline to week 52; and a difference of at least 30 m in the change in the 6-minute walk distance from baseline to week 52. This end point was assessed with the use of a win-ratio approach. All participants in the semaglutide group were compared with all participants in the placebo group within each BMI stratum (<35 and ≥35). An imputation approach was used for missing data for KCCQ-CSS and 6-minute walk distance. The crude percentage of wins across all components of the end point are shown for each group.

Table 2. (Continued.)

‖ The value is an odds ratio. For supportive secondary and exploratory end points, the widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.
** The KCCQ overall summary score (KCCQ-OSS) ranges from 0 to 100, with higher scores indicating better health status.
†† A threshold of 17.2 points was chosen on the basis of the change from baseline to week 52 in the patient global impression of severity (PGI-S) that measures the participant's perception of heart failure symptoms. To establish the threshold, the mean change in KCCQ-CSS was calculated (using pooled data across the groups) in the group of 168 participants who had a one-category improvement.
‡‡ A threshold of 29.5 m was chosen on the basis of the change from baseline to week 52 in the PGI-S that measures the participant's perception of the ability to walk quickly. To establish the threshold, the mean change in 6-minute walk distance was calculated (using pooled data across the groups) in the group of 125 participants who had a one-category improvement.
§§ The ratio of the NT-proBNP level at week 52 to the level at baseline was 0.78 in the semaglutide group and 0.95 in the placebo group.
¶¶ The value is a hazard ratio. The time-to-event analysis of the first adjudicated heart failure event (in-trial period) was performed with a Cox regression model, with randomly assigned group used as a fixed factor.

and confirmatory secondary end points only) are summarized in Table S4.

For the treatment policy estimand, the mean change in KCCQ-CSS at week 52 was 16.6 points in the semaglutide group and 8.7 points in the placebo group (estimated difference, 7.8 points; 95% confidence interval [CI], 4.8 to 10.9; P<0.001) (Fig. 1A and Table 2). For the trial product estimand, the corresponding changes in KCCQ-CSS were 19.1 points and 10.3 points (estimated difference, 8.8 points; 95% CI, 5.9 to 11.7) (Fig. S4A).

For the treatment policy estimand, the mean percentage change in body weight at week 52 was –13.3% for semaglutide and –2.6% for placebo (estimated difference, –10.7 percentage points; 95% CI, –11.9 to –9.4; P<0.001) (Fig. 1B and Table 2). For the trial product estimand, the corresponding changes were –15.1% and –2.4% (estimated difference, –12.7 percentage points; 95% CI, –13.9 to –11.5) (Fig. S4B).

CONFIRMATORY SECONDARY END POINTS

For the treatment policy estimand, the mean change in the 6-minute walk distance at week 52 was 21.5 m in the semaglutide group and 1.2 m in the placebo group (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1; P<0.001) (Fig. 2A and Table 2). For the trial product estimand, the corresponding changes were 29.0 m and 8.3 m (estimated difference, 20.6 m; 95% CI, 9.5 to 31.8) (Fig. S5A).

In the analysis of the hierarchical composite end point, treatment with semaglutide resulted in more wins than placebo, with a stratified win ratio of 1.72 (95% CI, 1.37 to 2.15; P<0.001) for the treatment policy estimand. The wins favored semaglutide over placebo for all key components of the hierarchical composite end point (Fig. 2B and Table 2); a difference of at least 15 points in the change in KCCQ-CSS contributed the most wins for semaglutide. For the trial product estimand, the stratified win ratio was 2.10 (95% CI, 1.67 to 2.63) (Fig. S5B).

For the treatment policy estimand, participants in the semaglutide group had a 43.5% reduction in CRP level at 52 weeks (geometric mean ratio [week 52 value to baseline value], 0.56), as compared with a 7.3% reduction with placebo (geometric mean ratio [week 52 value to baseline value], 0.93) (estimated treatment ratio [i.e., the ratio between the two geometric mean ratios], 0.61; 95% CI, 0.51 to 0.72; P<0.001) (Fig. 2C and Table 2). The corresponding values for the trial product estimand were 0.51 (49.0% reduction) and 0.91 (9.1% reduction) (estimated treatment ratio, 0.56, 95% CI, 0.48 to 0.66) (Fig. S5C).

SUPPORTIVE SECONDARY AND EXPLORATORY END POINTS

The results for supportive secondary and exploratory end points are shown in Table 2. In total, 1 participant in the semaglutide group and 12 in the placebo group had an adjudicated event of hospitalization for heart failure or an urgent visit (hazard ratio, 0.08; 95% CI, 0.00 to 0.42) (Fig. S6).

SAFETY AND SIDE EFFECTS

The numbers and percentages of participants with serious adverse events and the types of events that occurred are summarized in Tables 3 and S5 for the treatment period and the in-trial period, respectively. Serious adverse events were reported in 35 participants (13.3%) in the semaglutide group and 71 participants (26.7%) in the placebo group (P<0.001); the between-group difference primarily reflected the lower number of cardiac disorder events in the semaglutide group (7 [2.7%] vs. 30 [11.3%] in the placebo group; P<0.001). Overall, 6 participants in the semaglutide group and 6 in the placebo group discontinued treat-

ment because of serious adverse events. The number of participants who discontinued treatment because of any adverse event was 35 in the semaglutide group and 14 in the placebo group; the adverse events that led to discontinuation were predominantly gastrointestinal events.

During the trial, 7 participants died — 3 in the semaglutide group and 4 in the placebo group. One adjudicated cause of death in the placebo group was cardiovascular, and the causes of the other 6 deaths were adjudicated as noncardiovascular (3 in each group). One death in each group was reported as being related to coronavirus disease 2019.

DISCUSSION

In this randomized, placebo-controlled trial involving patients with heart failure with preserved ejection fraction and obesity, once weekly semaglutide at a dose of 2.4 mg led to larger reductions in heart failure–related symptoms and physical limitations (as measured with the KCCQ-CSS) and a greater degree of weight loss than placebo at 52 weeks. In addition, semaglutide increased the 6-minute walk distance, resulted in more wins in the evaluation of the hierarchical composite end point, and reduced CRP levels to a greater extent than placebo. Clinically meaningful improvements

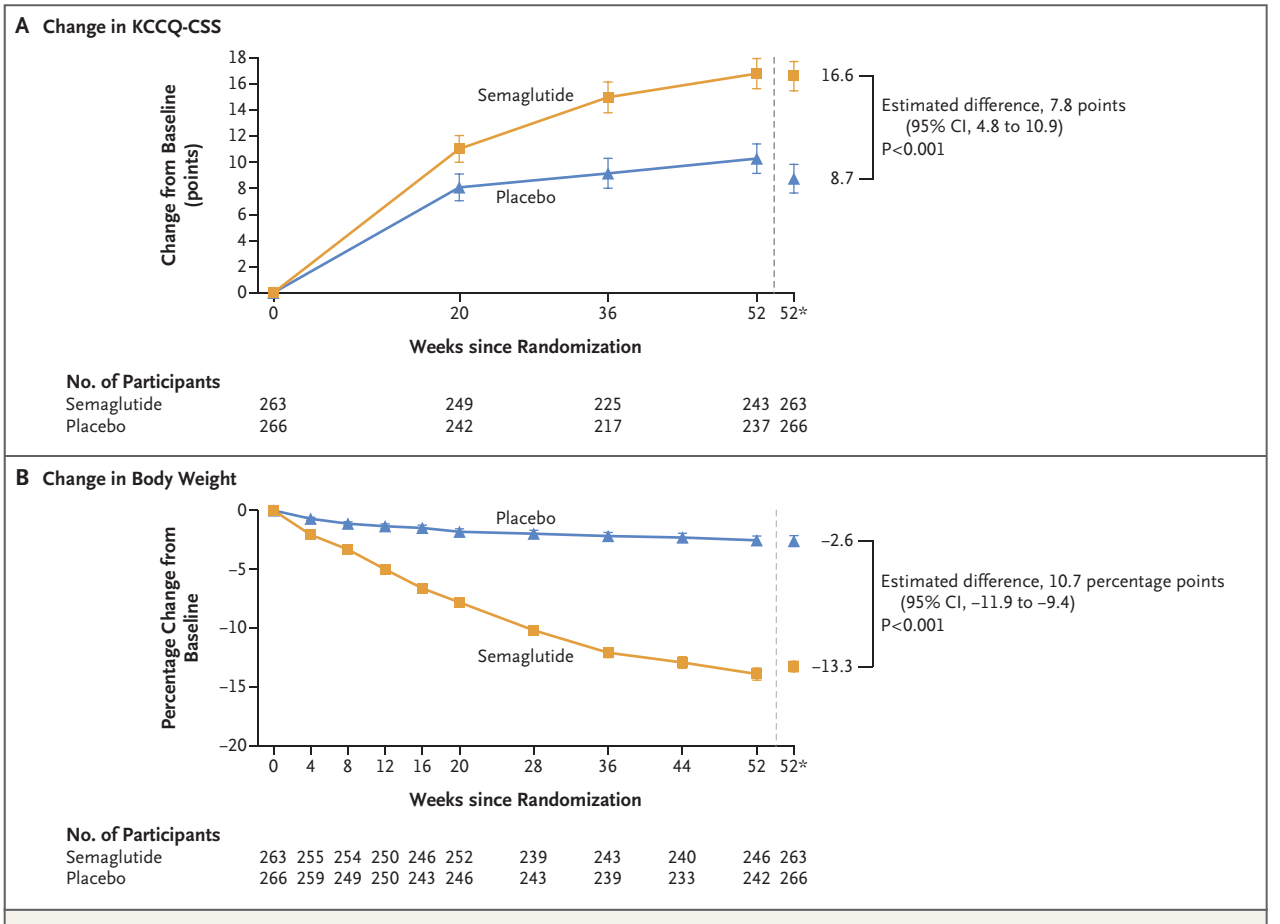


Figure 1. Changes from Baseline to Week 52 in the Dual Primary End Points.

Analyses are based on the treatment policy estimand, reflect the full analysis population, and are from the in-trial period. Shown are the observed (i.e., as-measured) mean changes from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and percentage changes in body weight. I bars indicate the standard error, and the numbers below the graphs are the numbers of participants contributing to the mean. The data at week 52* are the estimated mean changes from baseline to week 52 based on analysis of covariance (ANCOVA) and an imputation approach for missing data.

in the KCCQ-CSS and 6-minute walk distance were more common in the semaglutide group than in the placebo group. Treatment with semaglutide led to fewer serious adverse events than placebo and had a similar frequency of discontinuation due to serious adverse events.

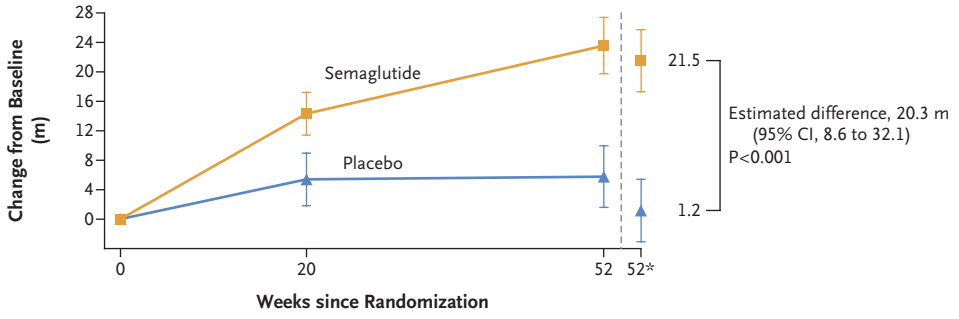
Patients with heart failure with preserved ejection fraction have an especially high burden of symptoms and physical limitations, as well as a poor quality of life.[2,19,20] Reductions in symptoms and improvements in physical function are therefore broadly considered to be key goals in the management of the condition, as important as avoidance of death and hospitalizations. Formal patient interviews indicate that patients with heart failure value reductions in symptoms and improvements in physical function at least as much as they value avoidance of death.[21-23] This finding has been recognized by regulatory agencies; the Food and Drug Administration has endorsed the view that a treatment for heart failure is potentially approvable on the basis of reductions in symptoms and improvements in physical function alone.[24] To date, there has been a dearth of treatments that affect these important outcomes in patients with heart failure with preserved ejection fraction, which highlights a major unmet need.

Although the condition is underrecognized,[19] especially in patients with obesity,[8] epidemiologic data indicate that the majority of patients with heart failure with preserved ejection fraction have obesity, and growing evidence suggests that adipose tissue may play a pivotal role in the development, progression, and adverse outcomes of heart failure with preserved ejection fraction.[4-8] The presence of visceral adiposity is associated with increased inflammation, left ventricular hypertrophy, insulin resistance, and diastolic and systolic left ventricular dysfunction, as well as with arterial, skeletal muscle, and physical dysfunction.[7] Among patients with established heart failure with preserved ejection fraction, those with the obesity phenotype have distinct clinical and hemodynamic features, including expanded plasma and stressed blood volume, reduced venous capacitance, elevations in exercise pulmonary wedge pressures, adverse hemodynamic response to diuresis, higher inflammatory markers, and more pronounced hypertension, as well as more severe symptoms and exercise intolerance.[9-12,25,26] Obesity also results in natriuretic peptide deficiency as a consequence of decreased production and increased clearance, which leads to a reduced capacity for vasodilation and natriuresis.[27-29]

Despite the relationships among obesity, excess adiposity, and worse outcomes and despite previous data suggesting that health status and exercise function improve with lifestyle modification–mediated weight loss in patients with heart failure with preserved ejection fraction and obesity,[30] prospective trials of pharmacologic treatments for the obesity phenotype of the condition have been lacking. The magnitude of the reductions in symptoms and physical limitations observed with semaglutide in our trial was substantial, with a mean increase in the KCCQ-CSS of nearly 8 points in favor of semaglutide. For perspective, previous global clinical trial programs of agents such as SGLT2 inhibitors, sacubitril–valsartan, and spironolactone for heart failure with preserved ejection fraction showed only modest changes in KCCQ scores (ranging from 0.5 to 2.3 points).[31-33] Furthermore, all responder analyses in our trial, even those examining very large improvements (≥15 points) in the KCCQ-CSS, consistently showed superiority of semaglutide to placebo; participants who received semaglutide had more than double the odds of having such benefits.

The improvement in the 6-minute walk distance that we observed in the trial is also clinically relevant. Even when patients have well compensated heart failure with preserved ejection fraction and are in stable condition, they have markedly impaired objectively measured physical function.[34] Impaired physical function is an independent predictor of poorer quality of life, hospitalization, loss of independence, nursing home placement, and death. To date, nearly all trials that have tested a variety of medications in heart failure with preserved ejection fraction for exercise function outcomes, such as the 6-minute walk distance or cardiopulmonary exercise testing, have shown neutral results.[34] The absolute magnitude of the increase in the 6-minute walk distance in our trial of semaglutide is notable: it is greater than that found in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training),[35] which tested exercise training in patients with heart failure with reduced

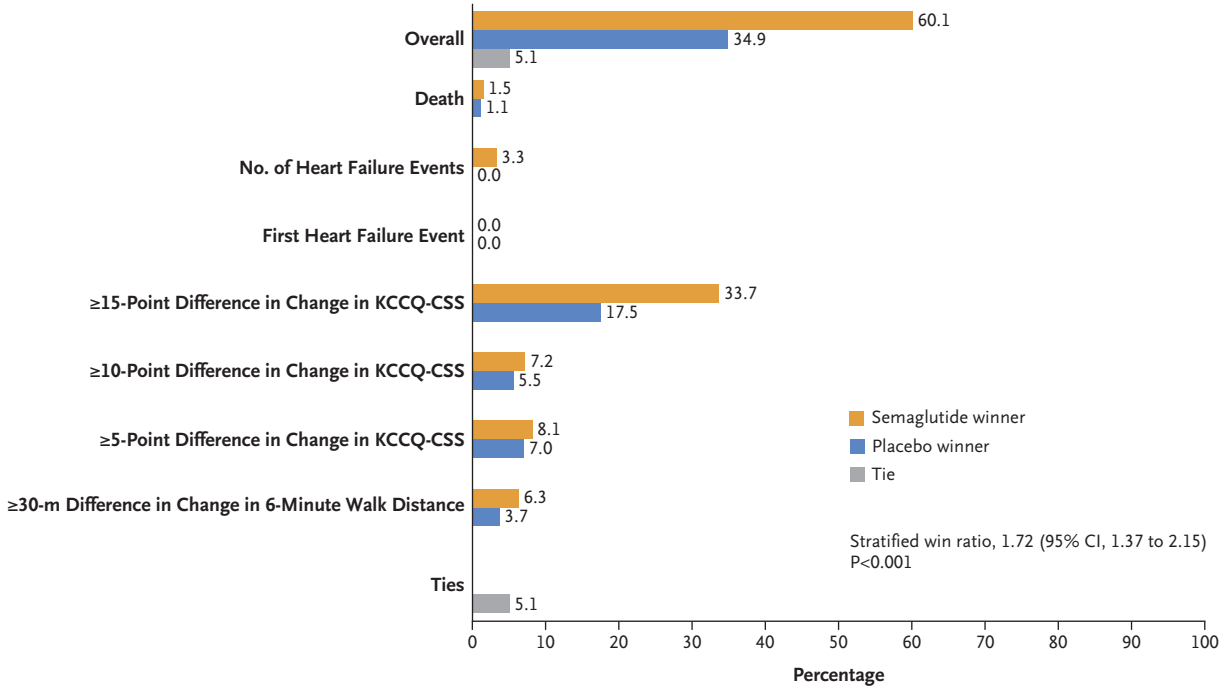
A Change in 6-Minute Walk Distance



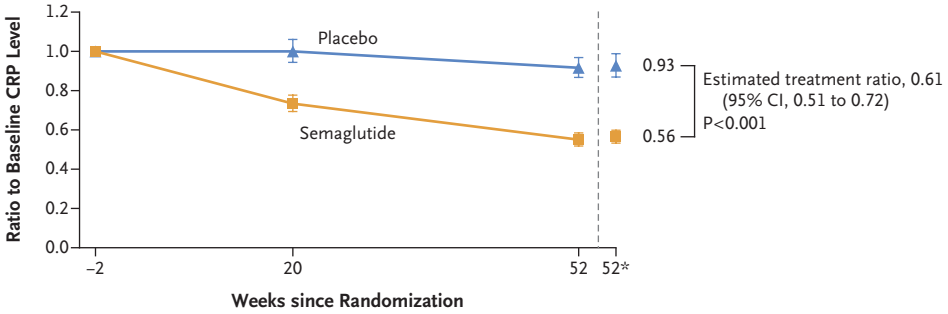
No. of Participants

Semaglutide	263	245	240	263
Placebo	266	232	225	266

B Stratified Win Ratio for Hierarchical Composite End Point



C Change in C-Reactive Protein Level



No. of Participants

Semaglutide	263	245	240	263
Placebo	266	232	225	266

Figure 2 (facing page). Changes from Baseline to Week 52 in Confirmatory Secondary End Points.

Analyses are based on the treatment policy estimand, reflect the full analysis population, and are from the in-trial period. Panel A shows the observed (i.e., as-measured) mean changes from baseline in the 6-minute walk distance; I bars indicate the standard error. Panel B shows the stratified win ratio for the composite hierarchical end point, which included death from any cause from baseline to week 57; the number and timing of heart failure events (defined as adjudicated events of hospitalization for heart failure or urgent visits in which intravenous therapy was administered); differences of at least 15, at least 10, and at least 5 points in the change in the KCCQ-CSS from baseline to week 52; and a difference of at least 30 m in the change in the 6-minute walk distance from baseline to week 52. Panel C shows the observed mean changes in the C-reactive protein (CRP) levels calculated on a logarithmic scale and back-transformed to a linear scale; I bars indicate the standard error. Numbers below the graphs are the numbers of participants contributing to the mean. The data at week 52* in Panels A and C are the estimated mean changes from baseline (from screening at week –2 for CRP) to week 52 for the treatment policy estimand based on ANCOVA and an imputation approach for missing data.

ejection fraction,[36] and is similar in magnitude to that observed in trials of exercise training in patients with heart failure with preserved ejection fraction.[34] Thus, collectively, our results indicate that semaglutide may represent a valuable therapeutic approach in the management of heart failure with preserved ejection fraction in patients with obesity.

Our findings of substantial reductions in symptoms and physical limitations and improvements in exercise function that parallel a greater degree of weight loss with semaglutide than with placebo may offer insights into the long-standing controversy surrounding weight (and weight loss) in persons with heart failure.[8] Previous observational reports have suggested that higher BMI may be associated with better prognosis in patients with heart failure[37] and that weight loss is associated with a worse prognosis (termed "the obesity paradox").[38] However, these observations did not distinguish between unintentional weight loss (often observed in association with cardiac cachexia, which would be expected to be a marker of poor prognosis) and intentional weight loss resulting from lifestyle-mediated, pharmacologic, or surgical interventions. Small observational studies evaluating intentional weight loss in patients with heart failure and obesity previously suggested an association with reductions in symptom severity and improvements in functional status.[39] A randomized trial of caloric restriction in patients with heart failure with preserved ejection fraction and obesity showed reductions in symptoms and improvements in exercise function and quality of life.[30] The data from our trial extend these findings and indicate that weight loss with semaglutide at a dose of 2.4 mg is a beneficial strategy in patients with heart failure with preserved ejection fraction and obesity. Whether this is also the case with other types of weight loss interventions or in other populations (such as those with heart failure with reduced ejection fraction and obesity) will be useful to evaluate in future trials.

Several key mechanisms may be responsible for the treatment benefits observed with semaglutide in this group of patients. The trajectory of reductions in symptoms and physical limitations and improvements in exercise function suggest that weight loss, with its attendant decrease in visceral adipose tissue, is likely to be an important contributor to these benefits. Decreases in the CRP level, systolic blood pressure, and NT-proBNP level were also greater in the semaglutide group than in the placebo group, which indicates that semaglutide may have favorable antiinflammatory and hemodynamic effects. The extent to which these benefits of semaglutide are attributable to weight loss, other direct mechanisms, or a combination of these factors is unknown. Despite the known association of higher BMIs with lower NT-proBNP levels[9,40] and previous observations suggesting that NT-proBNP levels increase with weight loss (in patients with type 2 diabetes and a normal NT-proBNP level at baseline),[41] we observed a substantially greater reduction in NT-proBNP levels with semaglutide than with placebo. Therefore, the lowering of NT-proBNP levels with semaglutide despite significant reductions in body weight, along with the lower number of adjudicated heart failure events (1 in the semaglutide group vs. 12 in the placebo group), suggest that the decongestive and favorable hemodynamic effects of semaglutide might be substantial. This idea is further buttressed by the fact that the number of cardiovascular serious adverse events reported was lower with semaglutide than with placebo; in addition to heart failure, these events also included atrial fibrillation and flutter — events that would be

Table 3. Reportable Adverse Events during the Treatment Period.*

Adverse Event	Semaglutide (N=263)			Placebo (N=266)			P Value†
	no. of participants (%)	*no. of events*	*events/100 person-yr*	*no. of participants (%)*	*no. of events*	*events/100 person-yr*	
Serious adverse event	35 (13.3)	60	23.4	71 (26.7)	133	50.1	<0.001
Serious adverse event leading to discontinuation of semaglutide or placebo	6 (2.3)	7	2.7	6 (2.3)	7	2.6	—
Gastrointestinal disorder	1 (0.4)	1	0.4	1 (0.4)	1	0.4	—
Adverse events leading to discontinuation of semaglutide or placebo	35 (13.3)	47	18.4	14 (5.3)	17	6.4	—
Gastrointestinal disorder	25 (9.5)	33	12.9	7 (2.6)	9	3.4	—
Fatal event	3 (1.1)	3	1.2	4 (1.5)	5	1.9	—
Most frequent serious adverse events‡							—
Cardiac disorder	7 (2.7)	8	3.1	30 (11.3)	43	16.2	<0.001
Atrial fibrillation	3 (1.1)	3	1.2	9 (3.4)	12	4.5	—
Cardiac failure	0	0	0	12 (4.5)	13	4.9	—
Atrial flutter	0	0	0	3 (1.1)	5	1.9	—
Congestive cardiac failure	0	0	0	3 (1.1)	3	1.3	—
Infection or infestation	4 (1.5)	5	2.0	17 (6.4)	22	8.3	0.006
Gastrointestinal disorder	7 (2.7)	9	3.5	7 (2.6)	8	3.0	1.00
Nervous system disorder	8 (3.0)	8	3.1	7 (2.6)	7	2.6	0.80
Renal or urinary disorder	6 (2.3)	7	2.7	4 (1.5)	6	2.3	0.54
Respiratory, thoracic, or mediastinal event	0	0	0	10 (3.8)	11	4.1	0.002
Musculoskeletal or connective-tissue event	4 (1.5)	5	2.0	4 (1.5)	5	1.9	1.00
Injury, poisoning, or procedural event	4 (1.5)	4	1.6	4 (1.5)	5	1.9	1.00
Metabolism or nutrition disorder	3 (1.1)	3	1.2	4 (1.5)	4	1.5	1.00
Hepatobiliary disorder	3 (1.1)	4	1.6	2 (0.8)	2	0.8	0.69
General disorder or administration-site reaction	1 (0.4)	1	0.4	3 (1.1)	3	1.1	0.62
Benign, malignant, or unspecified neoplasm	1 (0.4)	1	0.4	3 (1.1)	3	1.1	0.62

Safety focus areas§							
Covid-19–related event	39 (14.8)	39	15.2	45 (16.9)	48	18.1	—
Serious cardiovascular disorder	18 (6.8)	21	8.2	41 (15.4)	60	22.6	—
Serious gastrointestinal disorder	7 (2.7)	9	3.5	7 (2.6)	8	3.0	—
Medication error	0	0	0	0	0	0	—
Serious neoplasm	2 (0.8)	2	0.8	6 (2.3)	6	2.3	—
Serious acute gallstone disease	3 (1.1)	4	1.6	3 (1.1)	3	1.1	—
Serious acute renal failure	5 (1.9)	6	2.3	1 (0.4)	2	0.8	—
Serious malignant neoplasm	1 (0.4)	1	0.4	3 (1.1)	3	1.1	—
Acute pancreatitis	0	0	0	1 (0.4)	1	0.4	—
Serious rare event	0	0	0	1 (0.4)	1	0.4	—
Serious hypoglycemia	1 (0.4)	1	0.4	0	0	0	—
Misuse or abuse	0	0	0	0	0	0	—
Covid-19–related death	1 (0.4)	1	0.4	1 (0.4)	1	0.4	—
Adjudicated events¶							—
Death from any cause	3 (1.1)	3	1.0	4 (1.5)	4	1.4	—
Death from cardiovascular causes	0	0	0	1 (0.4)	1	0.4	—
Heart failure event	1 (0.4)	2	0.7	12 (4.5)	13	4.5	—

* Adverse events are shown for the safety analysis population (all randomly assigned participants exposed to at least one dose of semaglutide or placebo); since all participants received at least one dose, the safety population is the same as the full analysis population. Unless otherwise indicated, the events shown were observed during the treatment period (i.e., the period from the date of the first administration of semaglutide or placebo to the date of last administration, excluding potential intervals during which semaglutide or placebo was not being received [i.e., two or more consecutive missed doses]; for the evaluation of adverse events, the lag time for each treatment interval is 35 days).

† The overall comparison of serious adverse events and the comparisons of the most frequently reported serious adverse events between the two groups were performed with the use of Fisher's exact test and are reported as unadjusted two-sided P values.

‡ Events are grouped according to system organ class and are those that occurred in at least 1% of the participants in either group.

§ On the basis of therapeutic experience with glucagon-like peptide 1 receptor agonists and regulatory feedback and requirements, a number of safety focus areas were prespecified as being of special interest in the safety evaluation. Identified through searches of the *Medical Dictionary for Regulatory Activities*, these preferred terms were judged to be relevant for each of the safety focus areas. The listed safety focus areas include both serious and nonserious adverse events, Covid-19, misuse or abuse, medication errors, and acute pancreatitis.

¶ Events were adjudicated by an external committee and are from the in-trial period (the time from randomization to last contact with a trial site, regardless of whether treatment was discontinued or rescue intervention was received).

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expected to decline in frequency with improvements in hemodynamic status and inflammation. Collectively, these findings support the hypothesis that the range of benefits seen with semaglutide were not simply due to weight loss alone; rather, the pathophysiological processes that underlie heart failure with preserved ejection fraction syndrome itself improved at the same time that weight was lost.

This trial has several limitations. First, the number of non-White participants was low, which may limit the generalizability of our results; however, 23.2% of the participants recruited in the United States were Black, which is in line with what has been reported nationally among patients with heart failure with preserved ejection fraction.[42] Second, the trial was designed primarily to evaluate the effects of semaglutide on symptoms, physical limitations, and exercise function and was not adequately powered to evaluate clinical events such as hospitalizations for heart failure and urgent visits. Third, the duration of follow-up was limited to 1 year; although the trajectory of effects on the KCCQ-CSS, 6-minute walk distance, and weight loss indicated greater persistent improvements over time with semaglutide than with placebo, the durability of the observed effects beyond 1 year cannot be ascertained. However, the absence of a plateau effect in the semaglutide group at the end of the trial suggests that the clinical improvements may be durable beyond the observed treatment duration. Fourth, we did not collect data on specific glycated hemoglobin levels (beyond confirming the absence of diabetes during screening) at baseline or during follow-up; however, it is unlikely that the beneficial effects of semaglutide in this trial were mediated by changes in glycemia. Finally, although the use of standard therapies in our trial was consistent with that in other global trial programs involving patients with heart failure with preserved ejection fraction, the percentage of participants treated with SGLT2 inhibitors was low, which reflects both the period during which the trial was conducted and the exclusion of patients with diabetes. A separate, ongoing trial is investigating once-weekly semaglutide at a dose of 2.4 mg as compared with placebo in patients with heart failure with preserved ejection fraction, obesity, and type 2 diabetes and has a much larger percentage of participants receiving SGLT2 inhibitors (32%).[15]

In patients with heart failure with preserved ejection fraction and obesity, treatment with once weekly semaglutide at a dose of 2.4 mg led to larger reductions in heart failure–related symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo.

Supported by Novo Nordisk. Dr. Wolf is a member of SFB1425, funded by the Deutsche Forschungsgemeinschaft.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the trial participants, the trial-site staff who conducted the trial, and Jon Viney and Casey McKeown of Apollo, OPEN Health Communications, for administrative support and development of earlier versions of the figures and tables (funded by Novo Nordisk).

APPENDIX

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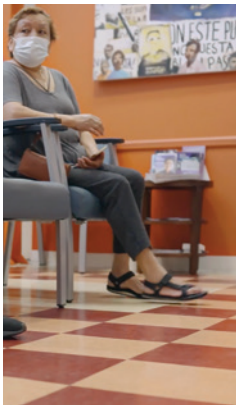
Double Take Video: Type 2 Diabetes, after the Diagnosis — Making a Plan and Addressing Social Determinants of Health



In this second episode of "Type 2 Diabetes — Controlling the Epidemic," a four-part Double Take video miniseries, Drs. Jane E.B. Reusch (University of Colorado), E. Dale Abel (UCLA), and Monica Peek (University of Chicago) describe the process of tailoring type 2 diabetes interventions and education to the individual patient. The video also highlights the impact that health inequities can have on diabetes management.