ORIGINAL ARTICLE

# Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes

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## ABSTRACT

### BACKGROUND

Obesity and type 2 diabetes are prevalent in patients with heart failure with preserved ejection fraction and are characterized by a high symptom burden. No approved therapies specifically target obesity-related heart failure with preserved ejection fraction in persons with type 2 diabetes.

### METHODS

We randomly assigned patients who had heart failure with preserved ejection fraction, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more, and type 2 diabetes to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The 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 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

A total of 616 participants underwent randomization. The mean change in the KCCQ-CSS was 13.7 points with semaglutide and 6.4 points with placebo (estimated difference, 7.3 points; 95% confidence interval [CI], 4.1 to 10.4; P<0.001), and the mean percentage change in body weight was −9.8% with semaglutide and −3.4% with placebo (estimated difference, −6.4 percentage points; 95% CI, −7.6 to −5.2; P<0.001). The results for the confirmatory secondary end points favored semaglutide over placebo (estimated between-group difference in change in 6-minute walk distance, 14.3 m [95% CI, 3.7 to 24.9; P=0.008]; win ratio for hierarchical composite end point, 1.58 [95% CI, 1.29 to 1.94; P<0.001]; and estimated treatment ratio for change in CRP level, 0.67 [95% CI, 0.55 to 0.80; P<0.001]). Serious adverse events were reported in 55 participants (17.7%) in the semaglutide group and 88 (28.8%) in the placebo group.

### CONCLUSIONS

Among patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, semaglutide led to larger reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo at 1 year. (Funded by Novo Nordisk; STEP-HFpEF DM ClinicalTrials.gov number, NCT04916470.)

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

This article was published on April 6, 2024, at NEJM.org.

N Engl J Med 2024;390:1394-407.
DOI: 10.1056/NEJMoa2313917


CME

Heart failure with preserved ejection fraction has become the predominant type of heart failure, partly owing to the increasing prevalence of obesity.[1-3] Excess adiposity plays an important role in the development and progression of heart failure with preserved ejection fraction and type 2 diabetes.[4-7] Type 2 diabetes is highly prevalent among patients with heart failure with preserved ejection fraction and is associated with adverse hemodynamic and clinical features, including greater symptom burden and worse functional capacity than in patients without type 2 diabetes.[8-13] There are few efficacious therapies in this patient group.

Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist that is administered once weekly at a dose of 2.4 mg, has been shown to induce substantial weight loss in persons with overweight or obesity, with favorable effects on cardiometabolic risk factors and a significant reduction in the likelihood of major adverse cardiovascular events among high-risk patients.[14-16] We have previously found in patients with heart failure with preserved ejection fraction and obesity, but without type 2 diabetes, that treatment with semaglutide led to larger reductions in heart failure–related symptoms and physical limitations, greater weight loss, and greater improvements in exercise function than placebo.[17] The effects of semaglutide in patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes may differ for several reasons. First, the magnitude of weight loss in trials of antiobesity pharmacotherapies is consistently smaller in patients with type 2 diabetes than in those without type 2 diabetes.[14,18] Second, patients with type 2 diabetes are more likely to receive sodium–glucose cotransporter 2 (SGLT2) inhibitors, which have emerged as the standard of care for heart failure with preserved ejection fraction.[11] Third, patients with heart failure with preserved ejection fraction and type 2 diabetes typically present with a more advanced phenotype.[11,19,20] All these factors may affect responsiveness to treatment with semaglutide. Accordingly, we sought to examine the efficacy and safety of once-weekly semaglutide at a dose of 2.4 mg in this patient group.

## Methods

### Trial Design and Oversight

We conducted the STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus) trial, a double-blind, randomized, placebo-controlled trial, at 108 sites in 16 countries in Asia, Europe, and North and South America. The steering committee designed the trial and was primarily responsible for trial-related academic publications. The trial design and the baseline characteristics of the trial participants have been published previously.[21] 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. All the participants provided written informed consent. The results of the primary and confirmatory secondary efficacy end points in the testing hierarchy were validated by a sponsor-independent statistician (employed by Statogen Consulting) who had access to all relevant data sets. The sponsor (Novo Nordisk) assumes responsibility for activities related to trial conduct, data collection, and statistical analysis. All drafts of the manuscript were prepared by the first author, who had full access to the primary source data. All the authors interpreted the data, contributed to the writing 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 the fidelity of the trial to the protocol. Additional information is provided in the Supplementary Appendix, available at NEJM.org.

*A Quick Take is available at NEJM.org*

### Trial Participants

Persons 18 years of age or older were eligible if they had documented heart failure, 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, and at least one of the following findings: elevated left ventricular filling pressures; elevated natriuretic peptide levels plus echocardiographic abnormalities; or hospitalization for heart failure within 12 months before screening plus echocardiographic abnormalities or ongoing treatment with diuretics. Participants were required to have received a diagnosis of type 2 diabetes at least 90 days before screening and to have a glycated hemoglobin level of no more than 10%. Key exclusion criteria were a change in body weight of more than 5 kg within 90 days before screening, a history of type 1 diabetes, use of a

GLP-1 receptor agonist within 90 days before screening, and uncontrolled diabetic retinopathy. The full list of eligibility criteria is provided in Table S1 in the Supplementary Appendix.

### RANDOMIZATION AND TRIAL PROCEDURES

Participants were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 52 weeks, with a 5-week follow-up period. Randomization was stratified according to BMI (<35 vs. ≥35). Semaglutide treatment was initiated at a dose of 0.25 mg for 4 weeks, and the dose was escalated every 4 weeks until the maintenance dose of 2.4 mg was reached by week 16 (Fig. S1).

Semaglutide or placebo was added to the baseline glucose-lowering medications, which could include any class other than GLP-1 receptor agonists. Modification of background glucose-lowering treatment or the addition of new treatments was implemented at the discretion of the investigator (see guidance in the Supplemental Methods section and in Tables S2, S3, and S4).

### END POINTS

The dual primary end points were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and the percentage change in body weight from baseline to week 52. The KCCQ is a 23-item, participant-administered instrument that quantifies heart failure–related symptoms, physical function, quality of life, and social function.[22-24] Scores range from 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 below), 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 a 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 S5.

Safety assessments included serious adverse events and adverse events of special interest (baseline to week 57), which included hypoglycemia (Table S6) and diabetic retinopathy. 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.

### STATISTICAL ANALYSIS

Details of the statistical methods, including sample-size calculations, are provided in the statistical analysis plan (available with the protocol at NEJM.org) and have been reported previously.[21] Efficacy end points were analyzed in the full analysis population according to the intention-to-treat principle; safety end points were analyzed in all the participants who underwent randomization and received at least one dose of semaglutide or placebo.

Two estimands were used to evaluate treatment efficacy: a treatment policy estimand (akin to an intention-to-treat analysis) and a hypothetical trial product estimand (if treatment was taken as intended, or an on-treatment analysis). The estimands accounted for intercurrent events, which encompassed discontinuation of treatment (which included 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 treatment policy estimand. All results are presented with two-sided 95% confidence intervals; two-sided P values are reported only for the hierarchically tested end points that involved the treatment policy estimand. The Supplementary Appendix and statistical analysis plan provide further details on the estimands, statistical testing hierarchy, 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. Single and multiple imputation were used to account for missing data (see the Supplementary Appendix). Treatment effects and standard errors were combined with the use of Rubin's rule. In a prespecified analysis, the effects of semaglutide as compared with placebo on KCCQ-CSS and body weight were examined within the subgroups of participants who did and did not receive SGTL2 inhibitors at baseline, by means of an analysis of covariance model with randomly assigned group by SGLT2 inhibitor use as an interaction term.

Analysis of the hierarchical composite end point was based on direct comparisons of each participant assigned to receive semaglutide and each participant assigned to receive placebo (stratified according to BMI). For each participant pair, a "winner" based on similar observation time was declared with the use of the end-point hierarchy, as reported previously.[21] The win ratio (the number of winners assigned to receive semaglutide divided by the number of winners assigned to receive placebo) was estimated with the use of 1000 imputations.

Strong control for the type I error was used for analyses of the dual primary and confirmatory secondary end points, as reported previously (see the statistical analysis plan, the Supplemental Methods section, and Fig. S2).[21] Analyses of the supportive secondary and exploratory end points were not controlled for multiple comparisons, and the confidence intervals should not be used to infer definitive treatment effects. Comparison of serious adverse events between the groups was performed with Fisher's exact test and reported with unadjusted two-sided P values.

## RESULTS

### PARTICIPANT CHARACTERISTICS

Between June 15, 2021, and August 19, 2022, a total of 616 participants underwent randomization: 310 were assigned to receive semaglutide and 306 to receive placebo. Premature discontinuation of treatment occurred in 50 participants (16.1%) in the semaglutide group and 46 (15.0%) in the placebo group, and 292 participants (94.2%) in the semaglutide group and 291 (95.1%) in the placebo group completed the trial. Among the participants who were still receiving treatment at week 52 (260 participants in each group), 209 (80.4%) were receiving the intended 2.4-mg dose of semaglutide and 248 (95.4%) were receiving the intended dose of placebo (Fig. S3).

The median age of the participants was 69 years, 44.3% were female, the median body weight was 102.7 kg, and the median BMI was 36.9; 396 participants (64.3%) had a BMI of 35 or more. The median KCCQ-CSS was 59.4 points, and the median 6-minute walk distance was 280 m. The median N-terminal pro–B-type natriuretic peptide (NT-proBNP) level was 493 pg per milliliter, the median glycated hemoglobin level was 6.8%, and the median duration of type 2 diabetes was 8.0 years (Table 1 and Table S7). Most participants received diuretics, renin–angiotensin system blockers, and beta-blockers; 32.5% received mineralocorticoid receptor antagonists, and 32.8% received SGLT2 inhibitors. In addition, 71.9% of the participants received metformin, 17.5% received sulfonylureas, and 20.8% received insulin.

### 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 (primary and confirmatory secondary end points only) are summarized in Table S8.

For the treatment policy estimand, the mean change in the KCCQ-CSS at week 52 was 13.7 points in the semaglutide group and 6.4 points in the placebo group (estimated difference, 7.3 points; 95% confidence interval [CI], 4.1 to 10.4; P<0.001) (Fig. 1A and Table 2). For the trial product estimand, the corresponding changes in the KCCQ-CSS were 16.6 points and 7.9 points (estimated difference, 8.6 points; 95% CI, 5.6 to 11.6) (Fig. S4A). The estimated difference between the semaglutide group and the placebo group in the change in the KCCQ-CSS was 5.3 points (95% CI, −0.2 to 10.7) among participants who received SGLT2 inhibitor therapy at baseline and 8.3 points (95% CI, 4.5 to 12.1) among those who did not receive SGLT2 inhibitor therapy at baseline.

For the treatment policy estimand, the mean percentage change in body weight at week 52 was −9.8% in the semaglutide group and −3.4% in the placebo group (estimated difference, −6.4 percentage points; 95% CI, −7.6 to −5.2; P<0.001)

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

| Characteristic | Semaglutide (N=310) | Placebo (N=306) |
|---|---|---|
| Female sex — no. (%) | 128 (41.3) | 145 (47.4) |
| Median age — yr | 69.0 (62.0–74.0) | 70.0 (63.0–75.0) |
| Race — no. (%)† | | |
| Asian | 45 (14.5) | 31 (10.1) |
| Black | 13 (4.2) | 5 (1.6) |
| White | 251 (81.0) | 268 (87.6) |
| Other | 1 (0.3) | 2 (0.7) |
| Median BMI (IQR) | 36.9 (33.6–41.5) | 36.9 (33.5–41.1) |
| Median NT-proBNP level (IQR) — pg/ml | 477.8 (251.2–969.2) | 502.3 (240.2–1114.6) |
| Median CRP level (IQR) — mg/liter | 3.7 (1.8–8.4) | 3.3 (1.6–8.4) |
| Median duration of diabetes (IQR) — yr | 8.0 (3.6–14.3) | 8.0 (4.1–15.2) |
| Median glycated hemoglobin level (IQR) — % | 6.7 (6.2–7.4) | 6.9 (6.2–7.7) |
| Median LVEF (IQR) — % | 57.0 (50.0–61.0) | 55.0 (50.0–60.0) |
| Median KCCQ-CSS (IQR) — points‡ | 60.4 (44.8–72.9) | 58.3 (41.1–70.8) |
| Median 6-minute walk distance (IQR) — m | 280.0 (205.1–357.6) | 280.0 (200.0–345.0) |
| Hospitalization for heart failure within 1 year — no. (%) | 49 (15.8) | 63 (20.6) |
| Coexisting conditions at screening — no. (%) | | |
| Atrial fibrillation | 117 (37.7) | 126 (41.2) |
| Hypertension | 255 (82.3) | 271 (88.6) |
| Coronary artery disease | 79 (25.5) | 69 (22.5) |
| Obstructive sleep apnea | 25 (8.1) | 28 (9.2) |
| NYHA functional class — no. (%) | | |
| II | 223 (71.9) | 212 (69.3) |
| III or IV | 87 (28.1) | 94 (30.7) |
| Concomitant medication — no. (%) | | |
| Diuretic | 246 (79.4) | 252 (82.4) |
| Loop diuretic | 186 (60.0) | 187 (61.1) |
| Thiazide | 42 (13.5) | 43 (14.1) |
| MRA | 105 (33.9) | 95 (31.0) |
| ACEI, ARB, or ARNI | 249 (80.3) | 253 (82.7) |
| Beta-blocker | 257 (82.9) | 253 (82.7) |
| SGLT2 inhibitor | 107 (34.5) | 95 (31.0) |

* Data are from the full analysis population. Overall, 51 participants (8.3%) qualified for participation in the trial on the basis of elevated left ventricular filling pressures, 107 (17.4%) on the basis of hospitalization for heart failure within 12 months in combination with ongoing diuretic treatment or echocardiographic abnormalities, and 458 (74.4%) on the basis of elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in combination with echocardiographic abnormalities. 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, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, NYHA New York Heart Association, and SGLT2 sodium–glucose cotransporter 2.

† Race was reported by the investigator.

‡ The Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) ranges from 0 to 100, with higher scores indicating fewer symptoms and physical limitations.

(Fig. 1B and Table 2). For the trial product estimand, the corresponding changes were −11.0% and −3.1% (estimated difference, −7.9 percentage points; 95% CI, −9.0 to −6.8) (Fig. S4B). The estimated difference between the semaglutide group and the placebo group in the change in body weight was −4.7 percentage points (95% CI, −6.7 to −2.8) among participants who received SGLT2 inhibitor therapy at baseline and −7.2 percentage points (95% CI, −8.7 to −5.8%) among those who did not receive SGLT2 inhibitor therapy at baseline.

#### CONFIRMATORY SECONDARY END POINTS

For the treatment policy estimand, the mean change in the 6-minute walk distance at week 52 was 12.7 m in the semaglutide group and −1.6 m in the placebo group (estimated difference, 14.3 m; 95% CI, 3.7 to 24.9; P=0.008) (Fig. 2A and Table 2). For the trial product estimand, the corresponding changes were 21.5 m and 3.4 m (estimated difference, 18.1 m; 95% CI, 8.9 to 27.2) (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 1.58 (95% CI, 1.29 to 1.94; P<0.001) for the treatment policy estimand. The wins favored semaglutide over placebo for most key components of the hierarchical composite end point (Fig. 2B and Table 2); a difference of at least 15 points in the KCCQ-CSS contributed the most wins for semaglutide. For the trial product estimand, the stratified win ratio was 1.86 (95% CI, 1.51 to 2.28) (Fig. S5B).

For the treatment policy estimand, participants in the semaglutide group had a 42.0% reduction in the CRP level at 52 weeks (geometric mean ratio [week 52 value to baseline value], 0.58), as compared with a 12.8% reduction with placebo (geometric mean ratio [week 52 value to baseline value], 0.87) (estimated treatment ratio [i.e., the ratio between the two geometric mean ratios], 0.67; 95% CI, 0.55 to 0.80; P<0.001) (Fig. 2C and Table 2). The corresponding values for the trial product estimand were 0.53 (47.4% reduction) and 0.92 (7.8% reduction) (estimated treatment ratio, 0.57; 95% CI, 0.49 to 0.67) (Fig. S5C).

#### SUPPORTIVE SECONDARY AND EXPLORATORY END POINTS

The results for supportive secondary and exploratory end points are shown in Table 2. The estimated treatment ratio for the change in the NT-proBNP level among participants receiving semaglutide as compared with those receiving placebo was 0.8 (95% CI, 0.7 to 0.9). In total, 7 participants in the semaglutide group and 18 in the placebo group had an adjudicated heart failure event (hospitalization or urgent visit for heart failure) (hazard ratio, 0.40; 95% CI, 0.15 to 0.92) (Fig. S6). The estimated difference in the change in glycated hemoglobin levels between participants receiving semaglutide and those receiving placebo was −0.8 percentage points (95% CI, −1.0 to −0.6).

#### SAFETY

Serious adverse events are summarized in Table 3 and Table S9 for the treatment period and the in-trial period, respectively. Safety focus areas for the treatment period are summarized in Table S10. Serious adverse events were reported in 55 participants (17.7%) in the semaglutide group and 88 (28.8%) in the placebo group (P=0.002). Cardiac disorder events were reported in 19 participants in the semaglutide group and 40 in the placebo group (P=0.004). Overall, 6 participants (1.9%) in the semaglutide group and 11 (3.6%) in the placebo group discontinued treatment because of serious adverse events. A total of 33 participants (10.6%) in the semaglutide group and 25 (8.2%) in the placebo group discontinued treatment because of any adverse event. There was no apparent between-group difference in the percentage of participants reporting clinically significant hypoglycemia. Overall, 16 participants died (6 in the semaglutide group and 10 in the placebo group). Five deaths were adjudicated as having cardiovascular causes (1 in the semaglutide group and 4 in the placebo group), 10 as having noncardiovascular causes (4 in the semaglutide group and 6 in the placebo group), and 1 (in the semaglutide group) as having an undetermined cause.

## DISCUSSION

In this trial involving patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, once-weekly semaglutide at a dose of 2.4 mg led to larger reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo at 52 weeks. Semaglutide also increased the 6-minute walk distance, resulted in more wins in the evalu-

**Table 2. Efficacy End Points.***

| End Point | Semaglutide (N=310) | Placebo (N=306) | Estimated Difference or Ratio (95% CI) | P Value |
|---|---|---|---|---|
| **Dual primary end points** | | | | |
| Change in KCCQ-CSS from baseline to week 52 — points | 13.7 | 6.4 | 7.3 (4.1 to 10.4)† | <0.001 |
| Percentage change in body weight from baseline to week 52 | –9.8 | –3.4 | –6.4 (–7.6 to –5.2)† | <0.001 |
| **Confirmatory secondary end points** | | | | |
| Change from baseline to week 52 in 6-minute walk distance — m | 12.7 | –1.6 | 14.3 (3.7 to 24.9)† | 0.008 |
| Hierarchical composite end point — crude percentage of wins‡ | 58.7 | 36.8 | 1.58 (1.29 to 1.94)§ | <0.001 |
| Change from baseline to week 52 in CRP level — %¶ | –42.0 | –12.8 | 0.67 (0.55 to 0.80)‖** | <0.001 |
| **Supportive secondary end points** | | | | |
| Change from baseline to week 52 in systolic blood pressure — mm Hg | –4.2 | –1.7 | –2.5 (–5.3 to 0.3)† | — |
| Change from baseline to week 52 in waist circumference — cm | –9.0 | –2.6 | –6.4 (–7.7 to –5.0)† | — |
| Change from baseline to week 52 in KCCQ-OSS — points†† | 13.5 | 6.2 | 7.3 (4.2 to 10.4)† | — |
| Change from baseline to week 52 in glycated hemoglobin level — % | –0.7 | 0.1 | –0.8 (–1.0 to –0.6)† | — |
| Percentage reduction in body weight at week 52 — % of participants | | | | |
| ≥10% reduction | 51.4 | 10.4 | 7.3 (4.7 to 11.4)§ | — |
| ≥15% reduction | 22.4 | 4.0 | 5.4 (2.8 to 10.2)§ | — |
| ≥20% reduction | 7.3 | 1.8 | 3.2 (1.3 to 8.2)§ | — |
| Increase in KCCQ-CSS at week 52 — % of participants | | | | |
| ≥5-point increase | 73.0 | 54.8 | 2.3 (1.6 to 3.3)§ | — |
| ≥10-point increase | 58.0 | 42.6 | 2.1 (1.4 to 2.9)§ | — |
| Attainment of anchor-based threshold for change in KCCQ-CSS — % of participants‡‡ | 42.7 | 30.5 | 2.0 (1.4 to 2.9)§ | — |
| Attainment of anchor-based threshold for change in 6-minute walk distance — % of participants§§ | 52.7 | 39.2 | 1.7 (1.2 to 2.3)§ | — |
| **Exploratory end points assessed in the overall population** | | | | |
| Change from baseline to week 52 in NT-proBNP level — % | –23.2 | –4.6 | 0.8 (0.7 to 0.9)‖¶¶ | — |
| Adjudicated heart failure event (hospitalization or urgent visit for heart failure), time-to-event analysis — no. of events (% of participants) | 7 (2.3) | 18 (5.9) | 0.40 (0.15 to 0.92)‖‖ | — |
| ≥15-point increase in KCCQ-CSS at week 52 — % of participants | 44.5 | 32.7 | 1.9 (1.3 to 2.8)§ | — |

* 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 (Table S13). For binary end points, odds ratios comparing semaglutide and placebo were estimated from a logistic-regression model 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 semaglutide or placebo was discontinued or a rescue intervention was received. CI denotes confidence interval.

† The value is the estimated between-group difference.

‡ 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 (defined as adjudicated events of hospitalization for heart failure or urgent visits in which intravenous therapy was administered, baseline to week 57); 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 the participants assigned to receive semaglutide were compared with all the participants assigned to receive placebo 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.

§ 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 estimated CRP levels (non–log-transformed) at week 52 were 4.44 mg per liter in the semaglutide group and 6.08 mg per liter in the placebo group. The changes in estimated CRP levels (non–log-transformed) from baseline to week 52 were –2.48 mg per liter and –0.84 mg per liter, respectively.

**Table 2. (Continued.)**

‖ 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 0.58 in the semaglutide group and 0.87 in the placebo group. The estimated treatment ratio is calculated as 0.58/0.87=0.67.

†† The KCCQ overall summary score (KCCQ-OSS) ranges from 0 to 100, with higher scores indicating better health status.

‡‡ A threshold of 16.3 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 190 participants who had a one-category improvement.

§§ A threshold of 16.2 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 168 participants who had a one-category improvement. Patient global impression of change (PGI-C) was also used in a sensitivity analysis of anchor-based evaluations of thresholds for 6-minute walk distance. The percentages of participants improving by at least 25.6 m were 43.8% in the semaglutide group and 30.6% in the placebo group, with a threshold of 25.6 m chosen on the basis of the change from baseline to week 52 in the PGI-C that measures the participant's perception of the ability to walk quickly (category "moderately better"). To establish the threshold, the mean change in 6-minute walk distance was calculated (using pooled data across the groups) in the group of 79 participants in the category "moderately better." The treatment odds ratio for the anchor-based sensitivity analysis (PGI-C) of 6-minute walk distance for semaglutide as compared with placebo was 1.7 (95% CI, 1.2 to 2.4).

¶¶ The ratio of the NT-proBNP level at week 52 to the level at baseline was 0.77 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 as a fixed factor.

ation of the hierarchical composite end point, and reduced CRP levels to a greater extent than placebo. More participants receiving semaglutide had clinically meaningful (anchor-based) improvements in the KCCQ-CSS and 6-minute walk distance than those receiving placebo. Semaglutide resulted in fewer serious adverse events than placebo, and the frequency of discontinuation due to serious adverse events was similar in the two groups.

Excess adiposity and insulin resistance form a common soil that can lead to the development of heart failure with preserved ejection fraction and type 2 diabetes.[6,7,25] Among persons with heart failure and preserved ejection fraction, those with type 2 diabetes have a more severe phenotype, characterized by a greater degree of myocardial, microvascular, mitochondrial, and skeletal muscle dysfunction and of inflammation and insulin resistance,[8,11-13,19,20] and have a greater burden of symptoms and physical limitations, worse exercise function, and poorer quality of life than those without type 2 diabetes.[9,11,12,26] Furthermore, the use of insulin and insulin secretagogues is specific to persons with type 2 diabetes and may be one of the reasons for the attenuated body-weight reduction in this group as compared with patients without type 2 diabetes observed in weight-loss trials.[14,18] Insulin promotes weight gain and has antinatriuretic effects that may exacerbate congestion in patients with heart failure.[27] Conversely, patients with type 2 diabetes are more likely to receive SGLT2 inhibitors, which reduce adverse heart failure–related events, improve health status,[28-30] and alleviate pulmonary congestion.[31,32] Thus, it was important to specifically examine the effects of semaglutide on key heart failure end points in this population.

The results of the STEP-HFpEF DM trial add to the previously reported findings of the STEP-HFpEF trial[17] in several ways. First, they extend the broad clinical benefits of semaglutide and safety findings to persons with heart failure with preserved ejection fraction and type 2 diabetes. Consistency between the findings of the two trials provides greater reassurance that semaglutide is an efficacious treatment option with a favorable safety profile in a broad population of patients with obesity-related heart failure with preserved ejection fraction (Table S11). Second, these consistent benefits with respect to heart failure occurred despite weight loss with semaglutide that was approximately 40% less than what was observed in patients without diabetes in the STEP-HFpEF trial, which suggests that the mechanisms of benefit with semaglutide may extend beyond weight loss and may include direct effects on decongestion; vascular, skeletal muscle, and mitochondrial function; epicardial adipose tissue; inflammation; and insulin resistance, factors that (unlike weight loss) may be more pronounced in patients with type 2 diabetes than in those with-

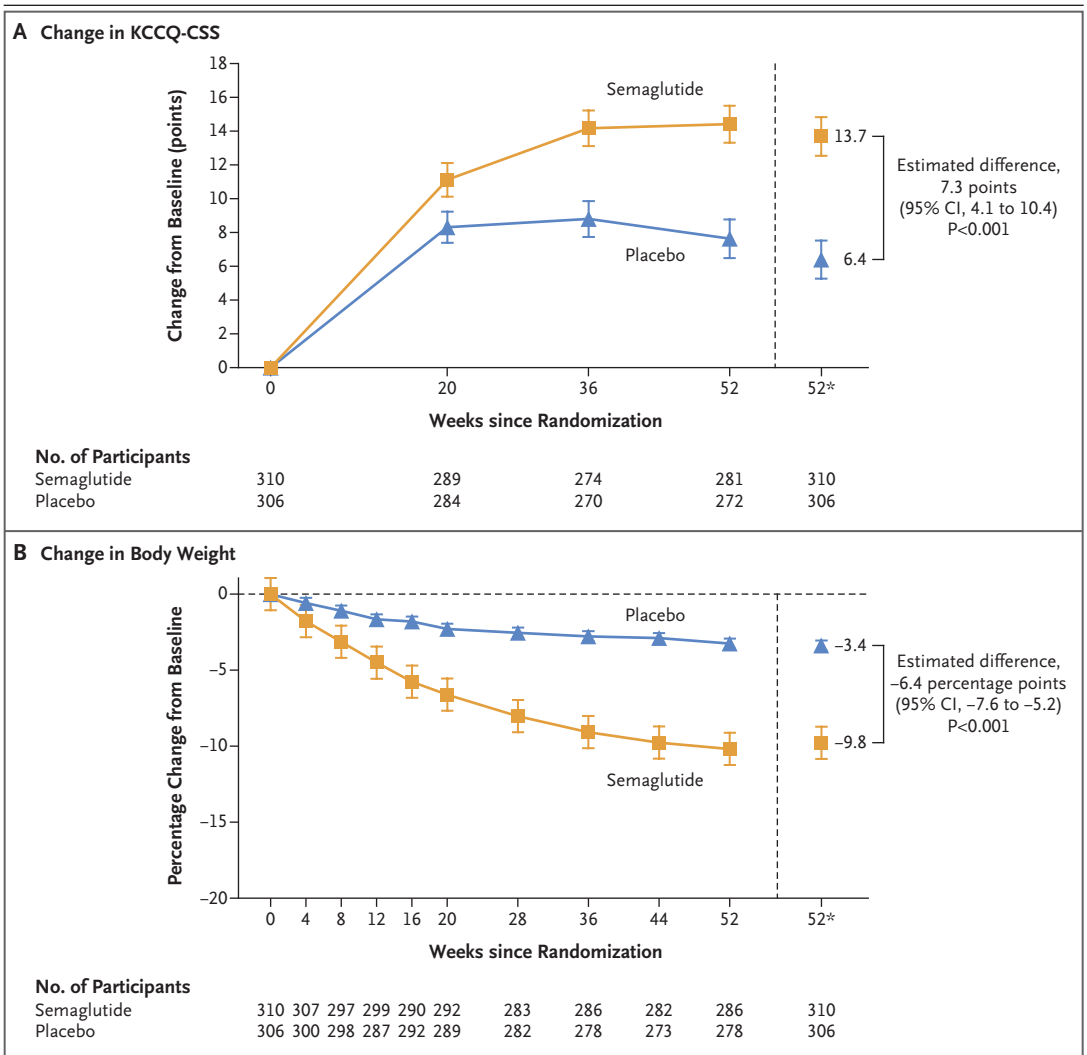


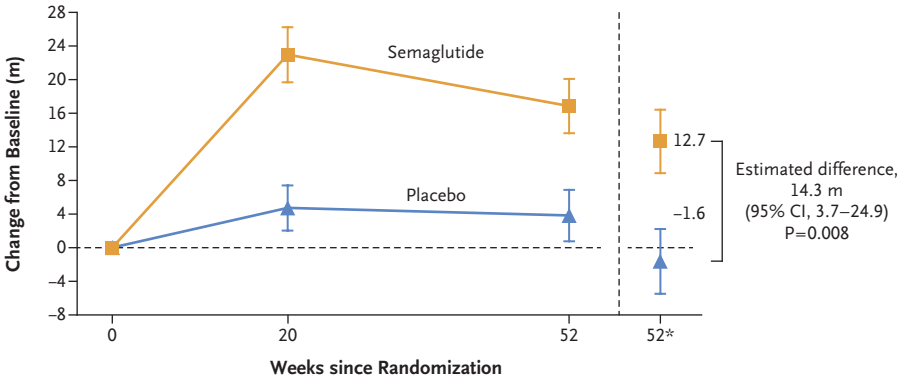

**Figure 1. Change from Baseline to Week 52 in the Dual Primary End Points.**

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 (with variations in participants attending certain trial visits). 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.

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

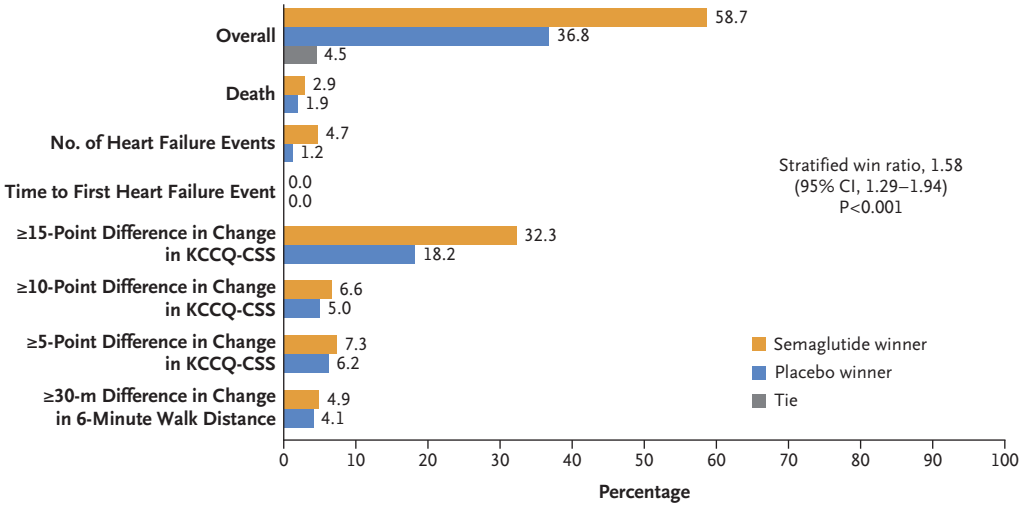
Analyses are based on the treatment policy estimand, reflect the full analysis population, and are from the in-trial period. Panel A shows the observed (i.e., as-measured) mean changes from baseline in the 6-minute walk distance; I bars indicate the standard error. Panel B shows the stratified win ratio for the hierarchical composite 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, 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 a 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.

**A** Change in 6-Minute Walk Distance

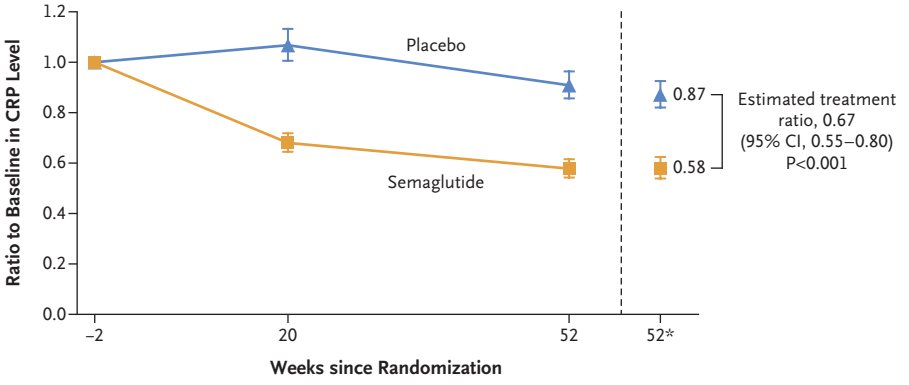



| No. of Participants | | | | |
|---|---|---|---|---|
| Semaglutide | 310 | 284 | 281 | 310 |
| Placebo | 306 | 277 | 265 | 306 |

**B** Stratified Win Ratio for Hierarchical Composite End Point




**C** Change in C-Reactive Protein Level




| No. of Participants | | | | |
|---|---|---|---|---|
| Semaglutide | 310 | 288 | 286 | 310 |
| Placebo | 306 | 285 | 277 | 306 |

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

| Adverse Event | Semaglutide (N=310) | | | Placebo (N=306) | | | 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 | 55 (17.7) | 101 | 33.1 | 88 (28.8) | 168 | 55.0 | 0.002 |
| Serious adverse event leading to discontinuation of semaglutide or placebo | 6 (1.9) | 6 | 2.0 | 11 (3.6) | 14 | 4.6 | — |
| Gastrointestinal disorder | 1 (0.3) | 1 | 0.3 | 0 | 0 | 0 | — |
| Adverse event leading to discontinuation of semaglutide or placebo | 33 (10.6) | 45 | 14.7 | 25 (8.2) | 34 | 11.1 | — |
| Gastrointestinal disorder | 20 (6.5) | 27 | 8.8 | 9 (2.9) | 10 | 3.3 | — |
| Fatal event | 4 (1.3) | 4 | 1.3 | 10 (3.3) | 15 | 4.9 | — |
| Most frequent serious adverse events‡ | | | | | | | — |
| Cardiac disorder§ | 19 (6.1) | 23 | 7.5 | 40 (13.1) | 58 | 19.0 | 0.004 |
| Cardiac arrhythmia | 12 (3.9) | 13 | 4.3 | 10 (3.3) | 12 | 3.9 | — |
| Coronary artery disorder | 5 (1.6) | 5 | 1.6 | 9 (2.9) | 10 | 3.3 | — |
| Heart failure | 4 (1.3) | 4 | 1.3 | 27 (8.8) | 35 | 11.5 | — |
| Vascular disorder | 5 (1.6) | 5 | 1.6 | 6 (2.0) | 6 | 2.0 | 0.77 |
| Infection or infestation | 12 (3.9) | 17 | 5.6 | 27 (8.8) | 38 | 12.4 | 0.01 |
| Gastrointestinal disorder | 5 (1.6) | 5 | 1.6 | 5 (1.6) | 5 | 1.6 | 1.00 |
| Nervous system disorder | 6 (1.9) | 7 | 2.3 | 6 (2.0) | 7 | 2.3 | 1.00 |
| Renal or urinary disorder | 2 (0.6) | 2 | 0.7 | 8 (2.6) | 8 | 2.6 | 0.06 |
| Respiratory, thoracic, or mediastinal event | 6 (1.9) | 6 | 2.0 | 6 (2.0) | 7 | 2.3 | 1.00 |
| Musculoskeletal or connective-tissue event | 5 (1.6) | 6 | 2.0 | 8 (2.6) | 8 | 2.6 | 0.42 |
| Injury, poisoning, or procedural event | 7 (2.3) | 11 | 3.6 | 2 (0.7) | 2 | 0.7 | 0.18 |
| Metabolism or nutrition disorder | 3 (1.0) | 3 | 1.0 | 4 (1.3) | 4 | 1.3 | 0.72 |
| General disorder or administration-site reaction | 1 (0.3) | 1 | 0.3 | 3 (1.0) | 3 | 1.0 | 0.37 |
| Benign, malignant, or unspecified neoplasm | 8 (2.6) | 8 | 2.6 | 7 (2.3) | 7 | 2.3 | 1.00 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Adjudicated events¶ | | | | | | | — |
| Death from any cause | 6 (1.9) | 6 | 1.8 | 10 (3.3) | 10 | 3.0 | — |
| Death from cardiovascular causes | 1 (0.3) | 1 | 0.3 | 4 (1.3) | 4 | 1.2 | — |
| Heart failure event | 7 (2.3) | 8 | 2.4 | 18 (5.9) | 23 | 7.0 | — |
| Death from undetermined cause | 1 (0.3) | 1 | 0.3 | 0 | 0 | 0 | — |

* Adverse events are shown for the safety analysis population (all randomly assigned participants who received at least one dose of semaglutide or placebo); because all participants received at least one dose, the safety population is the same as the full analysis population. Unless otherwise indicted, 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.
§ Cardiac disorder, arrhythmia, coronary artery disorder, and heart failure represent the high-level term. Cardiac arrhythmias were predominantly atrial fibrillation or flutter.
¶ 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 semaglutide or placebo was discontinued or a rescue intervention was received).

out type 2 diabetes. Third, the present trial provides evidence for the consistency of the effects of semaglutide on heart failure–related outcomes in patients who received SGLT2 inhibitors (which have emerged as a standard of care in heart failure with preserved ejection fraction[33]) and in those who did not receive them. Fourth, the favorable safety profile of semaglutide in patients with heart failure with preserved ejection fraction has now been extended to patients with type 2 diabetes, who have unique potential vulnerabilities. Semaglutide reduced glycated hemoglobin levels (despite well-controlled glycemia at baseline) without an increase in clinically significant hypoglycemia. Furthermore, there was no increase in diabetic retinopathy events with semaglutide, which has been a potential concern for GLP-1 receptor agonists in type 2 diabetes.[34]

Although the number of adjudicated heart failure events was small, the overall incidence of hospitalizations and urgent visits for heart failure was higher than in the STEP-HFpEF trial and similar to that in other recent trials involving patients with heart failure with preserved ejection fraction. Despite the relatively small number of events, they were distributed favorably to semaglutide as compared with placebo, which occurred in parallel with substantial reductions in NT-proBNP levels, a finding that offers further support for similar observations in the STEP-HFpEF trial[17] and suggests important disease-modifying effects of semaglutide. Collectively, these results provide a signal for a potential reduction in clinical events, which requires further confirmation in heart failure outcome trials.

This trial has several limitations. First, although the percentage of Black participants in the United States was 26%, which is higher than what has been reported nationally among patients with heart failure and preserved ejection fraction[35] (Table S12), the number of non-White participants in the overall trial was low, which limits generalizability. Second, the trial aimed to evaluate the effects of semaglutide on symptoms, physical limitations, and exercise function and was not designed to evaluate events such as hospitalizations and urgent visits for heart failure. Third, the duration of follow-up was limited to 1 year; although the trajectory of the effects of semaglutide suggested persistent improvements over time as compared with placebo, the durability of these effects beyond 1 year cannot

be ascertained. Fourth, as is the case for most trials, data were missing for some participants (Table S13).

In this trial involving patients with obesity-related heart failure with preserved ejection fraction and type 2 diabetes, 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 weight loss, and greater improvements in exercise function than placebo.

Supported by Novo Nordisk.

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.

## APPENDIX

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## REFERENCES

1. Roger VL. Epidemiology of heart failure: a contemporary perspective. Circ Res 2021;128:1421-34.
2. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. JAMA 2023;329:827-38.
3. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. Nat Rev Cardiol 2020;17:559-73.
4. Haass M, Kitzman DW, Anand IS, et al. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 2011;4:324-31.
5. Kitzman DW, Nicklas BJ. Pivotal role of excess intra-abdominal adipose in the pathogenesis of metabolic/obese HFpEF. JACC Heart Fail 2018;6:1008-10.
6. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovasc Res 2023;118:3434-50.
7. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nat Rev Cardiol 2021;18:291-304.
8. Reddy YNV, Rikhi A, Obokata M, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. Eur J Heart Fail 2020;22:1009-18.
9. Inzucchi SE, Claggett BL, Vaduganathan M, et al. Efficacy and safety of dapagliflozin in patients with heart failure with mildly reduced or preserved ejection fraction by baseline glycaemic status (DELIVER): a subgroup analysis from an international, multicentre, double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2022;10:869-81.
10. Kosiborod MN, Bhatt AS, Claggett BL, et al. Effect of dapagliflozin on health status in patients with preserved or mildly reduced ejection fraction. J Am Coll Cardiol 2023;81:460-73.
11. Lindman BR, Dávila-Román VG, Mann DL, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. J Am Coll Cardiol 2014;64:541-9.
12. Kristensen SL, Mogensen UM, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve trial (Irbesartan in Heart Failure with Preserved Ejection Fraction). Circulation 2017;135:724-35.
13. Jackson AM, Rørth R, Liu J, et al. Dia-

betes and pre-diabetes in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2022;24:497-509.
**14.** Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989-1002.
**15.** Kosiborod MN, Bhatta M, Davies M, et al. Semaglutide improves cardiometabolic risk factors in adults with overweight or obesity: STEP 1 and 4 exploratory analyses. Diabetes Obes Metab 2023;25:468-78.
**16.** Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023;389:2221-32.
**17.** Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med 2023;389:1069-84.
**18.** Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971-84.
**19.** Mthembu SXH, Mazibuko-Mbeje SE, Ziqubu K, et al. Impact of physical exercise and caloric restriction in patients with type 2 diabetes: skeletal muscle insulin resistance and mitochondrial dysfunction as ideal therapeutic targets. Life Sci 2022;297:120467.
**20.** Xu J, Pan X, Liang H, et al. Association between skeletal muscle mass to visceral fat area ratio and arterial stiffness in Chinese patients with type 2 diabetes mellitus. BMC Cardiovasc Disord 2018;18:89.
**21.** Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Design and baseline characteristics of STEP-HFpEF program evaluating semaglutide in patients with obesity HFpEF phenotype. JACC Heart Fail 2023;11:1000-10.
**22.** Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245-55.
**23.** Joseph SM, Novak E, Arnold SV, et al. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. Circ Heart Fail 2013;6:1139-46.
**24.** Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC state-of-the-art review. J Am Coll Cardiol 2020;76:2379-90.
**25.** Ramirez MF, Lau ES, Parekh JK, et al. Obesity-related biomarkers are associated with exercise intolerance and HFpEF. Circ Heart Fail 2023;16(11):e010618.
**26.** Yap J, Tay WT, Teng TK, et al. Association of diabetes mellitus on cardiac remodeling, quality of life, and clinical outcomes in heart failure with reduced and preserved ejection fraction. J Am Heart Assoc 2019;8(17):e013114.
**27.** DeFronzo RA, Cooke CR, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man. J Clin Invest 1975;55:845-55.
**28.** Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089-98.
**29.** Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451-61.
**30.** Adamson C, Kondo T, Jhund PS, et al. Dapagliflozin for heart failure according to body mass index: the DELIVER trial. Eur Heart J 2022;43:4406-17.
**31.** Borlaug BA, Reddy YNV, Braun A, et al. Cardiac and metabolic effects of dapagliflozin in heart failure with preserved ejection fraction: the CAMEO-DAPA trial. Circulation 2023;148:834-44.
**32.** Nassif ME, Qintar M, Windsor SL, et al. Empagliflozin effects on pulmonary artery pressure in patients with heart failure: results from the EMBRACE-HF trial. Circulation 2021;143:1673-86.
**33.** McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2023;44:3627-39.
**34.** Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834-44.
**35.** Shah KS, Xu H, Matsouaka RA, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol 2017;70:2476-86.