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

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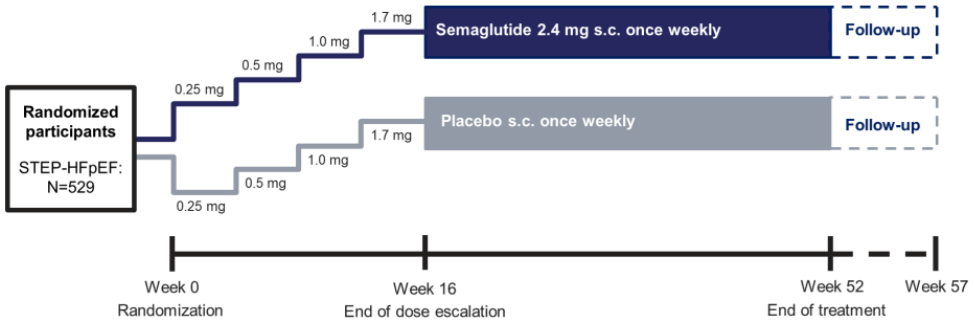
Procedures and Outcomes

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, followed by a 5-week follow-up period.

Randomization was stratified according to baseline BMI (<35 vs. ≥35).

Participants who discontinued treatment prematurely remained in the trial

Figure S1. Trial design



s.c. denotes subcutaneous, STEP-HFpEF Semaglutide Treatment Effect in People with obesity and heart failure with preserved ejection fraction.

Endpoints

The dual primary end points were: **Change in the KCCQ-CSS** and the **percentage change in body weight** from baseline to week 52.

The confirmatory secondary endpoints were:

The change in the 6-minute walk distance from baseline to week 52.

Change in the log-transformed C-reactive protein (CRP) level from screening (week −2) to week 52.

Inclusion

Left ventricular ejection fraction of at least 45%

Body-mass index of at least 30;

New York Heart Association functional class II, III, or IV symptoms;

Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) of less than 90 points;

6-minute walk distance of at least 100 m;

At least one of the following findings:

- Mean PWP >15 or LVEDP > 25 at rest or PA diastolic pressure >15 (on implantable monitor or LVEDP 25 with exercise
- Elevated natriuretic peptide levels (with thresholds stratified according to the BMI at baseline) plus echocardiographic abnormalities,
- Hospitalization for heart failure in the 12 months before screening plus ongoing treatment with diuretics or echocardiographic abnormalities

Exclusion

A patient-reported change in body weight of more than 5 kg within 90 days before screening

A history of diabetes

Myocardial infarction , stroke, or HF hospitalization 30 days prior to screening

SBP>160 at screening

Demographics

- White race: 96%
- Female: 56.1%
- Median BMI: 37 kg/m^2
- Hospitalization for HF within 1 year: 15.3%
- NYHA II: 66.2%
- Baseline medication: Diuretic: 80.7%, mineralocorticoid receptor antagonist: 34.8%, sodium–glucose cotransporter-2 (SGLT2) inhibitor: 3.6%

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.

Primary endpoint

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)

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)

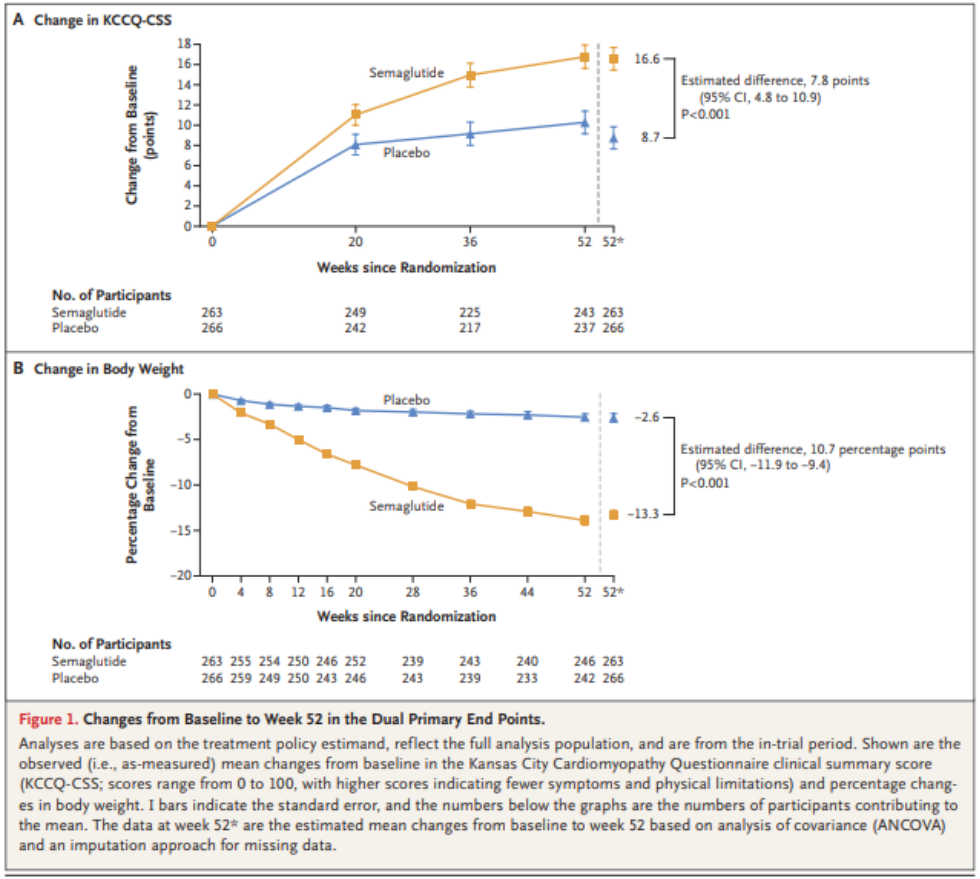
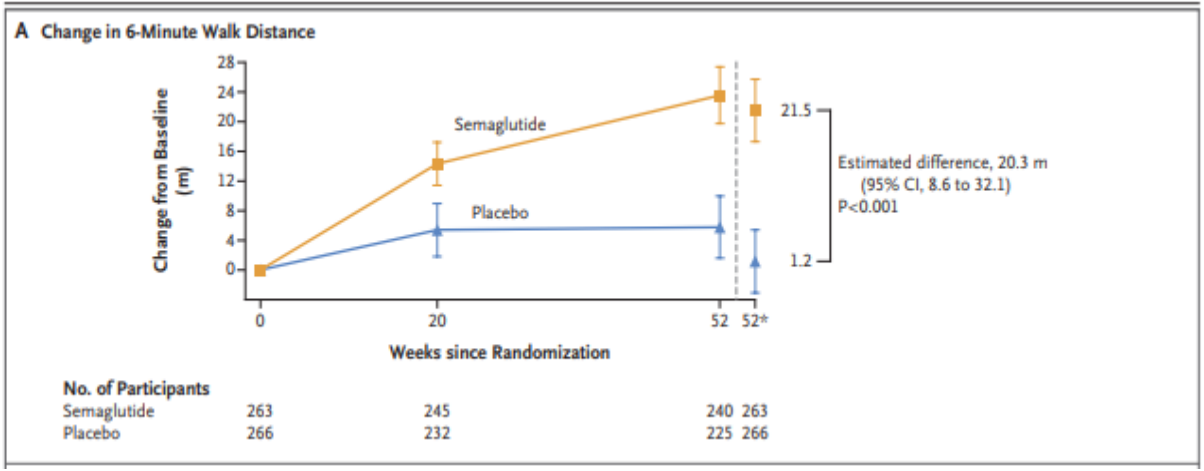


Figure 1. Changes from Baseline to Week 52 in the Dual Primary End Points.

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.

Secondary Endpoints

- Change in 6-minute walk distance from baseline to week 52: 21.5 vs. 1.2 m ($p < 0.001$)
- Percentage reduction from baseline to week 52 in NT-proBNP: -20.9 vs. -5.3 ($p < 0.05$)
- Hospitalization or urgent visit for HF: 1 vs. 12 events ($p < 0.05$)



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.

Limitations and criticisms

Low amount of SGLT2 concurrent use.

Were improvement from weight loss alone?

References

Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al., on behalf of the STEP-HFpEF Trial Committees and Investigators. Semaglutide in Patients With Heart Failure With Preserved Ejection Fraction and Obesity. *N Engl J Med* 2023;Aug 25