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ORIGINAL RESEARCH

Semaglutide and Exercise Function in Obesity-Related HFpEF

Insights From the STEP-HFpEF Program

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ABSTRACT

BACKGROUND Exercise function quantified by 6-minute walk distance (6MWD) is severely impaired in patients with heart failure with preserved ejection fraction (HFpEF).

OBJECTIVES This prespecified secondary analysis of pooled data from the STEP-HFpEF Program (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) examined factors associated with impaired exercise function at baseline, detailed effects of semaglutide on 6MWD, and on other key trial endpoints according to baseline 6MWD in patients with HFpEF.

METHODS Associates of 6MWD were assessed at baseline, and effects of semaglutide on 6MWD were evaluated at early (20 weeks) and final (52 weeks) time points, across subgroups, and according to the magnitude of weight loss achieved. Effects of semaglutide on the dual primary (changes in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score [KCCQ-CSS] and body weight) and secondary/exploratory endpoints were contrasted by tertiles of baseline 6MWD.

RESULTS The authors randomized 1,145 patients to semaglutide or placebo. Compared with patients who had obesity-related HFpEF and higher 6MWD, those with lower 6MWD were older and had lower KCCQ-CSS, higher body mass index and waist circumference, greater systemic inflammation (higher C-reactive protein), and more severe congestion (higher N-terminal pro-B-type natriuretic peptide, more diuretic use). Treatment with semaglutide increased 6MWD compared with placebo, an effect apparent at 20 weeks (treatment difference 14.6 m [95% CI: 8.6-20.7 m; $P < 0.0001$]) that was maintained at 52 weeks (treatment difference 17.1 m [95% CI: 9.2-25.0 m; $P < 0.0001$]). Increases in 6MWD with semaglutide (vs placebo) were similar across all relevant subgroups, with no significant interactions. Treatment with semaglutide increased KCCQ-CSS and reduced body weight, reduced C-reactive protein, improved the hierarchical composite (death, heart failure events, change in KCCQ-CSS and 6MWD), and reduced N-terminal pro-B-type natriuretic peptide across the spectrum of baseline 6MWD (all $P_{interaction}$ = NS). Each 1-unit decrease in body mass index on treatment with semaglutide was associated with a 4.1 m (95% CI: 2.4-5.7 m) increase in 6MWD ($P < 0.0001$).

CONCLUSIONS In patients with obesity-related HFpEF, impaired 6MWD is most strongly associated with excess adiposity, congestion, and inflammation. Semaglutide-mediated improvements in HF-related symptoms, physical limitations, and exercise function were consistent across the spectrum of baseline 6MWD, observed as early as 20 weeks after the initiation of treatment, preceding maximal weight loss. The effects were consistent across subgroups. There was strong correlation between greater magnitude of weight loss and greater improvements in 6MWD. (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity [STEP-HFpEF], NCT04788511; Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes [STEP-HFpEF DM], NCT04916470) (JACC Heart Fail. 2025;13:102660) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

BMI = body mass index

CRP = C-reactive protein

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SAE = serious adverse event

SGLT2 = sodium/glucose cotransporter 2

Exercise intolerance manifested as dyspnea and fatigue with exertion are the primary symptoms experienced by patients with heart failure with preserved ejection fraction (HFpEF).[1-3] The severity of exercise limitation can be quantified by the distance covered in the standardized 6-minute walk distance (6MWD).[4,5] Impairments in 6MWD are strongly associated with poorer health status, greater frailty, reductions in maximal aerobic capacity, and increases in risk for heart failure (HF) hospitalization or death.[6-9] In the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) Program, the glucagon-like peptide 1 receptor agonist semaglutide reduced HF-related symptoms and physical limitations and body weight in patients with obesity-related HFpEF.[10-12] Semaglutide also improved 6MWD and reduced inflammation and N-terminal pro-B-type natriuretic peptide (NT-proBNP), and in STEP-HFpEF, the magnitude of improvement in 6MWD in semaglutide-treated participants was associated with the magnitude of body weight lost.[13]

Few prospective studies have rigorously evaluated the factors associated with impaired baseline 6MWD in patients with obesity-related HFpEF. Furthermore, it is not known whether the effects of semaglutide on the broad range of HF outcomes is influenced by the extent of functional impairment at baseline in this patient group. Specifically, patients with obesity-related HFpEF and a lower baseline 6MWD may have frailty and sarcopenia, which could mute the beneficial effects of semaglutide as compared with individuals who have a higher baseline 6MWD.[14,15] In this prespecified secondary analysis, we performed a detailed assessment of the factors associated with a lower 6MWD at baseline in obesity-related HFpEF, tested the effects of semaglutide vs placebo on 6MWD over time and across a wide spectrum of patient baseline characteristics, and evaluated the association between change in 6MWD and the magnitude of weight loss during the trial. We also examined whether the extent of exercise function impairment at baseline modifies the effects of semaglutide (vs placebo) on primary, secondary, and exploratory endpoints in patients with obesity-related HFpEF. Because sex is well-known to influence 6MWD[16] (owing to differences in stride length, body composition, and hormone profiles), tertiles of 6MWD were also stratified by sex to evaluate for relevant interactions.

METHODS

This was a prespecified analysis of the randomized, international, multicenter, double-blind, placebo-controlled STEP-HFpEF Program, comprising 2 trials: STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity; NCT04788511) in patients with obesity-related HFpEF without type 2 diabetes; and STEP-HFpEF DM (Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes; NCT04916470) in patients with obesity-related HFpEF and type 2 diabetes. The design and primary results of the individual trials, and the overall program have been published previously.[10-12,17] The program was conducted at 129 sites across 18 countries in Asia, Europe, and North and South America. The steering committee, including academic members and representatives from the sponsor, designed both trials and was responsible for the academic

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publications. A global expert panel provided academic, medical, and operational input in each country. Institutional review board ethics approval was obtained at each study site and all patients provided informed consent to participate in the trial. The sponsor of the program was Novo Nordisk.

Patients were eligible to participate if they had a left ventricular ejection fraction of ≥45%, body mass index (BMI) of ≥30 kg/m^2, NYHA functional class II to IV, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) of <90 points, and objective evidence of HF, defined by ≥1 of the following: 1) elevated filling pressures (directly measured); 2) elevated natriuretic peptide levels (BMI stratified) in tandem with abnormalities in cardiac structure-function by echocardiography; or 3) HF hospitalization in the preceding 12 months while requiring ongoing diuretic treatment and/or echocardiographic abnormalities. Key exclusion criteria were a baseline 6MWD at screening of <100 m (with no upper limit exclusionary), prior or planned bariatric surgery, or self-reported change in body weight of >11 lbs (>5 kg) within 90 days preceding randomization. Full eligibility criteria are published elsewhere.[17]

After providing consent, eligible participants were randomized 1:1 to receive a once-weekly target dose of semaglutide 2.4 mg subcutaneously or matching placebo on top of standard of care for 52 weeks. Randomization was stratified by BMI <35 kg/m^2 vs ≥35 kg/m^2. The dual primary endpoints of the STEP-HFpEF Program were:1) change in KCCQ-CSS from baseline to 52 weeks; and 2) percent change in body weight from baseline to 52 weeks. Confirmatory secondary endpoints were: 1) change in 6MWD from baseline to 52 weeks; 2) a hierarchical composite endpoint comprising all-cause death, HF events, differences in several thresholds of change in KCCQ-CSS from baseline to 52 weeks; 3) differences in 6MWD change (of ≥30 m from baseline to 52 weeks); and 4) change in C-reactive protein (CRP) from baseline to 52 weeks. Change in plasma NT-proBNP levels was an exploratory endpoint.

Safety endpoints in the current analysis were serious adverse events (SAEs), which included cardiac SAEs and SAEs leading to permanent treatment discontinuation.

STATISTICAL ANALYSES. Baseline characteristics were evaluated across the baseline 6MWD tertiles (constructed within sex subgroups) and compared using tests for trend across these subgroups; continuous variables used the Jonckheere-Terpstra trend test and binary variables used a Cochran-Armitage trend test. Efficacy endpoints for semaglutide vs placebo, stratified by 6MWD tertiles, were assessed using the full analysis set (all randomized participants according to the intention-to-treat principle, while in trial, regardless of treatment discontinuation). For change in KCCQ-CSS and 6MWD, missing observations at week 52 caused by cardiovascular death or previous HF events were single imputed to the lowest observed value across both treatment arms and visits. Values missing for other reasons were multiple imputed from retrieved participants in the same randomized treatment arm (Supplemental Methods). For other endpoints, missing observations at week 52 were multiple imputed irrespective of death or prior HF events using the same imputation method.

Relationships between the baseline covariates and continuous baseline 6MWD were assessed by linear regression adjusted for sex and trial. The effects of semaglutide vs placebo on 6MWD were assessed both early (20 weeks) and at 52 weeks, and also evaluated across multiple prespecified subgroups, including age, sex, race, geographic region, BMI (<35 kg/m^2 or ≥35 kg/m^2), left ventricular ejection fraction (45%-49%, 50%-59%, or ≥60%), systolic blood pressure (<135 mm Hg or ≥135 mm Hg), NYHA functional class (II vs III or IV), CRP levels (<2 mg/L or ≥2 mg/L), baseline use of a loop diuretic, history of atrial fibrillation, and baseline use of renin-angiotensin system inhibitors. Multivariable linear regression models were also used to determine the relationship between the change in 6MWD and change in body weight during the trials; this analysis was performed in all participants (regardless of treatment assignment). Change in body weight was analyzed as an ordinal variable, including the following weight loss categories from baseline to 52 weeks: <5%, 5% to <10%, 10% to <15%, 15% to <20%, and ≥20%, adjusted for baseline 6MWD, baseline body weight, and trial.

Effects of semaglutide vs placebo on the continuous endpoints across 6MWD tertiles were assessed using analysis of covariance models, with the change in the corresponding endpoint at week 52 as the dependent variable. Fixed factors included randomized treatment, trial, BMI (<35 kg/m^2 or ≥35 kg/m^2), 6MWD tertiles, and treatment by 6MWD tertiles interaction, adjusted for the baseline value of the corresponding endpoint across 1,000 imputation data sets. For analyses of CRP and NT-proBNP, values were log-transformed. Estimates from the multiple imputations were derived using Rubin's rule. Interaction P values were derived from an F-test of equality between the treatment differences across the 3 6MWD tertiles. Furthermore, trend p values for

differences in semaglutide vs placebo treatment across the 6MWD tertiles were also derived for the various endpoints. In supportive analyses, the effects of semaglutide vs placebo on 6MWD were also evaluated using mixed models for repeated measurements with treatment adjusted for baseline of the endpoint variable, trial, sex, and BMI stratum all nested within trial visit using observed in-trial data. An unstructured covariance matrix was used.

Analyses of the hierarchical composite endpoint (win ratio) were performed stratified by 6MWD tertiles, based on direct comparisons of each participant randomized to semaglutide vs each participant randomized to placebo. For each of the participant pairs, a treatment winner based on similar observation time was declared from the endpoint hierarchy. The win ratio (ie, the proportion of winners randomized to semaglutide divided by the proportion of winners randomized to placebo) was estimated independently within each 6MWD tertile (using 1,000 imputations). The test for equality of the 6MWD tertiles for the win ratio was performed using a Cochran's Q test.

In addition, effects for semaglutide vs placebo on dual primary and confirmatory secondary endpoints in participants with the extreme values of the baseline 6MWD were analyzed by dichotomizing the baseline 6MWD as <150 m vs ≥150 m for the lower extreme, and baseline 6MWD as >450 m vs ≤450 m for the higher extreme. Analysis of covariance models were used using the full analysis set with fixed factors of randomized treatment, trial, BMI (<35 kg/m^2 or ≥35 kg/m^2), 6MWD dichotomized, and treatment by 6MWD dichotomized interaction, adjusted for the baseline value of the corresponding endpoint across 1,000 imputation datasets.

We further explored the relationship between baseline 6MWD and the continuous efficacy endpoints by incorporating treatment interaction with baseline 6MWD modeled continuously with restricted cubic splines, and the model stratified by BMI, sex and trial. Interaction *P* values between the 6MWD as a continuous variable (modelled as a spline) and randomized treatment at week 52 were derived to assess potential heterogeneity of treatment effects (semaglutide vs placebo) across the range of baseline 6MWDs.

Safety events across 6MWD tertiles were analyzed using the safety analysis set (all randomized participants exposed to ≥1 dose of treatment) and summarized as numbers of participants with an event and event rates. No adjustment for multiplicity was done in the pooled analyses, and a value of $P < 0.05$ was considered significant. All results from statistical analyses are presented with 2-sided 95% CIs and 2-sided *P* values. We used SAS (version 9.4, SAS Institute) for all analyses. Statistical analyses were performed by the independent statistical group at Saint Luke's Mid America Heart Institute using anonymized datasets.

RESULTS

A total of 1,145 participants were randomized across the STEP-HFpEF Program; 529 in STEP-HFpEF and 616 in STEP-HFpEF DM. As expected, the 6MWD was higher in men with obesity-related HFpEF compared with women (318 ± 100 m vs 274 ± 95 m; $P < 0.0001$). Tertiles of baseline 6MWD were 62 to 229 m, 229 to 319 m, and 320 to 600 m for women and 88 to 270 m, 270 to 365 m, and 365 to 600 m for men. Compared with participants who had HFpEF and a higher baseline 6MWD, those with lower 6MWD were older, had a higher BMI and waist circumference, lower KCCQ-CSS, higher CRP and NT-proBNP levels, and were more likely to have NYHA functional class III-IV symptoms and be treated chronically with loop diuretics (Table 1). They also had a greater prevalence of coronary artery disease and diabetes, but no differences in the prevalence of hypertension or atrial fibrillation.

CORRELATES OF 6MWD AT BASELINE. In linear regression analyses, older age, female sex, higher BMI, higher waist circumference, lower KCCQ-CSS, higher CRP, and higher NT-proBNP were associated with poorer baseline 6MWD (Table 2). Each 1-standard deviation increase in CRP, NT-proBNP, and BMI was associated with a 12.2 m, 12.8 m, and 21.5 m lower baseline 6MWD, respectively (Figure 1). There was a strong and highly significant positive relationship between baseline 6MWD and KCCQ-CSS (Table 2).

EFFECTS OF SEMAGLUTIDE VS PLACEBO ON 6MWD. Semaglutide (vs placebo) improved 6MWD, with a statistically significant improvement observed by week 20, which was maintained at 52 weeks ($P < 0.0001$ for both timepoints) (Central Illustration, Table 3). The mean estimated treatment difference at 20 weeks was 14.6 m (95% CI: 8.6-20.7 m) and at 52 weeks it was 17.1 m (95% CI: 9.2-25.0 m). The mean percentage increase in 6MWD at 20 weeks was 8.9% (95% CI: 6.9-10.9 m) for semaglutide and 3.2% (95% CI: 1.2-5.3 m) for placebo. The mean percentage increase in 6MWD at 52 weeks was 9.6% (95% CI: 7.4%) for semaglutide and 3.7% (95% CI: 1.6%-5.9%) for placebo. There was a consistent increase in 6MWD in semaglutide- vs placebo-treated patients across relevant participant subgroups, including across the baseline 6MWD tertiles (Figure 2, Table 3). Patients achieving more weight loss (regardless of treatment assignment) had greater improvements in 6MWD

TABLE 1 Baseline Characteristics

	6MWD Tertile 1 (n = 381)	6MWD Tertile 2 (n = 382)	6MWD Tertile 3 (n = 382)	Total (N = 1,145)	*P* Value
Female	190 (49.9)	189 (49.5)	191 (50.0)	570 (49.8)	NA
Age, y					<0.001
<65	91 (23.9)	118 (30.9)	159 (41.6)	368 (32.1)	
65-79	228 (59.8)	229 (59.9)	209 (54.7)	666 (58.2)	
≥80	62 (16.3)	35 (9.2)	14 (3.7)	111 (9.7)	
Race					0.009
Asian	39 (10.2)	20 (5.2)	17 (4.5)	76 (6.6)	
Black	11 (2.9)	17 (4.5)	11 (2.9)	39 (3.4)	
Other	0 (0.0)	1 (0.3)	3 (0.8)	4 (0.3)	
White	331 (86.9)	344 (90.1)	351 (91.9)	1026 (89.6)	
Body weight, kg	105.2 (93.0-121.7)	103.1 (89.5-117.7)	102.0 (91.8-117.1)	103.7 (91.3-119.0)	0.053
BMI, kg/m^2	39.8 (35.3-44.4)	37.6 (34.5-42.4)	37.0 (34.0-40.7)	38.0 (34.6-42.6)	<0.001
Waist circumference, cm	123.0 (114.0-133.5)	119.0 (111.0-128.5)	117.0 (109.5-126.5)	120.0 (111.0-129.0)	<0.001
Systolic blood pressure, mm Hg	132.0 (120.0-141.0)	135.0 (124.0-145.0)	134.0 (124.0-145.0)	133.0 (123.0-144.0)	0.031
NYHA functional class					
II	211 (55.4)	273 (71.5)	301 (78.8)	785 (68.6)	<0.001
III/IV	170 (44.6)	109 (28.5)	81 (21.2)	360 (31.4)	
LVEF, %	57 (50-60)	56 (51-60)	57 (50-60)	57 (50-60)	0.924
KCCQ-CSS, points	46.9 (33.3-63.0)	60.7 (44.8-72.9)	66.4 (53.6-77.1)	59.4 (42.7-72.4)	<0.001
6MWD, m	192.0 (157.5-220.0)	294.7 (270.3-323.0)	395.3 (368.0-440.0)	294.8 (220.0-368.0)	NA
CRP, mg/L	4.4 (2.0-9.9)	3.5 (1.8-7.4)	3.0 (1.7-6.6)	3.7 (1.8-8.1)	<0.001
NT-proBNP, pg/mL	638.9 (269.8-1231.3)	451.6 (240.2-1009.8)	378.9 (208.9-829.6)	475.3 (234.3-1,015.7)	<0.001
Comorbidities at screening					
Hypertension	315 (82.7)	334 (87.4)	310 (81.2)	959 (83.8)	0.566
Atrial fibrillation	177 (46.5)	163 (42.7)	178 (46.6)	518 (45.2)	0.968
Obstructive sleep apnea	40 (10.5)	47 (12.3)	32 (8.4)	119 (10.4)	0.336
Coronary artery disease	159 (41.7)	163 (42.7)	131 (34.3)	453 (39.6)	0.035
Type 2 diabetes	249 (65.4)	220 (57.6)	148 (38.7)	617 (53.9)	<0.001
Baseline medications					
Any diuretic	330 (86.6)	313 (81.9)	282 (73.8)	925 (80.8)	<0.001
Loop diuretics	284 (74.5)	231 (60.5)	187 (49.0)	702 (61.3)	<0.001
Thiazides	52 (13.6)	58 (15.2)	65 (17.0)	175 (15.3)	0.196
Beta-blockers	319 (83.7)	302 (79.1)	307 (80.4)	928 (81.0)	0.236
SGLT2 inhibitors	89 (23.4)	71 (18.6)	61 (16.0)	221 (19.3)	0.009
MRA	146 (38.3)	123 (32.2)	115 (30.1)	384 (33.5)	0.016
ACEI/ARB (ARNI)	292 (76.6)	317 (83.0)	290 (75.9)	899 (78.5)	0.806

Values are n (%) or median (Q1-Q3), unless otherwise indicated. *P* values for continuous variables computed from Jonckheere-Terpstra trend test, Cochran-Armitage trend test for binary variables, and Cochran-Mantel-Haenszel test for multinomial variables. Includes participants with baseline 6MWD of 62.0-228.5, 229.0-318.7, and 320.0-600.0 for women and 87.5-269.6, 270.3-365.0, and 365.4-600.0 for men.

6MWD = 6-minute walk distance; ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CRP = C-reactive protein; IQR = interquartile range; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NA = not available; SGLT2 = sodium-glucose cotransporter 2.

(**Central Illustration**). This relationship was maintained when baseline body weight was not included in the model ($P < 0.0001$). Decreases in body weight were associated with improved 6MWD in both the placebo and semaglutide groups when evaluated individually as well, though weight loss was expectedly much less common with placebo (Supplemental Figure 1).

EFFECTS OF SEMAGLUTIDE VS PLACEBO ON TRIAL ENDPOINTS BY BASELINE 6MWD. Semaglutide improved KCCQ-CSS scores across 6MWD tertiles in the overall population, with no significant treatment by 6MWD interaction (**Table 3**, **Figure 3A**), including when 6MWD was analyzed as a continuous variable (**Figure 3B**). In sex-stratified analyses, the treatment effect of semaglutide on KCCQ-CSS was more pronounced in women with lower vs higher baseline 6MWD (estimated difference: tertile 1: 13.2 points [95% CI: 8.0-18.5], tertile 2: 4.6 [95% CI: −0.6 to 9.8], tertile 3: 4.6 [95% CI: −0.4 to 9.7]) $P_{\text{interaction}} = 0.028$, but not in men (estimated difference: tertile 1: 6.7 [95% CI: 1.2-12.2], tertile 2: 8.2 [95% CI: 2.7-13.7],

TABLE 2 Correlates of Baseline 6MWD by Linear Regression

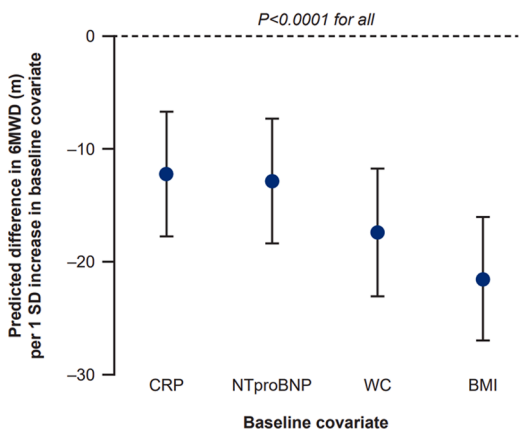
	Slope (95% CI)	*P* Value	Predicted Difference in Baseline Covariate per 20 m Lower Baseline 6MWD	Predicted Difference in 6MWD for 1 SD Increase in or Presence of Baseline Covariate	
				Slope (95% CI)	*P* Value
Age, y	−2.55 (−3.21 to −1.98)	<0.0001	7.85 (6.42 to 10.10)	−23.9 (−30.1 to 18.3)	<0.0001
Female vs male	−49.5 (−60.6 to −38.4)	<0.0001	–	–	–
BMI, kg/m^2	−3.31 (−4.15 to −2.48)	<0.0001	6.00 (4.82 to 8.06)	−21.5 (−26.9 to −16.0)	<0.0001
Waist circumference, cm	−1.19 (−1.58 to −0.8)	<0.0001	16.81 (12.66 to 25)	−17.3 (−23.0 to − 11.7)	<0.0001
CRP, mg/L[a]	−10.9 (−15.9 to −6.0)	<0.0001	1.83 (1.26 to 3.35)	−12.2 (−17.7 to −6.67)	<0.0001
NT-proBNP, pg/dL[a]	−11.6 (−16.5 to −6.6)	<0.0001	1.73 (1.21 to 3.02)	−12.8 (−18.3 to −7.3)	<0.0001
KCCQ-CSS, points	1.98 (1.73-2.24)	<0.0001	−10.1 (−11.56 to −8.93)	39.8 (34.7-45.0)	<0.0001

[a]Logarithmic transformation is used. Each model includes sex, trial, and the covariate listed in each row.
Abbreviations as in Table 1.

tertile 3: 8.1 [95% CI: 2.6-13.6]) $P_{interaction} = 0.91$) (Supplemental Tables 1 and 2), although this differential response was not statistically significant (3-way treatment × 6MWD × sex interaction; $P = 0.092$).

Semaglutide decreased body weight, NT-proBNP, waist circumference, and CRP to a similar extent across 6MWD tertiles (Table 3, Figure 3C). When 6MWD was analyzed as a continuous variable, the effects of semaglutide on decreasing body weight were consistent across all baseline values of 6MWD (Figure 3D). The effects of semaglutide on the hierarchical composite endpoint were favorable across all 6MWD tertiles, with no significant treatment by 6MWD interaction.

FIGURE 1 Predicted Change in 6MWD



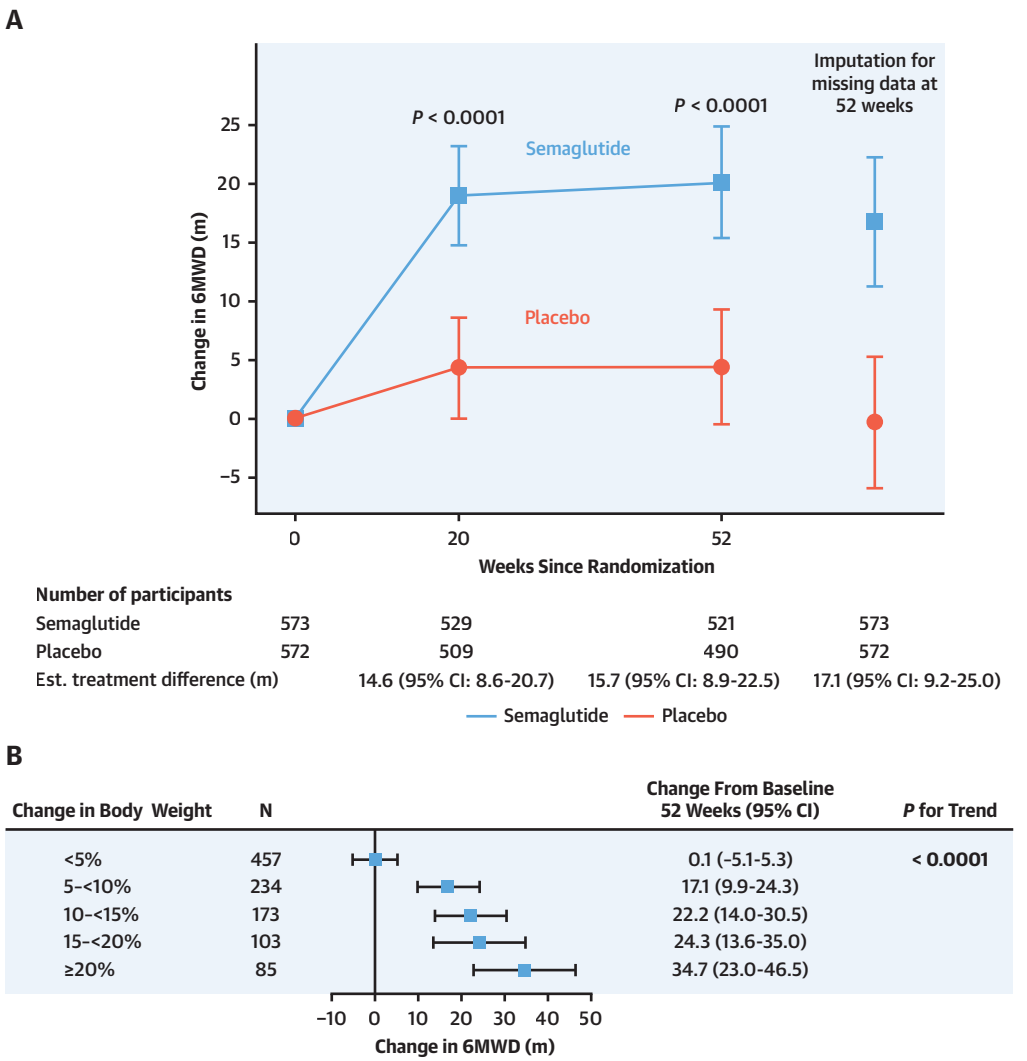
Predicted change in 6MWD for each 1 standard deviation increase in CRP, NT-proBNP, waist circumference, and BMI at baseline by linear regression. Point estimates for each regression coefficient and 95% confidence interval are plotted. 6MWD = 6-minute walk distance; BMI = body mass index; CRP = C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; WC = waist circumference.

SAFETY. The rates of SAEs in the overall population (regardless of treatment allocation) increased with lower baseline 6MWD (38.2 vs 46.5 vs 73.9 per 100 patient-years in the placebo arm) (Table 4), with a similar pattern for cardiovascular SAEs (14.1 vs 11.9 vs 27.3 per 100 patient-years). However, there were consistently fewer SAEs and cardiovascular SAEs in patients treated with semaglutide vs placebo across all tertiles of baseline 6MWD.

SEMAGLUTIDE EFFECTS AT THE EXTREMES OF BASELINE 6MWD. Individuals with very low or very high 6MWD are often excluded from clinical trials because of concerns that those with very poor baseline exercise function may not be responsive to treatment owing to frailty or other factors, whereas those with higher values may experience a ceiling effect, precluding the identification of potentially salutary effects. In the STEP-HFpEF program, treatment with semaglutide vs placebo resulted in consistently beneficial effects on dual primary and confirmatory secondary endpoints in patients with obesity-related HFpEF and a baseline 6MWD of <150 m (vs ≥150 m) and also among those with a baseline 6MWD of >450 m (vs ≤450 m) (Supplemental Tables 3 and 4), with no significant interactions. Similarly, safety profiles were similar when analyses were restricted to those individuals with a baseline 6MWD of <150 m or >450 m (Supplemental Table 5).

RELATIONSHIPS BETWEEN CHANGES IN 6MWD CORRELATES AND 6MWD ON SEMAGLUTIDE. In regression analyses evaluating changes in baseline correlates of 6MWD on treatment with semaglutide to changes in 6MWD at 52 weeks, each 1-unit decrease in BMI, log CRP, and log NT-proBNP was associated with a 4.1-, 5.4-, and 8.5-m increase in

CENTRAL ILLUSTRATION Change in 6MWD With Semaglutide



Borlaug BA, et al. JACC Heart Fail. 2025;13(11):102660.

(A) Increases in 6MWD were greater in participants randomized to semaglutide as compared with placebo after just 20 weeks, with an effect maintained out to end of study assessments at 52 weeks. Final results at 52 weeks with imputation for missing data shown at far right, and on-treatment results for those with available data at 20 and 52 weeks shown on the left. (B) Change in 6MWD relative to changes in body weight (regardless of treatment assignment) shown at 52 weeks relative to baseline. Points show mean change and whiskers show 95% confidence intervals. 6MWD = 6-minute walk distance; Est. = estimated.

6MWD, respectively; increases in KCCQ-CSS scores were also highly associated with increases in 6MWD on treatment with semaglutide (Table 5).

RELATIONSHIPS BETWEEN EARLY RATE OF WEIGHT LOSS ON SEMAGLUTIDE AND EFFICACY. The amount of weight loss after 1 month of treatment with semaglutide had no significant relationship with changes in 6MWD or KCCQ-CSS score at 52 weeks (Table 6). However, participants losing more body weight after 3 months of treatment had greater improvements in 6MWD and KCCQ-CSS, and greater decreases in CRP at 52 weeks.

DISCUSSION

This prespecified analysis of the STEP-HFpEF Program has several novel findings. First, patients with a

TABLE 3 Treatment Effects by Baseline 6MWD Tertile

	6MWD Tertile 1		6MWD Tertile 2		6MWD Tertile 3		*P* Values	
	Semaglutide (n = 191)	Placebo (n = 190)	Semaglutide (n = 190)	Placebo (n = 192)	Semaglutide (n = 192)	Placebo (n = 190)	P_{INT}	P_{TREND}
Dual primary endpoints								
Change in KCCQ-CSS (points)								
Change (52 weeks)	14	3.7	13.7	7.4	17.5	11.2		
Mean difference[a]	10.3 (6.4-14.1)	Ref.	6.3 (2.5-10.1)	Ref.	6.3 (2.6-10.1)	Ref.	0.247	0.150
Change in body weight (%)								
Change (52 weeks)	−11.8	−3.5	−11	−3.7	−11.4	−1.9		
Mean difference[a]	−8.3 (−9.8 to −6.7)	Ref.	−7.3 (−8.8 to −5.8)	Ref.	−9.5 (−11.0 to −8.1)	Ref.	0.103	0.238
Secondary endpoints								
6MWD (m)								
Change (52 weeks)	12.1	−2.2	14.8	−7.3	23.6	8.4		
Mean difference[a]	14.3 (0.5-28.0)	Ref.	22.1 (8.6-35.7)	Ref.	15.2 (1.9-28.5)	Ref.	0.680	0.922
CRP ratio								
Change (52 weeks)	0.59	0.95	0.61	0.86	0.52	0.88		
Treatment ratio[b]	0.62 (0.50-0.77)	Ref.	0.71 (0.58-0.88)	Ref.	0.59 (0.48-0.72)	Ref.	0.435	0.750
Hierarchical composite endpoint								
Win ratio	1.76 (1.37-2.28)		1.42 (1.10-1.83)		1.84 (1.41-2.40)		0.135	–
Waist circumference (cm)								
Change (52 weeks)	−10.7	−2.7	−9.8	−2.4	−10.4	−2.7		
Mean difference[a]	−7.9 (−9.7 to −6.2)	Ref.	−7.3 (−9.1 to −5.6)	Ref.	−7.6 (−9.4 to −5.9)	Ref.	0.880	0.807
NT-proBNP ratio								
Change (52 weeks)	0.8	1.01	0.81	0.92	0.72	0.93		
Treatment ratio[b]	0.8 (0.66-0.95)	Ref.	0.89 (0.74-1.06)	Ref.	0.78 (0.65-0.93)	Ref.	0.540	0.835

Tertiles 1, 2, and 3 include participants with baseline 6MWD of 62.0-228.5, 229.0-318.7, and 320.0-600.0 for women and 87.5-269.6, 270.3-365.0, and 365.4-600.0 for men. [a]Mean difference (95% CI) between the semaglutide and placebo treatment groups in terms of the change from baseline to 52 weeks adjusted for treatments, 6MWD tertiles, treatments × 6MWD tertiles, baseline value of the outcome variable, and BMI subgroup with placebo as the reference group. [b]These analyses were based on the log values; therefore, a treatment ratio is estimated, rather than a mean difference.

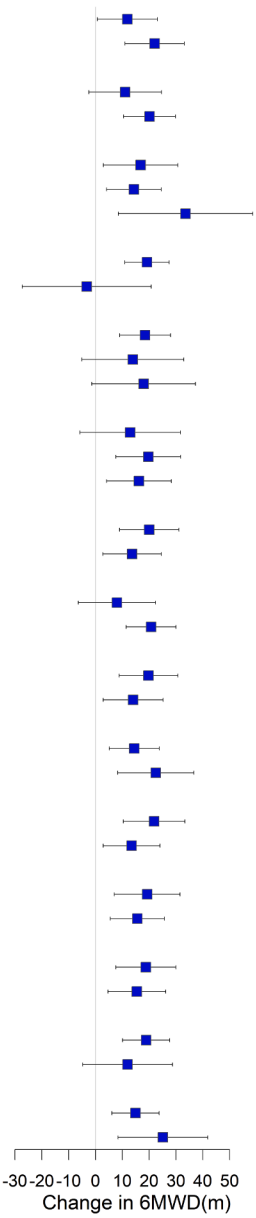
P_{INT} = *P* value for interaction; P_{TREND} = *P* value for trend; Ref. = Reference; other abbreviations as in Table 1.

lower baseline 6MWD displayed greater inflammation, congestion, and obesity severity, and there was a strong correlation between 6MWD and patient-reported severity of symptoms and physical limitations using the KCCQ-CSS. Second, semaglutide improved 6MWD very early, after just 20 weeks of treatment, and this effect was maintained to 52 weeks, as previously reported.[12] The favorable effect of semaglutide on 6MWD was consistent across the subgroups of 6MWD at baseline, and across a broad spectrum of participant demographic and clinical characteristics; however, improvements in 6MWD were more pronounced in patients who experienced more substantial weight loss. Third, the degree of improvement in 6MWD was strongly associated with the magnitude of weight loss during the trials. Fourth, semaglutide improved HF-related symptoms and physical limitations, increased exercise function, and decreased systemic inflammation and NT-proBNP regardless of baseline 6MWD, with no significant treatment by baseline 6MWD interactions, although there was a suggestion of a potentially greater improvement in KCCQ-CSS scores in women with the lowest 6MWD. Fifth, the effects of semaglutide on the key trial endpoints were observed consistently in patients with very low and the highest values of baseline 6MWD, mitigating potential concerns about semaglutide use in patients with the poorest exercise function at baseline, as well as concerns about ceiling effects in those with higher baseline 6MWD. Finally, the rate of SAEs was greatest in those with lowest baseline 6MWD, but patients treated with semaglutide had fewer SAEs and cardiac disorders across baseline levels of exercise function, even among those with lowest baseline 6MWDs.

We found that poorer exercise function in obesity-related HFpEF was associated with more pronounced systemic inflammation (higher CRP), more severe hemodynamic congestion (higher NT-proBNP and diuretic use), and greater adiposity (reflected by BMI and waist circumference), findings that agree with prior studies carried out in more selected HFpEF cohorts.[8] Notably, the strongest factors associated were related to excess body fat, providing further support for the importance of targeting adiposity in HFpEF.[18] This finding is further buttressed by the

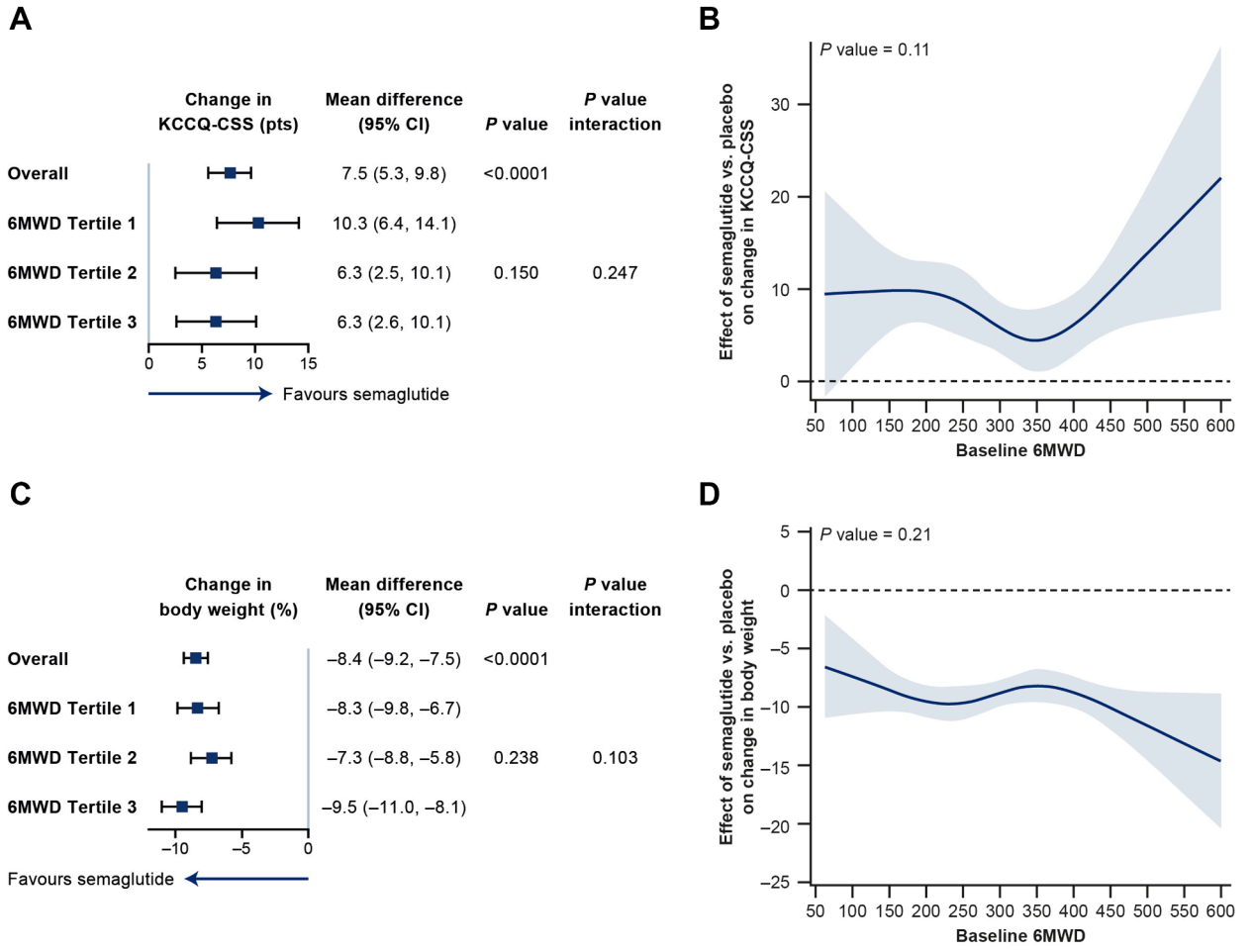
FIGURE 2 Forest Plot

	Semaglutide n	Semaglutide Change from baseline to week 52	Placebo n	Placebo Change from baseline to week 52	Between-group difference(95% CI)	P-Value Interaction
Sex						0.207
Female	252	12	251	0.1	11.91 (0.72, 23.1)	
Male	269	21.3	239	-0.7	22.05 (10.99, 33.1)	
BMI(kg/m2)						0.283
BMI < 35.0	175	12.4	178	1.3	11.07 (-2.46, 24.59)	
BMI >= 35.0	346	19	312	-1.1	20.17 (10.48, 29.86)	
Age group (years)						0.378
<65	165	21.9	156	5.1	16.83 (2.97, 30.69)	
>=65to<79	311	14.8	284	0.5	14.32 (4.15, 24.49)	
>=80	45	12.1	50	-21.5	33.58 (8.55, 58.61)	
Race						0.082
White	461	17	444	-2.1	19.2 (10.93, 27.47)	
Not White	60	14.7	46	18	-3.26 (-27.33, 20.81)	
Region						0.911
Europe	366	15.2	312	-3.3	18.49 (9.02, 27.97)	
North America	84	16.3	82	2.3	13.92 (-5.12, 32.96)	
Other	71	25.5	96	7.5	17.97 (-1.36, 37.3)	
LVEF						0.821
45-49%	86	18.3	89	5.3	12.94 (-5.84, 31.72)	
50-59%	212	16.6	202	-3.1	19.71 (7.65, 31.77)	
>=60%	223	16.3	199	0.1	16.2 (4.15, 28.25)	
NT-proBNP(pg/ml)						0.414
<475.3	244	14.8	257	-5.2	20.03 (8.96, 31.09)	
>=475.3	277	18.6	233	5	13.63 (2.71, 24.55)	
CRP(mg/L)						0.143
<2	153	18.6	144	10.6	8.02 (-6.36, 22.4)	
>=2	368	16	346	-4.7	20.73 (11.43, 30.02)	
SBP (mmHg)						0.469
<135	278	19.1	249	-0.7	19.76 (8.85, 30.68)	
>=135	243	14.1	241	0	14.05 (2.92, 25.18)	
NYHA class						0.347
II	371	16.5	332	2.1	14.45 (5.15, 23.75)	
III or IV	150	17.4	158	-5	22.47 (8.32, 36.63)	
Atrial fibrillation						0.286
Yes	225	22.3	235	0.4	21.85 (10.38, 33.32)	
No	296	12.5	255	-1	13.46 (2.87, 24.04)	
Loop diuretics						0.646
Yes	214	20.2	185	1	19.27 (7, 31.54)	
No	307	14.5	305	-1.1	15.6 (5.53, 25.66)	
Heart Rate(beats per min)						0.664
<70	245	15.5	236	-3.3	18.8 (7.62, 29.98)	
>=70	275	17.8	254	2.3	15.42 (4.66, 26.17)	
Coronary artery disease						0.469
Yes	402	19.6	393	0.7	18.87 (10.09, 27.66)	
No	119	7.4	97	-4.6	11.97 (-4.76, 28.7)	
RAAS inhibitor use						0.282
Yes	402	15.6	393	0.7	14.91 (6.13, 23.69)	
No	119	20.8	97	-4.3	25.13 (8.43, 41.82)	



Forest plot showing effects of semaglutide versus placebo on 6MWD according to prespecified subgroups. IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Figure 1.

FIGURE 3 Effects of Semaglutide vs Placebo



Effects of semaglutide vs placebo did not significantly differ on the dual primary endpoints of change in KCCQ-CSS [A, B] or change in body weight [C, D] when evaluated by tertile of baseline 6MWD or when evaluated as a continuous variable. KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; other abbreviation as in Figure 1.

greater degree of improvement in 6MWD observed with greater body weight reduction (Figure 1B). There was a strong relationship between 6MWD and KCCQ-CSS score,[6] which we interpret as an indicator of how objective functional impairments are experienced or interpreted by patients as orthogonal and complementary patient-centered outcomes above and beyond HF hospitalization. Although causality cannot be inferred from these cross-sectional relationships, a 20-m lower baseline 6MWD was associated with a 10.1-point lower KCCQ-CSS and 6.0-kg/m^2 higher BMI, providing new insight into the scale of inter-relationships between these measures in obesity-related HFpEF.

In patients with HF, exercise function measured by 6MWD or other metrics such as peak oxygen consumption consistently improves with exercise training,[19-22] but has been notoriously difficult to improve with pharmacological therapies.[23] Exertional limitation in HFpEF is caused by both cardiac and extracardiac factors.[1,2] Increases in left heart filling pressures during exercise lead to lung congestion and pulmonary hypertension in patients with HFpEF, impairing exercise capacity and increasing risk for adverse clinical outcomes.[24-30] Therapies that lower rest and exercise filling pressures and improve pulmonary vascular loading, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors,[31,32] have been shown to increase 6MWD in patients with HFpEF in some[33] (but not all[34,35]) trials, with greater symptomatic benefit in patients living with obesity.[36] Interestingly, these salutary

TABLE 4 Safety Findings by Baseline 6MWD

	Adverse Event Rate per 100 Patient-Years																	
	6MWD Tertile 1						6MWD Tertile 2						6MWD Tertile 3					
	Semaglutide (n = 191)			Placebo (n = 190)			Semaglutide (n = 190)			Placebo (n = 192)			Semaglutide (n = 192)			Placebo (n = 190)		
	n (%)	Events (n)	Events (per 100 Person-Years)	n (%)	Events (n)	Events (per 100 Person-Years)	n (%)	Events (n)	Events (per 100 Person-Years)	n (%)	Events (n)	Events (per 100 Person-Years)	n (%)	Events (n)	Events (per 100 Person-Years)	n (%)	Events (n)	Events (per 100 Person-Years)
Any SAE	36 (18.8)	66	34.9	63 (33.2)	138	73.9	28 (14.7)	53	29.2	57 (29.7)	90	46.5	26 (13.5)	42	22.0	39 (20.5)	73	38.2
Deaths[a]	4 (2.1)	4	1.9	6 (3.2)	6	3.0	5 (2.6)	5	2.5	6 (3.1)	6	2.9	0 (0.0)	0	0.0	2 (1.1)	2	1.0
Cardiac SAE	9 (4.7)	11	5.8	36 (18.9)	51	27.3	7 (3.7)	7	3.9	19 (9.9)	23	11.9	10 (5.2)	13	6.8	15 (7.9)	27	14.1
SAE leading to discontinuation	5 (2.6)	5	2.6	7 (3.7)	11	5.9	7 (3.7)	8	4.4	5 (2.6)	5	2.6	0 (0.0)	0	0.0	5 (2.6)	5	2.6

Data are adverse events during the on-treatment period in the safety analysis set, which included all randomly assigned participants who received at least one dose of semaglutide or placebo (all participants received at least 1 dose, and thus the safety analysis set was the same as the full analysis set). The on-treatment period spans from the date of first administration of semaglutide or placebo to the date of the last administration of semaglutide or placebo (excluding potential off-treatment time if 2 or more consecutive doses were missed). For the assessment of adverse events, each on-treatment period extends for 35 days from the date of most recent drug administration, unless otherwise stated. Investigators could report more than 1 event with a fatal outcome for the same participant. [a]Data are for the in-trial period (ie, the time from random assignment to last contact with a trial site, irrespective of treatment discontinuation or rescue intervention).

SAE = serious adverse event; other abbreviations as in Table 1.

hemodynamic effects of SGLT2 inhibitors are associated with the amount of weight lost,[31] particularly trunk fat, which includes visceral adipose tissue,[37] further supporting the important role for fat reduction.

Patients with the obesity phenotype of HFpEF have greater increases in filling pressures during exercise compared with those with HFpEF in the absence of obesity.[38] We observed that patients with more severely impaired 6MWDs had more substantial congestion, evidenced by higher NT-proBNP and greater diuretic use. Increases in visceral fat play a pivotal role in HFpEF, especially in women, and are more strongly correlated with hemodynamic perturbations.[39] The extent to which these decreases in visceral adipose might translate to improved hemodynamics remains unclear, but analyses from STEP-HFpEF have shown decreases in natriuretic peptide levels, suggesting a decrease in circulatory congestion.[40] Indeed, patients with obesity-related HFpEF and higher NT-proBNP, NYHA functional class, atrial fibrillation burden, and loop diuretic use all experienced greater improvement in HF-related symptoms with semaglutide, despite similar weight loss.[12,40-42]

Extracardiac mechanisms also importantly contribute to exercise intolerance in HFpEF.[2] Metabolic inflammation is increased in patients with HFpEF and more severe obesity,[13,43] and this finding is associated with impairments in peripheral oxygen uptake in the tissues.[44] Systemic inflammation, reflected by CRP, was markedly decreased with semaglutide in the STEP-HFpEF program,[10-12] which likely was related to decreased visceral and intermuscular fat, and this factor may have improved peripheral oxygen uptake and distribution in skeletal muscle. Excess, dysfunctional adipose and systemic inflammation also contribute to endothelial dysfunction and maladaptive impairments in venous and arterial compliance.[18,45] The SGLT2 inhibitor dapagliflozin was recently shown to improve arterial and venous compliance in HFpEF, and these improvements were again related to the magnitude of body weight reduction, suggesting another link between weight loss and clinical benefits on exercise tolerance.[46] It remains unclear whether similar effects may be observed with semaglutide-facilitated weight loss, but blood pressure was reduced in STEP-HFpEF. Finally, excess adipose tissue and systemic inflammation promote capillary loss and mitochondrial dysfunction within skeletal muscle, both of which have been shown to be present and contribute to exercise intolerance in patients with HFpEF, which may also have contributed.[47]

It is notable that benefits on 6MWD were apparent after just 20 weeks of treatment, before the maximal reduction in weight loss effect, and these benefits were maintained at 52 weeks. This pattern mirrors findings observed with NT-proBNP levels in the STEP-HFpEF program, which decreased by ~20% at 20 weeks and were maintained, but not further augmented after 52 weeks of treatment.[40] The improvement in exercise function at this earlier stage occurred just 4 weeks after patients had been titrated to the goal dose of 2.4 mg per week, and indicates

TABLE 5 Changes in Baseline 6MWD Correlates and Change in 6MWD on Semaglutide

Endpoints	Slope (95% CI)	*P* Value
BMI (kg/m^2)	−4.08 (−5.74 to −2.42)	<0.0001
CRP (mg/L)[a]	−5.44 (−10.59 to −0.30)	0.0382
NT-proBNP (pg/dL)[a]	−8.52 (−14.27 to −2.77)	0.0038
KCCQ-CSS (points)	1.01 (0.71-1.30)	<0.0001

Regression analysis of change in 6MWD (m) vs changes in continuous endpoints from baseline to 52 weeks controlled for baseline 6MWD (m), baseline value of endpoint, sex, and trial in patients treated with Semaglutide (predicted change per kg/m^2 of BMI, 1 log decrease in CRP and NT-proBNP, and 1 point change in KCCQ-CSS). [a]Logarithmic transformation of ratio of 52 weeks to baseline.

Abbreviations as in Table 1.

that benefits are observed early and do not take 1 year to achieve.

The benefits from semaglutide on primary and secondary endpoints were observed consistently across all tertiles of baseline 6MWD, with no significant treatment by 6MWD interactions overall. This finding is important, because there is potential concern that individuals with greater frailty (who also have a lower baseline 6MWD) may not benefit from treatment.[9] There was a notable increase in the rate of SAEs in patients with the lowest baseline 6MWD, reinforcing that this represents a more vulnerable cohort, but the safety of semaglutide was maintained in this group, with fewer adverse events observed compared with the placebo arm, similar to the pattern observed among patients with a higher baseline 6MWD. These data indicate that semaglutide is both safe and effective across the spectrum of baseline exercise function. Patients with very low or very high baseline 6MWDs are often excluded from trials because of concerns that they may be refractory to treatment (for low 6MWD), or that treatment benefits may not be detectable owing to a ceiling effect (for high 6MWD). Although the sample size of patients with very low (<150 m) and very high 6MWD (>450 m) was small, the point estimates for semaglutide effects vs placebo were similar compared to those with a 6MWD of ≥150 m or ≤450 m, respectively, with no significant treatment interactions.

In the community, HFpEF is more prevalent among women than men by a 2:1 margin, and there are important sex differences in pathophysiology, with women having smaller, stiffer ventricles,[48] greater arterial stiffness,[49] more severe inflammation,[44] and greater pathophysiological importance of visceral adiposity as compared with men.[39] In the STEP-HFpEF program, there was greater decrease in body weight observed in women vs men.[50] In this light, it is interesting that there was a signal of greater improvement in KCCQ-CSS scores in women with the lowest baseline 6MWD, although this difference did not attain statistical significance for the interaction (vs men). Women have a greater risk for HFpEF with obesity, and these data call for further study to better understand sex differences in the pathophysiology of obesity-related HFpEF.

STUDY LIMITATIONS. There are limitations to this analysis. The majority of participants in the STEP-HFpEF program were White, which may limit generalizability. The 52-week duration of treatment was relatively short, and whether the observed effects might have persisted (or been amplified) with longer treatment is not known, but it is notable that improvements in 6MWD were observed very early at 20 weeks. Use of SGLT2 inhibitors was low, because these agents were not yet approved for treatment of HFpEF at the time the trials were conducted, limiting the ability to determine how background therapy with these agents might influence the relationships observed. Direct assessments of body composition and muscle strength were not performed in this multicenter trial and would have provided additional insight.

TABLE 6 Relationship Between Rate of Early Weight Loss on Semaglutide and Efficacy at 52 Weeks

	Tertile 1	Tertile 2	Tertile 3	*P* Value
Weight loss at 1 month	+3.40% to −0.99%	−1.02% to −2.50%	−2.52% to −12.6%	
Change in 6MWD (m)	15.4 (6.2-24.6)	14.6 (5.4-23.7)	20.7 (11.6-29.8)	0.4162
Change in KCCQ-CSS (pts)	13.5 (10.8-16.1)	14.0 (11.3-16.6)	16.4 (13.8-19.0)	0.1274
Change in CRP (ratio)	0.65 (0.56-0.76)	0.52 (0.44-0.61)	0.56 (0.48-0.66)	0.2094
Weight loss at 3 months	6.53% to −3.13%	−3.15% to −5.91%	−5.92% to −15.3%	
Change in 6MWD (m)	10.3 (1.5-19.1)	19.0 (10.5-27.6)	26.2 (17.4-35.0)	0.0112
Change in KCCQ-CSS (pts)	12.0 (9.4-14.5)	14.2 (11.7-16.7)	19.2 (16.7-21.7)	<0.0001
Change in CRP (ratio)	0.69 (0.59-0.80)	0.61 (0.52-0.71)	0.46 (0.39-0.54)	0.0003

Abbreviations as in Table 1.

CONCLUSIONS

In patients with obesity-related HFpEF, poorer exercise function at baseline is associated with more severe congestion, systemic inflammation, and greater adiposity. Semaglutide improved exercise function, as measured by 6MWD, as early as 20 weeks, with sustained effects at 52 weeks, regardless of patient demographic and clinical characteristics. There was a strong association between greater improvements in exercise function and greater magnitude of weight loss. Semaglutide consistently improved HF-related symptoms, physical limitations, and decreased inflammation, congestion, and body weight across the range of 6MWDs at baseline, including those with very low or high baseline exercise function. These data provide new insights into the favorable impact of semaglutide on exercise function in patients with obesity-related HFpEF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Impairments in exercise function in obesity-related HFpEF are strongly tied to congestion, inflammation, and greater adiposity. Semaglutide improves exercise function in patients with obesity-related HFpEF across the spectrum of baseline exercise function, including those with very severe or very mild exercise intolerance at baseline, with a rapid effect that precedes maximal weight loss. The magnitude of improvement in exercise function is related to the rate and degree of weight loss achieved on treatment.

TRANSLATIONAL OUTLOOK: Further study is required to determine whether treatments that can achieve greater weight loss lead to even greater improvements in exercise function, and whether agents that specifically target adipose reduction while sparing or even augmenting skeletal muscle can further improve exercise capacity in HFpEF.

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APPENDIX For an expanded Methods section as well as supplemental tables and a figure, please see the online version of this paper.