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Semaglutide in Patients With Obesity and Heart Failure Across Mildly Reduced or Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Many therapies for heart failure (HF) have shown differential impact across the spectrum of left ventricular ejection fraction (LVEF).

OBJECTIVES In this prespecified analysis, the authors assessed the effects of semaglutide across the baseline LVEF strata in patients with the obesity phenotype of HF with preserved ejection fraction (HFpEF) in the STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and HFpEF) trial.

METHODS STEP-HFpEF randomized 529 patients (263 semaglutide; 266 placebo). For this prespecified analysis, patients were categorized into 3 groups based on LVEF: 45% to 49% (n = 85), 50% to 59% (n = 215), and ≥60% (n = 229).

RESULTS At 52 weeks, semaglutide improved the dual primary endpoints of Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (estimated treatment difference: EF [ejection fraction] 45%-49%: 5.0 points [95% CI: −2.7 to 12.8 points], EF 50%-59%: 9.8 points [95% CI: 5.0 to 14.6 points], and EF ≥60%: 7.4 points [95% CI: 2.8 to 12.0 points]; *P* interaction = 0.56) and body weight (EF: 45%-49%: −7.6 [95% CI: −10.7 to −4.4], EF 50%-59%: −10.6 [95% CI: −12.6 to −8.6] and EF ≥60%: −11.9 [95% CI: −13.8 to −9.9]; *P* interaction = 0.08), to a similar extent across LVEF categories. Likewise, LVEF did not influence the benefit of semaglutide on confirmatory secondary endpoints: 6-minute walk distance (*P* interaction = 0.19), hierarchal composite endpoint (*P* interaction = 0.43), and high-sensitivity C-reactive protein (*P* interaction = 0.26); or exploratory endpoint of N-terminal pro-brain natriuretic peptide (*P* interaction = 0.96). Semaglutide was well-tolerated across LVEF categories.

CONCLUSIONS In patients with HFpEF and obesity, semaglutide 2.4 mg improved symptoms, physical limitations, and exercise function, and reduced inflammation and body weight to a similar extent across LVEF categories. These data support treatment with semaglutide in patients with the obesity phenotype of HFpEF regardless of LVEF. (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity [STEP-HFpEF]; NCT04788511) (J Am Coll Cardiol 2023;82:2087–2096) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFrEF = heart failure with reduced ejection fraction

HFpEF = heart failure with preserved ejection fraction

hsCRP = high-sensitivity C-reactive protein

KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-brain natriuretic peptide

SGLT2 = sodium-glucose cotransporter-2

Patients with heart failure (HF) have been traditionally classified based on left ventricular ejection fraction (LVEF) into those with HF and reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).[1] Clinical trials have used this classification to determine eligibility; however, the criteria demarcating the 2 groups have ranged between >40%, >45%, or ≥50% for HFpEF and ≤40 or ≤35% for HFrEF, resulting in variations in definitions as well as an evidence gap for patients with an LVEF between 40% and 50%.[2,3] Recently, the universal definition of HF recommended classifying LVEF of 41% to 49% as HF with "mildly reduced" EF (HFmrEF) and HFpEF as ≥50%, bringing a consensus to the LVEF-based HF classification.[4]

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Sodium-glucose cotransporter-2 (SGLT2) inhibitors have now been proven to reduce the risk of HF hospitalization or cardiovascular death in patients with HFpEF, but trials evaluating angiotensin receptor-neprilysin inhibitors (ARNi), spironolactone, and candesartan have reported statistically nonsignificant reductions in the risk of this endpoint in the HFpEF populations studied.[5-8] Subgroup analyses in the latter neurohormone antagonist trials indicated that treatment benefits were largely confined to patients with HFmrEF, with no benefit in the group of patients with LVEF >55% to 60%, whereas SGLT2 inhibitors were found to improve outcomes across the range of LVEF.[9-12] These observations, coupled with mechanistic studies in HFpEF showing structural and functional cardiac differences in patients with LVEF <60% to 65% or >60% to 65%, have fueled a debate on the differential effects of interventions in patients with HFmrEF, and within the range of LVEF in those with "true" HFpEF.[13-16]

Obesity-related HFpEF has been well described as a distinct phenotype.[17,18] Semaglutide, a once-weekly long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, was recently tested in patients with HF and an LVEF of ≥45% and obesity (without type 2 diabetes) in the STEP-HFpEF (Semaglutide Treatment Effect in People with obesity and HFpEF) trial and shown to significantly improve symptoms, physical limitations, and exercise function, and reduce body weight compared with placebo.[19] Herein we describe the effects of semaglutide on the primary, confirmatory secondary, and select exploratory endpoints in a prespecified analysis, which was finalized in the statistical analysis plan before database lock, of patients with LVEF of 45% to 49%, 50% to 59%, and ≥60%.

METHODS

STUDY DESIGN. The study design and primary results of the STEP HFpEF trial (NCT04788511) have been published previously.[19,20] Briefly, the STEP-HFpEF trial was a randomized, international, multicenter, double-blind, placebo-controlled trial in patients with obesity phenotype of HFpEF and without type 2 diabetes. 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. Participants were eligible if they had an LVEF 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) <90 points and at least 1 of the following:

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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1) elevated filling pressures (based on right heart catheterization or remote pulmonary artery pressure sensor technology); 2) elevated natriuretic peptide levels (with thresholds stratified based on BMI) plus echocardiographic abnormalities; or 3) HF hospitalization in the previous 12 months plus requirement for ongoing diuretic treatment and/or echocardiographic abnormalities. Randomization was stratified by BMI <35 kg/m^2 vs ≥ 35 kg/m^2. Key exclusion criteria were prior or planned bariatric surgery, self-reported change in body weight >11 pounds (5 kg) within 90 days before randomization, or a systolic blood pressure of >160 mm Hg at screening. Patients were also excluded if they had a glycosylated hemoglobin of ≥6.5% or history of diabetes. Institutional Review Board ethics approval was obtained at each study site,[20,21] and all patients provided informed consent to participate in the trial. The sponsor of the trial was Novo Nordisk.

OUTCOMES. The primary aim of the study was to investigate the effects of semaglutide 2.4 mg once weekly on symptoms, physical limitations, and body weight compared with placebo. The dual primary endpoints were as follows: 1) change in KCCQ-CSS from baseline to 52 weeks; and 2) percent change in body weight from baseline to 52 weeks. The secondary objectives included assessing the effects of semaglutide on change in 6-minute walking distance (6MWD) from baseline to 52 weeks, the overall clinical benefit (hierarchical composite endpoint comprising of all-cause death, HF events, differences in several thresholds of change in KCCQ-CSS from baseline to 52 weeks, and differences in 6MWD change of 30 m or more from baseline to 52 weeks), and change in high-sensitivity C-reactive protein (hsCRP) from baseline to 52 weeks.

All serious adverse events (AEs) and the following AEs irrespective of seriousness were collected: AEs leading to premature treatment discontinuation, AEs of special interest, and AEs related to COVID-19. All deaths, HF hospitalizations, and urgent visits were adjudicated.

LEFT VENTRICULAR EJECTION FRACTION. Baseline LVEF was determined during the screening visit by using echocardiography in all participants, performed locally at each site (and not core-laboratory assessed). For the present analysis, patients were categorized into 3 groups based on baseline LVEF (45%-49%, 50%-59%, and ≥60%).

STATISTICAL ANALYSIS. Baseline characteristics were evaluated according to LVEF groups (45%-49%, 50%-59%, and ≥60%) and tests for trend were performed across these groups: Continuous variables used the Jonckheere-Terpstra trend test and binary variables used a Cochran-Armitage trend test. Efficacy endpoints were assessed using the full analysis set (all randomized participants according to the intention-to-treat principle, regardless of treatment discontinuation). For change in KCCQ-CSS and 6MWD, missing observations at week 52 caused by reasons other than CV death or previous HF events (if nonretrieved) were multiple imputed from retrieved participants in the same randomized treatment arm. For other endpoints, missing observations at week 52 were imputed irrespective of death or prior HF events using the same imputation method. Subgroup analyses within the LVEF subgroups for continuous endpoints were then performed using analysis of covariance models with 1,000 multiple imputations, adjusted for the baseline values for the relevant continuous outcome variable and BMI group (the stratification factor). 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 LVEF subgroups. To further explore the relationship between the LVEF at baseline and the dual primary endpoints (changes in KCCQ-CSS and body weight) in a more granular fashion, we employed mixed models incorporating LVEF as a continuous variable with a quadratic spline by randomized treatment adjusted for corresponding endpoints at baseline, all nested within visits and using in-trial data. An unstructured covariance matrix was used across visits. Interaction *P* values between the LVEF as a continuous variable (modeled 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 LVEF.

Subgroups analyses of the hierarchical composite endpoint (win-ratio) were performed stratified by the LVEF subgroups, based on direct comparisons of each participant randomized to semaglutide vs each participant randomized to placebo within each LVEF subgroup. For each of the participant pairs, a "treatment winner" based on similar observation time was declared based on the endpoint hierarchy. The win ratio (ie, the proportion of winners randomized to semaglutide divided by the winners randomized to placebo) was estimated independently within each LVEF subgroup (using 1,000 imputations as described in the previous text to establish the differences for change in KCCQ-CSS and 6MWD). Test for equality of

TABLE 1 Baseline Characteristics by Ejection Fraction Category

	LVEF 45%-49% (n = 85, 16.1%)	LVEF 50%-59% (n = 215, 40.6%)	LVEF ≥60% (n = 229, 43.3%)	*P* Value for Trend
Female	30 (35.3)	119 (55.3)	148 (64.6)	<0.001
Age, y	69.0 (59.0, 74.0)	69.0 (63.0, 76.0)	70.0 (62.0, 75.0)	0.35
Ethnicity				0.44
Hispanic or Latino	2 (2.4)	19 (8.8)	15 (6.6)	
Not Hispanic or Latino	83 (97.6)	196 (91.2)	214 (93.4)	
Race				0.07
Black	1 (1.2)	5 (2.3)	15 (6.6)	
Other	0 (0.0)	1 (0.5)	0 (0.0)	
White	84 (98.8)	209 (97.2)	214 (93.4)	
Body weight, kg	106.8 (96.7, 120.0)	103.7 (92.0, 121.7)	104.4 (90.5, 119.0)	0.25
BMI, kg/m^2	36.0 (33.9, 39.8)	36.9 (33.3, 41.5)	37.9 (34.0, 41.6)	0.12
Waist circumference, cm	122.0 (112.0, 128.5)	120.0 (110.5, 128.0)	117.0 (110.0, 127.2)	0.12
Systolic blood pressure, mm Hg	133.0 (120.0, 143.0)	133.0 (121.0, 145.0)	132.0 (122.0, 143.0)	0.76
LVEF, %	46.0 (45.0, 48.0)	55.0 (51.0, 56.0)	60.0 (60.0, 65.0)	NA
NT-proBNP, pg/mL	586.9 (314.6, 1160.3)	467.7 (206.4, 1053.7)	378.9 (204.7, 937.0)	0.01
hsCRP, mg/L	3.4 (1.7, 6.7)	3.8 (1.8, 8.6)	4.1 (2.1, 7.5)	0.22
KCCQ-CSS	62.5 (47.4, 75.0)	58.3 (40.6, 70.8)	57.8 (40.6, 74.0)	0.26
6MWD, m	365.0 (255.5, 415.6)	300.0 (238.4, 384.8)	318.7 (244.0, 382.0)	0.25
Comorbidities				
Hypertension	69 (81.2)	173 (80.5)	191 (83.4)	0.52
Atrial fibrillation	49 (57.6)	116 (54.0)	110 (48.0)	0.09
Obstructive sleep apnea	9 (10.6)	20 (9.3)	37 (16.2)	0.07
Coronary artery disease	35 (41.2)	78 (36.3)	67 (29.3)	0.03
NYHA functional class				0.23
II	55 (64.7)	146 (67.9)	149 (65.1)	
III-IV	30 (35.3)	69 (32.1)	80 (34.9)	
Concomitant medications				
Beta-blockers	71 (83.5)	169 (78.6)	178 (77.7)	0.32
Sodium-glucose cotransporter-2 inhibitors	7 (8.2)	7 (3.3)	5 (2.2)	0.02
Loop diuretic agents	58 (68.2)	144 (67.0)	127 (55.5)	0.01
Mineralocorticoid receptor antagonist	35 (41.2)	82 (38.1)	67 (29.3)	0.02
Angiotensin receptor neprilysin inhibitor	10 (11.8)	8 (3.7)	9 (3.9)	0.02
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	74 (87.1)	158 (73.5)	165 (72.1)	0.02

Values are n (%) or median (Q1, Q3). *P* values are for the test for trend across left ventricular ejection fraction (LVEF) groups. One participant with an LVEF of 33% was included in the LVEF 45%-<49% group.

6MWD = 6-minute walk distance; BMI = body mass index; hsCRP = high-sensitivity C-reactive protein; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP = N-terminal pro-brain natriuretic peptide.

the LVEF groups for the win ratio was performed using a Cochran's Q test.

No adjustment for multiple testing was performed. A significance level of 5% was considered significant. Results are presented as estimated changes from baseline to week 52 for continuous endpoints or a win-ratio (for the hierarchical composite endpoint), with a 95% CI and a 2-sided *P* value. N-terminal pro-brain natriuretic peptide (NT-proBNP) and hsCRP were log-transformed, and hence, treatment ratios at week 52 are reported. Safety events across the LVEF subgroups were assessed using the safety data set (all participants with at least 1 dose of randomized treatment) and either on-treatment or in-trial data sets depending on the type of safety event. Statistical analyses were performed using SAS version 9.4 (SAS/STAT version 15.1).

RESULTS

BASELINE PATIENT CHARACTERISTICS. A total of 529 patients (263 semaglutide; 266 placebo) were categorized into 3 groups based on LVEF: 45% to 49% (n = 85), 50% to 59% (n = 215), and ≥60% (n = 229) (Table 1); detailed distribution of study participants according to the baseline LVEF is presented in

TABLE 2 Effect of Semaglutide vs Placebo on Outcomes Across Ejection Fraction

	LVEF 45%-49% (n = 85, 16.1%)		LVEF 50%-59% (n = 215, 40.6%)		LVEF ≥60% (n = 219, 43.3%)		
	Semaglutide (n = 37)	Placebo (n = 48)	Semaglutide (n = 113)	Placebo (n = 102)	Semaglutide (n = 113)	Placebo (n = 116)	*P* Value for Interaction
Change in KCCQ-CSS at 52 weeks, points	17.3 (11.3 to 23.3)	12.2 (7.4 to 17.1)	16.9 (13.6 to 20.2)	7.1 (3.6 to 10.6)	16.1 (12.8 to 19.4)	8.7 (5.4 to 12.0)	
Adjusted mean difference, points	5.0 (−2.7 to 12.8)		9.8 (5.0 to 14.6)		7.4 (2.8 to 12.0)		0.56
Change in body weight at 52 weeks, %	−10.5 (−12.9 to −8.1)	−2.9 (−5.0 to −0.9)	−12.8 (−14.2 to −11.5)	−2.3 (−3.7 to −0.8)	−14.6 (−16.0 to −13.3)	−2.7 (−4.1 to −1.4)	
Adjusted mean difference, %-points	−7.6 (−10.7 to −4.4)		−10.6 (−12.6 to −8.6)		−11.9 (−13.8 to −9.9)		0.08
Change in 6MWD at 52 weeks, m	20.8 (−2.3 to 43.9)	24.3 (6.1 to 42.6)	20.1 (7.7 to 32.5)	−3.9 (−17.4 to 9.6)	23.3 (11.0 to 35.6)	−4.1 (−16.5 to 8.3)	
Adjusted mean difference, m	−3.5 (−33.0 to 26.0)		23.9 (5.6 to 42.3)		27.3 (9.9 to 44.8)		0.19
Hierarchical composite endpoint							
Win ratio	1.72 (0.95 to 3.09)		2.10 (1.46 to 3.04)		1.47 (1.04 to 2.07)		0.43
hsCRP ratio at 52 weeks, mg/L	0.45 (0.33 to 0.62)	0.92 (0.71 to 1.19)	0.62 (0.53 to 0.74)	0.88 (0.72 to 1.08)	0.55 (0.46 to 0.65)	0.97 (0.81 to 1.17)	
Treatment ratio, mg/L	0.49 (0.33 to 0.74)		0.71 (0.54 to 0.92)		0.56 (0.44 to 0.73)		0.26
NT-proBNP ratio at 52 weeks, pg/mL	0.81 (0.60 to 1.10)	0.99 (0.79 to 1.26)	0.83 (0.71 to 0.97)	0.97 (0.80 to 1.17)	0.75 (0.64 to 0.87)	0.91 (0.76 to 1.08)	
Treatment ratio, pg/mL	0.82 (0.56 to 1.19)		0.86 (0.67 to 1.10)		0.82 (0.65 to 1.04)		0.96

Values in parentheses are 95% CI.

6MWD = 6-minute walk distance; hsCRP = high-sensitivity C-reactive protein; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Supplemental Figure 1. With higher LVEF, patients were more often female, less likely to have a history of ischemic heart disease, and less likely to be treated with inhibitors of the renin-angiotensin system, diuretic agents, and mineralocorticoid receptor antagonists. Baseline NYHA functional class did not differ by LVEF category; however, with increasing LVEF, patients were more likely to have lower KCCQ-CSS, 6MWD, and NT-proBNP levels.

EFFICACY OUTCOMES ACCORDING TO EJECTION FRACTION. At 52 weeks, semaglutide improved KCCQ-CSS similarly across all LVEF categories (estimated treatment difference: LVEF 45%-49%: 5.0 points [95% CI: −2.7 to 12.8 points], LVEF 50%-59%: 9.8 points [95% CI: 5.0 to 14.6 points] and LVEF ≥60%: 7.4 points [95% CI: 2.8 to 12.0 points]; *P* interaction = 0.56) (Table 2, Central Illustration). Semaglutide also reduced body weight at 52 weeks to a similar extent in all LVEF subgroups (LVEF 45%-49%: −7.6% [95% CI: −10.7% to −4.4%], LVEF 50%-59%: −10.6% [95% CI: −12.6% to −8.6%], and LVEF ≥60%: −11.9% [95% CI: −13.8% to −9.9%]; *P* interaction = 0.08) (Table 2, Figure 1). The results were consistent when LVEF was analyzed as a continuous variable using quadratic splines (Supplemental Figure 2). LVEF categories did not influence the benefit of semaglutide on 6MWD (*P* interaction = 0.19), hierarchal composite endpoint (*P* interaction = 0.43), hsCRP (*P* interaction = 0.26), or NT-proBNP (*P* interaction = 0.96) (Table 2, Figure 1).

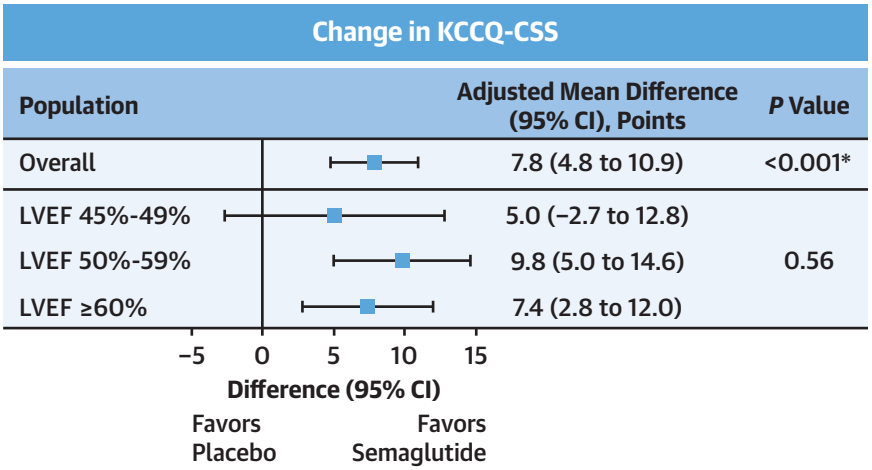
SAFETY OUTCOMES ACCORDING TO EJECTION FRACTION. Safety events according to LVEF categories are outlined in Table 3. The favorable safety profile of semaglutide was consistent across LVEF categories.

DISCUSSION

In this prespecified analysis of the 529 patients randomized in the STEP-HFpEF trial, semaglutide consistently improved HF-related symptoms and physical limitations as measured by KCCQ-CSS, as well as exercise function measured by 6MWD, and reduced body weight and inflammation across the range of LVEF, including in participants with LVEF ≥60%. Similar findings were observed for reductions in NT-proBNP. Last, semaglutide was generally well-tolerated, with fewer serious AEs than placebo across all 3 categories of LVEF.

Subgroup analyses across HFpEF trials evaluating neurohormonal antagonists have revealed less benefit in patients with HFpEF and the highest “truly

CENTRAL ILLUSTRATION **Treatment Effects (Semaglutide vs Placebo) on Kansas City Cardiomyopathy Questionnaire Clinical Summary Score Change Across Left Ventricular Ejection Fraction**



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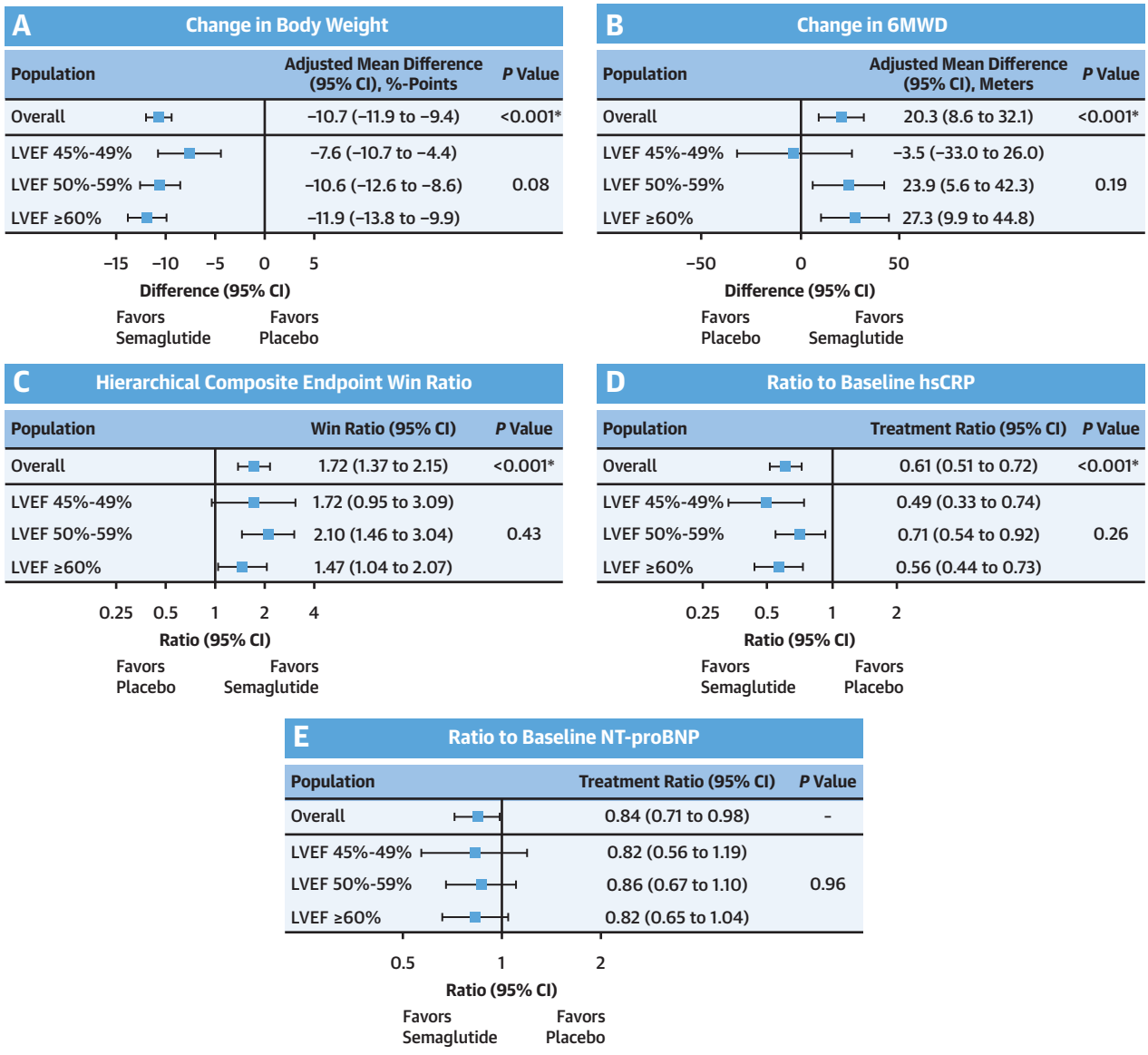
P values are for the test for interaction between treatment and LVEF subgroups except for *the treatment difference for semaglutide vs placebo. KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; LVEF = left ventricular ejection fraction.

normal" LVEF, suggesting the presence of disease-driving mechanisms not targeted by the respective intervention. In CHARM-Preserved (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity), candesartan significantly reduced the primary composite outcome in patients with LVEF 40% to 49%; however, no effect was observed for patients with LVEF ≥50%.[10] In TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), spironolactone was not effective in HFpEF overall defined as LVEF ≥45%; however, a potential efficacy was observed with lower LVEF and declining efficacy with increasing LVEF.[9] Similarly, in a combined analysis of the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trials suggested that patients with HFmrEF would most likely benefit from sacubitril/valsartan compared with renin-angiotensin system inhibitors, which was not the case in those with truly normal LVEF.[11]

EF-based discrepancies with neurohormonal antagonists have not been observed with cardiometabolic agents. In the combined analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) and DAPA-HF (Dapagliflozin and Prevention of Adverse-outcomes in Heart Failure) trials and the DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients with Heart Failure with Reduced Ejection Fraction) and PRESERVED-HF (Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with Preserved Ejection Fraction Heart Failure) trials, there were consistent benefits of dapagliflozin on both clinical events, as well as health status across the spectrum of LVEF, with no suggestion of attenuated benefit at higher LVEF.[22,23] Consistent results were also observed with participant-level pooled data in the EMPEROR (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure) Program.[12] The largest benefits of SGLT2 inhibitors on KCCQ were seen in the PRESERVED-HF trial, which included patients with the highest BMI and lowest KCCQ vs other SGLT2 inhibitor trial programs. In the current analysis of STEP-HFpEF, the benefits of semaglutide extended similarly across the LVEF spectrum, not only for symptoms, physical limitations, and exercise

FIGURE 1 Treatment Effects (Semaglutide vs Placebo) on Selected Outcomes Across LVEF



P values are for the test for interaction between treatment and left ventricular ejection fraction (LVEF) subgroups except for *the treatment difference between semaglutide vs placebo. 6MWD = 6-minute walk distance; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide.

function; but also, in the analysis of the hierarchical composite endpoint (which included death and HF events, although the total number of clinical events was small), as well as hsCRP and NT-proBNP. If anything, in the present analysis, the benefits of semaglutide on KCCQ-CSS appeared to be somewhat numerically larger in participants with higher LVEF, although the interaction was not statistically significant. STEP-HFpEF included exclusively patients with the obesity phenotype of HFpEF who had a greater burden of symptoms and physical limitations compared with other recent HFpEF trials of SGLT2 inhibitors and sacubitril/valsartan; the magnitude of improvements in symptoms and functional status was considerably greater with semaglutide in STEP-HFpEF than with other agents in prior

TABLE 3 Adverse Events in Semaglutide and Placebo Groups Across Ejection Fraction

	LVEF 45%-49%		LVEF 50%-59%		LVEF ≥60%	
	Semaglutide (n = 37)	Placebo (n = 48)	Semaglutide (n = 113)	Placebo (n = 102)	Semaglutide (n = 113)	Placebo (n = 116)
Serious adverse events	3 (8.1)	6 (12.5)	17 (15.0)	41 (40.2)	15 (13.3)	24 (20.7)
Cardiac serious adverse events[a]	0 (0.0)	3 (6.3)	5 (4.4)	17 (16.7)	2 (1.8)	10 (8.6)
Gastrointestinal serious adverse events[b]	2 (5.4)	0 (0.0)	5 (4.4)	4 (3.9)	0 (0.0)	3 (2.6)
Serious adverse events leading to premature treatment discontinuation	0 (0.0)	0 (0.0)	3 (2.7)	4 (3.9)	3 (2.7)	2 (1.7)
COVID-19-related adverse events[c]	9 (24.3)	3 (6.3)	18 (15.9)	27 (26.5)	12 (10.6)	15 (12.9)

Values are n (%). Data are from the on-treatment period. [a]Defined as events within the Medical Dictionary for Regulatory Activities cardiac disorder system organ class. [b]Defined as events within the Medical Dictionary for Regulatory Activities gastrointestinal disorder system organ class. [c]All events are reported irrespective of seriousness.
LVEF = left ventricular ejection fraction.

trials, likely because of both weight loss-related and weight loss-independent effects of semaglutide. Given that the majority of patients with "true" HFpEF have a cardiometabolic phenotype, with very high prevalence of overweight or obesity, it is likely that the treatment approach in this patient population may ultimately include combination therapy with SGLT2 inhibitors and GLP-1 receptor agonists, given their nonoverlapping and complementary mechanisms of action.[5-8,24]

There have been some concerns raised regarding the use of GLP-1 receptor agonist in patients with HFrEF based on 2 relatively small trials with liraglutide. The LIVE (Effect of Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients) trial randomized 241 patients with HFrEF with or without diabetes to placebo or liraglutide 1.8 mg for 24 weeks. No changes in LVEF, health status, or functional class were observed, but serious cardiac adverse events (including sustained ventricular tachycardia, atrial fibrillation requiring intervention, aggravation of ischemic heart disease, and worsening of HF) occurred more frequently in the liraglutide arm (n = 12, 10.0% vs n = 3, 3.0%; P = 0.04).[25] The FIGHT (Functional Impact of GLP-1 for HF Treatment) trial randomized 300 patients with HFrEF and recent decompensation to liraglutide or placebo for 6 months. The trial was neutral overall, but although not statistically significant, participants in the liraglutide arm experienced numerically higher risk for the composite outcome of death or HF hospitalization (HR: 1.30; 95% CI: 0.92-1.83; P = 0.14), particularly in patients with diabetes (HR: 1.54; 95% CI: 0.97-2.46; P = 0.07). Neither study was powered or of sufficient duration to allow conclusive comments regarding the efficacy or safety of these agents in HFrEF.[26] The favorable efficacy and safety results from the HFmrEF subgroup of participants in STEP-HFpEF provides important reassurance regarding the use of these agents in patients with mildly reduced LVEF and obesity, although the number of STEP-HFpEF participants with HFmrEF was small, and LVEF was only modestly reduced. Given that obesity may also contribute to the progression of HF-related symptoms and physical limitations in HFrEF, the efficacy and safety of GLP-1 receptor agonists in stable patients with HFrEF and obesity should be further investigated.

STUDY STRENGTHS AND LIMITATIONS. This study has certain strengths and limitations. Notably, it was a prespecified analysis of the first dedicated randomized, controlled trial of GLP-1 receptor agonists in patients with the obesity phenotype of HFpEF, and included participants across the range of mildly reduced, normal and high LVEF. However, LVEF was not measured in a central laboratory, and thus, may be subjected to normal variability of clinical practice (although this variability would be expected to be evenly distributed between treatment arms, and thus not have an impact on the findings). Additional measures such as left ventricular size or strain were also not available at the time of this analysis; these measures may influence HF outcomes.[16] Comparison of efficacy of different therapies across the LVEF spectrum should be interpreted with caution because of variation in patient and trial characteristics. The patients studied were predominantly White, which limits generalizability of these results to other racial and ethnic populations. As with most clinical trials, STEP-HFpEF was designed to have the appropriate statistical power for the analyses of the key endpoints

in the overall patient population, rather than within specific subgroups; subgroup analyses should be interpreted within the context of this limitation.

CONCLUSIONS

In the STEP-HFpEF trial, semaglutide improved symptoms, physical limitations, and exercise function, and reduced inflammation, NT-proBNP, and body weight in patients with the obesity phenotype of HFpEF across the range of EF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The long-acting GLP-1 receptor agonist semaglutide improves symptoms, physical limitations and exercise function, and reduces body weight across the spectrum of EF in patients with HF and left ventricular EF ≥45%, and BMI of 30 kg/m^2 or higher.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the benefit of semaglutide in patients with HFpEF and obesity who have type 2 diabetes.

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APPENDIX For supplemental figures, please see the online version of this paper.