JACC: HEART FAILURE VOL. ■, NO. ■, 2025

ORIGINAL RESEARCH

Frailty and Effects of Semaglutide in Obesity-Related HFpEF

Findings From the STEP-HFpEF Program

Ambarish Pandey, MD, MSCS,[a,b,*] Dalane W. Kitzman, MD,[c,d,*] Khaja M. Chinnakondepalli, MS,[e] Shachi Patel, PhD,[e] Barry A. Borlaug, MD,[f] Javed Butler, MD,[g] Melanie J. Davies, MD,[h,i] Sanjiv J. Shah, MD,[j] Subodh Verma, MD,[k] Cecilia Rönnbäck, MD, PhD,[l] Anne Domdey, PhD,[l] Karoline Liisberg, MS,[l] Morten Schou, MD, PhD,[m] Eduardo Perna, MD,[n] Fozia Z. Ahmed, MD,[o] Michael Fu, MD, PhD,[p] Mark C. Petrie, MD,[q] Mikhail N. Kosiborod, MD[r]

ABSTRACT

BACKGROUND Frailty is common in heart failure with preserved ejection fraction (HFpEF). In the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) program, semaglutide improved heart failure (HF) symptoms and physical limitations and reduced body weight (BW) in participants with obesity-related HFpEF. Whether the efficacy and safety of semaglutide vary by frailty and the effects of semaglutide on frailty are unknown.

OBJECTIVES This study sought to evaluate the efficacy of semaglutide in participants with obesity-related HFpEF according to frailty status at baseline.

METHODS The authors performed a prespecified, pooled, participant-level analysis of the STEP-HFpEF program that included participants with obesity-related HFpEF. Participants were randomized to once-weekly semaglutide, 2.4 mg, or placebo for 52 weeks. Dual primary endpoints were changes in Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and BW. Frailty was estimated using a cumulative deficit-derived frailty index comprising 34 variables across multiple domains at baseline and follow-up. Efficacy and safety of semaglutide were evaluated in participants across 3 baseline frailty strata. Effects of semaglutide on frailty burden were also assessed.

RESULTS Of the 1,145 participants, 110 (9.6%) were nonfrail, 343 (30.0%) were more frail, and 692 (60.4%) were most frail. Semaglutide-mediated weight loss was similar across frailty strata ($P_{interaction} = 0.38$). However, the effects of semaglutide on KCCQ-CSS varied by frailty status; participants who were most frail had the greatest improvement at 52 weeks (nonfrail mean difference: −1.5 [95% CI: −8.4 to 5.4]; more frail mean difference: 3.7 [95% CI: −0.2 to 7.6]; most frail mean difference: 11.0 [95% CI: 8.1-13.8]; $P_{interaction} < 0.001$). Semaglutide reduced the burden of frailty during follow-up (OR for being nonfrail at 52 weeks: 3.16 [95% CI: 2.44-4.09]; $P < 0.0001$).

CONCLUSIONS Semaglutide resulted in a similar reduction in BW across frailty subgroups but greater improvements in HF-related symptoms. Moreover, semaglutide reduced frailty burden after 52 weeks of treatment. (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity [STEP-HFpEF]; NCT04788511) and (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;■:102610) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2025.102610

ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walking distance

BMI = body mass index

CRP = C-reactive protein

FI = frailty index

GLP-1RA = glucagon-like peptide-1 receptor agonist

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

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

LVEF = left ventricular ejection fraction

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

QoL = quality of life

SAE = serious adverse event

SGLT2 = sodium-glucose cotransporter 2

Heart failure with preserved ejection fraction (HFpEF) is increasing in prevalence, particularly among older adults.[1,2] It is characterized by a high burden of morbidity, mortality, symptoms, and physical limitations.[1,2] Over the past decade, the understanding of HFpEF pathophysiology has evolved from solely a cardiac disease to a systemic, multiorgan condition that shares many pathophysiologic traits with other common, difficult to treat aging disorders.[3-5] This understanding has prompted a broader evaluation of new HFpEF therapies using a gerocentric framework incorporating geriatric syndromes such as frailty and physical dysfunction as meaningful effect modifiers and outcomes of interest.[3,4,6-8] Specifically, frailty, a geriatric syndrome characterized by increased physiologic vulnerability, is particularly relevant to managing HFpEF because of its high prevalence, shared pathophysiologic mechanisms, and association with worse functional and clinical outcomes.[3,7-11] Furthermore, patients with heart failure (HF) and frailty are often less likely to receive evidence-based therapies given a perception that they may have a higher risk of treatment intolerance and adverse drug effects.[12-15] Thus, older patients with HFpEF and frailty represent a vulnerable, high-risk group with a large clinical need for additional efficacious and safe therapies.

Among the emerging HFpEF therapies, incretin-based weight loss agents have shown great promise for the management of obesity-related HFpEF,[16-18] a distinct high-risk phenotype of HFpEF with severe cardiac hemodynamic impairment and poor long-term outcomes.[19-23] Obesity also predisposes patients to a high burden of physical dysfunction and frailty contributing to increased exercise intolerance and poor quality of life (QoL). In the recent STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity; NCT04788511) trials, semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), improved HF-related symptoms, physical limitations, and exercise function, reduced the biomarkers of inflammation and congestion, as well as body weight, and produced a signal for fewer HF events in patients with obesity-related HFpEF.[16-18] Whether the safety and efficacy of semaglutide in patients with obesity-related HFpEF vary by frailty status and the effects of semaglutide on frailty itself over time are unknown.

Addressing these knowledge gaps is critically important because GLP-1RA-induced weight loss has been associated with a substantial reduction in skeletal muscle and loss of bone mineral density in previous studies among individuals without HF.[24-27] This issue may be uniquely challenging in frail patients with HFpEF who have preexisting sarcopenia, skeletal muscle dysfunction, and increased physical function impairment.[28-30] Additional loss of skeletal muscle and bone mass may result in further decline of physical function and a higher risk of adverse outcomes and disability. To address these knowledge gaps, we conducted a prespecified, pooled, participant-level analysis of the STEP-HFpEF program trials to evaluate the efficacy of

From the [a]Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [b]Division of Geriatrics, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [c]Section on Cardiovascular Medicine, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA; [d]Section on Geriatrics/Gerontology, Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA; [e]Saint Luke's Mid America Heart Institute, Kansas City, Missouri, USA; [f]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA; [g]Baylor Scott and White Research Institute, Dallas, Texas, USA; [h]Diabetes Research Centre, University of Leicester, Leicester, United Kingdom; [i]NIHR (National Institute for Health and Care Research) Leicester Biomedical Research Centre, Leicester, United Kingdom; [j]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [k]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute of St Michael's Hospital, Unity Health Toronto, University of Toronto, Toronto, Ontario, Canada; [l]Novo Nordisk A/S, Søborg, Denmark; [m]Department of Cardiology, Herlev-Gentofte Hospital, University of Copenhagen, Herlev, Denmark; [n]J.F. Cabral Cardiology Institute, Corrientes, Argentina; [o]Keele University, Keele Cardiovascular Research Group, Keele, United Kingdom; [p]Section of Cardiology, Department of Medicine, Sahlgrenska University Hospital-Östra Hospital, Gothenburg, Sweden; [q]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom; and the [r]Department of Cardiovascular Disease, Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA. *These authors contributed equally to this work as first authors.
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.

Manuscript received February 18, 2025; revised manuscript received May 27, 2025, accepted May 30, 2025.

semaglutide according to frailty status by using the Rockwood cumulative deficit approach. We also evaluated the treatment effect of semaglutide on frailty burden during follow-up.

METHODS

STUDY DESIGN. We conducted a prespecified, pooled, participant-level analysis of the randomized, international, multicenter, double-blind, placebo-controlled STEP-HFpEF program trials.[16,17] The program comprised 2 trials: STEP-HFpEF, which was conducted in participants with obesity-related HFpEF (body mass index [BMI] ≥30 kg/m^2, left ventricular ejection fraction [LVEF] ≥45%) 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.[16-18,31] The 2 trials were conducted between 2021 and 2022 at 129 sites across 18 countries in Asia, Europe, and North and South America. Institutional Review Board or ethics committee approval was obtained at each study site, and all patients provided written, informed consent. The Steering Committee, which included academic members and representatives from the sponsor (Novo Nordisk), designed both trials and was responsible for the academic publications. A global expert panel provided academic, medical, and operational input in each country. The sponsor of the trial program was Novo Nordisk.

STUDY PARTICIPANTS. Eligible participants had symptomatic HF, LVEF ≥45%, BMI ≥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: 1) elevated filling pressures (by invasive hemodynamics or implantable pulmonary artery pressure sensor); 2) elevated natriuretic peptide levels (with stratified thresholds on the basis of BMI) and echocardiographic abnormalities; or 3) HF hospitalization in the previous 12 months and a requirement for ongoing diuretic treatment and/or echocardiographic abnormalities. Key exclusion criteria were previous or planned bariatric surgery, self-reported change in body weight >5 kg within 90 days before randomization, or systolic blood pressure >160 mm Hg at screening. The presence of uncontrolled diabetic retinopathy or maculopathy was also an exclusion criterion in the STEP-HFpEF DM trial. Eligible participants were randomized 1:1 to receive once-weekly semaglutide, 2.4 mg, or matching placebo in addition to standard care for 52 weeks. Randomization was stratified by BMI (<35 kg/m^2 vs ≥35 kg/m^2). Semaglutide or placebo was added to background therapy for type 2 diabetes in STEP-HFpEF DM.

FRAILTY INDEX. Frailty was assessed using the Rockwood cumulative deficit approach, as described previously.[32-34] We included variables that measure health status from the pooled STEP-HFpEF program data set (Supplemental Methods). The frailty index (FI) was derived from medical history, vital signs, laboratory data, and QoL questionnaires. Responses were coded on a scale from 0 (no deficit) to 1 (deficit). Categorical variables (eg, medical history of atrial fibrillation) were coded as 0 or 1 (absent or present). Ordinal variables (QoL questionnaire) were coded by converting the number of possible ranks into equally spaced scores ranging from 0 to 1, with a score of 1 indicating greatest severity. Variables were excluded if deficits were rare (<1%), too common (>80%), or had >15% missingness.[35-37] The FI was constructed using 34 variables that met the foregoing criteria and are shown in Supplemental Table 1. The FI was calculated by dividing the total number of deficits present by the total number of variables considered. The FI was categorized into 3 groups, as previously published: nonfrail (FI <0.210), more frail (FI: 0.211-0.310), and most frail (FI >0.310).[9,10] FI was calculated for the baseline visit, 20-week follow-up, and 52-week follow-up. Because LVEF was not available during follow-up, it was excluded, and a 33-variable FI was used for a follow-up FI. The FI calculation approach is consistent with previously published reports, and the parameters included in the FI are consistent with previous studies in patients with HFpEF.[11,38-42] Given that the proportional contribution of different domains, such as comorbidities and functional status or QoL, can vary on the basis of the variables included in the FI calculation, we also conducted a sensitivity analysis using an alternative FI model (modified FI, 29 variables) that had greater weighting of comorbidities and fewer variables corresponding to activities of daily living or QoL, which may be more affected by HF severity (Supplemental Table 2).

OUTCOMES. The dual primary endpoints of the STEP-HFpEF program were as follows: 1) change in KCCQ-CSS from baseline to 52 weeks; and 2) percentage change in body weight from baseline to 52 weeks. The confirmatory secondary endpoints were the following: change in 6-minute walk distance (6MWD) from baseline to 52 weeks; a hierarchical

composite endpoint (consisting of all-cause death [from baseline to 57 weeks], HF events [from baseline to 57 weeks], differences in several thresholds [≥5, ≥10, and ≥15 points] of change in KCCQ-CSS from baseline to 52 weeks, and a difference of at least 30 m in change in 6MWD from baseline to 52 weeks); and a change in high-sensitivity C-reactive protein (CRP) from baseline to 52 weeks. HF events (hospitalizations or urgent visits requiring intravenous therapy; an exploratory endpoint in both STEP-HFpEF trials) were adjudicated by a blinded clinical events committee, as previously described.[17] Change in the level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to week 52 by frailty category was also evaluated as an exploratory endpoint. We also evaluated the changes in other summary (Total Symptom Score) and individual (Physical Limitation Score, Social Limitations Score, and Quality of Life Score) Kansas City Cardiomyopathy Questionnaire (KCCQ) domains between baseline and 52 weeks by frailty category as exploratory endpoints. In addition, we examined safety endpoints, including serious adverse events (SAEs), SAEs leading to permanent treatment discontinuation, cardiac SAEs, and gastrointestinal SAEs.

STATISTICAL ANALYSIS. The pooled trial participants were stratified according to baseline FI into 3 categories: nonfrail (FI ≤0.210), more frail (FI: 0.211-0.310), and most frail (FI ≥0.311). Baseline characteristics were compared across the frailty strata by using the Jonckheere-Terpstra trend test for continuous variables, the Cochran-Armitage trend test for categorical variables, and the Cochran-Mantel-Haenszel test for multinomial variables. The efficacy endpoints were examined in the full analysis set according to the intention-to-treat principle. Safety endpoints, stratified by frailty category, were analyzed using the safety analysis set, which included randomized participants exposed to ≥1 dose of the investigational treatment. Analyses of continuous endpoints were performed using analysis of covariance models adjusted for the baseline value of the outcome variable, treatment arm, trial, and BMI (<35 kg/m^2 or ≥35 kg/m^2) as fixed factors by using 1,000 imputations; analyses also included an interaction term between the treatment arm and frailty category. Estimates were combined using Rubin's rule. For the analyses of 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. Missing values caused by other factors were multiple imputed from retrieved participants in the same randomized treatment arm. For other endpoints, missing observations at week 52 were multiple imputed irrespective of death or previous HF events by using the same imputation method. Analyses of all other KCCQ domains at week 52 used the same methodology and imputation methods as described earlier for KCCQ-CSS. The approach to the analysis of covariance analyses and handling of missing data for study outcomes is consistent with the prespecified statistical approach that was used across all STEP-HFpEF program analyses and agreed on with the regulatory agencies. Interaction *P* values were derived from an F-test of equality between the treatment differences across the frailty subgroups. Furthermore, trend *P* values for difference in semaglutide and placebo groups across the frailty subgroups were also derived for the various endpoints. The effects of semaglutide on outcomes of change in KCCQ-CSS and body weight were also examined across continuous measures of FI by using restricted cubic splines.

Analyses of the hierarchical composite endpoint (win ratio) were performed as stratified by FI, on the basis of direct comparisons of each participant randomized to semaglutide vs placebo as reported previously.[17,31] The win ratio, the proportion of winners randomized to semaglutide divided by the winners randomized to placebo, was estimated independently for each frailty FI category (using 1,000 imputations as described earlier). Test for equality for the win ratio was performed using Cochran's Q test.

For the responder analyses, we examined the proportion of participants by frailty category (on the basis of observed [ie, nonimputed] data) who experienced ≥5-point deterioration as well as ≥5-point (small), ≥10-point (moderate), ≥15-point (large), and ≥20-point (very large) improvement in the KCCQ-CSS between baseline and 52 weeks. Logistic regression models were constructed to calculate the ORs and corresponding 95% CIs for semaglutide effects on the likelihood for each threshold of KCCQ-CSS change (≥5-point reduction, and ≥5-, ≥10-, ≥15-, and ≥20-point improvement). Multiple imputations were used to account for missing data. Models were adjusted for baseline values of the outcome of interest, trial, and BMI group. Sensitivity analyses were conducted to evaluate the treatment effect of semaglutide on outcomes across frailty categories identified using the alternative frailty estimation models, including the modified FI (29 variables), with greater weighting of comorbidities and fewer variables corresponding to activities of daily living or QoL and the follow-up FI (33 variables), which excluded EF.

In additional post hoc analyses, the effects of semaglutide vs placebo on follow-up frailty status were also assessed, in which the FI was calculated at 20 weeks and 52 weeks post-randomization by using the Rockwood deficit index model described earlier. The primary analysis evaluating change in FI included participants with all 33 variables (excluding LVEF, which was not available on follow-up) available at baseline and follow-up visits (N = 990 of 1,145 [86.5% of the study cohort at 20 weeks]; and N = 994 of 1,145 [86.8% of the study cohort at 52 weeks]). The proportion of participants identified as nonfrail, more frail, and most frail on follow-up visits on the basis of the prespecified FI cutoffs were compared between the semaglutide and placebo groups. Logistic regression models were used to evaluate the effects of semaglutide vs placebo on the likelihood of being nonfrail during follow-up. In addition, responder analyses were performed to evaluate the odds of improvement or deterioration by ≥1 category of frailty between baseline and week 20, as well as baseline and week 52, by using logistic regression models adjusted for BMI, trial, and treatment arm. Sensitivity analyses also evaluated the effect of semaglutide on frailty burden on follow-up by using the modified FI (29 variables) as described earlier.

Safety endpoints were also analyzed by FI category in the safety analysis data set (randomized participants who received ≥1 dose of randomized treatment) and the in-trial or on-treatment data set, depending on the safety event. No adjustments were made for multiple comparisons, given the exploratory nature of the analyses. A 2-sided value of $P < 0.05$ was considered significant. Results are presented as estimated change from baseline to 52 weeks for continuous endpoints and a win ratio for the hierarchical composite endpoint, or an OR, with a 95% CI and a 2-sided *P* value. NT-proBNP and CRP were log-transformed; hence the treatment ratio with the corresponding 95% CI at week 52 is reported.

Statistical analyses were performed by the independent statistical group at Saint Luke's Mid-America Heart Institute, in collaboration with Novo Nordisk, using SAS software version 9.4 (SAS/STAT version 15.1, SAS Institute). All analyses were performed on anonymized data.

RESULTS

BASELINE CHARACTERISTICS BY FRAILTY CATEGORY. A total of 1,145 participants from the STEP-HFpEF and STEP-HFpEF DM trials were included in the analysis. The overall cohort had a high burden of frailty, with a mean FI of 0.359 ± 0.124 SD. Only 9.6% (n = 110) of participants were considered nonfrail with an FI <0.21, 30% (n = 343) were considered more frail with an FI between 0.211 and 0.310, and 60.4% (n = 692) were considered most frail with an FI ≥0.311. The distribution of frailty categories at baseline was similar between the semaglutide and placebo groups.

Baseline characteristics of study participants according to frailty categories are shown in **Table 1**. Compared with nonfrail participants, those with a higher frailty burden (more or most frail groups) were more often of Black race, female, and more likely to have cardiac and noncardiac comorbidities. They also had higher BMI, waist circumference, CRP, and NT-proBNP levels, worse functional status and exercise function (higher NYHA functional class and lower 6MWD), and worse health status (lower KCCQ-CSS). Among medications for HFpEF, the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors and angiotensin receptor-neprilysin inhibitors was lower, and the use of diuretic agents was higher among those patients with a higher frailty burden (vs nonfrail participants). Generally similar patterns of differences in baseline characteristics were noted across frailty categories by using the modified FI (Supplemental Table 3).

EFFICACY OF SEMAGLUTIDE VS PLACEBO BY BASELINE FRAILTY CATEGORIES. A summary of the proportional missing data for key outcomes is shown in Supplemental Table 4. The treatment effects of semaglutide vs placebo on the key endpoints across frailty strata are shown in **Table 2**. Baseline frailty modified the treatment effect of semaglutide on the dual primary endpoint of KCCQ-CSS. The magnitude of improvement in KCCQ-CSS with semaglutide (vs placebo) at 52 weeks gradually increased across increasing frailty categories, with the greatest treatment effect noted among most frail participants (treatment difference, nonfrail: −1.5 points [95% CI: −8.4 to 5.4 points]; more frail: 3.7 points [95% CI: −0.2 to 7.6 points]; most frail: 11.0 points [95% CI: 8.1-13.8 points]; $P_{trend} = 0.001$; $P_{interaction} < 0.001$). When FI was analyzed as a continuous variable, the treatment effect of semaglutide on KCCQ-CSS was greater, with higher FI values ($P_{interaction} = 0.018$) (**Figure 1A**). A similar pattern of treatment effect modification by baseline frailty status was noted for other domains of KCCQ, with the greatest magnitude of improvements in different KCCQ subscores observed among most frail participants (Supplemental Table 5). The effects of

TABLE 1 Baseline Characteristics of Participants in the STEP-HFpEF and STEP-HFpEF DM Trials Stratified by FI

	Total (N = 1,145[a])	Nonfrail FI ≤0.210 (n = 110)	More Frail FI: 0.211-0.310 (n = 343)	Most Frail FI ≥0.310 (n = 692)	*P* Value
Female	570 (49.8)	45 (40.9)	144 (42.0)	381 (55.1)	<0.001
Age, y					0.041
<65	368 (32.1)	34 (30.9)	119 (34.7)	215 (31.1)	
65-79	666 (58.2)	72 (65.5)	197 (57.4)	397 (57.4)	
≥80	111 (9.7)	4 (3.6)	27 (7.9)	80 (11.6)	
Race[b]					<0.001
Asian	76 (6.6)	9 (8.2)	40 (11.7)	27 (3.9)	
Black	39 (3.4)	3 (2.7)	8 (2.3)	28 (4.0)	
Other	4 (0.3)	0 (0.0)	2 (0.6)	2 (0.3)	
White	1,026 (89.6)	98 (89.1)	293 (85.4)	635 (91.8)	
Diabetes duration, y[c]	8.0 (3.9-14.8)	10.3 (5.9-18.3)	7.7 (3.7-13.9)	7.6 (3.9-15.0)	0.476
Body weight, kg	103.7 (91.3-119.0)	96.3 (83.7-104.6)	100.6 (89.0-115.9)	106.6 (94.6-123.3)	<0.001
BMI,[d] kg/m^2	38.0 (34.6-42.6)	34.1 (32.5-36.6)	36.4 (33.5-40.6)	39.4 (36.0-44.1)	<0.001
Waist circumference, cm	120.0 (111.0-129.0)	113.0 (106.0-120.7)	117.8 (109.0-126.0)	122.3 (114.0-132.1)	<0.001
SBP, mm Hg	133.0 (123.0-144.0)	128.0 (117.0-135.0)	132.0 (122.0-141.0)	136.0 (124.0-146.0)	<0.001
NYHA functional class					<0.001
II	785 (68.6)	101 (91.8)	304 (88.6)	380 (54.9)	
III	358 (31.3)	9 (8.2)	39 (11.4)	310 (44.8)	
IV	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)	
LVEF, %	57.0 (50.0-60.0)	55.0 (50.0-60.0)	57.0 (50.0-60.5)	57.0 (51.0-60.0)	0.063
KCCQ-CSS, points	59.4 (42.7-72.4)	83.3 (76.6-89.6)	71.8 (64.7-78.9)	47.2 (35.4-58.3)	<0.001
6MWD, m	294.8 (220.0-368.0)	359.5 (297.8-404.9)	329.5 (251.1-391.0)	263.5 (199.2-344.0)	<0.001
CRP, mg/L	3.7 (1.8-8.1)	2.1 (1.2-4.2)	3.0 (1.5-7.0)	4.4 (2.1-9.5)	<0.001
NT-proBNP, pg/mL	475.3 (234.3-1,015.7)	377.2 (266.4-608.1)	394.9 (199.6-954.8)	531.9 (256.2-1,119.7)	<0.001
Medical history					
Hypertension	959 (83.8)	87 (79.1)	286 (83.4)	586 (84.7)	0.164
Atrial fibrillation	518 (45.2)	31 (28.2)	152 (44.3)	335 (48.4)	<0.001
OSA	119 (10.4)	6 (5.5)	27 (7.9)	86 (12.4)	0.004
CAD	246 (21.5)	26 (23.6)	72 (21.0)	148 (21.4)	0.742
Medications					
Diuretic agents	925 (80.8)	78 (70.9)	255 (74.3)	592 (85.5)	<0.001
Loop diuretic agents	702 (61.3)	45 (40.9)	178 (51.9)	479 (69.2)	<0.001
Thiazides	175 (15.3)	15 (13.6)	60 (17.5)	100 (14.5)	0.625
Beta blockers	928 (81.0)	88 (80.0)	273 (79.6)	567 (81.9)	0.407
SGLT2 inhibitors	221 (19.3)	33 (30.0)	69 (20.1)	119 (17.2)	0.003
MRAs	384 (33.5)	37 (33.6)	89 (25.9)	258 (37.3)	0.015
ACEI/ARB/ARNI	899 (78.5)	89 (80.9)	269 (78.4)	541 (78.2)	0.591
ARNIs	58 (5.1)	10 (9.1)	21 (6.1)	27 (3.9)	0.011
Insulin and analogs	128 (11.2)	14 (12.7)	25 (7.3)	89 (12.9)	0.160
Sulfonylureas	108 (9.4)	15 (13.6)	37 (10.8)	56 (8.1)	0.034
DPP-4 inhibitors	92 (8.0)	10 (9.1)	40 (11.7)	42 (6.1)	0.015

Values are n (%) or median (Q1-Q3), unless otherwise indicated. [a]A total of 1,146 participants were randomized; however, 1 participant was randomized in error such that the full analysis set comprises 1,145 participants. [b]Race was reported by the investigator. [c]Diabetes was an exclusion criterion in the STEP-HFpEF trial; therefore, the data shown are from the STEP-HFpEF DM trial only. [d]BMI is the weight (kg) divided by the square of the height (m).

6MWD = 6-minute walk distance; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; DPP-4 = dipeptidyl peptidase 4; FI = frailty index; 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; OSA = obstructive sleep apnea; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2; STEP-HFpEF = Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity; STEP-HFpEF DM = Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes.

semaglutide on reducing body weight (second dual primary endpoint) were consistent across the frailty distribution in categorical ($P_{interaction}$ = 0.385) and continuous ($P_{interaction}$ = 0.18) (**Figure 1B**) analyses. In a sensitivity analysis using the modified FI (29 variable) or follow-up FI (33 variable) models, a similar pattern of results was noted, such that frailty burden significantly modified the treatment effect of semaglutide on KCCQ-CSS but not body weight outcomes (Supplemental Tables 6 and 7, Supplemental Figure 1).

Among confirmatory secondary endpoints, semaglutide led to numerically larger increases in

TABLE 2 Effect of Semaglutide Compared With Placebo on Outcomes by FI

	Nonfrail (FI ≤0.210) (n = 110)		More Frail (FI: 0.211-0.310) (n = 343)		Most Frail (FI ≥0.310) (n = 692)			
	Semaglutide (n = 59)	Placebo (n = 51)	Semaglutide (n = 172)	Placebo (n = 171)	Semaglutide (n = 342)	Placebo (n = 350)	$P_{interaction}$	P_{trend}
Dual primary endpoint								
Change in KCCQ-CSS at 52 wk, points	8.8 (3.6-14.0)	10.4 (4.9-15.8)	14.3 (11.3-17.3)	10.6 (7.6-13.6)	16.5 (14.3-18.7)	5.5 (3.3-7.7)	–	–
Adjusted mean difference, points	−1.5 (−8.4 to 5.4)		3.7 (−0.2 to 7.6)		11.0 (8.1-13.8)		<0.001	0.001
Change in body weight at 52 wk, %	−10.3 (−12.2 to −8.5)	−3.4 (−5.5 to −1.3)	−11.2 (−12.3 to −10.1)	−3.3 (−4.4 to −2.1)	-11.6 (−12.4 to −10.8)	−2.8 (−3.7 to −2.0)	–	–
Adjusted mean difference, %	−6.9 (−9.7 to −4.2)		−8.0 (−9.5 to −6.4)		−8.8 (−9.9 to −7.7)		0.385	0.219
Confirmatory secondary endpoints								
Change in 6MWD at 52 wk, m	16.3 (−0.6 to 33.1)	20.5 (1.9-39.1)	20.5 (10.6-30.5)	6.4 (−3.6 to 16.5)	15.0 (7.7-22.4)	−6.7 (−13.9 to 0.5)	–	–
Adjusted mean difference, m	−4.2 (−28.8 to 20.4)		14.1 (0.2-28.0)		21.7 (11.6-31.8)		0.141	0.055
Hierarchical composite endpoint, win ratio	1.02 (0.64-1.64)		1.38 (1.05-1.81)		2.00 (1.65-2.43)		0.0024	–
CRP ratio at 52 wk	0.71 (0.55-0.91)	1.00 (0.76-1.32)	0.48 (0.41-0.56)	0.78 (0.67-0.91)	0.60 (0.53-0.68)	0.94 (0.85-1.05)	–	–
Treatment ratio	0.70 (0.49-1.02)		0.62 (0.50-0.77)		0.64 (0.54-0.75)		0.832	0.635
NT-proBNP ratio at 52 wk	0.76 (0.61-0.95)	1.13 (0.88-0.44)	0.73 (0.64-0.84)	0.87 (0.76-1.00)	0.80 (0.73-0.89)	0.97 (0.88-1.07)	–	–
Treatment ratio	0.67 (0.49-0.93)		0.85 (0.70-1.02)		0.83 (0.72-0.95)		0.470	0.247

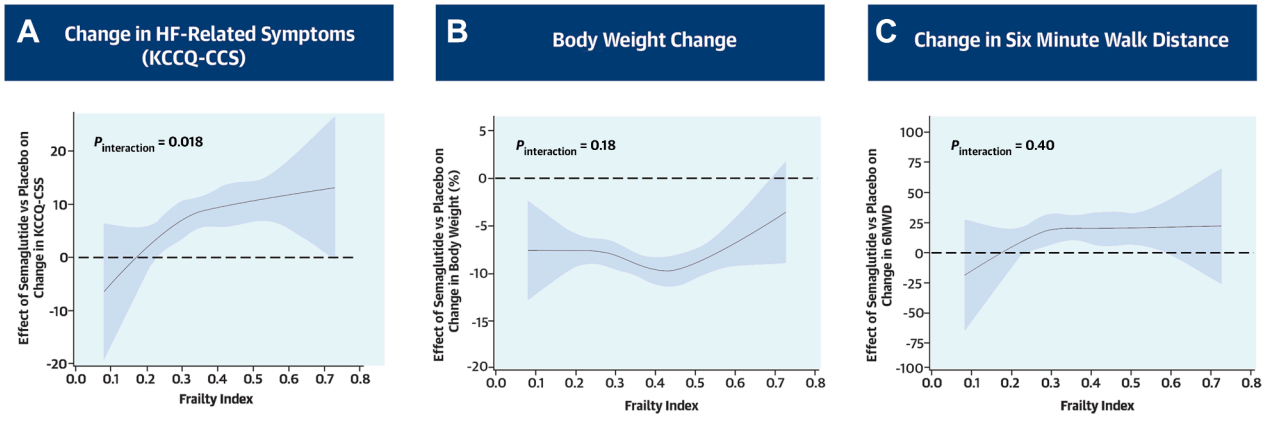
Values are HR (95% CI), unless otherwise indicated. *P* values are for interaction between treatment × FI. Data for in-trial period for participants.
Abbreviations as in Table 1.

6MWD among participants with higher frailty burden (treatment difference, nonfrail: −4.2 m [95% CI: −28.8 to 20.4 m]; more frail: 14.1 m [95% CI: 0.2-28.0 m]; most frail: 21.7 m [95% CI: 11.6-31.8 m]; $P_{trend} = 0.055$). However, this difference was not statistically significant ($P_{interaction} = 0.141$). When FI was analyzed as a continuous variable, effects of semaglutide on 6MWD were largely consistent across the FI distribution ($P_{interaction} = 0.40$) (**Figure 1C**). The effects of semaglutide on hierarchical composite endpoint differed across baseline frailty categories, with a more favorable win ratio among participants with a higher frailty burden (win ratio, nonfrail: 1.02 [95% CI: 0.64-1.64]; more frail: 1.38 [95% CI: 1.05-1.81]; most frail: 2.00 [95% CI: 1.65-2.43]; $P_{interaction} = 0.002$). Among other confirmatory secondary and supportive secondary endpoints, semaglutide resulted in a similar reduction in CRP and NT-proBNP across frailty categories (**Table 2**). In a sensitivity analysis using the modified FI, a similar pattern of results was noted for the treatment effect of semaglutide on confirmatory secondary endpoints and supportive secondary endpoints (Supplemental Table 6).

In the KCCQ-CSS responder analyses using prespecified thresholds (≥5-, ≥10-, ≥15-, and ≥20-point improvement), significant treatment effect heterogeneity was observed by baseline frailty burden ($P_{interaction} < 0.05$ for each threshold of KCCQ-CSS improvement). The odds of clinically meaningful improvements in KCCQ-CSS (for each prespecified threshold) with semaglutide (vs placebo) increased with a higher frailty burden, with the highest odds for treatment response among most frail participants (Supplemental Figure 2). Similarly, the odds of clinically relevant deterioration in KCCQ-CSS (>5-point deterioration) with semaglutide (vs placebo) decreased significantly with increasing baseline frailty burden ($P_{interaction} = 0.024$) with the lowest odds in the frailest group (OR: 0.28 [95% CI: 0.17-0.46]; $P < 0.0001$). A similar pattern of results was noted in a sensitivity analysis using the modified FI with a trend toward greater odds of clinically meaningful improvements in KCCQ-CSS with semaglutide among those patients with a higher frailty burden (Supplemental Figure 3).

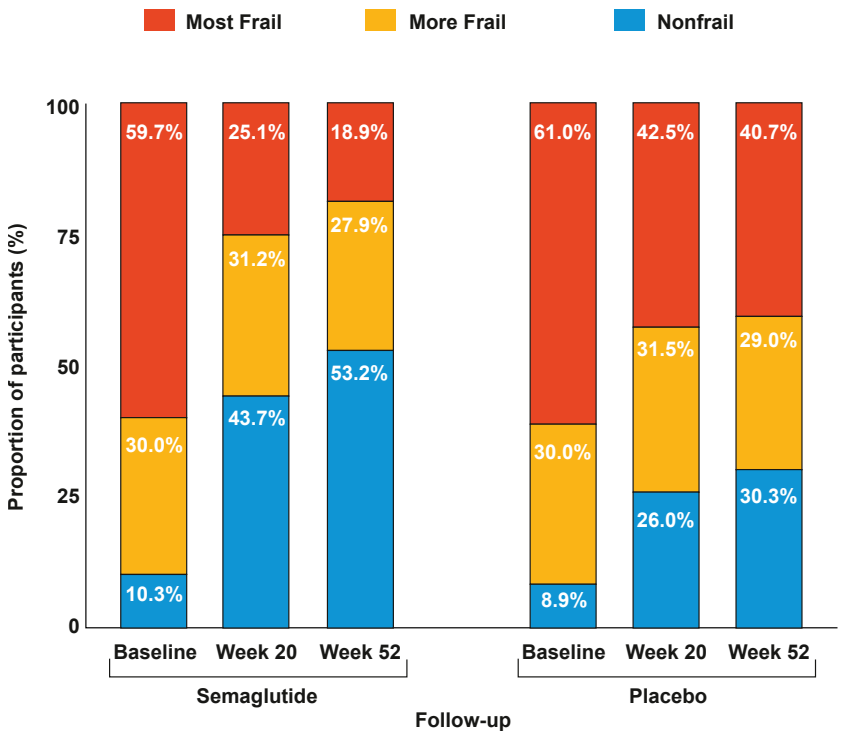
EFFECT OF SEMAGLUTIDE ON FRAILTY BURDEN DURING FOLLOW-UP. Semaglutide (vs placebo) reduced the burden of frailty during follow-up with a greater increase in the proportion of nonfrail participants and a concurrent decrease in the proportion of more frail and most frail participants at weeks 20 and

FIGURE 1 Effect on Outcomes of Semaglutide Compared With Placebo



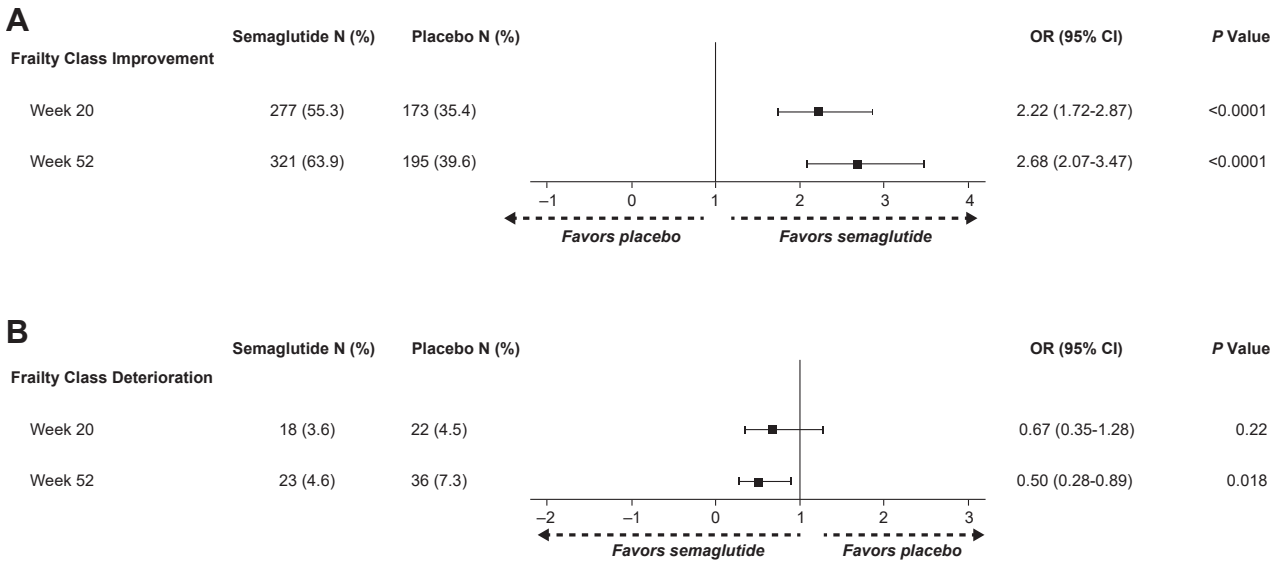
Change in KCCQ-CSS (A), change in body weight (B), and change in 6MWD across continuous distribution of the frailty index (FI) (C). Semaglutide-mediated weight loss was similar across the frailty distribution ($P_{interaction} = 0.18$). However, the effects of semaglutide on the KCCQ-CSS varied across frailty distribution, with greater improvements in KCCQ-CSS among those patients with a higher FI ($P_{interaction} = 0.018$). The effects of semaglutide on 6MWD were largely consistent across the FI distribution ($P_{interaction} = 0.40$). Models are adjusted for baseline value, treatment group, trial, and body mass index. $P_{interaction}$ for treatment effect × FI.
6MWD = 6-minute walk distance; FI = frailty index; HF = heart failure; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.

FIGURE 2 Relative Proportion of Participants in Different Frailty Strata at Baseline and Follow-Up Visits in the Semaglutide and Placebo Arms



FI was calculated at baseline, week 20, and week 52, and participants were categorized into different frailty strata as follows: nonfrail (FI <0.210), more frail (FI: 0.211-0.310), and most frail (FI >0.310). Abbreviation as in Figure 1.

FIGURE 3 Effect of Semaglutide on Frailty Status (Improvement or Deterioration By ≥1 Class of Frailty With Semaglutide vs Placebo)



(A) Odds of frailty class improvement. (B) Odds of frailty deterioration on follow-up. Logistic regression modeled the odds of improvement by ≥1 class in frailty status (ie, improvement from more frail to nonfrail, or most frail to more frail). The follow-up FI was calculated using 33 variables on follow-up. Abbreviation as in Figure 1.

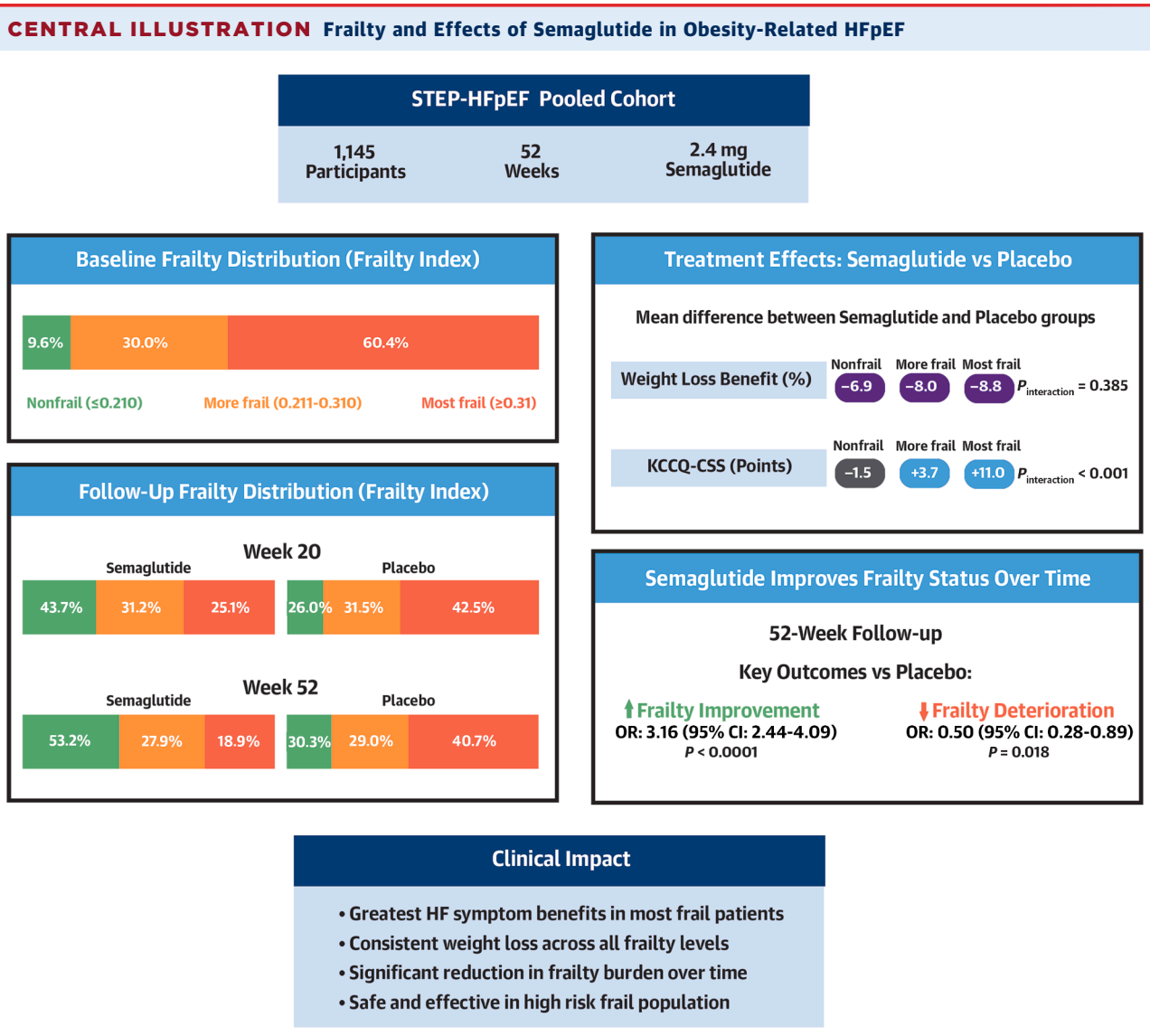
52 (Figure 2). In logistic regression models, semaglutide (vs placebo) led to significantly greater odds of being nonfrail at week 20 (OR: 2.56 [95% CI: 1.96-3.33]; $P < 0.0001$) and week 52 (OR: 3.16 [95% CI: 2.44-4.09]; $P < 0.0001$). Similarly, in responder analyses evaluating the odds of ≥1-class improvement or deterioration in frailty, semaglutide (vs placebo) led to significantly higher odds of improvement by ≥1 frailty category at 20 weeks (OR: 2.22 [95% CI: 1.72-2.87]; $P < 0.0001$) and 52 weeks (OR: 2.68 [95% CI: 2.07-3.47]; $P < 0.0001$) (Figure 3). Furthermore, semaglutide also resulted in significantly lower odds of deterioration of ≥1 frailty category at 52 weeks (OR: 0.50 [95% CI: 0.28-0.89]; $P = 0.018$). A similar pattern of results with greater improvement in frailty burden with semaglutide was noted when using a modified FI (Supplemental Table 8, Supplemental Figure 4).

SAFETY OUTCOMES. Participants with a higher frailty burden had numerically higher rates of serious gastrointestinal and cardiac disorders overall. However, fewer SAEs were noted in the semaglutide group compared with the placebo group across all frailty categories (Supplemental Table 9). Rates of treatment discontinuation resulting from SAEs were similar across frailty groups and were balanced between semaglutide and placebo.

DISCUSSION

In this prespecified, pooled patient-level, secondary analysis of the STEP-HFpEF and STEP-HFpEF DM trials, we observed a high burden of frailty among participants with obesity-related HFpEF. Participants with a higher frailty burden had a worse HF symptom burden and functional status, greater exercise intolerance, and greater HF disease severity. The reduction in body weight with semaglutide (vs placebo) did not differ across baseline frailty strata. However, despite comparable weight loss, semaglutide-mediated improvements in KCCQ-CSS and the hierarchical composite endpoint varied by baseline frailty burden, with the greatest improvements noted among participants in the most frail group. Furthermore, significant improvements in frailty burden were observed among semaglutide (vs placebo) treated participants by week 20, which persisted at week 52. Moreover, semaglutide consistently led to fewer SAEs than placebo across baseline frailty strata. Together, these findings suggest that semaglutide is safe, leads to larger HF-related treatment benefits among high-risk patients with obesity-related HFpEF and greater frailty burden, and has favorable effects on frailty itself in patients with obesity-related HFpEF, a vulnerable group with an especially high frailty burden (Central Illustration).

CENTRAL ILLUSTRATION **Frailty and Effects of Semaglutide in Obesity-Related HFpEF**



Pandey A, et al. JACC Heart Fail. 2025;■(■):102610.

In the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity) pooled cohort analysis, baseline frailty distribution showed that most participants (60.4%) had a high frailty burden as assessed by the deficit frailty index. Treatment with semaglutide (vs placebo) resulted in a significant weight loss benefit across all frailty categories and a greater improvement in KCCQ-CSS among the most frail participants. At 52-week follow-up, semaglutide (vs placebo) led to a significant improvement in frailty burden. HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score.

PREVALENCE AND OUTCOMES ACCORDING TO FRAILTY. The burden of frailty in participants in the STEP-HFpEF program was higher than in previous trials of HFpEF pharmacotherapies.[9-11] This difference is likely related to the differences in patient groups and the FI used across studies. STEP-HFpEF exclusively enrolled patients with obesity-related HFpEF, whereas the prevalence of obesity in other HFpEF trials was lower, ranging from 45% (DELIVER [Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure; NCT03619213] and EMPEROR-Preserved [EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; NCT03057951]) to 49% (PARAGON-HF [Efficacy and Safety of LCZ696 Compared to Valsartan,

on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction]; NCT01920711).[43] Obesity-related HFpEF is associated with a more severe disease phenotype with worse cardiac hemodynamics, more systemic inflammation, sarcopenic obesity with increased amounts of intermuscular and intramuscular fat, and microvascular and mitochondrial dysfunction in skeletal muscles leading to physical dysfunction and frailty.[3,19,20,44,45] Furthermore, although we used the Rockwood FI, a well-established and well-validated frailty assessment tool that has been extensively used in previous HF trials, there is variability in the components of FI used that may explain some of the differences in frailty burden across studies.[9-11,39,40,46,47] The variability in FI models used across different HF studies highlights the need for an informed and standardized approach to FI estimation in future to allow for better comparison across different groups.

We observed that baseline frailty modified the treatment effect of semaglutide in patients with HFpEF such that the most frail participants had the greatest semaglutide-mediated improvements in KCCQ-CSS and the hierarchical composite endpoint. Furthermore, the improvements in 6MWD with semaglutide were also numerically greater among patients with a higher frailty burden. The findings of greater semaglutide treatment benefits among the most frail patients with obesity-related HFpEF are consistent with earlier reports of treatment effect modification by frailty status for other HF therapies.[9,10,48,49] Specifically, in the DELIVER trial, dapagliflozin led to greater improvements in KCCQ among the most frail patients.[9] Similarly, in the PARAGON-HF trial, sacubitril-valsartan produced a greater reduction in the risk of HF hospitalizations among patients with a higher frailty burden.[10] These observations suggest that frailty-associated adverse functional and clinical outcomes in HFpEF are modifiable by using evidence-based therapies, including GLP-1RAs.

The greater treatment benefit of semaglutide in the most frail patients was noted despite a comparable semaglutide-mediated reduction in weight across the frailty strata. These observations suggest that the greater benefit of semaglutide in the most frail patients was not necessarily driven by greater weight loss but may reflect a more direct effect on shared pathobiology of obesity-related HFpEF and frailty consistent with previous analyses from the STEP-HFpEF program.[50-52] This finding was further confirmed by the significant improvement in the frailty burden during follow-up among patients with obesity-related HFpEF with semaglutide (vs placebo). Improvement in frailty burden with semaglutide is larger than that observed with other effective therapies for HFpEF, including SGLT2 inhibitors and exercise training.[11,48] The mechanisms underlying improvement in frailty burden with semaglutide are unclear but may be related to the favorable effects of GLP-1RAs on muscle quality. Specifically, frail patients with obesity-related HFpEF have a higher burden of sarcopenic obesity with increased skeletal muscle fat infiltration and associated muscle dysfunction that contributes to the greater impairment in physical function and worse QoL.[53] Insights from animal studies suggest that incretins may affect skeletal muscle directly and indirectly.[54] GLP-1RAs may improve skeletal muscle remodeling, enhance aerobic oxidation and mitochondrial biogenesis,[55] enhance protein synthesis,[56] and improve muscle insulin sensitivity through weight loss.[57] Evaluation of muscle composition by gold standard techniques (ie, magnetic resonance imaging) has shown that GLP-1RA-induced weight loss results in a reduction in muscle volume commensurate with body weight reduction and improved overall muscle composition and quality due to a decrease in intermuscular and intramuscular fat infiltration.[27]

Our study findings have important clinical implications. Despite the growing evidence demonstrating the cardiovascular benefits of GLP-1RAs among individuals with obesity with cardiovascular disease, including HFpEF,[16,17,58] using these therapies in frail patients with obesity has been a matter of debate. GLP-1RAs promote substantial weight loss; although most of the body weight reduction results from loss of adipose tissue, GLP-1RA use is associated with loss of up to ~6 kg of lean body mass, contributing up to 25% to 40% of the total weight loss.[25,53,59] Concerns have been raised that excess loss of lean body mass could worsen sarcopenia among older patients with HFpEF who have a high burden of sarcopenic obesity and may lead to higher frailty burden, including worse functional status, higher risk of falls, and adverse outcomes detrimental in older adults with frailty.[60-63] Our study findings alleviate these concerns and demonstrate greater HF-related benefits in most frail participants, alongside fewer SAEs with semaglutide (vs placebo) across the frailty strata. The greater treatment benefits of semaglutide among the most frail patients and its favorable effects on the frailty burden over time highlight its potential role as an effective treatment for these high-risk, vulnerable patients who have the most need for such therapies. These findings also highlight the critical importance of combating therapeutic

nihilism in the management of patients with obesity deemed to be frail with novel weight loss therapies.

It is noteworthy that the primary FI used in our analysis had greater representation of QoL and activities of daily living, which may be more affected by HFpEF severity, than some previous studies.[9,10] However, other studies have used similar FI models with greater representation of QoL factors in the frailty estimation.[11,40] The overlap in frailty and obesity-related HFpEF severity is biological and driven by shared mechanisms detailed earlier that contribute to reduced physiologic and exercise reserve across multiple organ systems.[7] The greater representation of QoL and functional traits in the deficit index-based FI allows for better capture of this shared pathophysiology and is consistent with previous approaches.[11,40,64] Furthermore, our study findings were consistent using an alternative modified FI that was less weighted for functional and QoL parameters, thereby highlighting the robustness of our observations, irrespective of the FI used.

STUDY LIMITATIONS. Several limitations of the present study are noteworthy. The findings from this prespecified secondary analysis of the STEP-HFpEF program are hypothesis generating, and corrections for multiple comparisons have not been made. Future studies are needed to confirm our observations. The STEP-HFpEF program was designed to assess HF-related symptoms, physical limitations, and exercise function and was not adequately powered for clinical events. Measures of body composition and adiposity depots were not available to characterize the actual change in body composition over the study duration. Frailty was assessed using an FI, and available variables were incorporated as described. This approach may overestimate frailty and does not incorporate important physical domains of frailty such as strength, exhaustion, slowness, and weakness. Moreover, the FI used in the present study contained relatively fewer comorbidities because of limited capture of these data, and greater representation of QoL parameters. Future studies are needed to assess frailty and physical dysfunction by using other objective tools such as the Fried frailty phenotype and Short Physical Performance Battery Score to confirm the robustness of our study findings with respect to greater treatment benefit of semaglutide in frail patients and improvement in frailty burden with semaglutide.

CONCLUSIONS

In the STEP-HFpEF program, the burden of frailty among adults with obesity-related HFpEF was high and was associated with a more severe disease phenotype, worse functional status, and poorer HF-related health status. Semaglutide led to greater improvements in KCCQ-CSS (reflecting fewer HF-related symptoms and physical limitations) and in the hierarchical composite endpoint in the most frail (vs less frail) patients. Semaglutide also significantly reduced the frailty burden over time in these high-risk patients and produced fewer SAEs than placebo regardless of frailty status. Together, these findings provide evidence supporting the use of semaglutide as an effective and safe therapy in the high-risk group of frail patients with obesity-related HFpEF.

DATA SHARING STATEMENT

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at https://www.novonordisk-trials.com. Data will be made available after research completion and approval of the product and product use in the European Union and the United States of America. Individual patient data will be shared in data sets in a deidentified/anonymized format.

ACKNOWLEDGMENTS The authors are indebted to the trial patients, the investigators, and the trial site staff. Administrative support was provided by Judah Lynch, MRes, of Apollo, OPEN Health Communications, funded by Novo Nordisk A/S.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This trial was funded by Novo Nordisk A/S, Søborg, Denmark. Administrative support for manuscript development was funded by Novo Nordisk A/S. Dr Pandey has received research support from the National Institutes of Health (NIH), American Heart Association, Ultromics, Roche, Applied Therapeutics, and Gilead Sciences; has received honoraria outside of the present study as an advisor or consultant for Tricog Health, Lilly USA, Rivus, Cytokinetics, Roche Diagnostics, Axon Therapies, Medtronic, Edwards Lifesciences, Science 37, Novo Nordisk, Bayer, Merck Sharp and Dohme, Semler Scientific, Sarfez Pharmaceuticals, and Emmi Solutions; has received nonfinancial support from Pfizer and Merck Sharp and Dohme; and is a consultant for Palomarin, with stock compensation. Dr Kitzman has received partial support from the Kermit Glenn Phillips II Chair in Cardiovascular Medicine and NIH grants U01AG076928, R01AG078153, R01AG045551, R01AG18915, P30AG021332, U24AG059624, and U01HL160272; and has received honoraria as a consultant for AstraZeneca, Bayer, Boehringer Ingelheim, Corvia Medical, Ketyo, Novartis, Novo Nordisk, Pfizer, and Rivus; has received grant funding from AstraZeneca, Bayer, Novartis, Novo Nordisk, Pfizer, and Rivus; and has held stock ownership in Gilead Sciences. Dr Borlaug has received research support from NIH grants R01HL128526, R01HL162828, and U01HL160226, the United States Department of Defense grant W81XWH2210245, and research grant funding from AstraZeneca, Axon Therapies, GlaxoSmithKline, Medtronic, Mesoblast, Novo Nordisk, Rivus, and Tenax Therapeutics; has served as a consultant for Actelion, Amgen, Aria, Axon Therapies,

BD, Boehringer Ingelheim, Cytokinetics, Edwards Lifesciences, Eli Lilly, Imbria, Janssen, Merck Sharp and Dohme, NGM, Novo Nordisk, NXT, and VADovations; and has been named inventor (U.S. patent No. 10,307,179) for the tools and approach for a minimally invasive pericardial modification procedure to treat heart failure. Dr Butler has served as a consultant to Abbott, American Regent, Amgen, Applied Therapeutics, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, CardioCell, Cardior, CSL Behring, CVRx, Cytokinetics, Daxor, Edwards Lifesciences, Element Science, Faraday, Foundry, G3P, Imbria, Impulse Dynamics, Innolife, Inventiva, Ionis, Levator, Lexicon, Lilly, LivaNova, Janssen, Medtronic, Merck Sharp and Dohme, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, PharmaIN, Prolaio, Pulnovo, Regeneron, Renibus, Roche, Salamandra, Salubris, Sanofi, scPharmaceuticals, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll. Dr Davies has acted as consultant, advisory board member, and speaker for Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; has served as an advisory board member for AstraZeneca, Carmot/Roche, Medtronic, Pfizer, and Zealand Pharma; has served as a speaker for Amgen and AstraZeneca; and has received grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk, and Sanofi-Aventis. Dr Shah has received research grants from AstraZeneca, Corvia, and Pfizer; and has received consulting fees from Abbott, Alleviant, Amgen, Aria CV, AstraZeneca, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Imara, Impulse Dynamics, Intellia, Ionis, Lilly, Merck Sharp and Dohme, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, ReCor, Regeneron, Rivus, Sardocor, Shifamed, Tenax, Tenaya, and Ultromics. Dr Verma has received speaker honoraria and/or consulting fees from Abbott, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Medical, Surgical Knowledge Translation Research Group, Eli Lilly, HLS Therapeutics, Janssen, Merck Sharp and Dohme, Novartis, Novo Nordisk, Pfizer, PhaseBio, and TIMI. Dr Rönnbäck is an employee and shareholder of Novo Nordisk. Dr Domdey is an employee and shareholder of Novo Nordisk. Ms Liisberg is an employee and shareholder of Novo Nordisk. Dr Shou has received speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Novo Nordisk. Dr Perna has received honoraria from Novo Nordisk. Dr Ahmed has served as a consultant or on an advisory board for AstraZeneca, Abbott, Medtronic, Novo Nordisk, Pfizer, and Pharmacosmos. Dr Fu has received honoraria for consultancy from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Novo Nordisk, and Otsuka; and has served as an advisor to US2.ai. Dr Petrie has received support from the British Heart Foundation Centre of Research Excellence Award (RE/13/5/30177 and RE/18/6/34217+); has received research funding from Boehringer Ingelheim, Roche, SQ Innovations, AstraZeneca, Novartis, Novo Nordisk, Medtronic, Boston Scientific, and Pharmacosmos; and has served as a consultant and on trial committees for Abbott, Akero, Applied Therapeutics, Amgen, AnaCardio, Biosensors, Boehringer Ingelheim, Corteria, Novartis, AstraZeneca, Novo Nordisk, AbbVie, Bayer, Horizon Therapeutics, Foundry, Takeda, Cardiorentis, Pharmacosmos, Siemens, Eli Lilly, Vifor, New Amsterdam, Moderna, Teikoku, LIB Therapeutics, 3R Lifesciences, Reprieve, FIRE 1, Corvia, and Regeneron. Dr Kosiborod has served as a consultant or on an advisory board for 35Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon Pharmaceuticals, Merck Sharp and Dohme (Diabetes and Cardiovascular), Novo Nordisk, Pfizer, Pharmacosmos, scPharmaceuticals, Structure Therapeutics, Vifor Pharma, and Youngene Therapeutics; has received research grants from AstraZeneca and Boehringer Ingelheim; has held stock in Artera Health and Saghmos Therapeutics; has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk; and has received other research support from AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Mikhail N. Kosiborod, Department of Cardiovascular Disease, Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri 64111, USA. E-mail: mkosiborod@saint-lukes.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with obesity-related HFpEF, semaglutide was associated with similar reduction in body weight and greater improvements in HF-related symptoms and physical limitations among those patients with the highest frailty burden.

TRANSLATIONAL OUTLOOK: Future studies are needed to determine the effects of semaglutide on prospectively assessed measures of frailty and physical dysfunction by using objective tools such as the Fried frailty phenotype and the Short Physical Performance Battery Score.

REFERENCES

1. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC scientific statement. *J Am Coll Cardiol*. 2023;81:1810-1834. https://doi.org/10.1016/j.jacc.2023.01.049

2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251-259. https://doi.org/10.1056/NEJMoa052256

3. Pandey A, Shah SJ, Butler J, et al. Exercise intolerance in older adults with heart failure with preserved ejection fraction: JACC state-of-the-art review. *J Am Coll Cardiol*. 2021;78:1166-1187. https://doi.org/10.1016/j.jacc.2021.07.014

4. Gorodeski EZ, Goyal P, Hummel SL, et al. Domain management approach to heart failure in the geriatric patient: present and future. *J Am Coll Cardiol*. 2018;71:1921-1936. https://doi.org/10.1016/j.jacc.2018.02.059

5. Upadhya B, Pisana B, Kitzman D. Evolution of geriatric syndrome: pathophysiology and treatment of heart failure with preserved ejection fraction. *J Am Geriatr Soc*. 2017;65:2431-2440.

6. Forman DE, Kuchel GA, Newman JC, et al. Impact of geroscience on therapeutic strategies for older adults with cardiovascular disease: JACC scientific statement. *J Am Coll Cardiol*. 2023;82:631-647. https://doi.org/10.1016/j.jacc.2023.05.038

7. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure: mechanisms, prevalence, prognosis, assessment, and management. *JACC Heart Fail*. 2019;7:1001-1011. https://doi.org/10.1016/j.jchf.2019.10.005

8. Talha KM, Pandey A, Fudim M, Butler J, Anker SD, Khan MS. Frailty and heart failure: state-of-the-art review. *J Cachexia Sarcopenia Muscle*. 2023;14:1959-1972. https://doi.org/10.1002/jcsm.13306

9. Butt JH, Jhund PS, Belohlavek J, et al. Efficacy and safety of dapagliflozin according to frailty in patients with heart failure: a prespecified analysis of the DELIVER trial. *Circulation*. 2022;146:1210–1224. https://doi.org/10.1161/CIRCULATIONAHA.122.061754

10. Butt JH, Dewan P, Jhund PS, et al. Sacubitril/valsartan and frailty in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2022;80:1130–1143. https://doi.org/10.1016/j.jacc.2022.06.037

11. Coats AJS, Butler J, Tsutsui H, et al. Efficacy of empagliflozin in heart failure with preserved ejection fraction according to frailty status in EMPEROR-Preserved. *J Cachexia Sarcopenia Muscle*. 2024;15:412–424. https://doi.org/10.1002/jcsm.13393

12. Vitale C, Jankowska E, Hill L, et al. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail*. 2019;21:1299–1305. https://doi.org/10.1002/ejhf.1611

13. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018;72:351–366. https://doi.org/10.1016/j.jacc.2018.04.070

14. Veenis JF, Brunner-La Rocca HP, Linssen GC, et al. Age differences in contemporary treatment of patients with chronic heart failure and reduced ejection fraction. *Eur J Prev Cardiol*. 2019;26:1399–1407. https://doi.org/10.1177/2047487319835042

15. Khan MS, Segar MW, Usman MS, et al. Frailty, guideline-directed medical therapy, and outcomes in HFrEF: from the GUIDE-IT trial. *JACC Heart Failure*. 2022;10:266–275. https://doi.org/10.1016/j.jchf.2021.12.004

16. Kosiborod MN, Petrie MC, Borlaug BA, et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N Engl J Med*. 2024;390:1394–1407. https://doi.org/10.1056/NEJMoa2313917

17. Kosiborod MN, Abildstrom SZ, Borlaug BA, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2023;389:1069–1084. https://doi.org/10.1056/NEJMoa2306963

18. Butler J, Shah SJ, Petrie MC, et al. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. *Lancet*. 2024;403:1635–1648. https://doi.org/10.1016/S0140-6736(24)00469-0

19. 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;118:3434–3450. https://doi.org/10.1093/cvr/cvac120

20. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation*. 2017;136:6–19. https://doi.org/10.1161/CIRCULATIONAHA.116.026807

21. Morgen CS, Haase CL, Oral TK, Schnecke V, Varbo A, Borlaug BA. Obesity, cardiorenal comorbidities, and risk of hospitalization in patients with heart failure with preserved ejection fraction. *Mayo Clin Proc*. 2023;98:1458–1468. https://doi.org/10.1016/j.mayocp.2023.07.008

22. Kitzman DW, Nicklas BJ. Pivotal role of excess intra-abdominal adipose in the pathogenesis of metabolic/obese HFpEF. *JACC Heart Fail*. 2018;6:1008–1010. https://doi.org/10.1016/j.jchf.2018.08.007

23. 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;4:324–331. https://doi.org/10.1161/CIRCHEARTFAILURE.110.959890

24. Houston DK, Miller ME, Kitzman DW, et al. Long-term effects of randomization to a weight loss intervention in older adults: a pilot study. *J Nutr Gerontol Geriatr*. 2019;38:83–99. https://doi.org/10.1080/21551197.2019.1572570

25. 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. https://doi.org/10.1056/NEJMoa2032183

26. Jensen SBK, Sorensen V, Sandsdal RM, et al. Bone health after exercise alone, GLP-1 receptor agonist treatment, or combination treatment: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2024;7:e2416775. https://doi.org/10.1001/jamanetworkopen.2024.16775

27. Pandey A, Patel KV, Segar MW, et al. Effect of liraglutide on thigh muscle fat and muscle composition in adults with overweight or obesity: results from a randomized clinical trial. *J Cachexia Sarcopenia Muscle*. 2024;15:1072–1083. https://doi.org/10.1002/jcsm.13445

28. Kitzman DW, Haykowsky MJ, Tomczak CR. Making the case for skeletal muscle myopathy and its contribution to exercise intolerance in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2017;10:e004281. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004281

29. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Cardiol*. 2014;113:1211–1216. https://doi.org/10.1016/j.amjcard.2013.12.031

30. Scandalis L, Kitzman DW, Nicklas BJ, et al. Skeletal muscle mitochondrial respiration and exercise intolerance in patients with heart failure with preserved ejection fraction. *JAMA Cardiol*. 2023;8:575–584. https://doi.org/10.1001/jamacardio.2023.0957

31. Kosiborod MN, Abildstrom 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;11:1000–1010. https://doi.org/10.1016/j.jchf.2023.05.010

32. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62:722–727. https://doi.org/10.1093/gerona/62.7.722

33. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323–336. https://doi.org/10.1100/tsw.2001.58

34. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24. https://doi.org/10.1186/1471-2318-8-24

35. Theou O, Brothers TD, Mitnitski A, Rockwood K. Operationalization of frailty using eight commonly used scales and comparison of their ability to predict all-cause mortality. *J Am Geriatr Soc*. 2013;61:1537–1551. https://doi.org/10.1111/jgs.12420

36. Blodgett JM, Theou O, Howlett SE, Rockwood K. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. *Geroscience*. 2017;39:447–455. https://doi.org/10.1007/s11357-017-9993-7

37. Blodgett J, Theou O, Kirkland S, Andreou P, Rockwood K. Frailty in NHANES: comparing the frailty index and phenotype. *Arch Gerontol Geriatr*. 2015;60:464–470. https://doi.org/10.1016/j.archger.2015.01.016

38. Ambagtsheer RC, Beilby J, Dabravolskaj J, Abbasi M, Archibald MM, Dent E. Application of an electronic frailty index in Australian primary care: data quality and feasibility assessment. *Aging Clin Exp Res*. 2019;31:653–660. https://doi.org/10.1007/s40520-018-1023-9

39. Evans JK, Usoh CO, Simpson FR, et al. Long-term impact of a 10-year intensive lifestyle intervention on a deficit accumulation frailty index: Action for Health in Diabetes trial. *J Gerontol A Biol Sci Med Sci*. 2023;78:2119–2126. https://doi.org/10.1093/gerona/glad088

40. Sanders NA, Supiano MA, Lewis EF, et al. The frailty syndrome and outcomes in the TOPCAT trial. *Eur J Heart Fail*. 2018;20:1570–1577. https://doi.org/10.1002/ejhf.1308

41. Sapp DG, Cormier BM, Rockwood K, Howlett SE, Heinze SS. The frailty index based on laboratory test data as a tool to investigate the impact of frailty on health outcomes: a systematic review and meta-analysis. *Age Ageing*. 2023;52:afac309. https://doi.org/10.1093/ageing/afac309

42. Theou O, Haviva C, Wallace L, Searle SD, Rockwood K. How to construct a frailty index from an existing dataset in 10 steps. *Age Ageing*. 2023;52:afad221. https://doi.org/10.1093/ageing/afad221

43. Sattar N, Butler J, Lee MMY, et al. Body mass index and cardiorenal outcomes in the EMPEROR-Preserved trial: principal findings and meta-analysis with the DELIVER trial. *Eur J Heart Fail*. 2024;26:900–909. https://doi.org/10.1002/ejhf.3221

44. Borlaug BA, Kitzman DW, Davies MJ, et al. Semaglutide in HFpEF across obesity class and by body weight reduction: a prespecified analysis of the STEP-HFpEF trial. *Nat Med*. 2023;29:2358–2365. https://doi.org/10.1038/s41591-023-02526-x

45. Verma S, Borlaug BA, Butler J, et al. A big STEP for treatment of heart failure with preserved ejection fraction. *Cell Metab*. 2023;35:1681–1687. https://doi.org/10.1016/j.cmet.2023.08.003

46. Chen L, You S, Ee N, et al. Impact of frailty on antihypertensive treatment in older adults. *Hypertension*. 2025;82:509–519. https://doi.org/10.1161/HYPERTENSIONAHA.124.24214

47. Dewan P, Jackson A, Jhund PS, et al. The prevalence and importance of frailty in heart failure with reduced ejection fraction - an analysis of PARADIGM-HF and ATMOSPHERE. *Eur J Heart Fail*. 2020;22:2123–2133. https://doi.org/10.1002/ejhf.1832

48. Pandey A, Kitzman DW, Nelson MB, et al. Frailty and effects of a multidomain physical rehabilitation intervention among older patients hospitalized for acute heart failure: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2023;8:167–176. https://doi.org/10.1001/jamacardio.2022.4903

49. Pandey A, Segar MW, Singh S, et al. Frailty status modifies the efficacy of exercise training among patients with chronic heart failure and reduced ejection fraction: an analysis from the HF-ACTION trial. *Circulation*. 2022;146:80–90. https://doi.org/10.1161/CIRCULATIONAHA.122.059983

50. Petrie MC, Borlaug BA, Butler J, et al. Semaglutide and NT-proBNP in obesity-related HFpEF: insights from the STEP-HFpEF program. *J Am Coll Cardiol*. 2024;84:27–40. https://doi.org/10.1016/j.jacc.2024.04.022

51. Schou M, Petrie MC, Borlaug BA, et al. Semaglutide and NYHA functional class in obesity-related heart failure with preserved ejection fraction: the STEP-HFpEF program. *J Am Coll Cardiol*. 2024;84:247–257. https://doi.org/10.1016/j.jacc.2024.04.038

52. Shah SJ, Sharma K, Borlaug BA, et al. Semaglutide and diuretic use in obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF-DM trials. *Eur Heart J*. 2024;45:3254–3269. https://doi.org/10.1093/eurheartj/ehae322

53. Neeland IJ, Linge J, Birkenfeld AL. Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. *Diabetes Obes Metab*. 2024;26:16–27. https://doi.org/10.1111/dom.15728

54. Muller TD, Finan B, Bloom SR, et al. Glucagon-like peptide 1 (GLP-1). *Mol Metab*. 2019;30:72–130. https://doi.org/10.1016/j.molmet.2019.09.010

55. Wu L, Zhou M, Li T, et al. GLP-1 regulates exercise endurance and skeletal muscle remodeling via GLP-1R/AMPK pathway. *Biochim Biophys Acta Mol Cell Res*. 2022;1869:119300. https://doi.org/10.1016/j.bbamcr.2022.119300

56. Abdulla H, Phillips BE, Wilkinson DJ, et al. Glucagon-like peptide 1 infusions overcome anabolic resistance to feeding in older human muscle. *Aging Cell*. 2020;19:e13202. https://doi.org/10.1111/acel.13202

57. Tian X, Gao Y, Kong M, et al. GLP-1 receptor agonist protects palmitate-induced insulin resistance in skeletal muscle cells by up-regulating sestrin2 to promote autophagy. *Sci Rep*. 2023;13:9446. https://doi.org/10.1038/s41598-023-36602-6

58. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389:2221–2232. https://doi.org/10.1056/NEJMoa2307563

59. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. *N Engl J Med*. 2022;387:205–216. https://doi.org/10.1056/NEJMoa2206038

60. Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A review of the effects of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors on lean body mass in humans. *Endocrinol Metab (Seoul)*. 2019;34:247–262. https://doi.org/10.3803/EnM.2019.34.3.247

61. Kim JE, O'Connor LE, Sands LP, Slebodnik MB, Campbell WW. Effects of dietary protein intake on body composition changes after weight loss in older adults: a systematic review and meta-analysis. *Nutr Rev*. 2016;74:210–224. https://doi.org/10.1093/nutrit/nuv065

62. McCrimmon RJ, Catarig AM, Frias JP, et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. *Diabetologia*. 2020;63:473–485. https://doi.org/10.1007/s00125-019-05065-8

63. Locatelli JC, Costa JG, Haynes A, et al. Incretin-based weight loss pharmacotherapy: can resistance exercise optimize changes in body composition? *Diabetes Care*. 2024;47:1718–1730. https://doi.org/10.2337/dci23-0100

64. Segar MW, Keshvani N, Singh S, et al. Frailty status modifies the efficacy of ICD therapy for primary prevention among patients with HF. *JACC Heart Fail*. 2024;12:757–767. https://doi.org/10.1016/j.jchf.2023.06.009

KEY WORDS **frailty, glucagon-like peptide-1 receptor agonist, heart failure with preserved ejection fraction, obesity, weight loss**

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