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Inflammation in Obesity-Related HFpEF

The STEP-HFpEF Program

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ABSTRACT

BACKGROUND Inflammation is thought to be an important mechanism for the development and progression of obesity-related heart failure with preserved ejection fraction (HFpEF). In the STEP-HFpEF Program, once-weekly 2.4 mg semaglutide improved heart failure–related symptoms, physical limitations, and exercise function, reduced the levels of C-reactive protein (CRP), a biomarker of inflammation, and reduced body weight in participants with obesity-related HFpEF. However, neither the prevalence nor the clinical characteristics of patients who have various magnitudes of inflammation in the context of obesity-related HFpEF have been well described. Furthermore, whether the beneficial effects of semaglutide on the various HF efficacy endpoints in the STEP-HFpEF Program are modified by the baseline levels of inflammation has not been fully established. Finally, the relationship between weight reduction and changes in CRP across the STEP-HFpEF Program have not been fully defined.

OBJECTIVES This study sought to: 1) evaluate baseline characteristics and clinical features of patients with obesity-related HFpEF that have various levels of inflammation in the STEP-HFpEF Program; 2) determine if the effects of weekly semaglutide 2.4 mg vs placebo across all key outcomes are influenced by baseline levels of inflammation assessed by CRP levels; and 3) determine the relationship between change in CRP and weight loss in the STEP-HFpEF Program.

METHODS This was a secondary analysis of pooled data from 2 international, double-blind, placebo-controlled, randomized trials (STEP-HFpEF and STEP-HFpEF DM). The outcomes were change in the dual primary endpoints (health status [measured by the Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score (KCCQ-CSS)] and body weight) from baseline to 52 weeks according to baseline CRP levels. Additional efficacy endpoints included change in 6-minute walk distance (6MWD), a hierarchical composite endpoint that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6MWD, and levels of CRP in semaglutide- vs placebo-treated patients. Patients were stratified into 3 categories based on baseline CRP levels (<2, ≥ 2 to <10, and ≥ 10 mg/L).

RESULTS In total, 1,145 patients were randomized, of which 71% of patients had evidence of inflammation (CRP ≥ 2 mg/L). At baseline, those with higher levels of inflammation were younger, were more likely to be female, and had higher body mass index, worse health status (KCCQ-CSS), and shorter 6MWD. Semaglutide vs placebo led to reductions in HF-related symptoms and physical limitations as well as body weight, and to improvements in 6MWD and the hierarchical composite endpoint that were consistent across baseline CRP categories (all P interaction nonsignificant). Semaglutide also reduced CRP to a greater extent than placebo regardless of baseline CRP levels (P interaction $= 0.32$). Change in CRP from baseline to 52 weeks was similar regardless of the magnitude of weight loss (P interaction $= 0.91$).

CONCLUSIONS Inflammation is highly prevalent in obesity-related HFpEF. Semaglutide consistently improved HF-related symptoms, physical limitations, and exercise function, and reduced body weight across the categories of baseline CRP. Semaglutide also reduced inflammation, regardless of either baseline CRP or magnitude of weight loss during the trials. (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity [STEP-HFpEF; NCT04788511]; Research Study to Look at How Well Semaglutide Works in People Living With Heart Failure, Obesity and Type 2 Diabetes [STEP HFpEF DM; NCT04916470]) (JACC. 2024;84:1646-1662) © 2024 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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Inflammation is a crucial factor in the development of heart failure with preserved ejection fraction (HFpEF).[1-5] Studies suggest that visceral adiposity is the primary trigger of inflammation in HFpEF.[3,6,7] As such, inflammation is often regarded to be a pathophysiologic hallmark of obesity-related HFpEF, the most prevalent clinical phenotype of this disease condition.[8] Visceral adipose tissue serves as a reservoir for the aberrant production of adipocytokines (eg, interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-α),[9,10] which in turn incite local and systemic immune dysregulation, widespread inflammation, and resultant microvascular and mitochondrial dysfunction—key factors that promote both cardiac and noncardiac manifestations of the HFpEF syndrome.[11-14] Indeed, markers of inflammation—such as IL-6 and C-reactive protein (CRP)—are associated with worse symptoms, quality of life, exercise capacity, and prognosis in HFpEF.[15-21] Moreover, pharmacologic inhibition of inflammation (with canakinumab) has been shown to reduce heart failure (HF) events in patients with previous myocardial infarction and elevated CRP (with a greater risk reduction in those with larger reductions in IL-6 and CRP).[22]

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In the STEP-HFpEF (Research Study to Investigate How Well Semaglutide Works in People Living With Heart Failure and Obesity; NCT04788511) 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) trials (collectively, the STEP-HFpEF Program), once-weekly 2.4 mg semaglutide improved HF-related symptoms, physical limitations, and exercise function, and reduced body weight and biomarkers of inflammation in individuals with obesity-related HFpEF.[23-25] Beyond the key findings of the STEP-HFpEF Program, a number of questions remain regarding the intersection of obesity-related HFpEF and inflammation. First, despite our understanding of the adiposity-inflammation axis in the pathobiology and clinical course of HFpEF, most evidence in this regard has been drawn from studies not specifically evaluating patients with obesity-related HFpEF.[26-28] Consequently, there is a paucity of data on the prevalence of various levels of inflammation and their relationship with participants' baseline characteristics in the context of obesity-related HFpEF. Addressing this question is of clinical importance, because of the overlap between the obesity and proinflammatory phenotypes of HFpEF as well as recent efforts to develop antiinflammatory therapies to reduce the risk of worsening HF in this patient group.

The second knowledge gap relates to whether the efficacy of semaglutide on all key trial outcomes in the STEP-HFpEF Program was influenced by baseline levels of CRP. Although the mechanisms of benefit for semaglutide in HFpEF remain unclear, it has been suggested that reduction in inflammation may be one important pathway that mediates it. Before the STEP-HFpEF Program, we published data to support a large effect of semaglutide to lower CRP levels in people with overweight or obesity but without HF.[29] Indeed, this efficacy on CRP reduction was confirmed in the STEP-HFpEF and STEP-HFpEF DM trials individually and in the pooled analyses of the 2 trials.[23-25] Although we have shown a consistent benefit of semaglutide on Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score (KCCQ-CSS) by

ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

BMI = body mass index

GLP-1 = glucagon-like peptide 1

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

IL = interleukin

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

LVEF = left ventricular ejection fraction

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

TNF = tumor necrosis factor

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categories of CRP (≥2 mg/L) in the pooled analyses from the STEP-HFpEF Program,[25] we have not previously examined other key trial outcomes (eg, 6-minute walk distance [6MWD] and hierarchical composite endpoint) by baseline CRP. In addition, we have not evaluated this relationship using alternative CRP clinical cutoff points or using CRP as a continuous variable.

The third unanswered question is whether the degree of semaglutide-mediated reduction in inflammation is related to the magnitude of weight loss in obesity-related HFpEF. In a previous analysis, done solely with the data from STEP-HFpEF trial, Borlaug et al reported that a greater reduction in body weight in the semaglutide group was associated with larger decrease in the levels of CRP.[30] However, this analysis was done exclusively in people treated with semaglutide and did not include participants in the placebo group. Furthermore, it was derived from only one of the trials (STEP-HFpEF) and did not include the results from the STEP-HFpEF DM trial participants. Evaluating whether there is heterogeneity in the efficacy of semaglutide vs placebo on CRP when stratified by the magnitude of weight loss during the trial remains an open and important question, and therefore was another objective of the present study.

Accordingly, this prespecified, pooled, patient-level analysis aimed to evaluate: 1) baseline clinical characteristics according to categories of inflammation (as assessed according to CRP); 2) the efficacy of semaglutide vs placebo on the key trial endpoints according to CRP levels, examined both categorically and continuously, as well as the safety of semaglutide across CRP categories; and 3) the effect of semaglutide on inflammation (as assessed according to CRP) according to the baseline levels of CRP and the magnitude of weight loss during the trial.

METHODS

STUDY AND PROGRAM DESIGN. The key elements of analysis were prespecified in the academic statistical analysis plan of the pooled trials which was finalized before the database lock of STEP-HFpEF DM trial. The STEP-HFpEF Program consisted of 2 trials: STEP-HFpEF (for patients with obesity-related HFpEF without diabetes) and STEP-HFpEF DM (for patients with obesity-related HFpEF and type 2 diabetes). The design and primary outcomes of the individual trials, as well as the overall Program, were previously published.[23-25] Patients were recruited from 129 sites across 18 countries in Asia, Europe, North America, and South America. The Steering Committee, comprising academic members and representatives from the sponsor (Novo Nordisk), designed both trials and oversaw academic publications. A global expert panel provided input on academic, medical, and operational aspects in each country. Each study site obtained Institutional Review Board or ethics committee approval, and all patients provided informed consent. Novo Nordisk sponsored the Program.

STUDY PROGRAM PATIENTS AND RANDOMIZATION. Eligible patients had left ventricular ejection fraction (LVEF) ≥45%, body mass index (BMI) ≥30 kg/m^2, NYHA functional class II to IV, KCCQ-CSS <90 points, 6MWD ≥100 m, and at least 1 of the following: elevated filling pressures (invasively measured), elevated natriuretic peptide levels plus structural echocardiographic abnormalities, and a history of HF hospitalization in the preceding 12 months plus ongoing diuretic treatment and/or echocardiographic abnormalities. Key exclusion criteria included previous or planned bariatric surgery, significant recent weight change, and high systolic blood pressure. Patients with uncontrolled diabetic retinopathy or maculopathy were excluded from STEP-HFpEF DM. Eligible patients were randomized 1:1 to receive once-weekly subcutaneous semaglutide at a target dose of 2.4 mg or matching placebo in addition to standard of care for 52 weeks, after which patients had safety follow-up for 5 weeks. Randomization was stratified by BMI (<35 kg/m^2 vs ≥35 kg/m^2). Semaglutide or placebo were added to background glucose-lowering medications for patients with type 2 diabetes in STEP-HFpEF DM, with treatment adjustments at the investigator's discretion in conjunction with guidance supplied by the trial team.

EFFICACY AND SAFETY OUTCOMES. The main objective of this analysis was to assess the effects of once-weekly 2.4 mg semaglutide vs placebo on the dual primary and confirmatory secondary endpoints in the STEP-HFpEF Program by baseline CRP categories (<2, ≥2 to <10, and ≥10 mg/L). The <2 vs ≥2 mg/L threshold were prespecified in the academic statistical analysis plan, and used as eligibility criteria in the CANTOS (Cardiovascular Risk Reduction Study [Reduction in Recurrent Major CV Disease Events]; NCT01327846)[31] and HERMES (A Research Study to Look at How Ziltivekimab Works Compared to Placebo in People With Heart Failure and Inflammation; NCT05636176) trials. Instead of restricting our analysis to just values ≥2 and <2, we opted to explore 3 distinct groups with the ≥10 mg/L subgroup added post hoc). This approach helps to mitigate potential confounding factors from significantly elevated values, which could suggest ongoing

inflammatory conditions that may distort the interpretation of CRP as an acute-phase reactant. Nonetheless, we also performed the analyses using the data categorized by the prespecified cutoff of <2 vs ≥2 mg/L.

The dual primary endpoints were changes in KCCQ-CSS and percentage change in body weight from baseline to week 52. Confirmatory secondary endpoints included changes in 6MWD, a hierarchical composite endpoint (which included all-cause death from baseline to week 57; number and timing of HF events [adjudicated hospitalizations for HF or urgent visits requiring intravenous therapy, baseline to week 57]; differences ≥15, ≥10, and ≥5 points in the KCCQ-CSS change from baseline to week 52; a difference ≥30 m in the 6MWD change from baseline to week 52); and changes in CRP levels from baseline to week 52. Changes in systolic blood pressure (a supportive secondary endpoint) and levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (an exploratory endpoint) from baseline to week 52 by CRP categories also were evaluated in the present analysis. We also assessed the effects of semaglutide vs placebo on CRP levels according to different categories of weight loss (<5%, 5% to <10%, 10% to <15%, 15% to <20%, and ≥20%) achieved during the trial. Safety endpoints included serious adverse events (SAEs), SAEs leading to discontinuation of study medication, and deaths, evaluated within the CRP subgroups.

STATISTICAL ANALYSIS. Baseline characteristics were evaluated according to baseline CRP categories. Continuous variables used the Jonckheere-Terpstra trend test and binary variables used a Cochran-Armitage trend test. The effects of semaglutide vs placebo on all efficacy endpoints were examined with the full analysis set (all randomized patients according to the intention-to-treat principle, while in trial regardless of treatment discontinuation). The effects of semaglutide (vs placebo) on KCCQ-CSS by CRP were also assessed across key subgroups including age (≤69 y vs >69 y), BMI (<35 kg/m^2 vs ≥35 kg/m^2), and LVEF (<57% vs ≥57%); this was done post hoc. Analyses of the efficacy endpoints, including systolic blood pressure and NT-proBNP, were performed with analysis of covariance models, adjusted for the baseline value of the relevant continuous outcome variable, with treatment, trial, and BMI (<35 kg/m^2 vs ≥35 kg/m^2) as fixed factors using 1,000 imputations; the subgroup analyses also included an interaction term between treatment and relevant subgroup. Estimates were then 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 reasons were multiple imputed from retrieved patients in the same randomized treatment arm. For other endpoints, missing observations at week 52 were multiple imputed irrespective of death or prior HF events using the same imputation method. Interaction *P* values were derived from an *F*-test of equality between the treatment differences across the subgroups. To further explore the relationship between baseline CRP and the dual primary endpoints (changes in KCCQ-CSS and body weight) at week 52, we used mixed models incorporating CRP as a continuous variable with study and BMI stratification as fixed factors and a quadratic spline by randomized treatment adjusted for corresponding endpoint at baseline, using all nonmissing values for the in-trial period. Interaction *P* values between CRP 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 CRP.

Analyses of the hierarchical composite endpoint (win ratio) were performed stratified by CRP categories, based on direct comparisons of each patient randomized to semaglutide vs each patient randomized to placebo. For each of the patient 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 by CRP categories (with the use of 1,000 imputations as described above). Test for equality for the win ratio was performed with the use of Cochran's *Q*-test. For KCCQ-CSS, we also constructed the cumulative response curves by CRP that plotted observed changes in KCCQ-CSS scores between baseline and week 52 against the cumulative proportions of patients in the semaglutide and placebo groups experiencing those changes; this was done post hoc. Logistic regression models were then used to calculate the ORs and corresponding 95% CIs for semaglutide effects on the likelihood of ≥5-point deterioration, as well as ≥5-, ≥10-, ≥15-, and ≥20-point improvements in KCCQ-CSS, with 1,000 multiple imputations to account for missing data, adjusted for the baseline KCCQ-CSS, trial, and BMI group (the stratification factor) as factors, with the subgroup and an interaction term between treatment and subgroup was also included for the subgroup analysis. An

TABLE 1 Baseline Characteristics of the STEP-HFpEF Program,[a] Stratified by Baseline CRP Category

	Baseline CRP, mg/L			
	<2 (n = 332)	≥2 to <10 (n = 591)	≥10 (n = 218)	*P* Value
Sex				<0.0001
Female	135 (41)	299 (51)	134 (61)	
Male	197 (59)	292 (49)	84 (39)	
Age, y	71 (65-76)	69 (63-75)	67 (59-73)	<0.0001
Race[b]				0.1306
White	297 (89)	539 (91)	186 (85)	
Asian	26 (8)	31 (5)	19 (9)	
Black/African American	9 (3)	19 (3)	11 (5)	
Other	0 (0)	2 (<1)	2 (1)	
Region				0.2013
Europe	237 (71)	396 (66)	136 (62)	
North America	52 (16)	100 (17)	39 (18)	
Other	43 (13)	98 (17)	43 (20)	
Ethnicity[b]				0.0561
Hispanic or Latino	27 (8)	56 (9)	29 (13)	
Not Hispanic or Latino	305 (92)	535 (91)	189 (87)	
Body weight, kg	100 (90-114)	105 (92-121)	107 (95-125)	<0.0001
BMI, kg/m^2	35 (32-38)	37 (34-42)	40 (35-45)	<0.0001
BMI stratification				<0.0001
30 to <35 kg/m^2	169 (51)	186 (31)	45 (21)	
≥35 kg/m^2	163 (49)	405 (69)	173 (79)	
Waist circumference, cm	117 (109-126)	120 (112-130)	124 (113-134)	<0.0001
HbA_{1c},[c] %	6.7 (6.2-7.4)	6.8 (6.2-7.5)	7.0 (6.3-8.0)	0.0225
Systolic blood pressure, mm Hg	133 (122-142)	135 (123-145)	132 (124-144)	0.6222
Diastolic blood pressure, mm Hg	78 (71-85)	78 (71-84)	78 (70-84)	0.6540
NT-proBNP, pg/mL	478 (249-993)	453 (227-1,016)	486 (240-1,142)	0.8121
CRP, mg/L	1.1 (0.7-1.6)	4.2 (2.8-6.3)	15.0 (12.1-22.2)	NA
LVEF,[d] %	56 (50-61)	57 (50-60)	57 (50-60)	0.4497
LVEF stratification				0.3119
≥45% to <50%[d]	58 (17)	98 (17)	35 (16)	
≥50% to <60%	148 (45)	228 (39)	94 (43)	
≥60%	126 (38)	265 (45)	89 (41)	
KCCQ-CSS, points	61 (45-74)	59 (44-72)	56 (36-69)	0.0001
6MWD, m	318 (237-382)	295 (230-366)	262 (192-358)	<0.0001
HF hospitalization within previous 1 y	53 (16)	97 (16)	43 (20)	0.2860
Comorbidities at screening				
Atrial fibrillation	149 (45)	290 (49)	77 (35)	0.0767
Type 2 diabetes[e]	193 (58)	300 (51)	121 (56)	0.3572
Hypertension	273 (82)	505 (85)	178 (82)	0.9519
Coronary heart disease	147 (44)	234 (40)	69 (32)	0.0036
Obstructive sleep apnea	35 (11)	63 (11)	21 (10)	0.7661

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additional analysis using spline regression was performed with a quadratic spline examining the continuous relationship between CRP ratio (baseline to week 52) and changes in KCCQ-CSS, 6MWD, and NT-proBNP (semaglutide vs placebo, baseline to week 52) with the use of observed values.

Safety endpoints by CRP were analyzed using the safety analysis set (all randomized patients exposed to at least 1 dose of randomized treatment) and either on-treatment or in-trial data sets depending on the type of safety event. No adjustment for multiple testing was performed. A 2-sided *P* value of <0.05 was considered to be significant. Results are presented as estimated changes from baseline to week 52 for continuous endpoints, a win ratio (for the hierarchical composite endpoint), or an OR (for responder analyses), with a 95% CI and a 2-sided *P* value. NT-proBNP and CRP were log-transformed; therefore, treatment ratios with the corresponding 95% CIs at week 52 are reported. Statistical analyses were performed with the use of SAS version 9.4, SAS/STAT version 15.1 (SAS Institute, Inc).

TABLE 1 Continued

	Baseline CRP, mg/L			
	<2 (n = 332)	≥2 to <10 (n = 591)	≥10 (n = 218)	*P* Value
NYHA functional class				0.0170
II	241 (73)	412 (70)	130 (60)	
III-IV	91 (27)	179 (30)	88 (40)	
Concomitant medications				
Beta-blockers	276 (83)	476 (81)	172 (79)	0.1997
Diuretics	263 (79)	481 (81)	178 (82)	0.4360
Loop diuretics	183 (55)	366 (62)	151 (69)	0.0008
MRAs	100 (30)	208 (35)	76 (35)	0.1902
Thiazides	50 (15)	99 (17)	26 (12)	0.4359
ACE inhibitor/ARB (ARNI)	259 (78)	469 (79)	168 (77)	0.8767
ARNI	15 (4)	32 (5)	11 (5)	0.7248
SGLT2 inhibitors	66 (20)	110 (19)	45 (21)	0.9062

Data are for the full analysis set. Percentages may not equal 100% due to rounding. Data are median (Q1-Q3) or n (%) and are from the full analysis set. Continuous variables used the Jonckheere-Terpstra trend test, and binary variables used a Cochran-Armitage trend test. [a]Pooled data from the STEP-HFpEF and STEP-HFpEF DM trials (n = 1,145); A total of 1,146 patients were randomized; however, 1 patient was randomized in error so that the full analysis set comprises 1,145 patients. [b]Race and ethnicity were reported by the investigator. [c]HbA_{1c} values are from the HFpEF DM trial only. [d]Includes 1 patient with an LVEF of 33%. [e]Diabetes was an exclusion criterion in the STEP-HFpEF trial; therefore, the data shown are from the STEP-HFpEF DM trial only, which included only patients with T2D.

6MWD = 6-minute walk distance; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BMI = body mass index; CRP = C-reactive protein; DM = diabetes mellitus; HbA_{1c} = glycated hemoglobin; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; N/A = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2 = sodium-glucose cotransporter 2.

RESULTS

BASELINE DIFFERENCES ACCORDING TO CRP. Among 1,145 randomized patients, baseline mean CRP levels were 3.7 mg/L (5th-95th percentiles: 0.6-21.9 mg/L). Categorically, 332 (29.0%), 591 (52.0%), and 218 (19.0%) patients had observed baselines CRP <2, ≥2 to <10, and ≥10 mg/L, respectively. Baseline characteristics and demographics are presented in Table 1. Compared with patients who had lower CRP, those with higher CRP were younger and more often female, and had evidence of greater

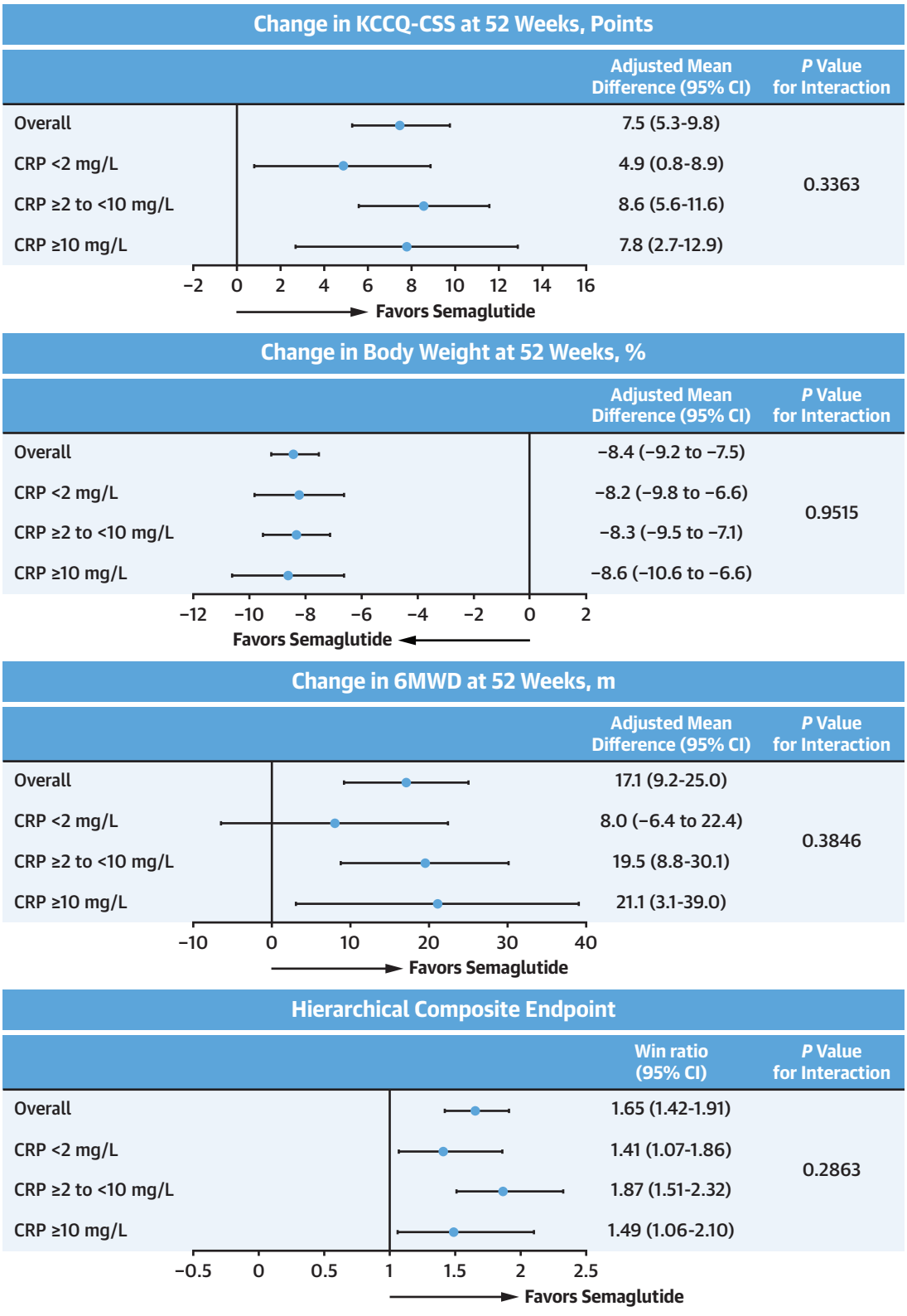
TABLE 2 Effects of Semaglutide vs Placebo on the Dual Primary, Confirmatory Secondary, and Select Supportive Secondary and Exploratory Endpoints by Baseline CRP Category

	Baseline CRP, mg/L												
	<2 (n = 332)				≥2 to <10 (n = 591)				≥10 (n = 218)				
	Semaglutide		Placebo		Semaglutide		Placebo		Semaglutide		Placebo		*P* Value for Interaction
	n	Outcome	n	Outcome	n	Outcome	n	Outcome	n	Outcome	n	Outcome	
Change in KCCQ-CSS at week 52, points	154	15.0	149	10.1	286	16.1	263	7.5	84	11.5	97	3.7	
Adjusted mean difference,[a] points		4.9 (0.8-8.9)				8.6 (5.6-11.6)				7.8 (2.7-12.9)			0.3363
Change in body weight at week 52, %	155	−11.2	152	−3.0	291	−11.5	266	−3.2	86	−11.3	102	−2.7	
Adjusted mean difference,[a] %		−8.2 (−9.8 to −6.6)				−8.3 (−9.5 to −7.1)				−8.6 (−10.6 to −6.6)			0.9515
Change in 6MWD at week 52, m	153	18.7	144	10.7	283	19.2	251	−0.3	85	5.5	95	−15.6	
Adjusted mean difference,[a] %		8.0 (−6.4 to 22.4)				19.5 (8.8 to 30.1)				21.1 (3.1 to 39.0)			0.3846
Hierarchical composite endpoint, win ratio[a]		1.41 (1.07-1.86)				1.87 (1.51-2.32)				1.49 (1.06-2.10)			0.2863
CRP ratio to baseline at week 52, mg/L	154	0.58	151	0.82	288	0.55	267	0.94	85	0.64	102	0.90	
Treatment ratio[a]		0.70 (0.56 to 0.87)				0.58 (0.49 to 0.69)				0.71 (0.53 to 0.97)			0.3185
Change in SBP at week 52, mm Hg	155	−4.1	152	−1.5	291	−5.1	267	−1.2	86	−3.8	102	−3.2	
Adjusted mean difference,[a] %		−2.5 (−6.2 to 1.1)				−3.9 (−6.6 to −1.2)				−0.7 (−5.4 to 4.0)			0.4806
NT-proBNP ratio to baseline at week 52	155	0.75	151	0.99	289	0.82	267	0.93	85	0.70	102	0.96	
Treatment ratio,[a] %		0.76 (0.62-0.92)				0.89 (0.77-1.02)				0.73 (0.57-0.93)			0.2630

Values in parentheses are 95% CI. Data are for the full analysis set. [a]Semaglutide vs placebo.

SBP = systolic blood pressure; other abbreviations as in Table 1.

FIGURE 1 Effects of Semaglutide vs Placebo According to Baseline CRP Category on the Dual Primary, Confirmatory Secondary, Select Supportive Secondary, and Exploratory Endpoints



6MWD = 6-minute walk distance; CRP = C-reactive protein; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure.

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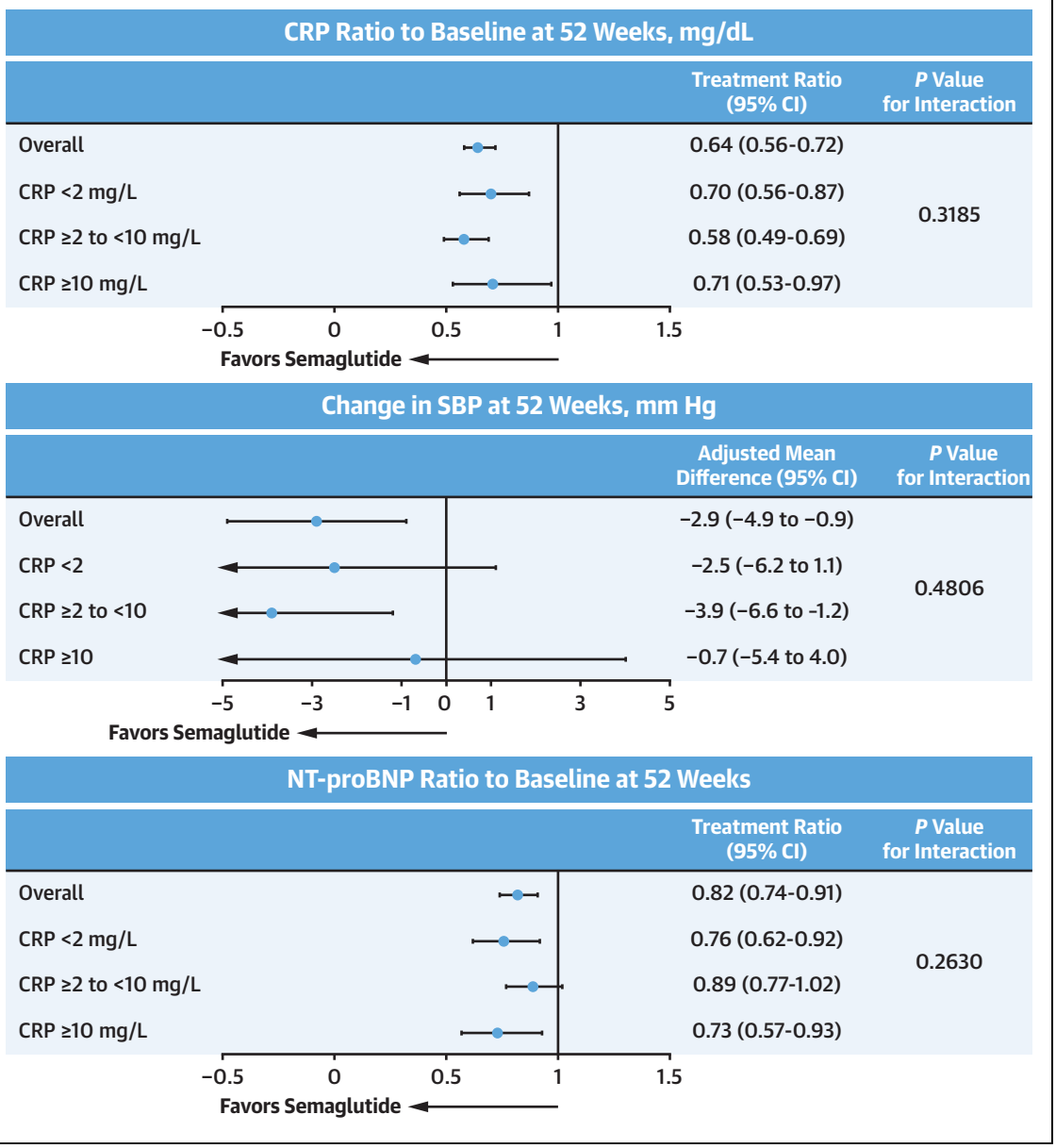
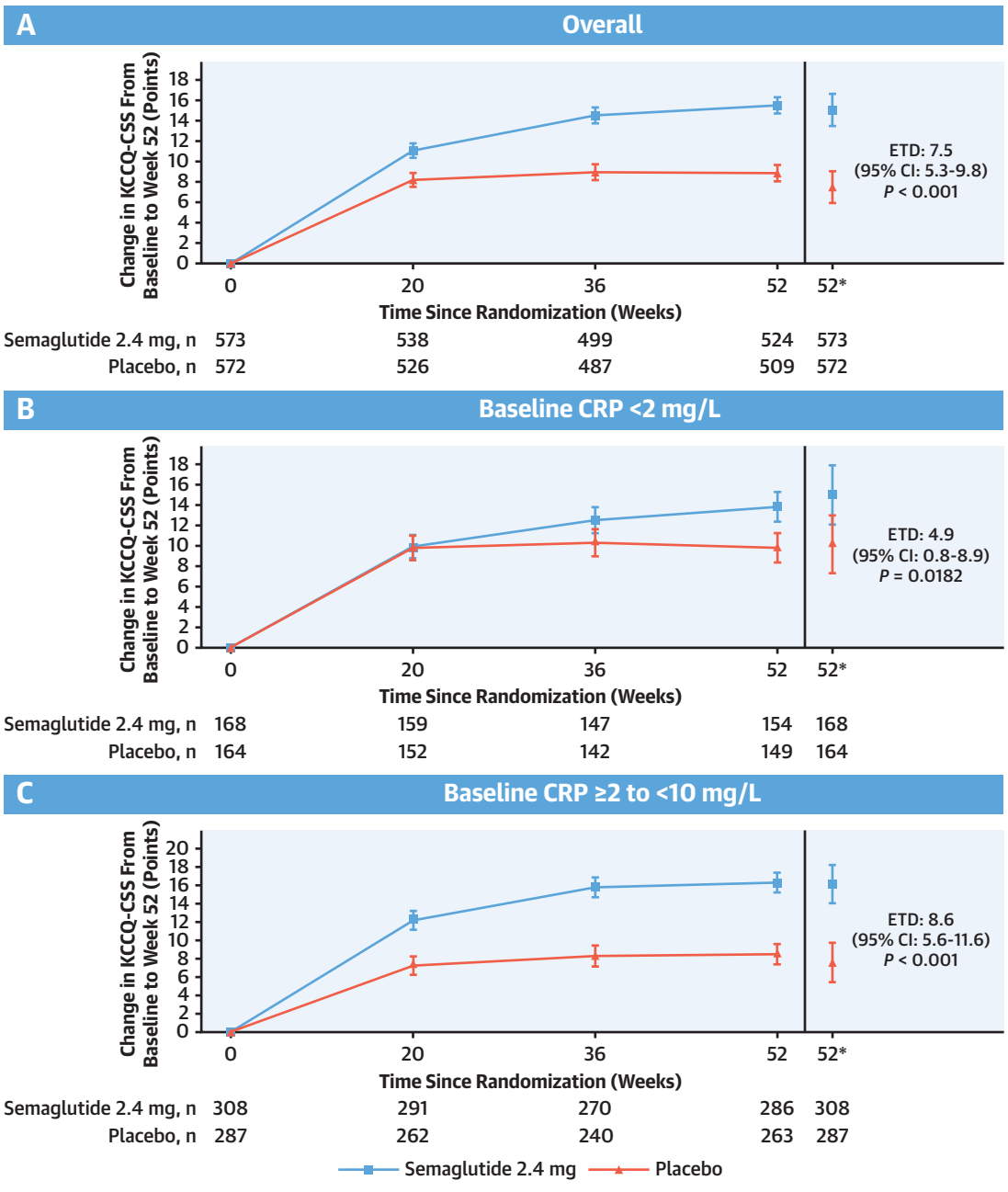
FIGURE 1 Continued



adiposity (higher weight, BMI, and waist circumference) (Table 1). Those with higher CRP had lower rates of coronary artery disease. Notably, those with higher CRP, compared with lower CRP, had lower KCCQ-CSS and 6MWD, higher proportion of NYHA III/IV symptoms, and greater use of loop diuretics (Table 1). LVEF, blood pressure, and NT-proBNP levels were similar between groups.

EFFICACY OF SEMAGLUTIDE VS PLACEBO BY CRP LEVELS. Compared with placebo, semaglutide improved KCCQ-CSS similarly across CRP groups; the adjusted mean difference was +4.9 points (95% CI: 0.8-8.9 points) in the CRP <2 mg/L group, +8.6 points (95% CI: 5.6-11.6 points) in the CRP ≥2 to ≤10 mg/L group, and +7.8 points (95% CI: 2.7-12.9) in the CRP ≥10 mg/L (*P* interaction = 0.34) (Table 2,

FIGURE 2 Change From Baseline in KCCQ-CSS Over 52 Weeks Overall and by Baseline CRP Categories



Change from baseline in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) over 52 weeks (A) overall and (B-D) by baseline C-reactive protein (CRP) categories observed from the in-trial period. Error bars are ±SEM. *Estimated means are from the analysis of covariance. Numbers shown below graphs are subjects contributing to the mean.

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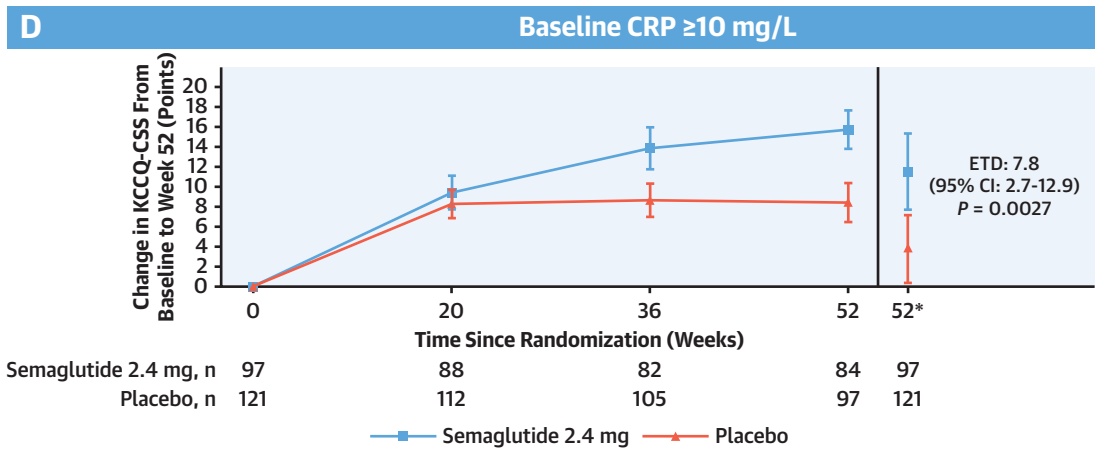
Figure 1). The trajectories of improvement in KCCQ-CSS were overall similar across CRP categories in the pooled population (Figure 2). The observed benefits on KCCQ-CSS were seen consistently in all CRP categories across key subgroups (age, BMI, and LVEF) (Supplemental Figure 1). When CRP was analyzed as a continuous variable, semaglutide vs placebo improved KCCQ-CSS across the entire range of CRP

FIGURE 2 Continued



levels (*P* interaction = 0.4006) (Figure 3A). Semaglutide reduced body weight consistently across CRP categories, as well as when it was examined as a continuous variable (Table 2, Figures 1 and 3B). Semaglutide vs placebo improved 6MWD in all groups, with numerically more effect in those with higher levels of CRP (Table 2, Figure 1) (*P* interaction = 0.3846). Semaglutide also resulted in a greater number of wins vs placebo for the hierarchical composite endpoint, and reduced CRP, systolic blood pressure, and NT-proBNP regardless of CRP levels (Table 2, Figure 1).

When the data were categorized by cutoff ≥2 vs <2 mg/L, the results were similar (Supplemental Table 1, Supplemental Figure 2).

In the responder analyses, semaglutide- vs placebo-treated patients had a significantly lower odds of ≥5-point deterioration (OR: 0.49; 95% CI: 0.35-0.69; $P < 0.001$), with no heterogeneity by baseline CRP category. In addition, semaglutide- vs placebo-treated patients had a significantly higher odds of ≥5-, ≥10-, ≥15-, and ≥20-point improvement in KCCQ-CSS consistently across CRP groups (Supplemental Figure 3).

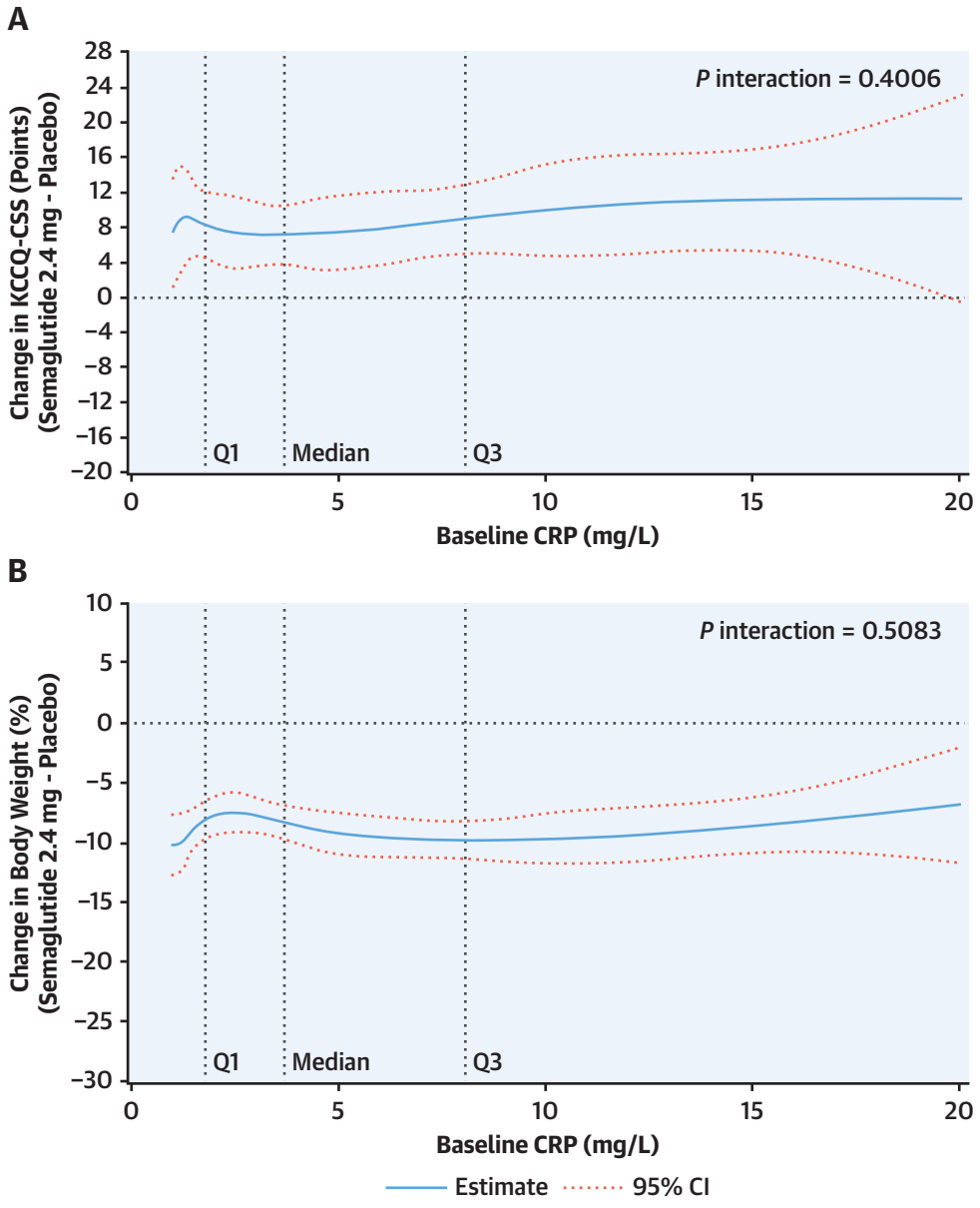
The cumulative response analysis among those with observed KCCQ-CSS values at week 52 showed continuous separation of KCCQ-CSS change curves in favor of semaglutide vs placebo across the 3 CRP subgroups (Supplemental Figure 4). In those with CRP <2 mg/L, 40.5% of patients treated with semaglutide experienced an increase in KCCQ-CSS of ≥20 points, compared with 20.5% of those treated with placebo. The corresponding numbers in those with CRP ≥2 to <10 mg/L were 36.0% and 20.2% and in those with CRP ≥10 mg/L were 31.4% and 16.5%.

EFFECT OF SEMAGLUTIDE ON CRP. Across the STEP-HFpEF Program, as shown previously, semaglutide reduced CRP by 20 weeks, with further reductions at week 52. The CRP ratio to baseline at week 20 was 0.70 with semaglutide and 1.04 with placebo (treatment ratio: 0.68; 95% CI: 0.61-0.75; $P < 0.0001$). As shown previously,[23-25] the CRP ratio to baseline at week 52 was 0.57 with semaglutide and 0.90 with placebo (treatment ratio: 0.64; 95% CI: 0.56-0.72; $P < 0.0001$); a similar reduction in CRP with semaglutide was seen in STEP-HFpEF (0.56 vs 0.93; treatment ratio: 0.61; 95% CI: 0.51-0.72; $P < 0.0001$) as in STEP-HFpEF-DM (0.58 vs 0.87; treatment ratio: 0.67; 95% CI: 0.55-0.80; $P < 0.0001$). Semaglutide reduced CRP to a similar extent regardless of baseline CRP category (Figure 1, Table 2). There was no heterogeneity in the efficacy of semaglutide vs placebo on CRP when stratified by the magnitude of weight loss during the trial (*P* interaction = 0.9154) (Figure 4).

ASSOCIATION OF CHANGE IN CRP AND HF OUTCOMES. As shown in Figure 5, there was no relationship between changes in CRP and semaglutide-mediated changes in either KCCQ-CSS or 6MWD. However, greater reduction in CRP was associated with larger semaglutide-mediated reductions in NT-proBNP levels (*P* interaction = 0.0045).

SAFETY OUTCOMES. There were fewer SAEs and serious cardiac disorders, regardless of baseline CRP category, in patients treated with semaglutide vs placebo (Supplemental Table 2). Gastrointestinal SAEs and SAEs leading to premature discontinuation

FIGURE 3 Treatment Effects of Semaglutide vs Placebo on KCCQ-CSS and Body Weight According to Baseline CRP (as a Continuous Variable)



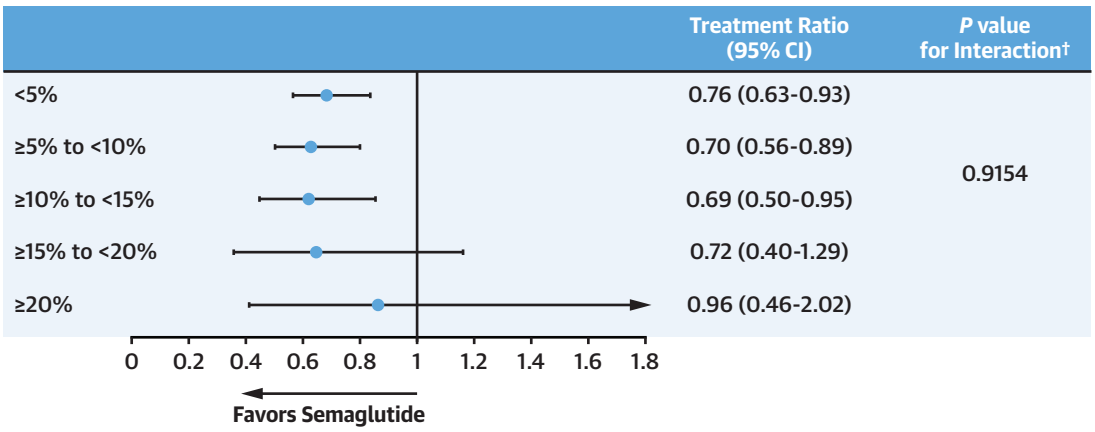
Treatment effects of semaglutide vs placebo on (A) KCCQ-CSS and (B) body weight by continuous CRP at baseline. All nonmissing responses in the in-trial period were included in an analysis of covariance model with trial, BMI strata, and treatment by CRP spline interaction as factors, and baseline CRP as covariate. CRP was log-transformed for analysis. Abbreviations as in Figure 2.

were similar between treatment groups across the CRP subgroups.

DISCUSSION

In this prespecified, patient-level, pooled analysis of STEP-HFpEF and STEP-HFpEF DM trials (STEP-HFpEF Program), we observed a high prevalence of inflammation as well as notable differences in participant characteristics according to baseline CRP categories. The prevalence of heightened inflammation (defined as CRP ≥2 mg/L) was found in approximately 70% of individuals with obesity-related HFpEF. Of interest, nearly 1 in 5 participants had very

FIGURE 4 Ratio to Baseline in CRP at Week 52[a] by Weight Loss Categories (Semaglutide vs Placebo)



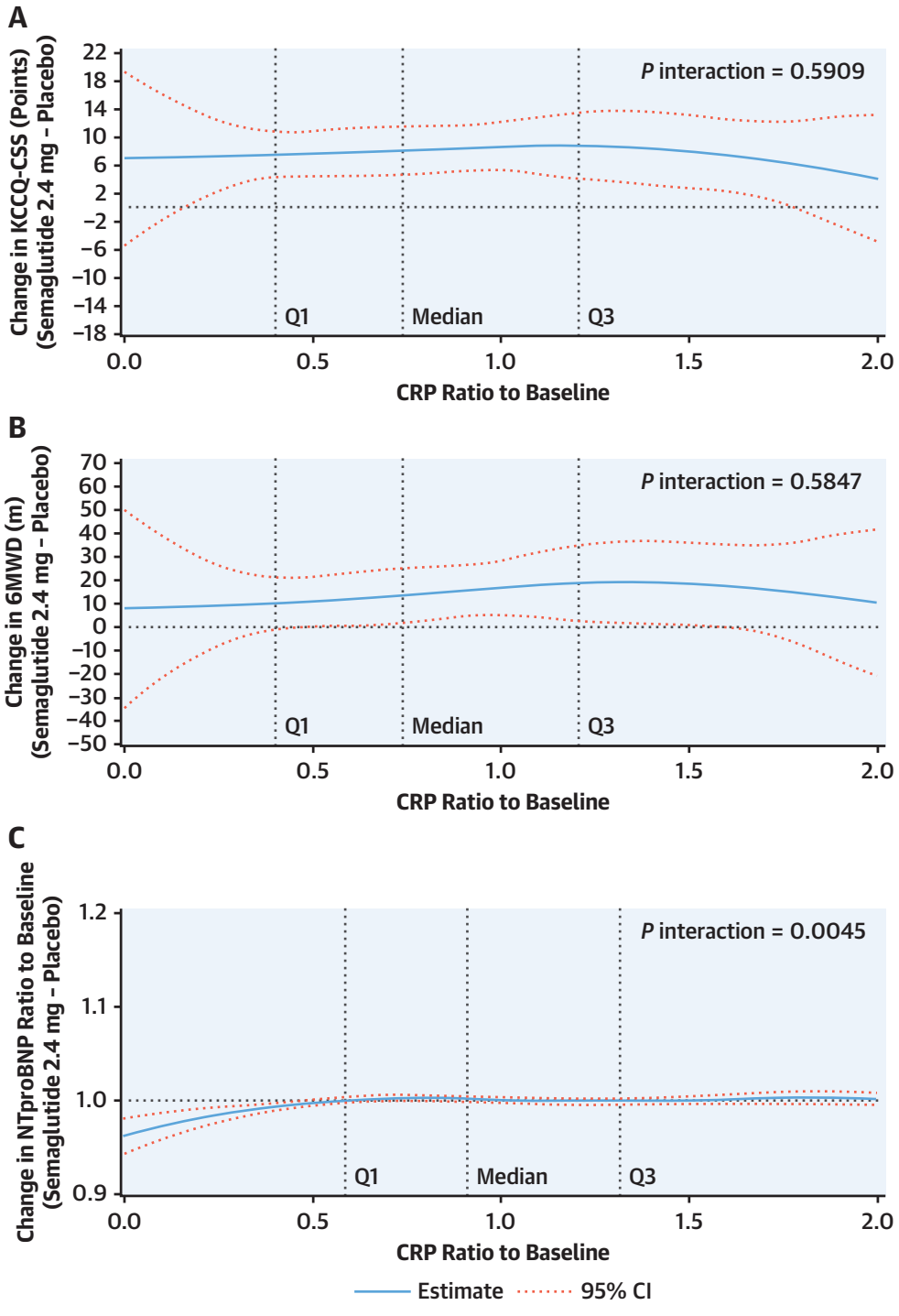
Only patients with observed C-reactive protein (CRP) and body weight values at baseline and week 52 are included. Data were analyzed using an ANCOVA with study, treatment, weight loss subgroup and treatment by weight loss subgroup interaction as factors and the baseline body weight and baseline value of the CRP as covariates. The ratio to baseline and the corresponding baseline value were log-transformed before analysis. CRP values are geometric mean (coefficient of variation). [a]Patients with change from baseline in body weight at week 52 and change from (ratio to) baseline in CRP at week 52. †Interaction test within treatment group.

high levels of inflammation (CRP ≥10 mg/L), potentially suggesting a presence of ongoing inflammatory conditions—a finding that to our knowledge has not been previously described in this patient group. Patients with higher CRP were more likely to be younger and female and had greater adiposity, including weight, BMI and waist circumference, compared with those who had lower CRP. Importantly, higher CRP levels at baseline were associated with more severe HF-related symptoms, physical limitations, and reduced exercise tolerance. These data provide some of the first insights about how baseline inflammation in the context of obesity-related HFpEF is related to patient demographics and clinical features of heart failure.

The second key finding of this analysis is that the beneficial effects of semaglutide on all key trial endpoints were consistent regardless of baseline CRP. In previous STEP-HFpEF Program studies, we demonstrated a consistent benefit of semaglutide on KCCQ-CSS and body weight by categories of CRP (≥2 and <2 mg/L); however, those analyses did not examine this relationship for any of the secondary or exploratory endpoints, and did not evaluate these relationships across more granular thresholds of CRP (<2, ≥2 to <10, and ≥10 mg/L) or by continuous spline analyses. We herein confirm that semaglutide led to similar degrees of improvement in KCCQ-CSS and reductions in body weight when assessed by CRP categorically and continuously. Semaglutide also led to consistent improvements in 6MWD and the hierarchical composite endpoint, as well as systolic blood pressure and NT-proBNP, across the CRP level categories. The improvements in 6MWD with semaglutide vs placebo were numerically larger in participants with higher CRP levels, although there was no statistical evidence of heterogeneity per se. Finally, semaglutide consistently reduced CRP levels regardless of the baseline levels of CRP or the magnitude of weight loss during the trials. This differs from our prior report, which assessed the data from only 1 (STEP-HFpEF) of the 2 trials, likely owing to the fact that the previously reported data were not placebo corrected.[30]

A substantial body of evidence supports the paradigm that inflammation is a causal factor in both the pathogenesis of incident obesity-related HFpEF[1-5] and in the propagation of prevalent obesity-related HFpEF. Excess adipose tissue strongly promotes inflammation and sustains unabated innate and adaptive immune pathway dysregulation.[2] The inflammatory environment in people with obesity is largely ascribed to increased production of adipocytokines from visceral adipose tissue deposits.[11] The inflammatory stimulus leads to the development of myocardial and systemic microvascular and macrovascular dysfunction, insulin resistance, and altered myocardial function.[11,32] These proinflammatory cytokines lead to activation of oxidative stress and promote profibrotic signaling pathways characterized

FIGURE 5 Association Between Change in CRP and Semaglutide-Mediated Changes in KCCQ-CSS, 6MWD, and NT-proBNP Between Baseline and Week 52



Figures represent quadratic spline regression models of the CRP ratio to baseline at week 52 (*x*-axis) on treatment difference (solid blue lines) in change from baseline to week 52 for (A) KCCQ-CSS, (B) 6MWD, and (C) NT-proBNP (*y*-axis). Dotted red lines represent 95% CIs. Data derived from the in-trial period. Models adjusted for trial and stratified by body mass index (<35 vs ≥35 kg/m^2). *P* value reported for test of interaction between treatment and change in CRP. Overall treatment differences reported for KCCQ-CSS; 6MWD, and NT-proBNP were 7.5 points (95% CI: 5.3 to 9.8), 17.1 m (95% CI: 9.2-25.0) and 0.82 (95% CI: 0.74–0.91), respectively.[25] Abbreviations as in Figures 1 and 2.

by myofibroblast activation and extracellular matrix degradation, which are thought to cause the development of myocardial stiffness in HFpEF.[3,32] Inflammation also alters cardiac energetics and substrate utilization in both cardiac and skeletal muscle.[33,34] Chronic inflammation also promotes marked systemic mitochondrial dysfunction, reduces endothelial bioavailability of nitric oxide and cyclic guanosine monophosphate, and inhibits phosphorylation of titin, which collectively alter myocardial energetics, sustain diastolic dysfunction in HFpEF, and promote exercise intolerance.[3,35] Therefore, sustained and unresolved inflammation, particularly in the setting of obesity, is a key determinant of the central and peripheral manifestations of the HFpEF syndrome.[1,3,36]

The IL-1/TNF-α-IL-6-CRP pathway plays a significant role in the inflammatory phenotype of HFpEF.[20,37,38] Visceral adiposity and other cardiometabolic stressors are thought to trigger activation of this axis and sustain chronic inflammation in HFpEF.[20] CRP, a nonspecific acute-phase protein, is widely regarded as a reliable barometer of activation of the upstream IL-1/IL-6 pathway and has been shown to be associated with worse symptoms and prognosis in HFpEF.[20,39] In a recent study, Alogna et al have carefully evaluated the role of this pathway in 4 prospective HFpEF studies.[20] In that analysis, elevated levels of IL-6 were observed in people with increased total and regional adiposity and were strongly related to reduced exercise capacity, exercise intolerance, significant physical limitations, and greater cardiac congestion.

In addition to central (myocardial) abnormalities, peripheral (skeletal muscle) derangements significantly contribute to the development and progression of exercise limitation in HFpEF.[40] Inflammation in obesity-related HFpEF is thought to promote skeletal muscle microvascular rarefaction and mitochondrial dysfunction, leading to changes in arteriovenous oxygen content difference (ΔAVO_2).[41-43] If inflammation is indeed critical in these peripheral manifestations of exercise intolerance in obesity-related HFpEF, it follows that such patients would benefit more from interventions aimed at reducing inflammation. Notably, body composition, particularly the degree of adiposity, and inflammation correlate with ΔAVO_2, with increased fat associated with reduced ΔAVO_2 and greater exercise intolerance in HFpEF.[41-43] Recent evidence from Tada et al suggests that inflammation in HFpEF exacerbates peripheral defects by diminishing the ability to enhance ΔAVO2 during exercise, thereby limiting aerobic capacity.[43] Indeed, this notion is supported by our analyses, which indicate greater improvements in 6MWD with semaglutide vs placebo in all patients, with a somewhat larger numeric improvement in those with the highest baseline levels of CRP.

The results of our present analysis confirm a high prevalence of inflammation in patients with obesity-related HFpEF and thus a substantial overlap between the obesity and proinflammatory phenotypes of this disease condition. Previous trials of lifestyle-mediated weight loss have shown a significant reduction in CRP and other HF-related benefits in obesity-related HFpEF. Kitzman et al evaluated the impact of caloric restriction or aerobic exercise training in people aged ≥60 years with obesity-related HFpEF.[44] That study demonstrated that CRP levels were elevated at baseline and that there was a large reduction in CRP with caloric restriction-mediated weight loss. Furthermore, the reduction in fat mass was strongly correlated with the reduction in CRP, and weight loss improved physical function (peak VO_2) and KCCQ scores. The findings of the present analysis from the STEP-HFpEF Program, along with our previously published data, show not only that semaglutide significantly improves various HF-related endpoints and produces large reductions in CRP regardless of the baseline levels of inflammation, but also that the declines in the CRP levels do not vary by the magnitude of weight loss during the trials. This suggests that semaglutide may also have direct non-weight loss-mediated effects on reducing inflammation. Other analyses from STEP-HFpEF (including, notably, its NT-proBNP-lowering effects despite and regardless of concomitant weight loss) indicate that the observed HF benefits of semaglutide are also not fully explained by weight loss and likely include direct disease-modifying properties.[45]

It is challenging, within a context of clinical trials, to ascertain the degree to which the beneficial HF effects of semaglutide are mediated by its effects on inflammation vs its other actions. Semaglutide has a plethora of benefits on interconnected cardiometabolic pathways, and ascribing a causal role of one specific mechanism is difficult. However, if inflammation is indeed a dominant mechanism, we would expect that patients with the highest level of inflammation would exhibit greater benefits. However, the observation that the efficacy of semaglutide vs placebo on all trial endpoints was relatively

agnostic regarding the levels of CRP suggests that inflammation reduction may not be the only (or the dominant) pathway. In support of this observation, we did not find a relationship between change in CRP and semaglutide-mediated improvement in either KCCQ-CSS or 6MWD. Of interest, greater reduction in CRP was associated with larger semaglutide-mediated reductions in NT-proBNP, suggesting (within the constraints of post hoc exploratory analyses) that reduction in inflammation may play a role in the decongestive effects of semaglutide. The ongoing HERMES trial, in which 5,600 patients (estimated enrollment) with HFpEF and inflammation (CRP ≥2 mg/L) are being randomized to the IL-6 antibody ziltivekimab (which does not appear to have any effects on body weight or other cardiometabolic parameters) vs placebo, with a primary outcome of cardiovascular death or HF event, may offer additional insights regarding the potential therapeutic effects of direct inflammation suppression in HFpEF.

We acknowledge limitations of the current analyses: We did not collect biomarkers of inflammation beyond CRP (eg, IL-1 or IL-6) in the current study; we did not consistently collect measures of renal function (estimated glomerular filtration rate) or hemoglobin, which are known to be important in the inflammatory phenotype of HFpEF; some analyses were done post hoc; mechanistic insights are limited; and we had a limited number of non-White patients, limiting the generalizability of the data. Alternative analytic models (eg, repeated measures) were not used, and follow-up was relatively short (52 weeks).

CONCLUSIONS

In the STEP-HFpEF Program, which enrolled patients with obesity-related HFpEF, inflammation, as assessed according to CRP ≥2 mg/L, was seen in >70% of subjects. Those with more baseline inflammation were more likely to be younger and female, to have a higher BMI, and to have worse health status and exercise function. Semaglutide improved all HF outcomes regardless of baseline CRP, and consistently reduced CRP regardless of baseline levels of CRP or the magnitude of weight loss during the trials.

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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. Individual patient data will be shared in data sets in a deidentified/anonymized format.

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