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STEP-HFpEF: GLP-1 agonists the next class of HFpEF therapies?

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Introduction

Heart failure with preserved ejection (HFpEF) is a condition underlined by impaired left ventricular (LV) diastolic function in the presence of normal contractile function, occurring due to the complex interplay between cardiometabolic comorbidities, inflammatory changes, volume overload and increased stiffness resulting in abnormal LV remodelling (1). HFpEF patients who are obese have been shown to demonstrate worse clinical and haemodynamic features compared to patients without obesity (2). Therefore, this patient population may respond favourably to weight loss measures. Glucagon-like peptide 1 (GLP-1) receptor agonists are an established treatment for type 2 diabetes mellitus and obesity, and have been shown to achieve effective weight loss and reduce major adverse cardiovascular events in those with concomitant cardiovascular or renal disease (3). Although a high proportion of patients with HFpEF are also obese, there is a paucity of obesity-targeting therapies in this particular population.

Take Home Messages

- Heart failure with preserved ejection fraction (HFpEF) is a debilitating condition associated with troubling symptoms and physical limitations, especially in those with obesity. No therapies have been developed to address obesity-related HFpEF.
- The STEP-HFpEF trial examined the effect of semaglutide treatment in patients diagnosed with HFpEF who had concomitant obesity.
- The study found semaglutide treatment in patients with HFpEF and obesity led to greater reductions in both symptoms and physical limitations as well as weight loss compared to placebo.
- Further large-scale studies are needed to evaluate the long-term effects of GLP-1 receptor agonists as well as their impact on hard clinical endpoints in this patient population.

STEP-HFpEF trial

The STEP-HFpEF trial was a multinational, double-blind, randomised, placebo-controlled trial assessing the effect of semaglutide, a GLP-1 receptor agonist utilised in the treatment of weight loss, on symptoms and physical limitations attributed to heart failure in patients with HFpEF and obesity (4). The primary endpoints were the change in points of the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; range of 0-100 with higher scores suggesting less symptoms and physical limitations) and the percentage change in weight from baseline to 52 weeks.

Inclusion criteria included adults with an LV ejection fraction ≥45%, BMI ≥30, New York Heart Association class II, III, or IV symptoms, KCCQ-CSS ≤90, 6-minute walk distance ≥100m, and at least one of the following: raised LV filling pressures (based on direct invasive measurements), elevated N-terminal pro-B-type natriuretic peptide (NT-pro-BNP; thresholds stratified according to baseline BMI) plus echocardiographic abnormalities, or heart failure-related hospitalisation in the 12 months before screening with echocardiographic abnormalities or ongoing diuretic treatment. Exclusion criteria included a history of diabetes and a change in body weight over 5kg within 90 days prior to screening. Patients were recruited from 96 sites in 13 countries across Europe (including United Kingdom), Asia, North and South America.

529 patients with a BMI ≥30 were randomly assigned in a 1:1 allocation to either semaglutide 2.4mg subcutaneous treatment (n = 263) or placebo (n = 266) once weekly. Baseline characteristics were generally similar between the two groups (**Table 1**). The study found that both the mean difference in KCCQ-CSS (7.8 points) and the mean difference in body weight (-10.7%) between the groups at 52 weeks were significantly greater with semaglutide treatment compared to placebo ($p<0.001$ for both primary endpoints) (**Figure 1**). Furthermore, there were less serious adverse events in the semaglutide treatment group than with the placebo group (13.3% vs. 26.7%, $p<0.001$).

Table 1. Baseline characteristics of patients

Characteristic	Semaglutide (n=263)	Placebo (n=266)	Total (n=529)
Female sex — no. (%)	149 (56.7)	148 (55.6)	297 (56.1)
Median age (IQR) — yr	70 (62–75)	69 (62–75)	69 (62–75)
Ethnic group — no. (%)			
Hispanic or Latino	15 (5.7)	21 (7.9)	36 (6.8)
Not Hispanic or Latino	248 (94.3)	245 (92.1)	493 (93.2)
Race — no. (%)			
Black	8 (3.0)	13 (4.9)	21 (4.0)
White	255 (97.0)	252 (94.7)	507 (95.8)
Other	0	1 (0.4)	1 (0.2)
Median body weight (IQR) — kg	104.7 (92.4–120.1)	105.3 (92.4–122.0)	105.1 (92.4–120.8)
Median BMI (IQR)	37.2 (33.9–41.1)	36.9 (33.3–41.6)	37.0 (33.7–41.4)
BMI stratum — no. (%)			
30 to <35	89 (33.8)	91 (34.2)	180 (34.0)

Table 1. Baseline characteristics of patients

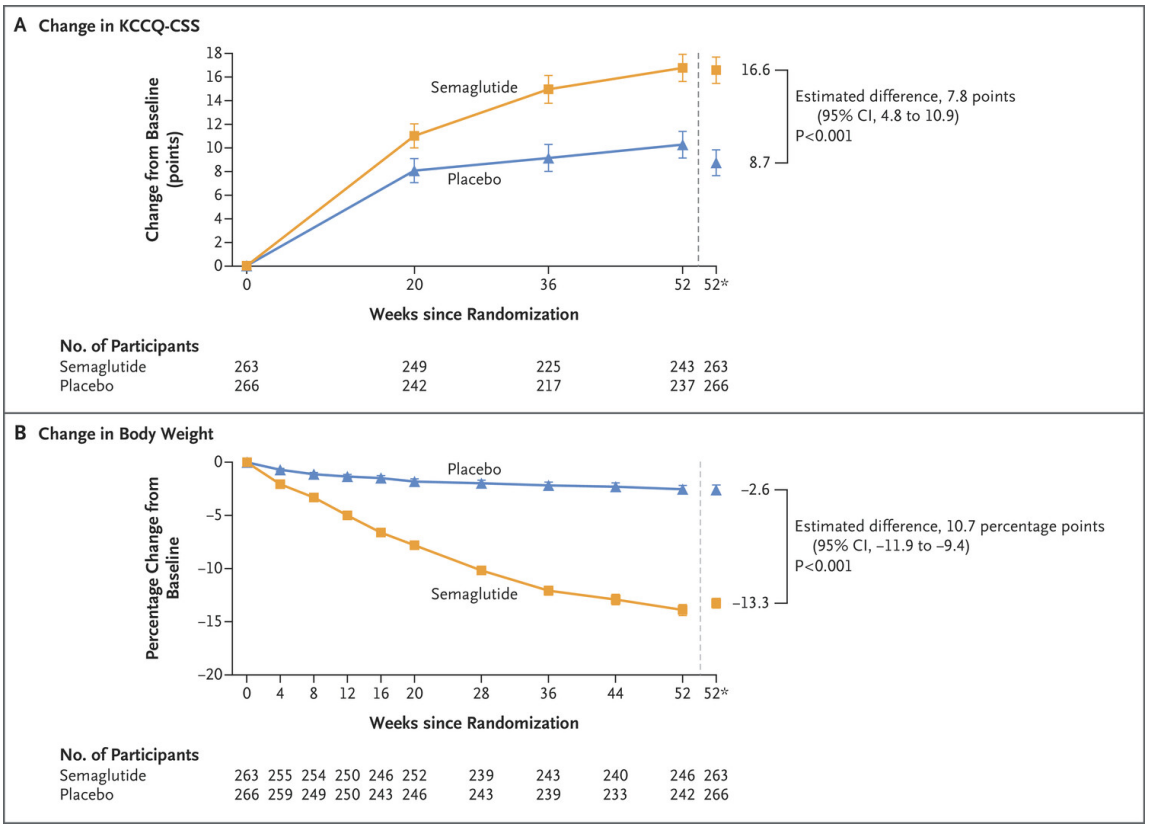
Characteristic	Semaglutide (n=263)	Placebo (n=266)	Total (n=529)
≥35	174 (66.2)	175 (65.8)	349 (66.0)
Median systolic blood pressure (IQR) — mm Hg	133 (122–145)	132 (120–142)	133 (121–144)
Median NT-proBNP level (IQR) — pg/ml	414.4 (229.2–1014.0)	499.8 (204.7–1025.0)	450.8 (218.2–1015.0)
Median LVEF (IQR) — %	57.0 (50.0–60.0)	57.0 (50.0–60.0)	57.0 (50.0–60.0)
LVEF stratum — no. (%)			
45 to <50%	37 (14.1)	48 (18.0)	85 (16.1)
50 to 59%	113 (43.0)	102 (38.3)	215 (40.6)
≥60%	113 (43.0)	116 (43.6)	229 (43.3)
Median KCCQ-CSS (IQR) — points	59.4 (42.7–72.9)	58.3 (40.5–72.9)	58.9 (41.7–72.9)
Median 6-minute walk distance (IQR) — m	316.0 (251.0–386.0)	325.8 (232.4–392.0)	320.0 (240.0–389.0)
Hospitalization for heart failure within 1 year — no. (%)	42 (16.0)	39 (14.7)	81 (15.3)
Coexisting conditions at screening — no. (%)			
Atrial fibrillation	135 (51.3)	140 (52.6)	275 (52.0)
Hypertension	216 (82.1)	217 (81.6)	433 (81.9)
Coronary artery disease	53 (20.2)	45 (16.9)	98 (18.5)
NYHA functional class — no. (%)			
II	183 (69.6)	167 (62.8)	350 (66.2)
III or IV	80 (30.4)	99 (37.2)	179 (33.8)

Table 1. Baseline characteristics of patients

Characteristic	Semaglutide (n=263)	Placebo (n=266)	Total (n=529)
Concomitant medication — no. (%)			
Diuretic	207 (78.7)	220 (82.7)	427 (80.7)
Loop diuretic	158 (60.1)	171 (64.3)	329 (62.2)
Thiazide	40 (15.2)	50 (18.8)	90 (17.0)
MRA	89 (33.8)	95 (35.7)	184 (34.8)
ACEI, ARB, or ARNI	210 (79.8)	214 (80.5)	424 (80.2)
Beta-blocker	201 (76.4)	217 (81.6)	418 (79.0)
SGLT2 inhibitor	8 (3.0)	11 (4.1)	19 (3.6)

Adapted from STEP-HFpEF (4). Data are median (interquartile range) or n (%). (Abbreviations) ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprolysin inhibitor, BMI, body mass 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; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter-2.

Figure 1. Changes in primary endpoints from baseline to week 52 (adapted from STEP-HFpEF (4)). KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score.



Analysis

The authors are to be commended for their research that aimed to address a novel and thought-provoking question. The study explored the efficacy of semaglutide in patients with both HFpEF and obesity, highlighting some key findings including alleviation of symptoms and physical limitations as well as weight loss. From these findings one could postulate that weight loss may lead to similar outcomes in HFpEF patients with obesity, however, previous studies have shown no improvement in diastolic function following weight loss achieved through caloric deficit (5) or liraglutide use (6) (albeit symptoms were not assessed).

Given the recent emergence of SGLT2 inhibitors as a disease-modifying therapy for HFpEF following both the DELIVER (7) and EMPEROR-Preserved (8) trials in tandem with the findings from this study, one can infer a significant metabolic component to the disease process. These studies also demonstrated SGLT2 inhibitors to have prognostic benefit in those with heart failure with reduced ejection fraction, suggesting a common metabolic factor amongst heart failure irrespective of ejection fraction. It would be interesting to investigate the effect of semaglutide in patients with heart failure with reduced ejection fraction and obesity, as similar benefit to that observed in the STEP-HFpEF trial would corroborate the aforementioned hypothesis.

The STEP-HFpEF trial has some limitations. The study participants may not be representative of the general population given the high proportion of Caucasian ethnicity. Furthermore, the sample size was not large enough to examine the effects of semaglutide treatment on hard clinical endpoints such as heart failure-related hospitalisations and major adverse cardiovascular events. Although the effects of semaglutide observed in this trial after 1 year of treatment seem promising, it is unclear if these would be maintained after the study period. Lastly, an LV ejection fraction cut-off of ≥45% was used in light of the evolving definition of HFpEF, however true HFpEF would be defined by an LV ejection fraction of ≥50%.

Conclusions

In conclusion, results from the STEP-HFpEF trial support semaglutide treatment in patients with HFpEF and obesity and therefore provide an additional therapy option for these particular patients. Larger studies are warranted to assess the longer-term effects of GLP-1 receptor agonists as well as their impact on hard clinical endpoints in patients with HFpEF.

Disclosures

No disclosures to declare.

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