Weekly Journal Scan

Weekly Journal Scan: a ‘thousand-mile’ journey in obesity-related heart failure treatment begins with a few STEPs

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Comment on ‘Semaglutide in Patients with Obesity-Related Heart Failure and Type 2 Diabetes’ which was published in the New England Journal of Medicine, https://doi.org/10.1056/NEJMoa2313917.

Key Points
• The STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus) is a company-funded, double-blind, multicentre, randomized, placebo-controlled trial aimed at assessing the efficacy and safety of the long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide, in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) and type 2 diabetes mellitus (T2DM). 1
• The study was conducted at 108 centres in Asia, Europe, North, and South America. Key inclusion criteria included a documented HF, with a left ventricular ejection fraction (LVEF) ≥ 45% and New York Heart Association (NYHA) class II–IV, a body mass index (BMI) of at least 30 kg/m2, a diagnosis of T2DM at least 90 days before screening, and a glycated haemoglobin level of no more than 10%.
• The dual primary endpoints were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS, a 23-item questionnaire evaluating HF-related symptoms, physical function, quality of life, and social function in a range from 0 to 100, with higher scores reflecting better health status) and the percentage change in body weight (BW), from baseline to week 52. Confirmatory secondary endpoints were (i) the change in the 6-min walking distance; (ii) a hierarchical composite endpoint including death from any cause, the number and timing of HF events (hospitalization or urgent visits requiring intravenous therapy), differences of at least 15, 10, and 5 points in the change in the KCCQ-CSS, and difference of a least 30 m in the change in the 6-minute walking distance; (iii) and the change in C-reactive protein level.
• A total of 616 participants were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg (n = 310) or placebo (n = 306) for 52 weeks, as an add-on to standard-of-care therapy, with a follow-up period of 5 weeks. Randomization was stratified according to BMI (<35 vs. ≥35). During the first 16 weeks, the doses of semaglutide or placebo were gradually escalated from .25 mg once weekly up to the maintenance dose. Ninety-four per cent of participants completed the trial. The median age of the enrolled subjects was 69 years (44% female, 84% White), and ~70% were in NYHA class II. The median BW was 103 kg, the median BMI was 37, with about two-thirds having a BMI of 35 or more, and the median duration of diabetes was 8 years. The median KCCQ-CSS was 59 points, and the median 6-min walking distance was 280 m. Most participants received diuretics, renin–angiotensin system blockers, and beta-blockers; approximately one-third of patients were also on mineralocorticoid receptor antagonists and sodium-glucose cotransporter (SGLT)-2 inhibitors.
• The mean change in the KCCQ-CSS at week 52 was 13.7 points in the semaglutide group and 6.4 points in the placebo group [estimated difference, 7.3 points; 95% confidence interval (CI), 4.1–10.4; P < .001], and the mean percentage change in BW was −9.8% in the semaglutide group and −7.6% in the placebo group [estimated difference, −6.4 percentage points; 95% CI, −7.6 to −5.2; P < .001]. The estimated differences in both endpoints were ~40% lower among participants receiving SGLT-2 inhibitors than among those who did not receive SGLT-2 inhibitor therapy at baseline. The mean change in the 6-min walking distance at week 52 was 13 m in the semaglutide group and −2 m in the placebo group (estimated difference, 15 m; 95% CI, 4–25; P = .008). The hierarchical composite endpoint analysis also favoured the semaglutide group compared with placebo (stratified win ratio 1.58; 95% CI, 1.29–1.94; P < .001). Seven participants in the semaglutide group and 18 in the placebo group had an adjudicated HF event (hospitalization or urgent visit) (hazard ratio, 40; 95% CI, 15–92). Serious adverse events were reported in 55 participants (18%) in the semaglutide group and 88 (29%) in the placebo group (P = .002).
Comment

Obesity is now recognized as a major predisposing condition for the development and progression of HFpEF. Similarly, T2DM has a prevalence of ∼45% in HFpEF. Both conditions are synergistically involved in the induction of low-grade inflammation and in promoting pro-oxidative and pro-fibrotic pathways leading to left ventricular hypertrophy and diastolic dysfunction, neurohumoral activation, and haemodynamic abnormalities.6,7

To date, there are no approved therapies targeting obesity-related HFpEF, and, only recently, trials assessing the potential clinical impact of specific treatments have been performed. Previous studies have shown the beneficial effects of GLP-1 receptor agonists in obesity and T2DM.6,8 In two distinct trials with a similar protocol, STEP-HFpEF and STEP-HFpEF DM, a weekly dose of semaglutide significantly reduced HF-related symptoms and physical limitations, improved functional capacity, and led to greater weight loss compared with placebo in obese patients (BMI of at least 30 kg/m2), with HFpEF, independently of the presence of T2DM,6,9

The majority of participants in the STEP HFpEF DM trial received guideline-directed medical therapy, with a percentage of patients taking SGLT-2 inhibitors at baseline significantly higher than that reported in the STEP HFpEF trial. Although significantly attenuated, the additional effect of semaglutide in the subgroup of patients receiving SGLT-2 inhibitors suggests independent effects on weight loss and quality of life.

The STEP HFpEF trial demonstrated an improvement in physical limitations and a reduction of the symptoms in the patients treated with semaglutide, with an estimated difference in the KCCQ-CSS of 7 points vs. placebo. In spite of the unavoidable limitations related to comparisons of subjective endpoints in different trials and in patients with different baseline clinical conditions, the improvement in quality of life seen in HFpEF DM exceeds that observed in previous trials assessing the effects of therapies recommended for HF, such as SGLT-2 inhibitors or sacubitril–valsartan.7,8 Of note, the improvement in KCCQ-CSS is accompanied by roughly 40% less weight loss with semaglutide in people with diabetes (compared with those without diabetes), again suggesting effects that may be independent of the BW reduction. It should be noted that the results should be interpreted in the light of a substantial placebo effect and of a potential persistence of the beneficial effects of semaglutide.

A major limitation of this trial derives from the adoption of soft endpoints such as those related to the use of questionnaires, physical activity, and quality of life. Other limitations include the low number of non-White participants, which affects the generalizability of the results, and the short-term follow-up, which prevents an assessment of the persistence of the beneficial effects of semaglutide.

Although reductions in HF events were reported, the trial was clearly underpowered for assessing the effects on clinical events. In this regard, however, data derived from a pre-specified pooled analysis of STEP-HFpEF and STEP-HFpEF DM trials may provide a more robust assessment of the effects of semaglutide on the primary and confirmatory secondary endpoints, thanks to the inclusion of a larger and more representative population encompassing the whole spectrum of obese patients with HFpEF (no diabetes, pre-diabetes, and T2DM), and with greater geographical diversity.9 The larger sample size permits to catch a glimpse of the effect of semaglutide on HF events and safety as well as a more thorough view of the effects of the drug across different subgroups (including LVEF range, atrial fibrillation, NYHA class, C-reactive protein levels, and coronary artery disease).9

It should be noted that the choice of a threshold of 45% of LVEF to define HFpEF includes a significant proportion of HF patients with mildly reduced EF according to European guidelines.10 Thus, the results of these studies may extend the observed clinical benefits of semaglutide beyond the tighter boundaries of HFpEF.

Taken together, the main findings of the individual STEP-HFpEF and STEP-HFpEF DM studies and the pooled analysis may contribute to paving the way for the use of semaglutide in patients with obesity-related HFpEF, and possibly in a broader population across the LVEF spectrum, irrespective of clinical characteristics. Further studies assessing hard endpoints, however, are needed to confirm the positive signals arising from this trial and the pooled analysis. While waiting for such evidence, the present results represent a STEP forward in the direction of a more personalized management of HF in an often neglected group of patients.

Declarations

Disclosure of Interest

D.P. received speaker’s fees from Daichi Sanokey, outside the submitted work. M.V. reports personal fees for speaker bureau and/or consulting in Advisory Boards from Astra Zeneca, Bayer, GSK, Menarini Int, Novartis Pharma, Novo Nordisk, Pfizer, Sanofi Pasteur, and Servier, outside the submitted work. M.V. is supported by a research grant from the Italian Ministry of Health (‘Ricerca corrente’).

References


