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Review Article

Semaglutide For Treatment of Obesity-Related Heart Failure with Preserved Ejection Fraction in Patients with And Without Diabetes

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Abstract

The glucagon-like peptide 1 receptor (GLP-1R) agonist semaglutide is effective for treatment of obesity and type 2 diabetes but its therapeutic role for obesity-related heart failure with preserved ejection fraction (HF-pelf) is unknown. The STEP-HFpEF and STEP-HFpEF DM are 2 randomized trials of similar design and endpoints that evaluated efficacy and safety of semaglutide 2.4 mg/w in obese subjects without and with type 2 diabetes, respectively. The 2 primary endpoints were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) and the percentage change in body weight. After 52 weeks, placebo-corrected amelioration in the KCCQ-CSS was similar in subjects without and with diabetes, 7.8 points (95% CI, 4.8 to 10.9; P<0.001) and 7.3 points (95% CI, 4.1 to 10.4; P<0.001), respectively. However, placebo-corrected weight loss appeared more marked in subjects without diabetes, -10.7 percentage points (95% CI, -11.9 to -9.4; P<0.001) but -6.4 percentage points (95% CI, -7.6 to -5.2; P<0.001) in patients with diabetes. In both trials, semaglutide improved the 6-minute walking distance (6-MWD) albeit more so in subjects without diabetes with placebo-adjusted difference of 20.3 meters (m) (95% CI, 8.6 to 32.1, P<0.001) and 14.3 m (95% CI, 3.7 to 24.9; P< 0.0001) in subjects without diabetes and with diabetes, respectively. In addition, semaglutide decreased levels of C-reactive protein (CRP) similarly in patients with and without diabetes. In the diabetes trial, the effects of semaglutide on the KCCQ-CSS and weight reduction were attenuated in patients receiving sodium-glucose co-transporter 2 (SGLT2) inhibitors. Subgroup analysis of pooled data from the 2 trials suggested that beneficial effects of semifluid on the KCCQ-CSS might be more evident in patients with more advanced HFpEF. Adverse effects led to semaglutide discontinuation in 12% of patients compared with 7% with placebo. The most common cause of semaglutide discontinuation was gastrointestinal (GI) disorders. Overall, semaglutide improved physical performance and reduced weight in obese subjects with HF-pEF with and without diabetes. Long-term randomized trials are needed to evaluate the effects of semaglutide on cardiovascular (CV) events and mortality in obesity-related HF-pEF.

Keywords: heart failure, preserved ejection fraction, semaglutide, obesity, type 2 diabetes

Introduction

HFpEF is defined by left ventricular ejection fraction (LVEF) of ≥ 50% and accounts for approximately half of cases of HF [1]. Obesity is considered one of the strongest risk factors for development of HFpEF [2]. In fact, 60 to 70% of patients with HFpEF are obese [1]. The obese phenotype of HFpEF is characterized by more severe symptoms and decreased quality of life [3]. Type 2 diabetes is a common co-morbidity present in 45% with HFpEF in the USA [4]. Type 2 diabetes is a bad prognostic sign in HFpEF associated with increased mortality independently of other characteristics of HFpEF [5]. The efficacy of the GLP-1 R agonist semaglutide as anti-obesity and anti-diabetic agent is well-established [6-7]. In addition, semaglutide decreased CV events in patients with obesity and diabetes [8-9]. Therefore, semaglutide was recently evaluated in 2 randomized trials as specific treatment for obesity-related HFpEF [10-11]. The first trial called STEP-HFpEF included obese patients without diabetes, whereas the second trial STEP-HFpEF DM enrolled exclusively obese patients with type 2 diabetes [10,11]. Because the 2 trials had similar design and outcomes, their data were pooled in one-specified analysis [12]. The main purpose of this article is to provide an appraisal of semaglutide as a potential therapeutic agent for obese subjects with HFpEF based on the results of the 2 STEP-HFpEF trials.

The STEP-HFpEF and STEP-HFpEF DM trials

The 2 STEP-HF-pEF studies were randomized, double-blind, placebo-controlled and multinational trials of 52-week duration each [10,11]. The 2 co-primary endpoints were the change in KCCQ-CSS and weight from baseline to the end of treatment at 52 weeks [10,11]. The KCCQ-CSS is a questionnaire that measures symptoms, physical and social limitations in patients with heart failure [8]. It is scored from 0 to 100, with higher score reflects less symptoms [8]. Intervention consisted of semaglutide 2.4 mg given subcutaneously once weekly [10,11]. No specific caloric restriction or exercise program was provided [10,11]. Inclusion criteria were body mass index (BMI) ≥30 kg/m^2, New York Heart Association (NYHA) class II-IV, left ventricular ejection fraction (LVEF) ≥45%, KCCQ-CSS of < 90 points and a 6-MWD of at least 100 meters [10,11]. In addition, participants had to have one of the following: elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels plus echocardiographic abnormalities, elevated cardiac filling pressure documented during catheterization, or hospitalization due to heart failure in the previous 12 months of screening plus ongoing treatment with diuretics [10,11]. At study entry, 65% of patients in the 2 trials had BMI of ≥35 kg/m^2, and 69% had NYHA class II symptoms [10,11]. Whereas the median age in both trials was 69, there were some differences between the 2 trials in other patients' demographics (table 1).

Results of the STEP-HFpEF and STEP-HFpEF DM

In patients without diabetes, the mean change in KCCQ-CSS was significantly higher with semaglutide at 52 weeks compared with placebo, 16.6 points and 8.7 points, respectively; estimated difference 7.8 points (95% CI, 4.8 to 10.9; P<0.001) [10]. In patients with diabetes, the mean change in the KCCQ-CSS was similar, 13.7 points and 6.4 points in the semaglutide and placebo group, respectively, estimated difference 7.3 points (95% CI, 4.1 to 10.4; P<0.001) [11]. With respect to weight loss, in subjects without diabetes, the mean percentage weight loss with semaglutide at 52 weeks was -13.3% and -2.6% with semaglutide and placebo, respectively; estimated difference -10.7 percentage points (95% CI, -11.9 to -9.4; P<0.001) [10]. However, in patients with diabetes, weight loss with semaglutide was less pronounced, being -9.8% in the semaglutide group and -3.4% in the placebo group, difference -6.4 percentage points (95% CI, -7.6 to -5.2; P<0.001) [11]. It follows that there was substantial heterogeneity in terms of weight loss according to diabetes status, $P_{interaction}$ <0.0001 [12]. There are 2 explanations for the lesser weight loss in the diabetes trial. First, for unclear reasons, it was repeatedly shown, that weight reduction with incretin-based therapy was less evident in patients with diabetes compared to those without diabetes [13-16]. Second, the proportions of women in the diabetes trial was less than in the trial excluding diabetes 44% and 56%, respectively (table 1). It is known that women exhibit greater weight loss in response to GLP-1 agonists compared with men (see below) [17-18]. Differences in response to semaglutide in patients without diabetes versus those with diabetes are depicted in table 1.

Confirmatory secondary endpoints

Confirmatory secondary endpoints in the 2 STEP-HF-pEF studies included the changes in 6-MWD, change in CRP, and hierarchical composite end point (that included death, heart failure events, differences in KCCQ-CSS and 6-MWD) [10,11]. The latter outcome was calculated by the win ratio statistical approach [10,11]. In subjects without diabetes, the 6-MWD was significantly greater with semaglutide vs placebo, 21.5 m vs 1.2 m; estimated difference, 20.3 m (95% CI, 8.6 to 32.1, P<0.001) [10]. Meanwhile, in patients with diabetes, this difference seemed less prominent. Thus, the 6-MWD increased 12.7 m with semaglutide and decreased 1.6 m with placebo, estimated difference 14.3 m (95% CI, 3.7 to 24.9; P< 0.0001) [11] (table 1). Regarding the hierarchical composite endpoints, treatment with semaglutide resulted in more wins than placebo, with win ratios of 1.72 (95% CI, 1.37 to 2.15; P<0.001) and 1.58 (95% CI,1.29 to 1.94; P<0.001) in participants without diabetes and with diabetes, respectively [10,11]. In both types of patients, the main contributor to the wins for semaglutide was the amelioration of at least 15 points in the KCCQ-CSS [10,11]. Participants randomized to semaglutide had 43% reduction in CRP levels (mean ratio of week 52 value to baseline value was 0.56) compared with 7.3% reduction in those randomized to placebo, estimated treatment ratio 0.61 (95% CI, 0.51 to 0.72), P<0.001 [10]. Similar reductions in CRP levels were observed in the diabetes trial, 42.0% reduction with semaglutide vs 12.8% reduction with placebo, estimated treatment ratio 0.67 (95% CI, 0.55 to 0.80) [11]. Interestingly, in the diabetes trial, glycated hemoglobin levels were significantly decreased in the semaglutide group; placebo-adjusted difference -0.8 percentage points (95% CI, -1.0 to -0.6) [11].

Effect of concomitant therapy with SGLT2 inhibitors on semaglutide efficacy

In the STEP-HFpEF DM trial, 34.5% and 31.0% of patients randomized to semaglutide and placebo, respectively were taking an SGLT2 inhibitor at baseline [11]. Results suggested that the effects of semaglutide on the KCCQ-CSS score and body weight were attenuated in presence of concomitant therapy with SGLT2 inhibitor [11]. Thus, the difference between the semaglutide group and the placebo group in the change in the KCCQ-CSS was 5.3 points (95% CI, -0.2 to 10.7), i.e. non-significant, among participants receiving SGLT2 inhibitors, and 8.3 points (95% CI, 4.5 to 12.1) among those who did not receive SGLT2 inhibitors [11]. Likewise, the placebo-corrected weight reduction was 4.7% (95% CI, 6.7 to 2.87) among subjects receiving SGLT2 inhibitors and 7.2% (95% CI, 8.7 to 5.8%) among those who were not receiving SGLT2 inhibitors [11]. Unfortunately, the authors did not mention whether a significant interaction existed between KCCQ-CSS or weight loss and the use of SGLT2 inhibitors [11]. Nevertheless, these results implied that the beneficial effects of semaglutide combined with SGLT2 inhibitors on HFpEF were less than additive possibly due to some overlap in mechanisms of actions between the 2 drug classes.

Subgroup analysis

Pooling results from the 2 STEP-HFpEF trials resulted in sufficient number of patients that allowed subgroup analysis [12]. Regarding the KCCQ-CSS, pooled data showed greater improvement in placebo-adjusted KCCQ-CSS with semaglutide among patients not receiving RAAS inhibitors 12.4 points (95% CI, 7.7 to 17.1) compared with those receiving RAAS inhibitors 6.2 points (95% CI, 3.8 to 8.7) $P_{interaction}$=0.02 [12]. On the other hand, use of loop diuretics was associated with better KCCQ-CSS (9.3 points, 95% CI, 6.5-12.1) compared with no use of loop diuretics (4.7 points, 95% CI, 1.2-8.2; $P_{interaction}$ =0.04) [12]. In addition, the beneficial effects of semaglutide on KCCQ-CSS were more marked in patients with concomitant atrial fibrillation, and those with median NT-proBNP levels above 475.3 pg/ml [12]. Taken together, this subgroup analysis suggested that beneficial effects of semaglutide on physical functioning might be more evident in patients with more advanced HFpEF.

Effects of gender

By combining data from the 2 trials, there was greater placebo-corrected weight loss with semaglutide in women (n=525) compared with men (n=527) being -9.6% (95% -10.9 to -8.4) and -7.2% (95% -8.4 to -5.9), respectively; $P_{interaction}$ = 0.006 [12]. This finding was consistently observed in trials of GLP-1R based therapy [17,18]. The reasons of greater weight loss in women than in men with GLP-1R agonists are unclear but could be related to lower BMI in women and therefore more exposure to GLP-1 agonists [17,18].

Effects of semaglutide on cardiovascular events

While the 2 STEP-HFpEF were not powered to examine CV events, there was a trend towards reduction of such events in the semaglutide groups. Thus, heart failure hospitalization occurred in 1% (8 of 573) of participants in the semaglutide group versus 5% (30 of 572) in the placebo group, hazard ratio (HR) 0.27 (95% CI, 0.15-0.62; P=0.0004) [12]. Moreover, the risk of CV death or heart failure event was lower in the semaglutide group than placebo, 2% and 6%, respectively, HR 0.31 (95% CI 0.15-0.62; P=0.0008) [12].

Safety of semaglutide

In the pooled data of the 2 STEP-HFpEF trials, semaglutide was discontinued due to adverse effects in 12% of patients compared with 7% with placebo [12]. The most common cause of drug discontinuation were GI disorders, 8% and 3% with semaglutide and placebo, respectively [12]. On the other hand, serious adverse effects occurred in fewer semaglutide-treated patients (16% versus 28% with placebo) owing to decreased serious cardiac disorders in the semaglutide group (5% versus 12% with placebo) [12]. During the 2 trials, 1% and 2% of patients randomized to semaglutide and placebo, respectively died [12]. In the diabetes trial, no increase in clinically significant hypoglycemia was reported in the semaglutide group [12].

Mechanisms of cardiac benefits of semaglutide

Weight loss appears to be a major mechanism whereby semaglutide improved outcomes in obese patients with HFpEF. Thus, amelioration in KCCQ-CSS, 6 MWD and CRP increased in parallel to the magnitude of weight reduction [19]. For instance, for each 10% weight loss, the increase in KCCQ-CSS was 6.4 points (95% CI, 4.1 to 8.8) and in the 6-MWD was 14.4 m (95% CI, 5.5 to 23.3), and the reduction in CRP levels was 28% (95% CI 16 to 37) [19]. However, the fact that patients with diabetes had similar improvements in KCCQ-CCS and 6-MWD despite losing less weight compared with subjects without diabetes suggest other mechanisms besides weight loss [10,11]. Such mechanisms may include decrease inflammation as reflected by reduction in CRP levels, amelioration of glycemic control and microvascular function [20]. Direct effects of semaglutide on cardiac structures are an unlikely mechanism because localization of GLP-1 receptors in human cardiomyocytes and cardiac blood vessels remain elusive [21].

Semaglutide versus sodium-glucose cotransporter 2 inhibitors for treatment of heart failure with preserved ejection fraction

The EMPEROR and DELIVER were 2 landmark trials that showed that the 2 SGLT2 inhibitors, empagliflozin and dapagliflozin decreased rates of hospitalization for heart failure by approximately 23 to 29% in patients with HFpEF irrespective of obesity and diabetes status [22,23]. In the EMPEROR and DELIVER studies, patients were much less obese than in the STEP-HFpEF trial with mean baseline BMI of approximately 29.8 kg/m^2 compared with a median of 37.0 kg/m^2 in the STEP-HFpEF trials (table 2) [12,22,23]. Moreover, empagliflozin therapy was associated with significant increase in the KCCQ-CSS score, although the magnitude of the increase was minimal; difference from placebo being 1.32 (95% CI, 0.45 to 2.19) [22]. Hence, SGLT2 inhibitors are currently considered the treatment of choice for patients with HFpEF [2]. The mechanisms of cardiac benefits of SGLT2 inhibitors are not totally unclear, but their diuretic actions represent a major factor. Weight loss induced by SGLT2 inhibitors is unlikely to play a major role. Indeed, the placebo-adjusted weight loss with empagliflozin in the EMPEROR trial was modest -1.28 kg (95% CI, -1.54 to -1.03) [22]. Table 2 illustrates the main differences between semaglutide and the 2 SGLT2 inhibitors, empagliflozin and dapagliflozin, for treatment of HFpEF.

Advantages and limitations of semaglutide for treatment of HF-Pef Advantages

Semaglutide offers several advantages for treatment of obese patients with HFpEF. First, the significant amelioration in exercise capacity coupled with weight loss. Second, in patients having type 2 diabetes, addition of semaglutide to standard care improved glycemic control without causing hypoglycemia despite the fact that patients' diabetes was fairly controlled at baseline (median glycated hemoglobin a study entry was 6.8 percentage points) [11].

Limitations

Several limitations exist regarding the use of semaglutide in obesity-related HFpEF. First, the 2 available trials were underpowered to examine the effects of semaglutide on hard CV outcomes and mortality. Second, the duration of the trials was relatively short [10-11]. Third, approximately 90% of patients were Whites [10,111]. Therefore, results may not necessarily be applied to non-White races. Fourth, although semaglutide was generally safe, 12% of patients could not tolerate the drug (versus 7% placebo) largely due to GI adverse effects [12]

Conclusion and future needs

No doubt, semaglutide is a promising addition to the management of obesity-related HFpEF with and without type 2 diabetes [10,11]. Its main limitations are absence of data regarding its effects on CV outcomes and mortality and relatively high rates of drug discontinuation due to GI adverse effects [12]. Concomitant therapy with SGLT2 inhibitors seems to attenuate benefits of semaglutide with respect to the KCCQ-CSS and weight reduction [11]. Long-term randomized trials of adequate statistical power are urgently needed to evaluate the impact of semaglutide on CV events and mortality in obese patients with HFpEF. Since most patients in these trials are expected to be on empagliflozin or dapagliflozin therapy as part of standard care, it will be interesting to see whether addition of semaglutide will confer further benefit in terms of CV events and mortality.

Conflict of interest

The authors have no conflict of interest to declare.

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