European Heart Journal Supplements (2024) **26** (Supplement 1), i127–i130
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae011

ESC
European Society
of Cardiology

Role of glucagon-like peptide-1 agonists in obesity and heart failure with preserved ejection fraction

Pier Luigi Temporelli*

Division of Cardiac Rehabilitation, Istituti Clinici Scientifici Maugeri, IRCCS, Gattico-Veruno, Italy

KEYWORDS
Heart failure with preserved ejection fraction;
Obesity;
Semaglutide

Heart failure with preserved ejection fraction (HFpEF) currently represents the majority of all heart failure cases in the community. Glucagon-like peptide-1 agonists represent a class of medications used to treat type 2 diabetes mellitus and, in some cases, obesity. This class includes semaglutide. In the available data from the Semaglutide Treatment Effect in People with Obesity (STEP) trials that were done, looking at weight loss effects of semaglutide, there was a 30–40% reduction in C-reactive protein levels, and that suggests that there is a significant anti-inflammatory effect. Recently, the STEP-HFpEF trial enrolled 529 non-diabetic patients with HFpEF and obesity who were randomly assigned to once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. A statistically significant improvement in the quality of life score and in weight loss was observed. Statistically significant improvements were also seen in the 6 min walk distance, levels of C-reactive protein, and N-terminal pro-B-type natriuretic peptide levels. Interestingly, the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity trial has shown that semaglutide produced a consistent reduction of around 20% vs. placebo across major cardiovascular event endpoints over the ~3-year follow-up in patients with overweight or obesity and cardiovascular disease but not diabetes.

Introduction

The burden of heart failure (HF), particularly heart failure with preserved ejection fraction (HFpEF), currently represents the majority of all HF cases in the community and is not just affecting older individuals.[1] We see more younger folks with obesity coming in with symptoms of shortness of breath and fluid buildup. Our understanding of HFpEF has evolved over the past two or three decades. Initially, it was thought to be a disease of largely impaired myocardial relaxation. Walter Paulus was one of the pioneers who proposed the concept of inflammation leading to HFpEF and obesity being one of the important drivers of the inflammation that leads to the development of HFpEF.[2] Now, our understanding of HFpEF has evolved to it being a multisystem disorder that leads to dysfunction in different organ systems.[3] One of the cardinal features that drives this dysfunction is the up-regulation of inflammatory pathways and increased inflammatory burden, and a lot of that is driven by obesity. Obesity is one of the most important modifiable risk factors for HFpEF.[4] However, a lot of work needs to be done to really understand the key drivers of inflammation and what pathways are being up-regulated. As we know, inflammation is most commonly identified by elevation in levels of C-reactive protein (CRP), which serves as a marker of increased inflammation, but the upstream up-regulation in IL-1- and IL-6-mediated pathways has also been implicated in inflammation that drives the development of diseases like HFpEF.

Are glucagon-like peptide-1 inhibitors anti-inflammatory?

Glucagon-like peptide-1 (GLP-1) agonists (also known as GLP-1 receptor agonists, incretin mimetics, or GLP-1

*Corresponding author. Email: pierluigi.temporelli@icsmaugeri.it

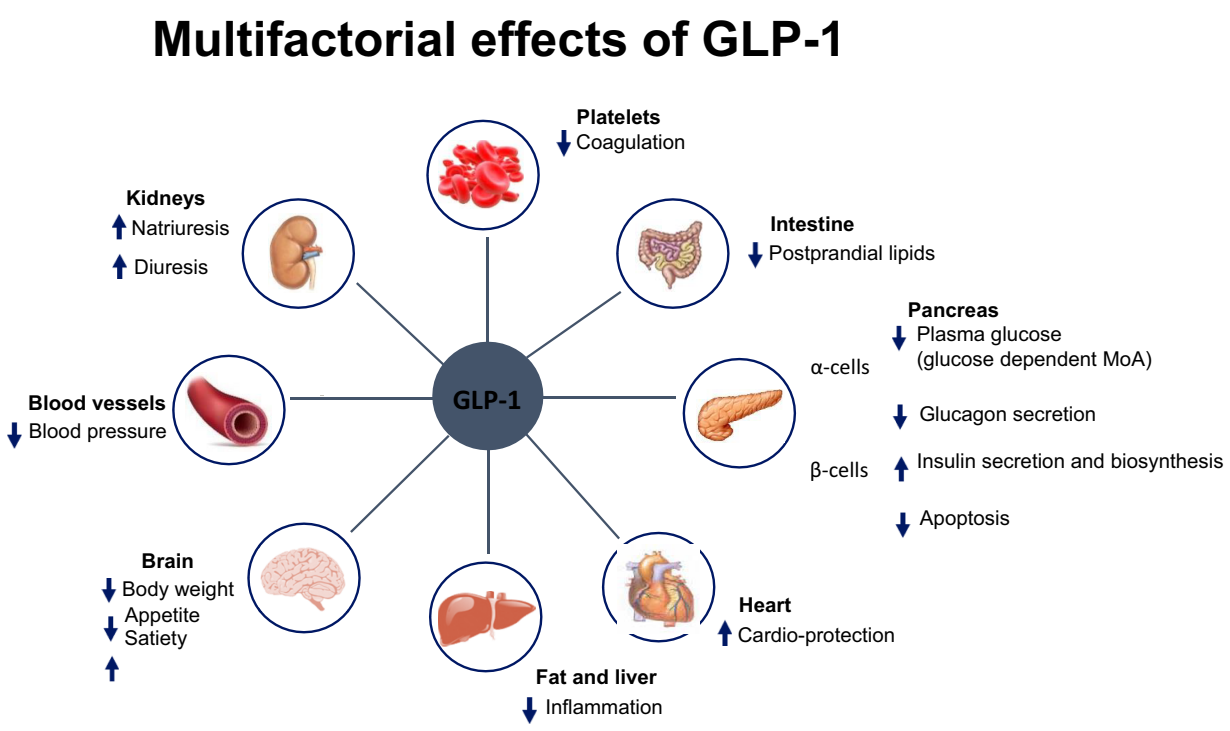

Figure 1 Effects of GLP-1 on various organ systems.

analogues) represent a class of medications used to treat type 2 diabetes mellitus and, in some cases, obesity. Examples of drugs in this class include exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide. According to the American Diabetes Association, metformin remains the preferred first-line therapy for treating type 2 diabetes. However, the addition of a GLP-1 analogue should be considered in patients with a contraindication or intolerance to metformin, in patients with a haemoglobin A1c > 1.5% over target, or in patients who do not reach their target A1c in 3 months, particularly in patients with atherosclerosis, HF, or chronic kidney disease.[5,6] The multifactorial effects of GLP-1 are depicted in *Figure 1*.

The GLP-1 receptor agonists have been on the market for 17 years. The long-acting ones have been on the market for 15 years. GLP-1s, by virtue of causing weight loss and reduction in visceral adiposity and the bad fat depots that exist in our body, have a significant anti-inflammatory effect. In the available data from the Semaglutide Treatment Effect in People with Obesity (STEP) trials that were done, looking at weight loss effects of semaglutide, a commonly used GLP-1 inhibitor, there was a 30–40% reduction in CRP levels, and that suggests that there is a significant anti-inflammatory effect.[7] Now, whether it is a direct effect on anti-inflammatory pathways or is related to weight loss is a matter of debate. In any case, in HFpEF patient population, the majority is obese and has an indication based on diabetes or obesity for the use of weight loss agents like GLP-1s. Recently, semaglutide has been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) as pharmacologic treatments for obesity or can be prescribed to overweight patients with comorbidities.

The STEP-HFpEF trial

The STEP-HFpEF trial combines three of the biggest topics in medicine today: GLP-1 agonists, obesity, and HFpEF. Heart failure with preserved ejection fraction is the most common cause of HF. Obesity worsens the quality of life in patients with HFpEF. Obesity is a likely cause of HFpEF. The GLP-1 agonists have clearly been shown to induce significant weight loss in patients with obesity.

Thus, STEP-HFpEF combines these two givens. That is, if the drug induces weight loss, it ought to improve functional capacity and quality of life. The trial enrolled 529 non-diabetic patients with HFpEF and obesity[8] who were randomly assigned to once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. Patients had to have a body mass index (BMI) > 30 kg/m^2 and an ejection fraction (EF) ≥ 45%. Heart failure with preserved ejection fraction meant having an elevated filling pressure at catheterization, an implantable monitor, or an elevated NT-proBNP with typical echocardiographic features of HFpEF or a hospitalization for HF requiring IV diuretic within the previous 12 months and two other clinical/haemodynamic/echocardiographic features of HFpEF. Average age of the enrolled patients was 69 years, average BMI was 37, and 56% were female. Mean left ventricular EF (LVEF) was 57%. Half had atrial fibrillation, 80% had hypertension, and one-third had coronary artery disease. The dual primary endpoint was weight loss and quality of life as measured by the Kansas

Table 1 Outcomes at 52 weeks, adjusted mean changes by left ventricular ejection fraction category in STEP-HFpEF

Endpoints	LVEF 45–49%, $n = 85$	LVEF 50–59%, $n = 215$	LVEF ≥ 60%, $n = 229$
Change in KCCQ-CSS	+5.0	+9.8	+7.4
% change in body weight	−7.6	−10.6	−11.9
Change in 6MWD (m)	−3.5	+23.9	+27.3
NT-proBNP pg/mL ratio, active vs. control	0.82	0.86	0.82

6MWD, 6 min walk distance; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LVEF, left ventricular ejection fraction; STEP-HFpEF, Semaglutide Treatment Effect in People with Obesity and Heart Failure with preserved Ejection Fraction.

City Cardiomyopathy Questionnaire (KCCQ), which is how patients judge their well-being, on multiple parameters. If both of those endpoints met statistical significance for superiority, then investigators would test secondary endpoints in a hierarchical fashion. First, investigators calculated a win ratio of multiple outcomes, a 6 min walk test, and then a CRP ratio. The win ratio is the proportion of winners randomly assigned to semaglutide divided by the winners randomly assigned to placebo.

Results were quite exciting. Improvements in KCCQ were double the size in the semaglutide arm, which was highly significant. Weight loss was largely greater in the semaglutide arm: 13% loss of body weight in the semaglutide vs. 3% in the placebo arm, which is highly significant. Thus, since both were significant, the secondary endpoints were reported. The 6 min walk was significantly better by 215 m in the semaglutide arm. Win ratio was better for semaglutide by a whopping 1.72–72% better. Finally, mean change in CRP for semaglutide vs. placebo was −43% vs. −7.3%.

Additional pre-specified analyses

In the STEP-HFpEF trial, treatment with once-weekly subcutaneous semaglutide 2.4 mg produced large improvements in symptoms, physical limitations, and exercise function, reduced inflammation, and resulted in greater weight loss compared with placebo in participants with HFpEF and obesity.[8] However, it is not known whether these benefits of semaglutide in STEP-HFpEF vary depending on the degree of health status impairment at baseline. Furthermore, it is important to have a clearer understanding regarding the effects of semaglutide on all key aspects of health status, which include symptoms, physical limitations, quality of life, and social limitations, and on the proportion of patients that experience deterioration, as well as small, moderate, large, and very large improvements across these domains. A pre-specified analysis of the STEP-HFpEF trial answered these questions.[9] Semaglutide consistently improved HF-related symptoms, physical limitations, and exercise function and reduced body weight, CRP, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) regardless of KCCQ-Clinical Summary Score (CSS) at baseline. Moreover, semaglutide-treated patients experienced large improvements in all key health status domains, which collectively reflect symptoms, physical limitations, social limitations, and quality of life. In addition, a greater proportion of semaglutide- vs. placebo-treated patients experienced small, moderate, large, and very large improvements across all of these domains.

In a subsequent pre-specified analysis, which was finalized in the statistical analysis plan before database lock, the effects of semaglutide on the primary, confirmatory secondary, and select exploratory endpoints in patients with LVEF of 45–49%, 50–59%, and >60% were described.[10] At 52 weeks, semaglutide improved the dual primary endpoints of KCCQ-CSS {estimated treatment difference: EF 45–49%: 5.0 points [95% confidence interval (CI): 2.7–12.8 points], EF 50–59%: 9.8 points [95% CI: 5.0–14.6 points], and EF > 60%: 7.4 points [95% CI: 2.8–12.0 points]; *P* interaction = 0.56} and body weight [EF: 45–49%: 7.6 (95% CI: 10.7–4.4), EF 50–59%: 10.6 (95% CI: 12.6–8.6), and EF > 60%: 11.9 (95% CI: 13.8–9.9); *P* interaction = 0.08], to a similar extent across LVEF categories (*Table 1*). Likewise, LVEF did not influence the benefit of semaglutide on confirmatory secondary endpoints: 6 min walk distance (6MWD) (*P* interaction = 0.19), hierarchal composite endpoint (*P* interaction = 0.43), and high-sensitivity CRP (*P* interaction = 0.26) or exploratory endpoint of NT-proBNP (*P* interaction = 0.96). These data support treatment with semaglutide in patients with the obesity phenotype of HFpEF regardless of LVEF. Of relevance, the NT-proBNP finding was very meaningful with respect to understanding potential mechanisms of the drug effects observed in the trial. For example, people with obesity tend to have lower than average natriuretic peptide levels that actually go up a bit when they lose weight. But in the trial, a reduction in NT-proBNP in spite of the weight loss was seen, regardless of LVEF category. This raises the question whether weight loss was the sole semaglutide effect responsible for the improvement in HF status and biomarkers. The accompanying NT-proBNP reductions—when the opposite might otherwise have been expected—may point to a possible mechanism of action that is something more than just weight loss. If that were the case, it becomes very important, because it means that this treatment might do good things in non-obese patients or might do good things in patients with other types of HF. It remains unknown, however, whether the improvement in health status, functional status, and reduced inflammation will translate to reduced risk of cardiovascular death or HF hospitalization. It is a question for future studies whether semaglutide would confer similar benefits for patients with obesity and HF with LVEF < 45% or in non-obese HF patients.

In summary, adults with HFpEF but without diabetes showed significant improvements in their HF-related symptoms and physical limitations, exercise function, and weight loss when treated with a weight-reducing dose of semaglutide for 52 weeks compared with placebo in the randomized STEP-HFpEF trial. The results, which also showed the treatment's safety in these patients, indicate that treatment with semaglutide is a valuable therapeutic approach in the management of patients with HFpEF and obesity. The findings establish semaglutide as a second class of medication with proven efficacy and safety for people with HFpEF, joining two agents also proven beneficial for people with HFpEF, dapagliflozin and empagliflozin, both from the class of sodium–glucose cotransporter 2 (SGLT2) inhibitors.

A new pathway to cardiovascular disease risk reduction: SELECT

Final results of the SELECT trial have shown that the anti-obesity drug semaglutide produced a consistent reduction of around 20% vs. placebo across major cardiovascular event endpoints over the ~3-year follow-up in patients with overweight or obesity and cardiovascular disease but not diabetes.[11] The trial involved 17 604 patients with a history of cardiovascular disease and a BMI of 27 or above (mean BMI was 33), who were randomly assigned to the GLP-1 agonist semaglutide, given by subcutaneous injection once weekly at a gradually escalating dose up to 2.4 mg, or placebo. The mean baseline glycated haemoglobin level was 5.8%.

Patients lost a mean of 9.4% of body weight over the first 2 years with semaglutide vs. 0.88% with placebo.

The primary cardiovascular endpoint—a composite of death from cardiovascular causes, non-fatal myocardial infarction (MI), or non-fatal stroke—was reduced significantly, with a hazard ratio (HR) of 0.80 (95% CI, 0.72–0.90; $P < 0.001$). Death from cardiovascular causes, the first confirmatory secondary endpoint, showed a 15% reduction (HR, 0.85; $P = 0.07$), but this missed meeting criteria for statistical significance, and because of the hierarchical design of the trial, this meant that superiority testing was not performed for the remaining confirmatory secondary endpoints. However, the HR for the HF composite endpoint was 0.82 (95% CI; 0.71–0.96), and the HR for death from any cause was 0.81 (0.71–0.93). Non-fatal MI was reduced by 28%, HR 0.72 (95% CI; 0.61–0.85). Moreover, nephropathy and revascularization were also reduced, and even stroke was numerically lower. The effects of semaglutide on the primary endpoint appeared to be similar across all pre-specified subgroups.

These data prove that losing weight can reduce cardiovascular morbidity and mortality. This has been described as great news for patients living with obesity and the beginning of a whole new era for patients with obesity. Since the obesity epidemic is out of control, therapies that improve cardiovascular outcomes caused by obesity are very welcome and semaglutide appears to do that.

Conclusions

The STEP-HFpEF and SELECT results will trigger a paradigm shift for cardiologists, who will now need to consider prescribing a weight loss medication to many of their patients, agents that until now were not part of the usual pharmacologic toolbox for cardiologists. The encouraging findings for semaglutide in patients with HFpEF potentially add a much needed extra option for these patients and provide another upstream treatment for patients with signs of this condition plus a high BMI. How these findings translate to hard endpoints remains to be established and will be important in determining the role of GLP-1 agonism.

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, *et al*. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;**391**:572–580.
2. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–271.
3. Redfield MM, Borlaug BA. Heart failure with preserved ejection fraction: a review. *JAMA* 2023;**329**:827–838.
4. Sorimachi H, Omote K, Omar M, Popovic D, Verbrugge FH, Reddy YNV, *et al*. Sex and central obesity in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2022;**24**:1359–1370.
5. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care* 2019;**42**:S90–S102.
6. Davidson MH. Cardiovascular effects of glucagonlike peptide-1 agonists. *Am J Cardiol* 2011;**108**:33B–41B.
7. Verma S, Bhatta M, Davies M, Deanfield JE, Garvey WT, Jensen C, *et al*. Effects of once-weekly semaglutide 2.4 mg on C-reactive protein in adults with overweight or obesity (STEP 1, 2, and 3): exploratory analyses of three randomised, double-blind, placebo-controlled, phase 3 trials. *EClinicalMedicine* 2022;**55**:101737.
8. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M *et al*. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med* 2023;**389**:1069–1084.
9. Kosiborod MN, Verma S, Borlaug BA, Butler J, Davies MJ, Jon Jensen T, *et al*. Effects of semaglutide on symptoms, function, and quality of life in patients with heart failure with preserved ejection fraction and obesity: a prespecified analysis of the STEP-HFpEF trial. *Circulation* 2024;**149**:204–216.
10. Butler J, Abildstrøm SZ, Borlaug BA, Davies MJ, Kitzman DW, Petrie MC, *et al*. Semaglutide in patients with obesity and heart failure across mildly reduced or preserved ejection fraction. *J Am Coll Cardiol* 2023;**82**:2087–2096.
11. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, *et al*. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221–2232.