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EDITORIAL
Heart failure and cardiomyopathies

STEPping down diuretic therapy with semaglutide in obesity-related heart failure with preserved ejection fraction: decongestion or disease modification?

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This editorial refers to 'Semaglutide and diuretic use in obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF-DM trials', by S.J. Shah *et al.*, https://doi.org/10.1093/eurheartj/ehae322.

Congestion is a clinicopathological hallmark of heart failure (HF) and remains the primary driver of HF hospitalization.[1] As such, decongestive therapies, primarily loop diuretics, have long been firmly recommended in HF clinical practice guidelines to alleviate HF-related signs and symptoms.[2] However, while loop diuretics remain critically important interventions when necessary, their use identifies individuals with more severe and/or progressive disease, and may additionally provoke hypotension, electrolyte and metabolic abnormalities (e.g. hypokalaemia, hypochloraemia, hyperuricaemia, and reduced plasma osmolality), neurohormonal activation, and adverse kidney events.[1,3] Hence, prevention or de-escalation of loop diuretic therapy with newer HF treatment approaches may be an attractive ancillary benefit and may even provide evidence of disease modification.

Indeed, sacubitril/valsartan, mineralocorticoid receptor antagonists (MRAs), and sodium–glucose co-transporter 2 inhibitors (SGLT2i), therapies shown to be effective in ameliorating clinical outcomes, have been shown to reduce loop diuretic requirements among individuals with HF with preserved ejection fraction (HFpEF).[4–8] However, prior trials did not explicitly target obesity-related HFpEF, which is associated with higher filling pressures and other unique mechanisms of congestion—such as higher resting and stressed intravascular volume, enhanced ventricular interaction, and reduced pulmonary vasodilator reserve—that may be less effectively targeted by conventional decongestive strategies.[9] Indeed, individuals with obesity often have attenuated diuretic responsiveness, leading to higher decongestive therapy requirements.[3–6,10] Individuals with obesity-related HFpEF also appear to be at enhanced risk of decongestion-related adverse effects, especially worsening kidney function.[3,10] As such, there is a particularly high demand for loop diuretic-sparing treatment strategies targeting phenotype-specific congestive mechanisms in this population.

In the STEP-HFpEF (Semaglutide Treatment Effect in People with Obesity and HFpEF) and STEP-HFpEF DM (Semaglutide Treatment Effect in People with Obesity, HFpEF, and Type 2 Diabetes) trials, semaglutide (2.4 mg)—a glucagon-like peptide-1 receptor agonist (GLP-1RA)—improved body weight, HF-related symptoms and physical limitations, exercise function, systemic inflammation, natriuretic peptides, and adjudicated HF events (albeit based on few captured events) compared with placebo.[11] However, whether treatment effects of semaglutide vary in relation to background diuretic therapy, and whether semaglutide influences post-baseline diuretic use, remains uncertain.

In this issue of the *European Heart Journal*, Shah *et al.* report the findings of a pre-specified secondary analysis of the pooled STEP-HFpEF and STEP-HFpEF DM trials,[12] providing further insight into (i) the safety and efficacy of once-weekly semaglutide (2.4 mg) by baseline diuretic use, and (ii) effects of semaglutide compared with placebo on loop diuretic dose, initiation, and discontinuation among individuals with obesity-related HFpEF. Overall, higher loop diuretic dose at baseline was associated with higher body mass index and waist circumference, worse HF-related symptoms and exercise function, lower left ventricular ejection fraction, higher natriuretic peptide levels, and greater use of MRAs and insulin. Between baseline and 52 weeks, semaglutide was well tolerated and consistently improved body weight, 6-min walk distance, natriuretic peptide levels, and high-sensitivity C-reactive protein levels irrespective of baseline loop diuretic use. However, despite similar body weight reduction, participants using loop diuretics at baseline appeared to have greater benefit on HF-related symptoms and physical

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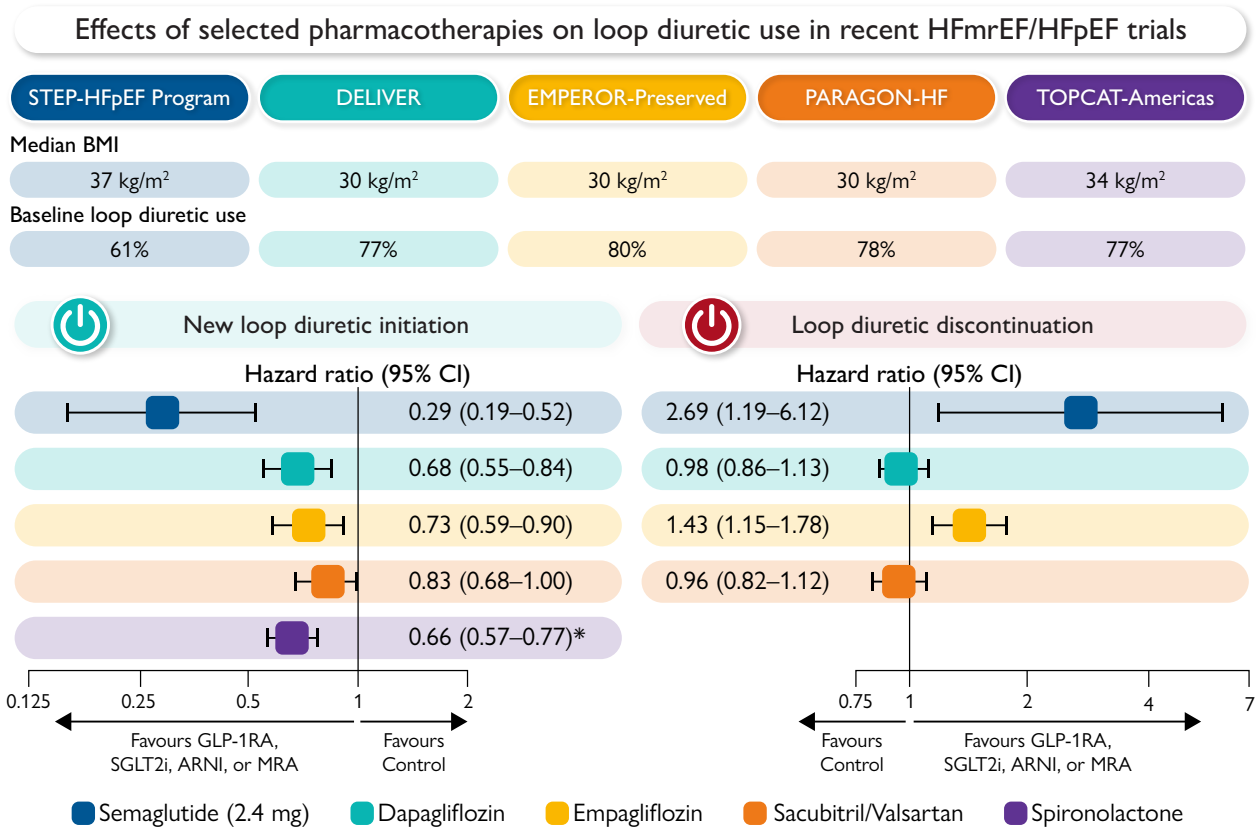
Graphical Abstract



*Hazard ratio reflects reported treatment effects of spironolactone vs. placebo on outpatient loop diuretic intensification (either new introduction or dose escalation). Discontinuations were not evaluated.

The median loop diuretic dose in each trial was 40 mg furosemide equivalents per day. Although between-trial comparisons should be cautiously interpreted (only the STEP-HFpEF Program explicitly targeted obesity-related HFmrEF/HFpEF), loop diuretic therapy initiations and discontinuations appear greater with once-weekly semaglutide (2.4 mg) compared with SGLT2i and ARNI. These findings are broadly consistent with between-trial treatment effects on loop diuretic dose escalations and reductions, supporting a decongestive effect of semaglutide in obesity-related HFmrEF/HFpEF, potentially as part of a broader disease-modifying role.

Abbreviations: ARNI = angiotensin receptor–neprilysin inhibitor; BMI = body mass index; DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; GLP-1RA = glucagon-like peptide-1 receptor agonist; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid receptor antagonist; PARAGON-HF = Prospective Comparison of ARNI with ARB [angiotensin -receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction; STEP-HFpEF = Semaglutide Treatment Effect in People with Obesity and HFpEF; SGLT2i = sodium–glucose co-transporter 2 inhibitor; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

limitations compared with those not using loop diuretics at baseline [Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS), +9.3 vs. +4.7; $P_{interaction} = .042$]. Further, participants treated with semaglutide had nearly three-fold higher rates of diuretic dose reduction (including sustained reductions) and diuretic discontinuation, as well as approximately three-fold lower rates of diuretic dose escalation and new initiation, when compared with placebo. The authors concluded that these findings support a primary decongestive effect of semaglutide in obesity-related HFpEF.

Taken together, the authors should be congratulated for a rigorous, timely, clinically relevant, and mechanistically informative analysis of two landmark clinical trials. However, it is important to emphasize several key limitations. First, the trials were not designed to evaluate treatment effects of semaglutide on decongestion, or its relationship to weight change, natriuretic peptides, or systemic inflammation. As such, subgroup analyses may be underpowered, and the lack of direct measurement of urine output, natriuresis, and filling pressures limits mechanistic insights. Second, between-subgroup variation in background medications known to influence congestion and diuretic responsiveness, such as insulin, was not explicitly addressed and may have contributed to study findings. Third, diuretics may be de-escalated for reasons other than improvements in disease status or congestion (e.g. changes in kidney function, suspected or confirmed volume depletion, electrolyte derangements, improvements in venous insufficiency, or reduced dietary sodium intake related to the anorexigenic effects of semaglutide); systematic capture of drivers of the observed changes diuretic therapy may have facilitated greater mechanistic understanding. Fourth, because the first post-baseline time point assessed in this analysis was 20 weeks (vs. ~2 weeks in prior trials), the timing of any decongestive effects of semaglutide remains unclear.

The above limitations notwithstanding, this analysis offers several important messages of immediate and future relevance to both clinical care and research efforts. First, higher adiposity at baseline in the STEP-HFpEF Program was associated with a more advanced HF phenotype. These

findings support and extend those from other HFpEF trials,[4–6] emphasizing the importance of positioning weight management as a core component of holistic HFpEF care targeting root causes of HF onset and progression.

Second, treatment with semaglutide improved body weight and HF-related symptoms and physical limitations irrespective of baseline diuretic therapy. Owing to their established gastrointestinal and chronotropic effects, there may be theoretical concerns regarding implementation of incretin-based therapies among individuals with more advanced obesity-related HFpEF phenotypes. This analysis suggests that once-weekly semaglutide can be safely and effectively initiated and titrated even among individuals with the highest loop diuretic requirements—a population characterized by older age, substantial HF-related health status impairment, greater comorbidity burden, and highest natriuretic peptide levels in this analysis.

Third, while more modest effects of sacubitril/valsartan and SGLT2i on diuretic therapy in other HFpEF trials (*Graphical Abstract*) have argued against anticipatory loop diuretic dose reduction,[4,5] the relatively high rate of loop diuretic de-escalation in the STEP-HFpEF Program (~1 in 7 participants) suggests that clinicians should be aware of the potential need for diuretic dose adjustment after semaglutide initiation. However, the somewhat lower background loop diuretic use (including lower use of higher-dose diuretic therapy) among STEP-HFpEF Program participants may have contributed to the higher rates of discontinuation compared with other HFpEF trials. As weight change may be a less reliable surrogate for volume status among semaglutide-treated individuals, other forms of monitoring (e.g. timely clinical follow-up and physical examination) may be needed to ensure appropriate diuretic management. More evidence is needed to guide diuretic management following introduction of incretin-based therapies in HF populations.

Fourth, the observation that, despite comparable weight reduction, benefits on KCCQ-CSS appeared to be greater among those with loop diuretic use at baseline is of immense interest and highlights potential for weight-independent benefits—in addition to previously observed weight-related benefits[13]—of semaglutide in obesity-related HFpEF. Critically, this finding should be interpreted with caution due to important between-subgroup differences in baseline characteristics, potential for post-randomization factors (e.g. insulin may have been de-escalated in the semaglutide arm, but not in the placebo arm), and lack of observed heterogeneity for other outcomes. However, it might be reasonable to propose that higher dose loop diuretic use in the STEP-HFpEF Program identified individuals with persistent congestion or mechanisms of health status impairment (including congestion) inadequately addressed by loop diuretic therapy. Hence, this population may have been most 'sensitive' to the decongestive effects of semaglutide. Synergistic effects of GLP-1RAs with other HF pharmacotherapies might also be possible.

There are several potential decongestive mechanisms of GLP-1RAs and other incretin-based therapies in obesity-related HFpEF. First, GLP-1RA administration has been shown to enhance short-term afferent renal arteriolar vasodilation, renal blood flow, and natriuresis—effects possibly mediated via the canonical GLP-1R, inactivation of the Na^+/H^+ exchanger 3, and reduced neurohormonal activation—all potentially enhanced in the presence of circulatory congestion.[14] Similar mechanisms may attenuate reflex renal vasoconstriction in response to loop diuretic therapy, a major driver of diuretic resistance. GLP-1RAs have also been shown to reduce kidney inflammation and preserve kidney structure and function—the latter demonstrated in the recent FLOW (Evaluate Renal Function with Semaglutide Once Weekly) trial[15]—which may be especially relevant for individuals with high decongestive therapy requirements.[14] Further, GLP-1RAs may target congestion and volume expansion by reducing adiposity, pericardial restraint, and adverse ventricular interaction—core features of obesity-related HFpEF.

In conclusion, this is an important analysis providing key insights into the role and mechanisms of once-weekly semaglutide (2.4 mg) in obesity-related HFpEF. The consistent safety and efficacy of semaglutide, irrespective of baseline diuretic use, supports broad implementation to improve HF-related health status in this population (especially among those with congestion inadequately addressed with loop diuretic therapy), but more robust outcome data are needed to formalize these recommendations. The potential for weight-independent benefits is of substantial interest and aligns thematically with GLP-1RA cardiovascular outcome trials in type 2 diabetes (wherein body weight reduction was more modest) and recently reported findings from SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity), in which cardiovascular benefits were similar irrespective of the degree of weight reduction.[16] Overall, the totality of evidence—including weight-independent and weight-dependent benefits, amelioration of pathobiological root causes, and prevention/reduction of loop diuretic requirements—supports a broader disease-modifying effect of semaglutide in obesity-related HF, rather than decongestion alone.

Declarations

Disclosure of Interest

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