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REVIEW

Obesity, heart failure with preserved ejection fraction, and the role of glucagon-like peptide-1 receptor agonists

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Abstract

Heart failure with preserved ejection fraction (HFpEF) has a high prevalence, affecting more than 50% of patients with heart failure. HFpEF is associated with multiple comorbidities, and obesity is one of the most common. A distinct phenotype has been proposed for obese patients with HFpEF. Recent data show the beneficial role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for weight loss in diabetic and non-diabetic patients with obesity or overweight when given as adjunctive therapy to diet and exercise. The mechanisms of action are related to paracrine and endocrine signalling pathways within the gastrointestinal tract, pancreas, and central nervous system that delay gastric emptying, decrease appetite, augment pancreatic beta-cell insulin secretion, and suppress pancreatic glucagon release. These drugs are therefore potentially indicated for treatment of patients with HFpEF and obesity or overweight. Efficacy and safety need to be shown by clinical trials with a first one, Semaglutide Treatment Effect in People with obesity and heart failure with preserved ejection fraction (STEP HFpEF), recently concluded. The aim of the present review is to provide the pathophysiological and pharmacological rationale for GLP-1 RA administration to obese patients with HFpEF.

Keywords Heart failure with preserved ejection fraction; Glucagon-like peptide-1 receptor agonists; Obesity

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Background: role of obesity in heart failure with preserved ejection fraction

The prevalence of heart failure (HF) with preserved ejection fraction (HFpEF) is around 4.9% in the general population aged over 60 years, and HFpEF affects more than 50% of the patients admitted for HF.[1–4] Thus, several millions of people are affected by HFpEF in Europe and the United States. The prevalence of obesity is growing in many developed countries. In the United States, more than 40% of the general population is obese, and it is projected that at least half of the population will be obese in 2030.[5,6] A specific and independent relationship exists between obesity and HFpEF so that these patients have peculiar clinical and haemodynamic features and obesity may be considered not a mere comorbidity but rather a direct cause of HFpEF itself.[7–10] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have recently been shown to be an effective treatment of obesity and diabetes. They are therefore potentially useful, if not of choice, for the patients with HFpEF and obesity.[9,11] This article will review the rationale for this treatment.

The obesity heart failure with preserved ejection fraction phenotype

Mechanisms

Obesity leads to a biological transformation of the adipose tissue towards an inflammatory state, and this may have adverse effects on the structure and function of the vasculature and most visceral organs.[12,13] Expansion of visceral adipose tissue causes oxidative stress, release of pro-inflammatory adipokines, activation of renin–angiotensin–aldosterone system, adipocyte apoptosis, autophagy, and gut microbiota dysbiosis: these mechanisms lead to insulin resistance with type 2 diabetes mellitus (T2DM), dyslipidaemia, increased vascular stiffness and hypertension, coronary artery disease, and eventually HF, namely, HFpEF.[14–16]

Inflammation can also cause microvascular impairment and fibrosis in the heart and also in the lungs, kidneys, liver, pancreas, and skeletal muscle, leading to the characteristic comorbidities of HFpEF.[17–21] Coronary microvascular endothelial dysfunction is observed with increased expression of endothelial adhesion molecules in myocardial biopsy samples of HFpEF patients, including vascular cell adhesion molecule and E-selectin.[22,23] Pro-inflammatory cytokines are also known to elicit endothelial production of reactive oxygen species through activation of nicotinamide adenine dinucleotide phosphate oxidases.[24] This can cause the high nitrosative/oxidative stress, which has been observed in HFpEF myocardium[22,25] and which is also exacerbated in typical comorbidities of HFpEF patients, such as T2DM, and physiological processes, such as ageing.[26,27]

Moreover, it has been shown that overall obesity and higher amount of visceral adipose tissue are associated with greater abnormalities in cardiac structure and function, with higher left ventricular (LV) mass, greater LV concentric hypertrophy, and higher degree of LV diastolic dysfunction.[28] A higher amount of adipose tissue is also associated with plasma volume expansion and impairment in LV relaxation potentially through systemic inflammation. This may contribute to limited ventricular distensibility, higher LV filling pressures, and signs and symptoms of HF.[29–32]

Obesity also affects both resting and exercise-related respiratory physiology. Severe obesity classically produces a restrictive ventilatory abnormality.[33] A peculiarity in these subjects is that decreased peak work rates are usually seen in a setting of normal or decreased ventilatory reserve and normal cardiovascular (CV) response to exercise.[34–36]

On the other hand, even asymptomatic severely obese subjects may develop abnormal echocardiographic indices of LV diastolic filling during exercise, as compared with matched lean controls.[37] This may represent a subclinical form of cardiomyopathy in obese subjects. Considering the poor prognosis of HFpEF in obese patients, we believe that the early identification of these patients and their relatively targeted treatment could represent the turning point in the natural history of the pathology.

Clinical characteristics

There is a high prevalence of T2DM in patients with HFpEF, and the presence of T2DM has been shown to increase mortality of patients with HFpEF by 30–50% even after adjustment for age, gender, hospital factors, and other patient characteristics. Unlike HF with reduced ejection fraction (HFrEF), HFpEF has distinct clinical phenotypes, and the obese–diabetic phenotype is the most often encountered phenotype in clinical practice.[38,39]

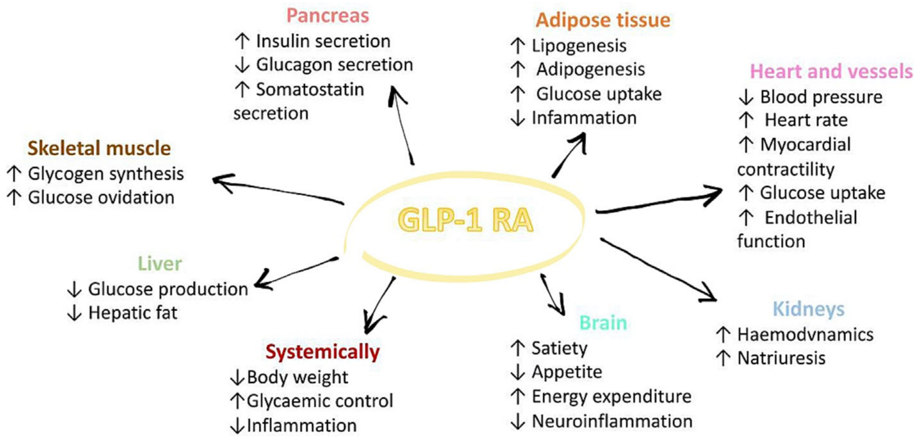
In the Phosphodiesterase-5 inhibition to improve clinical status and Exercise capacity in Diastolic HF (RELAX) trial,[40] body mass index (BMI) was 37.1 vs. 30.7 kg/m^2 in patients with and without T2DM. In this category of patients, LV remodelling was more relevant and associated with reduced ventricular compliance with increased systemic and pulmonary venous pressures and congestion despite preserved systolic function.[41]

In addition to the systemic inflammatory state, obesity is also associated with peculiar abnormalities in patients with HFpEF (*Figure 1*). Specific circulating biomarkers patterns have been identified in obese HFpEF patients, supporting the clinical definition of a distinct obese HFpEF phenotype.[42] Obese HFpEF patients exhibit higher circulating biomarkers of volume expansion [adrenomedullin (ADM)], myocardial fibrosis (thrombospondin-2), and systemic inflammation (galectin-9 and glycoprotein CD4) compared with obese non-HFpEF or lean HFpEF patients.[42] With the only exception of CD4, these proteins were linearly related with increased left atrial (LA) pressure. Importantly, ADM and CD4 were associated with increased mortality in obese HFpEF patients.[42]

The characteristics of the obese patients with HFpEF were compared with those of the normal subjects and with those of the non-obese patients with HFpEF, thus showing the peculiarity of the obese HFpEF phenotype. Obese patients with HFpEF had an increased plasma volume, epicardial fat thickness, and total heart volume. LV mass was increased with concentric LV hypertrophy, and right ventricular (RV) volume was larger with more severe RV dysfunction. The increase in heart volume and in ventricular interdependence was attended by an increased ratio of right- to left-sided heart filling pressures, higher pulmonary venous pressure, relative to LV transmural pressure, and greater LV eccentricity index, defined as the ratio of the anterior–inferior and septal–posterolateral cavity dimensions at the mid-ventricular level. Pulmonary capillary wedge pressure was slightly but significantly correlated with body mass and plasma volume in obese HFpEF (r = 0.22 and 0.27, both $P < 0.05$) but not in non-obese HFpEF ($P \geq 0.3$).[10] Venous compliance is decreased, thus contributing, in addition to the increased blood volume, to increased filling pressure and peripheral congestion.[15]

Compared with the non-obese HFpEF patients and control subjects, obese patients with HFpEF displayed worse exercise capacity (peak oxygen consumption, 7.7 ± 2.3 vs. 10.0 ± 3.4 and 12.9 ± 4.0 mL/kg/min; $P < 0.0001$), higher biventricular filling pressures with exercise, and impaired pulmonary artery vasodilator reserve.[10]

Figure 1 Direct and indirect effects of glucagon-like peptide-1 receptor agonist (GLP-1 RA) in heart failure with preserved ejection fraction (HFpEF). The figure shows currently known or suggested direct and indirect effects of GLP-1 RA in HFpEF in all human organs.



Along with abnormalities related to obesity, increased epicardial adipose tissue (EAT) has been shown to be associated with cardiac abnormalities and represents a pathological feature of obese HF patients.[43–45] Among obese patients with HFpEF, the presence of increased EAT is associated with greater haemodynamic impairment at rest and exercise, with a greater elevation in cardiac filling pressures, more severe pulmonary hypertension, and greater pericardial restraint.[46] The greater external restraint on the heart may alter the relationship between intravascular pressures and stress markers among obese patients complaining dyspnoea. In this context, standard biomarkers, namely, natriuretic peptides, may underestimate circulatory congestion leading to under-recognition of its clinical signs in patients with obesity.[47]

EAT is greater in obese HFpEF patients compared with the HFrEF ones and is associated with worse LA and LV function as shown by echocardiographic strain analysis.[48] Among HFpEF patients, increased EAT was also associated with worse haemodynamic and metabolic profile expressed by proteomic markers of inflammation, insulin resistance, and endothelial dysfunction,[45] expressed by effort intolerance, and impaired left atrioventricular and right ventriculo-arterial coupling.[49]

Glucagon-like peptide-1

Glucose homeostasis is dependent upon a complex interplay of multiple hormones: (i) insulin and amylin, produced by pancreatic beta cells; (ii) glucagon, produced by pancreatic alpha cells; and (iii) gastrointestinal peptides, including glucagon-like peptide-1 (GLP-1), and gastric inhibitory polypeptide, a glucose-dependent insulinotropic polypeptide.[50] The role of GLP-1 in glucose homeostasis is related to its incretin effect and is shown by the greater stimulatory effect on insulin secretion of oral glucose compared with intravenous glucose, as GLP-1 is released from intestinal L cells in response to nutrients.[51]

GLP-1 is produced from the proglucagon gene in L cells of the small intestine and is secreted in response to nutrients and binds to a specific GLP-1 receptor, which is expressed in various tissues, including pancreatic beta cells, kidney, lung, heart, brain, gastric mucosa, and other organs.[52] GLP-1 exerts its main effect by stimulating glucose-dependent insulin release from the pancreatic islets, but it also slows gastric emptying and inhibits inappropriate post-meal glucagon release, thus also reducing food intake. The satiety effect of GLP-1 may involve both meal entero-enteric reflexes and central signalling mechanisms that mediate changes in appetite and promote satiety.[53,54] Given its effects on slowed gastric emptying and on appetite centres in the hypothalamus, therapy with GLP-1 and its receptor agonists is associated with weight loss (*Figure 1*).[55]

Glucagon-like peptide-1 receptor agonists

Synthetic GLP-1 RAs are variably resistant to degradation by the enzyme dipeptidyl peptidase 4 and therefore have a longer half-life, with consequent favourable pharmacological effects. They bind to the GLP-1 receptor and stimulate glucose-dependent insulin release from the pancreatic islets, as described above. They do not usually cause hypoglycaemia in the absence of therapies that otherwise can cause it.[56]

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Results in patients with type 2 diabetes

GLP-1 receptor agonists reduce the risk of myocardial infarction (MI), stroke, and CV death in patients with T2DM.[11,57] Randomized controlled trials (RCTs) have demonstrated a reduction in CV events with liraglutide,[58] once-weekly semaglutide,[59] dulaglutide,[60] and albiglutide,[61] whereas lixisenatide, extended-release exenatide, and oral semaglutide showed a neutral effect (*Table 1*).[65–67]

In the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, the primary composite outcome of CV death, non-fatal MI, or non-fatal stroke was significantly lower in the liraglutide group as compared with the placebo group (13% vs. 15%, $P < 0.001$ for non-inferiority.[58] These beneficial effects observed in patients with no history of HF were, however, not replicated in patients with HF at baseline.

Results in patients with heart failure

Given the results derived from RCTs, international scientific societies currently recommend the use of GLP-1 RAs as part of a comprehensive strategy to reduce the risk of CV events in patients with T2DM,[11,57] though, not yet, for the prevention of HF in patients with diabetes.[2]

Overall, although hospitalization for HF did not represent the primary endpoint of the main RCTs, GLP-1 RAs slightly reduced the risk of hospitalization for HF by 11% (*Figure 2*).[77,78] However, their effects on HF-related events were different depending on the patients treated. HF events were reduced in diabetic patients with no HF at baseline whereas they were generally not changed in the RCTs enrolling patients with HF. A further distinction is possible depending on the HF phenotype with a possible increased risk of HF events in the patients with HFrEF at baseline and, on the opposite, beneficial effects in the patients with HFpEF above all with concomitant obesity.[79–81]

With respect of the results in patients with HFrEF, liraglutide had no effect on LV ejection fraction (LVEF), increased heart rate, and increased serious cardiac events in a randomized placebo-controlled trial in 241 patients with HFrEF with and without diabetes.[82] A significant increase in serious cardiac events, although with small numbers, 12 (10%) with liraglutide vs. 3 (3%) with placebo ($P = 0.04$), occurred in another small randomized trial in patients with HFrEF.[83] Results could be ascribed to the increase in heart rate with liraglutide. Similar trends were observed also with other GLP-1 RAs.[60,61]

In a *post hoc* analysis of the Harmony Outcomes trial,[61] albiglutide, compared with placebo, reduced the composite of CV death or HF hospitalization as well as HF hospitalizations alone in patients without HF history but not in those with a history of HF (interaction $P = 0.062$ and 0.025, respectively). In a *post hoc* analysis from REWIND, dulaglutide was not associated with a reduction in HF events in patients with T2DM regardless of baseline HF status over 5.4 years of follow-up.[60,84]

Different results are likely in patients with HFpEF, above all if the obesity phenotype (see below).

Results in patients with obesity

Along with the benefits on CV outcome, it has been shown that the administration of GLP-1 RA is associated with weight loss regardless of the diabetic status, although this may be less in patients with diabetes.[85–87] A systematic review comparing GLP-1 RA with placebo in patients with T2DM and suboptimal control on oral agents showed that all GLP-1 RAs except albiglutide reduce body weight.

Liraglutide has been shown to be effective for weight loss in non-diabetic patients with obesity or overweight when given as adjunctive therapy to diet and exercise (*Table 1*).[62-64,88] Semaglutide is also highly effective in both patients with and without T2DM (*Table 1*).[70,71,73,89–91] Its efficacy was greater compared with other agents. In the SUSTAIN trials, a slightly greater weight loss has been observed with subcutaneous once-weekly semaglutide, compared with exenatide, dulaglutide, or liraglutide.[91–93] Similarly, a secondary analysis of PIONEER 4 showed a greater weight loss with once-daily oral semaglutide compared with subcutaneous liraglutide.[71,90]

The 'STEP Program' trials have been designed to test the efficacy of semaglutide, at the higher dose of 2.4 mg/week, for weight loss in patients with and without type 2 diabetes. STEP 1 showed an average 14.9% reduction in body weight with semaglutide 2.4 mg plus a lifestyle intervention, compared with a 2.4% reduction in the placebo plus lifestyle intervention group (treatment difference of −12.4%, $P < 0.001$), among obese or overweight participants with related comorbidities, but not T2DM.[70] The STEP 2 trial showed an average body weight reduction of 9.6% and 6.9% with semaglutide 2.4 and 1.0 mg vs. 3.4% with placebo ($P < 0.001$) among participants with T2DM and overweight or obesity. The higher dose also achieved slightly better glycaemic control, reductions in cardiometabolic risk, and improved physical function relative to the standard dose.[71] In STEP 3, a weight reduction treatment difference of 10.3% was observed when treating overweight or obese people with related comorbidities, but not T2DM, with semaglutide 2.4 mg compared with placebo.[72] Patients who continued to take semaglutide after the first 20 weeks lost an additional 7.9% of their body weight in the STEP 4 trial.[73] Consistent results have been observed in other STEP trials.[94–96]

Recently, the Food and Drug Administration approved semaglutide injection 2.4 mg once weekly for chronic weight

Table 1 Randomized controlled trials of GLP-1 RA for body weight reduction in patients with and without T2DM

Trial	Design	Patients	Active drug	Patients	Main results
NCT00422058[62]	Double-blind, placebo-controlled trial	564	Liraglutide (1.2, 1.8, 2.4, or 3.0 mg) or placebo administered once a day subcutaneously, or orlistat three times a day orally	BMI of 30–40 kg/m^2 and fasting plasma glucose ≤7 mmol/L at run-in	Weight loss was proportional to liraglutide dose (mean 4.8–7.2 kg). With the highest doses of liraglutide (2.4 and 3.0 mg), there was higher weight lost compared with orlistat
SCALE Maintenance[63]	Randomized, double-blind, placebo-controlled trial	422	Liraglutide 3.0 mg/day or placebo (subcutaneous administration) for 56 weeks	BMI ≥ 30 or ≥27 kg/m^2 with dyslipidaemia and/or hypertension	Estimated weight loss difference of 6.1% in the liraglutide group ($P < 0.001$)
SCALE Obesity and Prediabetes[64]	Randomized, double-blind, placebo-controlled trial	731	Liraglutide 3 mg once daily vs. placebo injection	BMI ≥ 30 or ≥27 kg/m^2 with dyslipidaemia or hypertension	Estimated weight loss difference of 5.6% in the liraglutide group ($P < 0.001$)
LEADER[58]	Multicentre, double-blind, placebo-controlled trial	9340	1.8 mg of liraglutide or placebo	≥50 years with at least one CV coexisting condition or an age of ≥60 years with at least one CV risk factor	Weight loss was 2.3 kg higher in the liraglutide group
SUSTAIN-6[59]	Randomized, double-blind, placebo-controlled, parallel-group trial	3297	0.5 or 1.0 mg of once-weekly subcutaneous semaglutide or placebo	≥50 years with CV disease, chronic HF (NYHA II or III) or CKD of stage ≥3, or ≥60 years with at least one CV risk factor	Weight loss was greater in patients taking higher doses of semaglutide ($P < 0.001$)
PIONEER 6[65]	Randomized, placebo-controlled, Phase 3a trial	3183	Once-daily oral semaglutide (14 mg) or placebo	Established CV disease or CKD if ≥50 years or with at least one cardiovascular risk factor if ≥60 years	Weight loss was 3.4 kg higher in the semaglutide group
REWIND[60]	Randomized, double-blind, placebo-controlled trial	9901	Weekly subcutaneous dulaglutide (1.5 mg) or placebo	• ≥50 years with T2DM and HbA1c ≤ 9.5% and BMI ≥ 23 kg/m^2 or CV disease • ≥55 years with CAD, carotid or PAD, LV hypertrophy, and CKD • ≥60 years with at least two of tobacco use, dyslipidaemia, hypertension, or abdominal obesity	Lower least squares mean body weight of 1.46 kg in the dulaglutide group ($P < 0.001$)
ELIXA[66]	Multicentre, randomized, double-blind, placebo-controlled trial	6068	10–20 μg of subcutaneous lixisenatide or placebo in addition to other diabetes medications	T2DM and either an MI or hospitalization for unstable angina in the past 180 days	Weight loss was 0.6 kg higher in the lixisenatide group ($P < 0.001$)
EXSCEL[67]	Randomized, double-blind, placebo-controlled, event-driven trial	14 752	Subcutaneous injections of extended-release exenatide at a dose of 2 mg or placebo once weekly	T2DM with or without previous CV events	Lower least squares mean of 1.27 kg in the exenatide group ($P < 0.001$)
FREEDOM[68]	Non-inferiority, randomized controlled trial	4156	Subcutaneous exenatide (ITCA 650) or placebo	T2DM with or at risk for atherosclerotic CV disease	Weight loss was higher in the exenatide group (−4.24 kg; $P < 0.001$)

(*Continues*)

Table 1 (continued)

Trial	Design	Patients	Active drug	Patients	Main results
AMPLITUDE-O[69]	Randomized, placebo-controlled trial	4076	Weekly doses of efpeglenatide or placebo	T2DM and an HbA1c ≥ 7%, with history of CV disease (defined as CAD, stroke, or PAD) or if they had CKD and at least one additional CV risk factor	Weight loss was higher in the efpeglenatide group (2.6 kg, $P < 0.001$)
Harmony Outcomes[61]	Randomized, double-blind, placebo-controlled trial	9463	Subcutaneous albiglutide (30–50 mg) or of a matched volume of placebo once a week	≥40 years old with T2DM and established CAD, cerebrovascular disease, or PAD with an HbA1c ≥ 7%	Weight loss was higher in the albiglutide group (−0.66 kg at 8 months and −0.83 kg at 16 months)
STEP 1[70]	Randomized, double-blind, placebo-controlled trial	1961	Once-weekly subcutaneous 2.4 mg semaglutide or placebo, plus lifestyle intervention	Adults without T2DM and a BMI of ≥30 kg/m^2 (or ≥27 with ≥1 weight-related comorbidity)	Estimated weight loss difference of 12.4% in the semaglutide group ($P < 0.001$)
STEP 2[71]	Randomized, double-blind, double-dummy, placebo-controlled, Phase 3 trial	1210	Semaglutide 2.4 mg or semaglutide 1.0 mg or placebo once a week for 68 weeks, plus a lifestyle intervention	BMI ≥ 27 kg/m^2 and HbA1c 7–10% and diagnosis of T2DM at least 180 days before screening	Estimated weight loss difference of 6.2% in the semaglutide group ($P < 0.001$)
STEP 3[72]	Randomized, double-blind, parallel-group, 68 week, Phase 3a study	611	Once-weekly subcutaneous semaglutide 2.4 mg vs. placebo as an adjunct to intensive behavioural therapy with initial low-calorie diet	Adults without T2DM and with either overweight (BMI ≥ 27 kg/m^2) plus at least one comorbidity or obesity (BMI ≥ 30 kg/m^2)	Estimated weight loss difference of 10.3% in the semaglutide group ($P < 0.001$)
STEP 4[73]	Randomized, double-blind, 68 week, Phase 3a withdrawal study	902	Once-weekly treatment with subcutaneous semaglutide, 2.4 mg, compared with switching to placebo	Adults with overweight or obesity after a 20 week run-in with subcutaneous semaglutide titrated to 2.4 mg weekly	Estimated weight loss difference of 14.8% in the semaglutide group ($P < 0.001$)
NCT05111912[74] (recruiting)	Phase 2, open-label, randomized, interventional, dose-finding study	200	Once-weekly human GLP-1 analogue, compared with once-daily liraglutide 3 mg	BMI ≥ 30.0 and ≤40.0 kg/m^2 at screening, in the absence of type 2 or any other type of diabetes	Percentage change in participants' body weight (%) from the baseline to Week 26
NCT03671733[75] (recruiting)	Randomized, interventional open-label, Phase 3 study	150	Liraglutide vs. exenatide vs. exenatide microspheres for injection	BMI ≥ 28 kg/m^2 or with abdominal obesity and with weight stable for ≥3 months	Weight change at 3 months measured in kilograms
NCT05005741[76] (recruiting)	Multicentre, open-label, randomized controlled, Phase 4 trial	120	Three times a day of subcutaneous beinaglutide or once weekly of 1.5 mg subcutaneous dulaglutide for 16 weeks	Adults with T2DM and overweight or obesity (BMI from 24 to 35 kg/m^2) or waistline longer than 90 cm (male)/85 cm (female)	Change from baseline to Week 16 in HbA1c. The secondary endpoint is the change from baseline to Week 16 in weight

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus.

Figure 2 Reduction of adverse events in type 2 diabetes patients treated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs). The figure is adapted from Sattar *et al.*,[77] showing the beneficial effects on mortality, hospital admission for heart failure (HF), and MACE meta-analysed from GLP-1 RA clinical trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, Harmony Outcomes, REWIND, PIONEER 6, and AMPLITUDE-O). MACE included cardiovascular death, myocardial infarction, and stroke. *X* axis represents the % reduction of the analysed endpoints. CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events.

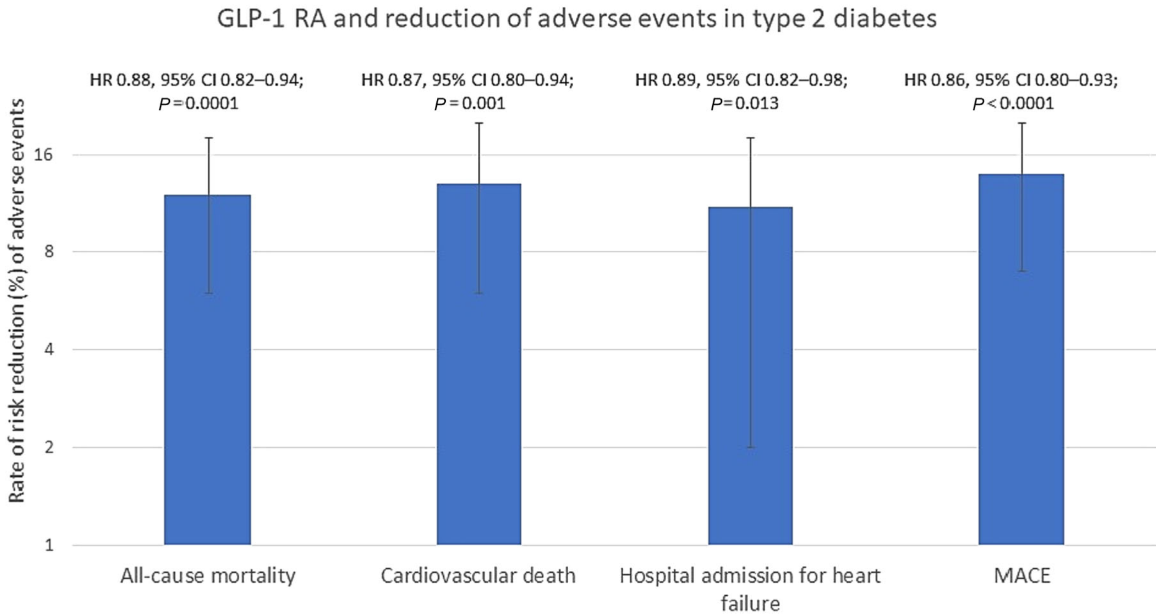
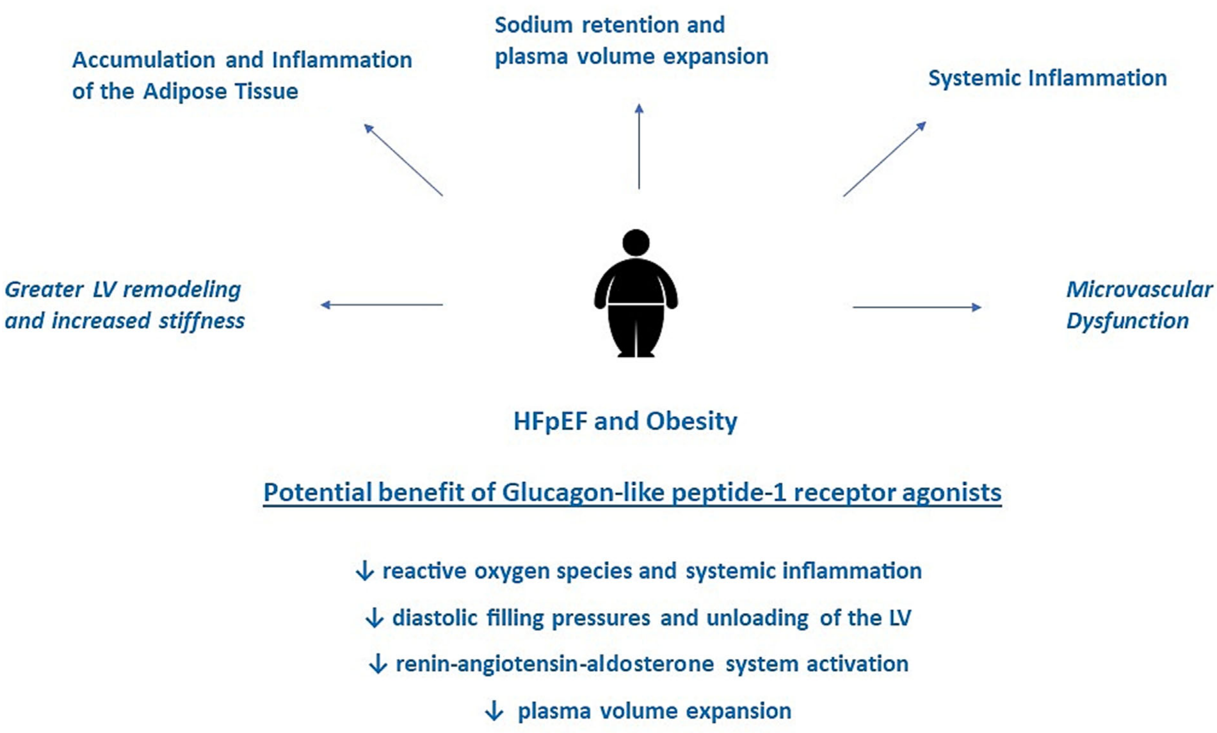


Figure 3 Obesity and heart failure with preserved ejection fraction (HFpEF). The figure shows the clinical feature and pathophysiology of obesity and HFpEF and the potential benefit deriving from glucagon-like peptide-1 receptor agonists. LV, left ventricular.



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management in adults with obesity or overweight with at least one weight-related condition (such as high blood pressure, T2DM, or high cholesterol), for use in addition to a reduced calorie diet and increased physical activity. Semaglutide is the first drug approved for chronic weight management in adults with general obesity or overweight since 2014. Although tirzepatide is at an earlier stage of development, it has shown a similar, if not greater, efficacy for weight loss.[97]

Treatment of patients with heart failure with preserved ejection fraction

With the recent exception of the sodium–glucose cotransporter-2 inhibitor (SGLT2i),[98,99] trials in patients with HFpEF have failed to show significant results so that no specific treatment was recommended in the 2021 European Society of Cardiology (ESC) guidelines for HF.[2] It can be, however, hypothesized that, similarly to the beneficial effects of caloric restriction and physical activity leading to weight loss, also treatment with weight reducing GLP-1 RA may be an effective for the patients with the obese HFpEF phenotype (*Figure 3*) (see below).

Treatment of the obese heart failure with preserved ejection fraction phenotype

Treatment of obesity includes a variety of modalities including lifestyle intervention, medications, and bariatric surgery.[100,101] The effect of weight loss in HF patients is still partially unsettled. The significance of obesity and, more specifically, increased epicardial fat is likely different in patients with HFrEF or HFpEF. It is associated with a reduced risk of events in HFrEF, whereas it is associated with worse symptoms and likely outcomes in HFpEF patients.[44,45,48,49,102,103]

Weight loss should be a target of treatment only in obese patients with HFpEF. In the FLAGSHIP study, non-obese HFpEF patients with weight loss had higher all-cause mortality and re-hospitalization rates than their pairs without weight loss.[104] Furthermore, at 6 months of hospital discharge, a high proportion of patients in the weight loss group in the non-obesity group presented with functional limitations and anorexia, suggesting that their physical function and nutritional status were deteriorating.

Conversely, weight loss had beneficial effects in obese patients with HFpEF. Kitzman *et al* showed that among obese older patients with clinically stable HFpEF, caloric restriction and/or aerobic exercise training increased peak oxygen consumption, and their effects were additive.[101] Similarly, dietary treatment/prevention programmes among obese

Table 2 GLP-1 RA and clinical outcomes in patients with heart failure and cardiovascular disease: ongoing trials

Study or trial	Type of study	Estimate enrolment	Drug vs. comparator	Inclusion criteria	Primary endpoints
STEP HFpEF[81]	Randomized, double-blind, placebo-controlled Phase 3 trial	529	Once-weekly subcutaneous semaglutide 2.4 mg add-on to standard of care vs. placebo	BMI > 30 kg/m^2, NYHA Class II–IV, and LVEF > 45%	1 7.8 points estimated difference in KCCQ from baseline to Week 52 2 −10.7 estimated difference in body weight from baseline to Week 52
STEP HFpEF DM[113] (recruiting)	Randomized, quadruple-blind, placebo-controlled Phase 3 trial	610	Once-weekly subcutaneous semaglutide 2.4 mg add-on to standard of care vs. placebo	Adults (>18 years old), with BMI > 30.0 kg/m^2, NYHA Class II–IV, LVEF > 45% at screening, T2DM diagnosed ≥90 days prior to the screening, and HbA1c ≤ 10%	1 Change in KCCQ clinical summary score from baseline to Week 52 2 Change in body weight percentage from baseline to Week 52
SUMMIT[97] (recruiting)	Randomized, double-blind, placebo-controlled Phase 3 trial	700	Tirzepatide administered subcutaneously vs. placebo	NYHA Class II–IV and elevated NT-proBNP, structural heart disease, or HF decompensation within 12 months	1 All-cause mortality, HF events, 6MWD test, and KCCQ from baseline to Week 120 2 6MWD test variation from baseline to Week 52
SELECT[114] (recruiting)	Randomized, quadruple-blind, placebo-controlled Phase 3 trial	17 500	Once-weekly subcutaneous semaglutide from 0.24 up to 2.4 mg add-on to standard of care vs. placebo	BMI ≥ 27 kg/m^2: prior myocardial infarction or prior stroke or PAD	Time to first occurrence of CV death, non-fatal myocardial infarction, or non-fatal stroke from 0 to 59 months

6MWD, 6 min walking distance; BMI, body mass index; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus.

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HFpEF patients showed that a loss of ≈7% body weight was associated with a 37% decrease in Minnesota Living With Heart Failure (MLWHF) score and a 29% increase in 6 min walking distance (6MWD) test at completion of the 15 week programme, compared with baseline.[105]

Also, bariatric surgery in obese patients with HFpEF has been shown to improve symptoms and New York Heart Association (NYHA) class, as well as reduce HF readmissions and reverse LV remodelling, and improve LV distensibility.[106–108] In a nationwide analysis, mortality was lower among obese HFpEF patients with bariatric surgery compared with obese HFpEF patients without bariatric surgery. Obese HFpEF patients with bariatric surgery also had lower total hospitalization charges and lower total hospitalization costs compared with obese HFpEF patients without bariatric surgery. These results suggest that bariatric surgery in morbidly obese HFpEF patients may reduce mortality and improve resource utilization.

Whereas cardiac rehabilitation and intentional weight loss through caloric restriction, physical activity, and/or bariatric surgery are promising strategies to improve exercise capacity in these patients, future large studies are needed to test whether such interventions may modify the risk of long-term adverse clinical outcomes.[109]

Effects of glucagon-like peptide-1 receptor agonist

Agents that lead to a weight loss may be effective in patients with obesity and HFpEF. Also, the efficacy of GLP-1 RA to reduce the generation of reactive oxygen species and reduce systemic inflammation[110] could represent a key factor to promote their use in HFpEF. Preliminary data show that GLP-1 RA may improve diastolic function by reducing diastolic filling pressures and unloading the ventricle.[111] Beneficial effects of GLP-1 RA also exert on the kidney by the protection from oxidative injury and by reducing the renin–angiotensin–aldosterone system activation and thereby contributing to blood pressure lowering.[112] This may be particularly important in HFpEF. A recent meta-analysis of the main GLP-1 RA CV outcome trials (CVOTs) has shown a reduction of the composite kidney outcome (development of macroalbuminuria, doubling of serum creatinine, end-stage renal disease, and renal-related deaths) by 21%.[77,78]

RCTs are needed to test the efficacy of these drugs in this population. The STEP HFpEF trial has recently shown a significant improvement in symptoms, quality of life, and exercise tolerance, assessed by the 6MWD test, along with body weight reduction, in patients with obesity and HFpEF treated with semaglutide (2.4 mg) compared with placebo.[81] Similarly, the STEP HFpEF DM trial (NCT04916470) will test the effect of semaglutide in subjects with obesity-related HFpEF and with T2DM.[113]

SUMMIT is another ongoing RCT that will assess the efficacy and safety of tirzepatide (LY3298176), a combined gastric inhibitory peptide and GLP-1 RA, in participants with HFpEF and obesity, compared with placebo.[97] Finally, SELECT has tested the superiority of semaglutide, compared with placebo, when added to standard of care for preventing major adverse CV events in patients with established CV disease and overweight or obese but without T2DM. Given the potential inclusion of HFpEF patients and the assessment of hospitalization for HF as a secondary outcome, SELECT will have potential for exploring new approaches to reduce CV events and HF events while targeting obesity (*Table 2*).[114,115]

With worsening epidemiological trends for both the incidence and prevalence of HF worldwide, it is critical to implement optimal prevention and treatment strategies for patients with or without comorbidities as T2DM.[116] Consensus statements and guidelines have recommended GLP-1 RA and SGLT2i as additions to lifestyle interventions with or without metformin in those at high atherosclerotic CV disease risk.[57,117–120]

However, these recommendations fail to differentiate between the prevention and treatment of patients with HF and do not differentiate among those with different HF phenotypes.

From this perspective, GLP-1 RA could represent a cornerstone treatment to modify the natural history of HFpEF. This could potentially lead to a breakthrough in the treatment of HF, which is constantly evolving, especially if we consider the high prevalence and adverse prognosis of patients affected by HFpEF.[121,122]

Conclusions

The number of patients with HFpEF is expected to grow, given the increased life expectancy and the increasing prevalence of risk factors predisposing to HFpEF. It is well known that obesity is one of the most common and clinically relevant phenotypes of HFpEF with specific pathophysiological mechanisms. Therapies targeting body weight reduction are therefore promising. Trials with GLP-1 RA in obese patients, with or without T2DM, have shown their efficacy for weight loss. Future studies are ongoing to assess whether GLP-1 RA can prevent and treat patients with HFpEF and obesity.

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