Pugliese *et al. Cardiovascular Diabetology* (2025) 24:224
https://doi.org/10.1186/s12933-025-02778-6

Cardiovascular Diabetology

REVIEW Open Access

Refining the link between obesity and heart failure: insights from GLP-1 receptor agonist trials and studies adopting direct adiposity measures

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Abstract

Overweight and obesity are major risk factors for heart failure (HF), contributing to its development through metabolic, neurohormonal, haemodynamic, and inflammatory alterations. While overweight/obesity increases the risk of developing HF, its impact on patient outcomes remains complex. The "obesity paradox" suggests that a higher BMI may be associated with improved survival in patients with established HF. However, recent GLP-1 receptor agonist (GLP-1 RA) trials suggest that intentional weight loss positively influences outcomes in overweight/obese patients with HF. This seemingly contradictory evidence highlights the need for a deeper understanding of the mechanisms linking adiposity to HF outcomes. A more precise characterization of adiposity phenotypes using alternative and accurate measures of pathological fat accumulation is crucial in identifying individuals who may benefit most from anti-obesity treatments. In this context, recent research underscores the role of epicardial adipose tissue (EAT) in HF pathophysiology, as it directly influences cardiac function and structure through inflammatory, metabolic, and mechanical effects. This narrative review summarises current evidence on the impact of weight loss on HF outcomes, focusing on recent GLP-1 RA trial results. Additionally, it highlights epidemiological and molecular data supporting EAT as a novel adiposity measure that might allow refining patient selection for pharmacological weight-loss treatments. Finally, it emphasizes the need for future research to identify causal pathways linking alternative measures of visceral fat accumulation to HF outcomes. These efforts will be essential in optimizing the benefits of novel weight-loss treatments, ensuring effective and individualized therapeutic strategies for overweight or obese patients with HF.

Keywords Obesity, Heart failure, GLP-1 RA, Epicardial adipose tissue, Epigenetic

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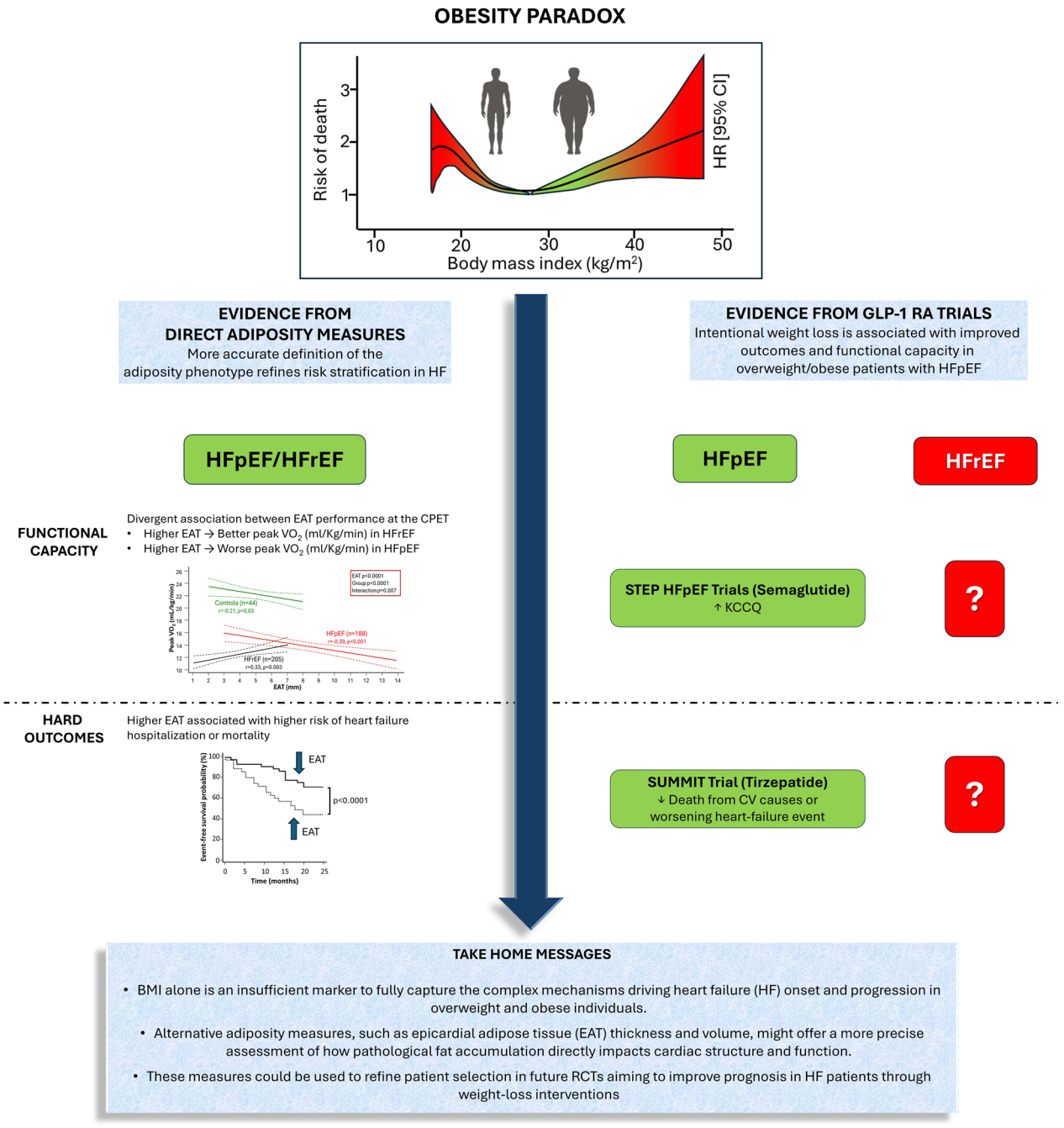
Graphical abstract



Introduction

The prevalence of overweight (defined as a body mass index, BMI ≥ 25 and < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) have nearly tripled over the past 50 years, and this trend spans all ethnicities, genders, geographical locations and age groups [1]. Overweight/obesity and their associated haemodynamic, metabolic, neurohormonal and inflammatory alterations promote a faster evolution of the cardiovascular disease (CVD) continuum toward heart failure (HF) development and progression [2, 3]. The Framingham heart study showed that participants with obesity had twice the risk of developing HF over a 14-year follow-up compared to participants with normal BMI [4], and other population-based studies confirmed this association [5]. While these earlier reports identified obesity as a major risk factor for both HF with

preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF), more recent studies suggested that obesity might be more strongly associated with the risk of developing HFpEF than HFrEF [3]. Furthermore, an elevated risk of developing HF has also been reported in overweight individuals, reinforcing the concept that the relationship between BMI and CVD risk is continuous, similar to other cardiovascular risk factors.

Once HF has developed, obesity remains associated with an increased risk of hospitalization, greater symptom burden, and poorer quality of life [6–8]. Randomized controlled trials (RCTs) have confirmed that treatments inducing a significant weight loss with Glucagon Like Peptide-1 receptor agonists (GLP-1 RAs) might substantially improve exercise tolerance and the quality of life of patients with HFpEF, while in patients with HFrEF, the results are still controversial [9]. The same trials have also suggested that the benefits obtained in HFpEF patients might be partially independent of type 2 diabetes and the patient's BMI when the treatment is initiated in patients with obesity [10].

These findings support the role of excessive fat accumulation in the development of HF. However, in patients with established disease, the relationship between overweight/obesity and the outcome may change direction, whereby overweight patients and those with mild obesity might have better survival [11–14]. This phenomenon, known as the "obesity paradox", has been observed not only in HF but also in other diseases, including coronary artery disease, chronic kidney disease, and chronic obstructive pulmonary disease [15, 16]. Several hypotheses have been proposed to explain this observation, including the influence of unaccounted confounders such as cardiorespiratory fitness (which is often impaired in overweight or obese subjects) [17], the reduced risk of hypotension with consequent higher tolerability to HF medications in HF-obese patients, the earlier diagnosis and treatment of HF driven by the earlier appearance of symptoms, the limitations of the BMI as an accurate measure of differentially distributed fat depots, and potential misinterpretations of the data.

This narrative review summarises recent evidence obtained in RCTs with GLP-1 RAs, suggesting a potential benefit of weight loss in patients with overweight or obesity and HF, with or without diabetes. Furthermore, we discuss the importance of using alternative measures of adiposity to improve understanding of cardiovascular risk related to excessive fat accumulation in HF, with a specific focus on the epicardial adipose tissue (EAT). Finally, we provide an overview of the potential molecular pathways by which different visceral fat accumulation (mainly EAT) can influence cardiac function and structure, increasing the risk of HF development and worsening. In doing so, we focused on epigenetic changes induced by excessive fat accumulation, given that they are emerging as key layers of gene regulation in response to environmental changes.

Targeting obesity in HF with GLP 1RAs in patients with heart failure, without and without type 2 diabetes mellitus

The 'obesity paradox' has a strong foundation in the evidence that *unintentional* weight loss is commonly associated with higher mortality and hospitalization risk in both HFpEF and HFrEF patients [18, 19], likely as a proxy of cachexia, widely observed in patients reaching the end-stage CVD trajectory [20]. In turn, intentional weight loss achieved through diet or physical exercise programmes in patients with established HFpEF and HFrEF could lead to improved exercise capacity, NYHA classification and quality of life, challenging the concept of the obesity paradox [21–23]. However, diet and physical exercise interventions require behavioral changes that are difficult to achieve and sustain for long periods, making it difficult to study their impact on the long-term HF prognosis in the context of randomized controlled trials (RCT) [24]. Interventions that can ensure a rapid and sustained reduction of body weight, such as bariatric surgery, could facilitate the assessment of the potential impact of weight loss on the risk of HF outcomes. For instance, bariatric surgery has been shown to reduce the risk of hospitalizations among patients with established HF [25–29]. Nevertheless, RCTs involving bariatric surgery in patients with established HF are challenging to design and conduct, as patients willing to undergo the surgical procedure might not accept the allocation to the control group involving alternative treatments. Given these issues with behavioural and surgical interventions, it has long been complicated to assess the impact of weight loss on the prognosis of patients at high risk for HF or with established disease.

Anti-obesity medications represent another potential option to promote effective and stable weight loss, but earlier drugs were linked to cardiovascular safety concerns, making their use in patients at high risk of CVD unfeasible [30–32]. More recently, GLP-1 RAs have provided an additional therapeutic option in treating obesity. While no trials with GLP-1 RA monotherapy have specifically assessed the impact of these drugs on hard CVD outcomes in patients with established HF (Table 1), post-hoc analyses of early studies have demonstrated significant but inconsistent reductions in HF-related hospitalizations (HHF) in individuals with obesity and type 2 diabetes [33, 34]. Notably, a meta-analysis of RCTs, including patients with type 2 diabetes, reported that GLP-1 RA therapy reduces the relative risk of hospital admission for HF by 11% (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.82–0.98) [35], confirming

Table 1 Phase III randomized, placebo-controlled trials involving GLP-1 agonists and reporting data on hard cardiovascular outcomes

Trial name	Type of GLP-1 agonist, administration and dose	Type of population	N	Duration	Primary outcome	Key outcomes
SUSTAIN-6 [143]	S/C semaglutide, 0.5—1.0 mg once- weekly	Type 2 Diabetes	3,297	104 weeks	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Semaglutide reduced the risk of CVD events vs placebo
PIONEER 6 [144]	OS semaglutide, 14 mg once-daily	Type 2 Diabetes	3,183	15.9 months	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Semaglutide was non-inferior to placebo for CVD safety
SOUL [145]	OS semaglutide, 14 mg once-daily	Type 2 Diabetes	9,650	5 years	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Semaglutide reduced the risk of major adverse CVD events by 14% vs placebo
SELECT [37]	S/C semaglutide, 2.4 mg once-weekly	Preexisting CVD, BMI ≥ 27 kg/m^2, no history of diabetes	17,604	39.8 months	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Semaglutide reduced the risk of CVD death, nonfatal MI, or nonfatal stroke by 20% vs placebo
FLOW [146]	S/C semaglutide, 1 mg once-weekly	Type 2 diabetes and CKD (eGFR 50–75 ml/min/ 1.73 m^2 + uACR > 300 and < 5000oreGFR 25 to < 50 ml/min/1.73 m^2 + uACR > 100 and < 5000	3,533	3.4 years	Composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of < 15 ml/min/1.73 m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes	Semaglutide reduced the risk of the primary outcome by 24% vs placebo, with a reduction in CVD mortality of 29% vs placebo
LEADER [147]	S/C liraglutide, 1.8 mg once-daily	Type 2 Diabetes	9,340	3.8 years	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Liraglutide reduced the risk of CVD events by 13% and mortality by 15% vs placebo
REWIND [148]	S/C dulaglutide, 1.5 mg once-weekly	Type 2 Diabetes	9,901	5.4 years	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Dulaglutide lowered the risk of major CVD events by 12% vs placebo
EXSCEL [149]	S/C Exenatide, 2 mg once-weekly	Type 2 Diabetes	14,752	5.6 years	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Exenatide was non-inferior to placebo for CVD safety but neither superior (P = 0.06 for superiority)
FREEDOM CVO [150]	Exenatide 20 mcg per day for 3 months followed by 60 mcg per day every 6 months or placebo	Type 2 Diabetes at high CVD risk	4,156	16 months	Composite of CVD death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina	Exenatide was non-inferior to placebo for CVD safety but not superior
HARMONY Outcomes [38]	S/C Albiglutide, 30–50 mg once-weekly	Type 2 Diabetes	9,463	1.6 years	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Albiglutide reduced the risk of major CVD events by 22% vs placebo
ELIXA [151]	S/C Lixisenatide, 10–20 µg once-daily	Type 2 Diabetes	6,068	25 months	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Lixisenatide was non-inferior to placebo for CVD safety but did not show superiority (P = 0.81 for superiority)
AMPLITUDE-O [36]	S/C Efpeglenatide, 4–6 mg once-weekly	Type 2 Diabetes	4,076	1.8 years	Composite of CVD mortality, nonfatal MI, or nonfatal stroke	Efpeglenatide reduced the risk of CVD events by 27% vs placebo

CVD Cardiovascular Disease, *MACE* Major adverse cardiovascular events, *S/C* Subcutaneous administration, *OS* Oral administration, *CKD* chronic kidney disease, *MI* Myocardial infraction *HF* Heart Failure, *HFpEF* Heart failure with preserved ejection fraction, *HFrEF* Heart failure with reduced ejection fraction

positive findings initially observed in the 4076 patients with type 2 diabetes at high CVD risk included in the AMPLITUDE-O [36] trial. Notably, treatment with efpeglenatide [36] in this trial resulted in relatively modest improvements in body weight (−2.6 kg versus placebo), raising the possibility that the benefits of GLP-1 RAs in HF may occur independently of weight loss. This hypothesis has been recently supported and expanded by the SELECT trial, including patients with a BMI ≥ 27 kg/m^2 and a history of CVD, but without type 2 diabetes, in which the rate of HF complications was reduced by semaglutide treatment and this protective effect occurred early after initiation of the trial, i.e., before substantial weight loss could be achieved [37]. Although the mechanisms by which GLP-1 RAs might confer early protection from the risk of HF outcomes remain largely unknown,

a potential protective effect against myocardial ischaemic damage has been suggested based on the evidence from the Harmony Outcomes study and the AMPLITUDE-O trial, demonstrating a reduction in the rate of myocardial infarction in patients treated with GLP-1 RAs [36, 38]. Proposed alternative mechanisms include enhanced myocardial glucose uptake [39, 40] and/or decreased cardiac inflammation, myocyte apoptosis, adverse left ventricular remodelling and atrial enlargement [40–42], which have not been consistently replicated across different trials [43, 44]. Remarkably, the mechanisms underlying the positive effects of GLP-1 RAs appear complementary to that of SGLT-2 inhibitors (SGLT2i), a therapeutic pillar of the treatment for both HFrEF and HFpEF, providing incremental benefits in reducing HF exacerbations and hospitalizations [45]. In a post hoc analysis of the AMPLITUDE-O trial, including the largest proportion (15.2%) of participants receiving baseline SGLT2i treatment among type 2 diabetes cardiovascular outcome trials (CVOTs) [36], the efficacy of efpeglenatide in preventing HHF was independent of baseline SGLT2i use, leading to a remarkable 77% risk reduction in patients treated with the combined therapy as compared with placebo (HR 0.23, 95% CI 0.05–0.97, p for interaction = 0.35) [46]. The incremental benefit of GLP-1 RAs in patients already on SGLT2i therapy has been reported also in a real-world study showing a significantly lower risk of HHF in overweight/obese individuals with type 2 diabetes receiving both treatments [47].

While GLP-1 RAs protect against new-onset HF, their impact on the prognosis of individuals with established disease remain controversial [48, 49], particularly in subjects with advanced HFrEF (LVEF < 40%). Early-phase clinical trials suggest that GLP-1 RA treatment may be neutral [43, 50] or even harmful in HFrEF patients, with or without diabetes, resulting in an increased risk of HF-related outcomes [51, 52]. Potential harms of GLP-1 RAs in advanced HFrEF may be mediated by their positive chronotropic effect, causing an increase in heart rate [52] and their potent weight-lowering effects that may aggravate HF-related cachexia [53]. A direct effect of GLP-1 RAs on the heart rate is supported by animal studies. Indeed, using a highly translational approach involving experiments in intact anaesthetized pigs, isolated pig hearts or isolated sinoatrial node tissues, Lubberding et al. documented that, independently of autonomic nervous system blockade or the presence of ivabradine, GLP-1 increases spontaneous action potential firing and diastolic depolarization slope in isolated pig sinoatrial node preparations [54].

A more recent prespecified analysis of the SELECT trial [55], however, suggested potential benefits derived from the treatment with GLP-1 RAs, extending also to patients with HFrEF. In a subsample of over 4000 patients with coexisting HF, the treatment with once-weekly semaglutide 2.4 mg was associated with a reduction in the risk of the composite outcome of cardiovascular death or worsening HF in both HFrEF and HFpEF patients [56]. Although this analysis included the largest population of patients with HFrEF recruited in cardiovascular outcome trials (CVOTs) and treated with a GLP-1 RA, concerns have been raised about the correct definition of the baseline HF phenotypes. Indeed, in the group of 1,341 patients that were classified as having HFrEF, the event rate for the composite of HHF or cardiovascular death recorded in the placebo arm was much lower (only 4%) compared to what was observed in other HFrEF CVOTs, including the EMPEROR-Reduced (21.0%) [57] and DAPA-HF (15.6%) [58] trials. Another unexpected result of this sub-analysis was that the risk reduction in those treated with semaglutide was mainly driven by a decrease in cardiovascular mortality rather than HHF [59], differently from what has been reported in previous trials enrolling patients with HFrEF [60]. In patients with HFpEF, instead, GLP-1 RAs might have a positive impact on the outcome, irrespective of type 2 diabetes. The STEP-HFpEF and STEP-HFpEF DM randomized, placebo-controlled trials [10], enrolling patients without and with type 2 diabetes, respectively, demonstrated that semaglutide 2.4 mg once-weekly improves HF-related symptoms and physical limitations in individuals with obesity and HFpEF (LVEF ≥ 45%). More recently, a prespecified analysis of the STEP-HFpEF DM trial documented that the improvement in the HF-related symptoms, physical limitations and amount of body weight reduction obtained with semaglutide 2.4 mg once-weekly compared to placebo were independent of baseline HbA1c, somewhat confirming a partial independence of the effects of semaglutide on these outcomes from the patient's glycometabolic status. In the same subanalysis, semaglutide resulted in lower rates of hypoglycaemia than placebo, suggesting its preferential use not only for controlling HF symptoms but also to improve glycemic control in diabetic patients as compared to more traditional glucose-lowering therapies [61].

While the limited sample size and follow-up duration of the STEP trials hindered the possibility of drawing definite conclusions on hard HF-related events, an updated pooled analysis of four randomized clinical trials (SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM) including 3743 patients with a history of HFpEF revealed that semaglutide 2.4 mg reduced the risk of worsening HF events (HR 0.59, 95% CI 0.41–0.82) and the combined risk of HF events and cardiovascular mortality (HR 0.69, 95% CI 0.53–0.89) in participants with HFpEF, the majority of whom were obese (although the SELECT trial also included overweight patients)[62]. These results have been more recently confirmed by the SUMMIT trial

[63], showing that a once-weekly injection of tirzepatide (a dual glucose-dependent insulinotropic polypeptide receptor and GLP-1 RA) in obese patients with HfpEF induced a very similar reduction in the rate of worsening HF events compared to placebo (HR 0.59, 95% CI 0.41–0.82). However, no difference in the rate of cardiovascular death was observed between the two study arms (HR 1.25, 95% CI 0.63–2.45).

In summary, GLP-1 RAs appear to be safe and beneficial in most patients with HF irrespective of the presence of type 2 diabetes, particularly those with HFpEF and obesity, representing a promising therapeutic option for improving health outcomes in this high-risk population (Table 2 and Fig. 2). Yet, it is important to emphasize the limitations of current CVOTs with GLP-1 RAs regarding HF patients. First, HF events were not included as the primary composite endpoint in most trials, so these outcomes were explored as secondary or exploratory endpoints. Second, as many CVOTs with GLP-1 RAs were not initially designed for patients with established HF,

Table 2 Randomized, placebo-controlled trials or their post-hoc analyses specifically assessing the impact of GLP-1 RAs on the outcome of patients with heart failure, stratified for type of heart failure and presence or absence of type 2 diabetes

	Trial name	Total no. and type of HF	HF outcomes
Type 2 diabetes	AMPLITUDE-O [36]	652 patients with history of HF at baseline. LVEF unknown	Efpeglenatide reduced the risk of HF hospitalization by 39% (0.61, 95% CI 0.38–0.98])
	EXSCEL [52]	4892 participants (with or without HF) with baseline LVEF available LVEF > 55%: 2925 LVEF 40–55%: 1498 LVEF < 40%: 469 Patients with a known diagnosis of HF at baseline: 2389	In patients with and without HF with available LVEF, exenatide increased the risk of HF hospitalization in those with reduced LVEF (< 40%) When restricting to participants diagnosed with HF, a similar pattern was observed
	STEP-HFpEF DM [140]	606 patients with HFpEF	Semaglutide significantly improved the Kansas City Cardiomyopathy Questionnaire clinical summary score and the 6-min walking test
	FLOW [141]	678 patients with history of HF at baseline HFpEF: 325 HFrEF: 123 Uknown: 230	Semaglutide increased time to first HF events or CVD death, HF events alone and CVD death alone The relative risk reduction for HF events and CVD death achieved with semaglutide was similar in HFpEF and HFrEF
No type 2 diabetes	SELECT [37]	4286 patients with a history of investigator-defined HF HFpEF: 2273 HFrEF: 1347 Uknown: 666	In patients with HFrEF semgalutide vs placebo reduced the risk of MACE by 35% (HR 0.65, 95% CI 0.49–0.87), CVD mortality by 37% (HR 0.63, 95% CI 0.43–0.91), all-cause mortality by 28% (HR 0.72, 95% CI 0.53–0.99) In patients with HFpEF semaglutide reduced the risk of MACE by 31% (HR 0.69, 95% CI 0.51–0.91) but not of CVD or all-cause mortality However, the interaction *p*-value for HFrEF and HFpEF was non statistically significant for any of the outcomes
	STEP-HFpEF [139]	529 patients with HFpEF	Semaglutide significantly improved the Kansas City Cardiomyopathy Questionnaire clinical summary score and the 6-min walking test
Mixed population	LIVE [50]	241 patients with a diagnosis of HFrEF	No difference in the change of LVEF between the liraglutide and the placebo group (mean difference: -0.8% [95% CI -2.1, 0.5]; $P = 0.24$) Heart rate increased with liraglutide (mean difference: 7 b.p.m. [95%CI 5, 9]; $P < 0.0001$) Serious cardiac events more common in the liraglutide (n = 12 [10%]) than placebo (3 [3%]) group ($P = 0.04$)
	FIGHT [51]	300 patients recently hospitalized for HF and with a diagnosis of HFrEF	No difference between the liraglutide and placebo groups in the primary end point, which was a global rank score including time to death, time to rehospitalization for HF, and time-averaged proportional change in N-terminal pro-B-type natriuretic peptide level from baseline to 180 days
	SUMMIT [63]	731 patients with HFpEF	Compared to placebo, tirzepatide reduced the risk of CVD death (HR 1.58, 95% CI 0.52–4.83), worsening HF event (HR 0.54, 95% CI 0.34–0.85), improved KCCQ-CSS, systolic blood pressure and high-sensitivity C-reactive protein (hsCRP)

CVD Cardiovascular Disease, *MACE* Major adverse cardiovascular events, *CKD* chronic kidney disease, *HF* Heart Failure, *HFpEF* Heart failure with preserved ejection fraction, *HFrEF* Heart failure with reduced ejection fraction, *LVEF* Left ventricular ejection fraction, *HR* Hazard ratio, *95% CI* 95% Coefficient interval

the characterization of disease severity was not standardized at baseline, and this impacted most of their post-hoc analyses, lacking detailed descriptions of symptoms and signs, natriuretic peptide levels, echocardiographic parameters, and functional status. Third, an increasing number of ancillary effects associated with GLP-1 RA treatment are being identified, some of which may contribute to the observed prognostic benefits in heart failure patients. For example, GLP-1 RAs are known to lower systolic blood pressure in hypertensive individuals, typically by 2 to 6 mmHg [64]. This effect occurs prior to weight loss, selectively lowers systolic but not diastolic pressure, and is substantially attenuated in normotensive individuals. While modest, this blood pressure–lowering effect could partly explain the differing benefits of GLP-1 RAs observed in HFpEF versus HFrEF, given that hypertension is highly prevalent in HFpEF, but less commonly seen in HFrEF [64]. Fourth, only the SELECT trial included overweight participants (BMI ≥ 27 kg/m^2); therefore, limited data is available to assess the impact of GLP-1 RAs on HF outcomes in this subgroup [65]. Similarly, the effects of GLP-1 RAs and, more generally, weight reduction strategies in patients with HFrEF and people with a BMI within the healthy range remain largely unexplored and controversial. This is an important issue as a normal or low BMI or body weight might be an indicator of sarcopenia in patients with advanced HF, thus representing a marker of poor prognosis [53, 66, 67]. These conditions may be worsened by GLP-1 RA therapy, which reduces appetite and food intake, leading to a sustained decrease in fat mass and, on a smaller scale, lean mass [68–70]. Addressing this research question might be difficult as, in these cases, the use of BMI as a marker of adiposity might be misleading. The use of alternative measures of adiposity that more directly reflect the amount of adipose tissue accumulation and its negative impact on different organ function has been recently emphasized by a position document of the Lancet commission, highlighting the limitations of using the BMI as an individual measure of health and recommending confirming the presence of excess adiposity by direct measurements of body fat [71].

Alternative measures of adiposity can refine the stratification of the cardiovascular risk related to obesity in patients with heart failure

From BMI to other systemic measures of adiposity

In people living with overweight/obesity, excess adipose tissue leads to insulin resistance and increased systemic inflammation, which can adversely affect cardiac function. The visceral fat accumulation is particularly harmful as it releases free fatty acids (FFAs) and inflammatory cytokines that promote myocardial stress and dysfunction. This can result in left ventricular hypertrophy, diastolic dysfunction, and effort intolerance, common precursors to HF [72, 73]. While the BMI might represent a broad measure of these metabolic rearrangements in obese patients, it does not directly measure the location of body fat and its amount, potentially leading to misinterpretations of its clinical information [74–77]. This issue is particularly relevant in patients with HF, especially those with reduced cardiac output (more common in HFrEF than in HFpEF) or advanced disease. Indeed, the neurohormonal activation that characterizes these conditions can lead to an increased BMI due to fluid rather than fat accumulation. As a result, the BMI is less accurate in reflecting a potential pathological fat accumulation in these subjects, particularly when considered alone and without appropriate adjustments for measures reflecting the patient's congestion. The integration of BMI with parameters that inform on the patient's fluid balance or the use of alternative anthropometric indices that more accurately reflect the amount of visceral fat might refine the estimation of the risk related to adiposity in these patients. A recent sub-analysis of 8000 patients with HFrEF enrolled in the PARADIGM-HF trial has shown that the 'obesity paradox' related to BMI was eliminated by comprehensive adjustment for variables reflecting disease severity or using alternative anthropometric indices [78]. Indeed, while in unadjusted analyses the risk of death due to cardiovascular or all causes was significantly lower in overweight and obese patients (in keeping with the 'obesity paradox'), after adjustment for prognostic variables, including NT-proBNP, the association was eliminated. In turn, greater adiposity assessed by BMI and waist-to-hip ratio was associated with a higher risk of HHF, but the association was stronger with the waist-to-hip ratio. A similar analysis of the Danish Study to Assess the Efficacy of ICDs [implantable cardioverter-defibrillators] in Patients with Non-Ischaemic Systolic Heart failure on Mortality (DANISH) trial documented that alternative anthropometric indices of adiposity, including waist circumference and height, were stronger predictors of mortality than BMI [79].

While alternative systemic measures of adiposity may significantly improve risk stratification in patients with HF compared to BMI, they remain indirect indicators of visceral fat. In patients with suspect or established CVD, who typically undergo cardiac imaging as part of their routine clinical evaluation, quantifying epicardial adipose tissue (EAT) thickness might offer easily available, additional insights into the mechanisms linking excessive visceral fat accumulation with impaired cardiac metabolism and function [80–83].

The pathophysiological mechanismsAssociation linking of EAT with the pathophysiologic abnormalities and prognosis of in HFHFpEF and HFrEF patients

EAT is situated between the visceral layer of the pericardium and the outer myocardial surface. A unique feature of EAT differentiating it from all other visceral fat depots is that there is no muscle fascia separating EAT from the myocardium, meaning the two tissues are in direct contact and share the same microcirculation. The absence of an anatomical barrier facilitates direct crosstalk between EAT and the adjacent myocardium [81]. In healthy subjects, this fat deposit regulates several processes, both at the local and systemic levels [81]. First, due to its efficiency in the uptake and breakdown of free fatty acids, EAT acts as an energy source and a buffer for excess free fatty acids in the underlying myocardium [84]. Moreover, it regulates the inflammatory and atherogenic balance in a paracrine fashion through the production and secretion of adipokines [85, 86]. Finally, EAT protects the heart from hypothermia thanks to brown fat-like features [87]; however, this feature tends to disappear with age, at least in the animal model [88].

In subjects with cardio-metabolic conditions, the accumulation and function of fat deposits (including EAT) is deregulated [89]. In obese subjects, the increased oxygen demand from enlarged adipose tissue is not paralleled by an appropriate increase in cardiac output and angiogenesis [90]. This leads to chronic adipose tissue hypoxia, which in turn induces the migration of immune cells inside fat depots and the production of pro-inflammatory cytokines acting locally and systemically [90, 91]. As a specific feature due to its location, EAT may also start directly compressing and even infiltrating the underlying myocardium, leading to both enhanced pericardial restraint and electrophysiological abnormalities [8, 92–94].

EAT is usually quantified non-invasively using transthoracic echocardiography, computed tomography, or cardiac magnetic resonance[4]. The two latter techniques allow for a three-dimensional evaluation of EAT and assess its precise regional distribution, which correlates to peculiar structural and functional cardiac abnormalities in individual patients [95]. Furthermore, computed tomography can evaluate EAT density, which is associated with heightened inflammation in the EAT and coronary circulation [96, 97]. However, echocardiography is a broadly available and reliable method to assess EAT thickness, requiring minimal training and costs. While echocardiography is indubitably an operator-dependent technique, good intra- and inter-observer reliability is reported in the studies that have applied it to the measurement of EAT [81]. Furthermore, inter-observer and inter-software variability may be an issue even for three-dimensional imaging techniques, such as computed tomography [98]. Thus, the measurement of EAT could be easily integrated into any routine echocardiographic assessment to refine the pathophysiologic characterization of overweight/obese patients and potentially capture changes induced by specific cardiometabolic treatments.

Increased EAT thickness has been described in patients with metabolic syndrome, diabetes mellitus, subclinical atherosclerosis, and coronary artery disease [73, 81, 85]. Furthermore, in patients free of CVD, increased EAT thickness directly correlates with incident HFpEF but not HFrEF [99]. In various conditions, thicker EAT is associated with structural and functional cardiovascular abnormalities, such as left ventricular hypertrophy, atrial dilation, and diastolic dysfunction, independent of BMI [95, 100, 101]. Specifically, in patients with HFpEF, increased EAT thickness shows a direct relationship with serum levels inflammatory and myocardial injury markers [102], and is associated with increased biventricular filling pressures [92, 93], right- and left-sided ventricular-arterial uncoupling [102], and impaired exercise tolerance, highlighted by reduced peak oxygen consumption and estimated peripheral oxygen extraction at cardiopulmonary exercise testing [102]. Also, enlarged EAT predicts an increased risk of adverse outcomes in patients with HFpEF, regardless of BMI [102, 103].

In turn, in patients with HFrEF, an opposite association between EAT and outcomes has been described, whereby subjects with thicker EAT might have a lower risk of HF-related complications than those with thinner EAT [102, 104]. Several hypotheses have been suggested to explain this divergent relationship of EAT with the outcome in HFpEF and HFrEF (Fig. 1). As mentioned, a thicker EAT might represent an important source of energetic substrates for the myocardium, acting as a metabolic reservoir [105]. Therefore, thinning of EAT in HFrEF might reflect underlying increased energy demands of the heart, leading to depletion of the surrounding epicardial fat pad. Indeed, a previous study showed depletion of intramyocardial fat in HFrEF, somewhat confirming that in conditions of cardiac cachexia, the myocardiocytes tend to consume the energetic reserves stored in their closer lipid depots [106]. This hypothesis is supported by the evidence that, compared to HFpEF, HFrEF is characterized by an upregulation of pathophysiological pathways related to increased metabolism [107]. Another explanation of the potential divergent effect of EAT on the outcome of HF patients lies in its endocrine role, which is substantially different depending on its amount [105]. Indeed, a relatively thin EAT is a rich source of anti-inflammatory adipokines (such as adiponectin) that might contribute to maintaining a physiological homeostasis of the cardiovascular system [108]. As such, within physiological ranges, a thicker EAT might represent an important ally to preserve physiological cardiac function

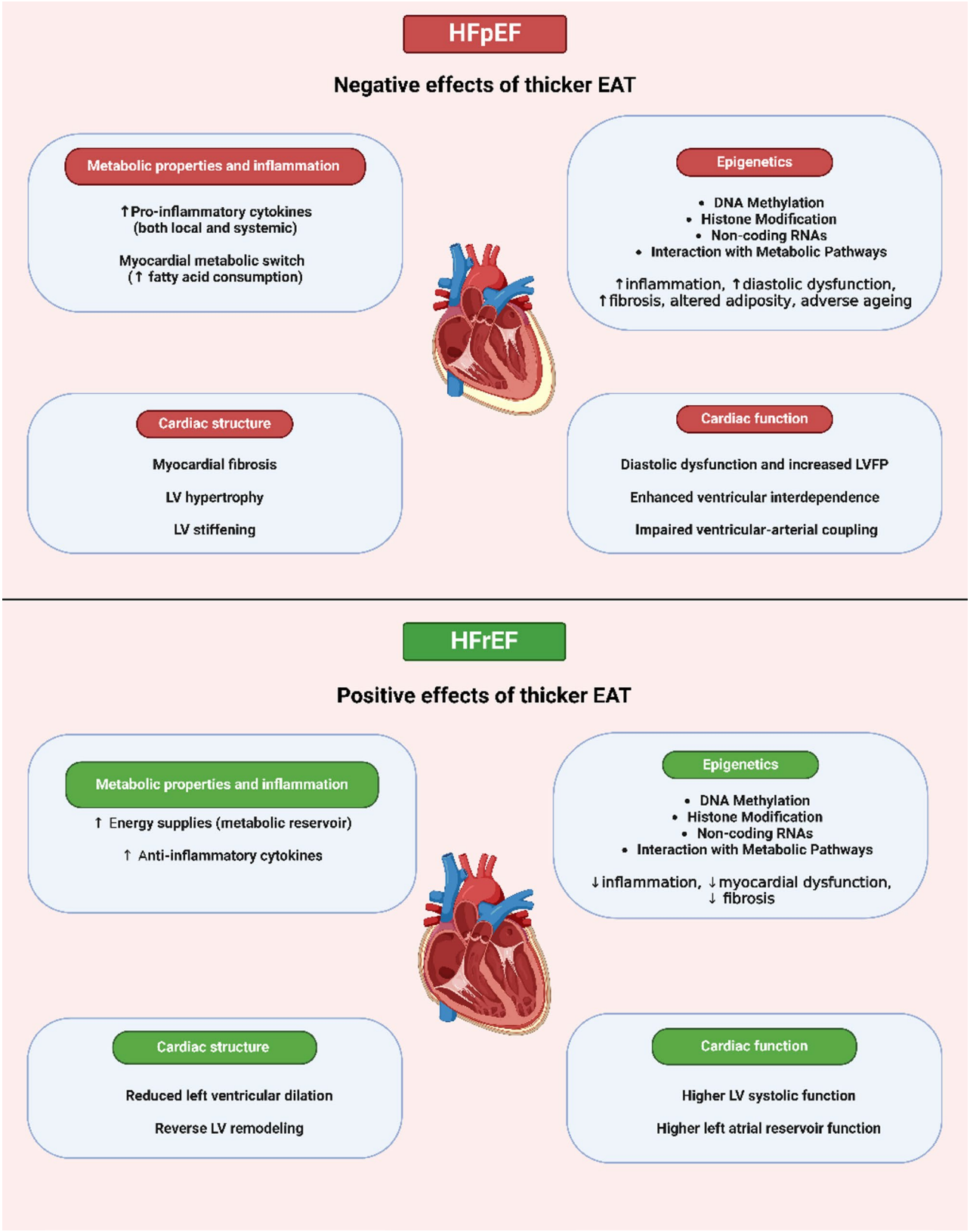


Fig. 1 Pathophysiological mechanisms through which epicardial adipose tissue (EAT) differently impacts myocardial function and structure in patients with heart failure with preserved or reduced ejection fraction

in patients with HFrEF. In patients with HFpEF, in turn, EAT is excessively increased, promoting a transition in its biology from an anti-inflammatory to a pro-inflammatory state [102]. Consequently, EAT may be a focal source of inflammatory cytokines in HFpEF, causing fibrosis and stiffening of the myocardium rather than representing an energetic reservoir [109]. This hypothesis might explain why the total EAT mass measured by magnetic resonance imaging poorly correlates with myocardial fibrosis in HFrEF while having strong correlations in HFpEF [110]. Finally, EAT might also influence cardiac mechanics. In obese individuals, increased EAT volume may impose an external constraint on the left ventricular relaxation, worsening diastolic dysfunction in HFpEF [8], while contributing to maintaining contractile efficiency in HFrEF.

Many therapeutic strategies employed in cardiometabolic conditions, such as dietary interventions, physical exercise, bariatric surgery, and antidiabetic drugs, such as GLP-1 RA and SGLT2i have been proven to reduce EAT volume and thickness [111]. Notably, GLP-1 receptors are expressed on EAT adipocytes, and their levels correlate with the expression of genes regulating fatty acid metabolism, adipogenesis, brown fat activation, and white-to-brown fat differentiation [112]. In fact, treatment with GLP-1 RAs substantially reduces EAT thickness, as documented by the results of the SUMMIT-CMR sub-study [113]. This is a cardiac magnetic resonance (CMR) sub-study of the larger SUMMIT trial [63] that explored the effects of tirzepatide on the cardiac structure and function of patients with HFpEF. Of the 176 patients recruited, 106 completed the CMR acquisitions at baseline and 52 weeks and had adequate image quality for analysis. The results documented that paracardiac adipose tissue and left ventricular mass were reduced by 45 mL (95% CI −69 to −22 mL; $P < 0.001$) and 11 g (95% CI −19 to −4 g; $P = 0.004$), respectively, when corrected for placebo. Intriguingly, left ventricular mass changes correlated with left ventricular end-diastolic volume and left atrial end-diastolic and end-systolic volumes. These and other results from meta-analyses [114] support the role of EAT in conditioning left ventricular function and structure. They also confirm the effects of GLP-1 RA in reducing EAT, potentially explaining, at least in part, the impact of these drugs on HF-related outcomes. However, it remains unclear whether changes in EAT thickness—and potentially its composition—merely reflect a general reduction in systemic adipose tissue, and thus simply mirror overall body weight loss in patients treated with GLP-1 receptor agonists, or whether these drugs may induce more specific modifications in EAT that are independent of body weight changes. A differential impact on systemic adiposity and EAT has been reported for other therapeutic approaches aimed at achieving weight loss. For instance, while bariatric surgery leads to significant reductions in overall body weight and visceral adipose tissue (VAT), the decrease in EAT is comparatively modest [115]. In contrast, a more recent study highlighted that even though EAT reduction is less substantial than VAT loss, it still has notable effects on cardiac structure and function [116]. Specifically, the decline in EAT was associated with reduced pericardial restraint—reflected in changes to the left ventricular eccentricity index—which in turn contributed to improved cardiac chamber expansion and performance over time. These observations make it possible that the weight loss observed after starting GLP-1 RA treatment might not completely capture changes in the amount and composition of the EAT or its potential consequences on the cardiac function and structure of overweight/obese patients. Molecular studies, particularly those exploring epigenetic remodeling related to fat accumulation, might provide further support for the role of EAT in conditioning left ventricular functional and structural remodeling in patients with overweight/obesity.

Fat depots, epigenetic signals and HF

Epigenetic mechanisms provide a critical layer of gene regulation in response to environmental changes [117]. This is the case of obesity, where chronic metabolic stress alters chromatin accessibility to transcriptional factors, thus enabling the upregulation or repression of genes required for adipose tissue homeostasis [118, 119]. Although genetics remains a cornerstone of obesity-related phenotypic alterations and cardiovascular risk, epigenetics plays a major role by affecting gene expression trajectories and triggering pro-inflammatory and pro-adipogenic programs over the lifespan [118, 120]. Notably, weight loss cannot rescue obesity-related alterations of the chromatin landscape, suggesting the existence of an obesity-related "epigenetic memory" driving this phenomenon [121, 122]. A recent study showed that human and mouse adipose tissues retain cellular transcriptional changes after a significant weight loss [123]. This phenomenon was explained by persistent epigenetic changes (both activating or repressing chromatin marks) in adipocytes [123]. Such "epigenetic memory" also explained the accelerated rebound weight gain through persistently active transcriptional programs implicated in adipogenesis and inflammation. In line with these observations, previous work has demonstrated that postprandial glucose spikes trigger long-lasting epigenetic signatures, which account for persistent vascular oxidative stress and endothelial dysfunction in diabetic individuals [124, 125]. These studies indicate that metabolic stress induced-epigenetic remodeling may explain molecular and phenotypic alterations of different fat depots (visceral fat, paracardial fat, EAT) implicated in the link between obesity and HF. The importance of epigenetic

regulation in obesity is outlined by the observation that monozygotic twins with discordant BMI display significant differences in DNA methylation and deregulation of genes involved in defective mitochondrial metabolism and enhanced inflammation [126]. The visceral adipose tissue of insulin-resistant vs insulin-sensitive obese patients shows marked differences in the DNA methylation landscape, with the most relevant changes observed at the promoter of genes involved in adiposity, diabetes development, chronic inflammation and aging such as COL9A1, CD44, IGF2BP1, ADAM2, TET1, ZNF714, ADCY9, TBX5, and HDACM [127]. An epigenome-wide association study showed that elevated BMI is associated with changes in DNA methylation and that these alterations are mainly related to adiposity [128]. Most epigenetic modifications were found to regulate genes involved in lipid and lipoprotein metabolism, substrate transport as well as inflammatory pathways. Although DNA methylation signatures seem to reflect micro-environmental changes and gene expression alterations in adipose tissue, they have limited application in clinical practice both as biomarkers and therapeutic targets (i.e. lack of selectivity, off target effects) [129]. Among epigenetic signals, alterations of the non-coding genome are gaining increasing attention in the clinical context and could be employed to study cardiovascular risk, disease trajectories as well as response to treatment [130, 131]. Recent evidence suggests that microRNAs (miRNAs) are critically involved in the cross-talk between EAT and the myocardium. A recent screening of miRNA signatures in human EAT unveiled miR-92a-3p a pivotal miR implicated in myocardial oxidative stress [132]. EAT miR-92a-3p was related to lower oxidative stress in the human myocardium, and high miR-92a-3p levels in EAT were independently related to a lower risk of adverse cardiovascular events [132]. Mechanistic studies showed that EAT-derived miR-92a-3p exerted protective effects in the adjacent myocardium through a paracrine effect. Another study showed that extracellular vesicles (Evs) are important carriers of EAT-derived miRNAs. The EV concentration was higher in the EAT secretome than in the subcutaneous adipose tissue and control secretomes. miRNA screening followed by validation identified miR-1-3p and miR-133a-3p as pivotal miRs involved in conduction abnormalities and pro-arrhythmic effects [133]. Besides local action, circulating miRs can also provide information on EAT size and dysfunction. Profiling of plasma miRs involved in cardiac disease and HF showed a strong correlation of miRNAs 155-5p and 302a-3p with indexed EAT volume, as assessed by computed tomography. In silico analyses showed that these miRs were implicated in regulating cardiac hypertrophy, adipogenesis, interleukin-8 production, and nerve growth factor signaling [134]. Finally, a recent study showed that different cardiac fat depots (coronary fat vs atrial fat) display different miRs expression patterns, suggesting a different contribution of these depots to cardiac remodeling based on their anatomic location. Of clinical relevance, treatment with the GLP-1 RA liraglutide was able to modify the miRNA landscape in EAT with a significant modulation of miR155 and miR181a levels [135].

Although this body of evidence clearly highlights that EAT may serve as important sources of epigenetic signaling, eventually fostering cardiac remodeling and HF phenotypes, we currently lack targeted epigenetic interventions capable of addressing EAT dysfunction in heart failure. Such treatments could confirm the causal role of EAT-related epigenetic modifications as a key driver of maladaptive myocardial responses in patients with heart failure. Established epi-drugs (i.e. Sirt1 activators) have been proven effective in tackling inflammation and lipotoxicity in the heart, the vasculature and the liver [136–138]. However, it remains unclear whether these molecules are also capable of rewiring meta-inflammatory pathways in EAT, thus preventing detrimental secretome changes and cardiac dysfunction in cardiometabolic patients. Besides chromatin editing approaches, the current explosion of RNA therapies indicates great potential to develop miRNA-targeting intervention against EAT-related miRs, namely miR-92a-3p, miR155 and miR181a. Nevertheless, challenges related to the delivery and the cell specificity of miRNA therapies in this setting remain. Further translational research in preclinical models and human samples is needed to delineate a clear roadmap of epigenetic intervention to prevent or treat EAT dysfunction in obese patients.

Conclusions

The intricate relationship between overweight/obesity and heart failure (HF) continues to be an area of active research, with growing evidence highlighting the role of adipose tissue in influencing cardiac function and structure. While body mass index (BMI) offers certain advantages as a proxy measure of adiposity, it has intrinsic limitations in capturing the complex pathophysiology that drives the development and progression of HF in individuals with overweight or obesity. As such, it represents an imprecise marker of patient outcomes. In line with the position of the *Lancet* Commission on the redefinition of clinical obesity [71], alternative measures of adiposity that more directly affect cardiac function and structure—such as epicardial adipose tissue (EAT) thickness and volume—may provide a more nuanced understanding of how pathological fat accumulation contributes to HF outcomes.

The use of GLP-1 receptor agonists (GLP-1 RAs) has emerged as a promising strategy to reduce adiposity-related cardiovascular risk, with evidence supporting

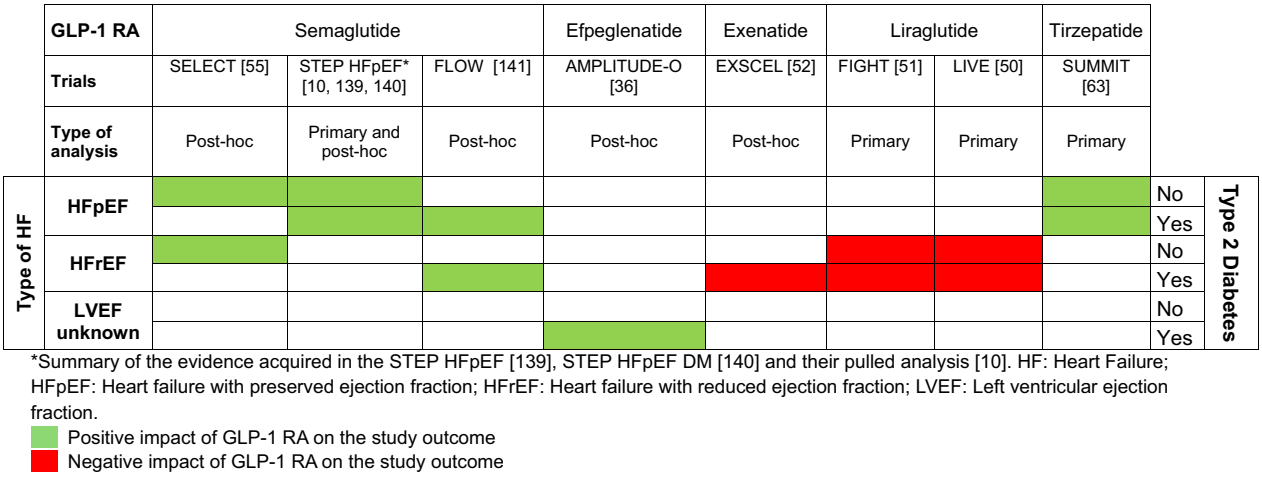


Fig. 2 Summary of the evidence supporting the use of GLP-1 RA in patients with heart failure, stratified based on type of GLP-1 RA and the presence or absence of type 2 diabetes

their beneficial effects on weight reduction and metabolic regulation. Although current data suggest a positive impact of GLP-1 RAs in patients with HF, several important questions remain unanswered. It is still unclear whether the benefits observed represent a class effect or differ between individual agents. Indeed, while semaglutide appears to benefit patients with both HFpEF and HFrEF, liraglutide and exenatide have shown potentially harmful effects in HFrEF populations [50–52] (Fig. 2). These discrepancies may reflect differences in the patient populations enrolled in the respective trials. For example, the FIGHT and LIVE trials included patients with advanced HFrEF [50, 51], whereas semaglutide trials primarily enrolled overweight, obese, or diabetic individuals—likely representing a more appropriate target population for GLP-1 RA therapy [37, 139–141]. Nevertheless, findings from the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM trials suggest that the benefits of semaglutide may be independent of BMI category or diabetes status [37, 139–141] (Fig. 2). While these findings are important, it should be noted that much of the available evidence for semaglutide comes from post hoc analyses of trials that were not originally designed for HF populations (Fig. 2). Currently, the SUMMIT trial remains the only study specifically enrolling patients with HFpEF and assessing the impact of GLP-1 RAs on HF-related primary outcomes. Therefore, before fully endorsing the use of other GLP-1 RAs in HFpEF or HFrEF, results from dedicated HF trials are needed [63].

Another important and unresolved question in daily clinical practice is when GLP-1 RA treatment should be combined with SGLT2 inhibitors, and which subgroups of HF patients are most likely to benefit from this combination therapy. Post-hoc analyses of randomized controlled trials [46] and real world evidence [47] support a complementary and thus additive cardiovascular protection achievable with the combination of GLP-1RAs and SGLT2i, but no dedicated trials have confirmed this preliminary evidence.

From a pathophysiological perspective, the mechanisms through which GLP-1 RAs improve prognosis in HF patients remain to be clarified. Weight loss is likely to improve quality of life and exercise tolerance in GLP-1 RA–treated patients [63, 139, 140], eventually leading to an enhanced ability to engage in daily physical activity and rehabilitation programs. It may also alleviate common comorbidities associated with HF progression, such as obstructive sleep apnea [142], potentially slowing the transition to more severe HF phenotypes. However, results from the SELECT trial—which included overweight patients—and the FLOW trial—which suggested a positive outcome mediated by improved renal function—support the hypothesis that the benefits of GLP-1 RAs in HF are likely multifactorial and only partially attributable to weight loss [37, 141]. Among other potential mechanisms, preliminary evidence suggests that GLP-1 RA can reduce EAT thickness [113, 114] and induce an epigenetic remodeling in the EAT [135]. These effects might account for a reduction in myocardial mechanical, metabolic and inflammatory stress that leads to the evolution towards more severe HF phenotypes. Given the increasing interest around selective and long-acting epigenetic therapies, a deeper characterization of the epigenetic modifications induced by GLP-1 RAs might lead to discovery of novel potential therapeutic targets, that might allow a better long-term management of HF.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02778-6.

Supplementary Material 1

Acknowledgements
The research leading to these results has received funding from the European Union–NextGenerationEU through the Italian Ministry of University and Research under PNRR-M4C2-I1.3 project PE_00000019 "HEAL ITALIA" to Stefano Taddei, CUP I53C22001440006. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them. This work was also supported by the Swiss National Science Foundation (n. 310030_197557) and the Swiss Heart Foundation (n. FF19045) to FP.

Author contributions
SM, NRP, FP, DT, reviewed the literature and wrote the initial draft of the paper. NDB, AB, HD, AM, AV, LG, RK, and KT critically reviewed the paper and contributed to its final draft.

Funding
The research leading to these results has received funding from the European Union–NextGenerationEU through the Italian Ministry of University and Research under PNRR-M4C2-I1.3 project PE_00000019 "HEAL ITALIA" to Stefano Taddei, CUP I53C22001440006. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them. This work was also supported by the Swiss National Science Foundation (n. 310030_197557) and the Swiss Heart Foundation (n. FF19045) to FP.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
DT reports receiving fees for serving on advisory boards from Amarin, Boehringer Ingelheim and Novo Nordisk, lecture fees from Eli Lilly, and travel support from AstraZeneca. FP reports receiving fees for serving on advisory boards from Novo Nordisk. He also serves as Guest Editor for the thematic collection to which the current manuscript has been submitted; as such, has not been involved in the peer review process for this article.

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Received: 28 February 2025 / Accepted: 6 May 2025
Published online: 22 May 2025

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