Beyond Weight Loss: the Emerging Role of Incretin-Based Treatments in Cardiometabolic HFpEF

Federico Capone[a,b,*], *Natasha Nambiar*[a,*] *and Gabriele G. Schiattarella*[a,c,d,e]

Purpose of review
Incretin-based drugs are potent weight-lowering agents, emerging as potential breakthrough therapy for the treatment of obesity-related phenotype of heart failure with preserved ejection fraction (HFpEF). In this review article, we will discuss the contribution of weight loss as part of the benefits of incretin-based medications in obese patients with HFpEF. Furthermore, we will describe the potential effects of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists on the heart, particularly in relation to HFpEF pathophysiology.

Recent findings
In the STEP-HFpEF trial, the GLP-1 receptor agonist semaglutide significantly improved quality of life outcomes in obese HFpEF patients. Whether the beneficial effects of semaglutide in obese patients with HFpEF are merely a consequence of body weight reduction is unclear. Considering the availability of other weight loss strategies (e.g., caloric restriction, exercise training, bariatric surgery) to be used in obese HFpEF patients, answering this question is crucial to provide tailored therapeutic options in these subjects.

Summary
Incretin-based drugs may represent a milestone in the treatment of obesity in HFpEF. Elucidating the contribution of weight loss in the overall benefit observed with these drugs is critical in the management of obese HFpEF patients, considering that other weight-lowering strategies are available and might represent potential alternative options for these patients.

Keywords
glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, heart failure with preserved ejection fraction, incretin-based treatments, metabolic dysfunction, obesity

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a type of heart failure for which only limited therapeutic options are available. Among the many classes of drugs that have been tested in patients with HFpEF, only two were able to improve clinical outcomes [1,2,3▪▪]. Both of these classes, namely sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), are glucose-lowering drugs originally approved for the treatment of type II diabetes mellitus (T2DM). GLP1-RAs, together with glucose-dependent insulinotropic polypeptide (GIP) agonists, act on the incretin axis, directly binding to their specific receptors which are mainly located in the pancreas – to stimulate insulin release –, and in the brain – to reduce appetite and delaying gastric emptying [4]. The role of glucagon-like peptide-1 (GLP-1) and GIP receptor agonists in HFpEF is currently under active investigation [3▪▪] [NCT04916470] [NCT04847557] making them among the most promising therapeutic strategies in this syndrome.

[a]Translational Approaches in Heart Failure and Cardiometabolic Disease, Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany, [b]Division of Internal Medicine, Department of Medicine, University of Padua, Padua, Italy, [c]Max Rubner Center for Cardiovascular Metabolic Renal Research (MRC), Deutsches Herzzentrum der Charité (DHZC), Charité -Universitätsmedizin Berlin, Berlin, Germany, [d]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany and [e]Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy

Correspondence to Gabriele G. Schiattarella, MD, PhD, Max Rubner Center for Cardiovascular Metabolic Renal Research (MRC), Deutsches Herzzentrum der Charité (DHZC), Charité -Universitätsmedizin Berlin, Berlin, Germany.
E-mail: gabriele.schiattarella@dhzc-charite.de

[*]Federico Capone and Natasha Nambiar are co-first Authors.

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KEY POINTS

- Incretin-based medications are weight-lowering agents that hold promise for the treatment of obese patients with heart failure with preserved ejection fraction (HFpEF).
- Whether the benefits of these drugs in obese HFpEF patients are only secondary to the body weight reduction is still unclear.
- A proper framework for incretin-based treatments based on clinical and mechanistic comparison with other weight-lowering strategies in obese HFpEF patients is warranted.

The notion of antidiabetic drugs being effective in heart failure may sound surprising, when – mistakenly – HFpEF is considered exclusively as cardiac-centric condition. This apparent discrepancy can be resolved when patients with HFpEF are considered as a whole. The majority of HFpEF individuals are obese, often suffering from a number of metabolic syndrome (MetS) hallmarks, such as arterial hypertension, dyslipidaemia, liver steatosis and T2DM [5–8]. At large, HFpEF can be considered the cardiac manifestation of MetS. SGLT2i and GLP-1RAs provide a broad range of beneficial effects in patients affected by MetS [9,10▪▪]. In the STEP-HFpEF trial, GLP-1RAs significantly improved clinical outcomes of quality of life in obese patients with HFpEF, collectively referred as cardiometabolic HFpEF. Considering the magnitude of body weight reduction observed with GLP-1RAs and, by design, the exclusion of lean HFpEF individuals from the STEP-HFpEF trial [3▪▪], it is legitimate to ask how much weight reduction alone contributed to the improvement of symptoms in patients with cardiometabolic HFpEF. If the majority of the observed benefits are exclusively weight related, losing body weight in cardiometabolic HFpEF should be the goal and could be reached by means other than pharmacological approaches (e.g. nutritional strategies, exercise training, bariatric surgery). Conversely if, beyond weight loss, there are clinical benefits of GLP-1RAs that are drug- (or class) specific, these compounds should be central for the management of obese HFpEF patients.

In this review, we will discuss the available evidence on the efficacy of incretin-based drugs in HFpEF treatment. In addition, we will provide an overview of the potential effects of GLP1-RAs and GIP agonists on the heart, especially in the context of HFpEF pathophysiology.

HEART FAILURE WITH PRESERVED EJECTION FRACTION AND OBESITY: WHAT DO INCRETINS TARGET IN CLINICAL TRIALS?

Among the different types of heart failure, HFpEF continues to gain attention. The combination of signs and symptoms of heart failure observed in HFpEF results, among others, from specific changes in cardiac mechanics [11] and derangements in energy metabolism [12], hindering both contractility and relaxation, especially during exercise [13]. HFpEF is not a single disease, but a constellation of different phenotypes [14]. Strikingly, about 80% of HFpEF patients are overweight or obese [5,6] and one-third suffer from T2DM [7]. These features mark the, arguably, most common HFpEF phenotype, the so-called cardiometabolic HFpEF.

Adipose tissue expansion has a pivotal role in cardiometabolic HFpEF pathogenesis [15,16], inducing systemic inflammation, excessive fatty acid uptake in cardiomyocytes and ultimately mechanical and energetic myocardial dysfunction. Of note, some of the whole-body derangements observed in cardiometabolic HFpEF are heart failure specific. Others are common among nonfailing obese individuals. Obesity itself promotes left ventricular hypertrophy [17], diastolic chamber stiffness [18], higher left ventricular filling pressure and lower mean mitral valve E/A ratio [19,20]. Weight gain is also associated with a greater risk of atrial remodelling [21] and atrial fibrillation [22]. Subclinical systolic dysfunction is observed in obese patients with HFpEF as evidenced by decreased longitudinal strain [23] and defective systolic reserve during exercise [24,25]. Obese HFpEF patients present more severe right ventricular dysfunction, lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels compared with nonobese HFpEF individuals and excessive epicardial adipose tissue (EAT) [23]. The enlarged EAT might have mechanical effects such as pericardial restraint [23] and, through secretion of soluble factors, can promote cardiac capillary rarefaction and fibrosis [26,27]. Specific to obese patients with HFpEF is plasma volume expansion, a condition caused by excessive systemic vasodilation and sodium retention [28], which is directly correlated with elevation in cardiac filling pressures [23].

Therefore, among the several cardiac and systemic changes typical of obese HFpEF patients, it is difficult to pinpoint which findings are common among obese individuals and which mark the progression to heart failure. Importantly, key clinical symptoms of heart failure, such as dyspnoea or fatigue, are highly prevalent in obese population without heart failure [29–31]. Dyspnoea on exertion

(DOE) is common in obesity, even in presence of normal cardiac function [32] and may depend on reduced expiratory volume, reduced lung and chest wall compliance, increased work of the inspiratory muscles and increased metabolic demand during exercise [33]. Also, obese patients with DOE have worse 6-min walking test (6MWT) distance and the severity of DOE is independently related to the fat mass distribution [34].

In the recently published STEP-HFpEF trial [3▪▪], 529 nondiabetic, obese HFpEF patients were randomized to GLP-1RA semaglutide or placebo. After 52 weeks, patients in the semaglutide group registered a significant improvement in the Kansas City Cardiomyopathy Questionnaire - Clinical Summary Score (KCCQ-CSS) as well as a longer walking distance in the 6MWT. In the intention-to-treat analysis, patients in the semaglutide group lost a mean of 13% of their body weight (compared with 2.6% in the placebo group). A significant reduction in C-reactive protein (CRP) level and NT-proBNP percentage from baseline was registered in the semaglutide group. The KCCQ-CSS is a questionnaire in which patients grade their symptoms (frequency and intensity of dyspnoea, fatigue and swelling) and physical limitations in activities such as dressing, showering or bathing [35,36]. In consideration of this, nonfailing obese individuals may register worse scores than lean individuals and, apart from signs of congestion, the majority of the KCCQ-CSS features are expected to improve after weight loss. In addition CRP is typically high in obesity and is independently related to BMI [37]. Considering the inverse relationship between natriuretic peptide levels and BMI, the reduction in NT-proBNP levels with semaglutide despite significant reductions in body weight stands for decongestive and favourable hemodynamic effects in the semaglutide group. The STEP-HFpEF trial was not powered to detect significant changes in clinical events, but a lower number of adjudicated HF events was registered with semaglutide.

In the recent SELECT trial [10▪▪], in a population of overweight individuals with preexisting cardiovascular disease, myocardial infarction in almost 70% of the cases – semaglutide-treated patients had a 20% reduction of cardiovascular events. Considering the lack of statical significance in the reduction of cardiovascular death and nonfatal stroke, it is likely that the fewer nonfatal myocardial infarction events recorded contributed the most to the overall benefit observed. Consistent with the STEP-HFpEF findings, a significant weight loss was observed, with a reduction in the body weight as soon as 4 weeks after randomization. Intriguingly, only patients with a baseline BMI less than 35 kg/m^2 had a significant improvement in the primary cardiovascular endpoint [10▪▪]. More than 4000 heart failure patients were enrolled in the SELECT trial. An absolute reduction in the number of hospitalization or urgent medical visit for heart failure was registered (hazard ratio 0.79) with a 95% confidence interval of 0.60–1.03.

More clinical trials are currently underway to evaluate the effects of semaglutide in diabetic obese HFpEF patients [NCT04916470] and the effects of the dual GIP/GLP-1 agonist tirzepatide in obese HFpEF patients with and without T2DM [NCT04847557]. The primary outcomes in these trials are still related to quality of life (KCCQ and 6MWT).

In summary, most of the benefits observed in the STEP-HFpEF trial, including the primary outcome, are related to weight loss [38▪]. Despite an early reduction in the occurrence of cardiovascular events in the SELECT trial, also in this case, the contribution of weight loss to the primary outcome improvement is substantial. Thus far, there is limited strong clinical evidence to support a cardiovascular benefit from GLP1-RAs beyond those mediated by weight loss and glycaemic control. This is not trivial, as GLP1-RAs are not the only available strategy to achieve a significant weight loss. In fact, losing weight through caloric restriction and/or aerobic exercise might be a more affordable strategy in the long term, significantly improving exercise capacity and/or quality of life in patients with obesity and HFpEF [39▪,40]. Consistently, supervised exercise training (SET) is a valuable intervention in these patients [41▪▪].

Considering the long-term cost of incretin-based treatments, a direct clinical comparison with dietary intervention, SET and/or bariatric surgery (in selected patients) [42] should be pursued, to establish if GLP1/GIP receptor agonists outperform other strategies in obese HFpEF patients. Moreover, the lack of cardiovascular benefits in patients with BMI at least 35 kg/m^2 in the SELECT trial supports a role for bariatric surgery option in these patients.

Routinary use of GLP1/GIP receptor agonists over nonpharmacological intervention in obese patients with HFpEF will benefit of gaining more insights in the biology of incretin-based treatments in HFpEF. To better understand the therapeutic potential of these drugs in heart failure, an overview of available preclinical data supporting direct effects of incretin axis modulation on the cardiovascular system is discussed below.

MECHANISMS UNDERLYING CARDIOPROTECTION OF GLUCAGON-LIKE PEPTIDE-1 AND GLUCOSE-DEPENDENT INSULINOTROPHIC POLYPEPTIDE AGONISTS

GLP-1 and GIP are two incretin hormones derived from the preglucagon gene that play a pivotal role in

several metabolic pathways [4]. While their primary effects are on the pancreas-gut axis, aiming to modulate insulin production, they also exert extra-pancreatic actions. A direct modulation of cellular energy substrates metabolism has been proposed, with effects on several peripheral organs including the heart [43,44▪▪].

Effect of incretins on cardiac metabolism

Changes in metabolism of major energy substrates have an important impact on cardiac remodelling. Upon GLP-1R stimulation, cardiac energy efficiency seems to be enhanced due to an increase in glucose uptake [45]. For example, GLP-1 infusion in hypertensive rats prone to heart failure, significantly increased myocardial glucose uptake (MGU) [46]. In dilated cardiomyopathy, a similar increase was observed *via* a nitric oxide and p38MAP kinase mediated mechanism [47]. In normal rat hearts, upon oleate treatment – that is, lipid overload –, the GLP-1R agonist reduced glucose uptake without affecting contractility. Conversely, GLP-1 treatment alone had a negative impact on contractile function while having no effect on glucose uptake, thereby suggesting distinct mode of actions between the incretin and the receptor agonist [48].

Cardiac hypertrophy is typically marked by changes in energetic substrates utilization with increased glucose oxidation and reduced fatty acid utilization (FAO). Whether the glucose oxidation to FAO ratio (GO/FAO) increase is beneficial or detrimental in heart failure has been long debated. GLP-1 administration in HFpEF mice is proposed to enhance the GO/FAO, potentially mitigating cardiac remodelling by reducing oxidative damage [49]. Despite this, only limited data support that GLP-1R stimulation increases glucose oxidation in cardiomyocytes. In addition, whether the observed metabolic shift after incretin-based treatments is beneficial in the context of cardiometabolic HFpEF is still partly unknown.

Despite the similarities in the physiological role between GIP and GLP-1, there are limited studies on the effect of GIP on the cardiovascular system. GIP agonists may positively impact systemic energy metabolism, as seen in transgenic mice with elevated GIP levels that exhibited improved glucose tolerance and insulin sensitivity [50]. In murine models of myocardial infarction, an association between GIP receptor activation and myocardial triacylglycerol metabolism has also been observed. Specifically, in cardiomyocytes, phosphorylation of ERK through GIPR seems essential for enhanced hormone-sensitive lipase phosphorylation leading to reduced ventricular injury and enhanced survival [51]. Direct GIPR antagonism was also shown to regulate lipid metabolism by decreasing fatty acid oxidation in cardiomyocytes indicating a potential metabolic approach to impact postischemic cardiac remodelling [51]. Taken together, these observations imply that the influence of GIP on cardiac remodelling may change based on the underlying cardiovascular alterations. However, the specific role for GIPR stimulation in cardiometabolic HFpEF is yet to be investigated.

Other proposed effects of incretins in preclinical models

Differently from the limited data available on the effects of incretins on cardiomyocyte metabolism, the role of GLP-1 and/or GIP in regulating body weight has been extensively investigated [43,52,53]. Their benefits on weight management and lowering glucose levels in clinical and preclinical studies are convincing. With respect to HFpEF, GLP-1 agonists are shown to decrease epicardial fat mass and reduce atrial enlargement [54]. In a cardiometabolic HFpEF model, treatment with the GLP-1 agonist liraglutide induced a 30% reduction in body weight, whereas treatment with SGLT2i dapagliflozin, minimally impacted the reduction of fat mass in these mice [54]. Similarly, a 15% reduction in fat mass was reported in obesity-related mouse model treated with semaglutide [55▪▪].

To investigate whether the cardiometabolic benefits are solely a product of weight loss, a comparison between the semaglutide effect with pair feeding-induced weight loss was recently performed [55▪▪]. While prolonged sustained weight loss effects were similar in both conditions, some specific cardioprotective features were observed exclusively in semaglutide-treated HFpEF mice. Apart from improving glycaemic control and exercise capacity, semaglutide-treated mice showed an overall improvement in cardiac performance by reduction in natriuretic peptide levels, inflammatory responses, fibrosis as well as attenuated left ventricular hypertrophy. Interestingly, GLP-1 receptor was mainly expressed in endothelial cells rather than cardiomyocytes. Furthermore, proteomics and transcriptomics analysis highlighted changes in several pathways (cytoskeleton organization, mitochondrial function, ATP synthesis and energy metabolism), which marked the HFpEF phenotype improvement observed in the semaglutide treated group [55▪▪]. Similar attenuation in myocardial dysfunction, as evidenced by an improvement in global longitudinal strain, was observed in the liraglutide-treated multihit HFpEF female mice model in response to a high-fat diet together with angiotensin II infusion. Here, inflammatory, fibrotic

and metabolic pathways are proposed as key in the development of cardiometabolic HFpEF phenotype [54]. These results collectively suggest that GLP-1 agonists may provide cardiometabolic advantages in HFpEF that go beyond the secondary impacts of weight reduction. While this marks a promising beginning towards exploring the incretin effects of HFpEF, caution is warranted. To date, only one study compared the effects of GLP-1RA with caloric restriction in cardiometabolic HFpEF [55▪▪]. Both studies mentioned above used female mice to demonstrate the effects of GLP-1 in HFpEF. Hence, exploring any sex-specific effects is worth doing. While multihit models are favourable to study HFpEF, there are inherited limitation of rodent models when it comes to translating findings in human participants. Overall, the field of mechanistic understanding of the effects of GLP-1-related drugs in cardiometabolic HFpEF is expected to continuously grow.

From a mechanistic perspective, there is limited evidence on the cardiovascular biology and long-term safety of selectively stimulating the GIPR in humans. The data available are still mostly in the preclinical space and incompletely understood. Moreover, given the heterogeneity of existing results [51,56], further studies need to be performed to better understand the role of GIPR agonists, particularly concerning the cardiometabolic effects they may have on HFpEF models.

CONCLUSIONS

HFpEF and obesity often coexist, and both represent a major challenge for public health. Incretin-based treatment is emerging as breakthrough therapy in obesity management. Recent clinical evidence suggests a role for GLP1-RAs in improving quality of life and exercise capacity in obese patients with HFpEF. Importantly, until now, the benefits observed in these patients may be all a direct or indirect consequence of the striking body weight reduction obtained with these medications. Preclinical data suggest a role for GLP1-RAs in modulating cardiac metabolism and overall cardiac function, but whether these can be considered, at least in part, weight-loss independent effects is still unclear. A direct comparison between incretin-based treatments and caloric restriction, exercise training or other weight-loss strategies in obese HFpEF patients has not been performed so far. With the use of GLP1 and/or GIP receptor agonists we are facing a paradigm change in the treatment of cardiometabolic HFpEF. Caution is warranted. Nutritional strategies combined with exercise training must be considered for the management of obese HFpEF individuals as part of long-term plan to treat this syndrome.

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Conflicts of interest

There are no conflicts of interest.

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