

# Heart failure and obesity: Translational approaches and therapeutic perspectives. A scientific statement of the Heart Failure Association of the ESC

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Obesity and heart failure (HF) represent two growing pandemics. In the general population, obesity affects one in eight adults and is linked with an increased risk for HF. Obesity is even more common in patients with HF, where it complicates the diagnosis of HF and is linked with worse symptoms and impaired exercise capacity. Over the past few years, new evidence on the mechanisms linking obesity with HF has been reported, particularly in relation to HF with preserved ejection fraction. Novel therapies inducing weight loss appear to have favourable effects on health status and cardiovascular risk. Against the backdrop of this rapidly evolving evidence landscape, HF clinicians are increasingly required to tailor their preventive, diagnostic, and therapeutic approaches to HF in the presence of obesity. This scientific statement by the Heart Failure Association of the European Society of Cardiology provides an up-to-date summary on obesity in HF, covering key areas such as epidemiology, translational aspects, diagnostic challenges, therapeutic approaches, and trial design.

**Keywords** Obesity • Heart failure • Risk factors • HFrEF • HFpEF

## Preamble

The prevalence of obesity is increasing dramatically, having reached pandemic proportions. In 2022, 43% of adults were overweight and 16% lived with obesity worldwide.<sup>1</sup> Obesity carries a high risk of cardiovascular diseases, especially heart failure (HF), both directly and indirectly through its association with other cardiovascular risk factors, including diabetes, sleep apnoea, hypertension, and dyslipidaemia. It often mimics symptoms and signs characterizing HF, for example fatigue, dyspnoea, and oedema, and can make diagnosis of HF challenging. Over the past few years, several novel therapeutic options specifically targeting obesity have become available, and many more are currently under development. Therefore, obesity warrants special consideration throughout all the steps of HF management, from prevention and diagnosis to treatment and drug development. This scientific statement by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) aims to provide a framework for approaching HF diagnosis, treatment, and trial design in the context of the obesity pandemic.

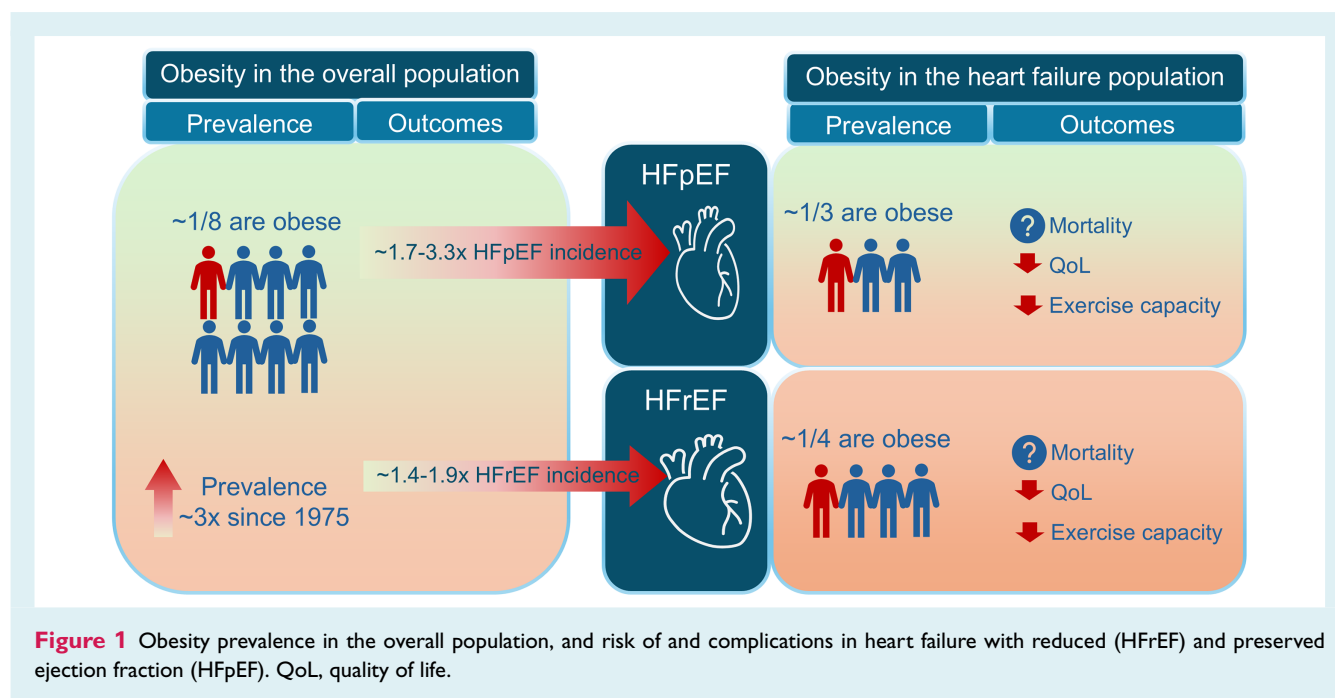
## Overweight and obesity: definitions and diagnosis

Obesity is characterized by excessive adiposity, with or without abnormal distribution or function of the adipose tissue.<sup>2</sup> In individuals with pre-clinical obesity, function of other tissues and organs is preserved, whereas there is predisposition to clinical obesity as well as, among other diseases, cardiovascular disease.<sup>2</sup> Conversely, clinical obesity is characterized by alterations in the function of tissues and organs due to excessive and/or abnormal adiposity.<sup>2</sup>

Excess adiposity is commonly estimated by the body mass index [BMI = body weight (kg)/height<sup>2</sup> (m<sup>2</sup>)].<sup>3</sup> BMI is not a direct measure of adiposity but rather correlates with the percentage of body fat, and this relationship is independently influenced by sex, age, and ethnicity.<sup>3–5</sup> In adults (aged 18 years and over), obesity is defined by

a BMI  $\geq 30$  kg/m<sup>2</sup> and overweight (also called pre-obesity) by a BMI between 25 and 30 kg/m<sup>2</sup>.<sup>3</sup> These cut-offs are internationally recognized as they are associated with health outcomes, cardiovascular risk, and mortality.<sup>6,7</sup> However, the optimal thresholds for defining obesity may differ by ethnicity. For example, in the Asian population, obesity is classified at a lower BMI ( $\geq 25$  kg/m<sup>2</sup>), with overweight defined as a BMI between 23 and 25 kg/m<sup>2</sup>.<sup>8,9</sup> Patients with higher BMI also exhibit a higher prevalence of other cardiovascular comorbidities, such as type 2 diabetes mellitus (T2DM) and arterial hypertension.<sup>10,11</sup>

Body mass index is easy to measure in everyday practice, but body weight can be affected by non-fat related mechanisms such as fluid retention in patients with HF. In addition, BMI does not distinguish between muscle and adipose mass, nor general and visceral adiposity. A larger abdominal or trunk fat content (also known as visceral, android, or central obesity) has been associated with an increased risk of metabolic syndrome, T2DM, high blood pressure, and heart disease,<sup>3,12,13</sup> with a stronger association than for BMI.<sup>14</sup> Central obesity is commonly assessed by measuring the waist-to-hip ratio or waist-to-height ratio, but it can also be more easily estimated by a single waist circumference (WC) measurement taken at the level of the midway horizontal distance between the lowest rib and the superior iliac crest (with cut-offs of 94 cm in European men and 80 cm in non-pregnant European women).<sup>3</sup> While there is a strong correlation between overall obesity and central obesity, some individuals may have abdominal obesity in the absence of overall obesity based on BMI (also known as normal-weight obesity), leading to an underestimation of the cardiovascular risk.<sup>12</sup> Conversely, some obese patients as defined by BMI may have limited abdominal and visceral obesity. Central obesity is best assessed by imaging techniques, such as dual-energy X-ray absorptiometry (DEXA) or magnetic resonance imaging (MRI), which are, however, often not easily accessible in daily practice. As a result, combining BMI and waist-to-height ratio is recommended over BMI alone to better detect fat accumulation in the body and to better assess cardiovascular risk.<sup>3,15,16</sup>



In addition, some adipose tissue-dependent metabolic derangements can have a negative impact on skeletal muscle and can lead to progressive loss of muscle mass and function or sarcopenia. The co-existence of obesity and sarcopenia defines sarcopenic obesity,<sup>17</sup> a condition associated with worse clinical outcomes including patients with HF.<sup>18,19</sup> Both sarcopenia and obesity are well documented as separate entities in patients with HF, but their combination is poorly investigated. The assessment of skeletal muscle functional parameters (e.g. handgrip strength, or chair stand test) is, thus, also useful in patients with obesity and HF.

## Epidemiology of obesity in relation to heart failure

### Prevalence of obesity

The World Health Organization reports tripled obesity prevalence since 1975, expressing concern about the subsequent rise in HF.<sup>20</sup> The prevalence of obesity varies geographically due to differences in diet, lifestyle, genetic factors, and healthcare access. Most recent statistics highlight a prevalence of ~17% in Europe (2019), 30–35% in North America (2022), ~25% in Latin America (2016), ~13% in Africa (2016), ~30% in Australia (2017–2018), 20–40% in Middle East (2018), from ~5% in Japan to ~20% in Malaysia (2019) in Asia, with large geographical variations. By 2025 worldwide prevalence of obesity is expected to reach 25%.<sup>1,21–24</sup>

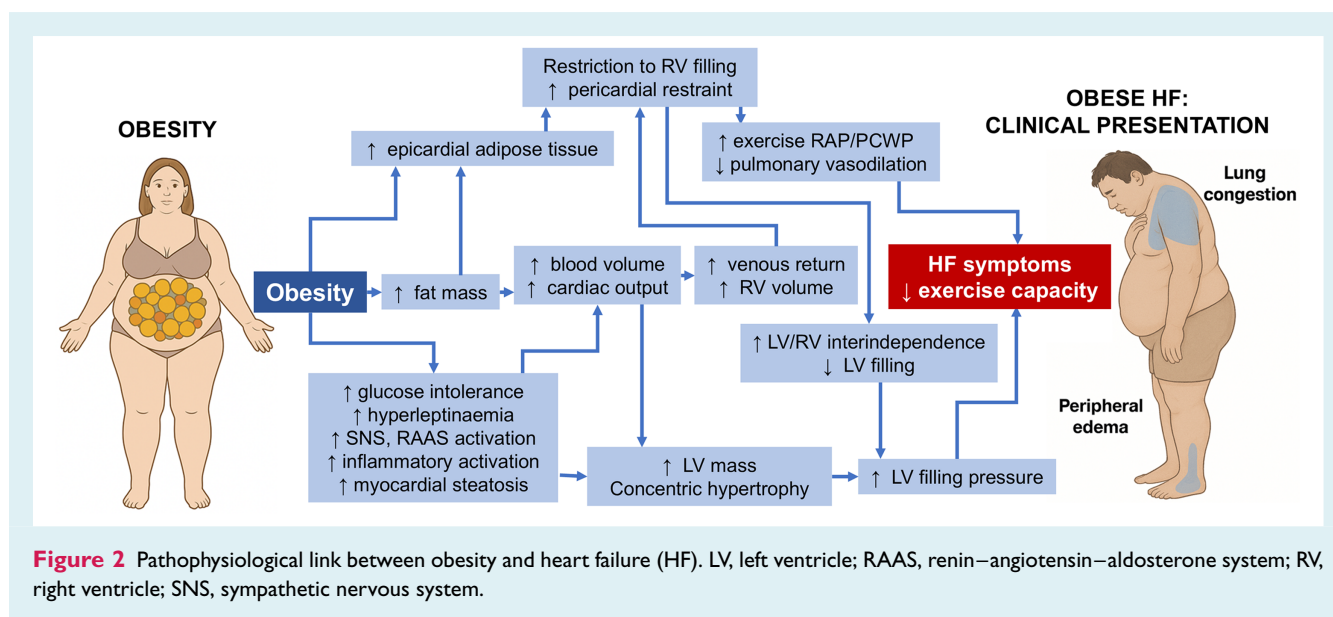
### Obesity and heart failure risk

Obesity increases the risk of HF by two-six-fold regardless of sex,<sup>25</sup> with a stronger adjusted (for age, sex, ethnicity, income, education, and physical activity) association with incident HF with preserved

ejection fraction (HFpEF) than incident HF with reduced ejection fraction (HFrEF)<sup>26</sup> (Figure 1). The differential association between BMI and HFpEF versus HFrEF has been reported to be more pronounced in women than men.<sup>27,28</sup> Consistently, prevalence of obesity in HF is overall high (~35% in the Global Congestive Heart Failure registry across 40 countries with different economic levels regardless of ejection fraction [EF]),<sup>29</sup> and higher in HFpEF versus HF with mildly reduced EF (HFmrEF) versus HFrEF, that is ~40% in CHAMP-HF (US) and ~30% in Get With The Guidelines-HF (US),<sup>30,31</sup> ~25% in the Swedish HF (SwedeHF) registry and in the TITRATE-HF study (The Netherlands) in HFrEF,<sup>32,33</sup> 28% and 31% in HFmrEF and HFpEF in SwedeHF,<sup>32</sup> respectively, 45% in the EMPEROR-Preserved and DELIVER trials enrolling patients with HFmrEF/HFpEF.<sup>34,35</sup>

### Obesity and heart failure prognosis

Patients with HF and obesity according to the BMI criteria have sometimes been reported to have better prognosis compared with those with lower BMI in different settings, that is chronic and advanced HF, HFpEF and HFrEF.<sup>36,37</sup> In the MAGGIC meta-analysis, the relationship between BMI and mortality was U-shaped regardless of EF, with a nadir at BMI at 30–34.9 kg/m<sup>2</sup>.<sup>36</sup> However, this 'obesity paradox', that is the apparent lower risk in patients with HF who are overweight/obese (vs. normal weight), has been questioned by more recent studies. When in the ASIAN-HF registry obesity was defined according to the waist-to-height ratio ( $\geq 0.55$ ), obesity was rather associated with increased risk of HF hospitalization or mortality, which was consistent with findings from the TOPCAT in HFpEF and only in women in the BIOSTAT-CHF, suggesting that measures of adiposity, such as waist-to-height ratio, could better reflect body composition than BMI.<sup>38–40</sup> In patients with HFrEF in the PARADIGM-HF, the 'obesity paradox' of BMI was



lost after adjustment for other prognostic variables, and reversed when BMI was replaced with alternative anthropometric measures of adiposity. Moreover, both BMI and waist-to-height ratio had a direct association with a higher risk of the primary outcome and HF hospitalization, and this was more evident after adjustment for other variables.<sup>41</sup> Another study found that the obesity paradox was mitigated when accounting for exercise tolerance.<sup>42</sup> Obesity is also associated with more adverse outcomes in patients with end-stage HF, following heart transplantation, and with a higher risk of left ventricular (LV) assist device thrombosis and infection.<sup>43</sup>

## Characteristics of patients with heart failure and obesity

In HF, regardless of EF, patients with versus without obesity are more likely to be women and younger, with medical history of hypertension, diabetes and atrial fibrillation (AF), although no differences in history of ischaemic heart disease have been observed.<sup>36</sup> They are also more likely to be symptomatic,<sup>36</sup> and, interestingly, in some studies, they have been shown more likely to receive HFrEF optimized guideline-directed medical therapy than their leaner counterparts.<sup>31,44</sup> Although this finding may be partly explained by the higher prevalence of comorbidities such as hypertension and diabetes in patients with obesity, thus contributing to the prescription of HF medical therapies for compelling indications, obesity itself has been associated with better and more intensive pharmacological treatment for HF, even after adjustments.<sup>45</sup>

## The link between obesity and heart failure

Approximately one third of patients with HF are obese, with a greater prevalence in HFpEF than HFrEF.<sup>30,32,46</sup> Of patients with

HFpEF, more than two thirds are overweight or obese,<sup>47</sup> with approximately 30% also having T2DM.<sup>48,49</sup> This association, linked to what is often termed cardiometabolic HFpEF – HFpEF stemming from metabolic syndrome –, underscores the profound impact of obesity on cardiovascular health. Obesity independently contributes to various cardiovascular alterations, such as LV hypertrophy,<sup>50</sup> diastolic dysfunction,<sup>51</sup> and plasma volume expansion,<sup>52</sup> which elevate cardiac filling pressures,<sup>53,54</sup> and manifests in symptoms like dyspnoea and peripheral oedema, even in individuals without overt HF (Figure 2). However, patients with HFpEF and obesity by definition present distinct HF symptoms related to lung and systemic congestion, along with inadequate cardiac output response to exercise.<sup>55</sup>

Adipose tissue expansion is central to the pathogenesis of cardiometabolic HFpEF, fostering systemic inflammation and metabolic dysregulation.<sup>56,57</sup> While some aspects of cardiac dysfunction observed in cardiometabolic HFpEF are unique to HF, others are common among individuals with obesity without manifest HF as well, including LV hypertrophy, diastolic stiffness, and atrial remodelling. Patients with HFpEF and obesity may also exhibit sub-clinical systolic dysfunction,<sup>55</sup> right ventricular dysfunction, and excessive epicardial adipose tissue, contributing to cardiac fibrosis and capillary rarefaction.<sup>58,59</sup> Obesity can contribute to mineralocorticoid receptor overactivation, which has deleterious effects in HF pathophysiology,<sup>60</sup> through aldosterone production by the adipocytes.<sup>61,62</sup>

Navigating through the myriads of cardiac and systemic changes associated with obesity and HF poses challenges in distinguishing between findings common in obese individuals and those related to HF progression. Clinical symptoms such as dyspnoea and fatigue are prevalent in the obese population, even in the absence of overt cardiac dysfunction.<sup>63</sup> Dyspnoea on exertion, a common complaint in obesity, can be attributed to various factors such as reduced lung compliance and increased metabolic demand during exercise, with its severity often linked with fat distribution.<sup>64</sup>

Compared with lean patients with HFpEF, in those with obesity the adaptive decrease in pulmonary vascular resistance during exercise is absent and thereby the increase in mean pulmonary artery pressure steeper, resulting in higher oxygen consumption per myocardial work (i.e. decreased myocardial efficacy).<sup>55</sup> Accordingly, patients with obesity who experience dyspnoea on exertion tend to exhibit poorer performance on functional tests like the 6-min walk test, highlighting the impact of obesity on physical capacity and cardiovascular health.<sup>65</sup>

Beyond the direct effects of body weight and adiposity on alterations in cardiac structure and function, its association with hypertension, T2DM, AF and ischaemic heart disease, further exacerbates the risk of HF, and also indirectly links obesity with HFrEF.

Even if obesity is more frequently associated with HFpEF, higher BMI determines an increased risk also of HFrEF, especially in men.<sup>27</sup> Excessive adiposity promotes coronary atherosclerosis progression and incident myocardial infarction which is the most common underlying aetiology in HFrEF and HFmrEF.<sup>66–68</sup> While obesity-driven HFpEF is primarily a consequence of metabolic dysfunction, systemic inflammation, and microvascular disease, in ischaemic HFrEF visceral adiposity accelerates atherosclerosis, contributes to plaque instability, and increases infarct size, leading to progressive systolic dysfunction.

Obesity-induced structural and functional cardiac changes, including left atrial enlargement, increased epicardial fat, and systemic inflammation, contribute to atrial remodelling and increased AF susceptibility, which in turn might lead to HF or worsen outcomes in patients with HF.<sup>69,70</sup> Haemodynamic alterations, such as increased cardiac output and preload, further exacerbate atrial stretch and AF risk.<sup>71–73</sup> The presence of obesity also complicates the clinical assessment of AF beyond HF, as symptoms, for example fatigue, dyspnoea, etc., may be attributed to excess weight rather than AF/HF-related haemodynamic compromise. Obesity is also associated with increased AF recurrence, with AF burden associated with worse outcome in HF patients.<sup>74,75</sup> N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are higher in patients with AF,<sup>76</sup> due to the atrial stretch and subsequent peptide release occurring during the chaotic atrial depolarization. Levels of natriuretic peptides are reduced in obesity (see below), thus the opposite effects of AF and increased adiposity should be considered when using NT-proBNP as diagnostic biomarker in the HF setting.

## Molecular aspects of cardiometabolic heart failure with preserved ejection fraction and obesity

Heart failure with preserved EF is a complex syndrome. In the most common phenotype, known as cardiometabolic HFpEF, obesity is a major driver of cardiac dysfunction. Excessive adiposity promotes several derangements, but the effects of obesity and metabolic syndrome on cardiac metabolism are pivotal in HFpEF

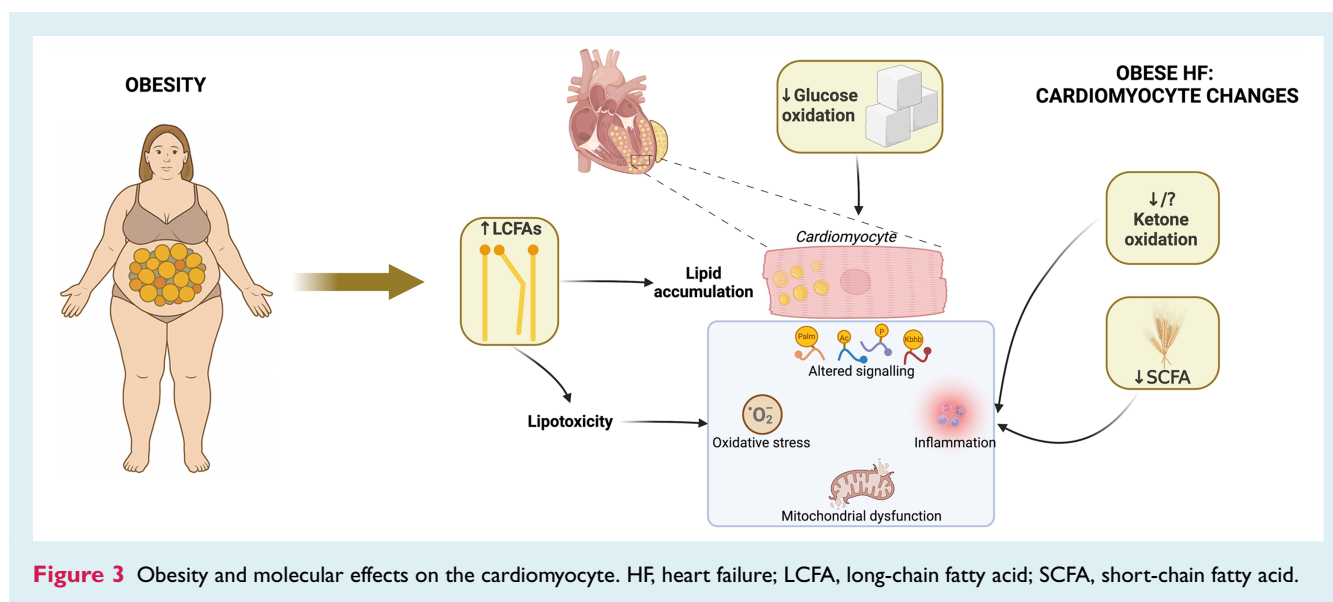
progression.<sup>77</sup> Cardiac energetics rely on the intricate interplay of various energy substrates, including fatty acids (FAs), ketone bodies (KBs), and glucose. In cardiometabolic HFpEF, the heart exhibits a distinct pattern of substrate utilization with significant changes in the balance between FAs, KBs, and glucose utilization (Figure 3).

Fatty acids, composed of an aliphatic chain and a carboxyl group, provide high energy yield upon oxidation. Long-chain fatty acids (LCFAs) are the predominant fuel for the healthy adult heart, given its high energy demand.<sup>78</sup> LCFA oxidation generates significant adenosine triphosphate (ATP) but requires substantial oxygen. In HFrEF, LCFAs metabolism is defective and an increase in alternative substrate oxidation is observed.<sup>79</sup> In cardiometabolic HFpEF, LCFAs overload in the myocardium and insulin resistance together contribute to a high reliance on FA oxidation compared with other substrates,<sup>80</sup> despite overall ATP production being defective.<sup>81</sup>

Long-chain FAs are primarily consumed as triglycerides and other esters, hydrolyzed with digestion, and transported to tissues where they are re-esterified or oxidized.<sup>82</sup> Pathologically high levels of LCFAs can lead to lipid overload and lipotoxicity, characterized by myocardial steatosis and diastolic dysfunction. Lipotoxicity involves increased reactive oxygen species production, primarily driven by intermediates like diacylglycerol and ceramides,<sup>83</sup> contributing to cardiomyocyte apoptosis and mitochondrial dysfunction. Beyond intracellular lipid accumulation, ectopic fat depots—epicardial, pericardial, and perivascular adipose tissue—play a crucial role in cardiovascular dysfunction. Epicardial adipose tissue surrounding the myocardium is highly metabolically active and secretes inflammatory cytokines and adipokines such as tumour necrosis factor- $\alpha$ , interleukin-6, and leptin, promoting myocardial fibrosis, oxidative stress, and microvascular dysfunction.<sup>84–86</sup> Excessive epicardial adipose tissue is linked to increased LV filling pressures, impaired relaxation, and worsened diastolic function.<sup>87,88</sup> Similarly, pericardial and perivascular fat depots contribute to coronary microvascular dysfunction and vascular inflammation by releasing vasoconstrictive and pro-atherogenic mediators, impairing endothelial function, increasing arterial stiffness, and exacerbating HFpEF pathophysiology. LCFAs also impact inflammation and epigenetic modulation, particularly through macrophage polarization and DNA methylation. Saturated FAs promote pro-inflammatory M1 macrophages via upregulation of DNA methyltransferases,<sup>89</sup> while polyunsaturated fatty acids (PUFAs) exhibit protective roles. For instance, n-3 PUFAs can modulate leptin expression and DNA methylation, thereby reducing the onset of diastolic dysfunction.<sup>90</sup>

Short-chain FAs (SCFAs), such as acetate, propionate, and butyrate, derive from gut microbiota fermentation and have beneficial effects in metabolic cardiomyopathy. Unlike LCFAs, SCFAs do not rely on the carnitine shuttle for mitochondrial entry, making them advantageous under conditions where FA oxidation is impaired.<sup>91,92</sup> SCFAs act as signalling molecules through G protein-coupled receptors,<sup>93,94</sup> influencing blood pressure, inflammation, and metabolic homeostasis.<sup>95</sup> They inhibit histone deacetylases, leading to anti-inflammatory effects and reduced lipid absorption, which can mitigate obesity and insulin resistance.<sup>96,97</sup>





Glucose serves as a crucial energy substrate for the heart, especially under ischemic conditions due to its lower oxygen requirement for ATP production. In HFpEF, insulin signalling is impaired and glucose oxidation is blunted,<sup>80,98</sup> highlighting the importance of substrate competition (Randle cycle) in metabolic adaptation.<sup>99</sup> KBs, primarily acetoacetate and  $\beta$ -hydroxybutyrate, are produced by the liver from FAs and serve as alternative energy sources during fasting or prolonged exercise. KB metabolism involves adipose tissue, liver, and peripheral tissues like the heart. Elevated FAs stimulate ketogenesis, providing an energy source during reduced glucose availability.<sup>100</sup> KBs play a role in cellular signalling and epigenetic regulation, and an increased use of KBs for energy is considered to be an adaptive response in patients with HFpEF.<sup>101</sup> However, in obese patients with HFpEF, studies suggest a decreased reliance on KBs for energy.<sup>80</sup> This shift in energy metabolism could contribute to the unique pathophysiology of HFpEF.

Acetylation, a reversible post-translational modification, impacts numerous proteins including histones, cytosolic proteins, and key mitochondrial enzymes, and can occur enzymatically or non-enzymatically, regulated by acetyl-CoA availability. Histone acetyltransferases and histone deacetylases transfer and remove acetyl groups, respectively, but these enzymes, now often referred to as lysine acetyltransferases and lysine deacetylases, highlight the importance of lysine residues in this modification.<sup>102</sup> Acetylation affects protein function, stability, and interactions, influencing cellular metabolism and disease progression, particularly in cardiometabolic conditions like HFpEF.<sup>103</sup>

In summary, in patients with obesity and HFpEF, cardiac metabolic remodelling alters the delicate balance between FAs, glucose, and KBs. LCFAs are primary fuels, but their pathological accumulation leads to lipotoxicity and diastolic dysfunction. A lower dietary fibre intake weakens the protective effects of SCFAs. Glucose utilization is defective and KB oxidation, usually providing an alternative energy source, is not increased in cardiometabolic

HFpEF.<sup>80</sup> Additionally, ectopic fat depots act as key mediators of myocardial and vascular dysfunction, amplifying inflammatory signalling, worsening diastolic compliance, and contributing to the adverse haemodynamic profile characterizing HFpEF. Understanding these molecular aspects is essential for developing targeted therapies to manage HFpEF and its cardiometabolic phenotype associated with obesity.

## Diagnostic considerations in subjects with heart failure and obesity

The diagnosis of HF in patients with obesity is challenging, due to partial overlap in symptoms and signs, such as dyspnoea and oedema. Distinguishing, among obese people, those with dyspnoea due to HF from those with non-cardiac dyspnoea, is critical. Characteristics clearly identifying dyspnoea as cardiogenic are (1) its causal relationship with lung congestion, (2) concomitant increase in cardiac filling pressures, at rest and during exercise. Therefore, especially when NT-proBNP levels are low as in obese individuals (see below), the assessment of congestion represents a key component of the diagnostic algorithm for HF. Further, there are specific issues in need to be considered when interpreting biomarker profiles and imaging tests.

## Biomarkers

### Natriuretic peptides

Body mass index is inversely correlated with natriuretic peptides, and obesity can therefore confound the assessment of natriuretic peptides in HF. However, in patients with HF, bariatric surgery (which induces significant weight loss) appears to increase natriuretic peptide levels despite being associated with improved cardiac function.<sup>104,105</sup>

Patients with HF and obesity have lower levels of plasma B-type natriuretic peptide (BNP) compared with those without obesity, and there is an inverse correlation between plasma BNP levels and BMI,<sup>106</sup> due to the high expression of natriuretic peptide receptor (NPR)-A and NPR-C in adipocytes,<sup>107</sup> and therefore the higher uptake of BNP by adipocytes and lower levels in the bloodstream. Obese patients with HF who do have elevated BNP (>35 pg/ml) are more likely to have right ventricular remodelling and elevated pulmonary artery pressure.<sup>108</sup>

Furthermore, NT-proBNP, which does not bind to NPR-A and NPR-C, is also found to be lower in obese patients, indicating that different mechanisms are involved. Indeed, in the context of HF with obesity, BNP production and secretion decrease as insulin resistance increases.<sup>109</sup> Additionally, increased levels of Thr71-glycosylated proBNP impair proBNP processing, leading to decreased levels of NT-proBNP and BNP.<sup>110</sup> Therefore, reduced BNP production, alterations in peripheral fat cell metabolism, and impaired proBNP processing are all mechanisms that together contribute to the decrease in plasma BNP/NT-proBNP levels in obese patients with HF,<sup>111</sup> challenging their assessment for diagnostic and prognostic purposes.

As a result, it has been suggested that lower NT-proBNP cut-off values should be used for ruling out HF in individuals with obesity. In a recent analysis, including multiple cohorts of HFpEF patients where diagnosis of cardiac dyspnoea was conclusively determined by exercise catheterization, a cut-off of 50 pg/ml has been proposed to reduce false negatives in outpatients with BMI  $\geq 35$  kg/m<sup>2</sup>.<sup>112</sup>

### Adipokines and other biomarkers

A number of adipokines and growth factors produced by the adipose tissue have been shown to be associated with increased cardiovascular risk including leptin, adiponectin, omentin, visfatin or apelin among others.<sup>113</sup> Leptin plays a key role on energy metabolism and homeostasis, neuroendocrine regulation and inflammation.<sup>114</sup> The leptin–aldosterone–neprilysin axis is involved in the development of cardiac inflammation and fibrosis across the spectrum of HF in patients with obesity.<sup>115</sup> In patients with HF and metabolic syndrome, circulating leptin was the most significantly elevated biomarker from a panel of 363 biomarkers.<sup>116</sup> On the other hand, adiponectin is an anti-inflammatory, anti-fibrotic and cardioprotective adipokine.<sup>114</sup> Leptin and adiponectin are regulated in an opposite manner, with obese individuals presenting high circulating levels of leptin but lower levels of adiponectin. Paradoxically, adiponectin levels increase during HF progression and are associated with adverse outcomes,<sup>117,118</sup> but this is probably due to the effect of wasting (i.e. unintentional loss of body mass during HF progression) that occurs during later HF stages and correlate with increased adiponectin levels. Therefore, higher levels of both these biomarkers might be indicative of HF in patients with obesity. Resistin is another adipokine secreted by the adipose tissue, that impairs glucose homeostasis.<sup>119</sup> Circulating plasma levels of both leptin and resistin are increased in patients with HF, and those patients with lower plasma leptin and resistin levels showed a greater improvement in EF and a decrease in NT-proBNP during follow-up,<sup>120</sup> suggesting a potential prognostic role for these biomarkers in the obese HF setting.

Fibroblast growth factor-21 (FGF-21) is expressed by the adipose tissue and by other organs such as skeletal muscle, liver or pancreas, it is involved in thermogenesis, and induces adiponectin secretion.<sup>121</sup> It is elevated in patients with obesity and metabolic syndrome,<sup>122</sup> and this paradoxical increase is thought to be related to a resistant state.<sup>123</sup> Elevated circulating levels of FGF-21 have been found to be associated with cardiovascular risk.<sup>119,124</sup> However, as circulating FGF-21 mainly has origin in the liver, its relevance in the obesity–HF axis needs to be further elucidated.<sup>125</sup> Growth differentiation factor-15 (GDF-15) is a stress-responsive cytokine that plays a role in regulating energy balance and is elevated in patients with HFpEF or HFpEF and particularly acute HF.<sup>126</sup> Elevated GDF-15 in patients with HF predicts risk of HF hospitalizations or mortality.<sup>127</sup> Although GDF-15 is linked with cachexia and is most elevated in underweight patients, those with HF and obesity had higher GDF-15 levels than normal weight patients in the SUPPORT trial.<sup>127</sup>

Inflammatory biomarkers are also correlated with obesity and adiposity measures. Interleukin-6 concentrations are elevated in HF and are associated with increased total body and trunk fat mass, as well as with poorer exercise capacity and symptoms in patients with HFpEF.<sup>128</sup> C-reactive protein (CRP) is highly positively associated with measures of adiposity such as BMI, WC, and waist-to-hip ratio.<sup>129,130</sup> Weight loss interventions, either lifestyle changes or surgical, were associated with significant decrease in CRP levels.<sup>131</sup> In recent clinical trials, semaglutide reduced CRP concentration irrespective of baseline BMI or glycemic status.<sup>132</sup>

### Adiposity measures

Heart failure has been shown to rank second among the cardiovascular diagnoses most strongly associated with BMI, and is also linked to other anthropometric measures like WC and waist-to-hip ratio.<sup>133</sup> However, measures of body composition by means of bioelectrical impedance analysis show a significant association of fat mass, but not fat-free mass index, with HF,<sup>133</sup> indicating that body composition measures may refine risk stratification for HF in individuals with obesity, as supported by the obesity paradox being observed when measures of body mass but not of body composition were applied.<sup>134</sup> Body composition and regional adiposity distribution measured by DEXA,<sup>135</sup> computed tomography (CT),<sup>136</sup> or MRI,<sup>137</sup> may add additional insights into the relations of alterations in fat, skeletal muscle, and bone mass with HF. Higher epicardial and visceral fat has been shown to have a stronger association with HFpEF risk compared with elevated subcutaneous fat.<sup>138</sup> Future developments in this field include to extend spatial fat tissue radiomics to HF incidence and outcomes.<sup>139</sup>

### Cardiac imaging

Obesity can complicate echocardiographic procedures and image acquisition, and therefore important considerations are needed when interpreting echocardiographic measures in these individuals. Indexing left atrial volume as well as LV volume and mass for body surface area may lead to underestimation of left atrial dilatation and LV hypertrophy in individuals with obesity, and consequently

affect the diagnostic and prognostic role of echocardiography in patients with or with suspected HF. Heighted-based indexing might be a valid option for more properly assessing left atrial size (or using lower body surface area-indexed thresholds) as well as LV mass in these patients.<sup>140</sup> Increased epicardial and pericardial fat is more common in patients with obesity and HFpEF.<sup>141,142</sup> In patients with HFpEF, an epicardial adipose tissue thickness of 9 mm or more has been associated with poorer metabolic profile, pericardial restraint, and elevated cardiac filling pressures.<sup>141–143</sup> Greater epicardial fat mass is associated with more LV dysfunction and fibrosis, as well as worse outcomes, in HFpEF but not HFrEF.<sup>144,145</sup> The measurement of epicardial fat could be useful for patient characterization and prognostication, and since the adipocyte hyperplasia rather than adipocyte hypertrophy is the main mechanism of adipocyte remodelling in the epicardium,<sup>146</sup> it may be an emerging therapeutic target.<sup>147</sup>

Use of echocardiographic contrast can improve image acquisition and may be particularly useful in individuals with obesity where image acquisition can be challenging. Cardiac magnetic resonance (CMR) is a viable alternative test to echocardiography to assess LV/right ventricular function as well as investigating the cause of HF by performing myocardial tissue characterization and rule out underlying significant coronary artery disease.<sup>148,149</sup> Importantly, excessive BMI or WC may limit accessibility to MRI machines, so technical limitations need to be considered when prescribing CMR in severe obesity.

## Exercise capacity

Exercise testing has a key risk stratification role in patients with HF. However, the assessment of exercise performance in obesity can be influenced by several factors. Obesity is commonly associated with other comorbid conditions (e.g. diabetes, sleep apnoea, musculoskeletal disease), which complicates the assessment of the independent role of obesity on cardiac performance during exercise.<sup>150,151</sup>

Performing cardiopulmonary exercise testing in individuals with obesity is challenging. Peak oxygen consumption ( $\text{VO}_2$ ) is conventionally indexed to body weight and reported as ml/kg/min. However, indexing exercise performance parameters to very large body weights can overemphasize the effects of scaling,<sup>152,153</sup> leading to retrieve an exaggerated exercise limitation in individuals with obesity. Indeed, in obese individuals, body fat is substantial but at the same time consumes almost no oxygen. Therefore, indexing to lean body mass might provide a better measure of exercise capacity and might be a better prognosticator.<sup>154</sup> A submaximal parameter, such as minute ventilation-to-carbon dioxide output ( $\text{VE}/\text{VCO}_2$ ) slope, may better risk stratify patients with obesity and HFrEF.<sup>42</sup>

## Prognostic role of weight reduction

Intentional weight loss in individuals with obesity with or without HF significantly reduces cardiovascular risk and improves outcomes, and can enhance mobility and quality of life

(QoL).<sup>155–159</sup> However, in patients with HF, weight loss can also be non-intentional and a marker of disease progression. Cachexia is known to be associated with worse outcomes and reduced exercise capacity. Several strategies have been proposed to counteract cachexia such as exercise, nutrition, appetites stimulants, anti-inflammatory drugs (including antibodies against GDF-15),<sup>160</sup> and muscle regeneration.<sup>161</sup> Still, in patients with obesity and HF, intentional body weight reduction, achieved through a combination of dietary modifications and exercise, plays a pivotal role in preserving muscle mass and improving exercise tolerance. On the contrary, if skeletal muscle mass and function is not preserved, that is skeletal muscle wasting, functional parameters as peak  $\text{VO}_2$  and 6-min walking distance, as well as long-term prognosis, are further impaired.<sup>106</sup> Prevalence of skeletal muscle wasting varies among HF populations, involving around 20% of patients with chronic HF and ~30% of those with acute decompensated HF.<sup>107</sup> While skeletal muscle wasting is more pronounced in HFrEF due to reduced cardiac output, molecular alterations, and catabolic wasting processes which are typical of advanced HF, it remains relevant also in HFpEF, especially due to pro-inflammatory cytokine activation, renin–angiotensin–aldosterone system overactivity, obesity and insulin resistance, all of which accrue to the metabolic burden of this syndrome. These molecular alterations may deeply contribute to exercise intolerance in both HFrEF and HFpEF.<sup>109</sup> Therefore, the role of physical activity and exercise training in HF is crucial not only to promote a proper intentional body weight reduction, which leads to better prognosis, but also to contrast skeletal muscle wasting, cachexia and frailty.<sup>162</sup>

## Treatments for obesity

### Rationale for treating obesity in heart failure

Obesity is a common and treatable comorbidity in patients with HF. Rather than a condition simply related to lifestyle, it must be considered a disease and treated as such.<sup>3,163,164</sup> Treating obesity might ameliorate inflammation, insulin resistance, and hypertension, that is key mechanisms that link obesity with HF. Weight loss has been observed to be beneficial in different populations of patients with HFpEF and HFrEF,<sup>165</sup> prompting the Heart Failure Society of America to advise a 5–10% weight loss in patients with HF and BMI  $\geq 35 \text{ kg/m}^2$ , regardless of EF.<sup>166</sup>

In both HFpEF and HFrEF, weight loss strategies, including lifestyle changes, pharmacological and surgical interventions, might reduce symptoms, improve exercise capacity, and reduce the risk of hospitalization for HF (Table 1),<sup>167–177</sup> as well as they can represent a ‘bridge to advanced therapy’, for example for LV assist device and heart transplantation in HFrEF, when a high BMI is an exclusion criterion.<sup>166,178–182</sup> Targeting obesity may be particularly important in HFpEF, given the specific pathophysiology and the high interplay between metabolic conditions and the clinical phenotype.

### Exercise interventions

Improving exercise capacity is a cornerstone in the management of obesity, and is associated with improved survival in patients



**Table 1** Selected trials investigating pharmacological or lifestyle interventions on weight loss in patients with HF

Trial	Sample size	Pharmacological/lifestyle intervention	Comparator arm	Effect on weight loss	Other key findings	Population
<b>Pharmacotherapy</b>						
Beck-da-Silva <i>et al.</i> <sup>167</sup>	21	Orlistat 120 mg 3x/d	Usual care	Weight loss -8.55 with orlistat vs. control, $p < 0.001$	Orlistat vs. usual care improved cardiometabolic risk factors, NYHA class, and 6MWT, but not QoL	HFpEF, BMI $> 30 \text{ kg/m}^2$
STEP-HFpEF <sup>168</sup>	529	Semaglutide (2.4 mg once weekly)	Placebo	13.3% vs. 2.6% reduction in body weight ( $p < 0.001$ )	6MWD increase, improved KCCQ-CSS, reduced CRP, reduced NT-proBNP	LVEF $\geq 45\%$ , BMI $\geq 30 \text{ kg/m}^2$ , no T2DM
STEP-HFpEF DM <sup>169</sup>	616	Semaglutide (2.4 mg once weekly)	Placebo	9.8% vs. 3.4% reduction in body weight ( $p < 0.001$ )	6MWD increase, improved KCCQ-CSS, reduced CRP, reduced NT-proBNP	LVEF $\geq 45\%$ , BMI $\geq 30 \text{ kg/m}^2$ , with T2DM
SUMMIT <sup>170</sup>	731	Tirzepatide (5, 10, or 15 mg)	Placebo	15.7% vs. 2.2% reduction in body weight ( $p < 0.001$ )	Improved both primary endpoints (urgent HF visit, HF hospitalization, oral diuretic intensification, and CV death; change in KCCQ-CSS)	HFpEF, obesity, age $\geq 40$ years
<b>Lifestyle modification</b>						
SECRET <sup>171</sup>	100	Caloric restriction (350–400 kcal/day deficit, 1.2 g protein per kg) and/or aerobic exercise 3x/week (walking/cycling 30–45 min)	Usual care	Diet main effect: -7 kg, $p < 0.001$ Exercise + diet: -11 kg, $p < 0.001$	Both diet and exercise improved peak $\text{VO}_2$ . Diet and exercise had additive effect	HFpEF, BMI $\geq 30 \text{ kg/m}^2$ , age $\geq 60$ years
Evangelista <i>et al.</i> <sup>172</sup>	14	HP hypocaloric diet or SP hypocaloric diet (walking/cycling 30–45 min)	Normocaloric diet	Greatest weight reduction with HP hypocaloric diet (-9.9 kg) vs. SP hypocaloric diet (-5.6 kg) vs. normocaloric diet (+1.5 kg), $p < 0.001$	HP hypocaloric diet had greatest percent body fat, total cholesterol, triglycerides, LDL cholesterol, and greater improvements in 6MWT, peak $\text{VO}_2$ , and QoL	HFpEF, T2DM, BMI $> 27 \text{ kg/m}^2$
Evangelista <i>et al.</i> <sup>173</sup>	99	Graduated, low-level exercise protocol $\geq 4$ times weekly consisting of light aerobic exercise and resistive training	Usual care	Greatest weight reduction in exercise group (-6.37 kg vs. -0.33 kg, $p = 0.002$ )	No significant differences in 6MWT or depression	BMI -27 kg/m <sup>2</sup> , advanced HF
Gonzalez-Islas <i>et al.</i> <sup>174</sup>	88	Low-carbohydrate normocaloric diet	Normocaloric diet	No significant weight loss	No significant difference in handgrip strength	HF, any EF (35% had obesity)
Pro-HEART <sup>175</sup>	76	HP hypocaloric diet (30% protein, 40% carbohydrate, 30% fat)	SP hypocaloric diet (15% protein, 55% carbohydrate, 30% fat)	Equivalent weight loss (-3.6 vs. -2.8 kg) and reduction in waist circumference (-1.9 vs. -1.3 cm)	HP hypocaloric diet exhibited greater decreases in HbA1c, total cholesterol, and triglycerides	HF, any EF, DM, BMI $> 27 \text{ kg/m}^2$
Brubaker <i>et al.</i> <sup>176</sup>	88	Resistance and aerobic training plus 300 kcal/day deficit 3x/week + diet (500–750 kcal/d deficit)	Aerobic training plus 300 kcal/d deficit	No significant differences in body weight or body fat	Peak $\text{VO}_2$ increased to similar degree in both groups	HFpEF, BMI $\geq 28 \text{ kg/m}^2$ , age $\geq 60$ years
Pritchett <i>et al.</i> <sup>177</sup>	20	The lifestyle intervention modelled on the Look AHEAD trial's behavioural programme including portion-controlled diet modification, behavioural techniques, physical activity, and social support	Usual care	No significant between-group difference in weight change	No significant difference in other defined endpoints	HFpEF (EF $\leq 50\%$ ), BMI $\geq 25 \text{ kg/m}^2$

6MWD, 6-min walk distance; 6MWT, 6-min walk test; BMI, body mass index; CRP, C-reactive protein; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; HP, high-protein; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; QoL, quality of life; SP, standard-protein; T2DM, type 2 diabetes mellitus;  $\text{VO}_2$ , oxygen consumption.

at risk of cardiovascular disease.<sup>183</sup> Few randomized clinical trials (RCTs) have provided data on the effects of weight loss achieved by exercise training in obese patients with HF (Table 7). The effects of exercise interventions are likely depending on whether the programme is supervised (allowing more structured guidance, support, and possibly adherence) or unsupervised (less resources required), duration, frequency, mode of exercise (e.g. resistance training, aerobic training, high-intensity interval training), and the ability of the patient to safely tolerate and adhere to the programme. In the SECRET randomized trial, which used a factorial design to assess diet (350–400 kcal/day deficit, 1.2 g of protein per kg/day) and/or supervised exercise (three times 1 h per week, mainly walking) in 100 patients with obesity and HFrEF, exercise and diet had an additive effect on weight loss and peak  $\text{VO}_2$ .<sup>171</sup> In a post-hoc analysis of the HF-ACTION randomized trial (2331 patients with HFrEF), 3 months of three weekly supervised aerobic exercise sessions had only negligible effects on weight loss regardless of BMI but with a significant improvement in QoL.<sup>184</sup> In a smaller RCT on 99 overweight/obese patients with HFrEF, a 6-month home-based low-level aerobic exercise programme  $\geq 4$  times weekly resulted in greater weight loss (−6.37 vs. −0.33 kg) than the control group.<sup>173</sup>

However, the benefits of exercise programmes in patients with obesity and HF extend well beyond weight loss, which should not be the sole target in treating obesity in HF. According to the 2021 ESC guidelines for HF, exercise is recommended in all patients with HF who are able to improve exercise capacity, QoL, and reduce HF hospitalizations.<sup>110</sup> The REHAB-HF trial demonstrated that a transitional exercise rehabilitation programme improved physical function in 349 patients hospitalized for HF. In REHAB-HF, the mean BMI was 33 kg/m<sup>2</sup> and BMI did not interact with the intervention's effect, suggesting that this evidence is likely highly applicable to obese patients with HF.<sup>185</sup> In meta-analyses, even short-term programmes (3–6 months) of supervised exercise training could improve peak  $\text{VO}_2$ , exercise duration, 6-min walking distance, and ultimately QoL in HFrEF.<sup>186–189</sup> Thus, exercise training should be promoted in patients with obesity and HF to improve functional capacity and QoL, and may be a useful supplement to other strategies to promote weight loss.

## Diet interventions

Caloric restriction is an effective strategy for weight loss. It stimulates autophagy and mitophagy, downregulates the mTOR pathway and activates AMP-activated protein kinase.<sup>190</sup> This, in turn, leads to improvements in several cardiovascular risk factors, such as hypertension and adiposity,<sup>191</sup> and at least partially, to reversing the cardiometabolic syndrome.<sup>192</sup> In a randomized study in elderly obese patients with multiple comorbidities, the CROSSROADS trial, caloric restriction improved quality of life and reduced total body fat and cardiometabolic risk factors, but did not significantly change body mass composition.<sup>193</sup> In patients with obesity and diabetes, but without history of HF, lifestyle modifications for weight loss have shown mixed results. While these interventions improve metabolic control and reduce the requirements for antidiabetic drugs, they do not always translate into a reduction of

cardiovascular events, highlighting the complexity of these conditions and the need for tailored approaches.<sup>194</sup> In the Look AHEAD trial, which tested an intensive lifestyle intervention promoting weight loss through decreased calorie intake and increased physical activity versus a support and education strategy for diabetes, there was no change in the incidence of cardiovascular events in overweight or obese patients with T2DM.<sup>195</sup> However, in a secondary analysis of the Look AHEAD trial, the intensive lifestyle modification was associated with a lower risk of cardiovascular events in patients who had a sustained weight loss.<sup>196</sup>

Fewer studies have evaluated dietary modifications specifically in patients with obesity and established HF. Besides the reduction in the absolute calorie count, it is key to maintain an adequate muscle mass to avoid compromising metabolic health and physical function, and skeletal muscle wasting in HF.<sup>106</sup> In 76 overweight/obese patients with HF across the EF spectrum and diabetes enrolled in the Pro-HEART randomized trial, both high-protein and standard protein calorie-restricted diets resulted in weight loss, but the high-protein calorie-restricted arm showed greater improvements in cardiometabolic risk factors.<sup>175</sup> In the SECRET trial,<sup>171</sup> the main effect of diet resulted in reduced weight and WC while improving body composition with increased lean body mass percentage. The diet + exercise arm showed the greatest reductions in weight and improvements in peak  $\text{VO}_2$ . Trials evaluating diet and exercise interventions for weight loss in patients with HF are summarized in Table 7, and in aggregate may suggest that the combination of adequate protein intake, caloric restriction, and exercise training is more effective than any strategy alone in reducing obesity and its related health risks.

Success of dietary interventions is highly dependent on adherence, which is hard to achieve for caloric restriction. In a study evaluating a 15-week weight loss programme supported by counselling and meal replacements in 60 patients with HFrEF and obesity, only two-third completed the programme, but those who did lose weight experienced improved exercise capacity and QoL.<sup>197</sup> This highlights both the challenges and importance of patient counselling, education, support, and adherence strategies (e.g. promoting satiety by increased fibre and protein intake) to target weight loss. Remote disease management and/or telemonitoring also represent promising tools to achieve patient empowerment and facilitate adherence for lifestyle interventions. The ongoing IDEAL-HF trial is investigating the use of a diet management app together with an intelligent weight scale in an estimated 830 patients with obesity and HFrEF, with a hierarchical primary endpoint (NCT06455878).

Ketogenic diets and intermittent fasting have been popular alternatives among those seeking to lose weight in the general population. Cardiac metabolism in HF may be more efficient if energy is derived from ketones, which have further been suggested to suppress cardiac inflammation, leading to hypotheses that increasing circulating KBs (e.g. by ketogenic diets) may have beneficial effects in HF.<sup>198</sup> However, there is a lack of clinical trial data on ketogenic and intermittent-fasting diets in HF.<sup>199</sup> Both these diets warrant special safety considerations in patients with HF as they may carry risk for ketoacidosis in insulin-deficient patients or sodium–glucose cotransporter 2 inhibitor (SGLT2i) users, hypoglycaemia in insulin users, and electrolyte abnormalities. Ketogenic

diets entail restricted carbohydrate intake, which has been associated with higher mortality in observational studies, although with minimal risk observed at 50–55% carbohydrate intake.<sup>200</sup> Patients with HF who adopt ketogenic diets should be closely monitored for electrolyte abnormalities, KBs, and elevated low-density lipoprotein cholesterol.<sup>201</sup> Moreover, considering that ketone oxidation is increased in the heart in HFrEF but is reduced in HFpEF, ketogenic diets may have different effects in these two populations, highlighting the importance of dedicated trials separately assessing the efficacy of these diets for a personalized prescription.

## Pharmacological treatment of obesity in heart failure

### Classical anti-obesity medications

Prior pharmacological treatments for obesity have seen limited use among patients with HF, partly due to concerns for cardiovascular safety. Fenfluramine was linked with the development of valve disease, sibutramine with elevated heart rate and blood pressure, cerebrovascular and myocardial infarctions, and phentermine with elevated heart rate and blood pressure, and are thus considered inappropriate to treat obesity in patients with HF.<sup>202,203</sup> Bupropion sustained release–naltrexone produced modest weight loss in obese patients, but can increase heart rate and blood pressure, and has undetermined safety in HFrEF.<sup>204</sup> Orlistat facilitated 8.6 kg weight loss, improved cardiometabolic risk factors, was safe, and improved exercise capacity in a small trial on 21 patients with HFrEF and obesity.<sup>167</sup> However, orlistat use predisposes patients to foecal urgency and steatorrhea, limiting compliance to this treatment.

### Sodium–glucose cotransporter 2 inhibitors

Recent years have seen the introduction of new drug classes that have shown efficacy in terms of weight loss as well as of reduction in cardiovascular risk, representing a compelling opportunity to target weight loss in HF by pharmacological treatment.

Sodium–glucose cotransporter 2 inhibitors reduce the risk of incident HF in patients with T2DM and high cardiovascular risk, and reduce the risk of cardiovascular mortality/HF hospitalizations in patients with HF across the EF spectrum.<sup>205</sup> SGLT2i had consistent effect across the BMI spectrum in patients with HFrEF and HFpEF in post-hoc analyses of the DAPA-HF and DELIVER trials.<sup>206,207</sup> SGLT2i also facilitate a modest but consistent weight loss.<sup>208</sup> The results of network meta-analyses suggest reductions in body weight, as compared with placebo, for all SGLT2i of about 1.5–2.0 kg in patients with T2DM.<sup>209,210</sup> Similar degrees of weight loss have been reported in patients with HFrEF and HFpEF.<sup>206,207</sup> In patients with HFpEF in the DELIVER trial, patients with higher BMI experienced greater weight loss and improvement in QoL with dapagliflozin.<sup>207</sup>

### Glucagon-like peptide-1 receptor agonists

In T2DM, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown to reduce risk of major adverse cardiovascular

events (MACE), that is a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke (0.5/1 mg weekly semaglutide vs. placebo: 24% lower risk<sup>211</sup>; 1.8 mg daily liraglutide vs. placebo: 13% lower risk).<sup>212</sup> GLP-1 RAs have a dose-dependent weight loss effect by promoting satiety, reducing appetite, slowing gastric emptying, and enhancing insulin secretion and energy expenditure. In patients with obesity, GLP-1 RAs have been demonstrated to produce significant weight loss when used at high doses (2.4 mg semaglutide weekly vs. placebo: 12.4% more weight loss<sup>213</sup>; 3.0 mg liraglutide daily vs. placebo: 5.6 kg more weight loss).<sup>214</sup> In patients with obesity but without T2DM in the SELECT trial (BMI  $\geq 27$  kg/m<sup>2</sup>), 2.4 mg weekly semaglutide was shown to lower the risk of MACE (a composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) by 20%.<sup>157</sup> The effect on these outcomes was shown before meaningful weight loss occurred, suggesting that GLP-1 RAs convey some cardiovascular benefits through weight loss-independent mechanisms, which may include improving metabolic parameters such as glycated haemoglobin, blood pressure, and lipid profiles.<sup>215–217</sup> They may also improve endothelial function and may ameliorate myocardial relaxation, reduce fibrosis, and inhibit oxidative stress and inflammatory pathways.<sup>216,218</sup>

In patients with HFpEF and obesity, recent trial data suggest that semaglutide, beyond promoting weight loss, can improve QoL and exercise capacity. In the STEP-HFpEF trial, patients with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) and HFpEF (EF  $\geq 45\%$ ) without diabetes assigned to semaglutide experienced greater weight loss (13.3% vs. 2.6%), and improvement in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS, +16.6 vs. +8.7 points) and 6-min walk distance (+21.5 vs. +1.2 m) as compared with placebo. The benefits were consistent irrespective of EF and baseline BMI.<sup>168</sup> Semaglutide also had favourable effects on the hierarchical composite endpoint including all-cause mortality, HF events, improvements in functional capacity and exercise tolerance.<sup>168</sup> In the STEP-HFpEF DM trial, which enrolled patients with obesity, HFpEF, and diabetes, treatment with semaglutide achieved slightly less weight reduction (9.8% with semaglutide vs. 3.4% with placebo) but similar effect on KCCQ-CSS, 6-min walk test, and NT-proBNP as in STEP-HFpEF.<sup>169</sup> Weight loss would typically be expected to be linked with an increase in NT-proBNP given the inverse relationship between NT-proBNP levels and BMI. Therefore, the observation that semaglutide users in the STEP-HFpEF programme experienced greater reductions in NT-proBNP might suggest that some of the benefits were mediated by factors other than weight loss. This view was recently supported by an echocardiography sub-study of the STEP-HFpEF programme, where semaglutide appeared to reduce adverse left atrial and right ventricular remodelling, without affecting LV dimensions or mass.<sup>219</sup> A recent pooled analysis included all patients from the STEP-HFpEF ( $n = 529$ ) and STEP-HFpEF DM ( $n = 616$ ) trials, as well as the HFpEF subgroups from the SELECT ( $n = 2273$ ) and FLOW ( $n = 325$ ) trials.<sup>220</sup> In 3743 patients with HFpEF, semaglutide reduced the risk of cardiovascular death/worsening HF events by 31%, worsening HF events by 41%, with non-significant effect on cardiovascular death (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.57–1.16). These data must, however, be considered mainly as hypothesis generating

because of the low number of primary outcome events ( $n = 241$ , event-rate per 100 person-years 2.1 with semaglutide and 3.0 with placebo), and the lack of systematic characterization of HF at baseline in SELECT and FLOW.

The dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA tirzepatide was evaluated against placebo in patients with BMI  $>27$  kg/m<sup>2</sup> in the SURMOUNT-1 trial, reporting even greater efficacy on weight loss ( $-15.0\%$  to  $-20.9\%$  with 5 to 15 mg weekly tirzepatide vs.  $-3.1\%$  with placebo).<sup>221</sup> The SUMMIT trial was a pivotal study evaluating the efficacy of tirzepatide in patients with HFpEF and obesity. This international, double-blind, randomized, placebo-controlled trial enrolled 731 patients who were assigned to receive either tirzepatide or placebo over a median follow-up of 104 weeks. Tirzepatide significantly reduced the incidence of the primary composite endpoint of death from cardiovascular causes or worsening HF events, with events occurring in 9.9% of the tirzepatide group as compared with 15.3% in the placebo group (HR 0.62, 95% CI 0.41–0.95).<sup>170</sup> This benefit was primarily driven by a decrease in worsening HF events.

Secondary analysis of the SUMMIT trial highlighted mechanistic insights, indicating an improvement in volume overload (lowered estimated blood volume by 0.58 L) and reduction in systolic blood pressure by 5 mmHg.<sup>222</sup> A reduction in troponin T and NT-proBNP levels, together with an improvement in estimated glomerular filtration rate by 2.90 ml/min/1.73 m<sup>2</sup> were also observed.<sup>222</sup> CMR findings showed reductions in LV mass and paracardiac adipose tissue with tirzepatide versus placebo.<sup>223</sup>

Overall, these data indicate a role for the use of semaglutide or tirzepatide in obesity-related HFpEF for effective weight loss as well as for improvement in symptoms and hard clinical outcomes. Importantly, a reduction in muscle mass (or in fat-free mass) has been observed in patients receiving GLP-1 RAs for weight loss, with higher levels than what observed in patients losing weight with alternative strategies, as well as in the SUMMIT trial in patients with HFpEF and obesity.<sup>224</sup> Whether this effect is really detrimental<sup>225</sup> or what is the impact in the context of HF warrants further investigations.

For patients with HFrEF, the evidence for treating obesity with GLP-1 RAs is less certain and their safety is debated. In the FIGHT trial, patients recently hospitalized for HFrEF with low EF (mean EF 27%) randomized to liraglutide experienced a numeric but non-significant increase in HF hospitalizations.<sup>226</sup> Similarly, in the LIVE study, patients with chronic HFrEF assigned to liraglutide had increased risk of adverse cardiac events, although there was only one death and one HF hospitalization, and the overall number of adverse cardiac events was low (12 [10%] with liraglutide vs. 3 [3%] with placebo,  $p = 0.04$ ).<sup>227</sup> However, neither FIGHT nor LIVE were trials focusing on an obese HFrEF population, and the GLP-1 RAs were not given in an obesity dose. In contrast, in a recently published post-hoc analysis of SELECT including 1347 patients with HFrEF (mean BMI 33.4 kg/m<sup>2</sup>), semaglutide reduced the risk of MACE by 35% and of the composite of cardiovascular death or hospitalization or urgent HF hospital visit by 21%, although the effect on HF hospitalizations alone was non-significant (HR 1.08;  $p = 0.11$ ).<sup>228</sup> Importantly, patients with HF and New York Heart Association (NYHA) class IV were excluded, and ~60% had

NYHA class II and, consistently, the rate of adverse events during follow-up was low (MACE  $n = 205$ , rate per 100 person-years 3.9 with semaglutide and 6.0 with placebo), indicating a less severe HF population than typically enrolled in modern HF trials. It should be noted that GLP-1 RAs, including semaglutide, are associated with a slight increase in heart rate (3–5 bpm).<sup>157,229</sup> Overall, incretin-based therapies should be tested in obese HFrEF populations in prospective, appropriately designed RCTs.<sup>230</sup>

Mechanistic RCTs of incretin-based therapies in obese HFrEF populations are warranted investigating effects on body composition (including adipose tissue in different organs and skeletal muscle), rhythm (atrial and ventricular dysrhythmias and heart rate) and effects on cardiac and kidney function. Robustly powered outcome RCTs are also necessary in obese HFrEF populations to determine the efficacy and safety of incretin-based therapies. Trials with various agents could target different body weights and use different pharmacological weight-loss strategies. These trials might avoid patients with very severe HFrEF (such as those enrolled in FIGHT).<sup>226</sup>

## Treatment of obesity by bariatric surgery in heart failure

Bariatric surgery is well-established as an efficient intervention to achieve weight loss in obese patients without pre-existing HF. In the GETAWAY trial, which randomized 100 obese hypertensive patients to bariatric surgery plus medical therapy versus medical therapy alone, bariatric surgery was an effective strategy to achieve better blood pressure control, cardiometabolic profile and reduce polypharmacy associated with obesity and cardiometabolic disease, both in the short and long term.<sup>231,232</sup> In patients with diabetes and obesity, without pre-existing HF, observational studies have suggested bariatric surgery to reduce the risk of incident HF.<sup>233,234</sup> Furthermore, sustained weight loss achieved with gastric bypass surgery is associated with a reduced risk of cardiovascular events, including the development of HF.<sup>235</sup>

To date, RCTs on bariatric surgery in patients with established HF are lacking, and evidence is therefore limited to observational studies. Prior bariatric surgery was associated with lower in-hospital mortality and shorter hospitalization duration in patients with obesity and HFpEF or HFrEF admitted due to decompensated HF,<sup>236,237</sup> especially if they had successfully lost weight. In obese patients with HFpEF, bariatric surgery was also associated with improved diastolic function, functional improvement, and lower readmission rates.<sup>238–241</sup> In a propensity-matched Canadian cohort study, bariatric surgery was associated with 56% lower risk of MACE (a composite of myocardial infarction, ischaemic stroke and all-cause mortality) in the subgroup with pre-existing HF.<sup>233</sup> In a systematic meta-analysis of observational studies on patients with obesity, bariatric surgery was associated with a 45% reduction in all-cause mortality, 41% reduction in cardiovascular mortality and 50% reduction in the incidence of HF.<sup>242</sup>

However, bariatric surgery carries potential surgical-related risks of complications, may promote nutritional deficiency requiring supplementation, and is available only in specific centres.<sup>243</sup> In observational studies on bariatric surgery, HF was associated



with an eight-fold higher risk of intraoperative cardiovascular complications (absolute risk increase of 1.2%),<sup>244</sup> and HFrEF with a three-fold higher risk of in-hospital mortality.<sup>245</sup> Therefore, the indication for bariatric surgery should be tailored to a case-by-case scenario. Further prospective RCTs tailored on the specific HF phenotypes and HF severity are needed to inform on acceptable risk thresholds for bariatric surgery in patients with HF. The ongoing BRAVE trial will assess bariatric surgery in an anticipated 2000 patients with severe obesity (BMI >35 kg/m<sup>2</sup>) and high-risk cardiovascular disease (including HFrEF and HFpEF), with MACE as primary outcome (NCT05531474).

### Other medical treatments for heart failure in patients with obesity

Obese patients represent overall up to 40% of patients with HFrEF, however they are underrepresented in RCTs.<sup>246</sup> In HFrEF, consistent effect across the BMI spectrum has been reported for SGLT2i,<sup>206</sup> and mineralocorticoid receptor antagonists (MRAs) potentially have greater benefit in those with abdominal obesity.<sup>247</sup> Although angiotensin receptor–neprilysin inhibitor efficacy was not examined across BMI subgroups in the PARADIGM-HF, the mean BMI in this trial was 28 kg/m<sup>2</sup>, suggesting generalizability of results to the overweight/obese population. Guideline-directed medical treatments are consistently recommended across the BMI spectrum.<sup>110,248,249</sup> However, obesity may affect the tolerability profile and pharmacodynamics of different drugs.<sup>250</sup> Indeed, obesity is associated with a higher activation of the renin–angiotensin–aldosterone system, more sympathetic stimulation and synthesis of adipokines, and a different response to MRAs.<sup>251–254</sup> Furthermore, in obese patients, the rate of absorption of several medications may be slowed due to delayed gastric emptying, the increased volume of distribution of lipophilic drugs and the changes in plasma protein level together with altered liver metabolism and excretion mechanism may impact the pharmacokinetics and pharmacodynamics of several HF drugs.<sup>255</sup> Data from large HF registries, including SwedeHF,<sup>44</sup> CHAMP-HF,<sup>31</sup> CHECK-HF,<sup>256</sup> and BIOSTAT-CHF,<sup>257</sup> suggest that obese patients are more frequently achieving target doses of guideline-directed medical therapies, potentially due to better tolerability, and this may be associated with improvement in longer-term outcomes.

In HFpEF, the only pharmacological class with a current class I recommendation to reduce HF hospitalizations or cardiovascular mortality, SGLT2i, has also demonstrated consistent effect regardless of BMI.<sup>207</sup> The recently delivered FINEARTS-HF trial showed the efficacy of the non-steroidal MRA finerenone in reducing worsening HF events or cardiovascular mortality by 16% in 6001 patients with HFpEF or HFmrEF.<sup>258</sup> Mineralocorticoid receptor blockade might be particularly appealing in obesity-related HFpEF, where adipocyte aldosterone production can contribute to mineralocorticoid receptor overactivation.<sup>61,62</sup>

## Clinical trial design

Clinical trial design for patients with obesity is becoming important considering the number of different interventions and novel agents

that are currently available in the pipeline and in need of being tested. These include existing but understudied interventions (such as specific lifestyle intervention programmes and bariatric surgery), novel pharmacological weight-loss treatments (such as novel GLP-1 RAs, GIP agonists, amylin agonists, glucagon agonists, peptide YY agonists, and combination therapies), and therapies targeting muscle wasting/cachexia which might occur in conjunction with weight loss (such as GDF-15 antagonists). Certain considerations that are very specific to obesity treatments need to be made in the design of such trials.

Heart failure trials have become increasingly reliant on inclusion criteria based on natriuretic peptides to ensure that enrolled patients have HF. The need for objective diagnostic criteria for HF diagnosis is perhaps even greater in HF trials on obesity, since symptoms between these two entities overlap. Determining appropriate cut-offs for natriuretic peptides in the obese population is, however, complicated by the inverse relationship between BMI and natriuretic peptides. Cut-offs stratified by BMI might be a feasible approach to address this issue. Alternatively, other objective criteria, such as right heart catheterization, might also be appropriate.

The effect of most evidence-based HF drugs to date is greater or only evident in HFrEF versus HFpEF (SGLT2i being the notable exception). Given the differential pathophysiological role of obesity and downstream metabolic factors in HFrEF versus HFpEF, it is plausible that many weight-loss treatments might also have effects that vary across the EF spectrum. Trials should therefore be encouraged to achieve sufficient power to investigate these phenotypes separately.

A perpetual question in trials on obese HF is whether the benefits that are being seen with obesity-modifying therapies are related to the drug directly affecting the cardiovascular system, or simply to weight loss. Mechanistic studies aiming to distinguish between these two factors may be helpful. Such studies might use as endpoints biomarkers and imaging (e.g. echocardiography, MRI, CT) to assess diastolic/systolic function, inflammation, fibrosis, and fat distribution (including epicardial adipose tissue). However, as outlined in previous sections, most if not all these endpoints can also change as an indirect effect of weight loss. Active control arms achieving similar degrees of weight loss as the studied intervention are therefore encouraged to identify potential direct cardiovascular effects.

Trials seeking to generate evidence for therapeutic indications might consider a range of outcomes that are both clinically relevant and plausible targets for weight-loss therapies, since obesity affects health status and outcomes both directly and through intermediary cardiometabolic steps. Death and worsening HF events remain the most accepted relevant clinical endpoints for the HF population. However, since obesity-modifying drugs tend to effect different organ systems and diseases, sufficiently powered trials might consider evaluating multiple endpoints in different organ systems, for instance reduction of cardiovascular outcomes and chronic kidney disease outcomes within the same clinical trial rather than focusing on one type of outcome per trial. In previous HF trials, the effect of HF drugs on kidney endpoints were highly dependent on the definition of events, which thus needs to consider characteristics of both the investigational drug and the target population.<sup>259</sup> Although

weight loss can be a valid therapeutic target for obese patients with HF, a demonstration of efficacy and safety on hard cardiovascular endpoints should precede widespread use in this population.

Patients with HF and obesity have substantial reductions in QoL and functional capacity,<sup>260</sup> so along with improvement in clinical outcomes, improvement in functional capacity and QoL may be endpoints of dedicated studies. Robust measures of exercise capacity (such as the 6-min walk test, peak  $\text{VO}_2$ , or  $\text{VE}/\text{VCO}_2$  slope) and QoL (such as the KCCQ) should be preferred over more crude measures with less clear associations with hard clinical outcomes, such as changes in NYHA class.<sup>261–263</sup> However, the profound weight loss exerted by GLP-1 RAs and GIP/GLP-1 RAs could reasonably risk unmasking treatment allocation, potentially warranting some caution when relying solely on soft endpoints.<sup>230</sup> Moreover, improvements in exercise capacity and QoL may be a result of the weight loss *per se* rather than modification of underlying HF.

Another consideration is the control arm treatment with placebo or active drug, considering the positive studies including for clinical outcomes some of the drugs in this category.<sup>220</sup> Comparative effectiveness of various drugs that impact obesity needs to be assessed. Because there is a difference in visceral adiposity distribution across different regions of the world – for example in South Asians, there is a higher visceral adiposity despite a lower BMI –<sup>264</sup> a good representation and a broader group of BMI patients should be studied with these drugs to assess their generalizability. These trials are probably best designed by a multidisciplinary team that includes cardiologists, internists, endocrinologists, and other specialties with expertise in both clinical trial design and various clinical specialties. Consideration should be given to basket trials, umbrella trials, and platform trials to either assess multiple outcomes with a given drug or multiple drugs for a given outcome.

## Conclusions

Obesity contributes to HF risk and is common in patients with established HF, where it adversely affects symptoms and QoL. The presence of obesity warrants a tailored approach throughout the HF disease journey, from prevention in pre-HF, diagnostic work-up of suspected HF, and treatment in established HF. Lifestyle modifications should balance the need for weight loss with the maintaining of lean muscle mass, and may be most effective when dietary and exercise interventions are combined. The advent of potent weight-loss therapies with simultaneous cardiovascular benefits, including GLP-1 RAs and GIP/GLP-1 RAs, have provided clinicians with new tools to pharmacologically treat obesity-related HFpEF. These therapies are potential alternatives also for selected patients with HFrEF and obesity, although more RCT data are needed.

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