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REVIEW ARTICLE

Implementation of guideline-directed medical therapy in patients with heart failure and obesity: *European Journal of Heart Failure* expert consensus document

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Abstract

Obesity is prevalent among patients with heart failure (HF), especially in those with preserved ejection fraction (HFpEF), and complicates diagnosis, therapy, and monitoring. It alters haemodynamics, biomarker interpretation, and drug pharmacokinetics, potentially influencing treatment response. Evidence from subgroup analyses of major HF trials suggests that renin–angiotensin system inhibitors (mainly sacubitril-valsartan), mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 inhibitors provide consistent benefits across body mass index (BMI) categories, with no major obesity-specific safety concerns. In contrast, data on beta-blockers in obese HF patients remains limited, largely reflecting the older design of pivotal trials. Management should include careful assessment of congestion, acknowledging the limitations of physical examination, and integrate natriuretic peptides measurement and imaging evaluation to guide individualised diuretic strategies. This expert consensus provides a comprehensive and pragmatic framework for the use of guideline-directed medical therapy in patients with HF and obesity, exploring the available evidence for each drug class and addressing efficacy, patient selection, safety, and monitoring.

Keywords Heart failure • Guideline-directed medical therapy • Obesity • Outcomes

Introduction

Obesity is common among patients with heart failure (HF), although prevalence estimates vary considerably depending on the definition and anthropometric measure applied. In those with preserved ejection fraction (HFpEF), reported prevalence reaches up to ~50%–60% when defined by body mass index (BMI), while alternative indices of adiposity, such as waist-to-height ratio or bioimpedance fat mass, suggest even

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higher estimates, highlighting central adiposity as an almost ubiquitous feature of the syndrome.[1–3] In patients with HF with reduced ejection fraction (HFrEF), prevalence is generally between 25% and 35%.[2,4] Building on these observations, Packer has recently proposed the 'adipokine hypothesis' of HFpEF, which conceptualizes the syndrome as a systemic disorder of adipose tissue. According to this framework, excess adiposity leads to dysregulated adipokine signalling, microvascular inflammation, and impaired cardiac and extracardiac reserve, providing a unifying explanation for the strong association between obesity and HFpEF.[5]

This frequent coexistence introduces complex challenges that span diagnosis, management, and longitudinal care. Obesity alters haemodynamics, promotes low-grade systemic inflammation, and complicates the interpretation of biomarkers, such as natriuretic peptides, and congestion assessment.[6] From a therapeutic perspective, obesity may attenuate the efficacy or tolerability of standard HF therapies by modifying drug pharmacokinetics and pharmacodynamics through increased volume of distribution, altered renal and hepatic clearance, and distinctive neurohormonal activation patterns including the renin–angiotensin–aldosterone system, sympathetic nervous system, and natriuretic peptide axis.[7,8] Historically, landmark trials did not stratify treatment effects by body size, and current clinical guidelines provide little guidance on BMI-specific dosing or management approaches.[9]

This scientific document aims to address these gaps in knowledge by providing a pragmatic, evidence-based review of guideline-directed medical therapy (GDMT) in patients with HF and obesity. The focus is restricted to GDMT and diuretics, as outlined in the 2021 ESC guidelines and their 2023 update,[9,10] while Glucagon-Like Peptide-1 receptor agonists (GLP-1 RAs) are discussed separately in a dedicated expert consensus document.[11] We examine here HF foundational therapies (i.e. renin–angiotensin system [RAS] inhibitors, beta-blockers, mineralocorticoid receptor antagonists [MRA], and sodium–glucose cotransporter 2 [SGLT2] inhibitors), focusing on their efficacy and safety, while also exploring challenges related to volume status assessment, diuretic responsiveness, and congestion monitoring. Given the absence of formal guidance, this document offers a practical framework to support individualized HF care in this growing population.

Differential impact of obesity in patients with HFpEF vs HFrEF

The impact of obesity is different in patients with HFpEF versus those with HFrEF.[12] In HFpEF patients, obesity and specifically adiposity with accumulation of visceral and epicardial fat, may contribute to cardiac dysfunction and worsening HF through adipokine release and inflammation.[5,13,14] In contrast, obesity does not appear to be the underlying cause of most HFrEF cases and was long thought to confer a survival advantage (the so-called obesity paradox).[15] More recent analyses of randomized clinical trials, however, indicate that this apparent benefit is largely attributable to confounding, as studies using alternative adiposity metrics (i.e. waist-to-hip ratio) no longer support the paradox and instead suggest an association with worse outcomes.[16]

Obesity has a larger prevalence in patients with HFpEF, compared with those with HFrEF. In addition, epidemiological data show a relationship between BMI and HFpEF but not HFrEF,[17,18] epicardial adipose tissue is increased in HFpEF and reduced in HFrEF,[19,20] while GLP-1 RAs have demonstrated clinical benefit in HFpEF but only heterogeneous evidence in HFrEF.[21–23] Finally, as discussed in the remainder of this article, the role of GDMT may differ substantially between HFrEF, where it improves outcomes, and HFpEF.

Practical guidance to GDMT use in HF patients with obesity

To guide clinical decision-making, we provide practical guidance for each foundational GDMT, using a structured framework that addresses (*Table 1*):

(A) Efficacy and treatment heterogeneity, assessing whether obese patients experience comparable benefits;
(B) Safety and monitoring, with attention to obesity-specific risks and strategies for their mitigation.

Renin-angiotensin system inhibitors

Efficacy and treatment heterogeneity

Treatment with an angiotensin-converting enzyme inhibitor (ACEi), angiotensin-receptor blockers (ARB), or angiotensin-receptor neprilysin inhibitor (ARNi) represents a cornerstone of pharmacotherapy in patients with HFrEF.[9]

The RAS and neprilysin activity are both upregulated in obesity,[24,25] but inhibition of these pathways appears to provide similar benefits in HFrEF patients, regardless of obesity status. Although most landmark trials of ACEi or ARB did not perform formal subgroup analyses based on obesity measures, the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated that the benefit of ARNi over enalapril on HF hospitalization or cardiovascular (CV) death was consistent across BMI categories (P-interaction = 0.50) and waist-to-height ratio quintiles (P-interaction = 0.72).[16] Real-world data from the Swedish Heart Failure Registry further support these findings, showing that treatment with RAS inhibitors (RASi) was independently associated with lower all-cause and cardiovascular mortality in patients with HFrEF, regardless of obesity status. After adjustments, RASi use was also associated with a reduced risk of HF hospitalization in obese, but not in non-obese patients.[26] Interestingly, observational data show that obese patients with HFrEF are more likely to achieve higher doses of ACEi, ARBs, or ARNi in clinical practice.[26–29] Preclinical data further suggest that neprilysin inhibition may confer additional benefits in obesity-related metabolic heart disease, as sacubitril/valsartan improved diastolic function, reduced interstitial fibrosis, and attenuated oxidative stress in a murine model of diet-induced obesity compared to valsartan alone.[30]

Beyond their haemodynamic effects, RAS inhibition may also offer metabolic benefit as they have shown to reduce adiposity and body weight. In animal models, inhibition of the RAS can decrease adipocyte size and the secretion of proinflammatory cytokines, thereby improving insulin sensitivity and limiting fat accumulation.[31] RAS blockade may also modulate energy metabolism by enhancing mitochondrial function and promoting the browning of white adipose tissue, leading to increased energy expenditure. Notably, treatment with ACEi and ARB lowers food intake, body weight, and fat mass in high-fat-fed mice, and these anti-obesity effects persist even when caloric intake is controlled.[31]

Although dedicated data on patients with both HF and obesity are limited, evidence from related populations provides useful mechanistic insights. For instance, a meta-analysis of 15 randomized controlled trials (RCTs) evaluating telmisartan in hypertensive patients with overweight/obesity, glucose intolerance, or metabolic syndrome showed a reduction in visceral fat compared with placebo or other antihypertensive agents, without a corresponding change in subcutaneous fat.[32] In a *post hoc* analysis of the CHARM (Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity) program, candesartan was associated with a lower risk of new-onset diabetes mellitus.[33] Similar metabolic effects have been reported for ACEi and ARBs in long-term hypertension trials.[34] Natriuretic peptides, whose effects

Table 1 Efficacy, safety, and expert advice on guideline-recommended drugs

	Efficacy and treatment heterogeneity	Safety and monitoring	Experts' advice
RASi	ARNI results in consistent benefits in HFrEF regardless of baseline BMI (i.e. PARADIGM-HF) Observational data suggest benefit regardless of obesity Obese patients often achieve higher doses in practice	No unique obesity-specific hazards Monitoring as in general HF population	Use at guideline-recommended target doses, irrespective of BMI.
Beta-blocker	No RCTs post-hoc analyses stratified by BMI Registry data show reduced mortality in HFrEF patients treated with BB irrespective of obesity		Use at guideline-recommended target doses, irrespective of BMI in HFrEF.
MRA	RCT post-hoc analyses suggest greater benefit in obese patients (i.e. EMPHASIS-HF: stronger effect in abdominal obesity; TOPCAT: benefit in obese/low NT-proBNP patients); FINEARTS: consistent benefit across BMI, with a possible greater benefit at higher BMI).		Use at guideline-recommended target doses, irrespective of BMI Potential additional benefit on clinical outcomes in obese patients
SGLT2i	No treatment-by-BMI interaction observed for primary outcome (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER) Improvements in symptoms and QoL often greater in obese patients		Use at guideline-recommended target doses, irrespective of BMI Potential additional benefit on symptoms/QoL in obese patients

AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life; RASi, renin-angiotensin system inhibitor; RCT, randomized clinical trial; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

are enhanced by ARNi therapy, have been shown to promote lipolysis and improve insulin sensitivity.[25,35] In the PARADIGM-HF trial, treatment with ARNi was associated with better glycaemic control and a slower progression to insulin dependence compared with enalapril in overweight patients (mean BMI 29 kg/m^2) with HFrEF and diabetes mellitus.[36] These metabolic effects might be particularly relevant in obese patients, who exhibit a markedly higher prevalence of diabetes mellitus.[26]

Safety and monitoring

From a safety perspective, obesity itself does not appear to introduce unique hazards in the context of ACEi, ARB, or ARNi use. Standard monitoring protocols apply, including regular assessments of renal function, serum potassium, and blood pressure, particularly during initiation and dose titration. However, obesity is strongly associated with a higher prevalence of diabetes mellitus,[26] which in turn elevates the risk for hyperkalaemia during RAS inhibition. Clinicians should therefore maintain heightened vigilance when managing obese patients with concomitant diabetes.

Experts' advice: In obese patients with HF, RAS inhibitor doses should be maintained at guideline-recommended target levels, as there is no evidence that obesity necessitates dose modification and full dosing is often well tolerated and optimizes cardiovascular and metabolic benefits.

Beta-blockers

Efficacy and treatment heterogeneity

No RCT testing beta-blockers in HF has pre-specified or reported outcomes stratified by BMI-defined obesity. As a result, data on their efficacy in this setting remain limited. In the Swedish Heart Failure Registry, the use of beta-blockers was associated with lower mortality in patients with HFrEF, irrespective of obesity status.[26] Interestingly, beta-blocker-induced weight gain has been associated with improved survival,[37] possibly due to attenuation of cachexia mechanisms predominantly seen in advanced HFrEF.[38,39] The overall evidence on the safety and efficacy of beta-blockers in HFpEF remains conflicting.[40–43] Currently, no data are available regarding the interaction between beta-blocker effects and obesity in HFpEF, as they are not guideline indicated.[44]

Safety and monitoring

Obese patients may have higher sympathetic activity, which theoretically could increase tolerability to beta-blockers. However, beta-blockers have raised concerns about potential adverse metabolic effects in obese patients, including changes in lipid profiles, reduced insulin sensitivity, and weight gain.[45,46] These effects are largely attributed to their inhibition of sympathetic nervous system activity, which plays a crucial role in regulating energy expenditure, fat metabolism, and glucose homeostasis.[47]

Despite some theoretical concerns, most of which are minor, anecdotal, or non-specific to obesity, the use of beta-blockers should not be limited in HFrEF patients, given their well-established mortality and morbidity benefit.[48] In contrast, due to the lack of clear evidence supporting a benefit of beta-blockers in HFpEF population, their use in those with obesity may still be appropriate, particularly in clinical situations where a specific benefit is expected, such as uncontrolled hypertension,[49] elevated heart rate in atrial fibrillation,[50] and symptomatic angina or inducible ischaemia.[51]

Experts' advice: In obese patients with HF, beta-blockers should be prescribed at guideline-recommended target doses, as their benefits on mortality and morbidity in HFrEF apply irrespective of body size. In HFpEF, where clear evidence of benefit is lacking, their use may be considered in patients with obesity when specific indications are present.

Mineralocorticoid receptor antagonists

Efficacy and treatment heterogeneity

Higher BMI has been associated with elevated aldosterone levels through multiple mechanisms, including the direct production of aldosterone-stimulating factors by adipocytes, many of which support a causal link to the development of HF, particularly in HFpEF.[52,53]

Several of these pathways appear to function independently of the classical RAS, as suggested by evidence that reduced neprilysin levels may impair aldosterone suppression and that leptin can directly stimulate aldosterone production.[53–55] Taken together, these mechanisms provide a strong rationale for targeting aldosterone signalling as a therapeutic strategy in obesity-related HF.[25,53] This approach may be particularly beneficial in individuals with excess visceral adiposity (as indicated by high waist circumference [WC]), where mineralocorticoid receptor antagonism may have a greater clinical impact.

In line with this pathophysiological background, analysis from major RCTs suggests that MRAs may provide a potentially greater benefit in HF patients with elevated BMI across both reduced and preserved ejection fraction phenotypes, a finding that has been consistently observed. In the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial, eplerenone significantly reduced the primary composite endpoint of CV death or HF hospitalization (and its individual components) in patients with New York Heart Association (NYHA) class II symptoms and an ejection fraction of ≤35%.[56] A post-hoc analysis showed that the magnitude of the risk reduction was more than twice as great in patients with abdominal obesity (WC ≥102 cm for men and ≥88 cm for women) than in those with a normal WC.[57] Specifically, eplerenone reduced the risk of the primary end point by 52% in patients with abdominal obesity, but by only 22% in those who were not obese (WC by treatment interaction $P = .01$). Moreover, abdominal obesity was associated with a nearly threefold greater reduction in cardiovascular mortality with eplerenone compared to those without abdominal obesity. These patients also tolerated the treatment better, with fewer discontinuations due to adverse effects. In this study, WC proved to be a better predictor of both efficacy and safety than BMI, highlighting abdominal obesity as a marker of a more favourable benefit–risk profile for long-term MRA therapy. Interestingly, in the EMPHASIS-HF trial, around 60% of patients across weight categories successfully achieved the target dose of 50 mg daily of eplerenone, indicating that obesity does not impair dose up-titration or tolerability.[57] Further evidence comes from a patient-level meta-analysis of the RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF trial, which demonstrated a greater benefit of MRAs on the primary composite outcome (CV death or HF hospitalization) and HF hospitalization in HFrEF patients with higher body weight.[58]

In HFpEF, a similar signal was observed in a post-hoc analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, where spironolactone was associated with a reduction in the primary endpoint (composite of cardiovascular death, HF hospitalization, or aborted cardiac arrest) of greater magnitude in obese patients with a BMI above 33 kg/m^2 or increased WC.[59] These findings were further supported by a machine-learning analysis of the same trial, showing a more pronounced reduction in the risk of the primary outcome among patients in phenogroup 3, characterized by obesity, diabetes, high renin levels, renal dysfunction, and liver fibrosis (hazard ratio [HR] 0.75, 95% confidence interval [CI] 0.59 to 0.95; p for interaction = 0.016).[60] The obesity-related reduction in natriuretic peptides may also influence the response to MRAs. Indeed, in patients with HF, hyperaldosteronism, plasma volume expansion, and profibrotic processes may be exacerbated by disproportionately low levels of natriuretic peptides, potentially due to increased neprilysin activity in obesity, which is responsible for the degradation of B-type natriuretic peptide.[61] Notably, in the TOPCAT trial, patients with low natriuretic peptide concentrations (likely reflecting abdominal obesity) experienced the greatest benefit from spironolactone, with an approximate 80% reduction in the primary endpoint, although this observation was based on a small number of events.[62]

A pre-specified analysis of the recent FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure) trial found that the effect of non-steroidal MRA finerenone on clinical events and symptoms was generally consistent across baseline BMI, with a possibly greater benefit on the primary composite outcome (cardiovascular death or worsening HF events) observed in patients with higher BMI (P for interaction = 0.005). Notably, no significant interaction between adiposity and treatment effect was observed when using waist-to-height ratio (P for interaction = 0.87) or BMI categories (underweight/normal weight, overweight, obesity class I, and obesity class II–III; P for interaction = 0.32).[63]

Safety and monitoring

The safety profile of MRAs in obese patients appears to be broadly comparable to that in non-obese patients, with no specific obesity-related safety concerns emerging in clinical trials. However, because obese individuals more frequently have diabetes and chronic kidney disease (i.e. two major risk factors for hyperkalaemia), the potential for adverse effects must be carefully monitored. The risk of hyperkalaemia is compounded when MRAs are used concurrently with RAS-modulating agents (i.e. ACEi, ARBs, or ARNi), a common therapeutic combination in HFrEF.

As with all patients on MRA therapy, renal function and serum potassium should be checked within one week of initiation, at dose adjustments, and periodically thereafter.[9] This is especially important in obese patients, who may experience unrecognized baseline renal dysfunction due to limitations in standard creatinine-based glomerular filtration rate (eGFR) calculations.[64] More accurate measures, such as cystatin C–based GFR estimates, may improve risk prediction, though this tool is not yet widely adopted in routine clinical settings.

Experts' advice: In obese patients with HF, MRAs should be prescribed at guideline-recommended target doses. Evidence from post-hoc analyses and meta-analyses suggests that MRAs may confer greater benefit (i.e. larger reduction in clinical events) in patients with excess adiposity across both HFrEF and HFpEF.

Sodium-glucose cotransporter 2 inhibitors

Efficacy and treatment heterogeneity

Foundational RCTs demonstrated the efficacy of SGLT2 inhibitors dapagliflozin and empagliflozin in reducing the risk of HF events and cardiovascular death in patients with HFrEF (DAPA-HF and EMPEROR-Reduced) and HFmrEF/HFpEF (EMPEROR-Preserved and DELIVER). Given the high prevalence of overweight and obesity in these populations (DAPA-HF: 36% overweight, 35% obesity; EMPEROR-Reduced: 36% overweight, 31% obesity; EMPEROR-Preserved and DELIVER: both 33% overweight, 45% obesity), understanding the consistency of efficacy and safety across BMI subgroups is clinically relevant.[65–68]

Across all major trials, there was no evidence of heterogeneity in the treatment efficacy of SGLT2 inhibitors by BMI. In DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), the benefit of dapagliflozin on the primary outcome (worsening HF or cardiovascular death) was consistent across baseline BMI categories.[69] Similarly, in the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction), empagliflozin reduced the risk of the primary outcome (HF hospitalization or cardiovascular death) and total HF hospitalization regardless of BMI.[70] In DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure), dapagliflozin consistently reduced the risk of the primary outcome (worsening HF or cardiovascular death) across BMI subgroups, with greater symptom improvement observed in patients with obesity.[71] In EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), empagliflozin showed consistent benefit on the primary outcome (first HF hospitalization or cardiovascular death) across BMI strata, with a trend toward greater absolute improvement in health status among those with higher BMI.[72] Finally, a study-level meta-analysis of EMPEROR-Preserved and DELIVER confirmed no significant treatment-by-BMI interaction for the primary composite outcome of HF hospitalization or cardiovascular death, total HF hospitalizations, CV

death, or eGFR slope.[72] These findings support that BMI should not influence the decision to initiate SGLT2 inhibitors in patients with HF.

Safety and monitoring

The safety profiles of SGLT2 inhibitors are generally consistent across BMI categories. Modest weight loss is typically observed (i.e. ~ 0.9 kg at 32 weeks in DAPA-HF and ~ 1.3 kg at 52 weeks in EMPEROR-Preserved), but this does not warrant dose adjustment or special monitoring. Adverse events (AEs), including discontinuations, volume depletion, renal events, and major hypoglycaemia were comparable across BMI subgroups in DAPA-HF and DELIVER.[69,71] In EMPEROR-Reduced, rates of symptomatic hypotension, acute renal failure, and confirmed hypoglycaemia were similar across BMI strata, though therapy discontinuation rates due to AEs was slightly more frequent in those with BMI <20 kg/m^2.[70] In EMPEROR-Preserved, AE rates were generally consistent across BMI categories, although a modest increase in renal failure and genital infections was observed in patients with higher BMI.[72] No BMI-specific safety precautions or monitoring are recommended. Standard monitoring of volume status, renal function, and glycaemic parameters remains appropriate for all patients, regardless of BMI.

Experts' advice: In obese patients with HF, SGLT2 inhibitors should be prescribed at the standard fixed doses recommended by guidelines, as there is no evidence that obesity modifies efficacy or tolerability. Across all pivotal HFrEF and HFpEF trials, the benefits of dapagliflozin and empagliflozin on HF events, cardiovascular mortality, and symptom improvement were consistent across BMI subgroups, with some signals of greater health status improvement in patients with obesity.

GDMT in obesity: summary of efficacy, dosing, and safety evidence

Across all major classes of GDMT for HFrEF and for SGLT2 inhibitors for HFpEF, there is no consistent evidence of treatment effect heterogeneity across BMI categories with standard dosing, with the exception of MRAs, which appear to provide greater benefit in patients with HF and obesity. Similarly, no obesity-specific safety concerns have been identified, and monitoring recommendations remain similar to those of the general HF population. Some comorbidities that are more prevalent in individuals with obesity (i.e. diabetes mellitus, chronic kidney disease) may increase the risks of certain AEs, but do not fundamentally alter safety strategies (*Figure 1*; *Table 1*).

Volume status assessment and diuretic strategy in obesity

Obesity poses challenges to the assessment of volume status. For example, physical exam findings of congestion are even more difficult to monitor than in non-obese patients.[73] Natriuretic peptides and echocardiography are key tools in the evaluation of haemodynamic congestion in individuals with HF.[9] However, known limitations of natriuretic peptides include inaccurate estimation of the degree of decompensation with demographic variables and certain comorbidities (i.e. age, atrial fibrillation, obesity).[74–76] Specifically, BMI is inversely related to natriuretic peptide levels,[76] and with increasing BMI, the association between natriuretic peptides and risk is shifted upward (i.e. at any given natriuretic peptide level, higher BMI confers greater risk of adverse events).[77] Echocardiographic measures, such as *E*/*e*' ratio, may also underestimate haemodynamic congestion in people with obesity and HF.[78] Lung ultrasound may offer incremental information regarding pulmonary congestion among individuals with obesity and HF beyond natriuretic peptide levels.[79] Notably, B-lines, like natriuretic peptide levels, decline with increasing BMI in HF patients, which may limit their accuracy for detecting congestion. However, the reduction in B-lines is less pronounced than for natriuretic peptides (i.e. decrease by 18% in chronic HF and by 12% in acute HF for every 5 unit increase in BMI, compared with a 28% decrease in NT-proBNP for the same

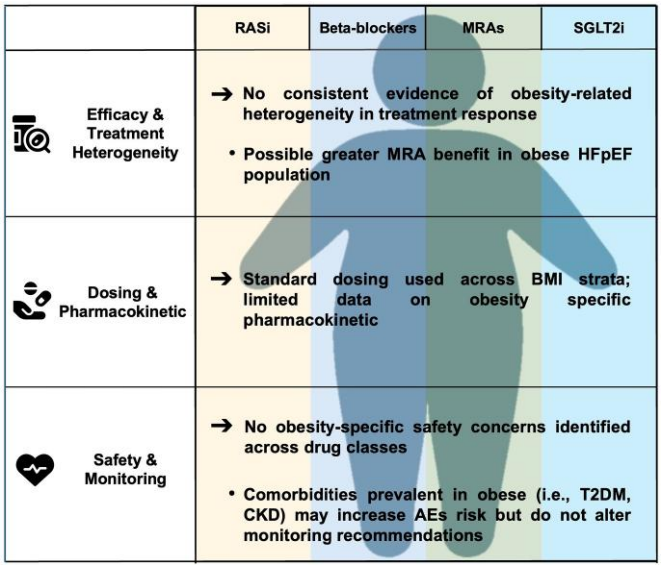

Figure 1 Summary of key evidence on the efficacy, safety, and dosing of guideline-directed medical therapy in patients with heart failure and obesity. Abbreviations: AEs, adverse events; BMI, body mass index; CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus. Part of the figure was created with BioRender.com

BMI increase),[79] making them a more reliable congestion marker in obese patients.[80]

Once congestion is established, loop diuretics remain the primary therapeutic intervention. Diuretics are recommended irrespective of ejection fraction to alleviate symptoms, improve functional status, and reduce hospitalization risk (Class I-C recommendation per European Society of Cardiology).[9] However, obesity can blunt natriuretic response to diuretics, a phenomenon potentially linked to altered renal handling of sodium, higher neurohormonal activation, and larger distribution volume.[8] Incorporating acetazolamide into the diuretic regimen may be particularly beneficial for obese HF patients who exhibit inadequate response to standard loop diuretic therapy, addressing the underlying mechanisms of diuretic resistance and facilitating more effective fluid management.[81] In addition, obese individuals often have increased intra-abdominal and/or renal vein pressure, which may specifically contribute to greater resistance to glomerular filtration.[82] As a result, obese patients may require higher initial diuretic doses or more aggressive up-titration to achieve euvolemia. For example, weight-based furosemide dosing (i.e. ≥2 mg/kg intravenous in diuretic-resistant patients) may be more appropriate in select cases, although formal guidelines do not yet differentiate dosing strategies by body weight.

At the same time, patients with obesity may be more vulnerable to renal function deterioration during natriuresis. In a pooled analysis of four RCTs (DOSE, CARRESS, ROSE, and ATHENA) including 332 patients hospitalized with decompensated HFpEF, obese individuals experienced greater renal deterioration during decongestive therapy, despite achieving similar weight loss. Compared to non-obese patients, those with obesity had a more pronounced rise in serum creatinine and greater decline in eGFR, with a twofold higher incidence of mild worsening renal function (creatinine increase ≥0.3 mg/dl; 28% vs 14%, $P = .008$) and a markedly higher incidence of severe worsening (creatinine increase >0.5 mg/dl; 9% vs 0%, $P = .002$).[83] However, misinterpretation of kidney function is a leading cause of inadequate decongestion in acute HF and of underdosing GDMT more generally, and should be avoided, particularly in high-risk patients like those with obesity.[84,85]

In patients treated with anti-obesity medications, especially GLP-1 RAs or dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RAs agents, careful coordination with diuretic therapy is warranted. These agents can induce early-phase gastrointestinal symptoms, reduced oral intake, and modest natriuresis, potentially favouring volume depletion and electrolyte disturbances.[86,87] In patients with HF, monitoring renal function and electrolytes during initiation and up-titration of these agents is advisable, with corresponding adjustments to diuretic and antihypertensive therapy as needed. Particular vigilance is needed in the presence of nausea, vomiting, or reduced fluid intake, which can exacerbate hypovolemia.[86]

Conclusion

Obesity is highly prevalent among patients with HF, mainly with HFpEF, and introduces unique diagnostic and therapeutic challenges. Available data, largely from subgroup analyses of major HF trials, suggest that RAS inhibitors (especially ARNI) and SGLT2 inhibitors retain efficacy and safety across BMI categories, whereas MRAs appear to provide even greater benefit in patients with obesity. On the contrary, evidence for beta-blockers remains scarce, mainly owing to the older design of the landmark studies. Accurate assessment of volume status is challenging in this setting, and individualized diuretic strategies remain essential.

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Declarations

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