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2025 ACC Scientific Statement on the Management of Obesity in Adults With Heart Failure

A Report of the American College of Cardiology

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ABSTRACT

Obesity confers increased risks of HF, coronary artery disease, and stroke, and weight loss can reduce cardiovascular disease risk. Given emerging evidence of the benefits of semaglutide and tirzepatide in individuals with HFpEF and obesity in concert with healthy behavioral interventions, clinicians should be aware of optimal diagnosis, risk assessment, and management of obesity in individuals with HF. Despite the early promise of anti-obesity medications in HFpEF, challenges remain, including whether BMI is the optimal metric to identify obesity and subsequent benefit from anti-obesity medications; the safety profile of anti-obesity medications for individuals with HF, particularly HFrEF; and whether the benefits of anti-obesity medications are attributed mainly to the magnitude of weight loss or due to other mechanisms of action. Motivated by this emerging evidence and ongoing challenges, this scientific statement: 1) reviews the diagnosis, evaluation, and risk assessment of obesity in HF; 2) describes HF-specific management strategies from lifestyle intervention to medications to surgery; and 3) addresses evidence gaps and future directions in obesity-related HF. With accurate evaluation of obesity as well as administration and monitoring of safe and effective interventions, clinicians may improve quality of life and functional capacity and potentially reduce HF events in individuals living with HF and obesity.

INTRODUCTION

The American College of Cardiology (ACC) has a long history of developing documents to complement clinical practice guidelines. Scientific statements represent a novel approach to inform clinicians about areas where evidence is new and evolving or where sufficient data are more limited.

The writing committee convened in early 2025 via a confidential conference call attended only by writing committee members and ACC staff. A review of outstanding questions was facilitated. Writing assignments were configured according to areas of expertise. Email correspondence was used to edit contributed content. Differences were resolved by consensus among the group. The work of the writing com-

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Obesity is a chronic disease defined by the presence of abnormal or excessive adipose accumulation that negatively affects health outcomes including increased risk of heart failure (HF), coronary artery disease, and stroke.[1,2] For individuals with HF with preserved ejection fraction (HFpEF), intentional weight loss to treat obesity is associated with improved health status and lower event rates in clinical trials[3-5]; for individuals with HF with reduced ejection fraction (HFrEF), small lifestyle trials and observational bariatric surgery data suggest benefits, but definitive trials are lacking.[6-8]

Historically, a lack of safe and effective weight-loss interventions have been available. Although sodium-glucose cotransporter-2 inhibitors show benefits in the treatment of HF, their effect on weight loss is modest.[9] However, novel anti-obesity medications (AOM) offer significant advances. AOM include agents with effects on glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP; formerly known as gastric inhibitory polypeptide).[10] Semaglutide, a GLP-1 receptor agonist, and tirzepatide, a dual GLP-1 and GIP receptor agonist, demonstrate improved cardiovascular outcomes in individuals with type 2 diabetes mellitus (T2DM) without[11] and with[12-14] high cardiovascular risk or established disease as well as a reduction in incident HF events.[15] Furthermore, the benefit of these therapies extends to those without T2DM but with cardiovascular disease[16] and HFpEF.[4,5]

Despite the early promise of AOM in HFpEF, challenges remain, including whether body mass index (BMI) is the optimal metric to identify obesity and subsequent benefit from AOM; the safety profile of AOM for individuals with HF, particularly HFrEF; and whether the benefits of AOM are attributed mainly to the magnitude of weight loss or due to other mechanisms of action.

Motivated by this emerging evidence and ongoing challenges, this scientific statement will (1) review the diagnosis, evaluation, and risk assessment of obesity in HF; (2) describe HF-specific management strategies from lifestyle intervention to medications to surgery; and (3) address evidence gaps and future directions in obesity-related HF. The specific focus of this scientific statement will be Stage C HFpEF, as reported and ongoing trials target this population (Table 1).

TABLE 1 Table of Consensus Recommendations

Epidemiology of obesity in HF
Avoidance of excess adiposity throughout the lifespan is key to the prevention of incident HF, particularly HFpEF.
The "HF obesity survival paradox" in part represents the negative implications of unintentional weight loss.
Obesity treatments offer opportunities for improved HF symptom burden, functional capacity, quality of life, and hospitalizations.
Diagnosis of obesity
Although BMI is an inexpensive, easily acquired, and readily reproducible metric that is strongly embedded in research and clinical practice, significant limitations exist in the detection of excess adiposity, the location of adiposity, and applicability to diverse populations.
To determine a diagnosis of clinical obesity in individuals with BMI <35 kg/m^2, direct assessment of excess adiposity with an anthropometric criterion (eg, waist circumference [the most readily obtainable], waist-to-hip ratio, or waist-to-height ratio) or body composition assessment (eg, dual X-ray absorptiometry, when available) may be used.
Clinicians should be aware that obesity remains a stigmatized condition and that some individuals may experience discomfort with being weighed, abdominally measured, or talking about weight during a medical visit.
Risk assessment and evaluation of obesity and HF
Because individuals with obesity have lower natriuretic peptide concentrations, lower thresholds are used in those who have obesity and exertional dyspnea to avoid underdiagnosis of HF in this population, although specific thresholds are not currently established.
For individuals with HF and obesity, monitoring for T2DM, hypertension, atrial fibrillation, sleep-disordered breathing, and objective evidence of exercise intolerance can identify the need for targeted interventions.
Management of obesity in HF: lifestyle and behavioral interventions
Behavioral changes aimed at intentional weight loss are appropriate to attempt for individuals with obesity because even modest changes in body weight can result in improvements in risk of cardiovascular events, although weight loss is often unsustainable.
Exercise can improve functional status in individuals with HFpEF.
Management of obesity in HF: pharmacologic interventions
The STEP-HFpEF program and SUMMIT trial show that, in people with BMI $\geq$30 kg/m^2 and HF with EF $\geq$45% (semaglutide) and EF $\geq$50% (tirzepatide), weight loss is associated with improvements in symptoms and functional capacity.
Insufficient evidence exist to date to confidently conclude that semaglutide and tirzepatide reduce HF events in individuals with HFpEF and obesity (with stronger evidence for tirzepatide), although exploratory analysis indicates favorable changes in biomarkers and imaging parameters suggesting potential distinct mechanistic advantages outside of weight loss.
During early-phase gradual dose escalation of semaglutide or tirzepatide, which occurs every 4 weeks, monitor kidney function and electrolytes with adjustment of diuretics, antihypertensive agents, and antihyperglycemic agents as indicated, particularly if gastrointestinal adverse effects are prominent.
Management of obesity in HF: invasive interventions
For individuals with HF and obesity, metabolic and bariatric surgery appears effective for intentional weight loss and potentially to reduce risk of HF events, including hospitalization for HF and death, although these possibilities are based only on data from observational studies.
Individuals with HF who are undergoing metabolic and bariatric surgery have an increased risk of postoperative cardiovascular morbidity and death, suggesting the need for preoperative optimization and perioperative care by clinicians with expertise in HF management.

BMI = body mass index; EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; STEP-HFpEF = Semaglutide Treatment Effect in People with Obesity and HFpEF; SUMMIT = A Study of Tirzepatide [LY3298176] in Participants With Heart Failure With Preserved Ejection Fraction [HFpEF] and Obesity; T2DM = type 2 diabetes mellitus.

DEFINITIONS AND CLASSIFICATIONS

Heart failure (HF): defined as per the Universal Definition of Heart Failure:[17] symptoms and/or signs of HF caused by structural/functional cardiac abnormalities *and* at least 1 of: 1) elevated natriuretic peptides; or 2) objective evidence of cardiogenic pulmonary or systemic congestion.

Heart failure with reduced ejection fraction (HFrEF): clinical diagnosis of HF and left ventricular ejection fraction (LVEF) ≤40%.[18]

Heart failure with mildly reduced ejection fraction (HFmrEF): clinical diagnosis of HF and LVEF 41%-49%.[18]

Heart failure with preserved ejection fraction (HFpEF): clinical diagnosis of HF and LVEF ≥50%[18] not attributable to an underlying cause such as an infiltrative cardiomyopathy, hypertrophic cardiomyopathy, valvular disease, or pericardial disease.

Heart failure stages:

- **Stage A**: At risk of HF due to conditions such as hypertension, diabetes, or coronary artery disease
- **Stage B**: Pre-HF with no symptoms but evidence for structural heart disease including reduced EF, increased left ventricular wall thickness, valvular disease
- **Stage C**: Symptomatic HF with structural heart disease and HF symptoms
- **Stage D**: Advanced HF with marked symptoms despite attempts at optimization of guideline-directed medical therapy

Anti-obesity medications (AOM): U.S. Food and Drug Administration (FDA)-approved second-generation agents including orlistat, phentermine/topiramate, and naltrexone/bupropion have minimal efficacy and limiting side effects, particularly in individuals with HF. Third-generation agents comprise hormone-based therapies that target metabolic pathways and control appetite. Therapies studied in HF include the GLP-1 receptor agonists (ie, semaglutide) and the GLP-1/GIP dual receptor agonist (ie, tirzepatide), alternatively termed nutrient-stimulated hormone therapies.

Obesity: The World Health Organization defines obesity by the BMI threshold ≥30 kg/m^2, with classes describing obesity severity (class 1 obesity BMI ≥30 kg/m^2 to <35 kg/m^2, class 2 obesity BMI ≥35 kg/m^2 to <40 kg/m^2, and class 3 obesity BMI ≥40 kg/m^2); BMI ≥25 kg/m^2 is consistent with obesity in most Asian populations; see *Lancet Diabetes and Endocrinology* Commission for details.[19]

Anthropomorphic criteria for excess adiposity:

- Abnormal waist circumference: ≥35 inches (88 cm; women); ≥40 inches (102 cm; men). In most Asian populations, waist circumference ≥31.5 inches (80 cm; women); ≥35 inches (90 cm; men) is abnormal; see *Lancet Diabetes and Endocrinology* Commission on Obesity for details.[19]
- Abnormal waist-height ratio: ≥0.50
- Abnormal waist-hip ratio: ≥0.85 (women); ≥0.90 (men)

Excess adiposity: From the *Lancet Diabetes and Endocrinology* Commission, excess adiposity is defined as elevated BMI confirmed by either direct measurement of body fat or at least an anthropometric criterion (eg, waist circumference, waist-to-hip ratio, or waist-to-height ratio) in addition to BMI, using validated methods and sex-specific thresholds.[19]

Clinical obesity: From the *Lancet Diabetes and Endocrinology* Commission, clinical obesity is defined as a chronic, systemic illness characterized by alteration in the function of tissues, organs, the entire individual, or a combination thereof, due to excess adiposity.[19] For individuals with excess adiposity and no end-organ disease, a diagnosis of clinical obesity can alternatively be applied with substantial obesity-associated age-adjusted limitations of daily activity.

Preclinical obesity: From the *Lancet Diabetes and Endocrinology* Commission, preclinical obesity is a state of excess adiposity with preserved function of other tissues and organs.[19]

Abbreviation	Meaning/Phrase
AOM	anti-obesity medications
BMI	body mass index
BNP	B-type natriuretic peptide
EF	ejection fraction
EMBT	endoscopic metabolic and bariatric therapies
FDA	U.S. Food and Drug Administration
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVAD	left ventricular assist device
MBS	metabolic and bariatric surgery
MI	myocardial infarction
NP	natriuretic peptides
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAF	population attributable fraction
PCWP	pulmonary capillary wedge pressure
SDOH	social drivers of health
T2DM	type 2 diabetes mellitus

EPIDEMIOLOGY OF OBESITY IN HF

Prevalence

The prevalence of obesity in adults in the United States from 2017 to 2020, as defined by BMI ≥30 kg/m², was 41.9%,[20] with higher prevalence in men versus women, as well as in Black and Hispanic individuals versus White individuals.[20] Acknowledging the uncertainty in obesity trends given current therapeutic advances, the estimated U.S. prevalence of obesity is projected to increase to 60.6% by 2050.[21]

Similarly, the prevalence of HF in the United States is expected to rise, from about 6.9 million in 2024 to 11.4 million in 2050.[21] About 1 in 4 U.S. adults will develop HF, with sex-specific differences: lifetime risk for HFrEF is higher in men (10.6%) than women (5.8%) but similar for HFpEF (10.7% for men and 10.4% for women).[22] Like obesity, the projected prevalence of HF in U.S. adults will increase from 2.7% in 2020 to 3.8% in 2050,[21] with comparable global trends.[20]

Obesity is common in HF, which may be related to increased body fat and its attendant metabolic sequelae because of widespread effects on the cardiovascular system leading to symptomatic HFpEF.[23,24] In the National Health and Nutrition Examination Survey, 2015-2018, 64.2% of participants self-reported having obesity.[25] In the National (Nationwide) Inpatient Sample of people hospitalized for HF in 2018, obesity was observed in 23.2% of those with HFrEF and 32.8% of those with HFpEF[26]; the lower observed prevalence likely attributed to the frailty, cachexia, and sarcopenia in hospitalized individuals.

Risk factors

Obesity and HF share common multifactorial risks including genetic, environmental, psychological, and nutritional factors.[19] Obesity is strongly associated with adjusted risk of incident HF[27,28]; every 4 kg/m² of BMI increase carries a 1.2-fold risk for HF,[29] with a stronger relationship in HFpEF.[30,31] Furthermore, the population attributable fraction (PAF) of obesity (ie, the percentage of HF that can be attributed to obesity) is greater for HFpEF than HFrEF and in Black individuals versus White individuals in the United States: PAF 22% and 6.6% in White women and 40.4% and 4.5% in Black women.[32] Similar findings are observed in Europe, where the PAF of obesity for HFpEF is 20% (women) and 16% (men) and for HFrEF is 6% (women) and 10% (men).[33]

Outcomes

In individuals with HF, obesity is associated with greater symptom burden,[23,34,35] lower exercise capacity, worse quality of life,[23,35,36] greater HF instability,[34] and more hospitalizations.[36,37] However, the association between obesity and death in individuals with HF is less clear. In 1 meta-analysis, being underweight (BMI <25 kg/m²) carried a 40% higher risk of death while overweight and obesity were not associated with a risk of death.[38] In another meta-analysis, excluding those with intentional weight loss from medications or bariatric surgery, weight loss ≥5% was associated with a 75% higher risk of death.[39]

This "obesity paradox" has many explanations, including incomplete confounder adjustment,[40] unfavorable outcomes from unintentional weight loss (reverse causation), lead time bias (earlier HF diagnosis in individuals with obesity), greater optimization of HF medications for individuals with obesity,[41] selection bias from inclusion of retrospective studies,[39] or identification of individuals with less advanced HF.[41] Furthermore, this paradox highlights that obesity classification based on BMI alone may not be accurate because no paradox exists when obesity is defined by anthropomorphic measures of central obesity rather than BMI.[42-44] BMI is also inconsistent across age, sex, and racial/ethnic groups, and does not distinguish variations in adiposity from lean mass and fluid retention.[19,45]

Of note, the prevalence of obesity is higher in individuals with adverse social drivers of health (SDOH) including lower education as well as more food insecurity, economic instability, adverse neighborhood and health systems,[46] and rurality.[20] These SDOH adversely influence access to care, management, and complications of HF.[20,47-49] Thus, treating obesity is increasingly important in mitigating the individual and population health consequences of HF, particularly the care inequities based on demographic and socioeconomic factors, insurance status, and rural residence.[47,50]

Consensus recommendations

- Avoidance of excess adiposity throughout the lifespan is key to the prevention of incident HF, particularly HFpEF.
- The "HF obesity survival paradox" in part represents the negative implications of unintentional weight loss.
- Obesity treatments offer opportunities for improved HF symptom burden, functional capacity, quality of life, and fewer hospitalizations.

DIAGNOSIS OF OBESITY

The World Health Organization defines obesity by the BMI threshold ≥30 kg/m² with classes describing obesity severity (class 1 obesity BMI ≥30 kg/m² to <35 kg/m², class 2 obesity BMI ≥35 kg/m² to <40 kg/m², and class 3 obesity BMI ≥40 kg/m²).[51] BMI has historically been the key metric for identifying obesity and is deeply embedded in research and clinical practice: the current obesity-related HFpEF trials of semaglutide and tirzepatide recruited

participants based on BMI criteria (≥30 kg/m^2)[4,5,52] and FDA approval of these medications includes BMI thresholds for eligibility. However, although BMI is an inexpensive, easily acquired, and readily reproducible metric, it has significant limitations.[19,53,54]

The limitations of BMI

BMI, developed for prognostication in predominantly White men, has weaknesses in detection of excess adiposity as well as health consequences across diverse populations.[55,56] BMI does not discern adipose tissue from muscle mass or fluid retention, which is particularly relevant in HF where muscle wasting and hypervolemia are prevalent. Furthermore, it cannot distinguish the location or metabolic consequences of adipose tissue, with centrally located adiposity most strongly associated with metabolic dysfunction, inflammation, and cardiovascular mortality.[57,58] Individuals in Asia show greater metabolic and end-organ consequences of excess adiposity at lower BMIs compared with White populations; BMI ≥25 kg/m^2 is consistent with obesity in most Asian populations.[59,60] As a result, BMI may not be the most effective tool to diagnose clinical obesity.[61]

Anthropometric measure—such as waist circumference, waist-to-hip ratio, waist-to-height ratio, or body roundness index—may better represent visceral adiposity and the potential to derive clinical benefit from obesity treatment.[62] Increased central adiposity is associated with more adverse HF outcomes, although variability by HF phenotype exists.[43,44,63-66] Particularly among individuals with HFpEF, paracardiac adipose tissue appears functionally and symptomatically relevant.[66-69]

Evolving diagnostic approaches

Although the FDA released draft guidance on "Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction: Guidance for Industry" in January 2025 and it remains BMI-centric,[70] the *Lancet Diabetes and Endocrinology* Commission proposed a new definition of "clinical obesity" also in January 2025. The *Lancet Diabetes and Endocrinology* Commission defines clinical obesity as a chronic, systemic illness characterized by alteration in the function of tissues, organs, the entire individual, or a combination thereof, due to excess adiposity.[19] Conversely "preclinical obesity" is a state of excess adiposity with preserved function of other tissues and organs. However, for individuals with excess adiposity and no end-organ disease, a diagnosis of clinical obesity can alternatively be applied with substantial obesity-associated, age-adjusted limitations of daily activity.

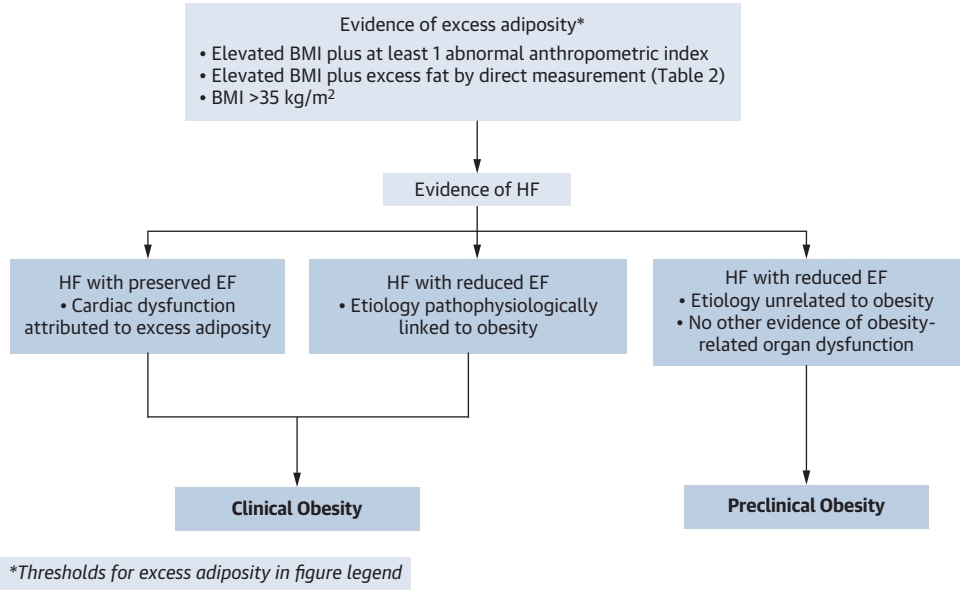
The *Lancet Diabetes and Endocrinology* Commission stipulates that excess adiposity should be confirmed by either direct measurement of body fat (eg, dual X-ray absorptiometry) (Table 2) or at least an anthropometric

TABLE 2 Strengths and Weaknesses of Adiposity Assessment Techniques in Individuals With HF

Technique	Strengths	Weaknesses
Body weight and BMI[19,53-59,61]	■ Quick ■ Low cost ■ Portable ■ Nonionizing	■ Does not perform well across racial/ethnic and sex groups ■ Does not distinguish fat mass specifically or location of adiposity ■ Variable patient acceptability
Waist circumference, waist-to-hip ratio, waist-to-height ratio[44,63-65,71-74]	■ Quick ■ Low cost ■ Portable ■ Nonionizing	■ Abdominal circumference may be increased during fluid retention ■ Differential prognostic performance of these indices across HF phenotypes and cohorts ■ Variable patient acceptability
Bioelectrical impedance analysis[75-78]	■ Low cost ■ Nonionizing ■ Validation of use specific to HF ■ Safety data available for transvenous pacemaker and defibrillator devices	■ Safety data unavailable with all implantable HF devices ■ Sex-specific normal ranges not fully established
Bioelectrical impedance spectroscopy[79-81]	■ Nonionizing ■ Segmental body compartment analysis possible ■ Validation of use specific to HF	■ Pending safety data with implanted cardiac devices
Whole-body dual X-ray absorptiometry[82]	■ Quick ■ Low radiation dose ■ Sex-specific normal ranges established	■ Intermediate cost ■ Ionizing (low-dose radiation) ■ Nonportable ■ Not widely accessible ■ Fat mass normal ranges not HF specific ■ Assessment of regional adiposity dependent on available software
CT[83,84]	■ Good spatial resolution ■ Comprehensive assessment of regional adiposity	■ Ionizing ■ Costly ■ Nonportable ■ Sex-specific normal ranges not fully established
MRI[85]	■ Good spatial resolution ■ Comprehensive assessment of regional adiposity ■ Nonionizing	■ Costly ■ Nonportable ■ Contraindicated with some implanted cardiac devices ■ Sex-specific normal ranges not fully established
Air displacement plethysmography[86]	■ High-fidelity assessment of body composition ■ Nonionizing ■ Quick	■ Costly ■ Nonportable ■ Sealed chamber may not be safe for individuals with HF ■ Fat mass normal ranges are not HF specific

BMI = body mass index; CT = computed tomography; HF = heart failure; MRI = magnetic resonance imaging.

FIGURE 1 **Diagnosis of Obesity in HF Based on the *Lancet Diabetes and Endocrinology* Commission[19]**



*Thresholds for excess adiposity: BMI threshold ≥30 kg/m^2; BMI ≥25 kg/m^2 is consistent with obesity in most Asian populations.[19] Abnormal waist circumference: ≥35 inches (88 cm; women); ≥40 inches (102 cm; men). In most Asian populations, waist circumference ≥31.5 inches (80 cm; women); ≥35 inches (90 cm; men) is abnormal.[19] Abnormal waist-to-height ratio: ≥0.5; abnormal waist-to-hip ratio: ≥0.85 (women); ≥0.90 (men). BMI = body mass index; EF = ejection fraction; HF = heart failure.

criterion (eg, waist circumference, waist-to-hip ratio, or waist-to-height ratio) in addition to BMI, using validated methods and sex-specific thresholds. Per this Commission, BMI should only be used as a surrogate measure of risk at a population level and not for individual assessment, although individuals with BMI ≥40 kg/m^2 may be assumed to have excess adiposity. For the adoption of this approach in routine practice, the time and cost of direct adiposity measurement are likely to have the highest yield when BMI <35 kg/m^2.

With an existing diagnosis of HFpEF, excess adiposity would fulfill the requirements for a clinical obesity diagnosis. Whether HFrEF qualifies would presumably depend on whether the cardiomyopathy pathophysiology is related to excess adiposity (eg, via ischemic, diabetic, hypertensive etiologies versus an unrelated pathophysiology [eg, a defined genetic, myocarditis, or infiltrative etiology]), although the presence of other obesity-related organ dysfunction would also qualify for a diagnosis of clinical obesity (**Figure 1**).

Of note, despite the endorsement of waist circumference as an anthropometric criterion, the feasibility and patient perceptions of conducting these measurements, especially within the HF clinic setting, are not established. Obesity is a highly stigmatized condition,[87] and clinicians should be sensitive to the potential for patient discomfort with either being weighed or abdominally measured during medical visits.[88]

Consensus recommendations

- Although BMI is an inexpensive, easily acquired, and readily reproducible metric that is strongly embedded in research and clinical practice, significant limitations exist in the detection of excess adiposity, the location of adiposity, and applicability to diverse populations.
- To determine a diagnosis of clinical obesity in individuals with BMI <35 kg/m^2, direct assessment of excess adiposity with an anthropometric criterion (eg, waist circumference [the most readily obtainable], waist-to-hip ratio, or waist-to-height ratio) or body composition assessment (eg, dual X-ray absorptiometry, when available) may be used.
- Clinicians should be aware that obesity remains a stigmatized condition and that some individuals may experience discomfort with being weighed, abdominally measured, or talking about weight during a medical visit.

RISK ASSESSMENT AND EVALUATION OF OBESITY AND HF

Risk assessment and evaluation of individuals with obesity and HF include understanding the challenges of the diagnosis of HF in the context of obesity and comprehensive assessment of obesity- and HF-related comorbidities.

Challenges of the diagnosis of HF in individuals with obesity

Given the lack of testing to definitively establish the diagnosis of HFpEF, the use of clinical scoring systems may be useful to aid in the diagnostic evaluation.[89-91] Nonetheless, excess adiposity can affect the sensitivity and specificity of the history, physical examination, echocardiogram, and natriuretic peptides (NP) for the diagnosis of HF as established in the Universal Definition.[17] Volume assessment remains particularly challenging in obesity-related HF, because traditional physical examination findings (eg, jugular venous distention, peripheral edema) are less reliable. In fact, even noninvasive hemodynamic markers including those obtained from echocardiography underestimate circulatory congestion in individuals with obesity.[92] Although not routinely performed, accurate diagnosis of HFpEF in individuals with dyspnea and obesity may include assessment of pulmonary capillary wedge pressure (PCWP) during a cycle exercise study, with generally accepted HFpEF thresholds of supine peak exercise PCWP ≥25 mmHg, or upright peak exercise PCWP ≥20 mmHg.[93,94]

Assessment of NP including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) can be challenging in the context of obesity. NP assessment is recommended to (1) guide the diagnosis of HF if it is uncertain and (2) to risk stratify individuals with existing HF.[17,18,95,96] However, obesity may suppress NP production resulting in lower NP levels compared with individuals without obesity despite similar or higher risk for HF events.[34,92,97] Furthermore, the current recommended rule-out NT-proBNP threshold of <125 ng/L had only 67% sensitivity in 1 analysis of individuals with a BMI >35 kg/m^2. In fact, with a BMI of >35 kg/m^2, using a rule-out NT-proBNP threshold of >50 ng/L offered 93% to 98% sensitivity and a rule-in NT-proBNP threshold of >220 ng/mL provided 82% to 89% specificity,[98] illustrating the value of BMI-dependent diagnostic thresholds for NP in individuals with obesity.[68,98] Thus, the use of NP to guide the diagnosis of HF and risk stratification in individuals with obesity is hindered by lower NP concentrations that belie true HF probability. Clinicians should have a high index of suspicion for HF in individuals with obesity if there are other clinical symptoms and signs of HF despite "normal" NP levels.

Assessment of comorbidities of obesity and HF

Individuals with metabolically unhealthy obesity—characterized by insulin resistance, chronic inflammation, and increased cardiovascular risk—are at particularly high risk for poor HF outcomes.[99] Routine metabolic profiling, including hemoglobin A1c (HbA1c) and lipid panels, can identify the effects of excess adiposity and guide targeted interventions. Additionally, assessment of liver enzymes and hepatic imaging can identify metabolic dysfunction-associated steatotic liver disease.

Echocardiography can identify left ventricular hypertrophy and pulmonary hypertension although it may underestimate congestion in individuals with obesity.[92] Blood pressure (BP) monitoring will detect masked and nocturnal hypertension, prevalent in obesity-related HF.[100] Given the higher risk of atrial fibrillation in obesity,[101] screening with symptoms and ambulatory ECG as indicated may uncover atrial fibrillation warranting intervention.

Sleep-disordered breathing is common in HFpEF[102-105] and obesity,[106] and thus for those with a high clinical suspicion of sleep apnea, polysomnography can identify obesity hypoventilation syndrome and obstructive sleep apnea warranting treatment.[18]

Objective assessments of functional capacity, sarcopenia, and frailty include 6-minute walk distance, gait speed, and handgrip strength. They may indicate a deficiency or decline for which targeted interventions such as resistance training or cardiac rehabilitation could be recommended.[3]

Consensus recommendations

- Because individuals with obesity have lower NP concentrations, lower thresholds are used in those who have obesity and exertional dyspnea to avoid underdiagnosis of HF in this population, although specific thresholds are not currently established.
- For individuals with HF and obesity, monitoring for T2DM, hypertension, atrial fibrillation, sleep-disordered breathing, and objective evidence of exercise intolerance can identify the need for targeted interventions.

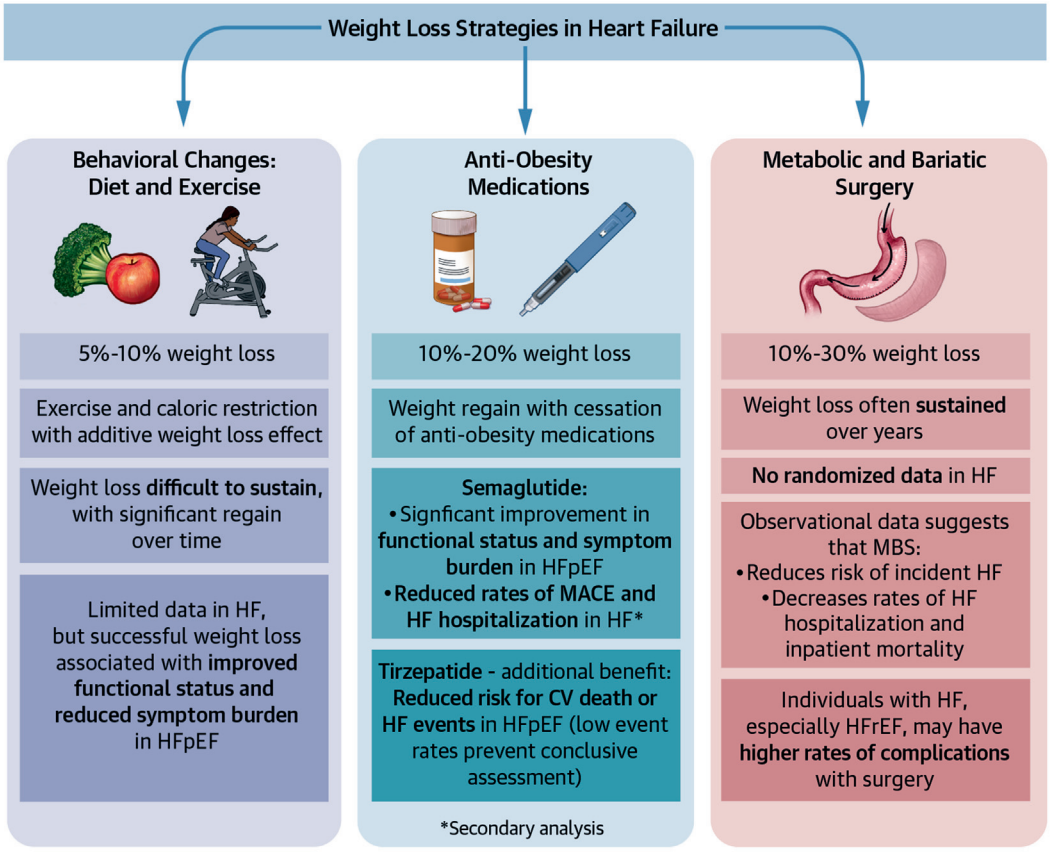
MANAGEMENT OF OBESITY IN HF

Management strategies for obesity range from lifestyle and behavioral interventions to medications to invasive interventions with varying evidence for safety and efficacy in individuals with HF. A summary of strategies is shown in the **Central Illustration**.

Lifestyle and behavioral interventions

Lifestyle and behavioral interventions have historically represented the foundation of intentional weight loss

CENTRAL ILLUSTRATION Evidence for Safety and Efficacy of Obesity Management Strategies in Individuals With HF



Kittleson MM, et al. JACC. 2025;■(■):■-■.

CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; MACE = major adverse cardiac events; MBS = metabolic and bariatric surgery.

efforts. There is a robust evidence base, and in line with the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease, that a plant-predominant dietary pattern can aid in weight loss while reducing cardiovascular co-morbidities.[107] Registered dieticians and health coaches can be helpful in the implementation of these approaches. Additionally, the Primary Prevention Guidelines recommend a period of 30 minutes a day of exercise at a level of breathlessness or its equivalent to aid in weight loss and reduction in cardiovascular morbidity and mortality.[107] Cardiac rehabilitation or structured coaching or exercise programs can aid in success with these lifestyle initiatives.

In individuals without HF, behavioral interventions, including caloric restriction, specific diets, and increases in physical activity, are associated with 1-year weight loss of 5% to 10% with wide variation across trials, even with similar interventions.[108] This variability likely reflects differences in adherence, metabolic adaptations, and genetic predisposition. Importantly, although this degree of weight loss may not resolve obesity, it has been associated with improvements in physical function,[109,110] prevention of/improvement in type 2 diabetes,[111,112] improved BP control,[113] improvements in cardiometabolic biomarkers,[113] and risk of cardiovascular events.[114]

Furthermore, although intentional weight loss via behavioral changes is challenging to achieve and sustain, when successful, it is associated with reduced cardiovascular risk and improved HF severity.[109,114,115] In the Look AHEAD (Action for Health in Diabetes) trial, 5,145 individuals with overweight or obesity and type 2 diabetes were randomized to an intensive lifestyle intervention, including caloric restriction and increased physical activity (intervention group) or diabetes support and education (control group).[115] Although individuals in

the intervention group had greater weight loss at 1 year (8.6% vs 0.7% in the control group), these differences were largely attenuated over time (6.0% vs 3.5% weight loss at a median follow-up of 9.6 years), suggesting inadequate long-term sustainability of behavioral interventions.

Although the Look AHEAD trial overall demonstrated no cardiovascular benefit (composite of cardiovascular death, nonfatal myocardial infarction [MI], nonfatal stroke and hospitalization for angina), those individuals who achieved ≥10% weight loss at 1 year had a 21% reduction in cardiovascular events, suggesting a potential threshold effect for cardiovascular benefit. Notably, 92% of those achieving ≥10% weight loss at 1 year had been assigned to the intensive lifestyle intervention arm, reinforcing the importance of structured weight loss programs.[114] Of note, achievement of optimal cardiometabolic health (including improvement in waist circumference, BP, HbA1c, and kidney function) was associated with lower HF risk.[116]

Similar findings have been observed in HFpEF. In a single-arm study of individuals with HFpEF and obesity undergoing a 15-week weight management program with meal replacements, weekly visits, and weight checks, only two-thirds of individuals completed the program, although 74% of those individuals lost >5% of their body weight. Individuals who did lose weight had improved 6-minute walk distance and quality of life, and improvements were highly correlated with the degree of weight loss.[109] These observations suggest that, although difficult to achieve, intentional weight loss via behavioral changes reduces cardiovascular risk and, among individuals with HFpEF, improves functional status and symptom burden.

Exercise is not an effective sole strategy for weight loss, although it does improve functional status in individuals with HF, and specifically HFpEF, and assists in the maintenance of weight loss in individuals of high cardiovascular risk. In a study of 100 older adults with HFpEF and obesity randomized in a 2 × 2 factorial design to 20 weeks of calorie restriction, exercise, or both, exercise alone was not associated with significant decreases in weight.[3] However, exercise provided additive benefits when combined with calorie restriction in functional capacity measured by maximal oxygen consumption. Exercise is also a strong predictor of successful weight loss maintenance over time. In one study, individuals who maintained an average weight loss of 13.6 kg for 5.8 years had exercised an average of 2,620 kcal/wk (~70 min/d of moderate intensity exercise).[117]

No evidence exists to support any single diet for weight loss; however, adherence to Mediterranean-style diets, particularly those supplemented with extra virgin olive oil or nuts, is associated with improved long-term weight maintenance and cardiovascular risk reduction.[118] A ketogenic diet may be effective for weight loss and may lower HF hospitalization risk in individuals with obesity and HF, although applicability and long-term safety (particularly for those who are taking sodium-glucose cotransporter 2 inhibitors) remain uncertain.[119] In individuals with HF, several small studies indicated that a high-protein diet may result in greater weight loss, improvement in cardiometabolic markers, functional status, and quality of life compared with a standard or low-protein diet.[120,121] However, the measured benefit is small, underscoring the difficulty of achieving meaningful weight loss through behavioral interventions.[122]

Consensus recommendations

- Behavioral changes aimed at intentional weight loss are appropriate to attempt for individuals with obesity because even modest changes in body weight can result in improvements in risk of cardiovascular events, although weight loss is often unsustainable.
- Exercise can improve functional status in individuals with HFpEF.

Pharmacologic interventions

Pharmacologic interventions for obesity have been hampered historically by inadequate efficacy or safety.[123,124] Fenfluramine, dexfenfluramine, sibutramine, and lorcaserin were withdrawn from the market because of safety concerns.[123,124] Currently available, FDA-approved, second-generation agents including orlistat, phentermine/topiramate, and naltrexone/bupropion have minimal efficacy and limited adverse effects, particularly in individuals with HF. However, the third-generation weight-loss medications have altered the pharmacotherapy landscape. These agents are more effective than lifestyle interventions and less risky than invasive procedures with increasing evidence of cardiovascular benefit in individuals with HFpEF. Of note, these agents have not been studied in individuals with HFrEF with safety concerns specifically for liraglutide potentially increasing the risk of hospitalizations for HF and arrhythmias in individuals with advanced HFrEF.[125-127]

Clinical trial summary of AOM in obesity-related HF

Semaglutide, a GLP-1 receptor agonist, and tirzepatide, a dual GIP/GLP-1 receptor agonist, have been evaluated in individuals with symptomatic HFpEF and BMI ≥30 kg/m^2 in 3 pivotal trials: the STEP-HFpEF program, comprising 2 trials separated by the inclusion of individuals with[128] or without[4] type 2 diabetes; and the SUMMIT trial.[5]

In the STEP-HFpEF program,[129] 1,145 individuals with EF ≥45% were randomized semaglutide or placebo, administered to target 2.4 mg once weekly for 52 weeks.

TABLE 3 Summary of Trials of Contemporary AOM in HF

	STEP-HFpEF (N = 1,145)	SUMMIT (N = 731)
Trial design		
Inclusion criteria		
Age, y	≥18	≥40
LVEF, %	≥45	≥50
NYHA functional class	II-IV	II-IV
KCCQ-CSS	<90	≤80
6MWD, m	≥100	100-425
BMI, kg/m^2	≥30	≥30
Additional criteria, at least 1 of:	a. Elevated filling pressure (hemodynamic) b. NT-proBNP ≥220 pg/mL (≥600 if AF); if BMI <35 (≥125/≥375 pg/mL if BMI >35) *and* LAE, LVH, Doppler evidence of elevated filling pressure, or elevated PASP c. Hospitalization for HF in prior 12 months *and* LAE, LVH, Doppler evidence of elevated filling pressure, or elevated PASP	a. Elevated filling pressure (hemodynamic or Doppler) b. NT-proBNP >200 pg/mL (>600 if AF) c. LAE *and* 1) eGFR <70 mL/min/1.73 m^2 *or* 2) Decompensated HF in prior 12 mo
Key exclusion criteria	■ End-stage kidney disease ■ Prior or planned bariatric surgery ■ Type 1 diabetes mellitus ■ History of pancreatitis ■ Multiple endocrine neoplasia	■ eGFR <15 mL/min/1.73 m^2 ■ Prior or planned obesity surgery ■ Type 1 diabetes mellitus ■ History of pancreatitis ■ Multiple endocrine neoplasia ■ Heart rate >100 bpm (>110 if AF)
Intervention and dose	Semaglutide SC injection once weekly Starting dose, 0.25 mg Maximum dose, 2.4 mg 5 dose steps/16 wk (0.25, 0.5, 1.0, 1.7, and 2.4 mg)	Tirzepatide SC injection once weekly Starting dose, 2.5 mg Maximum dose, 15 mg 6 dose steps/20 wk (2.5, 5, 7.5, 10, 12.5, and 15 mg)
Primary endpoints	■ Change in KCCQ-CSS (baseline, 52 wk) ■ Change in body weight (baseline, 52 wk)	■ Change in KCCQ-CSS (baseline, 52 wk) ■ Time to first composite of worsening HF event or cardiovascular death
Key secondary endpoints	■ Change in 6MWD (baseline, 52 wk) ■ Hierarchical composite outcome ■ Change in hs-CRP (baseline, 52 wk)	■ Change in 6MWD (baseline, 52 wk) ■ Change in body weight (baseline, 52 wk) ■ Change (%) in hs-CRP (baseline, 52 wk)
Baseline characteristics		
Age, y	69	65
Women, %	48	54
Black/African American, race, %	3.4	4.9
Hispanic/Latino, ethnicity %	9.8	54
NYHA functional class II, %	69	72
LVEF, %	57	61
KCCQ-CSS	59	52
6MWD, m	295	303
Waist circumference, cm	120	120
BMI, kg/m^2	37	38
NT-proBNP, pg/mL	472	~183
eGFR, mL/min/1.73 m^2	69	64
AF, %	45	25
Type 2 diabetes mellitus, %	54	48
Diuretic, %	81	74
ACEI/ARB/ARNI,* %	79	80
MRA	34	35
Beta-blocker	81	69
SGLT2 inhibitor	19	17

Continued on the next page

TABLE 3 Continued

	STEP-HFpEF (N = 1,145)	SUMMIT (N = 731)
Outcomes		
Follow-up, wk	Fixed 52	Median 104
Placebo-corrected mean change (95% CI)		
KCCQ-CSS points (out of 100)	7.5 (5.3-9.8)	6.9 (3.3-10.6)
Weight, %	-8.4 (-9.2 to -7.5)	-11.6 (-12.9 to -10.4)
6MWD, m	17.1 (9.2-25.0)	18.3 (9.9-26.7)
Waist circumference, cm	-7.6 (-8.7 to -6.6)	N/A
Systolic BP, mmHg	-2.9 (-4.9 to 0.9)	-4.7 (-6.8 to -2.5)
hs-CRP, %	-36 (-44 to -28)	-35 (-46 to -22)
NT-proBNP, %	-8 (-26 to -9)	-10 (-21 to 1)
Clinical events		
First HF event, active vs placebo, n	8 vs 30	29 vs 52
HR (95% CI)	0.27 (0.12-0.56)	0.54 (0.34-0.85)
First HF event or CV death, active vs placebo, n	10 vs 32†	36 vs 56
HR (95% CI)	0.31 (0.15-0.62)	0.62 (0.41-0.95)
Cardiovascular death, active vs placebo, n	2 vs 5	8 vs 5
All-cause death, active vs placebo, n	8 vs 14	19 vs 15

*Including sacubitril/valsartan.
†Only reported for STEP-HFpEF Diabetes.

6MWD = 6-minute walk distance; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AOM = anti-obesity medications; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BP = blood pressure; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EF = ejection fraction; HF = heart failure; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MRA = mineralocorticoid antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; SC = subcutaneous; SGLT2 = sodium-glucose cotransporter-2.

In the SUMMIT trial, 731 trial participants with or without type 2 diabetes and EF ≥50% were randomized to tirzepatide or placebo, to target 15 mg once weekly for a median follow-up of 104 weeks.[5]

In the STEP-HFpEF program, semaglutide improved quality of life by Kansas City Cardiomyopathy Questionnaire scores and functional capacity by 6-minute walk distance.[4,52,129] Semaglutide and tirzepatide were also associated with substantial weight loss, greater overall improvement in New York Heart Association functional class, and decreases in BP, NT-proBNP levels, and high-sensitivity C-reactive protein (Table 3).[4,5,128,129] The SUMMIT trial extended these observations with a co-primary endpoint of time-to-first composite of a worsening HF event or cardiovascular death. In the SUMMIT trial, tirzepatide was associated with a significant reduction in HF events, although the numbers of events were too small to offer a conclusive assessment of HF benefit.

The benefit of semaglutide and tirzepatide on "hard" clinical endpoints remains unclear, although the SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) trial offers insight. In 17,604 individuals with cardiovascular disease and BMI >27 kg/m^2, semaglutide was associated with 10.2% weight loss over 208 weeks, as well as a reduction in the primary composite endpoint of cardiovascular death, MI, and stroke.[16] Of the 24% of individuals with HF at baseline, the benefit of semaglutide was comparable to that of the entire trial population with an additional reduction in a composite HF outcome (cardiovascular death or hospitalization or urgent hospital visit for HF).[130] However, 90% of participants with baseline HF were New York Heart Association class I-II.

Role of AOM in HFpEF with obesity

The generalizability of the demonstrated clinical trial benefit to the real-world population of HFpEF and obesity is not clearly established. The inclusion criteria were complex and included indicators of congestion that may not be routinely assessed in clinical practice such as echocardiographic evidence of elevated filling pressures (Table 3). Second, the baseline characteristics indicate that the trial population differed in multiple aspects from that of other contemporary HFpEF trials,[131-134] including relatively younger individuals with higher EFs, higher BMI, lower NT-proBNP, and lower baseline Kansas City Cardiomyopathy Questionnaire scores (Table 3), although this may be a strength because this population may be more representative of clinical practice.

TABLE 4 Evidence-Based Approach to Patient Selection for FDA-Approved AOM Therapies Studied in HF

FDA-approved indications	Benefits based on clinical trials	Use with caution	Contraindications
Semaglutide ■ CVD and either obesity or overweight ■ Overweight with 1 weight-related comorbidity ■ Type 2 diabetes **Tirzepatide** ■ Overweight with 1 weight-related comorbidity ■ Obesity with sleep apnea ■ Type 2 diabetes	■ Adults ■ NYHA functional class II-IV symptoms ■ EF ≥45% (semaglutide) or EF≥50% (tirzepatide) ■ Additional criteria (at least 1 of): ○ Elevated left ventricular filling pressures ○ Elevated NT-proBNP HF decompensation in the prior 12 mo	■ HF with EF <45% ■ History of pancreatitis ■ Diabetes-related retinopathy ■ Use of insulin (monitor for hypoglycemia) ■ History of hypoglycemia ■ Suicidal ideation or behavior	■ Personal or family history of medullary thyroid cancer ■ Personal or family history of multiple endocrine neoplasia type 2 ■ Pregnancy or breast feeding ■ Type 1 diabetes

AOM = anti-obesity medications; CVD = cardiovascular disease; EF = ejection fraction; FDA = U.S. Food and Drug Administration; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

With these caveats, the current evidence suggests that, in people with BMI ≥30 kg/m² and HF with EF ≥45% (semaglutide) and EF ≥50% (tirzepatide), weight loss is associated with improvements in symptoms and functional capacity. An evidence-based approach to patient selection is shown in Table 4.

Monitoring of AOM in obesity-related HFpEF

The integration of AOM in obesity-related HF requires structured monitoring across initiation, titration with metabolic and HF-specific surveillance, and long-term follow-up to ensure safety and efficacy[36] (Figure 2). Pre-initiation assessment ensures clinical stability, postponing therapy in individuals with recent HF decompensation or arrhythmias, and baseline laboratory evaluation with kidney function, electrolytes, and HbA1c.

Adverse events reported in the trials were predominantly gastrointestinal, including nausea, vomiting, decreased appetite, constipation, and diarrhea. Other notable adverse effects include the potential for acute kidney injury from gastrointestinal-induced volume depletion, hypoglycemia in individuals with diabetes receiving insulin or insulin secretagogues, and rarely acute gallbladder disease, pancreatitis, and hypersensitivity reactions. Nonetheless, with the gradual dose uptitration approach used in the trials, overall discontinuation rates were only slightly more frequent in the active treatment group.

During early-phase gradual dose escalation, which occurs every 4 weeks, monitoring including kidney function and electrolyte reassessment with adjustment of diuretics, antihypertensive agents, and antihyperglycemic agents may be conducted as indicated, particularly if gastrointestinal adverse effects are prominent. In this situation, careful attention to hypovolemia and electrolyte imbalances is essential. For insulin-dependent individuals, glucose should be monitored to avoid hypoglycemia, in coordination with the clinician responsible for diabetes management.

Although the absolute relationship between weight loss and cardiovascular benefit with AOM remains unclear, in individuals with obesity who do not achieve at least 5% weight loss by 1 year, additional weight loss interventions are often pursued.

Consensus recommendations

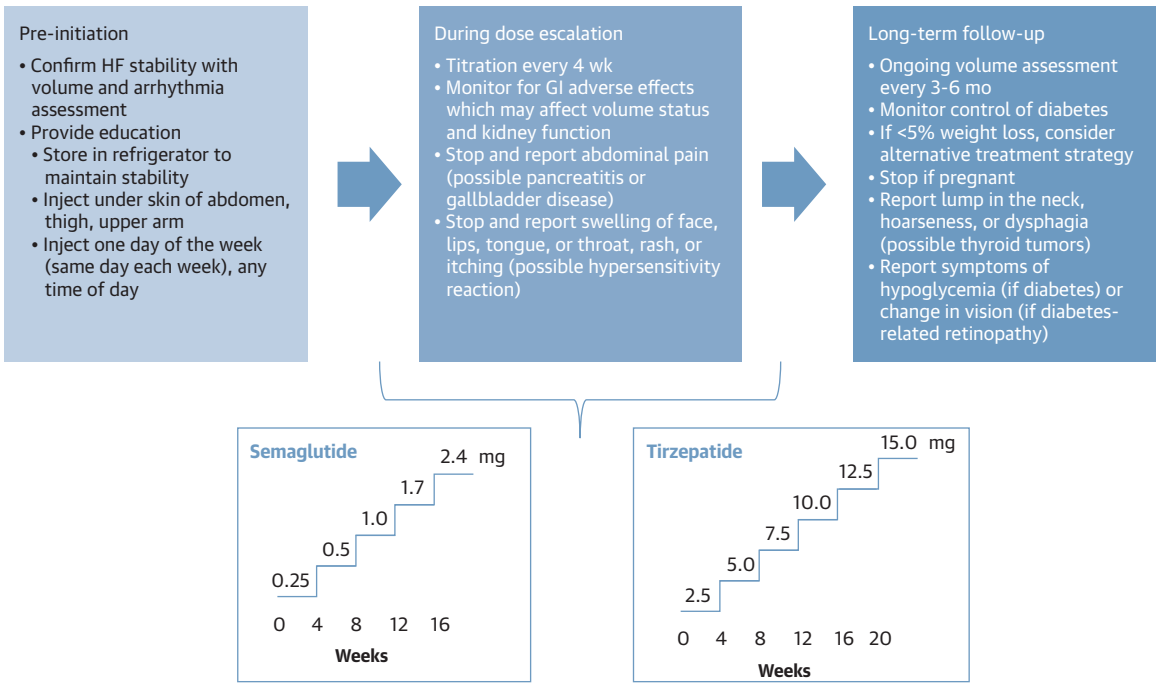
- The STEP-HFpEF program and SUMMIT trial show that, in people with BMI ≥30 kg/m² and HF with EF ≥45% (semaglutide) and EF ≥50% (tirzepatide), weight loss is associated with improvements in symptoms and functional capacity.
- Insufficient evidence exist to date to confidently conclude that semaglutide and tirzepatide reduce HF events in individuals with HFpEF and obesity (with stronger evidence for tirzepatide), although exploratory analysis indicates favorable changes in biomarkers and imaging parameters suggesting potential distinct mechanistic advantages outside of weight loss.
- During early-phase gradual dose escalation of semaglutide or tirzepatide, which occurs every 4 weeks, monitor kidney function and electrolytes with adjustment of diuretics, antihypertensive agents, and antihyperglycemic agents as indicated, particularly if gastrointestinal adverse effects are prominent.

Invasive interventions

Invasive interventions for weight loss include metabolic and bariatric surgery (MBS) and endoscopic metabolic and bariatric therapies (EMBT).[135-137] The most common MBS comprises Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding. EMBT, including gastric balloon and endoscopic sleeve gastrectomy, are less routinely used.

Among MBS, Roux-en-Y gastric bypass is most effective with an average 31% weight loss at 1 year; 70% of individuals maintain this weight loss at 10 years.[135] Sleeve gastrectomy confers average weight loss of 23% at 1 year, with 18% weight loss maintained at 4 years.[135] EMBT

FIGURE 2 **Management Considerations Across Phases of AOM Administration**



AOM = anti-obesity medications; GI = gastrointestinal; HF = heart failure.

methods offer an expected weight loss at 1 year of 12% to 15% with gastric balloon and 13% to 16% for endoscopic sleeve gastrectomy, although many recipients require long-term adjunctive therapies to sustain weight loss.[136,137] Gastric balloons are also limited by migration and symptom burden; up to 17% of recipients require removal because of adverse effects.[138] Current indications for MBS and EMBT include BMI ≥35 kg/m^2 (27.5 kg/m^2 in Asian individuals) or BMI ≥30 to 34.9 kg/m^2 with metabolic disease.[139]

There are no randomized trials of MBS and EMBT in individuals with HF. In individuals without established HF, MBS is associated with improved cardiac structure and mechanics[140,141] and lower risk of subsequent incident HF of almost 50%.[142-146] MBS is also associated with significant reductions in cardiovascular death, MI, and stroke, and significant improvements in cardiometabolic risk markers including systolic BP, total cholesterol, high-density lipoprotein, and HbA1c.[144,146-149]

Among individuals with established HF, MBS is associated with a decreased risk for hospitalization with HF and death during hospitalization for HF.[140,150-153] Of note, in a self-controlled case series of 524 individuals with HF undergoing MBS, a lower rate was observed for urgent visits and hospitalization for HF in the 2 years following MBS compared with the 2 years before MBS.[151] In addition, among individuals hospitalized for HF, those who had previously undergone MBS had a significantly lower risk of inpatient death than those with obesity without a previous MBS.[153] Although these analyses included weighting for between-group differences, individuals with MBS are often younger with fewer comorbidities. These analyses are therefore limited by a relatively high risk for residual confounding, and randomized controlled trials are needed to fully understand the effect of MBS on HF outcomes.

Additionally, despite evidence of cardiovascular benefit, individuals with HF have higher postoperative risks from MBS.[154-156] In analyses from the National (Nationwide) Inpatient Sample database, individuals with HF undergoing MBS had higher inpatient death rates; 3-fold for HFrEF and 1.5-fold for HFpEF, compared with individuals without HF.[156] Individuals with HF were also more likely to experience postoperative MI, pulmonary edema, atrial fibrillation, acute kidney injury requiring dialysis, respiratory failure, and sepsis. Although these

findings do not preclude MBS for individuals with HF, they do underscore the importance of patient selection and type of MBS. Individuals with HF should be appropriately stabilized with optimal medical therapy. Ensuring the availability of clinicians with HF experience at MBS centers could mitigate the perioperative HF risk.

Individuals with obesity and advanced HF, particularly those with left ventricular assist devices (LVADs), represent a unique patient subgroup. Individuals with obesity and LVADs experience higher rates of driveline infections, device thromboses, and neurologic events compared with individuals without obesity.[157] Historically, a BMI of ≥35 kg/m^2 has also been regarded as a barrier to heart transplant, leading individuals with obesity and LVADs to pursue weight loss to enable transplant eligibility.[157] As a result, understanding the safety and effectiveness of weight loss interventions is important in this group with case reports indicating feasibility,[158] although such surgeries are ideally undertaken only in centers with expertise in both high-risk MBS and HF.

Consensus recommendations

- For individuals with HF and obesity, MBS appears effective for intentional weight loss and potentially to reduce risk of HF events, including hospitalization for HF and death, although these possibilities are based only on data from observational studies.
- Individuals with HF who are undergoing MBS have an increased risk of postoperative cardiovascular morbidity and death, suggesting the need for preoperative optimization and perioperative care by clinicians with expertise in HF management.

EVIDENCE GAPS AND FUTURE DIRECTIONS

Numerous programs are now planned or are underway to investigate the effect of obesity treatments on clinical outcomes across a wide spectrum of cardiovascular disease states (**Table 5**).[159,160] Despite this enthusiasm, many questions remain.

What intentional weight loss strategy offers the greatest HF benefit?

There is no randomized controlled trial evidence regarding prognostic impact of intentional, nonmedication-based weight loss in individuals with HF. In a systematic review that compared studies of lifestyle intervention (n = 9), pharmacotherapy (n = 3; semaglutide or orlistat), or MBS (n = 10) in individuals with overweight or obesity and HF,[6] lifestyle intervention offered minimal adverse events and improvement in HF symptoms in both HFpEF and HFrEF. In another observational analysis of individuals with HF undergoing MBS or receiving GLP-1 receptor agonist, versus matched referents, both groups experienced a reduction in death, HF hospitalization, and weight compared with their respective matched referents.[146]

One emerging concern with AOM is the development of sarcopenic obesity, a condition characterized by the coexistence of low skeletal muscle mass (sarcopenia) and increased body fat. This poses a significant health risk particularly in older adults.[163,164] Trials of semaglutide and tirzepatide have not specifically included individuals with sarcopenic obesity, although body composition data suggest that up to one-third of weight lost within the treatment arms of STEP-1 (Semaglutide Treatment Effect in People) and SURMOUNT-1 (A Study of Tirzepatide [LY3298176] in Participants With Obesity or Overweight) was lean mass, as opposed to fat mass.[165,166] The key objectives in treating sarcopenic obesity are to combine exercise and nutritional interventions with the aim of reducing adipose tissue while preserving and ideally increasing muscle mass and function. Whether AOM can safely achieve this goal is not established and underscores the importance of studying concomitant behavioral interventions.

Thus, the sparse available data would suggest that intentional weight loss by any means might be expected to be associated with HF benefit, although behavioral interventions are less effective, and invasive approaches may offer greater risk.

What is the mechanism of benefit from AOM in HFpEF?

Whether the benefits of semaglutide and tirzepatide in obesity-related HF are attributable to weight loss or another mechanism distinct to the action of these therapies is not established and the subject of ongoing investigation (NCT05371496). The extent of weight loss likely mediates benefit,[167] although there may be distinct mechanistic advantages given observed improvements in diastolic function[168] and reductions in left ventricular mass and paracrine adipose tissue.[69] Semaglutide and tirzepatide are also associated with favorable effects on high-sensitivity C-reactive protein, estimated glomerular filtration rate, urine albumin-creatinine ratio, NT-proBNP, and high-sensitivity troponin.[169]

Furthermore, it is uncertain whether the encouraging findings from STEP-HFpEF and SUMMIT will be confirmed with a statistically robust, long-term reduction in cardiovascular death and hospitalization for HF and whether such benefits would be expected in those who are overweight (but who do not have obesity) or even be seen in those with normal BMI.[170]

TABLE 5 Weight-Loss Medications Currently Undergoing Evaluation

Medication	Mechanism of Action	Administration	Ongoing Trials		
			Name	Population	Endpoints
Semaglutide	GLP-1RA	Oral	SOUL NCT03914326	9,650 persons with T2DM and either CKD or ASCVD (no BMI requirement)	14% reduction in a composite of cardiovascular death, nonfatal MI and nonfatal stroke[161]
Semaglutide	GLP-1RA	Subcutaneous	CAMEO-SEMA NCT05371496	81 persons with BMI ≥30 kg/m^2 and HFpEF	Change in PCWP during exercise Estimated completion, August 2026
Tirzepatide	GLP-1R/GIP RA	Subcutaneous	SURMOUNT-MMO NCT05556512	15,374 persons with BMI ≥27 kg/m^2 and established atherosclerotic disease	Composite endpoint of death, MI, stroke, coronary revascularization and HF Estimated completion, October 2027
			SURPASS-CVOT NCT04255433	13,299 persons with BMI ≥25 kg/m^2 and established ASCVD (vs dulaglutide)	Noninferiority study for a composite of cardiovascular death, MI, and stroke Estimated completion, June 2025
Cagrilintide/ semaglutide	GLP-1RA/ amylin analogue	Subcutaneous	REDEFINE 3 NCT05669755	Goal 7,000 persons with BMI ≥25 kg/m^2 and ASCVD	Cardiovascular death, nonfatal MI, nonfatal stroke Estimated completion, October 2027
Orforglipron	GLP-1RA	Oral	ACHIEVE-4 NCT05803421	2,649 persons with BMI ≥25 kg/m^2 and T2DM with ASCVD or CKD (vs insulin glargine)	Composite outcome of cardiovascular death, HF event, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina Estimated completion, January 2026
Danuglipron	GLP-1RA	Oral	NCT04707313	628 persons with BMI ≥30 kg/m^2 without T2DM	Not published, reported 11.7% weight loss at 32 wk in persons with obesity and without T2DM; 50% discontinuation
Dapiglutide	GLP-1/GLP-2 RAs	Subcutaneous	DREAM NCT05788601	54 persons with BMI ≥30 kg/m^2	Not published; mean weight loss of up to 4.3% after 12 wk
Survodutide	GLP1-R/GCG RA	Subcutaneous	SYNCHRONIZE-CVOT NCT06077864	4,935 persons with BMI ≥27 kg/m^2 with ASCVD or 2 weight-related complications; or BMI ≥30 kg/m^2 with ASCVD or CKD or 2 weight-related complications	Composite outcome of cardiovascular death, nonfatal stroke, nonfatal MI, coronary revascularization or HF event Estimated completion, July 2026
Retatrutide	GLP-1/GIP/ GCG RA	Subcutaneous	TRIUMPH-3 NCT05882045	Goal 1,800 persons with BMI ≥35 kg/m^2 and ASCVD	Change in BMI Estimated completion, February 2026
Maridebart cafraglutide	GIP-RA and 2 GLP-1RAs	Subcutaneous (dosing monthly or less)	Maritime Program NCT05669599	592 persons with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with 1 weight-related comorbidity	Not published, reported ∼20% weight reduction without plateau at 52 wk; 11% discontinuation
Pemvidutide	GLP-1/GCG RA	Subcutaneous	MOMENTUM NCT05295875	391 persons with BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least 1 obesity-related comorbidity and without T2DM	Not published, 15.6% weight loss at 48 wk, 78% from adipose tissue
HU6	Controlled metabolic accelerator	Oral	HuMAIN-HFpEF NCT05284617	66 persons aged ≥30 y with BMI ≥30 kg/m^2	Reduction in body weight, total fat mass, and visceral adiposity while sparing skeletal muscle without improvement in peak volume of oxygen consumption[162]

ACHIEVE-4 = A Study of Daily Oral Orforglipron (LY3502970) Compared With Insulin Glargine in Participants With Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAMEO-SEMA = Evaluation of the Cardiac and Metabolic Effects of Semaglutide in Heart Failure With Preserved Ejection Fraction; CKD = chronic kidney disease; DREAM = Dutch Randomized Endovascular Aneurysm Management; GCG RA = glucagon receptor agonist; GIP-RA = glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1RA = glucagon-like peptide-1 receptor agonists; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HuMAIN-HFpEF = Exploratory Phase 2A, Double-Blind, Placebo-Controlled Dose Escalation Study of Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of HU6 for Subjects With Obese HFpEF; MI = myocardial infarction; MOMENTUM = Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3; PCWP = pulmonary capillary wedge pressure; REDEFINE 3 = A Research Study to See the Effects of CagriSema in People Living With Diseases in the Heart and Blood Vessels; SOUL = Semaglutide Cardiovascular Outcomes Trial; SURMOUNT-MMO = A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity; SURPASS-CVOT = The Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes; SYNCHRONIZE-CVOT = A Study to Test the Effect of Survodutide [BI 456906] on Cardiovascular Safety in People With Overweight or Obesity; T2DM = type 2 diabetes mellitus; TRIUMPH-3 = A Study of Retatrutide (LY3437943) in Participants With Obesity and Cardiovascular Disease.

Will more potent AOM be associated with more weight loss and greater HF benefits?

The dual GLP-1 receptor/GIP agonist tirzepatide is associated with greater weight loss than the single GLP-1 receptor agonist semaglutide.[4,5,171] A trial of individuals with obesity treated with tirzepatide or semaglutide (SURMOUNT-5; A Study of Tirzepatide in Participants With Obesity or Overweight With Weight Related Comorbidities) reported that the average weight loss was greater in those treated with tirzepatide (20.2% vs 13.7% at 72 weeks)[171]; this study did not specifically assess individuals with HF. Additional therapies with different mechanisms of action are being explored (Table 5).[172] It remains unclear at present whether more potent weight

loss effects would be expected to exert even more HF benefit and what degree weight loss will confer the greatest benefit; well-powered outcome trials are needed to answer these questions.

Will AOM improve outcome in individuals with HFrEF?

Beyond the relatively stable populations of study participants with HFpEF, the benefit of AOM is not clear. Given the potential gastrointestinal intolerances with possible deleterious effects on BP and volume status, a better understanding of safety and efficacy of AOM in individuals with recently decompensated HF is needed.

Additionally, the potential effects of some AOM on those with HFrEF are of specific importance. Two smaller trials in individuals with HFrEF using liraglutide,[125-127] and a post hoc analysis of individuals with T2DM and HF treated with exenatide raised concerns about the safety of GLP-1 receptor agonist in HFrEF,[173] possibly attributed to the increase in heart rate from these medications.[174] In contrast, larger cardiovascular outcomes trials did not identify risk for worse outcomes in those with HFrEF treated with liraglutide[175] or semaglutide.[130] Accordingly, the safety and efficacy of AOM in those who have obesity in HFrEF requires further investigation.

What is the role of cardiometabolic clinic in HF care?

Cardiometabolic conditions encompass a spectrum of related systemic diseases, including obesity, T2DM, dyslipidemia, metabolic dysfunction-associated steatotic liver disease, and chronic kidney disease, all of which share common pathological mechanisms and significantly contribute to the risk and progression of HF. Cardiometabolic clinics serve as a dedicated, multidisciplinary platform for the early detection, prevention, and comprehensive management of these conditions to mitigate their cardiovascular impact. These clinics integrate cardiology, endocrinology, nutrition, and behavioral therapy involving physicians, advanced practice professionals, pharmacists, and registered dieticians to optimize metabolic risk factors, personalize treatment strategies, including lifestyle interventions, pharmacotherapy (including titrating and tapering medications), and metabolic procedures, and provide structured follow-up to improve long-term outcomes.

By addressing the intersection of metabolic disease and HF, cardiometabolic clinics offer a targeted approach to improving symptom burden, functional status, and disease trajectory. However, widespread implementation remains challenging because of variations in clinical infrastructure, the need for standardized protocols, reimbursement limitations, and gaps in evidence guiding best practices for integration into HF care. Further research is needed to establish their role in routine management and optimize models of care delivery.[176]

CONCLUSIONS

Obesity confers increased risks of HF, coronary artery disease, and stroke[1,2] and weight loss can reduce cardiovascular disease risk.[177,178] Given emerging evidence of the benefits of semaglutide and tirzepatide in individuals with HFpEF and obesity in concert with healthy behavioral interventions, clinicians should be aware of optimal diagnosis, risk assessment, and management of obesity in individuals with HF. An essential future priority will be providing equitable access through policies and systems to ensure that individuals with adverse SDOH have access to evidence-based AOM, particularly so that we can avoid the unintended consequence of further exacerbating health inequities.[179,180] With accurate evaluation of obesity as well as administration and monitoring of safe and effective interventions, clinicians may improve quality of life and functional capacity and potentially reduce HF events in individuals living with HF and obesity.

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APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2025 ACC SCIENTIFIC STATEMENT ON THE MANAGEMENT OF OBESITY IN ADULTS WITH HEART FAILURE

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Michelle M. Kittleson, Chair	Smidt Heart Institute, Cedars-Sinai Medical Center—Professor of Medicine and Director of Education in Heart Failure and Transplantation	None	None	None	None	None	None
Emelia J. Benjamin	Boston Medical Center—Jay and Louise Coffman Professor in Vascular Medicine at Boston University Chobanian & Avedisian School of Medicine; Boston University School of Public Health	None	None	None	None	None	None
Vanessa Blumer	Inova Schar Heart and Vascular Institute—Associate Program Director, Cardiology Fellowship; Associate Director, Heart Failure Research; Advanced Heart Failure and Transplant Cardiologist	None	None	None	None	None	None
Josephine Harrington	University of Colorado Anschutz Medical Campus—Assistant Professor, Medicine-Cardiology	■ Novo Nordisk Inc.*	None	None	None	None	None
James L. Januzzi	Harvard Medical School—Hutter Family Professor of Medicine; Baim Institute for Clinical Research, Harvard— Chief Scientific Officer; Massachusetts General Hospital Cardiology Division	■ Abbott Laboratories ■ Abiomed ■ AstraZeneca* ■ Eli Lilly ■ Novartis* ■ Novo Nordisk ■ Prevencio* ■ Roche Diagnostics* ■ Siemens	None	None	■ Abbott Laboratories* ■ AbbVie, Inc. DSMB* ■ Bayer Healthcare Pharmaceuticals (DSMB) ■ CVRx (DSMB)* ■ Janssen Pharmaceuticals, Inc.* ■ Medtronic ■ Takeda Pharmaceuticals North American, Inc. (DSMB)*	■ Imbria* ■ Jana Care*	None

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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
John J.V. McMurray	British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow—Professor of Medical Cardiology	■ Alynylam Pharmaceuticals ■ AnaCardio ■ AstraZeneca Pharmaceuticals ■ Bayer Healthcare Pharmaceuticals ■ Biohaven Pharma ■ Cardurion ■ Chugai Pharma. ■ Cytokinetics ■ DalCor Pharma. ■ Medscape/ Heart Org. ■ Novartis Corporation ■ Protherics Medicine Developments Ltd. ■ Regeneron Pharmaceuticals ■ River Biomedics ■ RyCarma	■ AstraZeneca Pharmaceuticals ■ Centrix Healthcare* ■ Hikma Pharmaceuticals ■ IMEDIC Pharma ■ Intas Pharmaceuticals ■ Lupin Pharmaceuticals, Inc. ■ ProAdWise Communications ■ Radcliffe Cardiology ■ Sun Pharmaceuticals ■ Translational Medicine Academy	None	■ Novartis Corporation*† ■ Roche Pharma*† ■ WCG Clinical Services DSMB	■ Alynylam Pharmaceuticals† ■ AstraZeneca Pharmaceuticals*† ■ Bayer Healthcare Pharmaceuticals† ■ Cardurion† ■ Cytokinetics*† ■ Global Clinical Trial Partners Ltd.*	None
Amanda R. Vest	Cleveland Clinic—Section Head, Heart Failure & Transplant Cardiology, Heart, Vascular and Thoracic Institute	None	None	None	None	None	None

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*Significant relationship.

†No financial benefit.

ACC = American College of Cardiology; DSMB = data and safety monitoring board.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2025 ACC SCIENTIFIC STATEMENT ON THE MANAGEMENT OF OBESITY IN ADULTS WITH HEART FAILURE

Reviewer	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Barry Borlaug, MD, FACC	Mayo Clinic—Professor of Medicine	■ Axon* ■ Boehringer Ingelheim Pharmaceuticals, Inc* ■ BridgeBio Pharmacy* ■ Edwards* ■ Eli Lilly and Company* ■ Janssen Pharmaceuticals, Inc.* ■ Merck & Co., Inc.* ■ NGMBio* ■ ShouTi* ■ VADovations†	None	None	■ AstraZeneca Pharmaceuticals* ■ Corvia* ■ Department of Defense* ■ Medtronic* ■ NIH/NHLBI* ■ Novo Nordisk Inc.* ■ Rivus* ■ Tenax*	None	None
Rudolf A. de Boer. MD. PhD	Erasmus MC, Department of Cardiology, Rotterdam—Chair and Professor of Cardiology	■ Bristol-Myers Squibb Company ■ Novo Nordisk Inc.	■ Abbott Laboratories ■ AstraZeneca Pharmaceuticals ■ Zoll	None	■ Abbott Laboratories† ■ Alnylam* ■ AstraZeneca* ■ Bristol-Myers Squibb Company* ■ Novo Nordisk Inc.*	■ European Research Council† ■ Netherlands Heart Foundation†	None
Olivia Gilbert, MD, MSc	Wake Forest University School of Medicine—Associate Professor, Cardiovascular Medicine	None	None	None	None	None	None
Carl J. Lavie Jr., MD, FACC	Ochsner Heart and Vascular Institute, Ochsner Clinical School—Medical Director, Cardiac Rehabilitation and Preventive Cardiology	■ Amgen Inc.* ■ AstraZeneca Pharmaceuticals ■ Diagnostic and Statistical Manual of Mental Disorders ■ Esperion ■ GOED ■ New Amsterdam	■ Amgen* ■ AstraZeneca ■ Esperion	None	■ Novo Nordisk Inc. (DSMB)*	None	Testosterone replacement therapy and cardiovascular disease, 2023-2024, Defense*

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