Obesity and the Obesity Paradox in Heart Failure

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Abstract

Obesity has reached epidemic proportions in the general population, and is associated with increased risk for the development of new-onset heart failure (HF). However, in acute and chronic heart failure, overweight and mild to moderate obesity is associated with substantially improved survival compared to normal-weight patients. This phenomenon has been termed the “obesity paradox” in HF. The majority of data pertaining to the “obesity paradox” identifies obesity with body mass index; however the reliability of this method has been questioned. Newer studies have explored the use of other measures of body fat (BF) and body composition including waist circumference, waist-hip ratio, skinfold thickness, and bioelectrical impedance analysis of body composition. The relationship between the obesity paradox and cardiorespiratory fitness in HF is also discussed. Finally, this review explores the various potential explanations for the obesity paradox, and summarizes the current evidence and guidelines for intentional weight loss treatments for HF in the obese population.

Brief summary

Obesity has reached epidemic proportions in the general population, and is associated with increased risk for the development of heart failure (HF). However, in acute and chronic HF, obesity is associated with improved survival compared to normal-weight. This has been termed the “obesity paradox”. This review explores HF risk with obesity, potential explanations for the obesity paradox, and summarizes the current evidence and guidelines for intentional weight loss treatments in the obese HF population.
Prevalence of obesity in the general population

Obesity has increased in prevalence in recent years in the United States and worldwide. Between 2009 and 2010 the percentage of obese patients as identified by body mass index (BMI) ≥ 30kg/m$^2$ in the U.S. National Health and Nutrition Examination Survey nearly tripled, from 13.4% to 36.1%. Morbidly obese or super obese individuals with BMI ≥ 40kg/m$^2$ increased by a multiple of 6, from 0.9% to 6.6%. According to the U.S. National Health and Nutrition Examination Survey, more than one third of the U.S. population is obese and the distribution of BMI in the U.S. has drastically shifted towards higher values. Considering the adverse effects of obesity on left ventricular (LV) structure, diastolic and systolic function, and other risk factors for heart failure (HF), including hypertension and coronary artery disease, it is not surprising that HF incidence and prevalence, is increased in obese patients.

Obesity as a risk factor for heart failure

One of the first mentions of a causal relationship between obesity and HF was in 1956 in a case report entitled “Heart Failure due to Extreme Obesity,” An obese woman was described to develop cardiopulmonary failure due to the physical mass of adipose tissue weighing on her chest wall, leading to respiratory failure and subsequently cor pulmonale and death.\(^1\) A similar case was reported in the New England Journal of Medicine in 1957.\(^2\) Whereas early literature highlighted the purely physical effects of obesity on HF, we now understand that the role of obesity in heart failure is complex and that it has adverse effects on LV structure, LV function and other risk factors for HF, including hypertension and coronary artery disease. Salient studies thus far in this field are listed Table 2. In 1992, Kasper et al. first describes “the cardiomyopathy of obesity” based on hemodynamic and endomyocardial biopsy abnormalities associated with marked obesity when compared to lean controls.\(^3\) Analysis of 519 patients showed that body mass index was positively correlated with right heart pressures and cardiac output, pulmonary vascular resistance index and systolic blood pressure. A significantly higher percentage of obese patients were found to have idiopathic dilated cardiomyopathy compared with lean patients. A specific etiology for dilated cardiomyopathy was found in 64.5% of the lean patients compared with only 23.3% of the obese patients. The most common finding on endomyocardial biopsy in the obese group was mild myocyte hypertrophy (67%).

In 2002, Kenchaiah et al. published the first large study demonstrating the association of increased body-mass index and an increased risk of heart failure in 5881 participants of the Framingham Heart Study. BMI was found to correlate with HF risk in a dose-dependent fashion: HF risk increased by 5% in men and 7% in women for each single-unit increase in BMI, even after adjustment for demographics and other known risk factors such as diabetes, hypertension, and cholesterol.\(^4\) This positive correlation between BMI and HF risk for the
obese, and additionally overweight individuals, was confirmed in the larger Physicians’ Health Study of 21,094 men without known coronary artery disease. Overweight participants had a 49% increase in HF risk compared with lean participants and obese participants had a 180% increase (95% CI, 124-250).  

Similar trends have been demonstrated in non-U.S. populations. A study of 59,178 Finnish participants demonstrated the graded link between BMI and HF risk, with multivariate-adjusted hazard ratios of HF for normal, overweight and obese BMI of 1.00, 1.25, and 1.99 for men and 1.00, 1.33, and 2.06 for women, respectively. Levitan and colleagues analyzed two population-based prospective cohorts of 80,630 Swedish men and women; not only higher BMI but higher waist circumference (WC), waist–hip ratio, and waist to height ratio were associated with higher risk of HF hospitalization and mortality.  

In a recently published study in 2014, young adulthood obesity surfaced as an important risk factor for ischemic heart disease and HF without pre-existing ischemic heart disease. A population-based cohort study of 12,850 Danish males was conducted with a 36 year follow up starting at age 22. The 36-year risk was 7.3% for ischemic heart disease and 0.8% for HF without pre-existing ischemic heart disease among men of normal weight and 11.1% and 4.0% among obese men, respectively. Comparing obese men with men of normal weight, the adjusted hazard ratio was 6.68 (95% CI, 2.85-15.66) for HF without pre-existing ischemic heart disease. 

There are several plausible mechanisms for the association of obesity and increased risk for HF. An indirect, but well known and documented mechanism is the effect of obesity on HF through other risk factors. Increased BMI is a risk factor for hypertension, diabetes mellitus, and dyslipidemia, all of which augment the risk of myocardial infarction, an important antecedent of HF. In addition, hypertension and diabetes mellitus independently increase the risk of HF. Elevated BMI has also been shown to be associated with altered left ventricular remodeling, possibly owing to increased hemodynamic load, neurohormonal activation, and increased oxidative stress. Studies have suggested that obesity may have a direct effect on the myocardium by demonstrating loss of cardiac function through cardiac steatosis and lipoapoptosis. In 2013, a study by Graner et al. found that cardiac steatosis is associated with visceral obesity in nondiabetic obese men and suggested that visceral obesity is the best predictor of epicardial and pericardial fat in abdominally obese subjects.  

Notably, obesity is associated with obstructive sleep apnea (OSA) which is associated with incident HF. In a substantial proportion of patients with HF, OSA may play a role in the pathogenesis and progression of cardiac failure through mechanical, adrenergic, and vascular mechanisms. However, more research is required to determine basic mechanisms by which
OSA exerts its adverse effects on the cardiovascular system. Further research is also needed to clarify to what extent obstructive sleep apnea mediates the relationship between obesity and risk of heart failure.

**Structural and functional changes in the heart in obesity**

There is evidence that obesity is associated with structural and functional changes in the heart in both humans and animal models. These changes include but are not limited to left ventricular hypertrophy (LVH) and subclinical impairment of LV systolic and diastolic function and they are thought to be precursors to more overt forms of cardiac dysfunction and HF.\(^1\)

Studies have concluded that obesity is independently associated with LV hypertrophy and both LV cavity size and wall thickness are increased in obese subjects compared with age-matched controls.\(^13,14\) Wall thickness is commonly increased to a greater extent than cavity size, thus there appears to be a slight predominance of concentric cardiac hypertrophy compared with an eccentric pattern of hypertrophy.\(^12\) A few studies suggest that LV mass may be increased in obesity, but that the increase is appropriate for body size if obesity is without common comorbid conditions such as hypertension, diabetes and coronary artery disease.\(^15,16\)

Many studies have evaluated LV systolic function in obesity and the findings of these studies are variable. More recently several studies have found that LV ejection fraction is normal or even supranormal in the majority of obese subjects, even those with severe obesity.\(^13,16\) However, even if the EF is normal, myocardial function is often reduced when it is measured with more sensitive echocardiographic assessments of LV function such as midwall LV fractional shortening, systolic velocity measured with tissue Doppler, or systolic strain rate.\(^15,17,18\)

**Prevelence of obesity in the heart failure population**

The incidence and prevalence of HF and its associated mortality is increasing at alarming rates. Despite the progress made in the development of several new therapies in HF management, the overall 5-year mortality rate for HF remains extremely high at nearly 50%.\(^19\) Studies have determined that up to 32%-49% of HF patients are obese and 31% to 40% are overweight (BMI 25.0-29.9 kg/m\(^2\)).\(^20,21\) A very small proportion of patients with HF are classified as underweight. Patient who are overweight and obese commonly present with signs and symptoms of HF 10 years prior to their leaner counterparts. Of note, obesity is significantly more prevalent in HF patients with preserved ejection fraction as compared to those with reduced ejection fraction.\(^22\)
Obesity and BNP

The role of natriuretic peptides in the clinical expression of chronic HF has been established. Studies have shown that natriuretic peptide levels are reduced in the obese state, partly related to altered clearance receptors and peptide degradation. Mehra et al. compared brain natriuretic peptide (BNP) levels in obese and non-obese patients with respect to New York Heart Association functional class and lean body weight–adjusted peak aerobic oxygen consumption. Plasma levels of tumor necrosis factor-alpha, interleukin-6, and soluble intercellular adhesion molecule-1 were measured in a subset of patients. Levels of BNP were significantly lower in obese than in non-obese subjects (205 ± 22 and 335 ± 39 pg/ml, respectively), despite a similar severity of HF and cytokine levels. Multivariate regression analysis identified BMI as an independent negative correlate of BNP level demonstrating that obesity is an important and independent determinant of peripheral BNP expression in patients with HF. These findings not only speak to the usefulness of BNP as a diagnostic test in obese patients with HF, they also provide insight into certain potential underlying pathophysiologic mechanisms that relate to the development of HF in obese patients. Reduced levels of circulating BNP may lead to early loss of natriuretic-mediated vasodilation, lesser antagonism of the renin-angiotensin system, or loss of natriuretic ability in obese patients.

Obesity and survival in heart failure: the obesity paradox

Although elevated BMI is well established as a risk factor for HF, a surprising relationship between BMI and outcomes in those with established HF has been observed. This unexpected relationship between BMI and survival in HF was first described by Horwich et al. in 2001. Survival data for a cohort of 1,203 advanced systolic HF patients at a single university transplant center was analyzed and revealed that patients with higher BMI (> 27.8 kg/m²) were found to have significantly improved risk adjusted, transplant-free survival. The worst outcomes were seen in the underweight group, followed closely by normal-weight patients. Although elevated BMI is well established as a risk factor for HF, this study revealed that elevated BMI was not a risk factor for increased mortality, but rather was associated with a trend toward improved survival (Figure 2). This counterintuitive epidemiologic association between survival outcomes and traditional risk factors is termed reverse epidemiology or “obesity paradox,” and has now been well documented in numerous studies and in HF literature. In 2005, a subsequent analysis of 7767 stable outpatients with chronic HF enrolled in the Digitalis Intervention Group also revealed lower risk-adjusted mortality rates in the overweight and obese compared to normal-weight patients, with hazard ratios of 0.88 (0.80–0.96) and 0.81 (0.72–0.92), respectively. Another sub-analysis of a large, randomized controlled trial of 7599 patients with symptomatic HF with either reduced or preserved systolic function showed that patients in lower BMI
categories (underweight and normal weight) had a graded increase in the risk of death; the group with the highest BMI (>35 kg/m²) had similar risk to those with a BMI of 30.0–34.9 kg/m²). A meta-analysis of nine observational HF studies (n = 28,209) by Oreopoulos et al. also found that overweight and obese individuals respectively had reduced cardiovascular (−19% and −40%, respectively) and all-cause (−16% and −33%) mortality during 2.7 years of follow-up as compared with those without elevated BMI. Another analysis of BMI and its relationship to in-hospital mortality for 108,927 patients with decompensated HF identified a 10% reduction in mortality for every 5-unit increase in BMI.

The obesity paradox in different heart failure subgroups

The obesity paradox may not be uniform across all populations. Given the heterogeneity of those affected by HF, recent studies have made efforts to better characterize the obesity paradox in specific subgroups. A recent study of 6142 patients across four continents used cox proportional hazards models and net reclassification index to describe associations of BMI with all-cause mortality and found that the protective association of BMI with mortality was confined to persons of age older than 75 (hazard ratio (HR): 0.82), decreased cardiac function (ejection fraction <50%; HR: 0.85), no diabetes (HR: 0.86), and de novo HF (HR: 0.89). Another study by Zamora et al. found that when comparing mortality in obese and non-obese patients with different etiologies of HF, the obesity paradox was only observed in patients with non-ischemic HF.

Recently, the role of gender in HF outcomes was investigated in a prospective study following 2718 patients with HF at a single university center. BMI and WC were measured at baseline and in multivariate analysis revealed that normal BMI and normal WC were associated with higher relative risk for the primary outcome of death, urgent heart transplantation, or ventricular assist device placement in men (BMI 1.34, WC 2.02) and in women (BMI 1.38, WC 2.99). High BMI and WC were associated with improved outcomes in both genders.

Proposed mechanisms for the obesity paradox in heart failure

The exact mechanisms underlying the obesity paradox have not been clearly defined. Several theories exist (Figure 1). A common explanation for the increased survival seen in obese patients with HF is that the additional adipose tissue provides greater reserves against the catabolic changes associated with the disease process that can lead to cardiac cachexia. Cardiac cachexia is a syndrome involving progressive weight loss and alterations in body composition that carries a devastating prognosis in HF as well as in other disease states. In one HF
population, 50% of those with cachexia (defined as a non-intentional documented weight loss of at least 7.5% of previous normal weight over 6 months) had died at 18 month follow-up (HR 3.73; 95% CI 1.93-7.23 compared to those without cachexia). This highlights the possible protective role of adipose tissue in HF, as an energy reserve in the setting of chronic illness. One study from the Cleveland Clinic demonstrated that patients with morbid obesity experienced the highest all-cause mortality/transplant (HR 2.46; 95% CI 1.4-4.30), which was far greater than that of the non-obese group (HR 1.44; 95% CI 1.09-1.91), when both groups were compared to obese study participants. Another explanation for the obesity paradox is that obese patients may experience greater functional impairment and therefore may present earlier in their disease course.

Lastly, one potential explanation for the paradoxical link between obesity and HF is the way that most studies have chosen to identify obesity. For reasons of widespread acceptance and ease of use, BMI has been used to estimate body composition and identify overweight, obese and morbidly obese patients. However the reliability of BMI as a true representation of adiposity has been questioned. Some experts maintain that fat mass distribution, along with cardiorespiratory fitness and total fitness, are more accurate determinants of mortality in HF.

**Identifying obesity: looking beyond BMI to measure adiposity**

There are numerous alternative techniques that may prove to be more accurate to define obesity when compared to BMI (Table 1). These techniques include waist circumference (WC), waist-hip ratio, skinfold estimates of percent body fat (BF), dual X ray absorptiometry (DEXA), and bioelectrical impedance analysis (BIA) of body composition.

WC is an established predictor of cardiovascular risk in the general population and it is also a simple and inexpensive way to assess for abdominal obesity. In 344 patients with HF and systolic dysfunction, Clark et al. analyzed the prognostic value of BMI and WC and found lower total mortality in those patients with higher values of both parameters. In a recent study of 2254 patients in the Spanish Red Nacional de Investigación en Insuficiencia Cardiaca (REDINSCOR) Registry, BMI and WC were found to be independent predictors of lower total mortality in obese and overweight patients with chronic HF; however interestingly, the protective effect of BMI was lost in patients with a WC > 120cm. In future studies, WC should be measured together with BMI to better predict the prognosis of chronic HF.

BIA is another noninvasive, albeit slightly more costly and less readily available, technique to evaluate changes in body composition. In a community-based study in the United Kingdom, 1025 patients with chronic HF underwent BIA; percent BF, fat mass, and fat-free mass were associated with increased risk and percent BF was a significant predictor of mortality in a
multivariable model. A recent study found BIA to be safe for use with pacemakers and defibrillators, broadening its potential use in advanced HF populations. Preliminary data from a study by Horwich et al. that used BIA to assess body composition in 354 HF patients compared the relative contributions of lean body mass (LBM) and body fat mass (BFM) to the obesity paradox. They found that higher fat mass is protective in HF and higher lean mass may be protective in HF, but not significantly. The data also suggests that a body composition of low LBM and low BFM is the least protective in HF, whereas high LBM and high BFM is most protective.

One additional consideration is that DEXA and traditional BIA analysis both assume a constant fluid hydration status, which is likely not the case in the heart failure patient. Vectorial analysis of BIA (BIVA) is a promising method to evaluate body composition in HF patients. BIVA is a pattern analysis of impedance measurements (resistance and reactance) plotted as a vector in a coordinate system and most importantly, it is independent of hydration status. For a more complete understanding of the obesity paradox in HF, further investigations of body composition and outcomes in HF are warranted, keeping hydration status in mind.

**Cardiorespiratory fitness and prognosis in obese heart failure patients**

Cardiorespiratory fitness (CRF), measured as peak oxygen uptake (VO\(_2\)) or minute ventilation (V\(_E\))/carbon dioxide production (VCO\(_2\)), has been identified as an important predictor of survival in HF. Chase et al. studied a cohort of 744 HF patients and found that while obese patients had significantly lower V\(_E\)/VCO\(_2\) slopes than normal and overweight patients, V\(_E\)/VCO\(_2\) was a strong independent predictor of improved survival irrespective of BMI. A more recent study demonstrated that CRF level may actually mitigate or even negate the impact of the obesity paradox in HF. In a study of 2066 patients with systolic HF, Lavie et al. found that BMI was a significant predictor of age- and sex-adjusted survival in the group with low peak VO\(_2\) (< 14mL/O\(_2\)/kg), but not in the high-CRF group. These findings suggest that exercise training to improve CRF is reasonable.

In the largest multicenter randomized controlled study of exercise training in patients with HF, the HF ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial randomized 2,331 patients with HF into groups of standard care or standard care plus regular aerobic exercise training. The study demonstrated that after adjustment for highly prognostic predictors of all-cause mortality, exercise was associated with at least modest improvements in all-cause mortality, hospitalization and cardiovascular mortality. Therefore, exercise appears to be safe and beneficial in terms of improved quality of life for patients with HF.
Clinical implications for weight management in heart failure patients

Despite the potential benefits of weight loss in the prevention of HF, weight loss recommendations for other populations may not be appropriate for patients with established HF. There are no large-scale studies of the safety or efficacy of weight loss with diet, exercise, or bariatric surgery in obese patients with HF. And despite this gap in evidence, the major HF societies have variable recommendations regarding intentional weight loss interventions in HF. The American Heart Association does not have any specific recommendation for weight loss at any level of BMI. The Heart Failure Society of America recommends intentional weight loss for BMI > 30kg/m², and the European Society of Cardiology defers to other guidelines for management of obesity in HF. None of the major societies recommend weight loss for overweight patients with HF. The reasons for these variations are likely related to a lack of data regarding intentional weight reduction and long-term prognosis in HF. Further studies are needed to determine the impact of intentional weight loss in HF patients, including the safety and efficacy of bariatric surgery, which appears to be safe and effective in some small studies.

Conclusions

Obesity is a risk factor for the development of incident HF and population wide HF prevention efforts should include efforts to prevent and treat obesity. However, the association of obesity and improved survival in acute and chronic HF is also well established across multiple measures of adiposity. Further investigation is required for a more complete understanding of this substantial associated survival benefit in HF and the underlying pathophysiology involved (Table 3). A better understanding of the role of CRF in the relationship between obesity and outcomes may lead to better risk assessment. Furthermore, while intentional weight loss is known to improve hemodynamic function and cardiac structure in non-HF patients, additional research is needed to generate evidence-based guidelines for weight management in established HF in the overweight and obese population.
References

15. Iacobellis G. True uncomplicated obesity is not related to increased left ventricular mass and systolic dysfunction. J Am Coll Cardiol 2004;44:2257; author reply 2258.
49. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847.
Figure 1: Proposed pathophysiology of cardiomyopathy in obesity. This diagram shows the central hemodynamic alterations that result from excessive adipose accumulation in severely obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity, duration and severity of adverse LV loading conditions (particularly hypertension) and possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial hypertension from sleep apnea/obesity hypoventilation may be subsequently lead to right ventricular failure.

This figure and associated text adapted from Alpert et al. Impact of Obesity and Weight Loss on Cardiac Performance and Morphology in Adults. Progress in Cardiovascular Diseases, 2014;56:391-400. 51
Figure 2: Risk-adjusted survival curves for the four body mass index (BMI) categories at 5 years. The variables entered into the equation were age, gender, hypertension, diabetes mellitus, left ventricular ejection fraction, hemodynamic variables, peak VO2, mitral regurgitation, tricuspid regurgitation, medications and serum sodium, creatinine and lipid levels. Survival was significantly better for the overweight and obese BMI categories. (Adapted from Horwich et al.)²⁷
Table 1 – Different methods of identifying obesity in the HF population

<table>
<thead>
<tr>
<th>Method</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (BMI)</td>
<td>Widely used and studied</td>
<td>Reliability has been questioned</td>
</tr>
<tr>
<td>Waist circumference (WC)</td>
<td>Increased WC is associated with improved outcomes in advanced HF</td>
<td>Reliability has been questioned</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>Easy to obtain</td>
<td>Not widely studied in HF</td>
</tr>
<tr>
<td>Skinfold estimates of percent body fat (BF)</td>
<td>Increased BF is associated with improved outcomes in HF</td>
<td>Not widely studied in HF</td>
</tr>
<tr>
<td>Bioelectrical impedance analysis (BIA)</td>
<td>Potential to be used at bedside or in clinics</td>
<td>Not readily available</td>
</tr>
<tr>
<td>Dual-energy x-ray absorptiometry (DEXA)</td>
<td>A fairly accurate for assessing body composition</td>
<td>Expensive, requires technical expertise</td>
</tr>
<tr>
<td>Computed tomography (CT) and Magnetic resonance imaging (MRI)</td>
<td>Gold standards for assessing body composition</td>
<td>Expensive, radiation exposure</td>
</tr>
</tbody>
</table>
Table 2 – Select studies of obesity and outcome in patients with heart failure

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Population</th>
<th>NYHA class</th>
<th>Sample size</th>
<th>Mean age, % female</th>
<th>BMI categories reported (kg/m²)</th>
<th>Ottawa-Newcastle Quality Assessment Score (max total 9)</th>
<th>Mean follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bozkurt et al26 2005 (USA)</td>
<td>Post hoc analysis of the DIG database</td>
<td>I-IV</td>
<td>7788</td>
<td>63, 24%</td>
<td>24% Normal 18.5-24.9, overweight 25.0-29.9, obese ≥30</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Butler et al52 2005 (USA)</td>
<td>Post hoc analysis of 2 FDA-approved clinical trials for LVAD placement</td>
<td>IV</td>
<td>222</td>
<td>51, 13%</td>
<td>13% Underweight/low-normal &lt; 23.0, normal 23.0-26.3, overweight 26.4-29.4, Obese ≥29.4</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Cicoira et al53 2007 (Italy)</td>
<td>Post hoc analysis of the Val-HeFT Study</td>
<td>II-IV</td>
<td>4463</td>
<td>63, 18%</td>
<td>18% Underweight/low-normal &lt; 22.0, normal 22.0-24.9, overweight 25.0-29.9, Obese ≥30</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Davos et al54 2003 (UK)</td>
<td>Retrospective, single-center cohort</td>
<td>I-IV</td>
<td>525</td>
<td>61, 17%</td>
<td>17% Nonelevated BMI &lt; 25.0, overweight 25.0-29.0, obese ≥29-34.0, moderately/severely obese ≥34.0</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Gustafsson et al55 2005 (Denmark)</td>
<td>Post hoc analysis of the DIAMOND-CHF study</td>
<td>III-IV</td>
<td>4504</td>
<td>72, 39%</td>
<td>39% Underweight &lt; 18.5, normal 18.5-24.9, overweight 25.0-29.9, obese ≥30</td>
<td>9</td>
<td>6</td>
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<tr>
<td>Kenchaiah et al12 2007 (USA)</td>
<td>Post hoc analysis of the CHARM study</td>
<td>II-IV</td>
<td>7599</td>
<td>66, 32%</td>
<td>32% Underweight/low-normal &lt; 22.5, normal 22.5-24.9, overweight 25.0-29.9, Obese ≥30</td>
<td>9</td>
<td>3</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Age and Sex</td>
<td>BMI Classification</td>
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<tr>
<td>Hall et al. 2005 (USA)</td>
<td>Retrospective 20-hospital integrated health care system</td>
<td>NYHA class not given</td>
<td>2707</td>
<td>Age and sex not reported</td>
<td>Nonelevated BMI &lt; 24.3, overweight 24.4-28.5, obese 28.6-34.1, moderately/severely obese ≥34.2</td>
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<tr>
<td>Kristorp et al. 2005 (Denmark)</td>
<td>Prospective, single-center</td>
<td>I-III (1 patient had IV)</td>
<td>195</td>
<td>69, 28%</td>
<td>28% Nonelevated BMI &lt; 25, overweight 25-29.9, obese ≥30</td>
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<tr>
<td>Lavie et al. 2003 (USA)</td>
<td>Retrospective, single-center cohort</td>
<td>I-III</td>
<td>206</td>
<td>54, 19%</td>
<td>19% Normal 18.5-24.9, overweight 25.0-29.9, obese ≥30</td>
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<tr>
<td>Padwal et al. 2013 (Canada)</td>
<td>Sub-analysis of the MAGGIC meta-analysis</td>
<td>II-III</td>
<td>967</td>
<td>66.8, 32%</td>
<td>Nonelevated BMI &lt; 22.5-24.9, overweight 25-29.9, obese 30-34.9, moderately/severely obese ≥35</td>
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DIG, Digitalis Investigation Group; FDA, Food and Drug Administration; LVAD, Left ventricular assist device; DIAMOND, Danish Investigations of Arrhythmia and Mortality
### Table 3. Major Research Needed to Further Evaluate Obesity and the Obesity Paradox in Heart Failure

<table>
<thead>
<tr>
<th>Research Area</th>
<th>Details</th>
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<tbody>
<tr>
<td>Head to head comparison of the various methods to evaluate body composition</td>
<td>Evaluate body composition in heart failure patients and their associations with outcomes.</td>
</tr>
<tr>
<td>Using methods of body composition analysis, identify whether increased fat</td>
<td>Independent association with improved survival in heart failure.</td>
</tr>
<tr>
<td>mass, lean muscle mass, or both are independently associated with improved</td>
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<tr>
<td>survival in heart failure.</td>
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<tr>
<td>Measure visceral or ectopic fats, including pericardial fat, in heart failure</td>
<td>Correlate with HF characteristics and outcomes.</td>
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<tr>
<td>patients with CT or MRI and correlate with HF characteristics and outcomes.</td>
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<tr>
<td>Further evaluate with the causal association between obstructive sleep</td>
<td>Explore potential mechanisms which may account for the obesity paradox.</td>
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<tr>
<td>apnea, obesity, and incident heart failure.</td>
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<tr>
<td>Explore potential mechanisms which may account for the obesity paradox in</td>
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<td>patients with heart failure and other chronic disease states.</td>
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<tr>
<td>Evaluate in prospective randomized clinical trials if intentional weight</td>
<td>Determine degree therapeutic goals.</td>
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<td>loss results in improved quality of life and clinical outcomes in overweight</td>
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<tr>
<td>and obese heart failure patients.</td>
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<td>Ascertain optimal exercise and dietary recommendations for overweight and</td>
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<tr>
<td>obese patients with heart failure overall and in specific patient populations</td>
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<tr>
<td>based on age, sex, race/ethnicity, ejection fraction group and comorbid</td>
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<td>conditions.</td>
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