Body Mass Index and Adverse Cardiovascular Outcomes in Heart Failure Patients With Preserved Ejection Fraction
Results From the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) Trial

Markus Haass, MD; Dalane W. Kitzman, MD; Inder S. Anand, MD; Alan Miller, MD; Michael R. Zile, MD; Barry M. Massie, MD; Peter E. Carson, MD

Background—Obesity is a major risk factor for incident heart failure (HF). Paradoxically, in HF with reduced left ventricular ejection fraction (HFREF), a high body mass index (BMI) appears to be beneficial. Approximately 50% of HF patients have a preserved left ventricular ejection fraction (HFPEF). However, there are few data regarding the relationship between BMI and outcomes in HFPEF.

Methods and Results—Baseline characteristics and cardiovascular outcomes were assessed in the 4109 patients (mean age, 72 years; mean follow-up, 49.5 months) in the Irbesartan in HF with Preserved Ejection Fraction (I-PRESERVE) trial. Based on the BMI distribution, 5 BMI categories were defined: <23.5, 23.5 to 26.4, 26.5 to 30.9, 31 to 34.9, and ≥35 kg/m². Most patients (71%) had a BMI ≥26.5, 21% had a BMI between 23.5 and 26.4, and 8% had a BMI <23.5 kg/m². Patients with higher BMI were younger, more often women, and more likely to have hypertension and diabetes and higher left ventricular ejection fraction. Patients with BMI of 26.5 to 30.9 kg/m² had the lowest rate for the primary composite outcome (death or cardiovascular hospitalization) and were used as reference group. After adjustment for 21 risk variables including age, sex, and N-terminal pro-brain natriuretic peptide, the hazard ratio for the primary outcome was increased in patients with BMI <23.5 (hazard ratio, 1.27; 95% confidence interval, 1.04 to 1.56; \( P=0.019 \)) and in those with BMI ≥35 kg/m² (hazard ratio, 1.27; 95% confidence interval, 1.06 to 1.52; \( P=0.011 \)) compared with the referent group. A similar relationship was found for all-cause mortality and for HF hospitalization.

Conclusions—Obesity is common in HFPEF patients and is accompanied by multiple differences in clinical characteristics. Independent of other key prognostic variables, there was a U-shaped relationship, with the greatest rate of adverse outcomes in the lowest and highest BMI categories.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT000095238.

(Circ Heart Fail. 2011;4:324-331.)

Key Words: heart failure ■ body mass index ■ diastolic dysfunction ■ obesity ■ prognosis

Observational studies in the general population indicate that body mass index (BMI) is an independent predictor of prognosis with a J-shaped relation between BMI and risk of death, with the lowest risk at a BMI of 23 to 26.5 kg/m².1–3 Overweight is part of the metabolic syndrome, a major risk factor for coronary artery disease and stroke. Indeed, in middle-aged individuals, risk of death from atherosclerotic cardiovascular (CV) causes increases steadily with increasing BMI.2,4 In addition, obesity is a major risk factor for the development of heart failure (HF).5 However, even though increased BMI is associated with an increased incidence of coronary artery disease, a common cause of HF with reduced left ventricular ejection fraction (HFREF) and for incident HFREF, the prognosis in patients with established HFREF improves with increasing BMI. This phenomenon has also been called the “obesity paradox.”6–8

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Patients with HF and a preserved ejection fraction (HFPEF) comprise approximately 50% of the overall HF population.9 Compared with patients with HFREF, patients with HFPEF are usually older, are more frequently women, and have a higher incidence of diabetes and hypertension.10 However, relatively few data are available regarding the relationship...
between BMI and clinical events in patients specifically with HFPEF. In a post hoc analysis of the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) study, a BMI of 30 to 35 kg/m² was found to be associated with the lowest overall mortality not only in HREF but also in HFPEF, whereas BMI appeared to have no impact on the rate of hospitalization for worsening HF.11

The recently completed I-PRESERVE trial (Irbesartan in HF and PRESERVED Ejection fraction) is the largest randomized, controlled treatment trial in HFPEF.12 In the present analysis, we examined the relationship between BMI and CV morbidity and death in I-PRESERVE. We hypothesized that—similar to HREF—a higher BMI would be associated with a lower rate of CV events and mortality in HFPEF.

Methods

This post hoc analysis of the I-PRESERVE trial dataset was performed in all patients with a BMI value available at baseline. BMI was derived from body weight and height at the time of random assignment. A BMI value was missing in only 19 of 4128 patients, leaving 4109 patients for further analysis. The design and primary outcome of the I-PRESERVE trial have been previously published.12,13 Briefly, I-PRESERVE was a randomized, double-blind, placebo-controlled trial that evaluated the effect of irbesartan, an angiotensin AT1 receptor antagonist, in older HFPEF patients (age 60 years; left ventricular ejection fraction [LVEF] <45%). The mean follow-up was 49.5 months and the annual all-cause mortality rate was 5.2%. Irbesartan had no effect on the primary composite end point (death from any cause or hospitalization for a CV cause, that is, HF, myocardial infarction, unstable angina, arrhythmia, or stroke) or 2 secondary end points (death from any cause and hospitalization for worsening HF, the latter being defined as hospitalization with signs and symptoms of HF requiring a significant augmentation of HF therapy). The present subanalysis focused on the primary composite end point and these 2 secondary end points.

Statistical Analysis

BMI was evaluated as both a continuous and a categorical variable. Before defining the BMI categories, a density plot analysis of the BMI was performed (Figure 1). To create the BMI ranges, we strived to have clinically relevant categories, which excluded quartiles and quintiles for this particular sample because the resultant middle range would be too narrow. To allow for a sufficient number of patients in each category, the BMI cutoffs used were necessarily slightly different from those recommended by the World Health Organization (WHO).14 Based on the density plot and the 2 previous criteria, 5 BMI categories were defined: <23.5 (“underweight”), 23.5 to 26.4 (“normal” weight), 26.5 to 30.9 (overweight), 31.0 to 34.9 (“mild” obesity), and ≥35.0 kg/m² (“severe” obesity). The association of BMI with outcomes was examined in unadjusted and fully adjusted Cox proportional hazards models that contained age, sex, New York Heart Association (NYHA) class, heart rate, systolic blood pressure, left ventricular hypertrophy, LVEF, cause of HF, hospitalization for HF within the last 6 months, history of hypertension, myocardial infarction, stroke, chronic obstructive pulmonary disease and/or diabetes, use of diuretics, digoxin, a calcium-channel blocker, lipid-lowering agents, an angiotensin-converting enzyme (ACE) inhibitor, or a β-blocker, and N-terminal pro-brain natriuretic peptide (NT-proBNP) as covariates. The covariates were chosen for these multivariate analyses because they were found to be significant independent predictors of CV outcomes in previous publications. The BMI category with the lowest rate of the primary composite outcome (death or CV hospitalization) was selected and used as reference group for comparison regarding the relationship between BMI and all other predefined end points.

Results

Baseline Characteristics

The mean age (±SD) of the cohort was 71.6 (6.9) years; 29.4% were older than 75 years, and 60.4% were women. The mean LVEF was 59.4% (9.2%) and the median NT-proBNP was 339 pg/mL (range, 5 to 28 670 pg/mL). The baseline characteristics by BMI categories are shown in Table 1. The mean (±SD) BMI was 29.6 (5.3) kg/m² in the entire group. In respect to WHO-defined BMI ranges,14 16.5% of the patients had a BMI <25 kg/m², 42.4% between 25 and 30 kg/m², and 41.3% >30 kg/m². Age was inversely related to BMI, whereas average LVEF tended to increase with BMI. The percentage of women was highest in the BMI categories <23.5 kg/m² and ≥31 kg/m². The prevalence of arterial hypertension as an investigator-assigned etiology of HF increased with BMI, whereas that of coronary artery disease declined. The serum creatinine and hemoglobin did not significantly differ between the BMI subgroups. However, median NT-proBNP level markedly declined with increasing BMI (Table 1). The use of diuretics, ACE inhibitors, β-blockers, calcium channel blockers, and lipid-lowering agents increased with BMI, whereas the use of digoxin declined with BMI, and the use of antplatelets and spironolactone was unrelated to BMI.

Primary Composite End Point

The unadjusted Kaplan-Meier curves (Figure 2) indicated that the risk (the cumulative probability of adverse outcomes) correlated nonlinearly with BMI. The event rates for the primary outcomes in the 5 BMI groups are shown in Table 2. The lowest event rate (33.1%) was seen for BMI category 26.5 to 30.9 kg/m² and the highest event rate for BMI category <23.5 kg/m² (49.1%), with the 5 groups showing a U-shaped relationship. The components of the primary composite end point in general had a similar U-shaped relationship with BMI as the composite end point except for all-cause mortality which had a linear, inverse relationship with BMI (Table 2).
With the BMI category 26.5 to 30.9 kg/m² as the reference group, the unadjusted HR for the primary composite end point was mildly increased in patients with BMI 23.5 to 26.4 kg/m² (hazard ratio [HR], 1.18; 95% confidence interval [CI], 1.03 to 1.36; P=0.019) and even more so in patients with BMI <23.5 kg/m² (HR, 1.27; 95% CI, 1.04 to 1.56; P=0.019) and ≥35 kg/m² (HR, 1.27; 95% CI, 1.06 to 1.52; P=0.011), indicating a U-shaped relationship between BMI and the primary composite end point (Figure 3).

Predefined Secondary End Points and Mode of Death

Similar results were observed for all-cause mortality (Figure 4A). Compared with the reference group, the adjusted HR for
all-cause mortality was increased in patients with BMI <23.5 kg/m² (HR, 1.44; 95% CI, 1.12 to 1.84; \( P=0.005 \)) and in those with BMI \( \geq 35 \) kg/m² (HR, 1.31; 95% CI, 1.03 to 1.67; \( P=0.029 \)) in the fully adjusted model. However, mode of death differed among the 5 BMI categories. The unadjusted rate of sudden death and non-CV death tended to decrease with increasing BMI. However, on the contrary, the rate of HF death was highest in the lowest and highest BMI categories (BMI <23.5 kg/m² and BMI \( \geq 35 \) kg/m²), where it equaled the rate of sudden death. In patients with a BMI between 23.5 and 34.9 kg/m², the rate of sudden death and non-CV death was 2 to 3 times higher than the rate of HF death (Table 2 and Figure 5).

In the fully adjusted model, the risk of HF hospitalization was substantially increased, with BMI \( \geq 35 \) kg/m² (HR, 1.52; 95% CI, 1.19 to 1.94; \( P=0.001 \)) (Figure 4B), even though these patients had the highest LVEF and the lowest NT-proBNP (Table 1). HF hospitalization also tended to increase in the BMI category 31.0 to 34.9 kg/m² (HR, 0.82; 95% CI, 0.65 to 1.05; \( P=0.12 \)). However, in the lowest BMI category (<23.5 kg/m²) the risk for HF hospitalization was not significantly increased (HR, 1.11; 95% CI, 0.82 to 1.50; \( P=0.49 \)) (Figure 4B).

**Effect of Irbesartan**

Irbesartan had no significant effect on the relationships between BMI and the primary composite end point, all-cause mortality, or HF hospitalization.

**Discussion**

The major findings of the present study are (1) In patients with HFPEF, overweight and obesity are highly prevalent and are accompanied by multiple differences in clinical and demographic characteristics; (2) there is a U-shaped relationship between BMI and both the primary composite end point and all-cause mortality, with the highest event rates in those patients with the lowest BMI (<23.5 kg/m²) and those with the highest BMI (>35 kg/m²). These relationships were not

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**Table 2. Major Unadjusted Outcomes for the 5 BMI Categories**

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>&lt;23.5 (n=336)</th>
<th>23.5 to 26.4 (n=858)</th>
<th>26.5 to 30.9 (n=1506)</th>
<th>31.0 to 34.9 (n=813)</th>
<th>&gt;35.0 (n=596)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>165/49.1/152</td>
<td>329/38.4/109</td>
<td>499/33.1/92</td>
<td>280/34.4/95</td>
<td>225/37.8/108</td>
</tr>
<tr>
<td>All-cause mortality (death)</td>
<td>108/32.1/83</td>
<td>205/23.9/60</td>
<td>287/19.1/47</td>
<td>151/18.6/45</td>
<td>123/20.6/50</td>
</tr>
<tr>
<td>HF hospitalization and death</td>
<td>76/22.6/66</td>
<td>126/14.7/40</td>
<td>236/15.7/41</td>
<td>136/16.7/44</td>
<td>137/23.0/63</td>
</tr>
<tr>
<td>Cause-specific mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden death</td>
<td>28/8.3/22</td>
<td>61/7.1/18</td>
<td>74/4.9/12</td>
<td>43/5.3/13</td>
<td>24/4.0/10</td>
</tr>
<tr>
<td>HF death</td>
<td>25/7.4/19</td>
<td>18/2.1/5</td>
<td>42/2.8/7</td>
<td>17/2.1/5</td>
<td>21/3.5/9</td>
</tr>
<tr>
<td>All CV deaths</td>
<td>68/20.2/52</td>
<td>124/14.5/36</td>
<td>168/11.2/27</td>
<td>93/11.5/28</td>
<td>74/12.4/30</td>
</tr>
<tr>
<td>Non-CV deaths</td>
<td>26/7.7/20</td>
<td>64/7.5/19</td>
<td>101/6.7/16</td>
<td>43/5.3/13</td>
<td>32/5.4/13</td>
</tr>
<tr>
<td>Hospitalization for CV causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14/4.2/11</td>
<td>31/3.6/9</td>
<td>62/4.1/10</td>
<td>25/3.1/8</td>
<td>20/3.4/8</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>20/6.0/16</td>
<td>25/2.9/7</td>
<td>65/4.3/11</td>
<td>33/4.1/10</td>
<td>20/3.4/8</td>
</tr>
<tr>
<td>Stroke</td>
<td>22/6.5/17</td>
<td>44/5.1/13</td>
<td>69/4.6/11</td>
<td>43/5.3/13</td>
<td>22/3.7/9</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>14/4.2/11</td>
<td>31/3.6/9</td>
<td>55/3.7/9</td>
<td>42/5.2/13</td>
<td>32/5.4/14</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>0/0/0</td>
<td>2/0.2/ &lt;1</td>
<td>5/0.3/ &lt;1</td>
<td>2/0.2/ &lt;1</td>
<td>3/0.5/1</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HF, heart failure; and CV, cardiovascular.

\*n=No. of events.

\†Event rate=crude event rate (%).

\‡Event rate=per 1000 patient-years.
significantly altered by adjustment for 21 preselected clinical variables, including age, sex, NT-proBNP, and medication. Interestingly, the lowest incidence of adverse outcomes was observed in those patients with HFPEF who were moderately overweight (BMI between 26.5 and 30.9 kg/m²); and (3) HF hospitalization was only significantly increased in patients with a BMI ≥35 kg/m².

Clinical and Demographic Characteristics
More than 83% of the patients were overweight (BMI, 25 to 30 kg/m²) or obese (BMI, >30 kg/m²). This rate of obesity is similar to the population-based studies that have specifically examined older age patients with HF, including HFPEF specifically.¹⁵ In the present study, patients in the lowest BMI category (<23.5 kg/m²) were older and had a slightly lower LVEF, a higher NT-proBNP, and a lower rate of arterial hypertension and diabetes mellitus. NT-proBNP has been shown to be an independent marker of prognosis in both HFPEF and HFREF and to be lower in obese HF patients.¹⁶ Indeed, patients with the highest BMI (≥35 kg/m²) had a median NT-proBNP of only 254 pg/mL, and those with the lowest BMI (<23.5 kg/m²) had an almost 3 times higher median NT-proBNP level. Furthermore, patients with BMI <23.5 kg/m² had the lowest and those with a BMI ≥35.0 kg/m² the highest likelihood of ACE inhibitor, β-blocker, calcium channel blocker, diuretic, and lipid-lowering agents usage, whereas in patients with a BMI <23.5 kg/m², digoxin was most frequently administered. However, none of these agents has so far been shown substantially influence the prognosis in HFPEF.¹⁷

Despite marked differences in the key characteristics of patients with a BMI <23.5 kg/m² and those with a BMI ≥35.0 kg/m², both BMI categories had a similar risk of CV events after adjustment for 21 variables including age, LVEF, NT-proBNP, and medication, indicating an independent prognostic relevance of BMI. However, this does not exclude that the pathophysiological mechanisms related to the prognostic impact of a very low and very high BMI may differ. This is supported by the relatively low NT-proBNP and relatively high LVEF in the highest BMI category.

Adverse Outcomes
The rate of the primary composite end point was highest in patients with in the lowest BMI category (<23.5 kg/m²).
(Table 2), with 152 events per 1000 patient-years. This high event rate was driven mainly by the fact that this BMI category had the highest all-cause mortality rate and a high rate of worsening HF and stroke. However, there were no differences among the 5 BMI categories in the rates of myocardial infarction, unstable angina, and major arrhythmias. Likewise, a recent meta-analysis of 40 studies of patients with coronary artery disease found no difference in CV mortality between normal-weight patients and overweight or mildly obese patients, whereas patients with severe obesity had a 1.88-fold higher rate of major CV events.\(^7\) In the present study, the rate of CV events may have been too low to allow for further differentiation.

Similar to the primary end point, a U-shaped relationship was found for all-cause mortality. Again, patients in the lowest and highest BMI categories (<23.5 kg/m\(^2\) and >35 kg/m\(^2\), respectively) appeared to have the highest adjusted risk of death (Figure 4A). This finding is noteworthy because we previously reported in the I-PRESERVE patient cohort that the cause of death is twice as often non-CV as compared with HFREF (30% versus approximately 14% of total mortality).\(^19\) In contrast to all-cause mortality, the rate of HF hospitalization was only significantly increased in severely obese patients (ie, BMI \(\geq 35\) kg/m\(^2\)). It was lowest in patients with a BMI between 23.5 to 26.4 kg/m\(^2\) and only tended to increase in patients with a BMI \(<23.5\) kg/m\(^2\) (Figure 4B). In the present study, the rate of both sudden death and non-CV death declined with increasing BMI when focusing on the unadjusted event rates (Table 2). In contrast, HF death was relatively common, equaling rates of sudden death and non-CV death only in those patients with a BMI \(<23.5\) kg/m\(^2\) and in those with a BMI \(\geq 35\) kg/m\(^2\) (Figure 5).

### Comparison to Population-Based Studies

Three recently published large cohort studies based on general, unselected populations reported a J-shaped relationship between BMI and all-cause mortality. In US men ages 66 to 71 years, the optimum BMI was 25.0 to 26.4 kg/m\(^2\) and in women ages 66 to 71 years, 23.5 to 24.9 kg/m\(^2\), with a diminished impact of BMI at older age.\(^1\) Although the mean age in the present study was almost 72 years, BMI still had a significant influence on outcome, and although many patients in I-PRESERVE had coronary artery disease, the relationship between BMI and adverse CV outcomes rather resembled that between BMI and cancer death than that between BMI and death form atherosclerotic causes.\(^4,7\)

### Comparison to Other Databases With HFPEF

Data on the relationship between BMI and prognosis in HFPEF have been sparse. The results of the present study both confirm and extend the results of a previous report on BMI and prognosis in the CHARM-Preserved cohort.\(^11\) In that cohort, the lowest risk of all-cause death was observed in those with a BMI between 30.0 and 34.9 kg/m\(^2\) and the highest risk (HR, 1.99) in those with a BMI \(<22.5\) kg/m\(^2\). However, no significant relationship was found between BMI and hospitalization for HF.\(^11\) There are significant differences between the CHARM-Preserved and the I-PRESERVE cohorts, including (1) The LVEF inclusion criteria were higher in I-PRESERVE (>45% versus >40%), such that it that some patients with significantly reduced LVEF may have been included in CHARM-Preserved; (2) the I-PRESERVE cohort included a higher proportion of women (>60% versus <40%) and the patients were significantly older (mean age, 72 versus 65 years). The sex and age distribution of I-PRESERVE is more similar to that reported in population-based studies of HFPEF;\(^2\) (3) the inclusion criteria for I-PRESERVE required either prior HF-related hospital admission within the past year or NYHA functional class III symptoms plus echo abnormalities, whereas CHARM only required symptomatic HF (ie, NYHA functional classes II to IV).

### Potential Limitations

Although the data in the present study are consistent with a relatively large number of publications in HF, coronary disease, and other disorders, they are not sufficient to promote weight gain in underweight patients or to discourage weight loss in obese HF patients. In our study, similar to other published observational studies, we are unable to exclude occult, preexisting cancers or other chronic illnesses that affect BMI and prognosis.\(^23\) Furthermore, the significantly worse prognosis seen in the highest BMI category indicates the lack of a uniform mechanism to explain this phenomenon.

Our data analysis was based on a retrospective subanalysis of carefully characterized patients from a controlled trial (I-PRESERVE). Therefore, there was an unequal number of patients in each BMI category, and the most commonly used BMI ranges (WHO criteria) had to be slightly adjusted to allow for a sufficient number of subjects in each BMI category. Because HFPEF is mainly a disease of the elderly, the average age was higher than in previous studies in HFREF. However, if anything, this bolsters our key findings because most variables lose their prognostic power at a higher age.\(^2,4\)
Although 21 variables were used in the adjusted model, which all by themselves have been shown to influence adverse CV outcomes in the I-PRESERVE cohort, other residual confounders cannot completely be ruled out. The adjusted model included a previous myocardial infarction and a HF hospitalization 6 months before randomization, which was identical to the day of assessment of BMI. However, no information regarding the exact time intervals of these events and their potential influence on BMI and CV outcomes are available. Furthermore, the I-PRESERVE database does not contain any information on weight changes before and after randomization, which might have influenced the event rate.

Obese patients may have signs and symptoms resembling those of HF. This makes the ability to diagnose HFPEF in obese patients more difficult. However, the I-PRESERVE trial required that patients had a clinical diagnosis of HF along with either HF hospitalization or pertinent echocardiographic or Doppler criteria consistent with HFPEF. Obese patients fulfilled these criteria and had in fact the highest HF hospitalization rate.

Waist circumference, waist-to-hip ratio, and percent body fat may be better indicators of prognosis than BMI, but these data were unfortunately not assessed in I-PRESERVE. Furthermore, body composition was not analyzed, although fluid retention (eg, edema) not only increases BMI but also influences prognosis. However, only patients in stable clinical conditions at random assignment were included in the I-PRESERVE trial.

Independent from these potential limitations, we believe this to be the largest data set analyzed for the impact of BMI on adverse outcomes during long-term follow-up in HFPEF.

Conclusions

Obesity is highly prevalent in elderly HFPEF patients and is accompanied by multiple differences in clinical characteristics. Consistent with reports in patients with HFREF, HFPEF patients in the lowest BMI category (BMI <23.5 kg/m²) had the highest risk of subsequent events. The event rate was also significantly increased in HFPEF patients with severe obesity (BMI ≥35 kg/m²). This finding of a U-shaped relationship between BMI and adverse CV outcomes persisted even after adjustment for baseline imbalances for all end points.

Acknowledgments

We greatly acknowledge the statistical recommendations and initial analysis performed by Scott Hetzel, Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI.

Sources of Funding

The I-PRESERVE trial was funded by Bristol-Myers Squibb and Sanofi-Aventis, as was the present subanalysis. The study was also supported in part by National Institutes of Health grants 37AG18915 and P30AG21222 (Dr Kitzman).

Disclosures

The members of the steering committee (Drs Kitzman, Zile, Massie, and Carson) and of the end point committee (Drs Haass, Anand, Zile, and Miller) of I-PRESERVE received honoraria from Bristol-Myers Squibb for providing these services.
Obesity is a major risk factor for incident heart failure (HF). Paradoxically, in HF with reduced left ventricular ejection fraction (HFREF) a high body mass index (BMI) appears to be beneficial. However, approximately 50% of HF patients have a preserved left ventricular ejection fraction (HFPEF). Compared with HFREF, patients with HFPEF are usually older and more frequently female. The relationship between BMI and adverse cardiovascular (CV) outcomes was studied in the HFPEF patient cohort (n=4109) from the I-PRESERVE trial (mean age, 72 years, >60% female, mean BMI, approximately 30 kg/m²). Depending on their BMI, the patients were characterized by multiple differences in clinical variables. After adjustment for 21 key variables, patients in the lowest (BMI <23.5 kg/m²) and those in the highest BMI categories (BMI ≥35 kg/m²) had the highest CV event rate and the highest mortality. The lowest event rates were seen in overweight patients, that is, those with a BMI between 26.5 and 30.9 kg/m², indicating a U-shaped relationship. Only HF hospitalization was less frequently seen in normal-weight patients with HFPEF. This is the largest cohort of HFPEF patients studied so far, showing a significant impact of BMI on adverse CV outcomes. Whether weight changes, for example, weight gain in underweight and weight reduction in severe obesity, improve CV outcome in HFPEF patients could not be answered by the present study and requires a controlled trial.
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Circ Heart Fail. 2011;4:324-331; originally published online February 24, 2011;
doi: 10.1161/CIRCHEARTFAILURE.110.959890
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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