Body Mass Index and Prognosis in Patients With Chronic Heart Failure

Insights From the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program

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Background—In individuals without known cardiovascular disease, elevated body mass index (BMI) (weight/height\(^2\)) is associated with an increased risk of death. However, in patients with certain specific chronic diseases, including heart failure, low BMI has been associated with increased mortality.

Methods and Results—We examined the influence of BMI on prognosis using Cox proportional hazards models in 7599 patients (mean age, 65 years; 35% women) with symptomatic heart failure (New York Heart Association class II to IV) and a broad spectrum of left ventricular ejection fractions (mean, 39%) in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. During a median follow-up of 37.7 months, 1831 patients died. After adjustment for potential confounders, compared with patients with BMI between 30 and 34.9, patients in lower BMI categories had a graded increase in the risk of death. The hazard ratios (95% confidence intervals) were 1.22 (1.06 to 1.41), 1.46 (1.24 to 1.71), and 1.69 (1.43 to 2.01) among those with BMI of 25 to 29.9, 22.5 to 24.9, and <22.5, respectively. The increase in risk of death among patients with BMI ≥35 was not statistically significant (hazard ratio, 1.17; 95% confidence interval, 0.95 to 1.43). The association between BMI and mortality was not altered by age, smoking status, or left ventricular ejection fraction (P for interaction ≤0.20). However, lower BMI was associated with a greater risk of all-cause death in patients without edema but not in patients with edema (P for interaction <0.0001). Lower BMI was associated with a greater risk of cardiovascular death and noncardiovascular death. Baseline BMI did not influence the risk of hospitalization for worsening heart failure or due to all causes.

Conclusions—In patients with symptomatic heart failure and either reduced or preserved left ventricular systolic function, underweight or low BMI was associated with increased mortality, primarily in patients without evidence of fluid overload (edema). (Circulation. 2007;116:627-636.)

Key Words: heart failure ■ morbidity ■ mortality ■ obesity ■ prognosis

Elevated body mass index (BMI) is a major risk factor for the development of heart failure (HF).\(^1\)\(^-\)\(^4\) In individuals free of cardiovascular disease, a curvilinear association has been described between BMI and the risk of overall mortality, in which mortality was increased at the lowest and highest extremes and decreased in the middle.\(^5\)\(^-\)\(^6\) However, in patients with established HF, increased BMI has been noted to have an inverse,\(^7\)\(^-\)\(^13\) no,\(^14\) or nonsignificant\(^15\) association with the risk of mortality. Most of these studies were not conducted in a contemporary time period in patients receiving modern evidence-based treatments, and HF patients with a wide range of left ventricular ejection fractions were not evaluated. Thus, in patients with chronic HF, the prognostic significance of BMI on the risk of all-cause death, cause-specific death, and morbidity outcomes remains unclear.

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Accordingly, we examined the impact of BMI on prognosis in patients with symptomatic HF and either reduced or
preserved left ventricular systolic function from the Cande-
sartan in Heart failure: Assessment of Reduction in Mortality
and morbidity (CHARM) program. We hypothesized that in
patients with chronic HF, low BMI (and elevated BMI) would
be associated with an increased risk of death and unfavorable
cardiovascular outcomes.

Methods
The design and results of the CHARM program have been published
previously. Briefly, CHARM was a multinational, double-blind,
placebo-controlled program of clinical trials conducted between
March 1999 and March 2003 that evaluated the efficacy of cande-
sartan in 7599 men and women aged ≥18 years who had symptom-
atic chronic HF (New York Heart Association class II to IV,
regardless of left ventricular ejection fraction) and were either
receiving or not receiving an angiotensin-converting enzyme inhib-
itor at baseline. Patients with serum creatinine ≥265 mmol/L; serum
potassium ≥5.5 mmol/L; known bilateral renal artery stenosis;
symptomatic hypotension; critical aortic or mitral stenosis; recent
myocardial infarction, stroke, or open-heart surgery (within 4
weeks); use of an angiotensin-receptor blocker in the previous 2
weeks; any noncardiac disease judged likely to limit 2-year survival;
and those unwilling to provide consent, as well as women of
childbearing potential not using adequate contraception, were ex-
cluded. Planned duration of treatment and follow-up ranged from 24
to 48 months.

Covariates and Outcomes
All information on covariates including demographics, height and
weight, cardiovascular risk factors, symptoms and signs of HF, and
concomitant medications was ascertained at the time of enrollment.
Presence or absence of pitting edema in the feet, ankle, leg, or
sacrum was documented. BMI was calculated as weight in kilograms
divided by the square of the height in meters. The individual
outcomes considered in the present investigation were all-cause
death (the primary outcome of the CHARM overall program),
cardiovascular death, noncardiovascular death, hospitalization for
worsening HF, and hospitalization for all causes. The composite
outcomes evaluated were cardiovascular death or hospitalization for
worsening HF (the primary composite outcome of each of the 3
individual CHARМ trials), all-cause death or hospitalization for
worsening HF, and all-cause death or hospitalization for all causes.
The integrated end point assessed was days alive out of hospital
during 1 and 2 years of follow-up. All outcomes were determined by
an independent adjudication committee using prespecified defini-
tions and blinded to the baseline BMI status. A death was considered
cardiovascular unless a specific noncardiovascular cause was iden-
tified. Hospitalization for worsening HF was defined as an unex-
pected admission to hospital for treatment of HF or when HF became
a major component of the patient’s hospital admission. A patient
admitted for this reason had to show symptoms and signs of
worsening HF and require treatment with intravenous diuretics. 
Evidence of worsening HF had to include at least 1 of the following
items: increasing dyspnea on exertion, orthopnea, nocturnal dyspnea,
pulmonary edema, increasing peripheral edema, increasing fatigue
or decreasing exercise tolerance, renal hypoperfusion (ie, worsening
renal function), raised jugular venous pressure, and radiological
signs of HF.

Statistical Analyses
We evaluated BMI both as a continuous (for every 1-kg/m² change)
and as a categorical variable (≤22.5, 22.5 to 24.9, 25.0 to 29.9, 30.0
to 34.9 [referent], and ≥35.0 kg/m²). The BMI categories were
primarily based on cut points recommended by the World Health
Organization18 and endorsed by the National Institutes of Health.19
We calculated mean±SD for continuous variables and proportions
for categorical variables at baseline for each category of BMI. We
constructed linear or logistic regression models for baseline variables
with BMI as a continuous variable (per 1-kg/m² change) and
presented probability values as an estimate of their association. To
evaluate the association between BMI and the risk of various
outcomes defined as time to first event, we calculated unadjusted,
age- and sex-adjusted, and multivariable-adjusted hazard ratios
(HRs), 95% confidence intervals (CIs), and 2-sided probability
values using Cox proportional hazards regression models. We
performed linear regression analyses to assess the relation between
BMI and the integrated end point of days alive out of hospital during
1 year and 2 years of follow-up. In multivariable models, we adjusted
for all important predictors of mortality and morbidity identified in
a previous investigation in the CHARM program.20 These variables,
in the order of strength of association with all-cause death, were age
(per 10 years over age 60 years), left ventricular ejection fraction
(per 5% decrease below 45%), diabetes mellitus (none [referent],
insulin treated, and oral therapy or diet only), male sex, New York
Heart Association class II (referent), III, and IV, current smoking,
bundle-branch block, cardiomegaly, previous hospitalization for HF
(none [referent], ≤6 months, >6 months), diastolic blood pressure
(per 10-mm Hg decrease), duration of HF ≥2 years, previous
myocardial infarction, edema, heart rate (per 10-bpm increase),
pulmonary crackles, pulmonary edema, mitral regurgitation, atrial
fibrillation, rest dyspnea, and study treatment (candesartan versus
placebo). To assess the shape of the association between BMI and
all-cause death, we introduced terms with common transformations
of BMI inclusive of linear, quadratic, linear plus quadratic, logarith-
ic, squared root, exponential, and categorical (groups as specified
above) in multivariable models.

In multivariable models evaluating BMI as a continuous variable
(per 1-kg/m² change), we examined for interaction of the effect
of BMI on all-cause mortality and hospitalization for worsening HF by
age (per 1-year change and as a dichotomous variable: <median and
≥median), smoking status (never/past smokers and current smok-
ers), edema status (without edema and with edema), and left
ventricular ejection fraction (per 5% decrease below 45% and as a
dichotomous variable: ≤40% and >40%).

We performed all analyses using SAS software version 9.1.21 We
considered a 2-sided probability value of <0.05 as statistically
significant.

The authors had full access to and take full responsibility for the
integrity of the data. All authors have read and agree to the
manuscript as written.

Results
Baseline Characteristics
The mean (±SD) and median BMIs in the CHARM cohort were 28.3
(±5.4) and 27.6, respectively, and ranged from
14.3 to 57.4 kg/m². Approximately 40% of the patients with
HF had BMI between 25.0 and 30.0 kg/m², and ≈11% were
in the lowest (<22.5 kg/m²) and highest (≥35 kg/m²) BMI
categories, respectively.

BMI was inversely related to age; patients in the heaviest
category were on average 8.6 years younger than patients in the
least category (Table 1). Women were more likely to be
in the leanest or the heaviest BMI category. Increasing BMI
was associated with a higher New York Heart Association
functional class, heart rate, blood pressure, and left ventric-
ular ejection fraction. Greater proportions of individuals in
lower BMI categories were current cigarette smokers and had
previous history of myocardial infarction and bundle-branch
block. Although the duration of HF did not differ across
categories of BMI, a greater proportion of patients with lower
BMI were hospitalized for HF within 6 months before
enrollment. As anticipated, hypertension and diabetes melli-
tus were noted more commonly in higher BMI categories.
Whereas ischemic heart disease was the predominant cause of
HF in lower BMI categories, hypertension was the primary

| TABLE 1. Baseline Characteristics According to the Category of BMI in the CHARM Study* |
|----------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| BMI, kg/m²                            | <22.5 (n=889) | 22.5 to 24.9 (n=1277) | 25 to 29.9 (n=3063) | 30 to 34.9 (n=1579) | ≥35 (n=791) | P     |
| Demographic characteristics           |               |                 |                 |                 |                |      |
| Age, y                                | 68.8±11.4     | 67.8±10.4       | 65.8±10.7       | 63.6±10.6       | 60.2±11.2     | <0.0001 |
| Women, %                              | 41.2          | 29.4            | 26.1            | 33.3            | 42.1          | 0.0008 |
| Ethnic origin, %                      |               |                 |                 |                 |                |      |
| European origin                       | 85.5          | 90.8            | 92.7            | 90.4            | 86.6          | 0.0001 |
| Black                                 | 3.9           | 2.7             | 2.8             | 5.7             | 10.2          | <0.0001† |
| Other                                 | 10.6          | 6.4             | 4.6             | 3.9             | 3.2           | <0.0001† |
| Heart disease risk factors            |               |                 |                 |                 |                |      |
| NYHA class, %                         |               |                 |                 |                 |                | <0.0001 |
| II                                    | 43.8          | 47.3            | 47.1            | 44.6            | 35.0          | 0.0001 |
| III                                   | 52.6          | 50.5            | 50.4            | 53.3            | 61.7          | 0.0001 |
| IV                                    | 3.6           | 2.2             | 2.5             | 2.2             | 3.3           | 0.0001 |
| Heart rate, bpm                       | 73.2±12.7     | 72.0±13.1       | 72.4±13.0       | 73.4±13.5       | 74.6±12.3     | <0.0001 |
| Blood pressure, mm Hg                 |               |                 |                 |                 |                |      |
| Systolic                               | 125.9±19.3    | 129.1±19.9      | 130.9±19.0      | 133.3±18.3      | 134.2±18.8    | <0.0001 |
| Diastolic                              | 73.2±10.5     | 75.0±10.7       | 76.9±10.4       | 78.2±10.9       | 79.0±11.0     | <0.0001 |
| Left ventricular ejection fraction, % | 34.9±14.6     | 37.1±14.1       | 38.5±14.2       | 40.8±15.3       | 43.4±16.2     | <0.0001 |
| ≤30                                   | 38.4          | 31.6            | 26.9            | 23.4            | 22.6          | 0.0001 |
| 30 to <40                             | 31.0          | 29.4            | 30.7            | 28.6            | 20.6          | 0.0001 |
| 40 to <50                             | 11.7          | 17.6            | 18.4            | 18.4            | 17.3          | 0.0001 |
| ≥50                                   | 18.9          | 21.3            | 24.0            | 29.6            | 39.4          | 0.0001 |
| Medical history                       |               |                 |                 |                 |                |      |
| Duration of HF, y                     | 3.1±4.3       | 3.3±4.4         | 3.2±4.5         | 3.1±4.2         | 3.1±4.3       | 0.22   |
| Previous hospitalization for HF, %    |               |                 |                 |                 |                |      |
| Within 6 mo                           | 43.2          | 38.1            | 36.0            | 34.5            | 35.0          | 0.003  |
| After 6 mo                            | 34.4          | 33.4            | 34.3            | 34.9            | 37.6          | 0.19   |
| Current cigarette smoking, %          | 19.8          | 15.6            | 14.2            | 12.7            | 12.9          | <0.0001 |
| Pharmacologically treated hypertension, %| 35.3          | 40.8            | 45.2            | 58.5            | 67.1          | <0.0001 |
| Diabetes mellitus, %                  |               |                 |                 |                 |                |      |
| Insulin treated                       | 5.1           | 6.1             | 8.1             | 12.7            | 17.1          | <0.0001 |
| Oral therapy or diet only             | 13.0          | 15.0            | 18.4            | 22.7            | 28.6          | <0.0001 |
| Previous myocardial infarction, %     | 53.5          | 56.5            | 56.4            | 49.0            | 38.6          | <0.0001 |
| Current angina pectoris, %            | 18.7          | 23.4            | 25.3            | 23.4            | 25.2          | 0.064  |
| Stroke, %                             | 9.4           | 10.0            | 8.6             | 8.2             | 7.3           | 0.034  |
| Atrial fibrillation, %                | 28.9          | 28.8            | 26.9            | 27.2            | 25.9          | 0.072  |
| Cancer, %                             | 9.2           | 7.4             | 5.6             | 6.8             | 7.3           | 0.57   |
| Causes of HF, %‡                      |               |                 |                 |                 |                |      |
| Ischemic heart disease                | 71.3          | 72.4            | 73.7            | 66.7            | 55.5          | <0.0001 |
| Hypertension                          | 38.8          | 43.7            | 47.8            | 60.0            | 68.1          | <0.0001 |
| Mitral regurgitation                  | 25.9          | 20.1            | 17.8            | 14.6            | 10.1          | <0.0001 |
| Symptoms and signs of HF, %           |               |                 |                 |                 |                |      |
| Dyspnea on walking or climbing        | 97.0          | 96.8            | 96.5            | 96.1            | 96.6          | 0.20   |
| Rest dyspnea                          | 10.7          | 8.8             | 9.3             | 12.9            | 16.7          | <0.0001 |
| Orthopnea                             | 20.1          | 15.8            | 17.3            | 21.9            | 35.4          | <0.0001 |
| Paroxysmal nocturnal dyspnea          | 9.1           | 10.3            | 12.0            | 14.0            | 21.9          | <0.0001 |
| Edema                                 | 15.3          | 15.9            | 21.4            | 29.3            | 50.4          | <0.0001 |
| Venous congestion                     | 28.2          | 26.9            | 31.1            | 38.7            | 56.9          | <0.0001 |
| Jugular venous pressure >6 cm         | 10.6          | 8.1             | 8.9             | 7.9             | 11.8          | 0.46   |
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Concomitant medications, %</th>
<th>BMI, kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;22.5 (n=889)</td>
</tr>
<tr>
<td>S₃ gallop</td>
<td>14.7</td>
</tr>
<tr>
<td>Pulmonary crackles</td>
<td>17.4</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3.5</td>
</tr>
<tr>
<td>Bilateral pleural effusions</td>
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</tr>
<tr>
<td>Cardiomegaly</td>
<td>25.2</td>
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<tr>
<td>ECG, %</td>
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<tr>
<td>Bundle-branch block</td>
<td>24.5</td>
</tr>
<tr>
<td>Concomitant medications, %</td>
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<tr>
<td>Digitalis glycoside</td>
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<tr>
<td>Diuretics</td>
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<tr>
<td>β-Blocker</td>
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<tr>
<td>Calcium channel blocker</td>
<td>13.2</td>
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<tr>
<td>Lipid-lowering drug</td>
<td>31.4</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>44.4</td>
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<tr>
<td>Spironolactone</td>
<td>18.4</td>
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<tr>
<td>Study treatment, %</td>
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<tr>
<td>Candesartan</td>
<td>49.6</td>
</tr>
</tbody>
</table>

*P values indicate the association of each variable with BMI and were calculated from linear or logistic regression models with BMI as a continuous variable vs each covariate.
†Compared with European origin.
‡Categories were not mutually exclusive.

factor attributable to HF in higher BMI categories. Rest dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and edema were more likely to be noted in individuals with higher BMI, and S₃ gallop, pulmonary crackles, pulmonary edema, and cardiomegaly were more prevalent in patients with a lower BMI. A similar proportion of individuals were on candesartan therapy in each category of BMI.

BMI and Risk of Death

During a median follow-up of 37.7 months, 1831 patients (24.1%) died. For BMI categories <35.0 kg/m², crude cumulative incidence of all-cause death increased progressively with decreasing categories of BMI (Figure 1, log-rank P of test for equality <0.0001). In unadjusted analyses, every 1-kg/m² decrease in BMI was associated with a 5.3% increase in the risk of all-cause death (Table 2). After adjustment for age and sex, the increase in the risk of all-cause death was 3.3%, which did not change materially after additional adjustment for all other important predictors of all-cause death. In fully adjusted models, compared with patients with BMI between 30 and 34.9 kg/m², patients in lower BMI categories had a graded increase in the risk of all-cause death: 22.3% increase in patients with BMI between 25 and 29.9, 45.7% increase in patients with BMI between 22.5 and 24.9, and 69.4% increase among patients with BMI <22.5 kg/m² (Table 2). The 26.4% increase in the risk of all-cause death among patients with BMI ≥35 in age- and sex-adjusted analyses was attenuated to 16.8% and did not reach statistical significance in fully adjusted analyses.

In multivariable analyses evaluating the shape of the association between BMI and all-cause death, linear plus quadratic BMI terms had the best goodness of fit ($\chi^2 [2]=54.9, P<0.0001$), suggestive of a nonlinear (U- or J-shaped) association between BMI and all-cause death. Logarithmic ($\chi^2 [1]=41.8, P<0.0001$) and categorical ($\chi^2 [4]=48.5, P<0.0001$) terms had similar goodness of fit, followed by square root ($\chi^2 [1]=37.5, P<0.0001$), exponential ($\chi^2 [2]=30.6, P<0.0001$), and quadratic BMI ($\chi^2 [1]=24.7, P<0.0001$).

Patients in lower BMI groups were at a greater risk of cardiovascular death as well as noncardiovascular death (Table 2). A trend was evident toward increasing noncardiovascular deaths in the highest BMI category.

BMI and Risk of Hospitalization for Worsening HF

No linear association existed between BMI and the risk of hospitalization for worsening HF (Table 2). In age- and sex-adjusted models, compared with the group with BMI between 30.0 and 34.9 kg/m², an 18.3% (borderline statistical significance) and 26.6% increase existed in risk of hospitalization for worsening HF in the lowest and highest category, respectively (Table 2). This association was attenuated and no longer significant, however, in fully adjusted models.

No statistically significant association was present between BMI and the risk of composite of cardiovascular death or hospitalization for worsening HF (data not shown). The association of BMI with the risk of the composite of all-cause
death or hospitalization for worsening HF was similar to that with all-cause death alone (Table 2).

**BMI and Risk of Hospitalization for All Causes**

During follow-up, 4797 (63.1%; 40.8 per 100 person-years of follow-up) were hospitalized for all causes. Baseline BMI did not influence the risk of hospitalization for all causes. In fully adjusted models, compared with patients with BMI of 30 to 34.9, the HRs (95% CIs) were 1.07 (0.96 to 1.19; \( P < 0.20 \)), 0.98 (0.89 to 1.08; \( P = 0.73 \)), 1.03 (0.89 to 1.05; \( P = 0.39 \)), and 1.09 (0.94 to 1.17; \( P = 0.36 \)) for patients with BMI < 22.5, 22.5 to 24.9, 25 to 29.9, and \( \geq 35 \), respectively. The results for composite of all-cause death or hospitalization for all causes were similar to those for hospitalization for all causes (data not shown).

**BMI and Days Alive Out of Hospital**

In fully adjusted models, every 1-kg/m² decrease in BMI was associated with 0.6 (95% CI, 0.3 to 0.9; \( P < 0.0001 \)) and 1.9 (95% CI, 1.1 to 2.6; \( P < 0.0001 \)) fewer days alive out of hospital during 1 and 2 years of follow-up, respectively. In models evaluating BMI as a categorical variable, however, evidence existed of a possible inverted J-shaped association between BMI and days alive out of hospital characterized by a statistically significant stepwise decrease below and a decrease (albeit statistically nonsignificant) above BMI of 30 to 34.9 (Figure 2).

**Effect Modification**

The association between BMI and the risk of all-cause death and hospitalization for worsening HF did not depend on age, smoking status, or left ventricular ejection fraction (all \( P \) for interaction \( > 0.20 \)). Lower BMI was associated with higher risk of mortality in patients with impaired as well as preserved left ventricular ejection fraction (Table 3). However, lower BMI was associated with a greater risk of all-cause death in patients without edema but not in patients with edema (Table 3; \( P \) for interaction \( < 0.0001 \)). The HRs for each 1-kg/m² decrease in BMI were 1.05 (95% CI, 1.03 to 1.06; \( P < 0.0001 \)) in patients without edema and 1.00 (95% CI, 0.99 to 1.02; \( P = 0.71 \)) in patients with edema. Similar results were noted for both cardiovascular and noncardiovascular death (data not shown). Edema status or left ventricular ejection fraction at baseline did not influence the association between BMI and the risk of hospitalization for worsening HF (Table 3; \( P \) for interaction \( > 0.30 \)).

**Discussion**

In CHARM patients, lowest mortality was noted in patients with BMI between 30 and 34.9, a progressive increase in mortality was evident below this range, and a plateau or increase was observed above this range (U- or J-shaped association). By the same token, highest number of days alive out of hospital during 1 or 2 years of follow-up was observed in patients with BMI between 30 and 34.9, with a stepwise decrease in days alive out of hospital below and a modest decrease above this range (inverted J-shaped association). Lower BMI was associated with a greater risk of death, cardiovascular death, and noncardiovascular death (including cancer deaths). The relation between BMI and the risk of all-cause death was not altered by age, smoking status, or left
ventricular ejection fraction. The increased risk of death among patients with low BMI was evident primarily in the absence of edema, an indicator of fluid overload status.

Few studies have addressed the issue of shape of the association between BMI and all-cause death in chronic HF patients. In a report from the Digitalis Investigation Group (DIG) trial, unadjusted analyses using polynomial logistic regression revealed a nonlinear association between BMI and death. In the present investigation, age- and sex-adjusted as well as multivariable time-to-event analyses that accounted for major indicators of poor prognosis also suggest a nonlinear (U- or J-shaped) relation between BMI and mortality. Commensurate with this finding, an inverted J-shaped association was noted between BMI and days alive out of hospital, a type of quality of life-adjusted survival that accounted for multiple hospitalizations during the period of evaluation.

Edema increases BMI on the basis of fluid excess rather than solid tissue mass. Results of our investigation suggest that in patients with chronic HF, baseline BMI can be a useful indicator of mortality primarily in the absence of edema.

In the DIG trial as well as in our present investigation, in which relatively younger (mean age, 63 to 65 years) and stable HF patients were enrolled, left ventricular systolic dysfunction, as assessed by estimates of left ventricular ejection fraction, did not alter the effects of BMI on the risk of all-cause death. In the Danish Investigations of
Arrhythmia and Mortality (DIAMOND) congestive heart failure study, in which older (mean age, 72 years) HF patients admitted for new-onset or worsening HF were enrolled, in patients with left ventricular systolic dysfunction, as assessed by wall motion index, higher BMI was associated with a greater risk of all-cause death, whereas in patients with normal left ventricular systolic function, lower BMI posed a greater risk of all-cause death. The differences in study population and mode of ascertainment of left ventricular systolic function may partially explain the disparity in interaction of left ventricular function and BMI and the risk of mortality.

In our analyses as well as in the study by DIG investigators, BMI did not influence the risk of hospitalization for HF in multivariable analyses. The lack of association with this sensitive clinical measure of HF severity, along with the similarity of effect of BMI on cardiovascular and noncardiovascular deaths, suggests that low BMI is a general marker (not a causal factor) of ill health.

A number of hypotheses have been put forth to explain the association between lower BMI and increased risk of mortality in HF patients. Lower BMI in patients with "prevalent" HF, as in the present and other previously published studies, may have been due to preceding involuntary weight loss or cardiac cachexia, a heightened metabolic or increased catabolic state associated with worse prognosis. By the same token, higher BMI, except when produced by edema, might indicate a greater metabolic reserve, increased tolerance to metabolic stress, and/or a less severe form of HF, and consequently may have a better prognosis. Elevated BMI may be associated with reduced cardiac sympathetic activity, attended neurohormonal response to stress, lower proinflammatory cytokine levels, and lesser catabolic-anabolic imbalance, all of which bode a better prognosis. Increased production of leptin and soluble receptors of tumor necrosis factor in adipose tissues may reduce the detrimental effects of tumor necrosis factor, a proinflammatory cytokine. Individuals with higher BMI, presumably due to lower natriuretic peptide levels, may manifest symptoms and signs of HF at a younger age with consequent longer survival after diagnosis (lead-time bias).

Elevated BMI may increase the risk of death and unfavorable cardiovascular outcomes by promoting risk factors for cardiovascular disease and by influencing abnormal left ventricular remodeling. Extreme BMI may continue to pose greater hemodynamic stress on the heart that could be deleterious. The improvement in functional class and pump function noted in smaller studies in which extremely obese HF patients have undergone marked weight reductions lends credence to this notion.

The strengths of our investigation include a large sample size, multicenter setting, inclusion of a broad spectrum of left ventricular ejection fractions in patients with symptomatic HF on evidence-based treatments in a contemporary time period, assessment of edema status, availability of information on most covariates of interest (including duration of HF) for multivariable analyses, nearly complete follow-up of patients during the 2- to 4-year study period, and objective ascertainment of all study end points by an independent committee blinded to BMI status at enrollment. Several limitations of these analyses should also be noted. We did not have data on body weights at the time of first diagnosis of HF to ascertain the influence of weight change subsequent to the time of first diagnosis on the risk of death or cardiovascular outcomes. Selection bias is likely in all prognostic studies conducted on patients with prevalent HF (in which BMI at the time of onset of HF is unavailable, and changes in body weight preceding their inclusion in various categories of BMI are uncertain). For edema status, we did not have data on body composition or percent body fat to evaluate the impact of each component (muscle, bone,
and fat tissue) on the risk of clinical outcomes. Results of analyses stratified according to baseline edema status should be interpreted with caution given the small sample size of patients with edema in lower-BMI groups. We did not have other baseline data such as serum albumin levels for all participants, which may have allowed further elucidation of underweight status versus cardiac cachexia (or protein-calorie malnutrition) in patients with the lowest BMI values. Higher-BMI patients with HF were younger at the time of enrollment than lower-BMI patients, suggesting lead-time bias as a possible explanation for the association between higher BMI and better survival. However, the similar duration of HF in all BMI groups and absence of interaction between age and BMI and the risk of death in multivariable analyses do not support this explanation. Because a majority of patients studied were of European origin, the generalizability of our findings to other races and ethnic groups is another limitation.

We conclude that in patients with symptomatic and chronic HF, underweight status or low BMI is associated with a

**TABLE 3. Results of Multivariable Cox Proportional Hazards Models Examining the Relation of BMI to the Risk of All-Cause Death and Hospitalization for Worsening HF According to Left Ventricular Ejection Fraction and Edema Status at Baseline Examination**

<table>
<thead>
<tr>
<th>BMI Categories, kg/m²</th>
<th>&lt;22.5</th>
<th>22.5 to 24.9</th>
<th>25 to 29.9</th>
<th>30 to 34.9</th>
<th>≥35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular ejection fraction ≤40</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events/at risk (%)</td>
<td>258/641 (40.2), 15.5</td>
<td>274/818 (33.5), 12.4</td>
<td>527/1876 (28.1), 10.0</td>
<td>201/878 (22.9), 7.8</td>
<td>90/363 (24.8), 8.6</td>
</tr>
<tr>
<td>Multivariable HR (95% CI), P</td>
<td>1.69 (1.39 to 2.06), &lt;0.0001</td>
<td>1.44 (1.19 to 1.74), 0.0001</td>
<td>1.20 (1.02 to 1.41), 0.032</td>
<td>1.00 (referent)</td>
<td>1.19 (0.92 to 1.53), 0.18</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction &gt;40</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events/at risk (%)</td>
<td>70/248 (28.2), 10.4</td>
<td>91/459 (19.8), 6.9</td>
<td>183/1187 (15.4), 5.3</td>
<td>79/701 (11.3), 3.8</td>
<td>58/428 (13.6), 4.7</td>
</tr>
<tr>
<td>Multivariable HR (95% CI), P</td>
<td>1.99 (1.42 to 2.80), &lt;0.0001</td>
<td>1.67 (1.23 to 2.29), 0.0001</td>
<td>1.33 (1.01 to 1.74), 0.039</td>
<td>1.00 (referent)</td>
<td>1.25 (0.88 to 1.77), 0.21</td>
</tr>
<tr>
<td><strong>Without edema</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events/at risk (%)</td>
<td>272/753 (36.1), 13.6</td>
<td>285/1074 (26.5), 9.5</td>
<td>493/2409 (20.5), 7.0</td>
<td>174/1117 (15.6), 5.2</td>
<td>56/392 (14.3), 4.7</td>
</tr>
<tr>
<td>Multivariable HR (95% CI), P</td>
<td>1.92 (1.57 to 2.34), &lt;0.0001</td>
<td>1.56 (1.29 to 1.89), &lt;0.0001</td>
<td>1.22 (1.03 to 1.46), 0.024</td>
<td>1.00 (referent)</td>
<td>1.09 (0.80 to 1.47), 0.60</td>
</tr>
<tr>
<td><strong>With edema</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events/at risk (%)</td>
<td>56/136 (41.2), 16.3</td>
<td>80/203 (39.4), 15.2</td>
<td>217/654 (33.2), 12.5</td>
<td>106/462 (22.9), 8.1</td>
<td>92/399 (23.1), 8.3</td>
</tr>
<tr>
<td>Multivariable HR (95% CI), P</td>
<td>1.10 (0.78 to 1.56), 0.57</td>
<td>1.21 (0.89 to 1.64), 0.22</td>
<td>1.25 (0.99 to 1.59), 0.060</td>
<td>1.00 (referent)</td>
<td>1.24 (0.93 to 1.64), 0.14</td>
</tr>
</tbody>
</table>

| **Hospitalization for worsening HF** | | | | | |
| **Left ventricular ejection fraction ≤40** | | | | | |
| No. of events/at risk (%) | 182/641 (28.4), 12.4 | 210/818 (25.7), 10.8 | 454/1876 (24.2), 9.7 | 221/878 (25.2), 9.7 | 91/363 (25.1), 9.7 |
| Multivariable HR (95% CI), P | 1.18 (0.96 to 1.46), 0.11 | 1.08 (0.89 to 1.31), 0.45 | 1.00 (0.85 to 1.18), 0.99 | 1.00 (referent) | 1.00 (0.78 to 1.28), 1.00 |
| **Left ventricular ejection fraction >40** | | | | | |
| No. of events/at risk (%) | 47/248 (19.0), 7.6 | 71/459 (15.5), 5.7 | 192/1187 (16.2), 6.0 | 113/701 (16.1), 5.8 | 94/428 (22.0), 8.5 |
| Multivariable HR (95% CI), P | 1.02 (0.71 to 1.45), 0.93 | 0.97 (0.71 to 1.32), 0.83 | 1.09 (0.86 to 1.39), 0.47 | 1.00 (referent) | 1.28 (0.97 to 1.69), 0.087 |
| **Without edema** | | | | | |
| No. of events/at risk (%) | 182/753 (24.2), 10.1 | 217/1074 (20.2), 7.9 | 452/2409 (18.8), 7.1 | 198/1117 (17.7), 6.4 | 74/392 (18.9), 6.8 |
| Multivariable HR (95% CI), P | 1.18 (0.96 to 1.46), 0.12 | 1.11 (0.91 to 1.35), 0.30 | 1.07 (0.9 to 1.27), 0.43 | 1.00 (referent) | 1.14 (0.87 to 1.49), 0.35 |
| **With edema** | | | | | |
| No. of events/at risk (%) | 47/136 (34.6), 16.3 | 64/203 (31.5), 14.2 | 194/654 (29.7), 13.0 | 136/462 (29.4), 11.9 | 111/399 (27.8), 11.7 |
| Multivariable HR (95% CI), P | 0.95 (0.67 to 1.34), 0.75 | 0.93 (0.68 to 1.26), 0.63 | 0.98 (0.78 to 1.23), 0.88 | 1.00 (referent) | 1.06 (0.82 to 1.36), 0.67 |

*py indicates person-years.*

*See text for details.*
greater risk of all-cause death, and mild to moderate overweight status is associated with the lowest risk. The implication of moderate to extreme BMI on prognosis is uncertain. Lower BMI is an indicator of poor survival, primarily in the absence of fluid overload. Our findings warrant additional research, especially in community-based settings among patients with new-onset HF, to assess the impact of BMI, ascertained in close proximity to the first diagnosis of HF, on morbidity and mortality.

Source of Funding

The CHARM program was funded by AstraZeneca, which was responsible for data collection.

Disclosures

The data analysis for this article was performed independently by Drs Kenchaiah, Pocock, and Wang. The Executive Committee (Drs Pfeffer, Swedberg, Granger, McMurray, and Yusuf) supervised the management of the study and were primarily responsible for the interpretation of the data and review and approval of the manuscript. Dr Michelson is an employee of AstraZeneca. Drs Pocock, Pfeffer, Yusuf, Swedberg, Granger, McMurray, and Solomon have received research grants, honoraria for lectures, and/or consulting fees from AstraZeneca. The remaining authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

In 7599 symptomatic heart failure (New York Heart Association class II to IV) patients (mean age, 65 years; 35% women) with a broad spectrum of left ventricular ejection fractions (mean, 39%) in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) clinical trials, we examined the influence of body mass index (BMI) (defined as weight in kilograms divided by the square of height in meters) on prognosis. During a median follow-up of 38 months, 1831 patients died. Lowest mortality was noted in patients with BMI between 30 and <35, and progressive increase in mortality was evident below this range (22%, 46%, and 69% increase in patients with BMI 25 to <30, 22.5 to <25, and <22.5, respectively), and a plateau or increase was observed above this range (17% increase, albeit statistically nonsignificant, among patients with BMI ≥35). Similarly, highest number of days alive out of hospital was observed in patients with BMI between 30 and 34.9 (39, 29, 19, and 12 fewer days alive out of hospital during 2 years of follow-up in patients with BMI <22.5, 22.5 to <25, 25 to <30, and ≥35, respectively). The association between BMI and mortality was similar in patients with impaired as well as preserved left ventricular ejection fraction. However, lower BMI was associated with a greater risk of death primarily in patients without edema, an indicator of fluid overload status. Lower BMI (likely a consequence of involuntary weight loss or cachexia) was linked with a greater risk of cardiovascular death and noncardiovascular death (including cancer deaths), suggesting that among patients with heart failure, low BMI is a general marker of ill health.
Body Mass Index and Prognosis in Patients With Chronic Heart Failure: Insights From the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program

for the CHARM Investigators

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Correction

In the version of the article, “Body Mass Index and Prognosis in Patients With Chronic Heart Failure: Insights From the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program,” by Kenchaiah et al that was posted online on July 16, 2007 (DOI: 10.1161/CIRCULATIONAHA.106.679779), several errors occurred.

In the Methods and Results section of the abstract, line 11, the value of $P$ for interaction was shown as “$<0.001$” but should have been “$<0.0001$.” The same error occurred on page 5, column 2, line 7. Also, on page 2, column 2, line 18, the value “$=6$ months” should have been “$\leq 6$ months.” The authors regret these errors.

Two entries in Table 2 were inadvertently switched. In Table 2, line 17, the $P$ value for the age-and sex-adjusted model was listed as “1.00 (referent),” and the fully adjusted hazard ratio (95% confidence interval) was listed as “...” (ellipses to indicate a blank or nonapplicable cell). These should have been reversed so that the $P$ value was listed as “...” and the fully adjusted hazard ratio (95% confidence interval) was listed as “1.00 (referent).” The publisher regrets this error.

These errors have been corrected in the final print version of the article in the August 7, 2007, issue of the journal (Circulation. 2007;116:627–636) and in the current online version.

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