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Heart Failure

Body Mass Index and Mortality in Acutely Decompensated Heart Failure Across the World

A Global Obesity Paradox

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Objectives This study sought to define the relationship between body mass index (BMI) and mortality in heart failure (HF) across the world and to identify specific groups in whom BMI may differentially mediate risk.

Background Obesity is associated with incident HF, but it is paradoxically associated with better prognosis during chronic HF.

Methods We studied 6,142 patients with acute decompensated HF from 12 prospective observational cohorts followed-up across 4 continents. Primary outcome was all-cause mortality. Cox proportional hazards models and net reclassification index described associations of BMI with all-cause mortality.

Results Normal-weight patients (BMI 18.5 to 25 kg/m^2) were older with more advanced HF and lower cardiometabolic risk. Despite worldwide heterogeneity in clinical features across obesity categories, a higher BMI remained associated with decreased 30-day and 1-year mortality (11% decrease at 30 days; 9% decrease at 1 year per 5 kg/m^2; $p < 0.05$), after adjustment for clinical risk. The BMI obtained at index admission provided effective 1-year risk reclassification beyond current markers of clinical risk (net reclassification index 0.119, $p < 0.001$). Notably, the "protective" association of BMI with mortality was confined to persons with older age (>75 years; hazard ratio [HR]: 0.82; $p = 0.006$), decreased cardiac function (ejection fraction <50%; HR: 0.85; $p < 0.001$), no diabetes (HR: 0.86; $p < 0.001$), and de novo HF (HR: 0.89; $p = 0.004$).

Conclusions A lower BMI is associated with age, disease severity, and a higher risk of death in acute decompensated HF. The "obesity paradox" is confined to older persons, with decreased cardiac function, less cardiometabolic illness, and recent-onset HF, suggesting that aging, HF severity/chronicity, and metabolism may explain the obesity paradox. (J Am Coll Cardiol 2014;63:778–85) © 2014 by the American College of Cardiology Foundation

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Although a higher body mass index (BMI) is associated with a proportionally increased risk of incident heart failure (HF) (1), an elevated BMI in chronic HF is paradoxically associated with improved prognosis when compared with persons with "normal weight" (2–7). However, it is less clear whether adiposity influences outcomes in the acute HF setting. Although registry studies suggest a 10% lower in-hospital mortality for every 5 kg/m^2 increase in BMI, after adjustment for age, sex, renal, and hemodynamic profile (6), longer-term implications for patients surviving to discharge remain underexplored.

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Within the context of this HF obesity paradox, it is unclear how to reconcile general recommendations for ideal cardiovascular health (8), which articulate the importance of weight loss to preserve cardiometabolic health. Mechanistically, there is debate as to whether obesity itself may be protective in HF (e.g., as a marker of improved nutrition, less tumor necrosis factor-alpha activation and cachexia, or direct hemodynamic influences), or whether a low BMI is confounded by residual, unexplained factors that promote mortality (e.g., frailty). Although the obesity paradox itself has been documented in regional cohorts in different cardiovascular diseases (9), defining the role of adiposity in HF and addressing which specific aspects of the patient with advanced cardiac illness are important in modifying associations between BMI and mortality in a global setting is critical.

In a prospective, observational, intercontinental cohort of 6,142 patients, we examined the relationship between BMI and mortality after acute decompensated heart failure (ADHF) hospitalization worldwide, independent of traditional markers of risk. We defined specific factors in patients with ADHF that may mediate these associations between BMI and HF prognosis to clarify potential mechanisms of benefit (or harm) with adiposity. Ultimately, our overall goal was to clarify the prognostic impact of obesity in ADHF and to define subgroups within which adiposity may play a prominent role in mediating adverse prognosis.

Methods

Study population and adjudication of clinical outcomes. The study population was derived from a collection of 12 cohorts of patients with ADHF from 4 continents: Europe (n = 8; 2 in Italy, Austria, and the Czech Republic; 1 in France, Finland, Switzerland, the Netherlands, and Spain), North America (n = 2; United States), Asia (n = 1; Japan), and South America (n = 1; Argentina) (10–19). The principal investigators for each study submitted original patient-level data from admission. All patients had a diagnosis of ADHF on admission (regardless of new-onset HF or acute decompensation of chronic HF), according to clinical practice guidelines (20). Clinical details of presentation (medication use, hemodynamics, comorbidities), as well as demographic, echocardiographic, and biochemical data on admission were recorded prospectively in each cohort, with prospective adjudication of outcomes. A previous diagnosis of diabetes mellitus was based on self-report by the patient, ongoing antidiabetic therapy, or documentation in the patient's medical records. Estimated glomerular filtration rate was estimated by the Modified Diet in Renal Disease formula (21). As we sought to determine both short- and long-term prognosis by BMI, we excluded patients without BMI data available on admission and without adjudication of events at least 6 months after index admission. To adjust for possible frailty, we excluded patients with a BMI <18.5 kg/m^2 in all analyses. All-cause mortality was assessed at 30 days and 1 year by medical chart review at each specific institution as previously described (22). Cause-specific mortality was not available in this transnational cohort. All study procedures were approved by local institutional review boards/ethics.

Abbreviations and Acronyms

ADHF = acute decompensated heart failure
BMI = body mass index
CI = confidence interval
HF = heart failure
HR = hazard ratio
LV = left ventricular
LVEF = left ventricular ejection fraction
NRI = net reclassification improvement

Statistical analysis. Baseline demographic characteristics were expressed as median and interquartile range or frequency, and were compared using nonparametric techniques for continuous data (e.g., Wilcoxon or Kruskal-Wallis test) or chi-square testing for categorical covariates. The primary outcome of our study was all-cause mortality at 30 days and 1 year post-discharge for ADHF. Survival time was calculated from the date of admission until the date of death or last follow-up. Survival was plotted, and univariable and multivariable (covariate-adjusted) Cox proportional hazards regression models were used to estimate effects for each covariate, with simultaneous adjustment for potential confounders in multivariable models. Proportional hazards assumptions were verified. The log-linearity of BMI was confirmed in all patients for 30-day and 1-year mortality. Accordingly, the main exposure was defined by a 5-kg/m^2 increase in BMI (similar to the scaling reported by prior investigators [1]).

Covariates included for adjustment in multivariable models were age, sex, history of prior HF, history of coronary artery disease, atrial fibrillation, diabetes mellitus, blood pressure (systolic and diastolic), heart rate, presence of decreased renal function (as calculated by Crockault-Gault estimated

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glomerular filtration rate <60 ml/min/1.73 m^2), hyperglycemia (defined as glucose ≥7 mmol/l for nondiabetic subjects and ≥10 mmol/l for patients with prevalent diabetes mellitus [22]) and hyponatremia (serum sodium concentration <136 mmol/l). Our study was composed of a worldwide sample of patients with ADHF; given that patients were included from various centers, a potential cluster effect was taken into account using generalized linear models with a random intercept where the cluster of interest was the country.

In addition, to assess potential effect modification by certain clinical factors important in the diagnosis and treatment of HF on the association of BMI with all-cause mortality at 1 year, we performed multivariable Cox regression models for BMI in various subgroups relevant to ADHF prognosis, including de novo HF (defined as ADHF hospitalization without prior clinical diagnosis of HF), age (stratified at 75 years), sex, left ventricular ejection fraction (LVEF) (stratified at 50%), and diabetes. We adjusted for all covariates specified in the main multivariable Cox regression model for these subgroup analyses.

Finally, we assessed risk reclassification of BMI beyond a clinical model (composed of all covariates listed in the main multivariable model) using net reclassification analysis. Continuous net reclassification improvement (NRI) for BMI for the prediction of 1-year mortality was estimated by published techniques (23).

Statistical analyses were performed using R (version 2.15.0, R Foundation for Statistical Computing, Vienna, Austria). A 2-sided p value <0.05 was considered to be statistically significant.

Results

Study population. The derivation of the study population is shown in Figure 1. Of 9,158 patients originally included in the registry, patients were serially excluded for BMI data unavailable (n = 2,768), survival data beyond 30 days unavailable (n = 53), and BMI <18.5 kg/m^2 (n = 195). Our final population thus consisted of 6,142 patients, stratified by World Health Organization guidelines: normal weight (BMI 18.5 to 25 kg/m^2; n = 2,197); overweight (BMI 25 to 30 kg/m^2; n = 2,243), and obese (BMI ≥30 kg/m^2; n = 1,702).

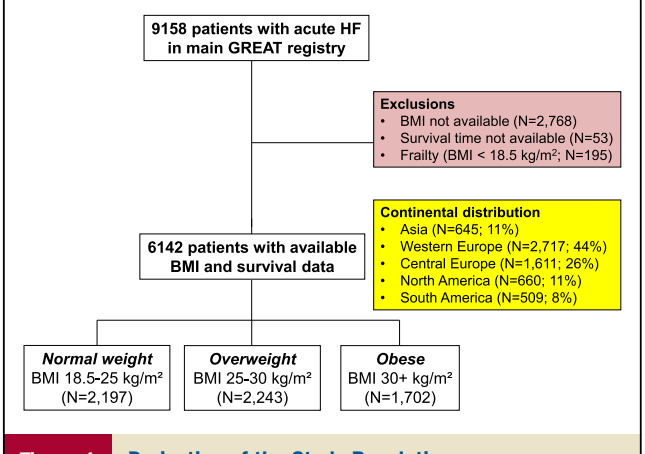

Figure 1 Derivation of the Study Population

BMI = body mass index; GREAT = Global Research on Acute Conditions Team; HF = heart failure.

Clinical, demographic, biochemical, and echocardiographic characteristics of the study population. Baseline characteristics of our intercontinental population stratified by obesity status are shown in Table 1. As expected, relative to overweight/obese ADHF patients, patients with normal weight were older and had a lower prevalence of obesity-related illness (e.g., diabetes, hypertension, and coronary artery disease). In addition, beta-blocker use, statin use, and renin-angiotensin system inhibition were less frequent among normal-weight patients. On admission, patients who were normal weight had lower systolic blood pressure and lower sodium concentration, LVEF, and hemoglobin. Concentrations of natriuretic peptides (B-type natriuretic peptide, N-terminal pro–B-type natriuretic peptide, and mid-regional pro-atrial natriuretic peptide) and serum troponin I were lower in obese persons (Table 1). In contrast, there were no differences in soluble ST2, C-reactive protein, mid-regional pro-adrenomedullin, or cystatin C across BMI categories.

Across the world, BMI was higher among patients admitted for ADHF in Europe and the Americas as compared with Asia. In addition, there was clinically significant heterogeneity across the world in sex, comorbid cardiometabolic illness (e.g., diabetes, hypertension, and coronary artery disease), drug therapy for HF, biomarkers of neurohormonal activation, and characteristics of initial presentation (Online Table 1).

Association of body mass index with short- and long-term HF mortality. In Cox regression models for 30-day and 1-year mortality in ADHF (Table 2), several well-known correlates of risk in HF (e.g., age, serum sodium, renal dysfunction, blood pressure) were associated with outcome in our cohort. When treated as a continuous covariate, BMI was associated with 30-day mortality (hazard ratio [HR]: 0.89 for every 5 kg/m^2 increase in BMI; 95% confidence interval [CI]: 0.80 to 0.98; p = 0.02) in unadjusted, but not in a multivariable (fully adjusted) model. Conversely, at 1 year, BMI was associated with mortality in both unadjusted and adjusted analyses (adjusted HR: 0.91 for every 5 kg/m^2 increase in BMI; 95% CI: 0.87 to 0.96; p < 0.001). When BMI was stratified by World Health Organization criteria for obesity (normal 18.5 to 25 kg/m^2, overweight 25 to 30 kg/m^2, obese ≥30 kg/m^2), event-free survival was greatest among obese subjects, followed by overweight and normal-weight persons, both at 30 days and at 1 year (Fig. 2). The association of greater BMI with improved 1-year outcome was maintained after further adjustment for B-type natriuretic peptide (HR: 0.86; 95% CI: 0.79 to 0.94; p = 0.001) and LVEF (HR: 0.89; 95% CI: 0.83 to 0.94; p < 0.001), and both (Online Table 2). In addition, a protective association of BMI with all-cause mortality at 1 year remained after excluding patients with grade 3 obesity (BMI >40 kg/m^2; HR: 0.85; 95% CI: 0.79 to

Table 1 Baseline Clinical, Demographic, and Biochemical Characteristics, Stratified by Weight Status on Admission

Covariate	Available	Normal Weight BMI 18.5–25 kg/m^2 (n = 2,197)	Overweight BMI 25–30 kg/m^2 (n = 2,243)	Obese BMI 30+ kg/m^2 (n = 1,702)	p Value
Demographics					
Age, yrs	6,140 (>99)	76.3 (67–83)	73.8 (64.6–79.9)	69.1 (60.3–76.9)	<0.001
Male	6,142 (100)	1,179 (54)	1,323 (59)	925 (54)	<0.001
BMI, kg/m^2	6,142 (100)	22.9 (21.3–24.1)	27.3 (26.1–28.4)	33.2 (31.2–36.3)	<0.001
Diabetes mellitus	6,112 (>99)	604 (28)	883 (40)	864 (51)	<0.001
COPD	5,990 (98)	355 (17)	388 (18)	320 (19)	0.09
Hypertension	5,343 (87)	1,024 (60)	1,393 (69)	1,248 (78)	<0.001
History of HF	5,943 (97)	1,095 (52)	1,060 (49)	837 (50)	0.18
Atrial fibrillation	5,808 (95)	681 (33)	645 (31)	491 (30)	0.12
History of CAD	6,023 (98)	962 (45)	1,164 (53)	788 (47)	<0.001
Medication use at admission					
Beta-blocker	5,417 (88)	884 (45)	954 (48)	742 (51)	<0.01
ACE inhibitor	5,141 (84)	733 (39)	858 (46)	632 (45)	<0.001
ARB	5,131 (84)	439 (24)	415 (22)	378 (27)	<0.01
Diuretics	5,338 (87)	1,123 (57)	1,055 (54)	799 (56)	0.16
Nitrates	4,706 (77)	317 (21)	343 (19)	255 (19)	0.33
Aspirin	4,502 (73)	589 (41)	677 (40)	560 (42)	0.47
Statin	4,305 (70)	344 (25)	499 (30)	409 (32)	<0.001
Hemodynamic and biochemical status on admission					
SBP, mm Hg	6,088 (99)	130 (110–157)	135 (115–160)	140 (120–160)	<0.001
DBP, mm Hg	6,070 (99)	77 (64–90)	80 (70–90)	80 (70–95)	<0.001
Heart rate, beats/min	6,075 (99)	89 (74–109)	88 (72–107)	88 (73–107)	0.11
LVEF, %*	3,157 (51)	38 (25–54)	38 (26–51)	43 (30–55)	<0.001
Hemoglobin, mg/dl	5,632 (92)	12.5 (11–14)	13 (11.6–14.4)	13.1 (11.7–14.6)	<0.001
Serum sodium, mEq/l	6,024 (98)	138 (136–141)	139 (136–141)	139 (136–141)	<0.001
Serum potassium, mEq/l	3,217 (52)	4.1 (3.8–4.5)	4.2 (3.8–4.6)	4.2 (3.8–4.6)	0.27
eGFR, ml/min/1.73 m^2	6,077 (99)	52.9 (37–71.5)	54.9 (39.7–71.8)	55.5 (40.7–73.2)	<0.001
Admission glucose, mmol/l	5,217 (85)	7.5 (5.8–12.9)	7.7 (6–11.1)	7.8 (6–11.4)	0.74
Biomarkers					
BNP, ng/l	2,585 (42)	1,002 (527–1,827)	885 (420–1,626)	666 (340–1,156)	<0.001
MR-proADM, nmol/l	344 (6)	1.58 (1.19–2.26)	1.51 (1.05–2.35)	1.62 (1.11–2.36)	0.61
MR-proANP, pmol/l	476 (8)	470 (301.8–665)	397 (259.6–590.8)	311.5 (205.2–463.5)	<0.001
NT-proBNP, ng/l	836 (14)	6,178 (2,607–13,884)	4,686 (1,991–9,490)	2,906 (1,403–5,876)	<0.001
Cystatin C, mg/l	257 (4)	1.26 (0.98–1.83)	1.12 (0.91–1.49)	1.19 (0.97–1.5)	0.14
sST2, ng/ml	302 (5)	49.7 (32.6–97.5)	47.5 (30.2–85)	44.6 (32.5–78.7)	0.74
hsCRP, mg/l	1,419 (23)	10.5 (4–38)	14 (5–42)	12 (5–33.4)	0.20
Troponin I, μg/l	948 (15)	0.02 (0.005–0.1)	0.01 (0.005–0.1)	0.005 (0.005–0.05)	<0.001

Values are n (%) or median (interquartile range). *Obtained during index hospitalization.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HF = heart failure; hsCRP = high-sensitivity C-reactive protein; LVEF = left ventricular ejection fraction; MR-proADM = mid-regional pro-adrenomedullin; MR-proANP = mid-regional pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure.

0.92; $p < 0.001$), excluding the largest referral center for our study (Czech Republic), or accounting for a fixed cluster effect. When classified by number of cardiovascular medications used on admission (with 1 point each for beta-blockade, angiotensin-converting enzyme inhibition, angiotensin-II receptor blockade, statin therapy, diuretics, and nitrates), nonobese patients (BMI <30 kg/m^2) receiving more medical therapy on admission appeared to have a better short-term (30-day) survival relative to obese patients (Online Fig. 1), although this result was not robust to multivariable adjustment. Finally, in an exploratory analysis of patients within the obese stratum (grade 1, 30 to 35 kg/m^2; grade 2, 35 to 40 kg/m^2; grade 3, 40+ kg/m^2), all patients except those in the highest obesity stratum (grade 3) had an equivalent or lower hazard of all-cause mortality relative to a reference BMI 18.5 to 25 kg/m^2 at 30 days and 1 year after full adjustment; the heaviest patients had a higher 30-day (but not 1-year) mortality. All sensitivity analyses were adjusted for the same covariates as in the fully adjusted multivariable model.

When compared with clinical risk assessments (as described by a multivariable model including all covariates in Table 2 except BMI), BMI provided significant reclassification of all-cause mortality at 1 year, with a continuous net reclassification index (NRI) of 0.119 (95% CI: 0.050 to 0.188; $p < 0.001$). Importantly, risk reclassification by BMI was

Table 2 Univariable and Multivariable Cox Regression Models for 30-Day and 1-Year Post-Discharge Mortality Among Patients With Acute HF

	30-Day Mortality				1-Year Mortality			
Covariate	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value	Univariable HR (95% CI)	p Value	Multivariable HR (95% CI)	p Value
BMI, per 5 kg/m^2	0.89 (0.80–0.98)	0.02	1.02 (0.92–1.12)	0.77	0.81 (0.73–0.90)	<0.001	0.91 (0.87–0.96)	<0.001
Diabetes mellitus	1.09 (0.82–1.45)	0.55	1.19 (0.92–1.54)	0.18	1.13 (0.90–1.42)	0.28	1.18 (0.96–1.46)	0.11
Hyperglycemia	2.15 (1.44–3.22)	<0.001	1.80 (1.37–2.35)	<0.001	1.27 (1.04–1.54)	0.02	1.15 (0.96–1.38)	0.12
Male	1.12 (0.86–1.45)	0.40	1.15 (0.90–1.47)	0.27	1.12 (0.93–1.35)	0.23	1.28 (1.13–1.44)	<0.001
Age, for 1 yr	1.03 (1.01–1.05)	0.001	1.04 (1.02–1.05)	<0.001	1.04 (1.03–1.04)	<0.001	1.04 (1.03–1.04)	<0.001
eGFR <60 ml/min/1.73 m^2	2.36 (1.93–2.90)	<0.001	1.70 (1.37–2.12)	<0.001	2.33 (2.03–2.66)	<0.001	1.78 (1.59–2.00)	<0.001
SBP, for 1 mm Hg	0.98 (0.97–0.98)	<0.001	0.98 (0.97–0.98)	<0.001	0.99 (0.98–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
DBP, for 1 mm Hg	0.97 (0.96–0.98)	<0.001	1.00 (0.99–1.01)	0.47	0.98 (0.97–0.98)	<0.001	0.99 (0.99–1.00)	0.02
Heart rate, per beat/min	1.00 (0.99–1.00)	0.75	1.00 (1.00–1.01)	0.33	1.00 (1.00–1.00)	0.07	1.00 (1.00–1.00)	0.15
Sodium <136 mmol/l	2.24 (1.71–2.94)	<0.001	1.74 (1.32–2.28)	<0.001	1.91 (1.63–2.23)	<0.001	1.56 (1.32–1.84)	<0.001
History of HF	0.70 (0.41–1.19)	0.19	0.58 (0.43–0.79)	<0.001	1.25 (0.93–1.68)	0.14	0.97 (0.81–1.16)	0.75
CAD	1.68 (1.18–2.38)	0.004	1.30 (0.95–1.77)	0.10	1.42 (1.25–1.61)	<0.001	1.15 (0.97–1.37)	0.12
Atrial fibrillation	0.78 (0.56–1.08)	0.14	0.82 (0.70–0.97)	0.02	1.15 (1.00–1.33)	0.05	0.99 (0.96–1.02)	0.48

A total of 4,917 patients were included in fully adjusted multivariable models.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

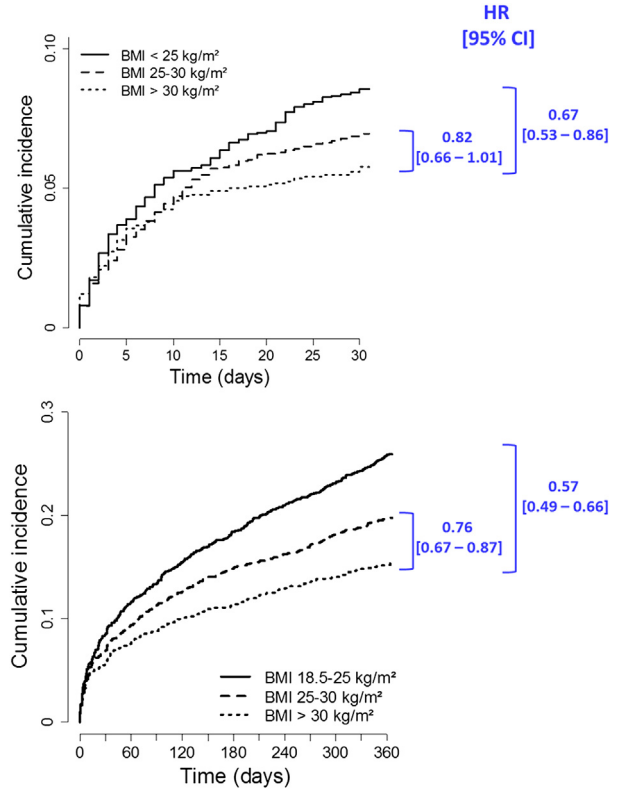

Figure 2 All-Cause Mortality 30 Days and 1 Year After Discharge

All-cause mortality to **(top)** 30 days post-discharge and **(bottom)** 1-year post-discharge after index hospitalization. Both survival curves are significant ($p < 0.001$). **Solid line** indicates body mass index (BMI) 18.5 to 25 kg/m^2; **dashed line** indicates BMI 25 to 30 kg/m^2; **dotted line** indicates BMI >30 kg/m^2. CI = confidence interval; HR = hazard ratio.

more prominent among patients who died (NRI for events: 0.190) relative to patients who remained alive during follow-up (NRI for nonevents: −0.07).

Obesity paradox is a global phenomenon and is confined to select subgroups within HF. The association of higher BMI with lower all-cause mortality persisted across the world in Asia (104 events, HR: 0.53; 95% CI: 0.39 to 0.72), Western Europe (520 events, HR: 0.71; 95% CI: 0.64 to 0.78), Central Europe (481 events, HR: 0.80; 95% CI: 0.74 to 0.87), and North America (125 events, HR: 0.85; 95% CI: 0.76 to 0.94); although comparable directional trends existed relative to outcomes of patients in South America (39 events, HR: 0.90; 95% CI: 0.63 to 1.28), the result was not statistically significant, likely limited by a reduced number of mortality events on this continent (Fig. 3).

Although a higher BMI was associated with generally favorable 1-year prognosis across the groups examined with comparable directional trends, heterogeneity existed when examined as a function of age, diabetes, and LVEF, with a higher BMI particularly associated with lower mortality among older persons (age >75 years, HR: 0.82; 95% CI: 0.72 to 0.95; $p = 0.006$), those with reduced ejection fraction (LVEF <50%, HR: 0.85; 95% CI: 0.79 to 0.92; $p < 0.001$), and those without diabetes mellitus (HR: 0.86; 95% CI: 0.79 to 0.93; $p < 0.001$). In addition, the protective association of BMI with all-cause mortality was present in patients with de novo HF (diagnosed on admission)—but not patients with established chronic HF admitted with acute decompensation. As expected, there were significant differences between patients with de novo HF and established ADHF, though BMI was not significantly different (Online Table 3). All subgroup analyses were fully adjusted using the same covariates as in the main multivariable model.

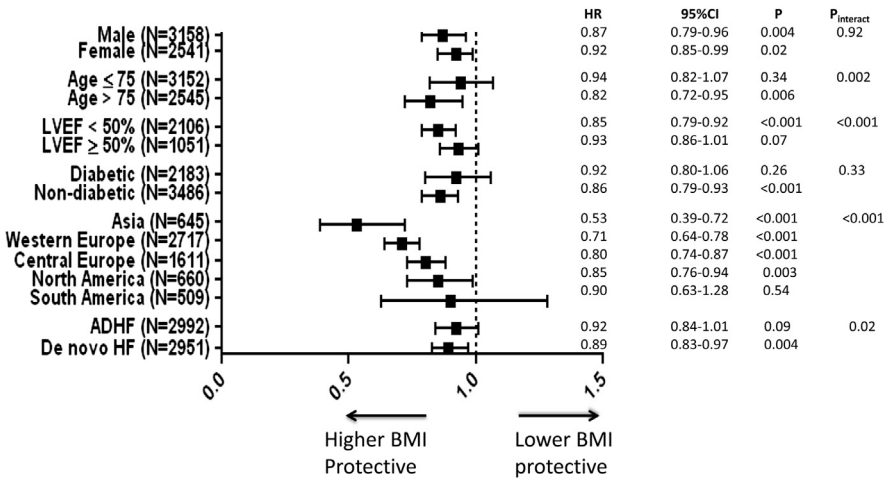

Figure 3 **Forest Plot of HR for Association of BMI With All-Cause Mortality**

Forest plot of HRs for association of BMI, per 5 kg/m^2 increments, with all-cause mortality by Cox regression. Each stratum-specific hazard ratio was adjusted for all covariates specified in Table 2. $p_{interact}$ represents the p value for the HR representing an interaction between each covariate and BMI. ADHF = acute decompensated heart failure; LVEF = left ventricular ejection fraction; other abbreviations as in Figures 1 and 2.

Discussion

Obesity is a global epidemic strongly associated with the development of a broad array of cardiovascular diseases. International clinical practice guidelines increasingly call for antiobesity efforts with the goal to prevent incident cardiovascular and metabolic disease. However, amidst this worldwide mandate for weight loss, an "obesity paradox" has been noted with a variety of cardiovascular ailments, wherein a higher BMI has been reported as "protective" against cardiovascular events, including HF (24). This observation has led to significant controversy as to the demerits of obesity once cardiovascular disease is established (9).

This special cohort provides a unique opportunity to examine ADHF prognosis and its determinants across continents, which allows us to refine an obesity paradox in HF across multiple geographic regions. We provide evidence for the existence of a global obesity paradox in ADHF, with a higher BMI associated with improved 30-day and 1-year mortality worldwide despite intercontinental heterogeneity in clinical and biochemical admission profiles, suggesting that an association between mortality and BMI is robust. In fully adjusted models, BMI was associated with all-cause mortality at 1 year but not at 30 days, suggesting that BMI may be a more specific marker of longer-term outcome. We demonstrate further that the association of BMI with outcome is specific to selected subgroups (nondiabetic persons, de novo HF diagnosis, older age, HF with reduced LVEF), suggesting a level of complexity beyond a simple protective effect of higher weights across all patients with HF. Finally, we demonstrate that a lower BMI effectively reclassifies the risk of long-term mortality beyond clinical indexes, suggesting an important opportunity to identify low BMI persons at high clinical risk for potential nutritional interventions.

Although an obesity paradox does not seem to be present in extreme obesity (25), explanations for the link between higher BMI and survival in HF remain speculative. Excess adiposity may putatively reflect a metabolic sink capable of resisting catabolic demands in HF (26–28). Indeed, a 6% weight loss in patients with advanced chronic HF is associated with a more than 2-fold increased risk of death (29). This nutritional hypothesis appears specifically important for older adults: in a study of 244 patients (mean age 83 years), obese persons with chronic HF were older, with greater absolute lymphocyte count and serum albumin level relative to normal-weight older HF patients, suggesting that BMI and nutritional status may be collinear in an older age range (30), a theory supported by our findings of higher risk particularly among older patients with lower body weight. Lower BMI in chronic HF is associated with negative energy balance in HF, systemic inflammation/catabolism (e.g., tumor necrosis factor-alpha, catecholamine, and glucocorticoid excess), decreased lean and fat mass, and poorer prognosis independent of age, functional status, left ventricular (LV) function, and aerobic capacity (31). Higher tumor necrosis factor-alpha, insulin resistance, and catecholamine excess are linked to cachexia in chronic HF with reduced LV function (32). Moreover, increased adiposity in rodent studies may defend mitochondrial function during pressure-overload (reduced LV function) HF (33), suggesting that BMI not only reflects cachexia and ambient inflammation, but also may be a marker of improved mitochondrial function in HF. Indeed, obesity in HF with reduced ejection fraction reflects both more lean muscle mass (associated with overall strength) and greater

adiposity, associated with improvements in strength and exercise capacity (34). Ultimately, frailty leads to increased hospitalization and cost in HF (35). Indeed, in an analysis including the 195 patients in our cohort with "cachexia" (as defined by BMI <18.5 kg/m^2), cachectic patients had a markedly increased hazard of death relative to other BMI categories (Online Fig. 2).

Although exercise- and dietary-mediated weight loss of obese persons with HF (specifically with normal LV function) remains supported by practice guidelines (36), our results suggest closer clinical surveillance for patients with unintentional weight loss who are hospitalized with HF. Although in aggregate our findings in ADHF agree with prior reports regarding chronic HF attesting to a protection from death with a higher BMI, our data suggest that the prognostic association of BMI with mortality is more complex than previously articulated, depending on age, LV function, and chronicity of HF, issues at the heart of ADHF risk stratification and management. Ultimately, the clinical implications of BMI are not region specific, but are specific to patient characteristics, severity, and type of HF. This insight also mandates that ongoing efforts in ADHF investigation consider differences in mortality by BMI categories, specifically as they interact with age, LV function, and chronicity. Failure to consider these emerging concepts in clinical trials design may lead to decreased event rates and underpowered, nongeneralizable results. In this context, we established that certain prognostic HF markers (e.g., ST2) are not affected by BMI, suggesting their centrality for clinical and research use in ADHF, independent of BMI.

Study limitations. The conclusions of our study should be viewed in the context of its design. Although every patient in this study has ADHF, the details of symptomatic status before admission (e.g., New York Heart Association functional class) and pre-hospital course are not specified. In addition, although weight assessed on admission may reflect some component of fluid overload, increased fluid (a higher BMI referable to more "HF") would be expected to worsen mortality (not improve mortality, as we observed in this study). Although patients without BMI data available (Fig. 1) were excluded, the remaining population was a large, multinational cohort with robust association between BMI and prognosis. In addition, the sample population was derived from a collection of prospectively enrolled studies of ADHF worldwide, and as such, data collection for certain markers of HF disease severity (e.g., echocardiography) was not uniform across continents. However, the strength of intercontinental patient recruitment, full adjudication of clinical outcome, and complete assessment of known clinical, hemodynamic, and biomarkers of prognosis increase the generalizability of our results. In addition, although we did not have data on specific cause of mortality in these persons, patients with active conditions limiting survival were excluded from the population. We did not have data regarding in-hospital management across different continents in this study; however, the lack of effect modification of location with the association between BMI and mortality suggests that the site-specific treatment differences may not greatly affect the strength of this relationship. Finally, given the lack of data on longitudinal changes in weight over time, associations among weight change (intentional or unintentional), BMI, and outcome could not be assessed.

Conclusions

Although these observations certainly do not endorse weight gain to "protect" patients with established HF, the general implication is that a lower BMI in ADHF identifies patients at particularly high risk. This phenomenon is evident in patients previously classified as "normal weight," thereby possibly resetting what is considered the lower normative bound for BMI in the ADHF setting. Ultimately, whereas a high BMI may not be the arbiter of prognostic benefit for patients hospitalized with HF, a normal BMI—especially in the context of cardiac function and older age—particularly signals adverse long-term prognosis. The clinical management of excess weight in patients hospitalized for ADHF needs specific tailoring at this sentinel stage in disease progression.

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Key Words: heart failure ■ obesity ■ obesity paradox.

APPENDIX

For supplemental tables and a figure, please see the online version of this article.