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NT-proBNP for Risk Prediction in Heart Failure



Identification of Optimal Cutoffs Across Body Mass Index Categories

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ABSTRACT

OBJECTIVES The goal of this study was to assess the predictive power of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the decision cutoffs in heart failure (HF) across body mass index (BMI) categories.

BACKGROUND Concentrations of NT-proBNP predict outcome in HF. Although the influence of BMI to reduce levels of NT-proBNP is known, the impact of obesity on prognostic value remains uncertain.

METHODS Individual data from the BIOS (Biomarkers In Heart Failure Outpatient Study) consortium were analyzed. Patients with stable HF were classified as underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5-24.9 kg/m²), overweight (BMI 25-29.9 kg/m²), and mildly (BMI 30-34.9 kg/m²), moderately (BMI 35-39.9 kg/m²), or severely (BMI ≥40 kg/m²) obese. The prognostic role of NT-proBNP was tested for the endpoints of all-cause and cardiac death.

RESULTS The study population included 12,763 patients (mean age 66 ± 12 years; 25% women; mean left ventricular ejection fraction 33% ± 13%). Most patients were overweight (n = 5,176), followed by normal weight (n = 4,299), mildly obese (n = 2,157), moderately obese (n = 612), severely obese (n = 314), and underweight (n = 205). NT-proBNP inversely correlated with BMI ($\beta = -0.174$ for 1 kg/m²; $P < 0.001$). Adding NT-proBNP to clinical models improved risk prediction across BMI categories, with the exception of severely obese patients. The best cutoffs of NT-proBNP for 5-year all-cause death prediction were lower as BMI increased (3,785 ng/L, 2,193 ng/L, 1,554 ng/L, 1,045 ng/L, 755 ng/L, and 879 ng/L, for underweight, normal weight, overweight, and mildly, moderately, and severely obese patients, respectively) and were higher in women than in men.

CONCLUSIONS NT-proBNP maintains its independent prognostic value up to 40 kg/m² BMI, and lower optimal risk-prediction cutoffs are observed in overweight and obese patients. (J Am Coll Cardiol HF 2021;9:653-663)

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**ABBREVIATIONS
AND ACRONYMS****BMI** = body mass index**eGFR** = estimated glomerular filtration rate**HF** = heart failure**LVEF** = left ventricular ejection fraction**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**SHR** = subdistribution hazard ratio

Despite recent advances in therapy, heart failure (HF) remains associated with significant morbidity and mortality (1,2). N-terminal pro-B-type natriuretic peptide (NT-proBNP) has a well-established role in risk stratification of patients with chronic HF, as it is associated with disease severity and poor outcomes (3-5). Circulating concentrations of NT-proBNP are influenced by several cardiac (eg, atrial fibrillation) and noncardiac (eg, age, renal function, pulmonary comor-

bidity) factors (6). Among noncardiac factors, body mass index (BMI) has also been consistently shown to inversely correlate with NT-proBNP both in healthy individuals and in patients with HF caused by numerous postulated mechanisms (7-12).

In the last decades, the prevalence of obesity has almost tripled worldwide according to the World Health Organization and frequently affects patients with HF (13). Obesity is a major risk factor for cardiovascular diseases, including hypertension and coronary artery disease (14); still, an “obesity paradox” has been reported to describe the lower mortality observed in HF patients with higher BMI, especially among those with nonischemic etiology (10). Furthermore, previous studies have provided conflicting evidence on the performance of natriuretic peptides for risk prediction in higher BMI classes (15-17), and whether sex-related differences may affect the relation between BMI and NT-proBNP levels in HF is debated (18).

The goal of the present study was to assess the impact of BMI on the association between NT-proBNP and outcome in a large international cohort of patients with chronic HF across the left ventricular ejection fraction (LVEF) spectrum.

METHODS

STUDY POPULATION. The population of the present study was selected from the BIOS (Biomarkers In

Heart Failure Outpatient Study) consortium, including 13 cohorts of patients with stable chronic HF and available NT-proBNP results. The data set was built starting from a core population collected in 2018 (from 11 original cohorts) and used to perform an individual patient data meta-analysis on the prognostic value of high-sensitivity troponin in chronic HF (n = 9,289, as detailed by Aimo et al [19]). Later, patients from other trials with similar inclusion criteria were included (up to 15,681 individuals). Only patients with stable, chronic HF were included, and data were prospectively collected within each study.

For the aim of the present study, only patients with available BMI data at enrollment (n = 12,763, from 8 different cohorts) were included (Supplemental Table 1) (10,20-26). Baseline characteristics, including NT-proBNP levels, of patients excluded caused by missing data on BMI were similar to the population included in the study. BMI was calculated as the ratio between weight in kilograms and the square of height in meters. According to the current nomenclature (27), patients were then distinguished into underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5-24.9 kg/m², considered as reference category), overweight (BMI 25-29.9 kg/m²), mildly obese (BMI 30-34.9 kg/m²), moderately obese (BMI 35-39.9 kg/m²), and severely obese (BMI ≥40 kg/m²).

LVEF was measured in the whole population by two-dimensional echocardiography by expert cardiologists or certified sonographers, using the modified Simpson’s rule (28). According to the latest European guidelines, patients were then classified into HF with reduced EF (LVEF <40%), HF with mid-range EF (LVEF 40%-49%), or HF with preserved EF (LVEF ≥50%) (29). Estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology collaboration equation (30). Plasma samples for NT-proBNP testing were collected at time of enrollment in each study, and the monoclonal electrochemiluminescence immunoassay method (Roche Diagnostics; coefficient

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

TABLE 1 General Features of the Study Population and Comparisons Across BMI Categories

	All Patients (N = 12,763)	Normal Weight (n = 4,299 [33%])	Underweight (n = 205 [2%])	Overweight (n = 5,176 [40%])	Mildly Obese (n = 2,157 [17%])	Moderately Obese (n = 612 [5%])	Severely Obese (n = 314 [3%])
Clinical features							
Age, y	66 ± 12	68 ± 13	69 ± 15	66 ± 12 ^a	64 ± 12 ^a	62 ± 13 ^a	58 ± 13 ^a
Male	9,566 (75)	3,149 (73)	108 (53) ^a	4,127 (80) ^a	1,611 (75)	400 (65)	182 (58) ^a
BMI, kg/m ²	27 ± 5	23 ± 2	17 ± 1 ^a	27 ± 1 ^a	32 ± 1 ^a	37 ± 1 ^a	45 ± 5 ^a
LVEF, %	33 ± 13	32 ± 12	32 ± 12	33 ± 12 ^a	35 ± 13 ^a	37 ± 15 ^a	39 ± 16 ^a
HFrEF	9,676 (76)	3,401 (79)	158 (77)	4,020 (77)	1,533 (70)	382 (60) ^a	182 (48) ^a
HFmrEF	1,519 (12)	489 (11)	21 (10)	607 (12)	272 (12)	95 (15)	35 (11)
HFpEF	1,568 (12)	409 (10)	26 (13)	550 (11)	351 (16) ^b	135 (21) ^a	97 (24) ^a
Ischemic etiology	6,744 (53)	2,318 (54)	97 (47)	2,890 (56)	1,079 (50)	261 (43) ^a	99 (32) ^a
NYHA functional class III-IV	4,131 (32)	1,462 (34)	79 (39)	1,571 (30) ^b	657 (31) ^b	229 (37)	133 (42)
NT-proBNP, ng/L	1,252 (492-2,915)	1,825 (748-4,217)	2,931 (1,247-7,716) ^a	1,132 (464-2,567) ^a	900 (357-1,954) ^a	736 (303-1,601) ^a	662 (261-1,461) ^a
Comorbidities							
Atrial fibrillation	2,816 (22)	858 (20)	41 (20)	198 (21)	542 (25) ^b	176 (29) ^a	101 (32) ^a
Hypertension	6,886 (54)	1,985 (46)	93 (45)	2,818 (54) ^a	1,355 (63) ^a	423 (69) ^a	212 (68) ^a
Diabetes mellitus	4,115 (32)	1,121 (26)	35 (17)	1,640 (32) ^a	860 (40) ^a	300 (49) ^a	159 (51) ^a
Hb, g/dL	13 ± 2	13 ± 2	13 ± 2 ^a	13 ± 2 ^a	14 ± 2 ^a	13 ± 2 ^a	14 ± 2 ^a
Anemia	3,798 (30)	1,449 (34)	83 (41)	1,453 (28) ^a	569 (26) ^a	167 (27) ^b	77 (25) ^b
Creatinine, mg/dL	1.2 (1.0-1.4)	1.2 (1.0-1.5)	1.1 (0.8-1.5) ^b	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (0.9-1.4)	1.1 (0.9-1.3) ^a
eGFR, mL/min/1.73 m ²	60 (46-75)	59 (44-75)	59 (40-82)	60 (46-74)	61 (48-77) ^a	63 (47-81) ^a	65 (48-81) ^a
CKD stage 3-5	6,191 (49)	2,184 (51)	103 (50)	2,532 (49)	981 (45)	272 (44)	119 (38) ^a
COPD	1,942 (15)	598 (14)	51 (25) ^a	747 (14)	365 (17)	105 (17)	76 (24) ^a
Therapy							
β-blockers	8,335 (65)	2,756 (64)	121 (59)	3,360 (65)	1,428 (66)	444 (73) ^b	226 (72) ^b
ACE inhibitors/ARB	10,629 (83)	3,554 (83)	167 (82)	4,298 (83)	1,849 (86)	495 (81)	266 (85)
MRA	4,089 (32)	1,356 (32)	75 (37)	1,615 (31)	712 (33)	205 (34)	126 (40) ^b

Values are mean ± SD, n (%), or median (interquartile interval). ^aP < 0.001 vs normal weight. ^bP < 0.05 vs normal weight.
 ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

of variation <3% at cutoff value [150 ng/L]) was used (31).

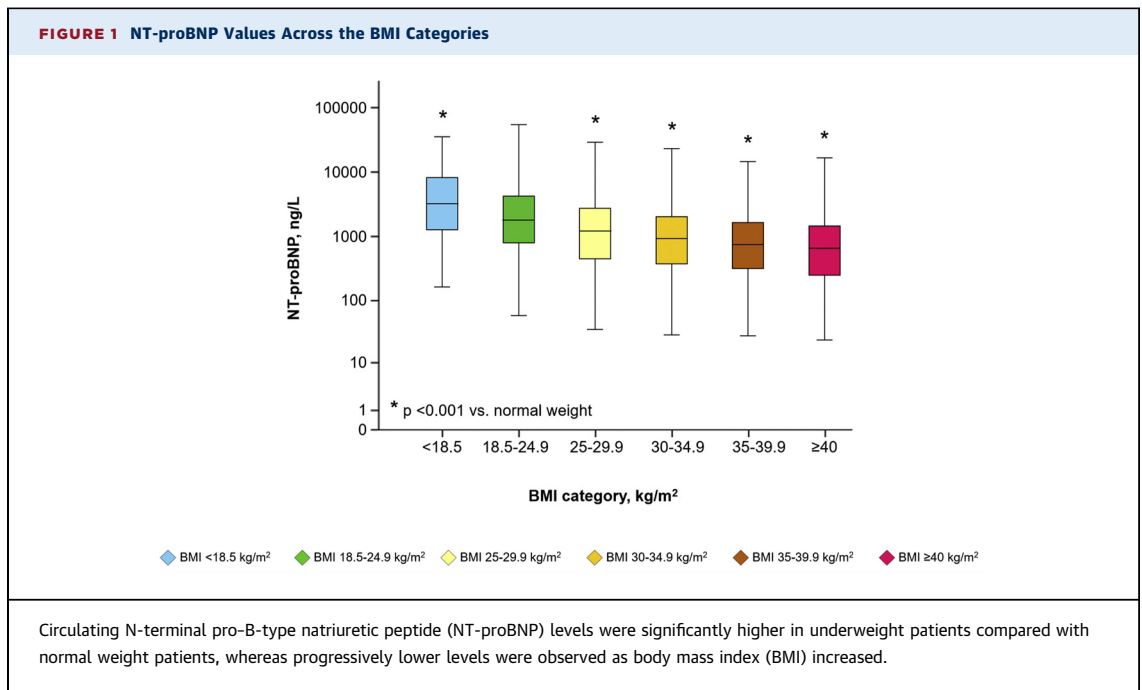
Follow-up data were retrieved for the primary and secondary endpoints of all-cause and cardiac death (including sudden cardiac death and death caused by HF progression or acute myocardial infarction), respectively. As detailed in the methods section of each included cohort, events have been adjudicated by either independent AD hoc committees (in 8,341 of 12,763 patients) (20-26) or by the study investigators based on follow-up visits, administrative databases, death certificates, and postmortem reports (10).

All patients were provided informed consent for the study, which was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki of the World Medical Association.

STATISTICAL ANALYSIS. The distribution of each variable was evaluated by using the Kolmogorov-Smirnov test. Normally distributed variables are reported as mean ± SD, whereas variables with skewed

distribution are reported as median (interquartile interval). Categorical data are reported as frequencies. Comparisons for quantitative variables between 2 groups were conducted by using Student’s *t*-test for independent samples or Mann-Whitney tests; analysis of variance or Kruskal-Wallis tests, as appropriate, were used to compare multiple groups, with post hoc Bonferroni correction for pairwise comparisons. Chi-square or Fisher exact tests were used for qualitative variables. Variables with a skewed distribution were ln-transformed before entering into regressions. Linear regression analysis was used to identify correlates of NT-proBNP among the variables reported in Table 1. Only significant univariable predictors were included in the final adjusted model, after excluding collinear predictors on the basis of the variance inflation factor.

Kaplan-Meier method and log-rank statistics (Mantel-Cox) were used to estimate survival according to BMI categories. The best cutoff of NT-proBNP in predicting either the primary or the secondary



endpoints at receiver-operating characteristic curves were assessed through the Youden's J statistic for each BMI category. Predictors of all-cause death were identified through Cox regression analysis, and competing-risks regression analysis was used for the endpoint of cardiac death, considering noncardiac death as competing outcome. Statistically significant univariable predictors were included in the final adjusted models for each BMI category. NT-proBNP was ln-transformed before entering into regressions, and thus risk estimation should be considered for each unitary increase in the ln-values.

Net reclassification improvement (with risk categories set at <10%, 10%-30%, and >30%), the integrated discrimination improvement, and the difference in Harrell's C-statistic were calculated to assess reclassification and discrimination improvements obtained by adding ln-transformed NT-proBNP to a clinical model (which included the univariable predictors of outcome for each BMI category). The prognostic value of NT-proBNP was also modeled with the p-spline smoothing method for the primary and secondary endpoints for each BMI category.

Statistical analysis was performed by using SPSS version 25.0, 2017 (IBM SPSS Statistics, IBM Corporation), R software version 3.2.3 (R Foundation for Statistical Computing), or Stata Statistical Software release 15, 2017 (StataCorp). A 2-tailed *P* value ≤ 0.05 was considered significant.

RESULTS

STUDY POPULATION. The entire cohort of the BIOS consortium included 15,681 patients. For the aims of the present study, 2,918 patients were excluded because of missing BMI data. Therefore, 12,763 patients constituted the study population; characteristics of these patients categorized according to BMI strata are reported in [Table 1](#). The study participants had an ischemic HF etiology in 6,744 individuals (53%), and 4,131 patients (32%) were in New York Heart Association functional class III to IV.

The mean BMI in the whole population was 27 ± 5 kg/m², and 40% of patients were overweight (n = 5,176), followed by normal weight (n = 4,299 [33%]), mildly obese (n = 2,157 [17%]), moderately obese (n = 612 [5%]), severely obese (n = 314 [3%]), and underweight (n = 205 [2%]). Men were more often overweight (43%), and normal weight was the most common BMI category among women (36%). The prevalence of underweight (3% vs 1%) and of moderate to severe obesity (11% vs 6%) was larger among women, whereas a similar rate of mild obesity was observed across the 2 sexes (17%) ([Supplemental Figure 1](#)).

HF with reduced EF was the most common diagnosis independent of BMI, whereas HF with preserved EF was significantly more common among obese patients than normal weight patients; there

was a similar prevalence of HF with mid-range EF among the BMI categories (Table 1). Most patients (82%) were on oral diuretic therapy, and no significant difference in diuretic use was observed across either LVEF or BMI strata.

BMI AND NT-proBNP. The median NT-proBNP value was 1,252 ng/L (492-2,915 ng/L) in the whole cohort. NT-proBNP values decreased as BMI increased and were significantly higher among underweight (2,931 ng/L [1,247-7,716 ng/L]) compared with normal weight (1,825 ng/L [748-4,217 ng/L]) patients. Conversely, overweight (1,132 ng/L [464-2,567 ng/L]), mildly obese (900 ng/L [357-1,954 ng/L]), moderately obese (736 ng/L [303-1,601 ng/L]), and severely obese (662 ng/L [261-1,461 ng/L]) patients exhibited lower values of NT-proBNP compared with normal weight patients (all; $P < 0.001$) (Figure 1). Women exhibited greater values of NT-proBNP compared with men (1,437 ng/L [561-3,372 ng/L] vs 1,194 ng/L [471-2,785 ng/L]; $P < 0.001$). However, when distinguished according to the BMI categories, such differences were statistically significant only in the overweight and mildly obese subsets (Supplemental Figure 2).

The univariable and multivariable predictors of NT-proBNP in the whole population are reported in Table 2. BMI was independently associated with NT-proBNP also after adjusting for other possible confounders (β -coefficient, -0.174; $P < 0.001$). Similar results were also observed when considering either women (β -coefficient, -0.178; $P < 0.001$) or men (β -coefficient, -0.174; $P < 0.001$) separately.

BMI AND OUTCOME. The median follow-up duration was 42 months (17 months-66 months). All-cause death was reported in 3,498 patients (27%), whereas cardiac death accounted for 2,145 (17%) events. Underweight patients had the highest rate of all-cause death (47%), followed by normal weight (29%), overweight (24%), mildly obese (20%), severely obese (20%), and moderately obese (19%) patients (log-rank = 167.1; $P < 0.001$). Similarly, the incidence of cardiac death was greater in underweight patients (27%), followed by normal weight (19%), overweight (16%), mildly obese (14%), moderately obese (12%), and severely obese (12%) patients (log-rank = 78.6; $P < 0.001$) (Supplemental Table 2, Supplemental Figure 3).

PREDICTORS OF MORTALITY AND RECLASSIFICATION ANALYSIS ACROSS BMI CATEGORIES. In multivariable Cox regression analyses, higher NT-proBNP concentrations were associated with a greater risk of all-cause death, independent of sex, LVEF, and other

TABLE 2 Univariable and Multivariable Predictors of NT-proBNP in the Study Population

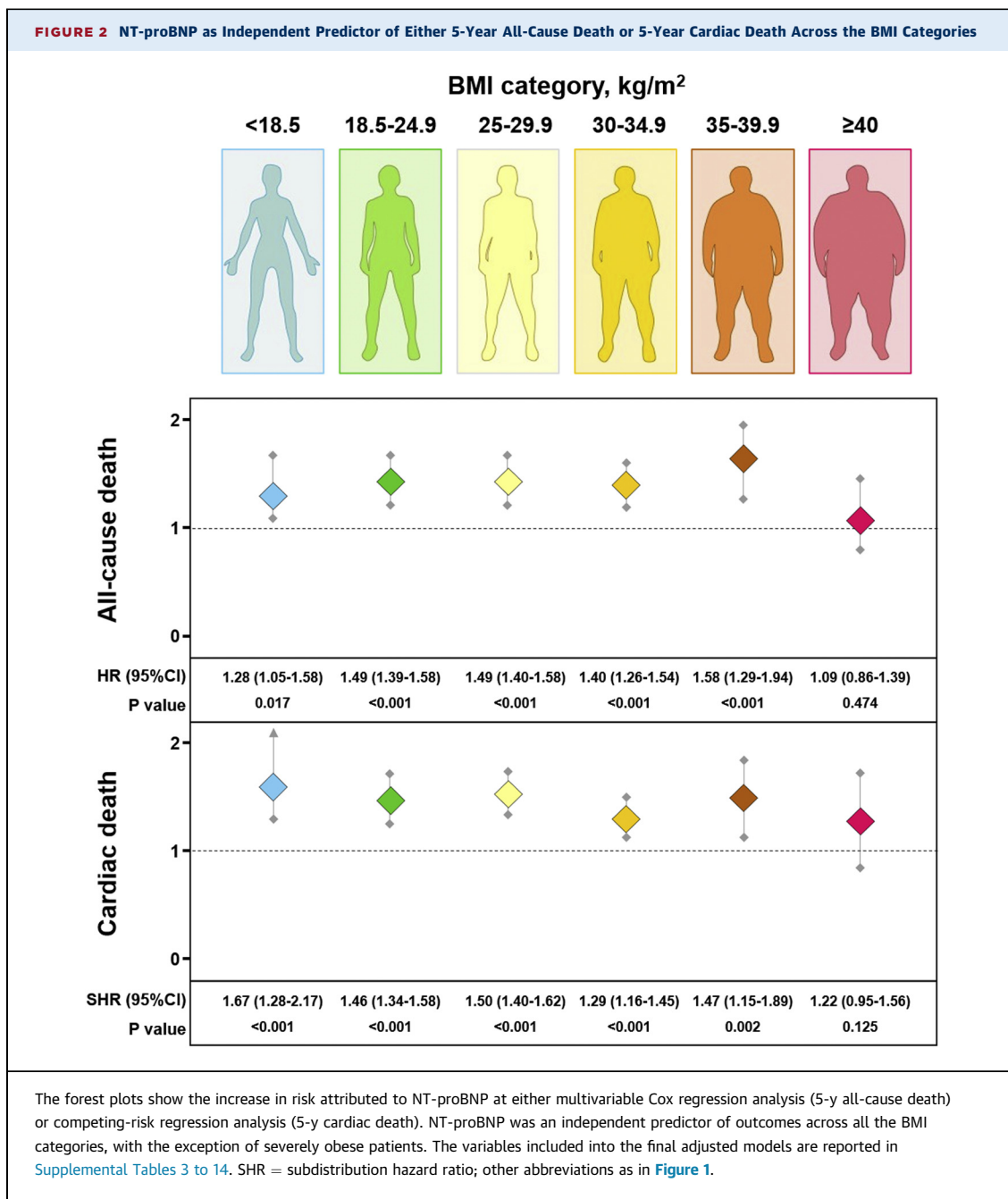
	Univariable Model		Multivariable Model	
	β -Coefficient	P Value	β -Coefficient	P Value
Age (y)	0.366	<0.001	0.162	<0.001
Male	-0.056	<0.001	0.003	0.669
BMI (kg/m ²)	-0.239	<0.001	-0.174	<0.001
LVEF (%)	-0.161	<0.001	-0.255	<0.001
Ischemic etiology	0.079	<0.001	-0.005	0.552
NYHA functional class III-IV	0.249	<0.001	0.107	<0.001
Atrial fibrillation	0.222	<0.001	0.194	<0.001
Hypertension	0.106	<0.001	0.042	<0.001
Diabetes mellitus	0.083	<0.001	0.028	<0.001
Hb (g/dL)	-0.295	<0.001	-0.172	<0.001
eGFR (mL/min/1.73 m ²)	-0.421	<0.001	-0.260	<0.001
COPD	0.057	<0.001	-0.013	0.099
β -Blockers	0.050	<0.001	0.082	<0.001
ACE inhibitor/ARB	-0.052	<0.001	-0.047	<0.001
MRA	0.075	<0.001	0.070	<0.001

Abbreviations as in Table 1.

covariates (as reported in Supplemental Tables 3 to 8) in underweight (HR: 1.28; 95% CI: 1.05-1.58; $P = 0.017$), normal weight (HR: 1.49; 95% CI: 1.39-1.58; $P < 0.001$), overweight (HR: 1.49; 95% CI: 1.40-1.58; $P < 0.001$), mildly obese (HR: 1.40; 95% CI: 1.26-1.54; $P < 0.001$), and moderately obese (HR: 1.58; 95% CI: 1.29-1.94; $P < 0.001$) patients but not in severely obese patients (HR: 1.09; 95% CI: 0.86-1.39; $P = 0.474$) (Figure 2).

In competing-risk regression, increasing NT-proBNP was independently associated with a greater risk of cardiac death in underweight (subdistribution HR [SHR]: 1.67; 95% CI: 1.28-2.17; $P < 0.001$), normal weight (SHR: 1.46; 95% CI: 1.34-1.58; $P < 0.001$), overweight (SHR: 1.50; 95% CI: 1.40-1.62; $P < 0.001$), mildly obese (SHR: 1.29; 95% CI: 1.16-1.45; $P < 0.001$), and moderately obese (SHR: 1.47; 95% CI: 1.15-1.89; $P = 0.002$) patients but not in severely obese patients (SHR: 1.22; 95% CI: 0.95-1.56; $P = 0.125$) (Figure 2). The other predictors of cardiac death are reported in Supplemental Tables 9 to 14. Notably, similar results were obtained when the cohort of origin was forced into the multivariable models, when merging the highest classes of BMI (ie, patients with BMI ≥ 35 kg/m²), and across the different LVEF classes (Supplemental Tables 15 to 19).

Net reclassification improvement, integrated discrimination improvement, and the difference in C-statistics were calculated for both the primary and



secondary endpoints by adding NT-proBNP to a clinical model, constituted by the other univariable predictors identified for each BMI category; the results are reported in Table 3. Including NT-proBNP allowed a significant improvement in risk prediction for the primary endpoint across all the BMI categories, with the only exception of severely obese patients. On the other hand, the inclusion of NT-proBNP improved the predictive models for cardiac death across all BMI categories.

BEST CUTOFFS OF NT-proBNP FOR RISK PREDICTION ACROSS BMI CATEGORIES. The best cutoffs of NT-proBNP for risk prediction across BMI categories are reported in Table 4. The best cutoff of NT-proBNP to predict 5-year all-cause death was 73% higher among underweight patients (3,785 ng/L) compared with normal weight individuals (2,193 ng/L). Conversely, it was 30% (1,554 ng/L), 52% (1,045 ng/L), 66% (755 ng/L), and 60% (879 ng/L) lower in overweight, mildly obese, moderately obese, and severely

TABLE 3 Improvement in Risk Prediction by Adding NT-proBNP to Clinical Models Across the BMI Categories

	NRI [95% CI]	P Value	IDI [95% CI]	P Value	Δ in C-Statistics	P Value
All-cause death						
BMI <18.5 kg/m ²	0.44 [0.40 to 0.48]	<0.001	0.05 [0.05 to 0.05]	<0.001	0.02	0.050
BMI 18.5 to 24.9 kg/m ²	0.38 [0.34 to 0.42]	<0.001	0.04 [0.04 to 0.04]	<0.001	0.04	<0.001
BMI 25 to 29.9 kg/m ²	0.35 [0.28 to 0.42]	<0.001	0.04 [0.03 to 0.04]	<0.001	0.03	0.049
BMI 30 to 34.9 kg/m ²	0.31 [0.19 to 0.42]	<0.001	0.03 [0.02 to 0.04]	<0.001	0.02	0.048
BMI 35 to 39.9 kg/m ²	0.38 [0.17 to 0.59]	<0.001	0.04 [0.02 to 0.07]	<0.001	0.04	0.044
BMI ≥40 kg/m ²	-0.02 [-0.01 to 0.02]	0.877	0.01 [-0.00 to 0.03]	0.165	0.00	0.680
Cardiac death						
BMI <18.5 kg/m ²	0.46 [0.12 to 0.80]	0.008	0.06 [0.02 to 0.10]	0.003	0.07	0.012
BMI 18.5 to 24.9 kg/m ²	0.66 [0.33 to 0.98]	<0.001	0.08 [0.03 to 0.12]	<0.001	0.06	0.009
BMI 25 to 29.9 kg/m ²	0.74 [0.42 to 1.06]	<0.001	0.08 [0.03 to 0.13]	<0.001	0.07	0.023
BMI 30 to 34.9 kg/m ²	0.67 [0.35 to 1.00]	<0.001	0.09 [0.05 to 0.15]	<0.001	0.04	0.047
BMI 35 to 39.9 kg/m ²	0.53 [0.19 to 0.86]	0.002	0.08 [0.03 to 0.12]	<0.001	0.03	0.037
BMI ≥40 kg/m ²	0.38 [0.00 to 0.77]	0.050	0.03 [0.00 to 0.06]	0.024	0.01	0.053

The clinical models included the univariate predictors identified for each BMI category through either Cox regression analysis (for the endpoint of all-cause death, as reported in Supplemental Tables 3 to 8) or competing-risk regression analysis (for the endpoint of cardiac death, as reported in Supplemental Tables 9 to 14).
 Δ = difference; IDI = integrated discrimination improvement; NRI = net reclassification index; other abbreviations as in Table 1.

obese patients compared with normal weight patients, respectively.

Although women exhibited NT-proBNP cutoffs approximately 30% higher compared with men across all the BMI categories, the association of increasing BMI with lower optimal cutoffs of NT-proBNP for risk prediction was maintained in both sexes (Table 5).

Finally, similar results were observed for the secondary endpoint of 5-year cardiac death and when considering either 1-year all-cause or cardiac death as endpoints (Supplemental Table 20).

The differences among the cutoffs identified at receiver-operating characteristic analysis were confirmed by smoothing the HR for increasing values of NT-proBNP through p-spline curves. The crossing-point between the curve and the neutral risk of all-cause death was shifted to the right (ie, toward higher values of NT-proBNP) in underweight patients, and to the left (ie, toward lower values of NT-proBNP) in overweight, mildly obese, moderately obese, and severely obese patients, compared with normal weight patients (Central Illustration, Supplemental Figure 4). A similar trend was observed when considering cardiac death (Supplemental Figure 5).

DISCUSSION

In a large international cohort of patients with chronic HF, NT-proBNP was inversely correlated to BMI independent of several possible confounding factors. Furthermore, NT-proBNP improved the risk prediction across nearly all BMI categories on top of a clinical model. Finally, in survival analysis, the best

cutoffs for risk prediction of NT-proBNP were significantly influenced by BMI and were higher in women than in men.

In line with previous studies, circulating concentrations of NT-proBNP were lower as BMI increased (10,17,32). Both cardiac and extracardiac factors may affect circulating levels of NT-proBNP, including age, HF etiology, and systolic function (11). Although normal weight patients were older and had lower LVEF and a higher prevalence of ischemic cardiomyopathy, other possible confounders increasing natriuretic peptides (namely atrial fibrillation, systemic arterial hypertension, and diabetes mellitus) were actually more prevalent across the higher BMI categories (33-35). Obesity-related renal alterations, characterized by higher circulating volume and glomerular hyperfiltration, may enhance the clearance of natriuretic peptides (7,36). Accordingly, obese patients exhibited slightly better renal function compared with lean individuals, and eGFR was inversely related to NT-proBNP. Variable enzymatic and/or fat cell-dependent clearance systems could participate as well (7,11,37-39). Although enhanced clearance of natriuretic peptides has been hypothesized to explain this finding, it is hard to support this as a mechanism, caused by the fact that both NT-proBNP and BNP (cleared via different mechanisms) are comparably affected by increased BMI. Accordingly, reduction of release of NT-proBNP likely plays a larger role. Increased epicardial adiposity could blunt ventricular transmural stress, thus lowering natriuretic peptide secretion in obese individuals (12), and a leading hypothesis is that higher androgen

TABLE 4 Best Cutoffs of NT-proBNP in Predicting Either 5-Year All-Cause or Cardiac Death Across the BMI Categories

	NT-proBNP Cutoff (ng/L)	AUC	Sensitivity	Specificity	P Value
5-y all-cause death					
BMI <18.5 kg/m ²	3,785	0.662	0.554	0.702	<0.001
BMI 18.5-24.9 kg/m ²	2,193	0.705	0.664	0.645	<0.001
BMI 25-29.9 kg/m ²	1,554	0.713	0.637	0.673	<0.001
BMI 30-34.9 kg/m ²	1,045	0.666	0.646	0.604	<0.001
BMI 35-39.9 kg/m ²	755	0.695	0.721	0.569	<0.001
BMI ≥40 kg/m ²	879	0.610	0.552	0.643	0.010
5-y cardiac death					
BMI <18.5 kg/m ²	3,866	0.720	0.706	0.683	<0.001
BMI 18.5-24.9 kg/m ²	2,194	0.705	0.700	0.615	<0.001
BMI 25-29.9 kg/m ²	1,413	0.718	0.707	0.619	<0.001
BMI 30-34.9 kg/m ²	1,044	0.662	0.656	0.585	<0.001
BMI 35-39.9 kg/m ²	691	0.664	0.739	0.532	<0.001
BMI ≥40 kg/m ²	1,058	0.663	0.576	0.694	0.002

AUC = area under the curve; other abbreviations as in Table 1.

concentrations (frequently associated with greater adiposity) may suppress expression of the *BNP* gene, thus contributing to lower concentrations of circulating BNP or NT-proBNP (40-42).

In the general population, NT-proBNP levels are significantly higher in women compared with men, and a possible sex interaction in the relation between BMI and natriuretic peptides has been described. Indeed, in a multivariable adjusted model, NT-proBNP levels were lower in women compared with men as BMI increased, whereas abdominal obesity was associated with lower NT-proBNP levels only among women (8). The role of body composition on natriuretic peptides has received recent interest, with

higher NT-proBNP concentrations associated with a more favorable adiposity profile, marked by less visceral and hepatic fat and lower skeletal muscle mass (43,44). This supports the potential role of androgen concentrations between women and men as a potential mediator of this finding, as originally suggested by Chang et al (45). More data are needed to better understand how adiposity affects both BNP and NT-proBNP, but the relationship is obviously far more complex than a simple, single pathway.

Whether BMI may affect the reliability of the prognostic power of NT-proBNP in patients with chronic HF is debated. In a study by Frankenstein et al (16), NT-proBNP was an independent predictor of all-cause mortality among patients with systolic HF in each of the 3 BMI subgroups examined (20-24.9 kg/m², 25-29.9 kg/m², and ≥30 kg/m²). Conversely, in a recent subanalysis of the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, the association between NT-proBNP and the primary outcome (a composite of death from cardiovascular causes or a first hospitalization for HF) was weaker in the highest BMI categories (17), similar to our findings. It could be hypothesized that other unknown factors might impair the predictive value of NT-proBNP in obese individuals. However, our results show, in a large international cohort that, although weakened, the additive prognostic significance of NT-proBNP is maintained in patients with HF across different BMI categories, with the exception of the most severely obese patients. As a further point, we chose all-cause death and cardiac death as primary and secondary endpoints, respectively, whereas the combination of all-cause mortality and heart transplantation (15,16) or of cardiovascular death and HF hospitalization (17) were considered in previous studies.

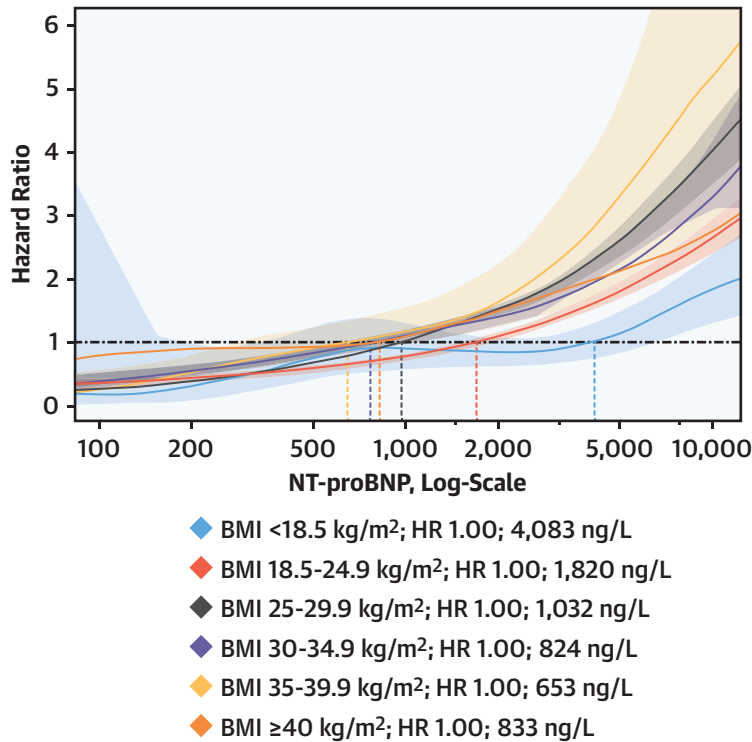
STUDY LIMITATIONS. BMI and the other clinical variables were only assessed at the time of recruitment, and thus any possible variation during follow-up could not be taken into account. In addition, BMI does not provide information on body fat distribution, nor does it discriminate lean from fat mass or weight gain related to edema/congestion. Nevertheless, BMI is significantly correlated with total body fat content and remains a commonly adopted index for the estimation of body composition, especially in larger populations (27), as the use of more accurate parameters (eg, waist-to-height ratio) is less applicable and holds uncertain additive clinical relevance (46). We found that NT-proBNP prognostic cutoffs are lower in patients with higher BMI. Because we used

TABLE 5 Best Cutoffs of NT-proBNP in Predicting 5-Year All-Cause Death Across the BMI Categories in Either Women or Men

		NT-proBNP Cutoff (ng/L)	AUC	Sensitivity	Specificity	P Value
BMI <18.5 kg/m ²	Female	3,385	0.651	0.575	0.661	0.010
	Male	2,953	0.683	0.635	0.667	0.002
BMI 18.5-24.9 kg/m ²	Female	2,728	0.694	0.614	0.695	<0.001
	Male	2,196	0.709	0.666	0.652	<0.001
BMI 25-29.9 kg/m ²	Female	2,021	0.719	0.621	0.709	<0.001
	Male	1,529	0.714	0.633	0.683	<0.001
BMI 30-34.9 kg/m ²	Female	1,591	0.716	0.625	0.730	<0.001
	Male	1,045	0.649	0.615	0.613	<0.001
BMI 35-39.9 kg/m ²	Female	1,049	0.664	0.575	0.632	0.001
	Male	864	0.711	0.690	0.641	<0.001
BMI ≥40 kg/m ²	Female	889	0.693	0.684	0.617	0.007
	Male	631	0.575	0.538	0.523	0.158

Abbreviations as in Tables 1 and 4.

CENTRAL ILLUSTRATION N-Terminal Pro-B-Type Natriuretic Peptide and Risk of All-Cause Death Across the Body Mass Index Categories



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The **spline curves** show how the risk of all-cause death changes according to N-terminal pro-B-type natriuretic peptide (NT-proBNP) circulating levels in each body mass index (BMI) category. The **colored shaded area around each curve** represents the upper and lower limits of the 95% CI. The **vertical dotted lines** indicate the projection on the horizontal axis of the crossing point between each spline curve and a HR of 1.00. Log-scale: base-10 log-scale.

the Youden method to calculate these cutoffs, assuming that false-positive findings were as undesirable as false-negative findings, they may be less applicable for specific purposes, needing the optimization of either sensitivity or specificity. The Chronic Kidney Disease Epidemiology collaboration equation was used to estimate GFR in the study population. Although considered a reliable method for the assessment of renal function in clinical practice in obese subjects (47), some underestimation and/or overestimation could not be excluded among the extreme BMI categories. Finally, the whole population included in the study, although composed only of patients with chronic HF, has been assembled from different cohorts with slightly different characteristics, and women accounted for only a minority (25%) of the study population; therefore, the survival analysis was not powered enough to perform sex-

specific analyses on the prognostic role of NT-proBNP in the extreme BMI categories.

CONCLUSIONS

Circulating levels of NT-proBNP are inversely correlated to BMI in chronic HF independently from other possible confounders, including sex. NT-proBNP maintained its independent prognostic value up to 40 kg/m² BMI, with lower cutoffs in overweight and obese patients. Testing the prognostic value of natriuretic peptides in patients with different BMI values is of major clinical relevance given the increasing prevalence of obesity in the general population and in patients with HF (13). Further to some possible implications of BMI-adjusted cut points in clinical practice (48), they may be important for designing the enrollment criteria in future population

studies and clinical trials, instead of the arbitrary BMI correction factor for natriuretic peptide sometimes adopted (49).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Both the circulating levels and the best cutoffs for risk prediction of NT-proBNP in chronic HF are significantly affected by BMI and patient's sex, being lower as BMI increases and higher in women than men. Lower cutoffs of NT-proBNP should be considered in overweight and obese patients with chronic HF, particularly when male.

TRANSLATIONAL OUTLOOK: Although sex hormones and body fat distribution may play major roles, additional studies are needed to clarify the pathophysiological links between natriuretic peptides, BMI, and sex in patients with HF.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.