

ORIGINAL RESEARCH

# Obesity and Serial NT-proBNP Levels in Guided Medical Therapy for Heart Failure With Reduced Ejection Fraction: Insights From the GUIDE-IT Trial

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**BACKGROUND:** Obese patients have lower NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels. The prognostic implications of achieving NT-proBNP levels  $\leq 1000$  pg/mL in obese patients with heart failure (HF) receiving biomarker-guided therapy are not completely known. We evaluated the prognostic implications of obesity and having NT-proBNP levels ( $\leq 1000$  pg/mL) in the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment in HF) trial participants.

**METHODS AND RESULTS:** The risk of adverse cardiovascular events (HF hospitalization or cardiovascular mortality) was assessed using multivariable-adjusted Cox proportional hazard models based on having NT-proBNP  $\leq 1000$  pg/mL (taken as a time-varying covariate), stratified by obesity status. The study outcome was also assessed on the basis of the body mass index at baseline. The predictive ability of NT-proBNP for adverse cardiovascular events was assessed using the likelihood ratio test. Compared with nonobese patients, obese patients were mostly younger, Black race, and more likely to be women. NT-proBNP levels were 59.0% (95% CI, 39.5%–83.5%) lower among obese individuals. The risk of adverse cardiovascular events was lower in obese (hazard ratio [HR], 0.48; 95% CI, 0.29–0.59) and nonobese (HR, 0.32; 95% CI, 0.19–0.57) patients with HF who had NT-proBNP levels  $\leq 1000$  pg/mL, compared with those who did not. There was no interaction between obesity and having NT-proBNP  $\leq 1000$  pg/mL on the study outcome ( $P > 0.10$ ). Obese patients had a greater risk of developing adverse cardiovascular events (HR, 1.39; 95% CI, 1.01–1.90) compared with nonobese patients. NT-proBNP was the strongest predictor of adverse cardiovascular event risk in both obese and nonobese patients.

**CONCLUSIONS:** On-treatment NT-proBNP level  $\leq 1000$  pg/mL has favorable prognostic implications, irrespective of obesity status. NT-proBNP levels were the strongest predictor of cardiovascular events in both obese and nonobese individuals in this trial.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01685840.

**Key Words:** cardiovascular outcomes ■ heart failure ■ mortality ■ natriuretic peptides ■ obesity

Obesity is a growing epidemic in the United States and a major risk factor for the development of heart failure (HF).<sup>1–7</sup> However, once HF develops, overweight and obese patients have paradoxically been reported to have a better prognosis compared with those

who are normal or underweight.<sup>8–15</sup> Natriuretic peptides (NPs) (specifically, B-type NP and NT-proBNP [N-terminal pro-B-type NP]) are the gold standard biomarkers for HF risk stratification, diagnosis, and prognostication. They are also unexpectedly lower in obese individuals.<sup>7,16–23</sup>

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## CLINICAL PERSPECTIVE

### What Is New?

- NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels, a strong prognostic biomarker, are ~59% lower in obese patients with heart failure with reduced ejection fraction.
- Increasing body mass index and obesity in patients with heart failure with reduced ejection fraction is associated with a higher risk of an adverse cardiovascular event, irrespective of whether the biomarker-based strategy guided clinical care was used or not.

### What Are the Clinical Implications?

- NT-proBNP levels are the strongest prognostic markers for adverse cardiovascular events, irrespective of the obesity status.
- Compared with those with NT-proBNP levels of >1000 pg/mL, patients with heart failure with reduced ejection fraction with on-treatment NT-proBNP levels of ≤1000 pg/mL have a lower risk of heart failure hospitalization or death.

## Nonstandard Abbreviations and Acronyms

<b>GDMT</b>	guideline-directed medical therapy
<b>GUIDE-IT</b>	Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment in Heart Failure
<b>HFrEF</b>	heart failure with reduced ejection fraction
<b>NP</b>	natriuretic peptide
<b>NYHA</b>	New York Heart Association

Despite having lower NP levels than nonobese patients, prior data indicate that NT-proBNP levels may retain diagnostic and prognostic significance among obese patients presenting with acute dyspnea or advanced HF.<sup>7,19–21,24,25</sup> The results from the multicenter, randomized GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment in HF) trial, evaluating the role of NT-proBNP levels to guide HF management, were neutral.<sup>26</sup> Secondary analyses from the GUIDE-IT trial and prior studies indicate that those who achieved the NT-proBNP levels of ≤1000 pg/mL had a lower risk of adverse cardiovascular events.<sup>17,27–30</sup> However, the prognostic implications of having on-treatment NT-proBNP ≤1000 pg/mL in obese patients with HF receiving biomarker-guided HF therapy are not known. Moreover, the implications of

obesity, a known NP deficient state, in the setting of a guided HF trial, are not known.

We hypothesize that obese patients with HF have a greater risk of adverse cardiovascular events than nonobese patients, which is predicted by NT-proBNP levels and improves with the attainment of NT-proBNP levels of ≤1000 pg/mL. We examined the participants of the GUIDE-IT trial to characterize HF with reduced ejection fraction (HFrEF) in obese patients by evaluating the prognostic implications of body mass index (BMI), baseline NT-proBNP, and having NT-proBNP levels of ≤1000 pg/mL in obese patients with HF receiving biomarker-guided HF therapy. We also analyzed the optimization of guideline-directed medical therapy (GDMT) during the study period, stratified by obesity status.

## METHODS

Anonymized study data are available at the National Heart, Lung, and Blood Institute BioLINCC data repository and can be accessed at <https://biolincc.nhlbi.nih.gov/home/>. The GUIDE-IT trial was a multicenter, controlled, unblinded trial that randomized 894 patients with HFrEF to biomarker-guided and standard evidence-based medical care for the management of HF.<sup>26,31</sup> The National Heart, Lung, and Blood Institute–sponsored study was conducted at 45 clinical sites in the United States and Canada, between January 16, 2013, and September 20, 2016. The local institutional review boards at the respective trial sites approved the study, and all participants provided written informed consent.<sup>26,31</sup>

### Inclusion and Exclusion Criteria

The study rationale, design, inclusion and exclusion criteria, and results of the trial have been previously described.<sup>26,31</sup> In brief, the trial enrolled patients with recently documented systolic HF (left ventricular ejection fraction ≤40% within 12 months before randomization), having had an HF event (HF hospitalization, emergency department visit for HF, or outpatient HF management with intravenous diuretics) in the preceding 12 months and elevated NP levels (B-type NP >400 pg/mL or NT-proBNP >2000 pg/mL) in the 30 days before randomization. We included 873 participants with baseline BMI and NT-proBNP data available.

### Study Procedures

The GUIDE-IT trial participants underwent extensive baseline testing and physical examination before simple, unrestricted randomization to respective HF management arms. Subjects were followed up at 2 weeks, 6 weeks, 3 months, and then every 3 months for the remaining study period. Each follow-up visit entailed the collection of blood for

**Table 1. Baseline Characteristics of Study Participants: Stratified by Obesity Status**

Characteristics	Nonobese (N=506)	Obese (N=367)	P Value
<b>Demographics</b>			
Age, y	66 (57–75)	58 (49–66)	<0.001
Black race	163 (30.9)	161 (43.9)	<0.001
Men	381 (72.3)	227 (61.9)	0.001
<b>Medical history</b>			
Alcohol abuse	69 (13.1)	33 (9.0)	0.69
Atrial fibrillation	82 (15.8)	63 (17.4)	0.60
Cancer	34 (6.5)	10 (2.7)	0.01
CKD	190 (36.1)	140 (38.2)	0.57
COPD	107 (20.3)	86 (23.4)	0.28
Depression treated with medication	79 (15)	62 (16.9)	0.46
Diabetes mellitus	211 (40.0)	199 (54.2)	<0.001
Duration of HF, mo	11.0 (1.0–60.0)	21.5 (1.0–81.5)	0.07
Dyslipidemia	302 (57.4)	222 (60.5)	0.37
History of IHD	295 (56.1)	152 (41.4)	<0.001
History of smoking	188 (35.7)	116 (31.6)	0.22
Hypertension	400 (76.1)	306 (83.4)	0.01
ICD or pacemaker	238 (45.3)	157 (42.8)	0.49
Peripheral arterial disease	62 (11.8)	32 (8.7)	0.15
Prior MI	174 (33.1)	77 (21)	<0.001
Sleep apnea	54 (10.3)	147 (40.1)	<0.001
Stroke	57 (10.8)	38 (10.4)	0.91
Ventricular tachycardia/fibrillation	99 (18.8)	61 (16.7)	0.42
<b>Clinical assessment</b>			
6-min Walk test distance, m	300.0 (199.0–375.0)	281.9 (165.0–365.7)	0.03
Ascites	30 (5.7)	16 (4.4)	0.50
BMI, kg/m <sup>2</sup>	25.2 (22.8–27.5)	35.1 (32.2–39.7)	<0.001
DBP, mm Hg	68 (60–78)	72 (63–80)	<0.001
Heart rate, beats/min	75 (66–85)	78 (68–88)	0.01
JVD	144 (28.9)	99 (29.2)	0.79
LVEF, %	23.0 (20.0–30.0)	24.0 (20.0–30.0)	0.63
NYHA class			0.006
I	39 (7.4)	39 (7.4)	
II	279 (53.2)	279 (53.2)	
III	193 (36.8)	193 (36.8)	
IV	7 (1.3)	7 (1.3)	
Orthopnea			0.27
None	158 (30.2)	158 (30.2)	
Mild	156 (29.8)	156 (29.8)	
Moderate	133 (25.4)	133 (25.4)	
Severe	52 (9.9)	52 (9.9)	
Percent oxygen saturation (SpO <sub>2</sub> )	98 (96–99)	97 (95–98)	0.003
Peripheral edema	199 (51.8)	185 (48.2)	0.47
Rales	63 (12.5)	37 (10.1)	0.06
S3 gallop	51 (9.7)	30 (8.2)	0.63
SBP, mm Hg	112 (100–126)	116 (103–130)	0.02

(Continued)

**Table 1. Continued**

Characteristics	Nonobese (N=506)	Obese (N=367)	P Value
Medications at baseline			
ACE inhibitor	333 (63.6)	232 (63.2)	0.94
ARBs	93 (17.8)	56 (15.3)	0.36
β-Blocker	499 (95.2)	346 (94.3)	0.47
CCB	29 (5.5)	39 (10.6)	0.01
GDMT score	6 (4–8)	7 (4–9)	<0.001
Loop diuretic	491 (93.7)	358 (97.6)	0.01
Mineralocorticoid receptor antagonist	256 (48.9)	188 (51.2)	0.50
Statin	309 (59)	221 (60.2)	0.87
Laboratory data			
BUN, mg/dL	22.0 (13.0–33.0)	23.0 (16.0–35.0)	0.04
Creatinine, mg/dL	1.29 (1.0–1.7)	1.3 (1.1–1.7)	0.48
NT-proBNP, pg/mL	3412.0 (1847.0–6771.0)	1964.0 (1145.0–3643.0)	<0.001
Serum potassium, mmol/L	4.4 (4.1–4.8)	4.2 (3.9–4.6)	<0.001
Serum sodium, mmol/L	138.0 (136.0–141.0)	139.0 (136.0–141.0)	0.40
Biomarker-guided therapy arm	266 (50.5)	180 (49.1)	0.68

Data represented as count (percentage) and median (25<sup>th</sup>–75<sup>th</sup> percentile). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

NT-proBNP assessment locally (in biomarker-guided arm only) and additional sample collection for centralized NT-proBNP testing (in both arms) at the biomarker core laboratory in Duke Clinical Research Institute, Durham, NC.<sup>31</sup> The results from core laboratory assessments were not transmitted back to the investigators. The follow-up visits also involved focused history collection, physical examination, and medication adjustment with the documentation of the rationale behind the adjustments. Although the specific medication adjustments were at the discretion of the treating physicians, prioritization of the neurohormonal antagonist titration was encouraged over diuretics in the absence of volume overload or congestion.<sup>26,31</sup> The prespecified primary outcome for the GUIDE-IT trial was the time-to-first HF hospitalization or cardiovascular cause of death, which was adjudicated by a blinded clinical events committee. The trial was discontinued by the National Heart, Lung, and Blood Institute–appointed data and safety monitoring board at 81% of planned enrollment after 50% of planned primary end point events had occurred, as the study met the prespecified inefficiency criteria.<sup>26</sup>

## Measures and Outcomes

The GUIDE-IT trial participants were stratified on the basis of baseline BMI into quartiles and into obese (BMI  $\geq 30$  kg/m<sup>2</sup>) and nonobese groups (BMI  $< 30$  kg/

m<sup>2</sup>). The medical therapy use was evaluated at each study visit and computed as the GDMT score.<sup>17</sup> Having NT-proBNP levels of  $\leq 1000$  pg/mL and the GDMT score were treated as time-varying covariates, computed at each visit. The change in New York Heart Association (NYHA) class from baseline was taken as a time-varying covariate in secondary analysis. Achievement of NT-proBNP levels  $\leq 1000$  pg/mL among patients with HF has been shown to be associated with a lower risk of adverse cardiovascular events.<sup>17,27–30</sup> Furthermore, the biomarker-guided treatment arm of the GUIDE-IT trial required titration of the medical therapy to an NT-proBNP target of  $< 1000$  pg/mL.<sup>26</sup> Hence, given the high clinical significance, the NT-proBNP levels were dichotomized at 1000 pg/mL in this study. The outcome of interest was the development of adverse cardiovascular events (composite of HF hospitalization and death attributable to cardiovascular causes).

## Statistical Analysis

The baseline characteristics were compared using descriptive statistics. The continuous variables were summarized as median and the interquartile range (25<sup>th</sup>–75<sup>th</sup> percentile), and compared using the Wilcoxon rank-sum or Kruskal-Wallis tests. The categorical variables were summarized as counts and percentages and compared using the  $\chi^2$  or Fisher exact tests. NT-proBNP was log transformed because

**Table 2. Baseline Characteristics of Study Participants: Stratified by BMI Quartiles**

Characteristics	Quartile 1 (<24.6 kg/m <sup>2</sup> ) (N=218)	Quartile 2 (24.6–28.8 kg/m <sup>2</sup> ) (N=218)	Quartile 3 (28.8–33.8 kg/m <sup>2</sup> ) (N=219)	Quartile 4 (>33.8 kg/m <sup>2</sup> ) (N=218)	P Value
Demographics					
Age, y	68 (58–77)	65 (56–74)	63 (54–71)	56 (46–65)	<0.001
Men	157 (72.0)	160 (73.4)	155 (70.8)	125 (57.3)	0.001
Black race	64 (29.4)	69 (31.7)	74 (33.8)	111 (50.9)	<0.001
Medical history					
Alcohol abuse	40 (18.4)	24 (11)	19 (8.7)	18 (8.3)	0.005
Atrial fibrillation	34 (15.7)	38 (17.8)	41 (18.8)	31 (14.5)	0.62
Cancer	19 (8.7)	13 (6)	7 (3.2)	5 (2.3)	0.01
CKD	68 (31.2)	79 (36.2)	85 (38.8)	92 (42.2)	0.11
COPD	48 (22)	42 (19.3)	47 (21.5)	52 (23.9)	0.71
Depression treated with medication	32 (14.7)	34 (15.6)	38 (17.4)	35 (16.1)	0.90
Diabetes mellitus	74 (33.9)	93 (42.7)	116 (53)	120 (55.1)	<0.001
Duration of HF, mo	5.0 (1.0–44.0)	13.0 (1.0–51.0)	24.0 (1.0–84.0)	24.0 (1.0–84.0)	0.003
Dyslipidemia	108 (49.5)	136 (62.4)	146 (66.7)	122 (56)	0.002
History of IHD	123 (56.4)	122 (56)	114 (52.1)	78 (35.8)	<0.001
History of smoking	85 (39)	76 (34.9)	68 (31.1)	69 (31.7)	0.28
Hypertension	152 (69.7)	175 (80.3)	174 (79.5)	189 (86.7)	<0.001
ICD or pacemaker	82 (37.6)	106 (48.6)	99 (45.2)	99 (45.4)	0.12
Peripheral arterial disease	27 (12.4)	29 (13.3)	24 (11.0)	14 (6.4)	0.08
Prior MI	80 (36.7)	66 (30.3)	61 (27.9)	41 (18.8)	<0.001
Sleep apnea	18 (8.3)	23 (10.6)	59 (26.9)	99 (45.4)	<0.001
Stroke	29 (13.3)	21 (9.6)	20 (9.1)	21 (9.6)	0.47
Ventricular tachycardia/fibrillation	35 (16.1)	43 (19.7)	37 (16.9)	41 (18.9)	0.73
Clinical assessment					
6-min Walk test distance, m	300.0 (195.6–366.5)	297.0 (196.5–372.0)	305.0 (204.0–381.2)	257.5 (148.2–356.8)	0.02
Ascites	10 (4.6)	16 (7.3)	9 (4.1)	9 (4.1)	0.60
BMI, kg/m <sup>2</sup>	22.4 (21.0–23.7)	26.5 (25.7–27.6)	30.9 (29.8–32.3)	38.8 (36–43.9)	<0.001
DBP, mm Hg	68 (60–76)	69 (60–79)	70 (60–82)	72 (64–80)	<0.001
Heart rate, beats/min	75 (65.5–85)	77 (67–86)	75 (68–86)	80 (68–88)	0.07
JVD	60 (28.8)	59 (28.6)	52 (25.1)	65 (32.7)	0.64
LVEF, %	20.0 (17.0–30.0)	25.0 (20.0–31.9)	24.0 (20.0–30.0)	25.0 (20.0–30.0)	0.08
NYHA class					
I	16 (7.3)	17 (7.8)	13 (5.9)	12 (5.5)	
II	111 (50.9)	125 (57.3)	112 (51.1)	92 (42.2)	
III	87 (39.9)	68 (31.2)	88 (40.2)	106 (48.6)	
IV	2 (0.9)	3 (1.4)	3 (1.4)	7 (3.2)	
Orthopnea					
None	73 (33.5)	64 (29.4)	62 (28.3)	64 (29.4)	0.55
Mild	58 (26.6)	73 (33.5)	63 (28.8)	53 (24.3)	
Moderate	56 (25.7)	51 (23.4)	58 (26.5)	55 (25.2)	
Severe	23 (10.6)	19 (8.7)	27 (12.3)	33 (15.1)	

(Continued)

**Table 2. Continued**

Characteristics	Quartile 1 (<24.6 kg/m <sup>2</sup> ) (N=218)	Quartile 2 (24.6–28.8 kg/m <sup>2</sup> ) (N=218)	Quartile 3 (28.8–33.8 kg/m <sup>2</sup> ) (N=219)	Quartile 4 (>33.8 kg/m <sup>2</sup> ) (N=218)	P Value
Percent oxygen saturation (SpO <sub>2</sub> )	98 (96–99)	98 (96–99)	97 (96–98)	97 (95–98)	0.005
Peripheral edema	68 (18.3)	94 (25.1)	96 (25.6)	117 (31.2)	0.51
Rales	31 (31.6)	21 (21.4)	23 (23.5)	23 (23.5)	0.33
S3 gallop	21 (9.6)	20 (9.2)	19 (8.7)	17 (7.8)	0.35
SBP, mm Hg	109 (98–122)	115 (103–129)	116 (101–130)	116 (104–131.5)	0.002
Medications at baseline					
ACE inhibitor	150 (68.8)	131 (60.1)	136 (62.1)	138 (63.3)	0.27
ARBs	33 (15.1)	46 (21.1)	30 (13.7)	36 (16.5)	0.19
β-Blocker	205 (94)	211 (96.8)	210 (95.9)	202 (92.7)	0.27
CCB	7 (3.2)	16 (7.3)	15 (6.9)	27 (12.4)	0.004
GDMT score	5 (3–8)	6 (4–9)	7 (4–9)	7 (5–9)	<0.001
Loop diuretic	205 (94)	204 (93.6)	211 (96.4)	213 (97.7)	0.12
Mineralocorticoid receptor antagonist	103 (47.3)	108 (49.5)	110 (50.2)	114 (52.3)	0.80
Statin	120 (55.1)	128 (58.7)	140 (63.9)	129 (59.2)	0.31
Laboratory data					
BUN, mg/dL	19 (11–29)	24 (16–34)	22 (16–33)	24 (17–38.5)	<0.001
Creatinine, mg/dL	1.23 (1.0–1.7)	1.3 (1.1–1.7)	1.3 (1.1–1.7)	1.3 (1.1–1.8)	0.13
NT-proBNP, pg/mL	3592.0 (1769.0–6774.0)	3299.0 (1780.0–7165.0)	2274.0 (1435.0–4065.0)	1935.0 (987.7–3846.0)	<0.001
Serum potassium, mmol/L	4.5 (4.1–4.8)	4.4 (4.1–4.8)	4.3 (4–4.7)	4.2 (3.9–4.5)	<0.001
Sodium, mmol/L	138 (136–140)	138 (136–141)	139 (136–141)	139 (137–141)	0.66
Biomarker-guided therapy arm	109 (50)	108 (49.5)	110 (50.2)	106 (48.6)	0.98

Data represented as count (percentage) and median (25th–75th percentile). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; JVD, jugular venous distension; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and SBP, systolic blood pressure.

of its skewed distribution, and log-transformed values were used in all analyses. The percentage difference in NT-proBNP levels between obese and nonobese individuals was computed, as previously described (Data S1, Table S1).<sup>16,17,30,32–34</sup> The NT-proBNP levels at each study visit were compared between the obese and nonobese groups.

The hazard for the development of adverse cardiovascular outcome in obese individuals, nonobese individuals, and across quartiles of baseline BMI was determined using multivariable-adjusted Cox proportional hazard models. The model was adjusted for known clinical correlates of NPs,<sup>16,17,30,32–34</sup> such as age, sex, race (Black race versus others), blood urea nitrogen, left ventricular ejection fraction, diabetes mellitus, GDMT score (time varying), systolic and diastolic blood pressure, NYHA class, ischemic heart disease, serum potassium, history of cancer in past 5 years, sleep apnea, log-transformed NT-proBNP

as a time-varying covariate, and treatment strategy (biomarker-guided versus usual care arm). The covariate description and model fit statistics are provided in Data S1. The proportional hazard assumption was assessed using Schoenfeld residuals for all covariates. Potential interaction by treatment strategy for the study outcome was assessed using a multiplicative interaction term (obese status×treatment group). In a sensitivity analysis, we performed nonlinear (restricted cubic spline) survival analyses, as described previously,<sup>33</sup> to assess the relationship of baseline BMI on the study outcome in the Cox regression model, adjusted for the above-mentioned covariates. The relative strength of association between the risk of adverse cardiovascular outcomes and various baseline characteristics, stratified by obesity status, was evaluated in multivariable-adjusted Cox models and compared using the likelihood ratio test, using previously described methods.<sup>16,35,36</sup> In brief, multivariate regression models with

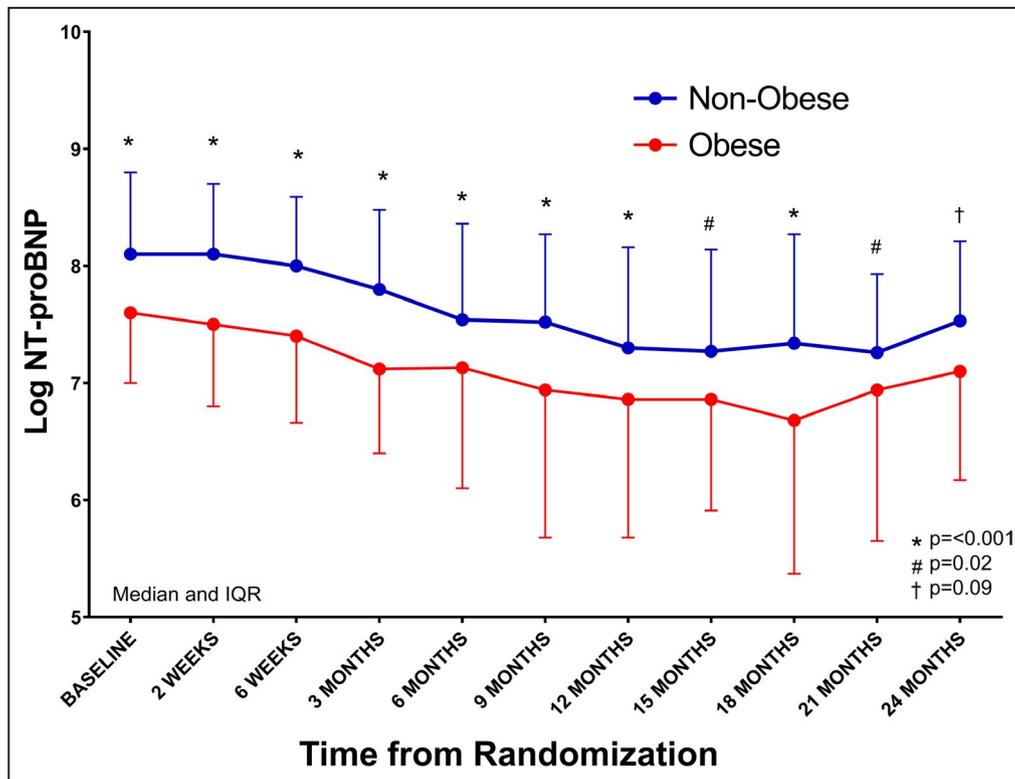
and without respective covariates were used to calculate the  $\chi^2$  values for each covariate.

The prognostic importance (risk of adverse cardiovascular events) of having NT-proBNP  $\leq 1000$  pg/mL, overall and in both obese and nonobese individuals, was assessed using Cox regression models, taking NT-proBNP  $\leq 1000$  pg/mL as a time-varying covariate. The model was adjusted for baseline log-transformed NT-proBNP levels and BMI, along with other above-mentioned covariates. The interaction between obesity and NT-proBNP  $\leq 1000$  pg/mL levels on the study outcome was done using a multiplicative interaction term (obese status  $\times$  having NT-proBNP  $\leq 1000$  pg/mL) in Cox regression analysis. Descriptive reporting of the reasons for the lack of titration of medications and inadequate medication adjustment in the biomarker-guided treatment arm (defined as having NT-proBNP  $\leq 1000$  pg/mL with no change in dosage of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker,  $\beta$ -blocker, or mineralocorticoid receptor antagonist) was assessed and stratified by obesity status. In the secondary analyses, we assessed the prognostic ability of per unit increase in log NT-proBNP baseline and on-treatment

log NT-proBNP levels in obese and nonobese individuals using multivariable-adjusted Cox regression. In an additional analysis, we also evaluated the prognostic ability of change in NYHA class (from baseline) for risk of adverse cardiovascular outcomes in obese and nonobese individuals using multivariable-adjusted Cox regression. The models were adjusted for the above-mentioned covariates. All statistical analyses were done using Stata SE 16.0 (StataCorp, College Station, TX), with a 2-sided type I error of 0.05 considered statistically significant.

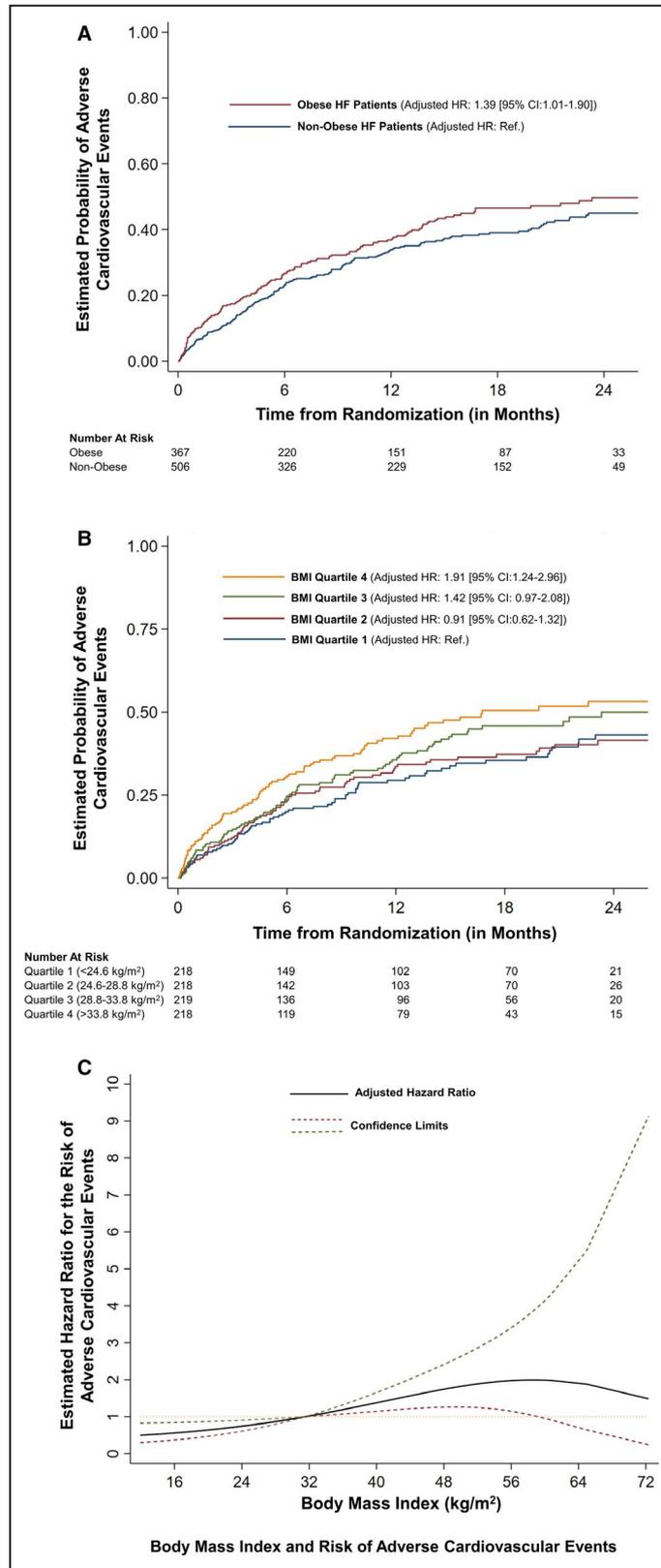
## RESULTS

Among 873 patients with HFrEF from the GUIDE-IT trial, 42% were obese. Obese patients were younger (58 [25th–75th percentile, 49–66] years versus 66 [25th–75th percentile, 57–75] years;  $P < 0.001$ ) and more likely to be women (38.1% versus 27.7%;  $P < 0.001$ ) and Black race (43.9% versus 30.9%;  $P < 0.001$ ) than nonobese patients. Obese patients also had a higher prevalence of hypertension (83.4% versus 76.1%;  $P = 0.01$ ) and diabetes mellitus (54.2% versus 40%;  $P < 0.001$ ), with a higher GDMT score (7 [25th–75th percentile, 4–9];  $P < 0.001$ ),



**Figure 1. NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels during study period: stratified by obesity.**

The data are represented as median (point) and interquartile range (error bars). Red represents obese, and blue represents nonobese. Adjusted for age, sex, race, blood urea nitrogen, left ventricular ejection fraction, diabetes mellitus, guideline-directed medical therapy score, systolic and diastolic blood pressure, New York Heart Association class, ischemic heart disease history, history of cancer in past 5 years, sleep apnea, and treatment arm. IQR indicates interquartile range.



than nonobese patients (Table 1). The median baseline NT-proBNP values were 59.0% (95% CI, 39.5%–83.5%) lower among obese individuals (1964 [25th–75th percentile, 1145–3643] versus 3412 [25th–75th percentile,

1847–6771] pg/mL; adjusted  $P<0.001$ ) than nonobese individuals. The baseline characteristics of the study population across the BMI quartiles are described in Table 2.

## Figure 2. Obesity and risk of adverse cardiovascular events.

The figure shows the risk of adverse cardiovascular events based on baseline body mass index (BMI), stratified on obesity status (A) and quartiles (B). C, The relationship of the risk of adverse cardiovascular events with baseline BMI. Adjusted for age, sex, race, blood urea nitrogen, left ventricular ejection fraction, diabetes mellitus, guideline-directed medical therapy score, systolic and diastolic blood pressure, log-transformed NT-proBNP (N-terminal pro-B-type natriuretic peptide) (time varying), New York Heart Association class, ischemic heart disease history, history of cancer in past 5 years, sleep apnea, and treatment arm. HF indicates heart failure; HR, hazard ratio; and Ref., reference.

### NT-proBNP Levels: Stratified by Obesity Status

The NT-proBNP levels were lower among obese individuals, both at baseline and through the entire trial period at the various study visits ( $P < 0.05$  at visits except month 24) (Figure 1).

### Risk of Adverse Cardiovascular Events: Stratified by Baseline BMI

In the multivariable-adjusted models, obese individuals had a greater risk of developing adverse cardiovascular events (hazard ratio [HR], 1.39; 95% CI, 1.01–1.90;  $P = 0.04$ ) compared with their nonobese counterparts (Figure 2A). Taking those in the lowest BMI quartile as a reference, individuals in the third (HR, 1.42; 95% CI, 0.97–2.08;  $P = 0.07$ ) and fourth BMI quartiles (HR, 1.91; 95% CI, 1.24–2.96;  $P = 0.003$ ) had a greater risk of development of adverse cardiovascular events (Figure 2B). There was no interaction between treatment strategy and obesity status on the study outcome ( $P > 0.10$ ). In sensitivity analyses, we evaluated the association of BMI with the study outcome using restricted cubic splines. This demonstrated that a higher BMI was associated with a worse prognosis, whereas those with a lower BMI had a relatively lower risk (Figure 2C). The absolute event rates for outcome analyses are depicted in Table S2.

### Ranking of the Relative Strength of Association of Risk Factors With Adverse Cardiovascular Events

Obesity status–stratified clinical and demographic correlates of the study outcome, ranked by their  $\chi^2$  values, are depicted in Figure 3. The NT-proBNP level was the strongest correlate for the development of HF hospitalization or cardiovascular death in both obese and nonobese patients with HF. Among obese individuals, NYHA class, age, blood pressure, race, and GDMT score were strong correlates of the study outcome. In contrast, race, ischemic heart disease, NYHA class, and GDMT score were strong clinical correlates for adverse cardiovascular outcomes among nonobese individuals.

### Risk of Adverse Cardiovascular Outcomes With NT-proBNP $\leq 1000$ pg/mL

In multivariable-adjusted models, having NT-proBNP levels of  $\leq 1000$  pg/mL was associated with a 58%

lower risk of adverse cardiovascular outcomes (HR, 0.42; 95% CI, 0.29–0.59;  $P < 0.001$ ) (Figure 4A). Among obese individuals, those with NT-proBNP  $\leq 1000$  pg/mL had a lower risk for adverse cardiovascular outcomes (HR, 0.48; 95% CI, 0.29–0.78;  $P = 0.003$ ). Similarly, among nonobese individuals, those with NT-proBNP levels  $\leq 1000$  pg/mL had a significantly lower risk for adverse cardiovascular outcomes (HR, 0.32; 95% CI, 0.19–0.57;  $P < 0.001$ ). There was no interaction between obesity and having NT-proBNP levels  $\leq 1000$  pg/mL on the study outcome ( $P > 0.10$ ). Per unit increase in on-treatment log NT-proBNP levels had a higher hazard for the prediction of the study outcome compared with per unit increase in baseline log NT-proBNP levels in both obese and nonobese individuals (Table S3).

The reduction in NYHA class from baseline indicated a 28% lower risk of study outcome in obese individuals and a 25% lower risk of the study outcome in nonobese individuals (Table S4).

### Optimization of GDMT in GUIDE-IT Trial: Stratified by Obesity Status

The GDMT score through the study period is depicted in Figure S1. The most common reason for not titrating medication was the clinician's decision in both obese and nonobese patients. Being at maximally tolerated therapy was more prevalent in nonobese individuals compared with obese individuals. In the biomarker-guided arm, the prevalence of inappropriate adjustment of medication during the visit was higher in nonobese individuals (51.4%) compared with obese individuals (41.6%) ( $P < 0.001$ ) (Figure S2).

## DISCUSSION

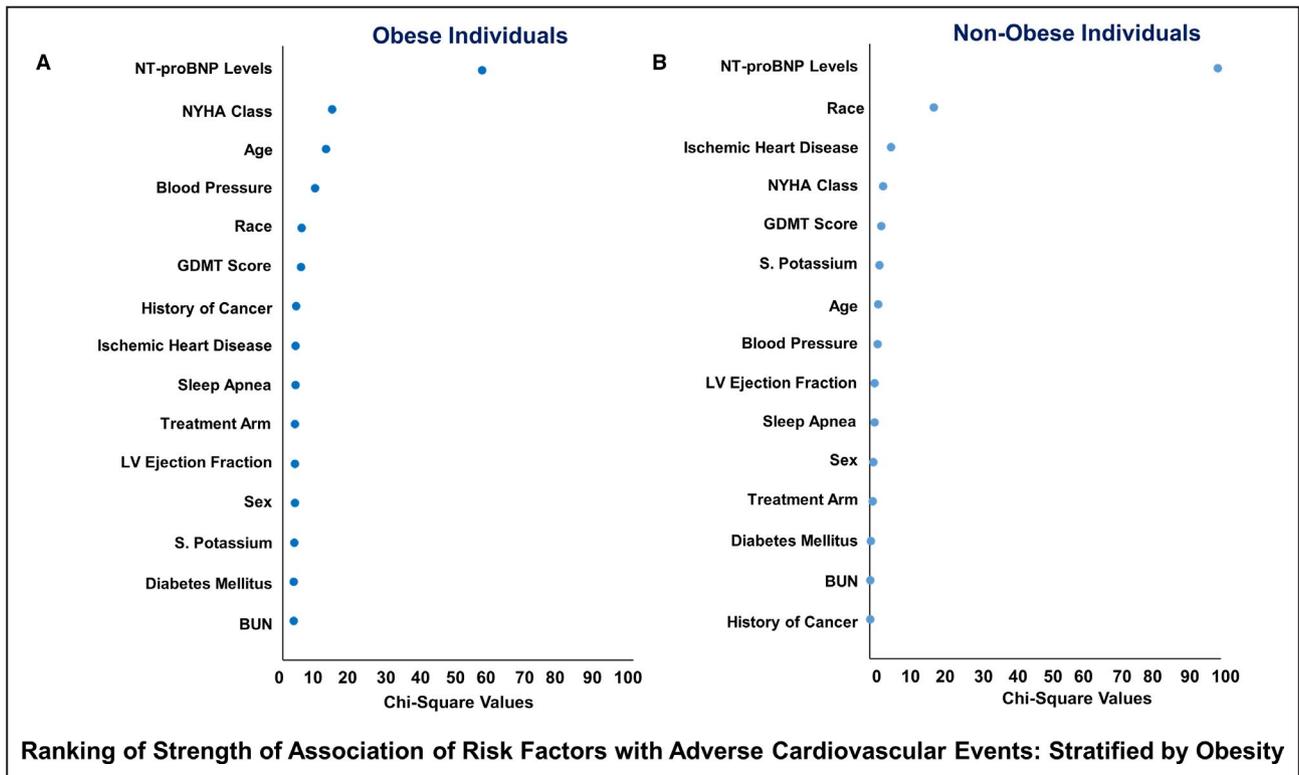
In this study, we observed that obese patients with HFREF had 59% lower NT-proBNP levels than nonobese patients at baseline, which remained consistent during the study period, indicating a similar reduction in NT-proBNP levels on HF treatment in both groups. Obesity or higher BMI was associated with worse functional status (NYHA class and 6-minute walk test) and a higher incidence of adverse cardiovascular events, irrespective of whether clinical care was guided by the biomarker-based strategy or not. The GDMT score remained similar through the study period, suggesting similar up-titration of HF medications, with clinician

decision being the most common reason for lack of medication up-titration. Baseline NT-proBNP level was a strong clinical predictor for the risk of adverse cardiovascular outcomes in both obese and nonobese individuals. Thus, having on-treatment NT-proBNP levels of  $\leq 1000$  pg/mL has favorable prognostic implications, irrespective of obesity status, with risk for HF hospitalization or death being 68% lower in nonobese and 52% lower in obese patients with HFrEF with NT-proBNP levels of  $\leq 1000$  pg/mL compared with those with NT-proBNP levels of  $>1000$  pg/mL.

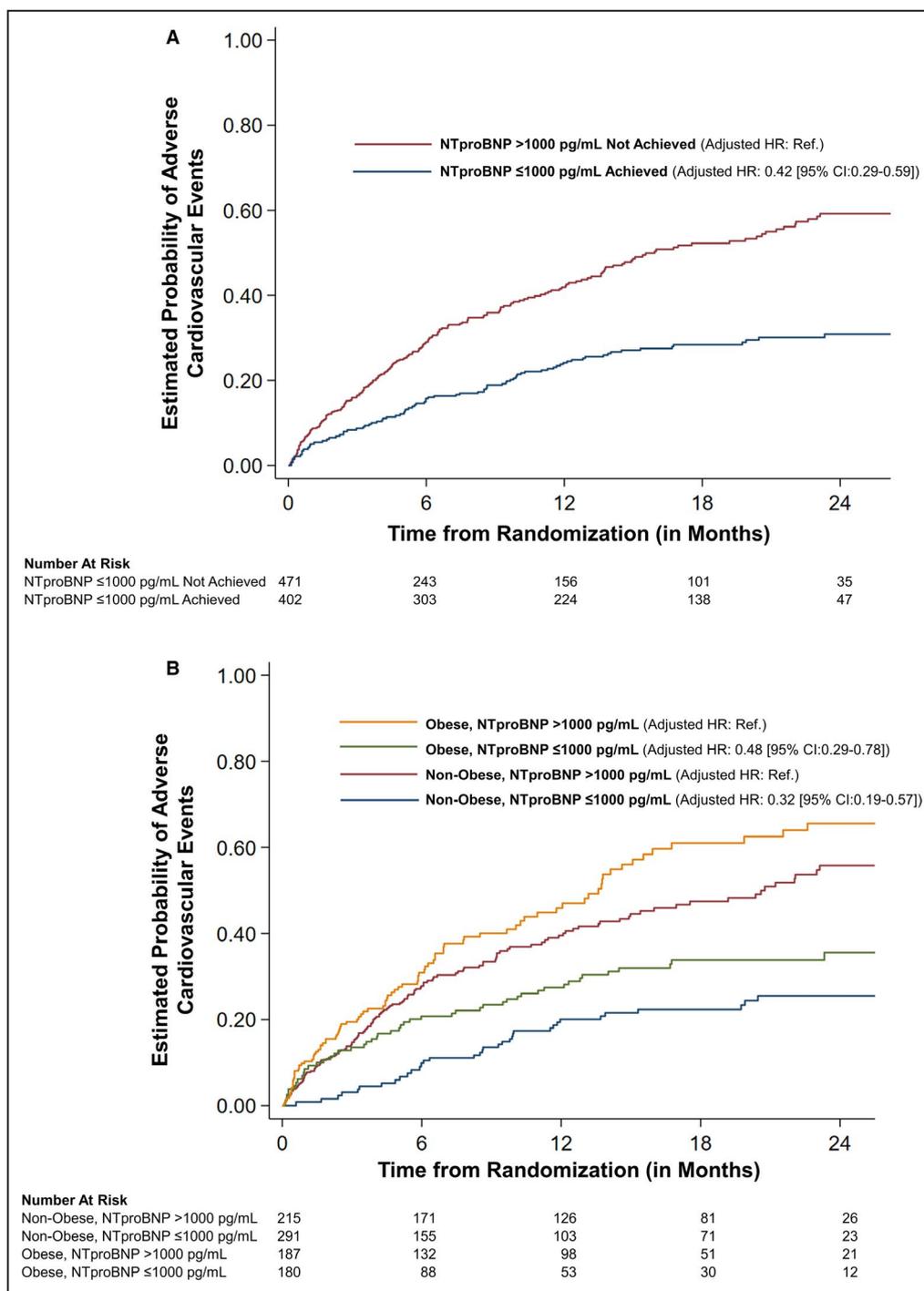
Obesity in the setting of HFrEF has often been attributed to being paradoxically "protective." The evidence for this is primarily from observational epidemiological studies, with limited data from a robust, well-phenotyped population of HFrEF in clinical trials.<sup>8-15</sup> Notwithstanding the prior investigations, the evidence in support of the mechanistic hypotheses postulated to support the obesity paradox in HF is lacking. Obesity adversely impacts the cardiac and vascular function, and remodeling, which is mediated by systemic microvascular endothelial inflammation.<sup>37,38</sup> Moreover, data from HF with preserved ejection fraction trials indicate that obesity, which is considered a unique HF with preserved ejection fraction disease phenotype,

is associated with worse clinical outcomes.<sup>39-41</sup> Previous investigations have looked into the impact of obesity on adverse outcomes, mostly in the setting of acute decompensated HF, or advanced HF, and may be limited because of potential information bias, with limited phenotyping of the baseline characteristics, inadequate accounting for the impact of unmeasured confounders, and infrequent follow-up.<sup>8-15</sup> Obese patients presenting earlier with noncardiac edema and dyspnea may be more quickly diagnosed with HFrEF, which introduces potential misclassification or lead-time bias in these investigations.<sup>8-15,42</sup> In the current investigation, a closely followed population with HFrEF in the setting of a multicenter, randomized clinical trial, we found that obese individuals have a higher risk of adverse cardiovascular events, despite being younger, having lower NT-proBNP levels, having similar ejection fraction, having greater GDMT scores, and having less frequent and inadequate medication up-titration. Further studies to shed light on the obesity paradox association are warranted.

The ascertainment of the clinical condition of obese patients with HF using physical examination may be challenging. This resultant inadequate characterization of the clinical state may, therefore,



**Figure 3. Ranking of strength of association of risk factors with adverse cardiovascular events: stratified by obesity.** The figure depicts the relative contribution of each variable to the risk of adverse cardiovascular events in terms of  $\chi^2$  values in obese (A) and nonobese (B) individuals. To ensure comparison on the same scale, the covariates were corrected for the degree of freedom. BUN indicates blood urea nitrogen; GDMT, guideline-directed medical therapy; LV, left ventricular; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and S., serum.



**Figure 4. NT-proBNP (N-terminal pro-B-type natriuretic peptide) ≤1000 mg/dL and risk of adverse cardiovascular events.**

**A**, The risk of adverse cardiovascular events stratified by achieved NT-proBNP levels. **B**, The risk of adverse cardiovascular events stratified by obesity and having NT-proBNP ≤1000 mg/dL. Adjusted for age, sex, race, blood urea nitrogen, left ventricular ejection fraction, diabetes mellitus, guideline-directed medical therapy score, systolic and diastolic blood pressure, body mass index, log-transformed baseline NT-proBNP, New York Heart Association class, ischemic heart disease history, history of cancer in past 5 years, sleep apnea, and treatment arm. HR indicates hazard ratio; and Ref., reference.

preclude adequate up-titration of medications among obese individuals with HFrEF. This consequently increases the reliance on surrogate biomarkers of clinical condition, such as NT-proBNP levels.<sup>7,19,21</sup> There are limited data assessing the value of NT-proBNP levels of  $\leq 1000$  pg/mL in treated obese patients with HFrEF, who represent a known NP deficient population. In our study, NT-proBNP levels were observed to be consistently lower in obese individuals. Numerous mechanisms have been suggested for this relative deficiency of NPs in obese individuals,<sup>9,43–45</sup> such as increased clearance or impaired processing NPs.<sup>7,45–47</sup> Recent data indicate that increased glycosylation of the precursor peptide in obese individuals may cause impairment of the posttranslational processing of the precursor peptide, resulting in low circulating NP levels identified by the clinical assays.<sup>46,47</sup> Lower circulating bioactive NP molecules reduce the beneficial effect of NPs on cardiovascular physiological features, which are mediated through natriuresis,<sup>48,49</sup> vasodilation,<sup>50</sup> and direct inhibition of the renin-angiotensin-aldosterone system.<sup>51–54</sup> This is of paramount importance in the state of cardiac dysfunction and congestion. This is consistent with our study findings, where NT-proBNP was observed to be a strong prognostic marker in obese patients with HFrEF, despite lower circulating NP levels. We advance the findings of the GUIDE-IT trial by demonstrating that having on-treatment NT-proBNP levels of  $\leq 1000$  mg/dL holds important prognostic implications in both obese and nonobese patients, irrespective of the treatment strategy. Furthermore, the interaction seen in the primary trial may have been attributable to the lesser inadequate up-titration of medication among obese individuals in the biomarker-guided arm, as noted in our analyses.

Our study has important clinical implications. The obesity burden is burgeoning in the United States and globally, and this may contribute to an increase in the incidence and prevalence of HF. Our study highlights that once these patients develop HFrEF, they are likely to have greater morbidity and mortality with higher BMI, despite a similar response to HF treatment. The lack of a treatment target is HFrEF, especially in the setting of limited physical examination, such as in obesity, leaves the titration of HF treatment to the physician's discretion. Even with the high prevalence of inadequate medication up-titration, reaching NT-proBNP levels of  $\leq 1000$  pg/mL holds prognostic importance.

Furthermore, NT-proBNP levels are frequently part of the inclusion criteria for clinical trials and have also been used as a surrogate therapeutic end point in HFrEF clinical trials. Since obesity is an natriuretic peptide NP deficient state, there may be a selection bias introduced in the enrollment into HFrEF clinical

trials.<sup>55</sup> The data from our study indicate that careful consideration of NP deficiency states in the inclusion criteria of HFrEF trials may warrant different NT-proBNP inclusion thresholds for these NP deficiency states.<sup>30,55</sup>

## Study Limitations

The use of BMI to categorize obesity may not be ideal, and other measures, such as waist/hip ratio, body fat proportion, and fat mass, have been suggested.<sup>44</sup> Despite this, BMI is a validated surrogate clinical measure of adiposity.<sup>11</sup> Although the dichotomization of variables, such as BMI and NT-proBNP levels, introduces bias and has several limitations, it allows for easier clinical interpretation of the data. However, we also evaluated the association of BMI as a continuous variable in our sensitivity analyses that demonstrated similar results as the categorical division of BMI. The GDMT score was developed to provide a comprehensive understanding of the HF medications being taken by the patients, and the medication used is likely to change through the course of the study period.<sup>17</sup> Therefore, we used the GDMT score as a continuous time-varying variable to account for the changing medication use throughout the study period. Because of the small study population, our study was underpowered to detect a significant interaction between obesity and NT-proBNP  $\leq 1000$  pg/mL on the study outcome. Our study does not provide information about how frequently the assessment of NT-proBNP levels must be performed in patients with HFrEF. Lowering of NT-proBNP beyond 1000 pg/mL is prognostically important, even in the NP deficient population of obese individuals with HFrEF. Reduction in NT-proBNP concentration along with aggressive, goal-oriented up-titration of medications can be part of the optimal management of HFrEF, irrespective of obesity status.<sup>17</sup>

## CONCLUSIONS

NT-proBNP concentration is a strong prognostic marker in HFrEF, irrespective of obesity status. On-treatment NT-proBNP level  $\leq 1000$  pg/mL, achieved through adequate GDMT, is associated with a more favorable prognosis in HFrEF, irrespective of obesity status.

## ARTICLE INFORMATION

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## Disclosures

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## Supplementary Material

Data S1

Tables S1–S4

Figures S1–S2

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# **SUPPLEMENTAL MATERIAL**

## Data S1.

### Supplemental Methods

The percentage difference in N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels between obese and non-obese individuals were computed as previously described.<sup>32, 34</sup> The relative percentage difference with 95% confidence interval was calculated by applying the following formula:  $(e^{\beta} - 1) \times 100$ .<sup>32, 34</sup> The NT-proBNP levels at each study visit were compared between the obese and non-obese group. These models were adjusted for known clinical correlates of natriuretic peptide levels: age (continuous variable), sex (categorical; male [reference] vs. females), race (Blacks vs. others [reference]), blood urea nitrogen (BUN) (continuous variable), left ventricular ejection fraction (LVEF) (continuous variable), diabetes (categorical variable; yes/no), GDMT score (continuous variable; time-varying), systolic and diastolic blood pressure (continuous variable), New York Heart Association (NYHA) class (ordinal variable ranging from class I [reference] to class IV), ischemic heart disease (categorical variable; yes/no), serum potassium (continuous variable), history of cancer in last five years (categorical variable; yes/no), sleep apnea (categorical variable; yes/no), and treatment strategy (categorical variable; biomarker-guided versus usual care arm [reference]).

The hazard for the development of adverse cardiovascular outcome in obese individuals, non-obese individuals, and across quartiles of baseline BMI was determined using multivariable-adjusted Cox proportional hazard models. The model adjustment covariates included important clinical correlates such as age (continuous variable), sex (categorical; male [reference] vs. females), race (Blacks vs. others [reference]), BUN (continuous variable), LVEF (continuous variable), diabetes (categorical variable; yes/no), GDMT score (continuous variable; time-

varying), systolic and diastolic blood pressure (continuous variable), NYHA class (ordinal variable ranging from class I [reference] to class IV ), ischemic heart disease (categorical variable; yes/no), serum potassium (continuous variable), history of cancer in last five years (categorical variable; yes/no), sleep apnea (categorical variable; yes/no), log-transformed NT-proBNP as a time-varying covariate (continuous variable), and treatment strategy (categorical variable; biomarker-guided versus usual care arm [reference]). We and other have shown that the included model covariates are important clinical correlates of NT-proBNP levels and adverse clinical outcomes in heart failure patients.<sup>16, 17, 30, 32-34</sup>

In the secondary analyses, we assessed the prognostic ability of per unit increase in log NT-proBNP at baseline and on-treatment log NT-proBNP levels in obese and non-obese individuals using multivariable-adjusted Cox regression. In additional analysis, we also evaluated the prognostic ability of change in NYHA class (from baseline) for risk of adverse cardiovascular outcomes in obese and non-obese individuals using multivariable-adjusted Cox regression. The models were adjusted for the abovementioned covariates.

The model fit statistics for all the analyses in this article are provided in **Table S1**.

**Table S1. Model Fit Statistics for Multivariable-Adjusted Cox Regression Analyses.**

Cox Regression Analyses	Model Fit (AIC)		Model Fit (SBC)		Model Fit (-2 Log Likelihood)	
	Without Covariates	With Covariates	Without Covariates	With Covariates	Without Covariates	With Covariates
<b>Association of Risk of Study Outcome with Obesity and BMI</b>						
<b>Obese versus Non-Obese</b>	3060.48	2836.44	3060.48	2892.72	3060.48	2804.44
<b>BMI Quartiles</b>	3060.48	2830.74	3060.48	2894.06	3060.48	2794.74
<b>BMI (Continuous Variable)</b>	3060.48	2830.40	3060.48	2886.68	3060.48	2798.40
<b>Association of Risk of Study Outcome with NT-proBNP <math>\leq</math> 1000 pg/mL</b>						
<b>Obese</b>	1310.58	1303.43	1310.58	1258.44	1310.58	1226.44
<b>Non-Obese</b>	1703.65	1642.61	1703.65	1690.89	1703.65	1610.61
<b>Association of Risk of Study Outcome with Baseline and On-Treatment NT-proBNP Levels*</b>						
<b>Obese</b>						
<b>Baseline NT-proBNP</b>	1310.58	1265.92	1310.58	1302.48	1310.58	1239.92
<b>On-Treatment NT-proBNP</b>	1140.90	1094.70	1140.90	1059.84	1140.90	1033.84
<b>Non-Obese</b>						
<b>Baseline NT-proBNP</b>	1703.65	1657.95	1703.65	1697.20	1703.65	1631.98
<b>On-Treatment NT-proBNP</b>	1579.92	1455.26	1579.92	1493.60	1579.92	1429.26
<b>Association of Risk of Study Outcome with Change in NYHA Class<sup>†</sup></b>						
<b>Obese</b>	1139.84	1066.35	1139.84	1101.22	1139.84	1040.35
<b>Non-Obese</b>	1554.96	1432.48	1554.96	1470.63	1554.96	1406.48

\*For per unit increase in log NT-proBNP. † For per unit decrease in NYHA Class

**Table S2. Event Rate for the Study Outcome.**

	<b>Study Outcome Rate (per 100 patients)</b>
<b>Obese</b>	39.2
<b>Non-Obese</b>	35.4
<b>BMI</b>	
Quartile 1	33
Quartile 2	33.9
Quartile 3	38.8
Quartile 4	42.2
<b>NT-proBNP ≤1000 pg/mL</b>	12.8
<b>NT-proBNP &gt;1000 pg/mL</b>	39.7
<b>NT-proBNP ≤1000 pg/mL</b>	
Obese	19.8
Non-Obese	6.9
<b>NT-proBNP &gt;1000 pg/mL</b>	
Obese	49.5
Non-Obese	34.2

BMI: body mass index; NT-proBNP: N-terminal-pro-B-type-natriuretic peptide

**Table S3. Baseline and On-Treatment NT-proBNP Levels and Risk of Adverse Cardiovascular Outcomes.**

	<b>Hazard Ratio (95% Confidence Interval)</b>
<b>Obese Individuals</b>	
Baseline NT-proBNP	1.30 (1.07-1.59)
On-Treatment NT-proBNP	2.00 (1.63-2.45)
<b>Non-Obese Individuals</b>	
Baseline NT-proBNP	1.40 (1.16-1.68)
On-Treatment NT-proBNP	2.29 (1.93-2.71)

Hazard ratios provided for per unit increase in log NT-proBNP levels. The models were adjusted of age, sex, race, blood urea nitrogen, left ventricular ejection fraction, diabetes, GDMT score (time-varying), systolic and diastolic blood pressure, New York Heart Association (NYHA) class, ischemic heart disease history, history of cancer in last five years, sleep apnea and treatment arm.

**Table S4. Change in NYHA Class and Risk of Adverse Cardiovascular Outcomes.**

	<b>Hazard Ratio (95% Confidence Interval)</b>
<b>Obese Individuals</b>	<b>0.72 (0.53-0.96)</b>
<b>Non-Obese Individuals</b>	<b>0.75 (0.58-0.99)</b>

Hazard ratios provided for per unit decrease in NYHA Class decrease in NYHA class. The models were adjusted of age, sex, race, blood urea nitrogen, left ventricular ejection fraction, diabetes, GDMT score (time-varying), systolic and diastolic blood pressure, log-transformed NT-proBNP (time-varying), New York Heart Association (NYHA) class, ischemic heart disease history, history of cancer in last five years, sleep apnea and treatment arm.

Figure S1. Change in GDMT Score During the Study Period.

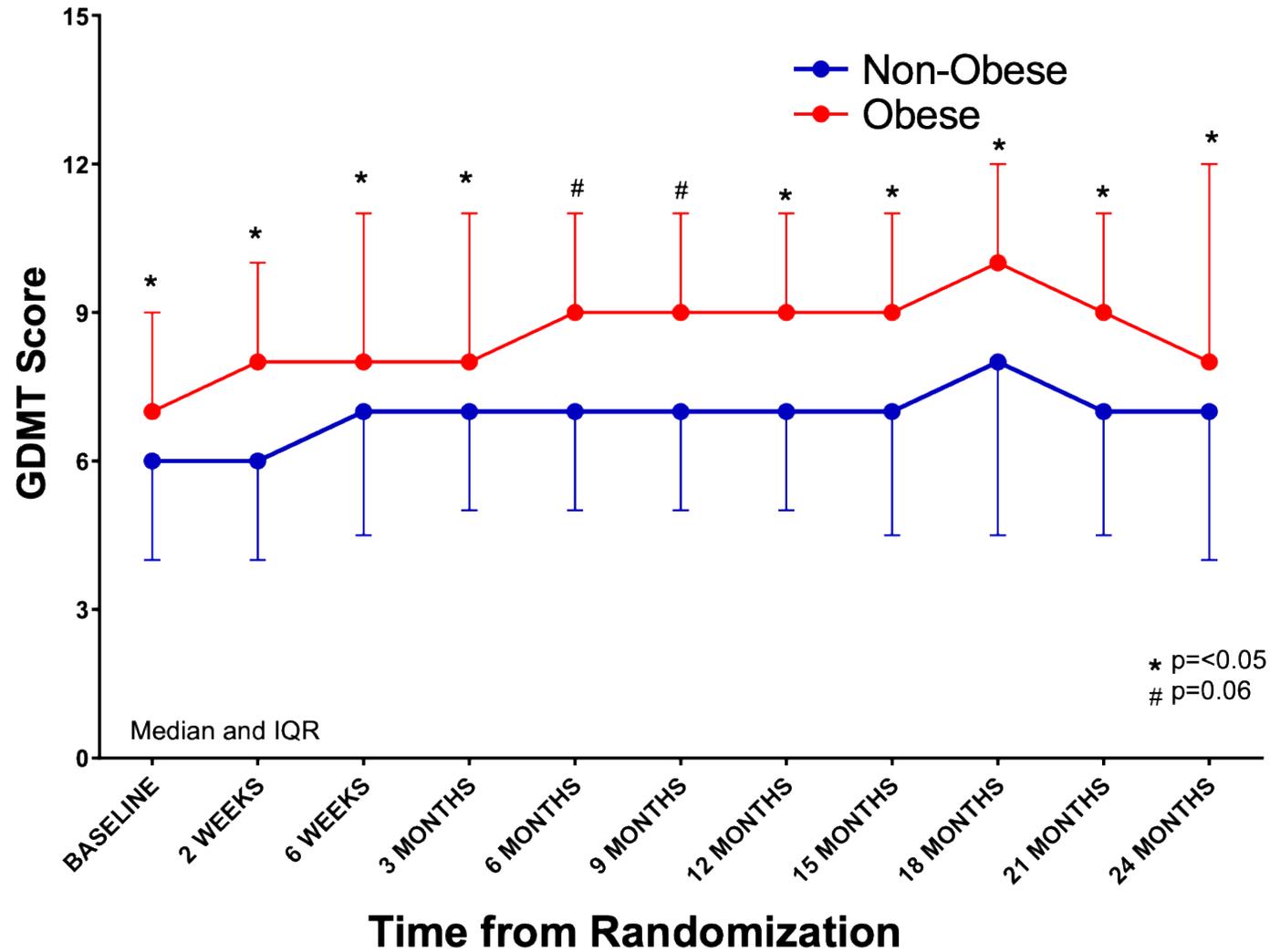
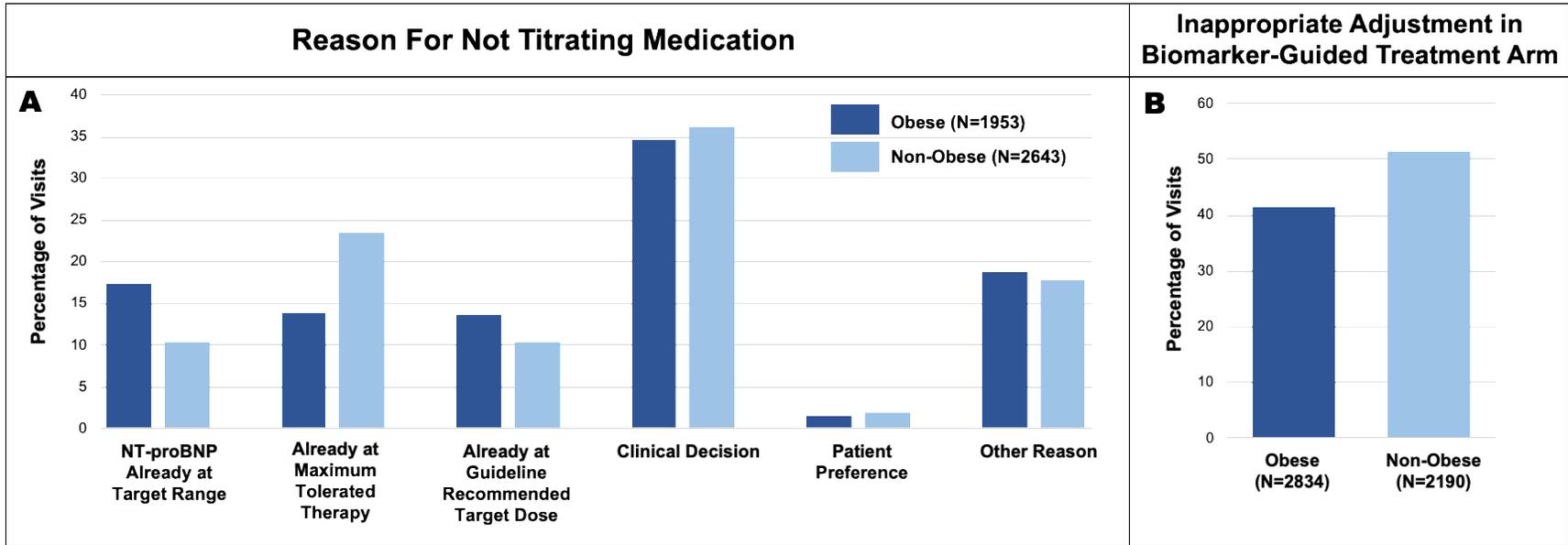


Figure S2. Medication Titration in GUIDE-IT: Stratified by Obesity.



N represents the total number of visits