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.[32, 34] The relative percentage difference with 95% confidence interval was calculated by applying the following formula: $(e^{\beta} - 1) \times 100$.[32, 34] 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.[16, 17, 30, 32-34]

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
Association of Risk of Study Outcome with Obesity and BMI						
Obese versus Non-Obese	3060.48	2836.44	3060.48	2892.72	3060.48	2804.44
BMI Quartiles	3060.48	2830.74	3060.48	2894.06	3060.48	2794.74
BMI (Continuous Variable)	3060.48	2830.40	3060.48	2886.68	3060.48	2798.40
Association of Risk of Study Outcome with NT-proBNP ≤ 1000 pg/mL						
Obese	1310.58	1303.43	1310.58	1258.44	1310.58	1226.44
Non-Obese	1703.65	1642.61	1703.65	1690.89	1703.65	1610.61
Association of Risk of Study Outcome with Baseline and On-Treatment NT-proBNP Levels*						
Obese						
Baseline NT-proBNP	1310.58	1265.92	1310.58	1302.48	1310.58	1239.92
On-Treatment NT-proBNP	1140.90	1094.70	1140.90	1059.84	1140.90	1033.84
Non-Obese						
Baseline NT-proBNP	1703.65	1657.95	1703.65	1697.20	1703.65	1631.98
On-Treatment NT-proBNP	1579.92	1455.26	1579.92	1493.60	1579.92	1429.26
Association of Risk of Study Outcome with Change in NYHA Class†						
Obese	1139.84	1066.35	1139.84	1101.22	1139.84	1040.35
Non-Obese	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.

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

	Hazard Ratio (95% Confidence Interval)
Obese Individuals	
Baseline NT-proBNP	1.30 (1.07-1.59)
On-Treatment NT-proBNP	2.00 (1.63-2.45)
Non-Obese Individuals	
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.

	Hazard Ratio (95% Confidence Interval)
Obese Individuals	**0.72 (0.53-0.96)**
Non-Obese Individuals	**0.75 (0.58-0.99)**

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.

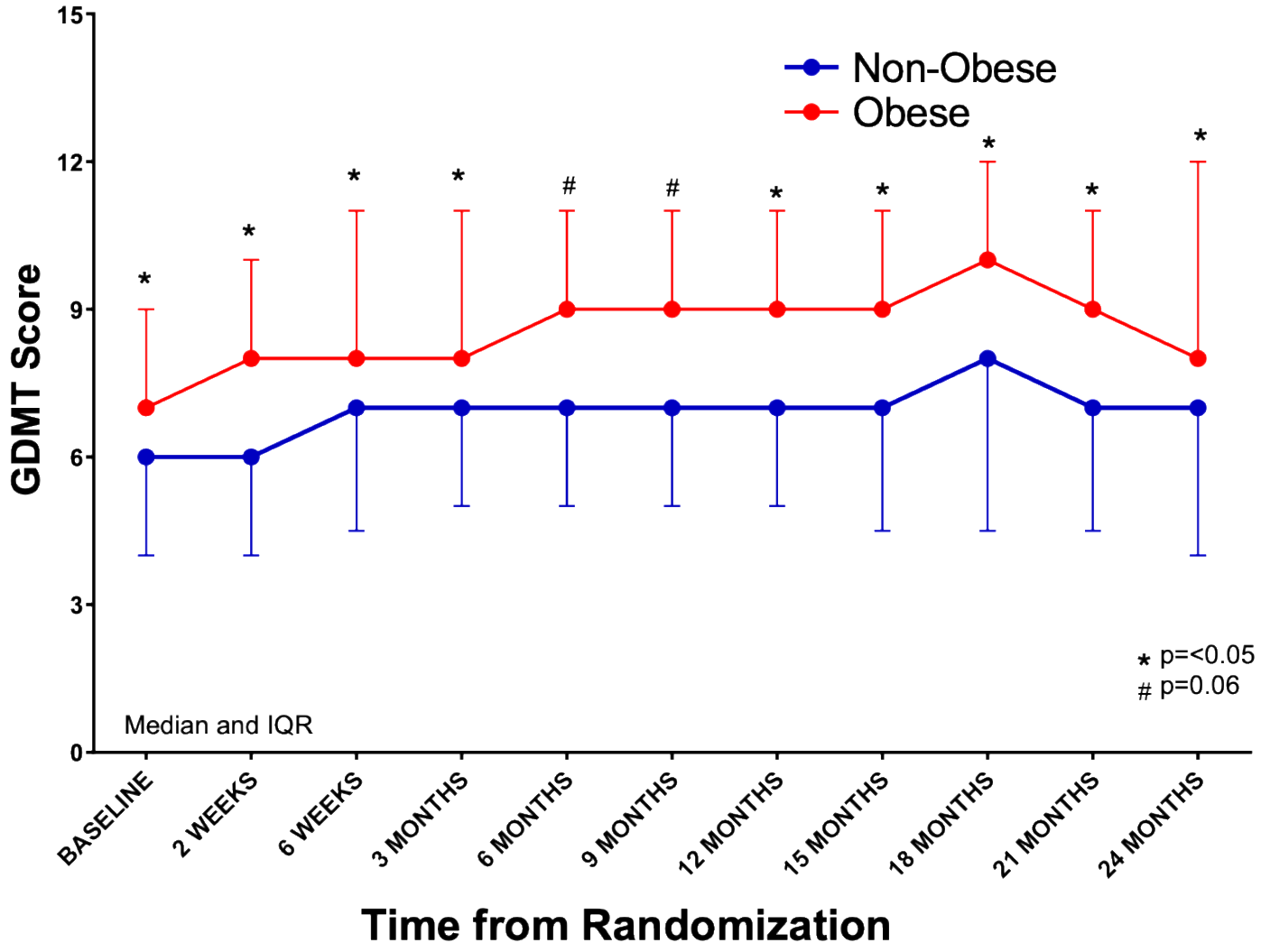
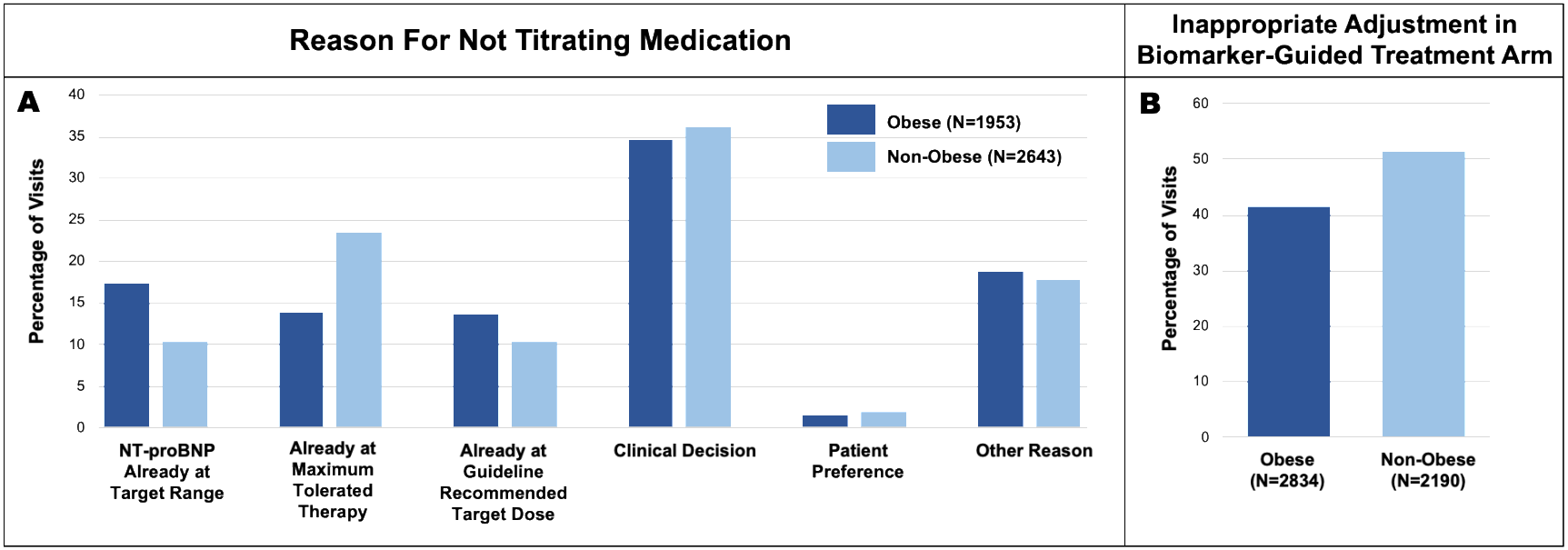


Figure S2. Medication Titration in GUIDE-IT: Stratified by Obesity.



N represents the total number of visits