5-18-2021

Differences in NT-proBNP Response and Prognosis in Men and Women With Heart Failure With Reduced Ejection Fraction.

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Journal of the American Heart Association

ORIGINAL RESEARCH

Differences in NT-proBNP Response and Prognosis in Men and Women With Heart Failure With Reduced Ejection Fraction

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BACKGROUND: NT-proBNP (N-terminal pro-B-type natriuretic peptide) is a prognostic biomarker in heart failure (HF) with reduced ejection fraction. However, it is unclear whether there is a sex difference in NT-proBNP response and whether the therapeutic goal of NT-proBNP ≤1000 pg/mL has equivalent prognostic value in men and women with HF with reduced ejection fraction.

METHODS AND RESULTS: In a secondary analysis of the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) trial we analyzed trends in NT-proBNP and goal attainment by sex. Differences in clinical characteristics, HF treatment, and time to all-cause death or HF hospitalization were compared. Landmark analysis at 3 months determined the prognostic value of early NT-proBNP goal achievement in men and women. Of the 286 (32%) women and 608 (68%) men in the GUIDE-IT trial, women were more likely to have a nonischemic cause and shorter duration of HF. Guideline-directed medical therapy was less intense over time in women. The absolute NT-proBNP values were consistently lower in women; however, the change in NT-proBNP and clinical outcomes were similar. After adjustment, women achieving the NT-proBNP goal had an 82% reduction in death or HF hospitalization compared with a 59% reduction in men.

CONCLUSIONS: Men and women with HF with reduced ejection fraction had a similar NT-proBNP response despite less intensive HF treatment among women. However, compared with men, the early NT-proBNP goal of ≤1000 pg/mL had greater prognostic value in women. Future efforts should be aimed at intensifying guideline-directed medical therapy in women, which may result in greater NT-proBNP reductions and improved outcomes in women with HF with reduced ejection fraction.

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

Key Words: N-terminal pro-B-type natriuretic peptide ■ heart failure ■ women

The prevalence of heart failure (HF) with reduced ejection fraction (HFrEF) increases with age for both men and women; however, there are intriguing sex-specific differences in predisposing factors, medical treatment, health-related quality of life (QoL), and clinical outcomes.[1–3] Women with HFrEF are frequently older and are more likely than men to have a nonischemic HF cause.[3–9] Women experience more severe symptoms and have a worse QoL for a similar burden of HF.[3,10] Guideline-directed medical therapy (GDMT) is often underutilized in women, and women are less likely to be referred for cardiac rehabilitation and cardiac resynchronization therapy, despite the greater mortality benefits of these interventions in women compared with men.[1–3,5,11,12] Finally, there are conflicting data regarding clinical outcomes in women

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Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.019712

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a population with advanced heart failure with reduced ejection fraction, women were treated less intensely with guideline-directed medical therapy than men.
- Absolute NT-proBNP (N-terminal pro-B-type natriuretic peptide) values were consistently lower in women, yet the adjusted change in NT-proBNP, NT-proBNP early goal achievement, and clinical outcomes were similar between men and women with heart failure with reduced ejection fraction.

What Are the Clinical Implications?

- Among men and women achieving the NT-proBNP goal of ≤1000 pg/mL at 3 months, there was a lower rate of death and heart failure hospitalization in women than in men, suggesting that women with heart failure with reduced ejection fraction may derive greater benefit from early NT-proBNP reductions.

Nonstandard Abbreviations and Acronyms

CHAMP-HF	Change the Management of Patients With Heart Failure
GDMT	guideline-directed medical therapy
GUIDE-IT	Guiding Evidence Based Therapy Using Biomarker Intensified Treatment
HFrEF	heart failure with reduced ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
KorHF	Korean Heart Failure Registry
NT-proBNP	N-terminal pro-B-type natriuretic peptide
QoL	quality of life

with HFrEF. Some studies indicate higher rates of death and HF hospitalization, while others have found that women with HFrEF have fewer HF hospitalizations and lower mortality compared with men with HFrEF.[3,4,13,14] Further evaluation of the biological mechanisms underlying these sex differences is needed to optimize the care of women with HFrEF.

Insight into the pathophysiologic underpinnings of sex-specific differences may be gained through observation of the longitudinal response in NT-proBNP (N-terminal pro-B-type natriuretic peptide), one of the more powerful diagnostic and prognostic biomarkers in HFrEF. Previous studies have evaluated baseline NT-proBNP concentrations and the association with clinical outcomes in men and women.[15–17] However, to date, no study has serially evaluated NT-proBNP and assessed the sex-specific NT-proBNP response and clinical outcomes in men and women with HFrEF. Furthermore, the therapeutic target of reducing NT-proBNP to <1000 pg/mL has been uniformly applied to both sexes; however, it is unclear whether this NT-proBNP goal has equivalent prognostic value in both men and women.

The GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) trial was a large, randomized clinical trial that evaluated the impact of biomarker-guided care at 45 sites in the United States and Canada by comparing NT-proBNP–guided management with usual care in the HFrEF population.[18] In this secondary analysis of the GUIDE-IT trial, we studied the longitudinal trends in NT-proBNP among men and women with HFrEF in order to increase the understanding of sex-specific differences in HFrEF and identify opportunities to optimize treatment and improve clinical outcomes.

METHODS

Data Availability

Qualified researchers trained in human subject confidentiality protocols may request access to the data that support the findings of this study by contacting the National Heart, Lung, and Blood Institute Biological Specimen and Data Repository Information Coordination Center.

Study Design and Population

The study design and outcomes for the GUIDE-IT trial have been previously published.[18,19] Briefly, between January 16, 2013, and September 20, 2016, stable patients with HFrEF (ejection fraction ≤40%) were enrolled and randomized to a strategy of usual care with NT-proBNP guidance or usual clinically directed care. Patients in the biomarker-guided arm were treated with usual care plus serial NT-proBNP measurements with a goal to decrease NT-proBNP concentration <1000 pg/mL, whereas those in the usual care arm received standard clinically guided care. Patients were to be followed for a minimum of 12 months and a maximum of 24 months. The GUIDE-IT trial was designed to include 1100 patients but was stopped by the data safety monitoring board for futility after 894 patients (81% of planned) were enrolled.[18] No difference in achieved NT-proBNP concentrations or clinical outcomes was found between the study arms and the medical management of both study groups was comparable. The study

was funded by the National Heart, Lung, and Blood Institute and approved by the institutional review board at each study site. All patients provided written informed consent to participate.

In both study arms, NT-proBNP levels were collected at baseline and every 3 months through 12 months and analyzed at a central core laboratory. Patients and providers were blinded to core laboratory NT-proBNP results. In the biomarker-guided arm, NT-proBNP levels were also ascertained at local laboratories for use by treating providers. The study protocol specified clinical interventions to be considered to achieve the NT-proBNP goal of <1000 pg/mL, but specific management decisions were at the discretion of the treating physician. Patients randomized to the usual care group received treatment based on clinical practice guidelines. Sites were asked not to perform open-label assessment of natriuretic peptides in the usual care group. Provider reasons for not titrating HF medications were collected at study visits.

All patients with an NT-proBNP measurement at baseline were included in this analysis cohort. Clinical characteristics, serial NT-proBNP concentrations, GDMT, and clinical outcomes through 24 months were evaluated according to sex. The GDMT score, as reported by Januzzi et al,[20] was used to assess sex differences in treatment with HF therapies associated with mortality reduction in HFrEF. The primary clinical outcome was time to a composite of all-cause death or HF hospitalization. Secondary outcomes were time to all-cause death, time to HF hospitalization, time to cardiovascular hospitalization, and time to a composite of cardiovascular death or HF hospitalization. All adverse events were adjudicated by a clinical end point committee using prespecified criteria. Health-related QoL was measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ), which is scored 0 to 100, with lower scores indicating a poorer health status.

Statistical Analysis

Descriptive data are presented as frequencies and percentages for categorical variables and mean±SD or median with 25th and 75th interquartile range (IQR) for continuous variables. For continuous variables, differences were assessed using Wilcoxon rank sum test, and for categorical variables, differences were assessed using chi-square test. In the case of low cell counts, the treatment group differences were tested using Fisher exact method. For count data, such as medication adjustments and visit frequency, Poisson regression with offset of follow-up time was used to assess differences. Sex differences in NT-proBNP concentrations were adjusted for age, race, body mass index (BMI), chronic kidney disease, diabetes mellitus, and ischemic cardiomyopathy.[21] For time-to-event analyses, with time starting at randomization, unadjusted event rates were estimated using Kaplan-Meier curves and 95% CIs; group differences were tested using log-rank test. Cox proportional hazards regression models were used to examine the associations between sex and outcomes while adjusting for covariates that were statistically significant in the univariate model or clinically relevant. The covariates included were age, race, BMI, hypertension, diabetes mellitus, smoking, chronic kidney disease, peripheral artery disease, atrial fibrillation, coronary artery disease, ischemic cardiomyopathy, myocardial infarction, New York Heart Association class III/IV, ejection fraction, duration of HF, log of baseline NT-proBNP, biomarker-guided arm, and QoL by KCCQ score. To minimize bias attributable to missing variables, multiple imputation using the fully conditional specification method was implemented for the modeling. Landmark time-to-event analyses at 3 months were performed on patients alive at that time. Cox regression analysis was performed and included the same covariates as above, as well as median visit count until the landmark, median dose adjustment until the landmark, GDMT score at the landmark, log of 3-month NT-proBNP, and NT-proBNP ≤1000 pg/mL at the landmark. To assess whether there was a differential benefit for women and men who achieved the NT-proBNP goal at 3 months, we assessed the interaction of sex and NT-proBNP goal achievement at the landmark in the Cox regression analysis. An exploratory analysis of adjusted data used a grid search to find the 3-month NT-proBNP concentration in men and women at which there was a shift in linear association with the time-to-event outcome of death or HF hospitalization.[22] A 2-piece cubic spline model with transformation was used to demonstrate the optimal 3-month NT-proBNP cut point, defined as the NT-proBNP concentration below which there was a significant decrease in the adjusted hazard for death or HF hospitalization. The threshold for statistical significance was 2-sided with a type I error rate of 0.05. The assumption of proportional hazards for sex was assessed using supremum test and found to be nonsignificant in the Cox regression models. Analyses were performed using SAS version 9.4 (SAS Institute Inc.).

RESULTS

There were 286 (32%) women and 608 (68%) men in the GUIDE-IT trial (Figure 1). The baseline characteristics of men and women are shown in Table 1. Women had greater racial diversity, a higher BMI, and fewer coronary artery disease risk factors compared with men. Women

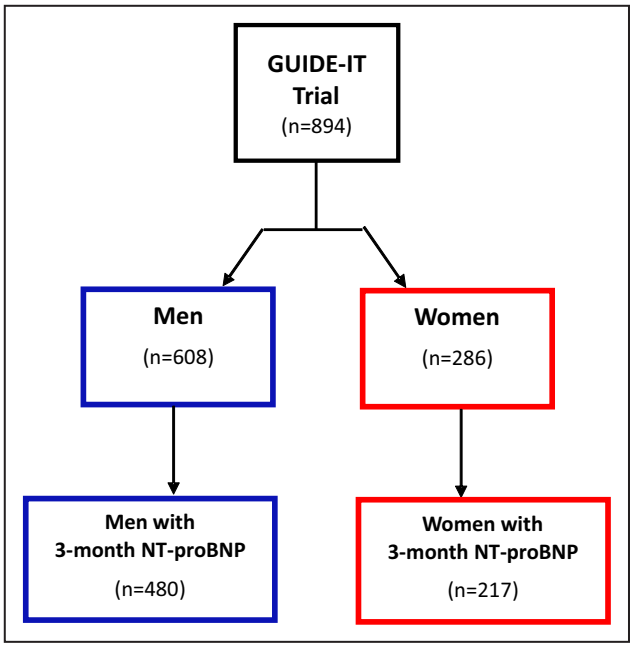

Figure 1. CONSORT diagram.
Study flow diagram of secondary analysis population and subgroup. GUIDE-IT indicates Guiding Evidence Based Therapy Using Biomarker Intensified Treatment; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

were more likely to have a nonischemic HF cause, a shorter duration of HF, and a higher ejection fraction at baseline, but, compared with men, women had a lower QoL score. There was no difference in biomarker-guided therapy allocation according to sex. Pharmacologic treatment by medication class was similar between men and women at baseline (Table 2). A relatively low percentage of either sex were at ≥100% of the target dose for β-blockers and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) at baseline. However, the GDMT score was significantly lower in women at baseline, 3 months, and 12 months. At 1 year, a significantly greater percentage of men than women were titrated up to ≥100% of target doses of β-blockers and a similar trend was seen for ACEIs or ARBs (Figure 2). Women had significantly fewer dose adjustments than men: 4.0 (IQR, 2.0–7.0) versus 5.0 (IQR, 2.0–8.0) (P<0.001). Reasons for not titrating dose are listed in Figure 3 and differed between men and women. Women also had significantly fewer clinical visits compared with men: 9.3±5.0 versus 10.0±5.8, respectively (P=0.002).

The absolute NT-proBNP values were consistently lower in women; however, the trend in NT-proBNP among men and women with HFrEF was similar over time (Figure 4). Univariate analysis of the sex-specific NT-proBNP response revealed that women had a significantly lower NT-proBNP concentration by 3 months, but after adjusting for age, race, BMI, chronic kidney disease, diabetes mellitus, and

Table 1. Baseline Clinical Characteristics in Men and Women in GUIDE-IT

	Women (n=286)	Men (n=608)	*P* Value
Age, y	60.6±15.0	61.9±13.3	0.36
Race (Black)	127 (44.4)	197 (32.4)	<0.001
BMI, kg/m^2	31.8±9.6	29.5±7.2	0.001
Hypertension	210 (73.4)	496 (81.6)	0.008
Hyperlipidemia	157 (54.9)	367 (60.4)	0.15
Diabetes mellitus	142 (49.7)	268 (44.1)	0.13
Smoking	80 (28.0)	224 (36.8)	0.01
Atrial fibrillation	99 (34.6)	259 (42.6)	0.03
Chronic kidney disease	87 (32.4)	243 (40.0)	0.007
Peripheral artery disease	17 (5.9)	77 (12.7)	0.002
Coronary artery disease	102 (35.7)	308 (50.7)	<0.001
Myocardial infarction	54 (18.9)	197 (32.4)	<0.001
Ischemic cardiomyopathy	111 (38.8)	336 (55.3)	<0.001
HF duration*, mo	8 (1.0–48.0)	20 (1.0–72.0)	0.003
NYHA class III/IV	127 (44.4)	248 (40.8)	0.34
Ejection fraction, %	25.1±8.2	23.9±8.3	0.03
QoL score by KCCQ	53.1±21.4	59.6±22.0	<0.001
Biomarker-guided therapy	139 (48.6)	307 (50.5)	0.62

Values are mean±SD or number (percentage) unless otherwise noted. BMI indicates body mass index; GUIDE-IT, Guiding Evidence Based Therapy Using Biomarker Intensified Treatment; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; and QoL, quality of life.
*Median (interquartile range).

ischemic cardiomyopathy, there were no significant sex differences in NT-proBNP response (Table 3). The median follow-up for clinical events was 14.7 months (IQR, 6.6–23.5 months) with a similar duration in men and women (14.7 months [IQR, 6.7–23.7 months] and 14.9 months [IQR, 6.2–22.6 months], respectively). There was no difference between men and women for the primary outcome of all-cause death or HF hospitalization (Figure 5). Unadjusted analysis of secondary outcomes demonstrated significantly fewer deaths among women at 12 months; however, this did not remain statistically significant after adjustment (Table 4).

To further explore the impact of early NT-proBNP goal achievement on outcomes among men and women, a 3-month landmark analysis was performed and included the 697 (77.9%) patients who were alive and had a 3-month NT-proBNP concentration. The analysis excluded 197 patients, of whom 49 had died, 53 had <3 months of follow-up, and 95 were missing

Table 2. Pharmacologic Treatment in Men and Women in the GUIDE-IT Trial

	Women (n=286)	Men (n=608)	*P* Value
Medications at baseline (% of patients)			
ACEI or ARB	78.1	80.1	0.53
β-blocker	95.4	94.7	0.74
Mineralocorticoid receptor antagonist	48.4	50.5	0.57
GDMT score*	6 (4–8)	7 (4–9)	<0.001
Percentage at ≥100% of target dose at baseline			
ACEI or ARB	15.0	20.3	0.11
β-Blocker	7.5	6.4	0.55
Mineralocorticoid receptor antagonist	79.3	69.5	0.04
Medications at 3 mo (% of patients)			
ACEI or ARB	79.5	77.1	0.51
β-Blocker	94.9	95.3	0.85
Mineralocorticoid receptor antagonist	55.8	58.7	0.47
GDMT score*	7 (5–10)	8 (5.75–10)	0.017
Percentage at ≥100% of target dose at 3 mo			
ACEI or ARB	21.5	26.3	0.25
β-Blocker	6.8	9.2	0.31
Mineralocorticoid receptor antagonist	80.3	75.6	0.32
Medications at 1 y (% of patients)			
ACEI or ARB	73.8	78.1	0.31
β-Blocker	93.1	93.9	0.70
Mineralocorticoid receptor antagonist	52.5	55.0	0.63
GDMT score*	7 (4.5–10)	8 (6–11)	0.009
Percentage at ≥100% of target dose at 1 y			
ACEI or ARB	22.	31.8	0.08
β-Blocker	6.2	16.3	0.003
Mineralocorticoid receptor antagonist	79.8	73.4	0.29

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GDMT, guideline directed medical therapy; and GUIDE-IT, Guiding Evidence Based Therapy Using Biomarker Intensified Treatment.
*Median (interquartile range).

the 3-month NT-proBNP measurement. Differences in clinical characteristics between men and women in this subgroup were similar to that of the whole cohort (Table S1). In the 3-month landmark analysis of the primary outcome of death or HF hospitalization, there was no difference between men and women for the primary outcome after adjustment (hazard ratio [HR], 1.11; 95% CI, 0.82–1.51 [*P*=0.48]). However, longer HF duration increased the hazard for death or HF hospitalization (HR, 1.22; 95% CI, 1.12–1.34 [*P*<0.001]), while achieving the NT-proBNP goal of ≤1000 pg/mL at 3 months decreased the hazard (HR, 0.41; 95% CI, 0.25–0.68 [*P*<0.001]).

Evaluation of sex differences in NT-proBNP goal achievement at 3 months revealed that women were more likely to achieve the early goal, but this did not remain statistically significant after adjustment for clinical characteristics and HF treatment (odds ratio [OR], 0.50; 95% CI, 0.08–3.03 [*P*=0.45]). However, among women achieving the NT-proBNP ≤1000 pg/mL at 3 months, there was an 82% reduction in death or HF hospitalization (HR, 0.18; 95% CI, 0.07–0.45 [*P*<0.001]). In comparison, men achieving the early NT-proBNP goal had a 59% reduction in the primary outcome (HR, 0.41; 95% CI, 0.25–0.68 [*P*<0.001]) (Figure 6). Exploration of the interaction between sex and achieved 3-month NT-proBNP goal on clinical outcomes suggested a trend that women benefitted more than men from early NT-proBNP goal achievement (interaction *P*=0.11).

Additionally, the 3-month NT-proBNP concentration below which women had a significant reduction in the adjusted hazard for the primary outcome was substantially lower than the NT-proBNP threshold in men (Figure S1). After adjustment, an NT-proBNP threshold of ≤5410 pg/mL at 3 months was associated with a significantly lower rate of death or HF hospitalization in men, whereas an NT-proBNP threshold of ≤1260 pg/mL at 3 months was predictive of lower mortality or HF hospitalization in women. Furthermore, the magnitude of benefit of lowering NT-proBNP was greater for women. For every 100-pg/mL reduction in NT-proBNP below the sex-specific threshold, women had a 21% lower rate of death or HF hospitalization (HR, 0.79; 95% CI, 0.68–0.91 [*P*=0.001]), whereas men only had a 4% reduction in the primary outcome (HR, 0.96; 95% CI, 0.95–0.98 [*P*<0.001]).

DISCUSSION

This secondary analysis of the GUIDE-IT trial revealed important insights about sex-specific management and the longitudinal NT-proBNP response among men and women with HFrEF. Compared with men, women had fewer clinical risk factors and received less intensive GDMT, especially by 12 months. Exploratory analysis suggested that when the difference in clinical risk and intensity of HF treatment between men and women is adjusted for, early NT-proBNP goal achievement may benefit women more than men. Furthermore, incremental reductions in NT-proBNP below sex-specific thresholds have greater prognostic significance in women than men.

Similar to prior studies, women with HFrEF in the GUIDE-IT trial were more racially diverse, had higher BMIs and fewer coronary artery disease risk factors, and were more likely to have a nonischemic cause of HF.[3–5,7,9] Baseline KCCQ scores were significantly lower

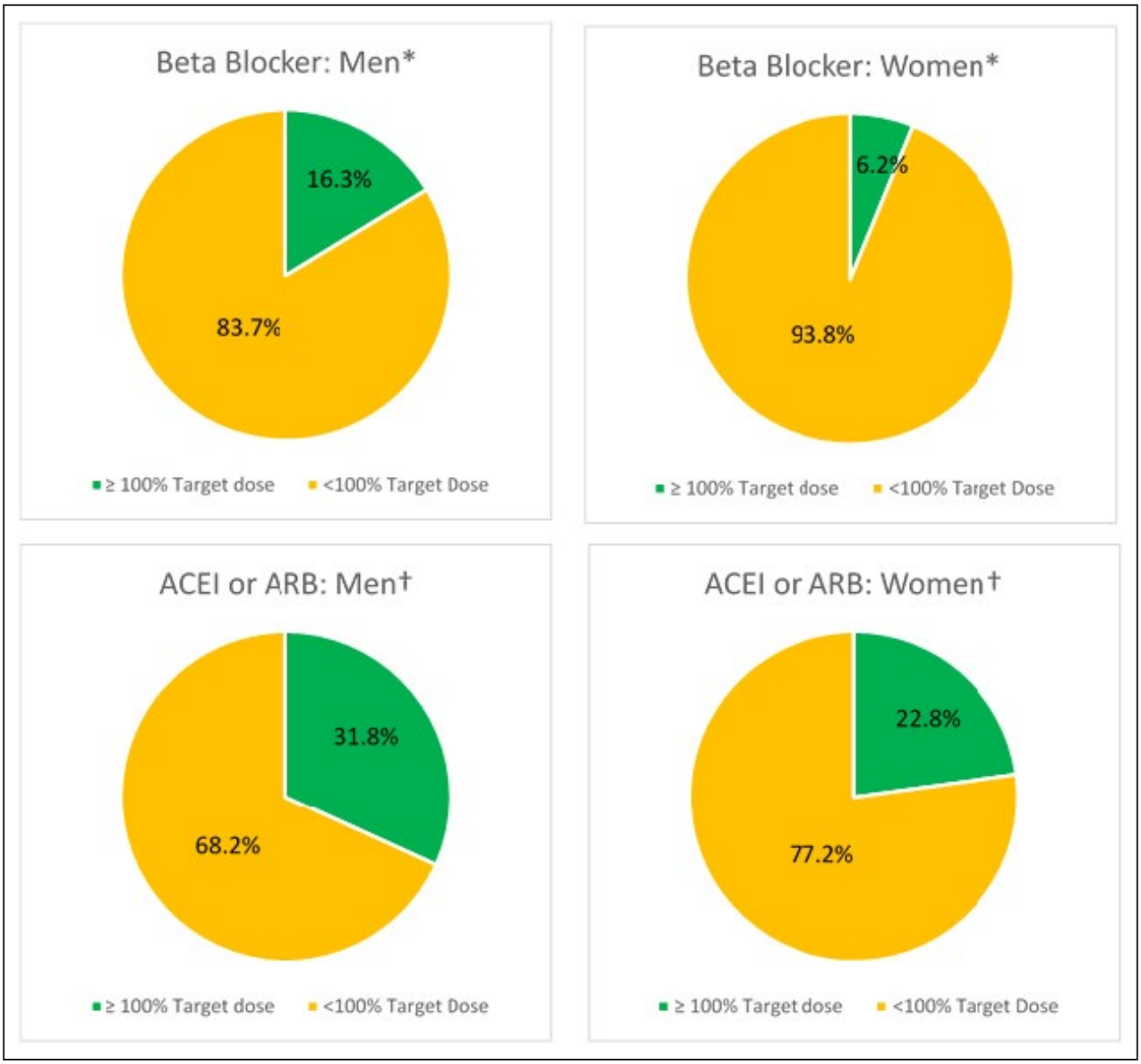

Figure 2. Sex differences in target dosing of guideline-directed medical therapy (GDMT) at 1 year.
Pie charts indicating the proportion of men and women achieving target doses of β-blocker therapy (top row) and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) therapy (bottom row) at 1 year. Men were significantly more likely to be at or above target doses than women. *P=0.003; †P=0.08. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

among women than men, despite having a shorter duration of HF and a higher mean ejection fraction. This sex disparity in KCCQ scores has also been observed in other HFrEF studies and warrants further investigation as to why HF imparts a lower QoL among women than men.[3,10] A greater understanding of psychosocial factors and the influence of comorbid conditions, such as anxiety and depression, that may be contributing to these sex differences could allow for more targeted therapeutic strategies.

Earlier HFrEF studies have reported pharmacologic undertreatment of women at baseline; however, more contemporary studies demonstrate this treatment differential is narrowing.[3–5,9,15] Yet even in these more recent studies, treatment was largely defined as the percent utilization in each class of GDMT. In contrast, the GUIDE-IT trial uniquely captured pharmacologic treatment over time with granular detail about the percentage of patients at or above target doses of GDMT and reasons for not titrating dose during clinical visits.[23] In this sex-stratified treatment analysis, a similar proportion of men and women were taking guideline-recommended medications for HF at baseline; however, women were at significantly

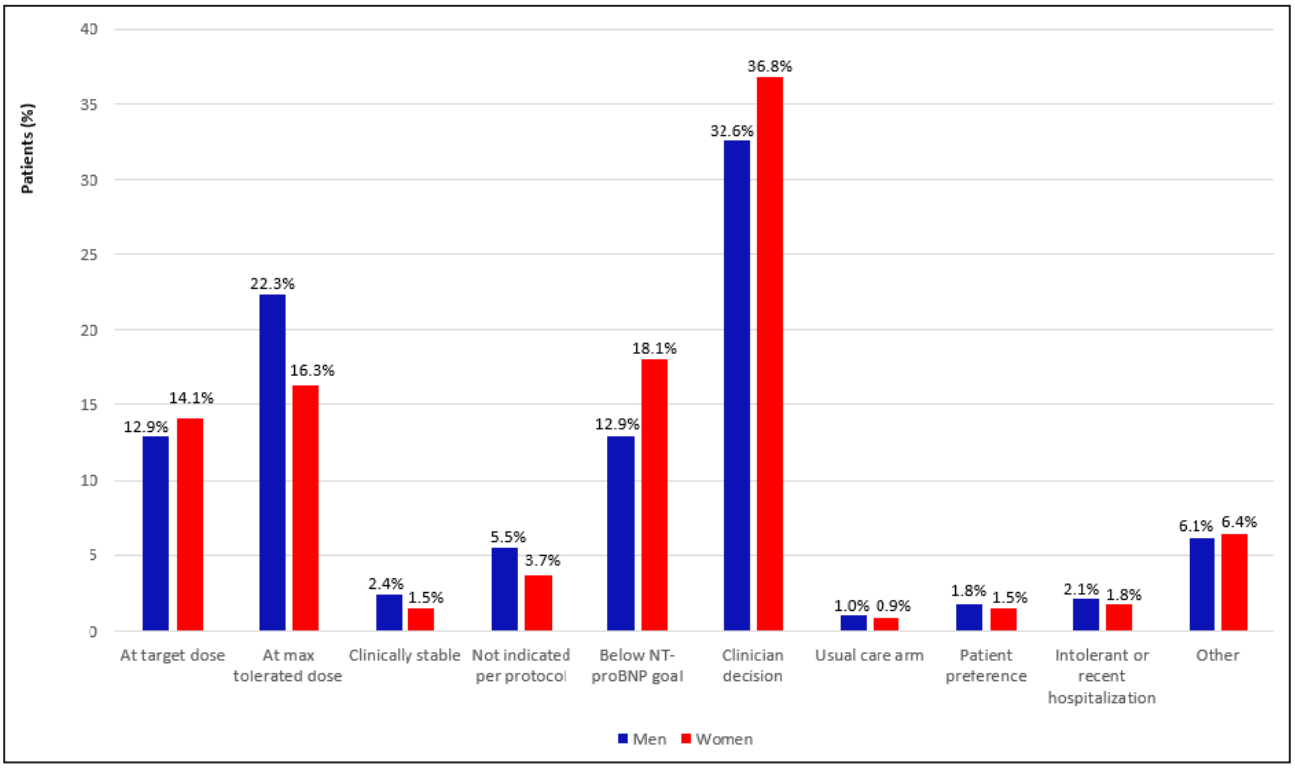

Figure 3. Reasons for not titrating medications by sex.
Bar graph indicating the reasons for not titrating medication dose in men and women. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

lower GDMT intensity at baseline and throughout the course of the study, indicating a lower dose application of HF therapies known to have a mortality benefit. At 1 year, men were significantly more likely to be at or above the target dose for β-blockers compared with women, and a similar trend was noted for ACEIs or ARBs. These results are consistent with findings from the CHAMP-HF (Change the Management of Patients With Heart Failure) registry, which found that female sex was associated with lower utilization of β-blockers and ACEIs or ARBs.[24] This undertreatment of women has important implications for clinical outcomes and is also significant for the potential impact on NT-proBNP. Januzzi et al[20] demonstrated that escalating the dose of β-blocker therapy has the greatest influence on lowering NT-proBNP concentrations (OR, 1.38; 95% CI, 1.10–1.72 [*P*=0.005]) followed by ACEI therapy (OR, 1.11; 95% CI, 1.01–1.21 [*P*=0.03]). Had women been treated as intensely as men over time with GDMT, women may have achieved even lower concentrations of NT-proBNP. Efforts should be made to increase the intensity of GDMT in order to optimize HF treatment and improve clinical outcomes in women with HFrEF.

The lower achievement of target dose and undertreatment among women is at least partly explained by the fewer dose titrations in women compared with men. Provider reasoning for not titrating dose differed between men and women with men more often being "at the maximum tolerated dose," while women were not titrated because they were "below NT-proBNP goal" or because of the provider's "clinical decision." Lack of titrating as a result of achieving the NT-proBNP goal may disadvantage women more than men. In the landmark analysis, women only began to have a significant reduction in adverse outcomes once NT-proBNP concentrations were <1260 pg/mL at 3 months. Therefore, women in whom GDMT was not intensified were denied the benefit that further biomarker reduction could have potentially conferred. Lack of dose titration because of the provider's discretion may reflect that women with HFrEF are perceived differently than men with HFrEF and such sex bias can influence clinical HF management.[25–27] Greater understanding of these perceived differences is needed to overcome the obstacles that may hinder the intensifying GDMT in women.

This is the first study, to our knowledge, to longitudinally evaluate the sex-specific NT-proBNP response to HF treatment and assess the association with clinical outcomes in men and women with HFrEF. Furthermore, existing data are conflicting as to whether NT-proBNP has the same prognostic significance in men and women with HFrEF.[15,16] In the study by Franke and colleagues,[15] NT-proBNP was

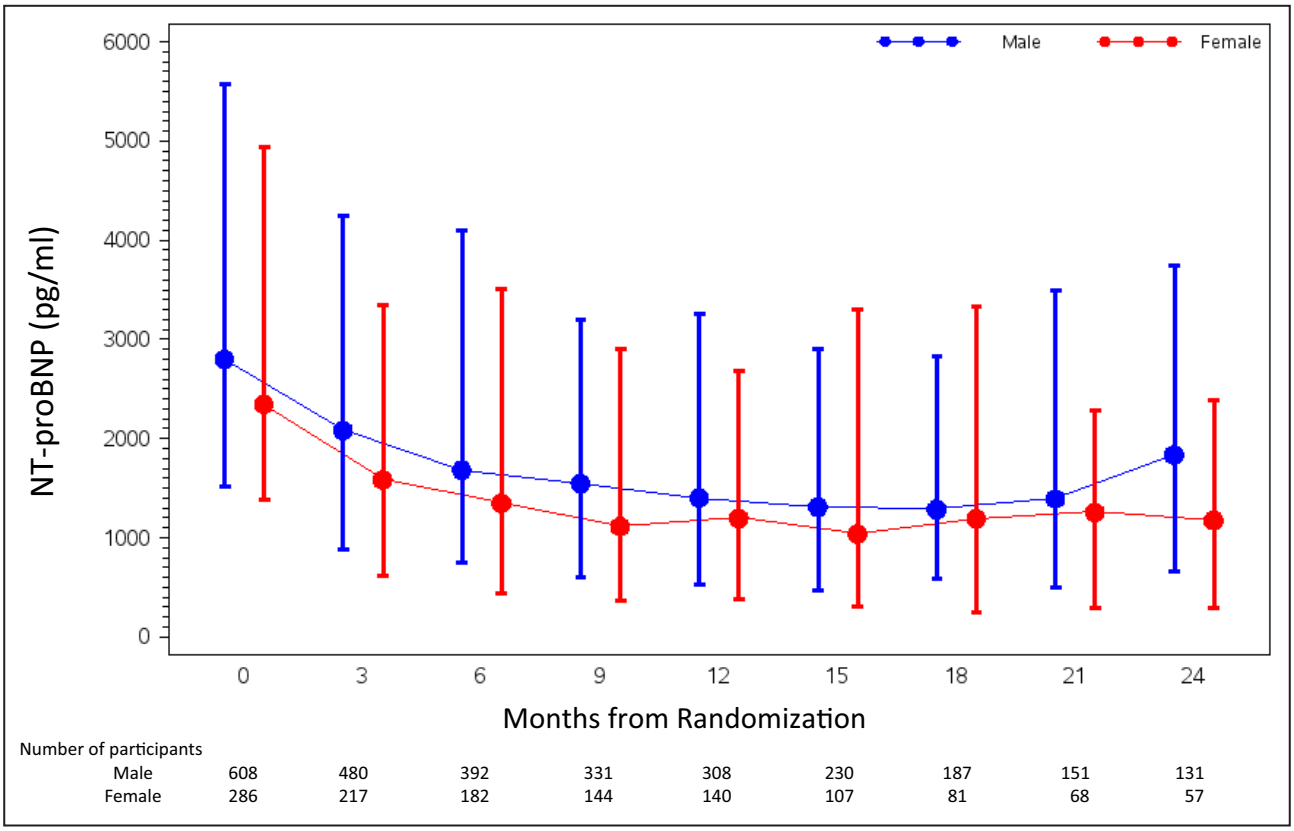

Figure 4. Change in NT-proBNP (N-terminal pro-B-type natriuretic peptide) in men and women with heart failure with reduced ejection fraction.
The trend in NT-proBNP was similar between men and women. Dots are median NT-proBNP (pg/mL); whiskers are interquartile range.

found to be equally predictive of mortality in men and women. In contrast, an analysis of KorHF (Korean Heart Failure Registry) found that NT-proBNP had greater predictive value for death and HF readmission in men than women.[16]

In GUIDE-IT, women had lower absolute NT-proBNP concentrations; however, the difference NT-proBNP goal achievement and absolute NT-proBNP reduction was not significantly different after adjustment for factors known to influence NT-proBNP levels.[21] This could

Table 3. NT-proBNP Response According to Sex

	Women (n=286)	Men (n=608)	Unadjusted *P* Value	Adjusted *P* Value*
NT-proBNP (pg/mL) at baseline	2349 (1382 to 4946)	2803 (1521 to 5573)	0.10	0.56
NT-proBNP (pg/mL) at 3 mo	1587 (623 to 3343)	2086 (883 to 4250)	0.01	0.61
NT-proBNP <1000 at 3 mo	79 (36.4)	135 (28.1)	0.03	0.46
NT-proBNP Δ from baseline to 3 mo	−401 (−1416 to 281)	−543 (−1709 to 280)	0.69	0.91
NT-proBNP (pg/mL) at 6 mo	1351 (446 to 3510)	1685 (748 to 4093)	0.09	0.99
NT-proBNP <1000 at 6 mo	77 (42.3)	129 (32.9)	0.03	0.17
NT-proBNP Δ from baseline to 6 mo	−554 (−1650 to 517)	−644 (−1861 to 358)	0.51	0.77
NT-proBNP (pg/mL) at 9 mo	1116 (361 to 2909)	1549 (600 to 3205)	0.07	0.67
NT-proBNP <1000 at 9 mo	61 (42.4)	105 (31.7)	0.03	0.09
NT-proBNP Δ from baseline to 9 mo	−574 (−2005 to 73)	−814 (−2244 to 151)	0.38	0.87
NT-proBNP (pg/mL) at 12 mo	1201 (387 to 2679)	1404 (529 to 3263)	0.15	0.15
NT-proBNP <1000 at 12 mo	65 (46.4)	126 (40.9)	0.30	0.63
NT-proBNP Δ from baseline to 12 mo	−661 (−2003 to 214)	−829 (−2256 to 127)	0.63	0.98

Values are median (interquartile range) or number (% of evaluable patients). Δ indicates change; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*Adjusted for age, race, body mass index, chronic kidney disease, diabetes mellitus, and ischemic cardiomyopathy.

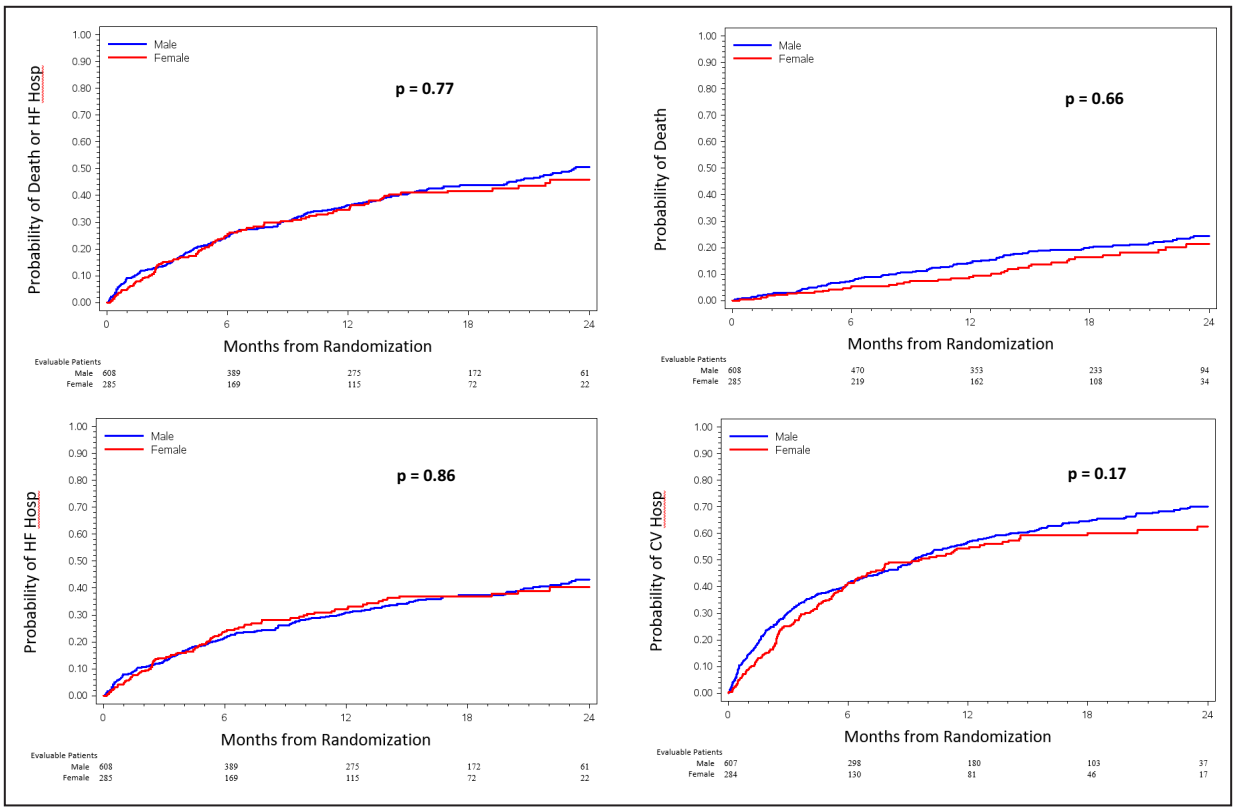

Figure 5. Clinical outcomes in men and women with heart failure (HF) with reduced ejection fraction.
The Kaplan-Meier curves for the primary outcome of death or HF hospitalization (upper left) and secondary outcomes of death (upper right); HF hospitalization (lower left) and cardiovascular hospitalization (lower right). Clinical outcomes were similar in men and women.

explain the similar clinical outcomes between men and women. Greater reductions in NT-proBNP have been associated with improved clinical outcomes.[28] It is possible that if women had received GDMT of equivalent intensity through 12 months, they may have had a greater absolute reduction in NT-proBNP and

Table 4. Clinical Outcomes in Men and Women With HFrEF Through 24 Months

	Women* (n=286)	Men* (n=608)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR† (95% CI)	*P* Value
12 mo						
Composite: death or HF hospitalization	85 (34.6)	198 (36.5)	0.94 (0.73 to 1.21)	0.64	0.91 (0.69 to 1.20)	0.49
Death	21 (8.9)	74 (14.4)	0.61 (0.37 to 0.99)	0.04	0.72 (0.43 to 1.21)	0.22
HF hospitalization	78 (32.0)	164 (31.0)	1.04 (0.80 to 1.36)	0.77	1.02 (0.76 to 1.37)	0.91
Cardiovascular hospitalization	134 (54.4)	309 (56.8)	0.91 (0.74 to 1.11)	0.36	0.87 (0.70 to 1.08)	0.20
Composite: cardiovascular death or HF hospitalization	84 (34.3)	190 (35.1)	0.97 (0.75 to 1.25)	0.81	0.92 (0.69 to 1.21)	0.55
24 mo						
Composite: death or HF hospitalization	101 (35.3)	243 (40.0)	0.93 (0.74 to 1.17)	0.54	0.96 (0.75 to 1.24)	0.77
Death	38 (21.3)	105 (24.3)	0.78 (0.54 to 1.13)	0.19	0.91 (0.61 to 1.37)	0.66
HF hospitalization	89 (40.3)	199 (43.1)	1.0 (0.78 to 1.28)	0.98	1.03 (0.78 to 1.35)	0.86
Cardiovascular hospitalization	145 (62.5)	351 (70.1)	0.87 (0.72 to 1.06)	0.16	0.86 (0.70 to 1.07)	0.17
Composite: cardiovascular death or HF hospitalization	98 (44.0)	230 (47.7)	0.95 (0.75 to 1.20)	0.68	0.96 (0.74 to 1.24)	0.75

HF indicates heart failure; HFrEF, heart failure with reserved ejection fraction; and HR, hazard ratio.
*Event rates are expressed as number (percentage).
†Adjusted for baseline clinical characteristics.

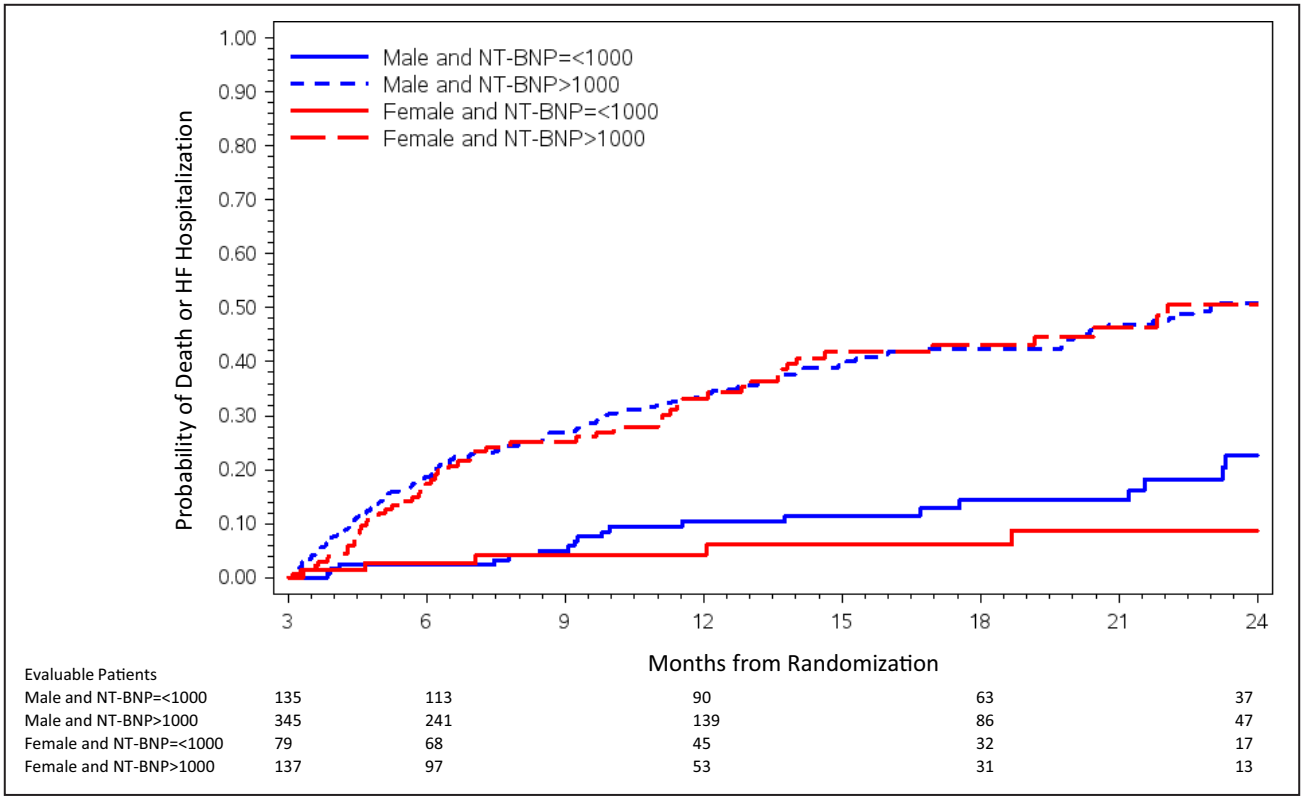

Figure 6. Clinical outcomes in men and women by early NT-proBNP (N-terminal pro-B-type natriuretic peptide) goal achievement.
Clinical outcomes were similar between men and women not achieving the early NT-proBNP goal (blue and red dashed lines). However, separation of the solid curves suggests a trend towards fewer events among women achieving the early NT-proBNP goal compared with men achieving the early NT-proBNP goal.

fewer clinical events compared with men. This would be consistent with previous studies that have demonstrated better clinical outcomes among women with HFrEF.[3,13]

Early achievement of the NT-proBNP goal of ≤1000 pg/mL is associated with significantly better outcomes than those not attaining goal.[20] After adjustment for clinical risk and HF treatment through 3 months, there was no sex difference in the ability to achieve the early NT-proBNP goal of ≤1000 pg/mL. However, women achieving the NT-proBNP goal of ≤1000 pg/mL at 3 months had a clinically significant lower rate of death and HF hospitalization than men achieving the early NT-proBNP goal (82% versus 59%, respectively). This difference did not meet statistical significance, likely because of the smaller number of patients in the landmark analysis and fewer events that consequently limited the power to detect a statistical difference. Nonetheless, these findings are still clinically meaningful and extend the current knowledge by suggesting that the early NT-proBNP goal of ≤1000 pg/mL may have greater prognostic significance in women than men. This finding is further supported by the observation that the prespecified therapeutic NT-proBNP goal of ≤1000 pg/mL was over 5 times lower than the adjusted NT-proBNP threshold of 5410 pg/mL needed for risk reduction in men; however, it was only minimally lower than the adjusted NT-proBNP threshold of 1260 pg/mL needed for women to demonstrate a reduction in adverse events. In other words, since the sex-specific NT-proBNP threshold for risk reduction was lower in women, there was greater benefit with incremental NT-proBNP reductions than in men, whose sex-specific NT-proBNP threshold was higher. This likely explains why women derived greater clinical benefit from lower NT-proBNP concentrations at 3 months than men.

Limitations

Several caveats should be considered in the interpretation of these results. First, women only comprised one third of the GUIDE-IT study population; therefore, it is possible that additional sex differences exist but were not detected because of the sample size and the abbreviated follow-up period with a relatively low number of events secondary to early trial termination. Efforts are needed to achieve equity in trial enrollment so that when sex differences exist, they can be detected and used

to inform sex-specific HF management. Second, although this study included an in-depth analysis of treatment differences between men and women with HFrEF, treatment with neprilysin inhibitors, a therapy that can lead to substantial NT-proBNP reduction, was not common in clinical practice during the timeframe in which the GUIDE IT trial was conducted. However, neprilysin inhibition does not appear to have a differential effect in men compared with women.[29,30] Finally, a landmark analysis at 12 months may have revealed whether the less intense GDMT in women negatively impacted NT-proBNP goal achievement and clinical outcomes more than men. Yet, such an analysis would have low power to detect a difference attributable to an even smaller population than in the 3-month landmark subgroup, which may not reflect the overall GUIDE-IT population as a result of survivor bias, and been limited by shorter follow-up duration with fewer events. Furthermore, the clinical value of a 12-month NT-proBNP analysis is uncertain. In contrast, the 3-month landmark is informative for guiding clinical management and informing the prognosis of men and women with HFrEF.

CONCLUSIONS

This study revealed several important insights on HF treatment, NT-proBNP response, and clinical outcomes among men and women with HFrEF. Women were undertreated with regards to target dosing of β-blockers and ACEIs or ARBs. Future efforts should be aimed at intensifying GDMT, achieving target doses, and reducing NT-proBNP in women, which may have even greater benefit for women than men.

ARTICLE INFORMATION

Received January 7, 2021; accepted April 1, 2021.

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Sources of Funding

The GUIDE-IT trial was funded by the National Heart, Lung, and Blood Institute.

Disclosures

Drs O'Connor and Felker have received grant support from the National Institutes of Health. Drs Cooper, Leifer, and Desvigne-Nickens are employees of the National Heart, Lung, and Blood Institute and were members of the GUIDE-IT Steering Committee. Dr Januzzi is a trustee of the American College of Cardiology; has received grant support from Novartis Pharmaceuticals, Innolife, Applied Therapeutics, and Abbott Diagnostics, and consulting income from Abbott, Janssen, Novartis, Pfizer, Merck, and Roche Diagnostics; and participates in clinical end point committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, and Takeda. The remaining authors have no disclosures to report.

Supplementary Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

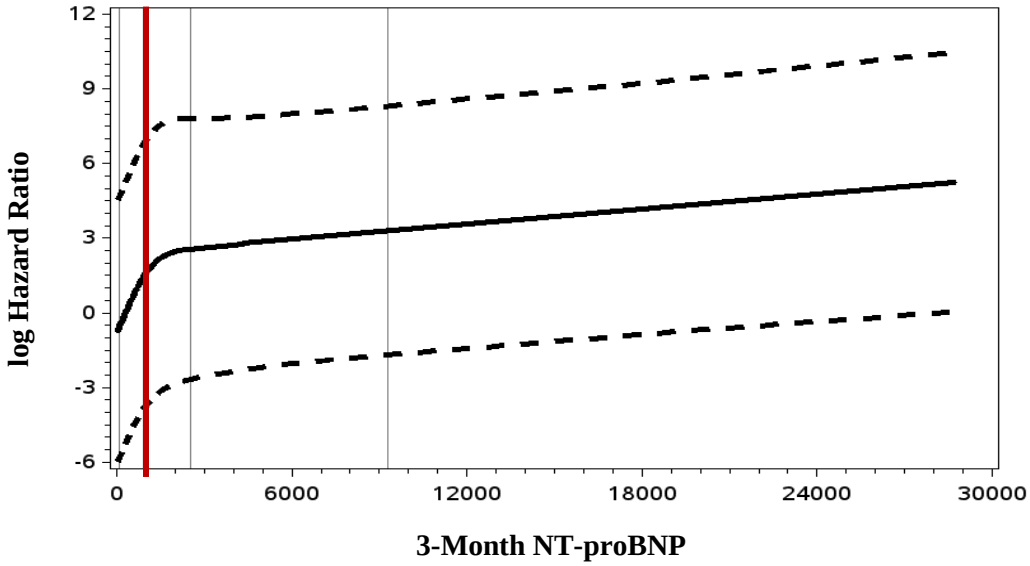
Table S1. Baseline Clinical Characteristics of Men and Women with NT-proBNP at 3 months.

	Women (n=217)	Men (n=480)	P-value
Age (years)	59.9±15.1	62.0±12.8	0.18
Race (Black)	97 (44.7%)	148 (30.8%)	<0.001
Body mass index (kg/m^2)	32.5±10.1	29.4±7.1	<0.001
Hypertension	155 (71.4%)	391 (81.5%)	0.004
Hyperlipidemia	120 (55.3%)	288 (60.0%)	0.25
Diabetes mellitus	109 (50.2%)	213 (44.4%)	0.16
Smoking	52 (24.0%)	174 (36.3%)	0.001
Atrial fibrillation	72 (33.2%)	206 (42.9%)	0.02
Chronic kidney disease	63 (29.0%)	186 (38.8%)	0.01
Peripheral artery disease	8 (3.7%)	61 (12.7%)	<0.001
Coronary artery disease	68 (31.3%)	245 (51.0%)	<0.001
Myocardial infarction	38 (17.5%)	155 (32.3%)	<0.001
Ischemic cardiomyopathy	75 (34.6%)	267 (55.6%)	<0.001
Heart Failure Duration* (mos)	6 (1.0-45.0)	20 (1.0-72.0)	0.003
NYHA Class III/IV	88 (40.6%)	195 (41.1%)	0.93
Ejection Fraction (%)	25.0±8.3	23.9±8.4	0.09
Biomarker-guided Therapy	106 (48.8%)	243 (50.6%)	0.68
Quality of Life Score by KCCQ	54.5±21.0	59.9±22.1	0.002

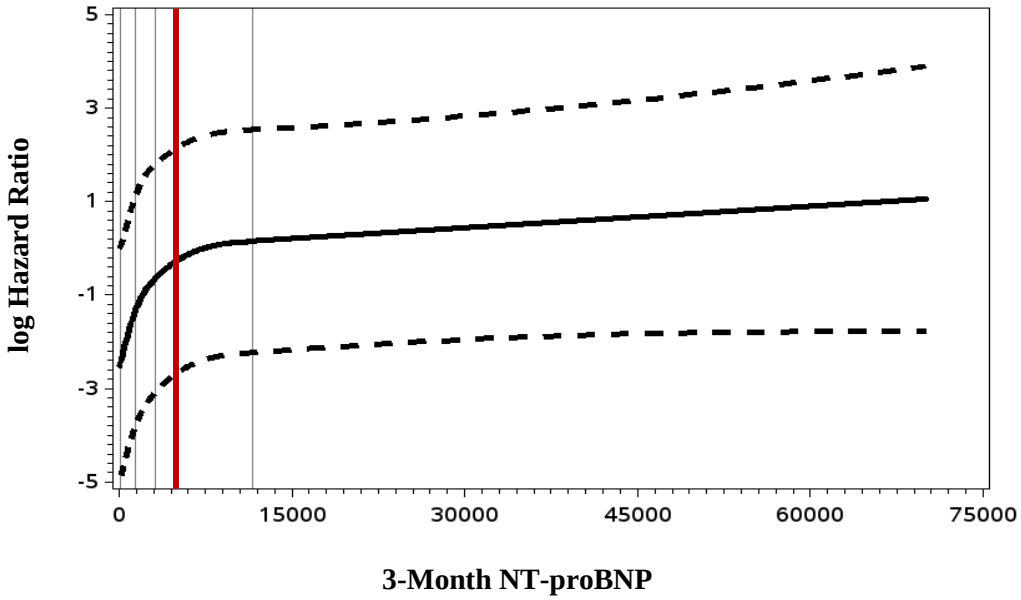
Values are mean±SD or n (%). *Median (interquartile range) NYHA= New York Heart Association; KCCQ= Kansas City Cardiomyopathy Questionnaire

Figure S1. Relationship between 3-month NT-proBNP and Death or HF Hospitalization.

A. Women with HFrEF



B. Men with HFrEF



The vertical red line indicates the inflection point at which there was a significant decrease in the adjusted hazard for death or HF hospitalization (women: 1260 pg/ml; men: 5410 pg/ml).