JAMA Cardiology | Original Investigation

Assessment of Limitations to Optimization of Guideline-Directed Medical Therapy in Heart Failure From the GUIDE-IT Trial
A Secondary Analysis of a Randomized Clinical Trial

Mona Fiuzat, PharmD; Justin Ezekowitz, MB BCh, MSc; Wendimagegn Alemayehu, PhD; Cynthia M. Westerhout, PhD; Marco Sbolli, MD; Dario Cani, MD; David J. Whellan, MD, MHS; Tariq Ahmad, MD; Kirkwood Adams, MD; Ileana L. Piña, MD; Chetan B. Patel, MD; Kevin J. Anstrom, PhD; Lawton S. Cooper, MD, MPH; Daniel Mark, MD, MPH; Eric S. Leifer, PhD; G. Michael Felker, MD, MHS; James L. Januzzi, MD; Christopher M. O'Connor, MD

IMPORTANCE Despite evidence that guideline-directed medical therapy (GDMT) improves outcomes in patients with heart failure (HF) and reduced ejection fraction, many patients are undertreated. The Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial tested whether a strategy of using target concentrations of N-terminal pro–brain natriuretic peptide (NT-proBNP) to guide optimization of GDMT could improve outcomes.

OBJECTIVE To examine medical therapy for HF in GUIDE-IT and potential reasons why the intervention did not produce improvements in medical therapy.

DESIGN, SETTING, AND PARTICIPANTS GUIDE-IT, a randomized clinical trial performed at 45 sites in the United States and Canada, was conducted from January 16, 2013, to September 20, 2016. A total of 894 patients with HF and reduced ejection fraction (≤40%) were randomized to NT-proBNP–guided treatment with a goal to suppress NT-proBNP concentrations to less than 1000 pg/mL vs usual care. This secondary analysis examined the medical therapy titration and reasons why the intervention did not produce improvements in care and outcomes. Data were analyzed March 27 to June 28, 2019.

MAIN OUTCOMES AND MEASURES For each encounter, medication titrations were captured. A reason was requested if a modification was not made. A Cox proportional hazards regression model was used to assess the independent association of drug class with outcomes.

RESULTS Among the 838 patients available for analysis (566 men [67.5%]; median age, 62.0 years), 6223 visits occurred during 24 months. Adjustments of HF medication were made during 2847 of 5218 qualified visits (54.6%) (all usual care visits and all guided care visits with NT-proBNP level ≥1000 pg/mL) in 862 patients (96.4%). Most adjustments occurred within the first 6 months, primarily within the first 6 weeks. The most common reasons for not adjusting were "clinically stable" and "already at maximally tolerated therapy." Only 130 patients (15.5%) achieved optimal GDMT (≥50% of the target dose of β-blockers or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or any dose of mineralocorticoid antagonists) at 6 months, an increase from the baseline (79 of 891 [8.9%]) but not different by treatment arm. Higher doses of β-blockers were associated with reduced risk of the composite outcome of HF hospitalization and cardiovascular death (hazard ratio [HR], 0.98; 95% CI, 0.97-1.00; $P = .008$) and of all-cause death (HR, 0.97; 95% CI, 0.95-0.99; $P = .01$). Higher doses of angiotensin-converting enzyme inhibitors (HR, 0.84; 95% CI, 0.75-0.93; $P < .001$) and angiotensin receptor blockers (HR, 0.84; 95% CI, 0.71-0.99; $P = .04$) were associated with reduced risk of all-cause death. Increasing doses of mineralocorticoid antagonists did not appear to be associated with improved outcomes.

CONCLUSIONS AND RELEVANCE Despite a protocol-driven approach, many patients in GUIDE-IT did not receive medication adjustments and did not achieve optimal GDMT, including those with known elevated NT-proBNP concentrations. These results suggest that opportunities exist to titrate medications for maximal benefit in HF. GUIDE-IT may have failed to achieve treatment benefit because of therapeutic inertia in clinical practice, or current GDMT goals may be unrealistic.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01685840

JAMA Cardiol. doi:10.1001/jamacardio.2020.0640
Published online April 22, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Mona Fiuzat, PharmD, Duke University Medical Center, DUMC Box 3850, Durham, NC 27710 (mona.fiuzat@duke.edu).

High-quality evidence has established that the use of guideline-directed medical therapy (GDMT) at target doses reduces morbidity and mortality in heart failure with reduced ejection fraction (HF-rEF). Despite this fact, many patients in clinical practice are not treated with these agents or are treated with lower-than-recommended doses.[1,2] This disconnect between evidence and practice is not well understood. When patients appear to be stable or are perceived to be doing well, there may be a natural reluctance by clinicians or patients to alter therapy and potentially cause adverse effects. We hypothesized that this therapeutic inertia might be overcome by providing biomarker feedback that some apparently stable patients may still need therapy intensification, which served as the basis of the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial. Concentrations of amino-terminal pro-B type natriuretic peptide (NT-proBNP) were chosen because they are strongly associated with outcomes in patients with HF and may be lowered using standard therapies in HF-rEF, such as β-blockers, angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs). Smaller trials examining the use of NT-proBNP concentrations to "guide" GDMT have suggested that the approach leads to more assiduous application of GDMT along with better outcomes compared with usual care.[3-5]

To test the prognostic benefits of biomarker-guided care for HF in a large, multicenter randomized clinical trial, Felker et al[6] performed the GUIDE-IT trial at 45 sites in the United States and Canada by comparing NT-proBNP–guided HF management vs usual care. Patients in the biomarker-guided arm were treated with usual care plus a goal to suppress NT-proBNP to less than 1000 pg/mL (to convert NT-proBNP to nanograms per liter, multiply by 1), whereas those in the usual care arm received standard clinically guided approaches to treatment decisions. GUIDE-IT planned for an enrollment of 1100 patients but was stopped early by the data safety monitoring board owing to futility. No difference in achieved NT-proBNP concentrations between the 2 study arms was reported, and initial analysis showed comparable administration of GDMT between both study groups.[7] In this secondary analysis, we aimed to examine the medical therapy titration in greater detail to understand potential reasons why the intervention did not produce the hypothesized improvements in care and outcomes.

Key Points

Question What heart failure medication was used and what were reasons for not titrating therapy in the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment study?

Findings In this secondary analysis of a randomized clinical trial including 838 patients with heart failure and reduced ejection fraction, medication adjustments were made during 2847 of 5218 qualified visits (54.6%). The most common reasons for not adjusting were "clinically stable" and "already at maximally tolerated therapy," and at 6 months, only 130 patients (15.5%) achieved optimal guideline-directed medical therapy (≥50% of the target dose of β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, or any dose of mineralocorticoid antagonists).

Meaning These results suggest that opportunities exist to titrate medications for maximal benefit in patients with heart failure.

Methods

Patient Cohort and Medical Therapy Protocols

The GUIDE-IT trial design and outcomes have been previously reported.[6,7] GUIDE-IT was a multicenter randomized clinical study, conducted from January 16, 2013, to September 20, 2016, that tested the strategy of augmented guideline-based therapy to suppress NT-proBNP concentrations to less than 1000 pg/mL vs usual care. The study was approved by the institutional review board at each study site, and all participants provided written informed consent.

The primary end point was the composite of time to HF hospitalization or cardiovascular death; 894 patients were randomized to the biomarker-guided or usual care groups. At each clinical encounter, sites evaluated the need for medication titration. The study protocol specified interventions to be considered to achieve the NT-proBNP target in the biomarker-guided arm (eMethods 1 in the Supplement), but specific treatment decisions were at the discretion of the treating physician. Specific changes in therapy and the rationale for them (eg, in response to clinical change or NT-proBNP concentration) were captured on the case report form. Patients randomized to the usual care group received care based on clinical practice guidelines.[8] Investigators were provided with specific information on target doses of neurohormonal antagonists (β-blockers, ACEis/ARBs, and MRAs) from clinical trials. Diuretic therapy was titrated based on clinical judgment of the treating physician and was considered a medication adjustment or titration. Sites were asked not to perform open-label assessment of natriuretic peptides in the usual care group. Among the 894 patients in the trial, all patients with a record of at least 1 visit during any of the study visits (ie, at baseline, 2 weeks, 6 weeks, and every 3 months throughout to a maximum of 2 years) were included in our analysis cohort.

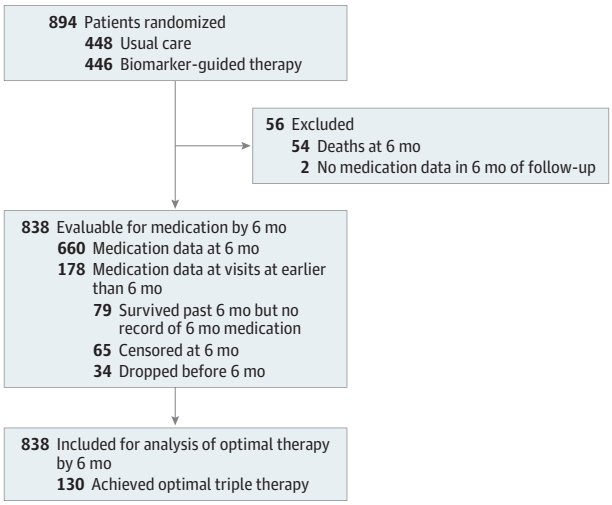
Reasons for Not Titrating Medication

A reason was requested if a modification was not made at the study visit. Reasons were provided by the site in categorical and free-text formats and mapped to appropriate groupings.

Optimal GDMT at 6 Months

Optimal GDMT was defined as receiving 50% or more of the target dose of β-blockers or ACEis/ARBs or any dose of MRAs by the 6-month study visit. If the patient did not have a medication record but was known to be alive by the 6-month study visit, the medication dose at the last visit was carried forward. Patients who died before the 6-month visit and/or never had a medication dose recorded in the first 6 months of follow-up were excluded from the optimal GDMT analysis (**Figure 1**).

Figure 1. Study CONSORT Diagram



The last medication data before 6 months are carried forward.

Qualified Visits

Qualified visits in the usual care arm were defined as all visits. Qualified visits in the guided-therapy arm were defined as those with an NT-proBNP concentration greater than or equal to 1000 pg/mL or higher (by local laboratory).

Clinical Outcomes

The clinical outcomes included the composite of time to first HF hospitalization or cardiovascular death and all-cause mortality. For the landmark analyses at 3 months, patients with the respective event observed or censored before the landmark time point were excluded. For HF hospitalization or cardiovascular death, patients who survived the 3-month landmark without HF hospitalization were included. Similarly, patients who were alive at 3 months regardless of their history of HF hospitalization were included for all-cause mortality analysis.

Statistical Analysis

Data were analyzed from March 27 to June 28, 2019. Descriptive data were summarized as frequencies and percentages for categorical variables and medians with 25th and 75th percentiles (interquartile range [IQR]) for continuous variables. Summary data on baseline characteristics of patients who achieved optimal GDMT at 6 months were compared with those who did not use the Pearson χ^2 test or the Wilcoxon rank-sum test, as appropriate. The change over time of the relative frequency of patients receiving guideline-recommended therapies for a number of drug classes (ACEis/ARBs, β-blockers, MRAs, loop diuretics, double target therapy, and triple target therapy) was evaluated. We specifically tested for significance of the change at 12 months relative to baseline applying generalized estimating equations to fit a logistic regression model that takes into account the correlation between pairs of visits of the same patient. The comparison was performed at the aggregate level and in subgroup analyses by stratifying according to sex (male or female), race/ethnicity (white or nonwhite), and age group (≥65 or <65 years).

For the analysis of reasons for not titrating medication, the frequency distribution of whether there was titration (yes or no) and the specific reasons if there was no titration were determined at each study visit. The proportion of visits with titration was compared between the treatment arms and stratified by NT-proBNP concentration (≥1000 or <1000 pg/mL), applying the generalized equalizing equation approach to fit a logistic regression model that takes into account the correlation between multiple visits per patient.

To evaluate how much the decision to change or adjust dosages at each appropriate visit was based on physiologic variables, we examined the nature of the association of heart rate, systolic blood pressure (SBP), potassium level, and serum creatinine (SCr) level with the probability of change in medication, applying a spline-smoothed regression. To further examine specific reasons for no change that included "at maximally tolerated dose," "at guideline-recommended target dose," and "clinically stable," summary tables were created of median (IQR) values for doses of β-blockers, ACEis/ARBs, diuretics, and MRAs and median (IQR) values of heart rate, SBP, potassium level, SCr level, glomerular filtration rate, and NT-proBNP concentration at the 6-month point.

The association of medication classes with clinical outcomes was assessed in landmark analyses at 90 days. A multivariable Cox proportional hazards regression model was used to examine the independent association of each drug class, including β-blockers (per 5-mg dose), ACEis (per 5-mg dose), ARBs (per 25-mg dose), and MRAs (per 25-mg dose), with the outcomes (HF hospitalization or cardiovascular death and all-cause mortality) 90 days after randomization. The hazard ratio (HR) and 95% CI from the Cox proportional hazards regression fit was estimated as the measure of the change in relative risk per the rescaled unit increase in dose. The choice of the rescaling factors for the doses followed previous work by Januzzi et al.[9] Briefly, the dose was converted to dose equivalents (carvedilol equivalents for β-blockers, lisinopril equivalents for ACEis, losartan equivalents for ARBs, and spironolactone equivalents for MRAs) according to a previously published conversion table (eMethods 2 in the Supplement).

A 2-sided $P < .05$ was regarded as significant. All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Inc) and R statistical software, version 3.5.0 (R Project for Statistical Computing).

Results

A total of 838 patients (272 women [32.5%] and 566 men [67.5%]; median age, 62.0 [IQR, 53.0-71.0] years) had data available for analysis at 6 months (Figure 1). Only 130 patients (15.5%) were receiving optimal GDMT at 6 months (≥50% of the target dose of β-blockers or ACEis/ARBs or any dose of MRAs) (**Table 1**). This proportion was significantly increased from the baseline (79 of 891 [8.9%]) (eTable 1 in the Supplement) but was similar between groups (70 of 423 [16.5%] patients in the intervention arm and 60 of 415 [14.5%] in the usual

Table 1. Baseline Demographics of Patients Who Achieved vs Did Not Achieve Optimal GDMT at 6 Months[a]

Characteristic	Patient group		*P* value
	Achieved optimal GDMT (n = 130)	Did not achieve optimal GDMT (n = 708)	
Age, median (IQR), y	56 (47-64)	64 (54-72)	<.001
Women	35 (26.9)	237 (33.5)	.14
Race/ethnicity[b]			
White	63 (50)	392 (57)	.12
Black	55 (43)	254 (37)	.17
Other	8 (6.2)	42 (5.9)	.92
Hispanic	7 (5.4)	49 (6.9)	.52
Duration of HF, median (IQR), mo	19 (1-65)	12 (1-66)	.94
LVEF at baseline, median (IQR)	22 (17-30)	25 (20-30)	.28
NYHA class at enrollment			
I	8 (6.2)	50 (7.2)	.76
II	72 (55.8)	360 (51.5)	
III	48 (37.2)	278 (39.8)	
IV	1 (0.8)	11 (1.6)	
Missing	1 (0.8)	9 (1.3)	
Risk factors			
Ischemic heart disease	44 (33.8)	363 (51.3)	<.001
Diabetes	44 (33.8)	337 (47.6)	<.001
Atrial fibrillation	51 (39.2)	281 (39.7)	.92
Chronic kidney disease	29 (22.3)	270 (38.1)	.005
SBP, median (IQR), mm Hg	119 (106-136)	113 (102-128)	.005
Heart rate, median (IQR), beats/min	78 (68-86)	76 (67-86)	.58
NT-proBNP level, median (IQR), pg/mL	1786 (988-3549)	2726 (1517-5373)	<.001
SCr level, median (IQR), mg/dL	1.2 (1.0-1.4)	1.3 (1.1-1.7)	<.001
GFR, median (IQR), mL/min/1.73m^2	72 (57-89)	58 (42-74)	<.001
Treatments			
β-Blocker	126 (96.9)	658 (92.9)	.10
ACEi/ARB	127 (97.7)	522 (73.7)	<.001
MRA	100 (76.9)	313 (44.2)	<.001
Implantable cardioverter-defibrillator	54 (41.5)	277 (39.1)	.60
Cardiac resynchronization therapy	21 (16.2)	131 (18.5)	.52
Study site			
Community	55 (42.3)	317 (44.8)	.60
Academic	75 (57.7)	391 (55.2)	
Treatment arm			
Guided therapy	70 (53.8)	353 (49.9)	.40
Usual care	60 (46.2)	355 (50.1)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SCr, serum creatinine.

SI conversion factors: To convert NT-proBNP to nanograms per liter, multiply by 1; SCr to micromoles per liter, multiply by 88.4.

[a] Optimal GDMT is increased dosage of 50% or more of β-blockers or ACEis/ARBs or any dose of MRA. Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100.

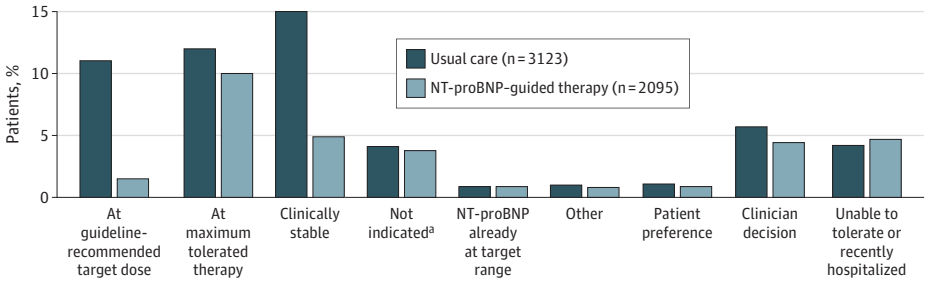
[b] Some patients identified as more than 1 racial/ethnic group.

care arm; *P* = .40). Three hundred sixty-three patients (43.3%) achieved double HF therapy (any combination of ≥50% of the target dose of β-blockers or ACEis/ARBs or any dose of MRAs) at 6 months. There was no difference between the treatment arms in the likelihood of achieving double HF therapy (194 of 423 [45.9%] in the intervention arm and 169 of 415 [40.7%] in the usual care arm; *P* = .13).

Patients who achieved optimal GDMT were younger (median age, 56 [IQR, 47-64] vs 64 [IQR, 54-72] years), with fewer comorbidities (ischemic heart disease, 44 [33.8%] vs 363 [51.3%]; diabetes mellitus, 44 [33.8%] vs 337 [47.6%]; and chronic kidney disease, 29 [22.3%] vs 270 [38.1%]) and a more stable clinical profile, including higher SBP (median, 119 [IQR, 106-136] vs 113 [IQR, 102-128] mm Hg), lower NT-proBNP concentration (1786 [IQR, 988-3549] vs 2726 [IQR, 1517-5373] pg/mL), and lower SCr level (median, 1.2 [IQR, 1.0-1.4] vs 1.3 [IQR, 1.1-1.7] mg/dL). There was no difference by race or sex in likelihood of achieving optimal GDMT and no difference between academic or community sites.

A total of 894 patients completed the trial, which represented 6223 study visits over a maximum of 24 months. Medication adjustments were made in 2847 of 5218 qualified study visits (54.6%) (all visits in the usual care arm and visits in the guided arm with NT-proBNP level ≥1000 pg/mL). These visits represented 862 patients (96.4%) (eTable 2 in the Supplement), including 1429 of 2095 visits (68.2%) in guided-arm patients with NT-proBNP greater than or equal to 1000 pg/mL in whom titration would have been expected according to study

Figure 2. Reasons for Not Titrating Medications by Treatment Arm



Data include all qualified visits, that is, all visits in the usual care arm and all visits in the guided therapy arm with N-terminal pro–brain natriuretic peptide (NT-proBNP) levels of greater than or equal to 1000 pg/mL, determined by local laboratories. To convert NT-proBNP to nanograms per liter, multiply by 1.

[a] Includes laboratory draw, telephone visit, or end of study.

Table 2. Reasons for Not Titrating Medication Dose

Visit	No. of visits								
	At guideline-recommended target dose (n = 174)	At maximum tolerated therapy (n = 257)	Clinically stable (n = 276)	Not indicated[a] (n = 174)	NT-proBNP level at target range (n = 33)	Other (n = 40)	Patient preference (n = 40)	Clinician decision (n = 215)	Unable to tolerate or recent hospitalization (n = 176)
All	366	577	581	206	46	48	51	270	228
Usual care	334	367	479	127	27	31	33	178	130
Guided therapy	32	210	102	79	19	17	18	92	98

Abbreviation: NP-proBNP, N-terminal pro–brain natriuretic peptide.

[a] Includes laboratory draw, telephone visit, or end of study.

protocol (eTable 4 in the Supplement). Most of the GDMT adjustment occurred within the first 6 months, primarily within the first 6 weeks of enrollment.

The primary reasons reported by investigators for not adjusting therapy were "clinically stable" (581 of 5218 visits [11.1%]) and "already at maximally tolerated therapy" (577 of 5218 [11.1%]) (eTable 2 in the Supplement). In the intervention arm, when the NT-proBNP concentration was greater than or equal to 1000 pg/mL (qualified visit), the most common reason for not titrating medication was reported as "already at maximally tolerated therapy" (210 of 2095 [10.0%]) (eTable 3 in the Supplement, **Figure 2**, and **Table 2**). The results were consistent by sex, with these top 2 reasons reported for both men and women. In white patients, "at maximally tolerated therapy" was selected as the most common reason, whereas in black patients, "clinically stable" was the most common reason selected. In patients older than 65 years, "at maximally tolerated therapy" was the most common reason selected, whereas in patients 65 years or younger, "clinically stable" was most commonly selected. Investigators in the community setting were more likely to report "clinically stable" as the most common reason for not titrating (354 of 2323 [15.2%] visits in community sites vs 224 of 2895 [7.7%] visits in academic sites; $P < .001$), with both academic and community sites reporting "at maximally tolerated therapy" as the top 2 reasons. Academic sites reported "at guideline-recommended target dose" as the second most common reason.

In the usual care arm (where clinicians were blinded to NT-proBNP values), medication changes were made in 967 of 1973 visits (49.0%) when NT-proBNP was greater than or equal to 1000 pg/mL and 356 of 866 visits (41.1%) when NT-proBNP concentration was less than 1000 pg/mL. These findings indicated a high rate of titration in the usual care arm even when NT-proBNP concentration was low (eTable 4 in the Supplement).

The eFigure in the Supplement demonstrates the association of physiologic variables and likelihood of medication change. Heart rate, SBP, potassium level, and SCr level were important physiologic considerations in the probability of whether or not a medication change was made. Patients with a higher heart rate or elevated potassium level had increased probability of a medication change. Systolic blood pressure showed a linear relationship, and SCr level did not have an association with the probability of medication change. For patients with the selected reason "at maximally tolerated therapy," maximum therapy was likely based on important parameters (eg, heart rate of 70 bpm; SBP of 102 mm Hg; potassium level of 4.3 mEq/L; SCr level of 1.4 mg/dL; and estimated glomerular filtration rate of 57 mL/min/1.73 m^2) (eTable 5 in the Supplement). When "at guideline-recommended target dose" was selected, the median β-blocker daily dose was 50 mg; ACEi dose, 19 mg; ARB dose, 100 mg; MRA dose, 25 mg; and loop diuretic dose, 40 mg (eTable 6 in the Supplement). When "clinically stable" was selected, mean daily doses of medications were not at target, and physiologic parameters appear to allow for further medication change (eTable 7 in the Supplement). In these visits (clinically stable but no medication change occurred), the median NT-proBNP level was 3045 (IQR, 1829.0-5870.0) pg/mL in the intervention group, indicating that these 66 visits could have included a medication titration per the study protocol.

Higher doses of β-blockers were associated with improvement in both the primary composite outcome (HR, 0.98; 95% CI, 0.97-1.00; $P = .008$) and all-cause mortality (HR, 0.97; 95% CI, 0.95-0.99; $P = .01$), with approximately 2% to 3% reduction in risk for every 5-mg increase in dose (**Table 3**). Higher

Table 3. Outcomes by Medication Class

Medication class	Composite HF hospitalization or cardiovascular death (n = 714)[a]		All-cause mortality (n = 808)[b]	
	Outcome analysis	*P* value	Outcome analysis	*P* value
No. of events	207	NA	119	NA
No. censored	507	NA	689	NA
HR (95% CI) per 5-mg increase in dose				
β-Blocker	0.98 (0.97-1.00)	.008	0.97 (0.95-0.99)	.01
ACEi	0.99 (0.95-1.05)	.95	0.84 (0.75-0.93)	<.001
HR (95% CI) per 25-mg increase in dose				
ARB	1.05 (0.99-1.13)	.13	0.84 (0.71-0.99)	.04
MRA	1.01 (0.82-1.23)	.95	1.14 (0.90-1.44)	.28

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; HF, heart failure; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NA, not applicable.

[a] Among the 894 patients in the trial, a total of 180 (121 with HF hospitalization and/or cardiovascular death; 59 censored for the events before landmark) were excluded, leaving 714 available for the primary end point analysis.

[b] Among the 894 patients in the trial, a total of 86 were censored for all-cause mortality (n = 62) or death before the 3-month landmark (n = 24), leaving 808 available for the effect on mortality analysis.

doses of ACEis (HR, 0.84; 95% CI, 0.75-0.93; $P < .001$) and ARBs (HR, 0.84; 95% CI, 0.71-0.99; $P = .04$) were associated with a reduction in risk of all-cause mortality with increasing doses, but such an observation was not present for the primary end point of HF hospitalization or cardiovascular death. In this analysis, increasing doses of MRAs were not associated with improved outcomes for either end point.

Discussion

There were several important findings from this analysis. First, the rate of optimized GDMT in the trial was disappointingly low, with only 15.5% of patients achieving optimal GDMT at 6 months despite this objective being clear to all investigators with performance feedback for the intervention arm during the conduct of the trial. The fact that the investigative group consisted of experienced HF clinicians who had substantial familiarity and comfort with the drugs in question and their use in patients with difficult HF is particularly notable. Furthermore, sex, race/ethnicity, and type of center (academic vs community) did not appear to influence the likelihood of therapy changes; however, younger patients with fewer comorbidities were more often titrated to more comprehensive GDMT. Third, most dose adjustments occurred within the first 6 weeks of enrollment, suggesting that once a period of apparent clinical stability has been achieved, there may be a reluctance to push drug therapy further toward a theoretical target. This therapeutic inertia may have several causes, including a reluctance by physicians or patients to risk adverse effects with higher doses and uncertain tangible benefits for individual patients. However, we found that when "maximally tolerated" or "at guideline target" was selected, the general clinical profile indicated these reasons were likely accurate. Nonetheless, some visits may have had room for titration, particularly when patients were deemed to be clinically stable. This finding supports the notion that apparently clinically stable patients may have room for medication titration, but generally patients may be maximized before reaching target GDMT. Heart rate, SBP, and potassium levels are important variables associated with the likelihood of a medication adjustment, whereas SCr level is important but not as strongly correlated.

Finally, those patients in the biomarker-guided arm did not receive more intensive titration of GDMT despite an NT-proBNP target level less than 1000 pg/mL. Reasons for not titrating were often subjective, including clinician impression that patients were medically at their maximally tolerated doses, even in the face of elevated NT-proBNP concentrations. Our data are similar to results from the Change the Management of Patients With Heart Failure (CHAMP) registry, which reported a similar finding of only 1% of eligible patients receiving target doses of GDMT combined.[1] On the other hand, 43.3% of patients in our study achieved double "optimal" HF therapy, indicating that perhaps few patients achieve optimal therapy but many may achieve double GDMT. In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure) Trial, in 280 patients receiving usual care, there were a total of 1061 HF medication adjustments over 6 months, driven by diuretics (585 adjustments).[10] There were no changes in the use or doses of neurohormonal antagonists (ACEi/ARB or β-blockers) in the usual care arm. Together, these findings indicate a mean of 4 medication changes per patient during 6 months, with more than half of the changes attributed to diuretic adjustments. This further indicates that even in the setting of a protocol-driven approach, significant opportunity remains to titrate doses of life-saving therapies for HF-rEF.

We found significant improvement in outcomes with increasing doses of β-blockers. This finding is consistent with previous findings, emphasizing the dose-related benefit from this class of therapy.[11] As well, higher doses of ACEis/ARBs were associated with a reduction in the risk of all-cause mortality, consistent with previous data.[12,13] We found no signal for improved outcome associated with increased doses of MRAs in this study, consistent with other trials. The heterogeneity of response to MRAs relative to

improved outcome deserves further assessment. However, these nonrandomized comparisons should be interpreted cautiously in this context.

Limitations

This analysis has several limitations. Patients not meeting eligibility criteria for GUIDE-IT were excluded from the study. Compared with HF registries, GUIDE-IT represents a relatively young cohort of patients, and therefore very elderly and frail patients are less represented. GUIDE-IT included a relatively sick cohort of patients, with recent hospitalization and relative instability (hospitalization and high NT-proBNP concentrations within last 30 days). On the other hand, GUIDE-IT includes one of the largest cohorts of Hispanic, black, and female patients in a clinical trial for HF, and therefore the characterization of special populations and their importance in predictive models is important. Combined sacubitril and valsartan (Entresto) was new to the market during the course of the GUIDE-IT trial, so this therapy could not be evaluated in the context of other GDMT. Finally, causal relationships were not recorded, so the association between aggregate clinical profile and medication adjustment decisions are inferred and not determined on an individual basis.

Conclusions

Despite a protocol-driven approach implemented by experienced HF cardiologists, many patients in the GUIDE-IT trial did not receive GDMT adjustments, particularly in the long term, even in those with known elevated NT-proBNP concentrations. These results suggest that GUIDE-IT may have failed to achieve the treatment benefit postulated because of therapeutic inertia in clinical practice or that current GDMT goals may be unrealistic. The opportunity to titrate GDMT remains in the care of patients with HF-rEF, although some patients may be maximized before achieving GDMT. Whether more assiduous titration of therapies for patients in the biomarker-guided arm—in whom NT-proBNP concentration often remained elevated above the target value—would have further improved outcomes remains speculative.

ARTICLE INFORMATION

Accepted for Publication: January 16, 2020.

Disclaimer: Dr O'Donnell is an associate editor of *JAMA Cardiology*, but he was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Published Online: April 22, 2020. doi:10.1001/jamacardio.2020.0640

Author Affiliations: University Medical Center and Duke Clinical Research Institute, Duke University, Durham, North Carolina (Fiuzat, Patel, Anstrom, Mark, Felker, O'Connor); Heart Function Clinic, Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada (Ezekowitz); Canadian VIGOUR Centre, Katz Group Centre for Pharmacy and Health Research, University of Alberta, Edmonton, Alberta, Canada (Ezekowitz, Alemayehu, Westerhout); Department of Cardiology, University of Brescia, Brescia, Italy (Sbolli, Cani); Inova Heart and Vascular Institute, Fairfax, Virginia (Sbolli, Cani, O'Connor); Division of Cardiology, Department of Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania (Whellan); Section of Cardiovascular Medicine, Yale University School of Medicine, New Haven, Connecticut (Ahmad); Department of Cardiology, University of North Carolina School of Medicine, Chapel Hill (Adams); Division of Cardiology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York (Piña); Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, Maryland (Cooper, Leifer); Baim Institute for Clinical Research, Cardiology Division, Massachusetts General Hospital, Boston (Januzzi).

Author Contributions: Dr Fiuzat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Fiuzat, Ezekowitz, Alemayehu, Whellan, Ahmad, Adams, Anstrom, Felker, O'Connor.
Acquisition, analysis, or interpretation of data: Fiuzat, Ezekowitz, Alemayehu, Westerhout, Sbolli, Cani, Whellan, Adams, Piña, Patel, Cooper, Mark, Leifer, Felker, Januzzi, O'Connor.
Drafting of the manuscript: Fiuzat, Ezekowitz, Alemayehu, Westerhout, Cani, Ahmad, Januzzi.
Critical revision of the manuscript for important intellectual content: Fiuzat, Ezekowitz, Alemayehu, Westerhout, Sbolli, Whellan, Ahmad, Adams, Piña, Patel, Anstrom, Cooper, Mark, Leifer, Felker, Januzzi, O'Connor.
Statistical analysis: Alemayehu, Westerhout, Anstrom, Mark, Leifer.
Obtained funding: Fiuzat, Mark, Felker, O'Connor.
Administrative, technical, or material support: Fiuzat, Ezekowitz, Whellan, O'Connor.
Supervision: Ezekowitz, Whellan, Ahmad, Felker, Januzzi, O'Connor.

Conflict of Interest Disclosures: Dr Fiuzat reported receiving grant or research support from Roche Diagnostics. Dr Ezekowitz reported receiving grant or research support from the Canadian Institutes of Health Research, Amgen, Inc, Bayer AG, Bristol-Myers Squibb, Merck & Co, and Novartis International AG and serving as a consultant for Amgen, Inc, Bayer AG, Merck & Co, and Novartis International AG. Dr Whellan reporting receiving grant support from the National Heart, Lung, and Blood Institute (NHLBI), the National Institute on Aging, CVR Global, Novartis International AG, and Aegerion Pharmaceuticals, Inc; serving as a consultant for CSL Behring and BDC Advisors; and serving on clinical end points committees for CVRx, Inc, and FibroGen, Inc. Dr Adams reported receiving grants and personal fees from Roche Diagnostics during the conduct of the study; grants and personal fees from Novartis and Amgen, personal fees from Cytokinetics, Relypsa, and Windtree Therapeutics, and grants from BMS, Boehringer Ingelheim, and Otsuka outside the submitted work. Dr Piña reported serving on the advisory board for Relypsa, Inc. Dr Ahmad reported receiving consulting income from Cytokinetics, Inc, and Amgen, Inc. Dr Anstrom reported receiving grant support from the NHLBI, Merck & Co, and Bayer AG. Dr Mark reported receiving grants from the National Institutes of Health (NIH)/NHLBI, Mayo Clinic, Merck & Co, Oxygen Therapeutics LLC, and HeartFlow outside the submitted work and consulting income from CeleCor Therapeutics, Cytokinetics, Inc, and Novo Nordisk A/S outside the submitted work. Dr Felker reported receiving grant support from Merck & Co, Amgen, Inc, Roche Diagnostics, the NIH, and the American Heart Association and consulting fees from Novartis International AG, Amgen, Inc, Cytokinetics, Inc, Medtronic plc, Bristol-Myers Squibb, MyoKardia, Inc, Innolife, Abbott Laboratories, Alnylam Pharmaceuticals, Inc, EBR Systems, Inc, Cardionomic, SphingoTec GmbH, scPharmaceutical, Inc, and Stealth BioTherapeutics Corp. Dr Januzzi reported receiving grant support from Roche Diagnostics, Abbott Diagnostics, Singulex, Inc, Prevencio, Inc, Novartis International AG, and Cleveland HeartLab, Inc, and consulting income from Roche Diagnostics, Abbott Diagnostics, Prevencio, Inc, and Critical Diagnostics; and participating in clinical end point committees/data safety monitoring boards for Siemens Healthcare Diagnostics, Inc, Novartis International AG, Bayer AG, AbbVie, Inc, and Amgen, Inc. Dr O'Connor reported receiving grant or research support from Roche Diagnostics and Merck & Co and consulting fees from Merck & Co, Bayer AG, Bristol-Myers Squibb, Windtree Therapeutics, Inc, and Arena Pharmaceuticals, Inc. No other disclosures were reported.

Funding/Support: The GUIDE-IT trial was supported by the NHLBI of the NIH. Additional substudies were supported by Roche Diagnostics.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the present study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72(4):351-366. doi:10.1016/j.jacc.2018.04.070

2. Thomas M, Khariton Y, Fonarow GC, et al. Association of changes in heart failure treatment with patients' health status: real-world evidence from CHAMP-HF. *JACC Heart Fail*. 2019;7(7):615-625. doi:10.1016/j.jchf.2019.03.020

3. Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2011;58(18):1881-1889. doi:10.1016/j.jacc.2011.03.072

4. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. *Am Heart J*. 2009;158(3):422-430. doi:10.1016/j.ahj.2009.06.018

5. Lainchbury JG, Troughton RW, Strangman KM, et al. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol*. 2009;55(1):53-60. doi:10.1016/j.jacc.2009.02.095

6. Felker GM, Ahmad T, Anstrom KJ, et al. Rationale and design of the GUIDE-IT study: Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in heart failure. *JACC Heart Fail*. 2014;2(5):457-465. doi:10.1016/j.jchf.2014.05.007

7. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;318(8):713-720. doi:10.1001/jama.2017.10565

8. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70(6):776-803. doi:10.1016/j.jacc.2017.04.025

9. Januzzi JL Jr, Ahmad T, Mulder H, et al. Natriuretic peptide response and outcomes in chronic heart failure with reduced ejection fraction: insights from the GUIDE-IT trial. *J Am Coll Cardiol*. 2019;74(9):1205-1217. doi:10.1016/j.jacc.2019.06.055

10. Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. *JACC Heart Fail*. 2016;4(5):333-344. doi:10.1016/j.jchf.2015.11.011

11. Fiuzat M, Wojdyla D, Kitzman D, et al. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. *J Am Coll Cardiol*. 2012;60(3):208-215. doi:10.1016/j.jacc.2012.03.023

12. Packer M, Poole-Wilson PA, Armstrong PW, et al; ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation*. 1999;100(23):2312-2318. doi:10.1161/01.CIR.100.23.2312

13. Konstam MA, Neaton JD, Dickstein K, et al; HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 2009;374(9704):1840-1848. doi:10.1016/S0140-6736(09)61913-9