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CLINICAL TRIALS (J. BUTLER, SECTION EDITOR)

The Future of Biomarker-Guided Therapy for Heart Failure After the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) Study

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Abstract

Purpose of Review Biomarker-guided management of patients with chronic heart failure with reduced ejection fraction (HFrEF) remains controversial.

Recent Findings Biomarkers have established roles for diagnosis and prognostication in HF. Pilot data suggested that use of natriuretic peptides might be helpful to guide HF care. The recent Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) randomized–controlled trial did not find therapy guided by NT-proBNP to be more effective than usual care in improving the primary endpoint of HF hospitalization or cardiovascular mortality amongst patients with chronic HFrEF. Patients in GUIDE-IT received similar care and had similar NT-proBNP lowering regardless of treatment allocation.

Summary Though biomarkers retain important standing for diagnosis and prognosis in HF, the GUIDE-IT trial results suggest carefully managed patients may not benefit from a biomarker-guided strategy. Future studies focusing this intervention on patients treated in a more real-world setting are needed.

Keywords Heart failure · Biomarkers · Natriuretic peptides · Guidelines · Heart failure therapy · Clinical trials

Recent heart failure (HF) clinical practice guideline updates have articulated a Class I standing for the natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro B-type natriuretic peptide [NT-proBNP]) for diagnosis and prognosis in those affected by the diagnosis. Guidelines have also given Class II recommendation for use of BNP or NT-proBNP for assessing risk for rehospitalization after hospital discharge for HF care, or in screening to prevent HF onset [1••]. These applications—particularly diagnosis and prognosis—are unassailable. On the other hand, much debate lies in the role of BNP and NT-proBNP use for "guiding" therapy in patients with chronic HF with reduced ejection fraction (HFrEF) [2••, 3••].

Conceptually, the use of BNP or NT-proBNP to guide HF care is based on the observation these two biomarkers are prognostic when measured serially—rising patterns are associated with worse outcome, while falling patterns are reassuring—and most guideline-directed medical therapies (GDMT) with benefit for HF including angiotensin-converting enzyme inhibitors (ACEi), beta blockers, aldosterone antagonists, and cardiac resynchronization therapy (CRT) tend to change BNP or NT-proBNP in a favorable direction after their initiation and up-titration [4–6, 7••]. Following significant reduction in NT-proBNP in this context, improved outcomes are observed, including fewer cardiovascular (CV) events [8, 9] and significant left ventricular (LV) reverse remodeling [10]. In contrast, those whose GDMT is titrated with persistent elevation and no response in natriuretic peptide concentration have persistently bad outcomes, despite such GDMT up-titration [11].

This article is part of the Topical Collection on *Clinical Trials*

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Notably, importance of GDMT lies not only in initiation of these therapies but even more importantly in titration to the doses achieved in clinical trials to maximize benefit [12–14]. Unfortunately, achievement of target GDMT falls short of the goal in most assessments outside of clinical trials for HF therapies [15]. Thus, higher risk patients may be under-treated, even beyond the context of what would be considered "target" therapy. Given links between natriuretic peptide trends during medical therapy appear to inform success or failure of such GDMT, it naturally led to the concept that natriuretic peptides might be used to serve as a tool to "guide" application of GDMT, triggering more aggressive therapy titration in those with persistently elevated concentrations of these biomarkers.

Guided Therapy Trials, Early Data

The outcomes of early trials of natriuretic peptide guided HF therapy were mixed [2••]. The earliest pilot study done to explore whether NT-proBNP-guided care would be superior than usual care was done by Troughton and colleagues in 69 patients with chronic HFrEF. During follow-up, there were fewer CV events including death, hospital admission, or HF decompensation in the biomarker-guided group compared to the usual care group (19 vs. 54, $P = 0.02$) and at 6 months 27% of patients in the biomarker-guided group compared to 53% of the usual care group experienced a first CV event ($P = 0.034$) [16•]. Following this study, three randomized–controlled trials showed biomarker-guided care to be superior to standard management without an increase in adverse events [8, 17, 18], while several other trials involving biomarker-guided care were neutral [19–24].

An understanding of successful guided therapy studies helped to inform a path forward. Such trials tended to use lower NT-proBNP or BNP targets (e.g., NT-proBNP < 1000 pg/mL, BNP < 100 pg/mL), had designs leading to more adjustments in GDMT in those within the guided therapy arm (versus usual care), and had significantly greater reduction in NT-proBNP or BNP concentrations in the guided therapy arm versus usual care. In contrast, those studies that were unsuccessful tended to have higher natriuretic peptide goals, less differences in GDMT adjustment between arms, and less difference in NT-proBNP or BNP lowering between arms. Overall findings suggested, however, that guided therapy was typically well tolerated [25], and if significant lowering in NT-proBNP occurred, prognosis was improved. Overall meta-analyses and combined individual patient data analyses combining findings from available natriuretic peptide-guided HF studies suggested a 20–30% mortality reduction associated with biomarker-guided HF management over standard HF care [9, 26, 27].

Because the available studies were relatively small, had varying designs, and returned conflicting data regarding the role of biomarker-guided management of chronic HFrEF, a large prospective randomized control trial was designed with the hope of putting the debate to rest.

The GUIDE-IT Trial

The Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) randomized–controlled trial of 894 patients with chronic HFrEF unfortunately did not find NT-proBNP-guided therapy to be more effective than usual care in improving outcomes including the primary endpoint of HF hospitalization or CV mortality amongst patients with chronic HFrEF [15]. The primary endpoint occurred in 164 patients (37%) in the biomarker-guided group and 164 patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.79–1.22; $P = 0.88$). CV mortality occurred in 12% ($N = 53$) of patients in the biomarker-guided group and 13% ($N = 57$) of patients in the usual care group (HR, 0.94; 95% CI, 0.65–1.37; $P = 0.75$) [28••]. However, there is much to learn from the design and results of the GUIDE-IT trial to better understand the future of biomarker-guided management of patients with chronic HFrEF.

Design of the GUIDE-IT Trial

The design of the GUIDE-IT trial has been previously published [29••]. Detailed inclusion and exclusion criteria for GUIDE-IT are listed in Table 1. Briefly, the original enrollment goal was 1100 high-risk patients with chronic HFrEF (LV ejection fraction < 40%), a HF event in the preceding 12 months, and a BNP > 400 pg/mL or NT-proBNP > 2000 pg/mL in the preceding 30 days. Patients were excluded if they had an acute coronary syndrome, revascularization, or CRT in the preceding 3 months, severe stenotic valvular disease, anticipated need for advanced therapies, complex congenital heart disease, or end-stage renal disease amongst other exclusion criteria [29••]. Patients were randomized to the NT-proBNP-guided arm targeting an NT-proBNP < 1000 pg/mL using GDMT versus the usual care arm. In the NT-proBNP arm, titration of neurohormonal antagonists was emphasized over titration of diuretics, except in the case of clinically apparent congestion or in the case of very high NT-proBNP concentrations (i.e., NT-proBNP > 5000 pg/mL) [29••].

In both arms, initial follow-up visit occurred 2 weeks after randomization and then every 3 months. Additionally, patients had 2-week follow-up visits after change in HF therapies. Follow-up visits continued every 2 weeks until therapeutic targets or maximum tolerated doses of GDMT were reached. Patients hospitalized for HF during the study had a 2–4-week follow-up study visit post-hospital discharge.

Table 1 Inclusion and exclusion criteria of the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial [29••]

Inclusion criteria
Age ≥ 18 years
HF event in prior 12 months (defined as any one of the following: (a) HF hospitalization, (b) treatment in the emergency department (or equivalent) for HF, and (c) outpatient treatment for HF with intravenous diuretics)
Recent documented LVEF ≤ 40% by any method within 12 months prior to randomization
BNP > 400 pg/mL or NT-proBNP > 2000 pg/mL in 30 days prior to randomization
Exclusion criteria
Clinical diagnosis of ACS or cardiac revascularization within 30 days
CRT within prior 3 months or current plans to implant CRT device
Severe stenotic valvular disease
Anticipated OHT or VAD within 12 months
Chronic inotropic therapy
Complex congenital heart disease
ESRD with renal replacement therapy
Non-cardiac terminal illness with expected survival less than 12 months
Women who are pregnant or planning to become pregnant
Inability to comply with planned study procedures
Enrollment or planned enrollment in another clinical trial

HF, heart failure; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; ACS, acute coronary syndrome; CRT, cardiac resynchronization therapy; OHT, orthotropic heart transplant; VAD, ventricular assist device; ESRD, end-stage renal disease

The primary endpoint of the GUIDE-IT trial was time to CV death or first HF hospitalization [29••]. Ultimately, 894 patients were enrolled in the trial ($N = 446$ in the NT-proBNP-guided arm and $N = 448$ in the usual care arm) when the study was halted early when NT-proBNP-guided therapy was found to not be more effective than usual care.

NT-proBNP Targets and Change During GUIDE-IT

The NT-proBNP target < 1000 pg/mL was chosen based on previous trials [30] and the favorable results of the Pro-BNP Outpatient Tailored Chronic HF Therapy (PROTECT) study in which patients with NT-proBNP < 1000 pg/mL had the lowest frequency of total CV events (0.45) compared with those with an NT-proBNP concentration between 1000 and 2000 pg/mL (1.1 events), between 2000 and 3000 pg/mL (1.25 events), and above 3000 pg/mL (2.0 events) ($P < 0.001$ for trend) [8]. Achievement of this target value was also associated with significantly greater LV reverse remodeling at one year in parallel with lower event rates [10]. Furthermore, in recent analyses, the NT-proBNP threshold was reaffirmed in an analysis by Zile et al., who found those with NT-proBNP concentrations < 1000 pg/mL either at baseline or at one month after treatment with sacubitril/valsartan had significantly better outcomes compared to those above this value [31•].

One extremely important observation to help understand lack of difference in outcome in the GUIDE-IT trial relates to NT-proBNP change in both the guided and usual care arm. At 12 months, the median NT-proBNP decreased from a median of 2568 pg/mL to 1209 pg/mL (53% decrease) in the biomarker-guided group and from a median of 2678 pg/mL to 1397 pg/mL (48% decrease) in the usual care group (Fig. 1). Thus, there were no differences seen with respect to achieved NT-proBNP concentration: 46% of participants in the biomarker-guided arm and 40% of the usual care group achieved an NT-proBNP < 1000 pg/mL at 12 months ($P = 0.21$) [28••]. The reduction in NT-proBNP achieved in both arms of GUIDE-IT exceeds that of most other studies in this area, particularly for the "usual care" arm. Given difference in the achievement of an NT-proBNP concentration < 1000 pg/mL in both study arms, it is not unexpected that there was no difference in the primary endpoint of time to CV death or first HF hospitalization between the two groups.

The results of GUIDE-IT do not imply lack of prognostic value of NT-proBNP changes during HF therapy. What remains yet unknown from the GUIDE-IT experience is whether patients with NT-proBNP < 1000 pg/mL in both treatment groups at study conclusion had lower CV events compared to those who did not achieve an NT-proBNP < 1000 pg/mL regardless of treatment arm. Furthermore, amongst those who achieved an NT-proBNP < 1000 pg/mL at study conclusion, it also remains uncertain whether patients with higher rates of achievement of target doses of GDMT fared better than those with lower rates of achievement of target doses of GDMT. That is, was it more important to achieve target doses of GDMT or to achieve an NT-proBNP concentration < 1000 pg/mL in order to maximize reduction in CV events? Such analyses are under way.

Guideline-Directed Medical Therapy

GDMT reduces morbidity and mortality in patients with chronic HFrEF [1••], and importantly, GDMT are titrated to target or maximum tolerated doses to maximize benefit. There was no difference in baseline GDMT between the biomarker-group and the usual care group with 93% in both groups taking a beta blocker, 77% in the biomarker-guided group, and 74% in the usual care group taking an ACEi/angiotensin receptor blocker (ARB)/angiotensin receptor blocker neprilysin inhibitor (ARNI), and 50% in the biomarker-guided group and 48% in the usual care group taking a mineralocorticoid antagonist (MRA) (all P values nonsignificant).

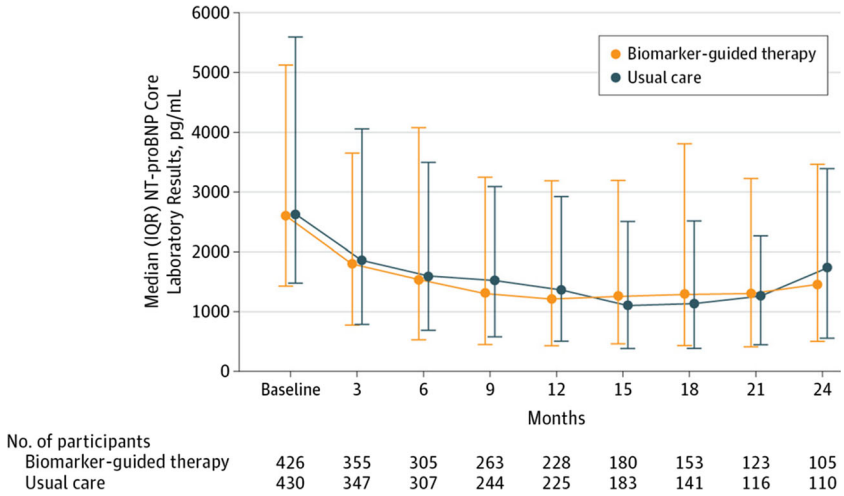

Fig. 1 Change in NT-proBNP concentrations in the biomarker-guided therapy arm versus the usual care arm. No difference was seen between both study arms. NT-proBNP = N-terminal pro B-type natriuretic peptide. Adapted from Felker et al. [28••] with permission

As noted earlier, besides lacking difference in NT-proBNP concentrations following study procedures, the other hallmark of neutral biomarker-guided studies was a lack of difference in achieved GDMT between study arms. In GUIDE-IT, achievement of an NT-proBNP < 1000 pg/mL in a similar number of patients in the usual care group as the biomarker-guided group is a testament to aggressive titration of GDMT: as part of the study design, even in the usual care group patients were followed-up 2 weeks after changes in GDMT and every 2 weeks until attainment of target or maximum tolerated medication doses [29••]. With respect to GDMT, over the course of the GUIDE-IT trial, there was modest intensification of GDMT in both groups, without statistically significant differences between those randomized to biomarker-guided therapy or usual care [28••] (Table 2).

It is striking that in the NT-proBNP-guided arm at 12 months, only 48% of patients achieved the target beta blocker dose and only 55% achieved the target ACEi/ARB/ARNI dose. Reasons for this are unclear and may include patient intolerance or it may be that in patients who reached an NT-proBNP concentration < 1000 pg/mL no further medication titration was attempted. Had more patients achieved target doses of GDMT, a difference between the biomarker-guided arm and the usual care arm may have been seen as in prior studies [17].

Follow-Up Strategy and Practice Setting

Thanks to the study design, in the GUIDE-IT trial, patients randomized to the biomarker-guided strategy had a modestly greater number of study clinic visits compared to those randomized to the usual care arm (median, 12 vs. 10, Wilcoxon $P = 0.002$); however, it is crucially important to emphasize on average patients were seen on a monthly basis in the usual care arm [28••], which calls the definition of "usual" care into question. Additionally, it is important to note that most of the GUIDE-IT study investigators practiced at academic tertiary care referral centers and most were HF specialists. As such, it is unclear if the usual care in the GUIDE-IT trial was a fair representation of usual HFrEF care in non-academic centers and/or care provided by non-HF specialists. Had the comparison been between biomarker-guided management and usual care in patients managed by non-HF specialists the results may differ. This has yet to be explored.

Future Directions

While the GUIDE-IT trial did not find NT-proBNP-guided therapy to be more effective than usual care, further exploration of biomarker-guided care is needed. A comparison of biomarker-guided care with usual care more representative of real-word treatment is needed. Additionally, an exploration amongst those who achieved NT-proBNP < 1000 pg/mL to determine if there was a difference in events between those who achieved target doses of GDMT and those who did not would be useful. Furthermore, a comparison between those who achieved target GDMT compared to those who achieved NT-proBNP concentrations < 1000 pg/mL without achieving

Table 2 Differences in medical therapy over the study duration between both treatment arms [28••]

	NT-proBNP-guided group ($N = 446$)		Usual care group ($N = 446$)		P
	Baseline	12 Months	Baseline	12 Months	
Taking beta blocker, N (%)	415 (93)	227 (91)	416 (93)	219 (91)	0.86
Mean dose achieved (% of target dose)	33	48	35	45	0.60
50% of target dose	152 (37)	136 (60)	139 (33)	125 (57)	0.97
100% of target dose	30 (7)	33 (15)	26 (6)	25 (11)	0.31
Taking ACEi/ARB, N (%)	342 (77)	187 (75)	333 (74)	172 (71)	0.63
Mean dose achieved (% of target dose)	41	55	43	53	0.35
50% of target dose	140 (41)	95 (51)	135 (41)	85 (49)	0.74
100% of target dose	59 (17)	58 (31)	67 (20)	47 (27)	0.11
Taking MRA, N (%)	223 (50)	136 (54)	217 (48)	126 (52)	<0.99
Mean dose achieved (% of target dose)	98	115	94	103	0.29
50% of target dose	219 (98)	135 (99)	216 (100)	125 (99)	0.42
100% of target dose	170 (76)	116 (85)	163 (75)	94 (75)	0.06
Loop Diuretics	77	86	76	77	0.26
Mean dose (mg furosemide equivalents)					

NT-proBNP, N-terminal pro B-type natriuretic peptide; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid antagonist

target GDMT would be an interesting area to explore. This may enlighten us on whether targeting a low NT-proBNP is as important as attainment of target doses of GDMT. Several questions regarding biomarker-guided management have yet to be explored, and the results of GUIDE-IT have not yet closed the door on this management strategy for patients with chronic HFrEF.

Conclusions

The natriuretic peptides remain a gold standard in HF care for numerous roles, including diagnosis, prognosis (including "therapy monitoring" of prognosis during treatment), as well as screening for HF risk. Enthusiasm to utilize NT-proBNP to improve precision of HFrEF care was based on numerous smaller pilot studies. Lessons learned from those studies suggested that in order to be successful, guided therapy needed to aim for (and achieve) a low NT-proBNP concentration, resulting from different therapies in the guided patients compared to usual care. The GUIDE-IT trial was based on such concept, but returned results suggest no difference between guided therapy and usual care. No results are yet available from GUIDE-IT to suggest lack of value of NT-proBNP for prognostication; such analyses are underway, but it is expected NT-proBNP change retains prognostic meaning in both study arms.

Though it is likely NT-proBNP changes will retain prognostic importance, results from GUIDE-IT suggest aggressively managed, frequently seen patients may not necessarily benefit from a biomarker-guided strategy to drive better care. It seems clear, however, that the study design in GUIDE-IT was hardly usual care, delivered in tertiary care centers by highly experienced HF specialists; nearly a dozen visits in a single year is hardly "usual" therapy. Future studies focusing this intervention on patients treated in a more real-world setting are needed. The GUIDE-IT trial affords opportunities for further exploration of strategies that may improve the care of chronic HFrEF patients including more frequent follow-up and aggressive titration of GDMT in settings more consistent with disease management programs.

Compliance with Ethical Standards

Conflict of Interest Nasrien E. Ibrahim declares no conflicts of interest. James L. Januzzi reports grants and personal fees from Roche and Abbott during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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