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Rationale and Design of the GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) Study

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Abstract

Objective—The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) Study was designed to determine the safety, efficacy, and cost effectiveness of a strategy based on achieving and maintaining an amino-terminal pro-B-type natriuretic peptide (NT-proBNP) target of less than 1000 pg/mL, compared with usual care in high risk systolic heart failure (HF) patients.

Background—Elevations in natriuretic peptide (NP) levels provide key prognostic information in patients with HF. Therapies proven to improve outcomes in HF patients are generally associated with decreasing levels of NPs, and observational data show that decreases in NP levels over time are associated with favorable outcomes. Results from smaller prospective randomized studies of
this strategy thus far have been mixed, and current guidelines do not recommend serial measurements of NPs to guide therapy in HF.

**Methods**—GUIDE-IT is a prospective, randomized, controlled, unblinded, multicenter clinical trial that aims to randomize approximately 1100 subjects with high risk systolic HF (left ventricular ejection fraction [LVEF] ≤ 40%) to either usual care (optimized guideline recommended therapy) or a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP target of <1000 pg/mL. Patients in either arm of the study are followed at regular intervals and after treatment adjustments for a minimum of 12 months. The primary end-point of the trial is time to cardiovascular death or first HF hospitalization. Secondary end points will include time to cardiovascular death and all-cause mortality, cumulative mortality, health related quality of life, resource utilization, cost effectiveness, and safety.

**Conclusions**—The GUIDE-IT study is designed to definitively assess the effects of a NP guided strategy in high risk systolic HF patients on clinically relevant end points of mortality, hospitalization, quality of life, and medical resource use.

**Keywords**
Heart Failure; Biomarkers; Clinical Trial

**Introduction**

Heart failure (HF) is a public health problem of massive proportions in both developed and developing countries (1). In the United States alone, over 5 million patients are estimated to have HF, more than 1 million hospitalizations and 270,000 deaths result annually from HF, and disease management accounts for over $30 billion in total costs per annum (2). Evidence based therapies such as β-blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors can significantly improve outcomes in HF, but available data suggest that many patients in clinical practice are either not treated with these agents or are treated with substantially lower than recommended doses (2-7).

What accounts for this underutilization of cardiac medications of proven benefit? Signs and symptoms suggestive of disease progression in HF may be subjective and subtle, and under-recognized by providers and patients (8). Additionally, “therapeutic inertia”—the reluctance on the part of both patients and providers to increase or modify therapy in face of apparent clinical stability and the additional follow-up required—may also play a role (9).

A variety of disease management strategies have been evaluated to improve the management of chronic HF patients, ranging from nursing-based interventions to technologically complex interventions using implantable hemodynamic monitors and telemedicine. The success of these approaches has been highly variable, and many are personnel intensive, complex, or costly to implement (10-12). Therefore, there is a need for a cost effective and objective measure of disease stability that can be used to favorably impact care of chronic HF patients and demonstrate improvements in outcomes (13).

The natriuretic peptides (NP), specifically B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP), provide a readily evaluable objective
biochemical marker that reflects many aspects of HF physiology and disease progression. It is well established that the NPs are among the most powerful predictors of adverse outcomes in HF (14-17). Concentrations decline in response to use of guideline-recommended HF therapies (Table 1), and rising levels portend poor patient outcomes (18-22). These observational data have led to the hypothesis that serial measurements of natriuretic peptides may be used to guide titration of chronic medical therapy in HF.

Previous clinical trials of varying size and design have tested this hypothesis over the last two decades, with mixed results (Table 2) (23-32). While pooled analyses of these studies indicate a 20-25% reduction in mortality with biomarker guided therapy, generalizability has been limited by the small size of studies as well as significant heterogeneity in the inclusion criteria, treatment strategies, and NP cut-points (33, 34). In light of this uncertainty, current guidelines do not recommend the use of serial measurements of NP to guide titration of therapy in HF (2). Thus, the GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial was designed to prospectively evaluate the efficacy of a biomarker-guided HF treatment strategy compared to optimal medical therapy alone, in a large cohort of high risk patients with systolic HF. GUIDE-IT is funded by the National Heart Lung and Blood Institute (www.clinicaltrials.gov identifier NCT01685840) and will be the largest study of biomarker-guided therapy in HF performed to date.

**Methods**

**Study Objectives**

The primary objective of GUIDE-IT is to determine the efficacy and safety of a strategy of biomarker-guided therapy compared with optimized care in high risk HF patients with left ventricular systolic dysfunction. The primary endpoint is time to cardiovascular death or first HF hospitalization. The secondary objectives of GUIDE-IT are to evaluate the effect of biomarker-guided therapy on hospitalizations, all-cause mortality, cardiovascular death, resource use, quality of life, cost, and cost-effectiveness.

**Study Population**

The GUIDE-IT study intends to enroll approximately 1100 patients in with known systolic HF (LVEF ≤40%) and high risk for HF events at sites in the United States and Canada. Inclusion and exclusion criteria are summarized in Table 3. Patients are considered high risk if they have had a HF hospitalization, emergency department visit for HF, or were treated with intravenous diuretics as an outpatient within the prior 12 months, AND an NT-proBNP >2000 pg/mL or BNP>400 pg/mL at any time during the 30 days prior to randomization. Patients must also have an LVEF of ≤40% determined by an accepted imaging method within 12 months prior to randomization.

**Study Design**

The overall scheme of GUIDE-IT is shown in Figure 1. The trial is a multicenter, prospective, randomized, parallel control group, unblinded, 2-arm clinical trial comparing
biomarker-guided therapy to usual care in high risk patients with systolic HF. Patients enrolled in GUIDE-IT are randomized in a 1:1 allocation to either:

- **Usual Care:** Titration of HF therapy based on target doses from current evidence based guidelines for the management of HF (2)
  
  OR

- **Biomarker-Guided:** Titration of HF therapy using guideline recommended therapies (Table 4) with a goal of achieving and maintaining a target NT-proBNP <1000 pg/mL.

**Usual Care**

Patients receive care based on the 2013 AHA/ACC guideline recommendations (2). Investigators are provided with specific information on evidence-based target doses of neurohormonal antagonists. Diuretics are titrated based on the clinical judgment of the treating physician. Importantly, routine assessment of NPs will not be performed in the usual care group except for compelling medical reasons, consistent with current guidelines (2). Follow-up visits are identical to the schedule of visits for the biomarker-guided arm, including interim visits when medication changes relevant to the treatment of HF occur.

**Biomarker-Guided Arm**

While both BNP and NT-proBNP are widely clinically available and have been used in previous trials of biomarker-guided therapy, NT-proBNP was selected as the marker to guide therapy in the GUIDE-IT study. The rational for this was that NT-proBNP has a longer half-life (6 hours vs. 20 minutes), a better ability to predict long-term morbidity and mortality in a head-to-head comparison in Val-HeFT, and stronger data supporting the validity of a specific natriuretic peptide target (35). The target of 1000 pg/mL was selected on the basis of prior data suggesting an inflection point in the risk curve at this concentration, as well as the favorable results of the PROTECT (Pro-BNP Outpatient Tailored Chronic HF Therapy) study using the same cut-point (16,28,36).

In the biomarker guided arm, NT-proBNP levels are ascertained at a local laboratory and utilized by treating physicians for the purpose of achieving values of less than 1000 pg/mL. The GUIDE-IT protocol specifies interventions to be considered to lower NT-proBNP levels in the biomarker-guided arm, but specific treatment decisions are at the discretion of the treating physician (Table 4). The order of implementation is based on clinical judgment, with more than one intervention allowed during a single encounter. Titration of neurohormonal antagonists are emphasized over titration of diuretics due to a mortality benefit of such agents, except in the case of clinically apparent congestion or in the case of very high NT-proBNP levels (>5000 pg/mL).

**Follow-up Visits**

For patients in either arm of the study, follow up visits occur 2 weeks after randomization and subsequently every 3-month basis for the duration of the study once optimal doses of therapies have been achieved. For patients in either arm of the study, there is a 2-week follow-up visit after a change in therapy for HF. These post-change in therapy follow-up
visits usually occur as a face-to-face encounter, but can also be done via a “laboratory only” visit to reduce patient hardship, at the discretion of the treating physician. Follow-up visits continue every 2 weeks until therapeutic targets are reached, or the investigator determines that further titration of therapy is not possible. Patients hospitalized for HF during the study have a 2-4 week follow-up study visit post discharge to reassess and adjust medical therapy, which includes all standard follow-up assessments as defined above.

**Study Duration and End Points**

The anticipated study duration is approximately 5 years; 6 months of start-up activities (i.e., finalizing of protocol, preparing study sites and contracts, and receiving site Institutional Review Board [IRB] approval), 36 months of active enrollment, 12 months of patient follow-up after the final patient is enrolled, and 6 months of study close-out, data analysis, and reporting of results.

The primary end point for the GUIDE-IT study is time to CV death or first HF hospitalization (Table 5). To minimize potential bias in an unblinded study, a Clinical Event Committee (CEC) blinded to treatment assignment adjudicates all deaths and hospitalizations. The components of the primary endpoint will also be considered separately in secondary analyses. Important secondary endpoints include cumulative morbidity, assessed by recurrent hospitalizations and total days alive and out of the hospital during follow-up. Other secondary endpoints will include measures of quality of life (QOL), resource utilization, cost, and cost effectiveness. An Economic and Quality of Life (EQOL) core will perform all QOL and economic analyses. QOL assessments will be performed at baseline, 3 months, 6 months, and then annually to a maximum of 24 months. Assessments at each visit will include the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Duke Activity Status Index (DASI), the Epidemiological Studies Depression Scale (CES-D), the Medical Outcomes Study Short Form (SF-12), the Medical Outcomes Study Short Form (SF-36) subscales, and the EQ-5D.

In addition to routine safety reporting of adverse events, events that could be related to the risks of aggressive titration of HF medications (hypotension, bradycardia, renal dysfunction, and hyperkalemia) will be specifically monitored and reported.

**Quality of Life Assessments**

**Statistical Analysis**

All major treatment comparisons between the randomized groups will be performed according to an intention-to-treat basis. Statistical comparisons of the two randomized arms with respect to the primary endpoint will be a time-to-event analysis (time from randomization to the first occurrence of CV death of HF hospitalization). The Cox proportional-hazards regression model will be the primary tool to assess the effect of biomarker guidance versus usual care on both the composite outcome, as well as each component. An adjusted model will be utilized for the primary efficacy analysis in order to maximize the precision of the estimate of treatment effect (37). The model will include an indicator variable for treatment group, and the following baseline variables: age, gender, NT-proBNP, diabetes mellitus, and LVEF. These variables were selected based on their
known association with outcomes in heart failure as well as the expectation of very little missing data for these variables. To avoid any potential for bias, the functional form of each adjustment variable will be prespecified in the statistical analysis plan. In subgroup analyses, we will examine the effect according to specific patient characteristics. The effect of the NT-proBNP-guided treatment strategy on all endpoints will be summarized using hazard ratios, with associated confidence intervals. For analysis of the total days alive and out of hospital endpoint, we will apply the inverse probability weighted estimators to account for potential bias due to censored and incomplete data (38).

**Statistical Power and Sample Size**

Sample size for this study (N=1100) has been selected based on the primary end point, time to CV death or first HF hospitalization. Based on the anticipated patient population and recently published clinical trial data, we have projected a 1 year CV-death and hospitalization rate of 40% for subjects randomized to the usual care arm (27,39). A meta-analysis by Felker et al. found an aggregate reduction of about 30% in all-cause mortality with biomarker-guided therapy, so the impact of biomarker-guided therapy can be conservatively expected to reduce the primary composite endpoint by 20% (33). If we account for reasonable estimates of drop-in and drop-out (5% for each over 2 years), loss to follow up (4% per year), and non-CV death (4% per year), 1100 subjects will provide approximately 90% power to detect a 20% relative reduction (from 40% to 32%) in the primary endpoint with biomarker guided therapy. Also, GUIDE-IT has a fixed sample size design with the flexibility of an event driven study design. For secondary endpoints, assuming at least 350 subjects per treatment group, the study will have >90% power for detecting a treatment differences of 1/4 standard deviation in secondary end points.

**Natriuretic Guided Treatment in the Elderly**

Two prior studies (TIME-CHF and BATTLESCARRED; Table 2) suggested a differential benefit of natriuretic guided treatment according to age, with elderly patients (≥ 75 years) deriving less benefit; however, other studies such as PROTECT have not reproduced these findings (26-28). As a result of the lack of clarity surrounding this question, and given that HF is primarily a disease of the elderly, the differential effect of NP guided treatment based on age will be examined in GUIDE-IT. We have pre-specified an interaction analysis, with the population stratified at age 75 years, and determined that we will have adequate power to detect statistically significant interactions.

**Data and Safety Monitoring Board Reviews**

The NHLBI-appointed Data and Safety Monitoring Board (DSMB) will meet every 6 months to review the accumulating data. Prior to each meeting, the coordinating center will conduct any requested statistical analyses and prepare a summary report along with the following information: patient enrollment reports, rates of compliance with the assigned testing strategy, frequency of protocol violations, and description of SAEs. For futility monitoring, the study will apply the inefficacy monitoring rule of Freidlin, Korn, and Gray to stop the trial if the biomarker-guided strategy is not beneficial (40). We plan to use the conservative boundary LIB0 along with a harm look at 25% of expected information,
including 7 interim looks scheduled at roughly 25%, 40%, 50%, 60%, 70%, 80%, and 90% trial completion. With the proposed design, a total of roughly 566 events are expected and the first interim review for futility and efficacy would be scheduled to occur after approximately 140 primary endpoint events have been observed. If the data suggested a benefit for the usual care arm with a P-value of <0.05, this approach would suggest stopping the trial at the 25% look. For the interim reviews at 40%, 50%, 60%, 70%, 80%, and 90%, the LIB0 conservative boundary would suggest stopping the trial for inefficacy if the biomarker-guided arm had a hazard ratio > 1.0 compared to usual-care arm. Lastly, an interim efficacy analyses will also be performed (41,42).

**Trial Organization**

An overview of trial organization is displayed in Figure 2. The study is conducted under the leadership of an Executive Committee comprised of cardiologists with extensive experience caring for patients with HF that has overall responsibility for study conduct. The clinical coordinating center (CCC), data coordinating center (DCC), and economics and quality of life cores are at the Duke Clinical Research Institute (DCRI). Given the importance of investigator adherence to the study protocol in order to successfully test the primary hypothesis, a Protocol Adherence Committee oversees investigator adherence with the study protocol. Specifically, investigators record their rationale for specific adjustments of HF medications at each encounter in the case report form. If investigators choose not to intensify therapy at a given patient visit in the biomarker guided arm despite an NT-proBNP level >1000 ng/mL, they record their clinical rationale for not making adjustments (e.g., hypotension limits further up-titration). The Adherence Committee reviews data on the extent to which investigators are responding to NT-proBNP levels >1000 ng/mL in the biomarker guided arm and perform educational interventions with investigators in need of additional training. If investigator adherence is persistently poor at a given site, the Adherence Committee may recommend halting enrollment at that site.

**Core Laboratories and Sub-studies**

In order to understand the mechanisms underlying the treatment effect of biomarker guided therapy (if any), core laboratories for biomarkers, genetics, and echocardiography have been established. At each clinical encounter, local laboratories are used for NT-proBNP assessments (biomarker guided arm only), but an additional plasma sample for centralized NT-proBNP testing is submitted to the biomarker core lab. These values are not transmitted back to investigators, but used to validate the results of local laboratory testing, as well as to provide NT-proBNP data on patients in the usual care arm at the conclusion of the study. In addition, DNA samples as well as serial plasma and serum samples are collected and stored at a central biomarker-genetics core laboratory for future use. An echocardiographic sub-study is performing baseline and 12-month echocardiograms on a subset of patients; these images are interpreted centrally by a core laboratory blinded to treatment allocation or other clinical data.
Discussion

Existing clinical guidelines for treatment of chronic systolic HF recommend that therapies be titrated to target doses from clinical trials, or maximally tolerated doses (2). This is unlike management of most chronic diseases that utilize a paradigm of therapeutic titration based on ‘biomarker’ targets known to be associated with patient outcomes; for example, hemoglobin A1C for diabetes and viral load for HIV. In HF, NPs have emerged as important biochemical gauges of disease state, with both baseline and serial levels having important prognostic value (22,34,43,44). However, since a landmark study in 2000 showed dramatic benefits with NP guided treatment of HF, several randomized trials that differed considerably in design and execution, have yielded varied results. Meta-analyses of these studies have determined that using NP levels to guide therapy in chronic systolic HF patients may lead to significant improvements in clinical outcomes, but these conclusions are susceptible to known limitations of meta-analyses in the face of small heterogeneous trials (33,34,44,45).

GUIDE-IT has attempted to incorporate lessons learned from prior studies about how best to apply NP guided therapy to high risk HF patients (43). First, since the advantages of NP guidance are limited by the benefits of specific HF therapies, it stands to reason that biomarker-guided therapy is most likely to be efficacious in patients in whom medical therapy is known to be effective. Therefore, we have focused on patients with systolic HF and not included patients with HF and preserved ejection fraction (HFrEF), given the lack of effective therapeutics for this group of patients. Second, many prior studies with neutral results may have set natriuretic peptide goals that were too high (i.e., not aggressive enough), potentially leaving patients “at target” but still with a persistent amount of residual risk (28,30). For GUIDE-IT, we have adopted the target of 1000 pg/mL, successfully used in the PROTECT study; while a significant percentage of patients may not achieve this value, data have indicated that even modest lowering of NT-proBNP and even intermittent periods of time at or below 1000 pg/mL is associated with superior outcomes compared to those with less reductions of the biomarker (28,46). Thus, while it would be desirable to reach the goal in every study participant, a concerted effort to produce reduction in NT-proBNP is hypothetically likely to produce favorable results. Third, while treating physicians in the biomarker guided arm will retain responsibility for specific treatment decisions, we will emphasize up-titration of therapies that have been shown to have mortality benefits such as β-blockers and RAAS antagonists over diuretics: trials emphasizing use of neurohormonal antagonists were more likely to show efficacy. Fourth, some prior studies have suggested a differential treatment effects of a biomarker-guided strategy by age, with greater efficacy in younger patients (34). For this reason, we pre-specified age (≥75 or < 75 years of age) as a key subgroup of interest, and GUIDE-IT adequately powered to examine this interaction appropriately.

GUIDE-IT will be an unblinded trial because blinding would eliminate one potentially important mechanism of treatment effect: the impact of patient knowledge of their own natriuretic peptide levels on adherence and health-related behaviors. Blinding GUIDE-IT would remove the patient from the critical role of active partnership in the management of his or her disease and would not reflect how biomarker-guided therapy will ultimately be
used in practice, thus raising important issues about generalizability. We have taken multiple steps to minimize potential biases related to lack of blinding, including the use of an objective primary endpoint (cardiovascular death or HF hospitalization), and centralized adjudication of events by a Clinical Event Committee blinded to treatment assignment.

The GUIDE-IT study is primarily designed to determine the efficacy of a strategy of biomarker-guided therapy compared with optimized medical care on clinical outcomes in high-risk patients with systolic HF. However, data from the trial may also clarify several other important unanswered questions. For example, it is unknown whether the hypothesized mortality benefits derived from aggressive attempts at lowering biomarker levels could occur at the expense of increased morbidity related to side effects of therapy, especially among elderly patients. The Economics and Quality of Life (EQOL) core laboratory will use a battery of validated instruments such as the Kansas City Cardiomyopathy Questionnaire that provide a comprehensive assessment of health-related quality of life and allow for assessment of differences in these measures between treatment arms. The EQOL laboratory will also collect wide-ranging economic data, thereby allowing for an evaluation of resource utilization and cost-effectiveness of a biomarker-guided strategy. This inclusion of detailed quality of life analysis and robust health economic measures will serve to enhance the overall value of the findings from GUIDE-IT. Furthermore, a robust bio-repository and echocardiography sub-study will be included and will provide insight into the mechanistic underpinnings of any observed impact of biomarker-guided therapy on clinical outcomes.

**Conclusion**

Numerous studies have found that elevations in the NPs are among the best predictors of adverse outcomes in patients with chronic systolic HF, and that use of guideline-based therapies is associated with a decrease in serial plasma levels of these markers. The results of several observational studies and small randomized controlled trials have suggested that a biomarker-guided strategy aimed at decreasing NP levels, compared with standard care, may lead to improvements in outcomes among patients with chronic systolic HF. The GUIDE-IT study is designed to provide the definitive answer about the safety, efficacy, and cost effectiveness of natriuretic peptide-guided therapy for treatment of chronic systolic HF.

**Acknowledgments**

**Funding Sources:** The GUIDE-IT study is funded by the following grants from the National Heart Lung and Blood Institute (grants 1R01HL105448-01A1, 1R01HL105451-01A1, and 1R01HL105457-01A1). Sub-studies for echocardiography as well as the GUIDE-IT biobank were funded by a grant from Roche Diagnostics.

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References


**Abbreviation List**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>HF</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>NP</td>
<td>Natriuretic Peptides</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Amino terminal pro-B-type natriuretic peptide</td>
</tr>
<tr>
<td>RASS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>EQOL</td>
<td>Economic and Quality of Life</td>
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<table>
<thead>
<tr>
<th>CCC</th>
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<tr>
<td>DCC</td>
<td>Data Coordinating Center</td>
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Figure 1. Schematic diagram for the GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in HF (GUIDE-IT) trial
GUIDE-IT aims to randomize approximately 1100 high risk chronic heart failure patients with left ventricular ejection fraction ≤40% to either optimized guideline recommended therapy or a strategy of adjusting therapy with the goal of achieving and maintaining a target NT-proBNP target of <1000 pg/mL. Patients in either arm of the study are followed at regular intervals and after treatment adjustments for a minimum of 12 months. Assessments during these visits are delineated in the figure.
Figure 2. Trial Organization

The study is being conducted under the leadership of an Executive Committee comprised of cardiologists with extensive experience caring for patients with HF that has overall responsibility for study conduct. The Duke Clinical Research Institute will house the clinical coordinating center (CCC), data coordinating center (DCC), and economics and quality of life cores are at the Duke Clinical Research Institute (DCRI).
### Table 1
Therapies for HF That May Lower Natriuretic Peptide Values

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis (loop or thiazide)</td>
<td>↓</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>↓</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>↓</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Transient ↑, mostly ↓</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists</td>
<td>↓</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>↓</td>
</tr>
<tr>
<td>Exercise</td>
<td>↓</td>
</tr>
<tr>
<td>Rate control of atrial arrhythmia</td>
<td>↓</td>
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</table>
### Table 2

Design of Selected RCTs of Biomarker-Guided Therapy in HF

<table>
<thead>
<tr>
<th>Study</th>
<th>GUIDE-IT*</th>
<th>Troughton et al.</th>
<th>STARS-BNP</th>
<th>Berger et al.</th>
<th>PROTECT</th>
<th>STARBRIT</th>
<th>TIME-CHF</th>
<th>BATTLE-SCARRED</th>
<th>PRIMA</th>
<th>SIGNAL-HF</th>
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<tr>
<td>Samples Size</td>
<td>1100</td>
<td>69</td>
<td>220</td>
<td>278</td>
<td>151</td>
<td>137</td>
<td>499</td>
<td>364</td>
<td>345</td>
<td>252</td>
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<tr>
<td>Marker</td>
<td>NT-proBNP</td>
<td>NT-proBNP</td>
<td>BNP</td>
<td>NT-proBNP</td>
<td>NT-proBNP</td>
<td>BNP</td>
<td>NT-proBNP</td>
<td>NT-proBNP</td>
<td>NT-proBNP</td>
<td>NT-proBNP</td>
</tr>
<tr>
<td>Target</td>
<td>1000 pg/mL</td>
<td>1692 pg/mL</td>
<td>100 pg/mL</td>
<td>2200 pg/mL</td>
<td>1000 pg/mL</td>
<td>1/2 × Discharge level</td>
<td>400 pg/mL if age&lt;75, 800 pg/mL if age&gt;75</td>
<td>1270 g/mL</td>
<td>Discharge level</td>
<td>50% decrease from entry</td>
</tr>
<tr>
<td>Length of f/u (months)</td>
<td>12-24</td>
<td>9.6</td>
<td>15</td>
<td>12</td>
<td>10</td>
<td>3</td>
<td>18</td>
<td>12</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>HFpEF Included</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>CV Death or HF Hospitalization</td>
<td>Death + CV hospitalization or worsening HF</td>
<td>Death + HF hospitalization time to endpoint</td>
<td>Days alive and out of hospital</td>
<td>Total CV events</td>
<td>Days alive and out of hospital</td>
<td>All-cause death or hospital</td>
<td>All-cause mortality</td>
<td>Days alive and out of hospital</td>
<td>Days alive and out of hospital</td>
</tr>
<tr>
<td>Favors BGT</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* Ongoing. RCT indicates randomized control trial; BNP, b-type natriuretic peptide; NT-proBNP, amino-terminal pro-B-type Natriuretic Peptide N, number; f/u, follow up; HFpEF, HF preserved Ejection Fraction; CV, cardiovascular; HF, HF.
### Table 3
GUIDE-IT Primary Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 years</td>
</tr>
<tr>
<td>HF event in Prior 12 months *</td>
</tr>
<tr>
<td>Recent documented LVEF ≤ 40% by any method within 12 months prior to randomization</td>
</tr>
<tr>
<td>BNP &gt; 400 pg/mL or NT-proBNP &gt; 2000 pg/mL in 30 days prior to randomization</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>Clinical diagnosis of ACS† or cardiac revascularization within 30 days</td>
</tr>
<tr>
<td>CRT within prior 3 months or current plans to implant CRT device</td>
</tr>
<tr>
<td>Severe stenotic valvular disease</td>
</tr>
<tr>
<td>Anticipated OHT or VAD within 12 months</td>
</tr>
<tr>
<td>Chronic inotropic therapy</td>
</tr>
<tr>
<td>Complex congenital heart disease</td>
</tr>
<tr>
<td>ESRD with renal replacement therapy</td>
</tr>
<tr>
<td>Non cardiac terminal illness with expected survival less than 12 months</td>
</tr>
<tr>
<td>Women who are pregnant or planning to become pregnant</td>
</tr>
<tr>
<td>Inability to comply with planned study procedures</td>
</tr>
<tr>
<td>Enrollment or planned enrollment in another clinical trial</td>
</tr>
</tbody>
</table>

* A HF Event in the prior 12 months is defined as any one of the following: (a) HF hospitalization (b) Treatment in the emergency department (or equivalent) for HF (c) Outpatient treatment for HF with intravenous diuretics.

† Diagnosis of ACS should not depend entirely on positive cardiac markers, as this can be noted in acute HF patients.

BNP indicates B-type natriuretic peptide; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; ACS, acute coronary syndrome; CRT, chronic resynchronization therapy; OHT, orthotropic heart transplantation; VAD, ventricular assist device; ESRD, end stage renal disease.
<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential Interventions to Decrease NT-proBNP Levels</strong></td>
</tr>
</tbody>
</table>

- Up-titrate or add Angiotensin Converting Enzyme (ACE)-inhibitor or Angiotensin II Receptor Blockers (ARB)
- Up-titrate or add beta-blocker (if not clinically congested)
- Up-titrate or add hydralazine-nitrates in African-American patients
- Increase loop diuretic dosage (if clinically congested or NT-proBNP > 5000 pg/mL)
- Add oral thiazide diuretic
- Add digoxin
- Consider adding ARB to ACE-I (if not on spironolactone)
- Consider optimization of cardiac resynchronization therapy (if CRT device implanted)
- Up-titrate or add spironolactone if tolerated by renal function and potassium
- Consider hydralazine-nitrates in non-African-American patients
- Intensified or repeated HF education regarding diet, sodium restriction, etc.
- Reconsider potential indications for CRT (if not previously implanted)
- If in atrial fibrillation, maximize rate control or consider more aggressive attempts at normal sinus rhythm
- Consider exercise training or cardiac rehabilitation

NT-proBNP indicates amino-terminal pro-b-type natriuretic peptide N, number; CRT, chronic resynchronization therapy.
### Table 5

**Trial End Points**

<table>
<thead>
<tr>
<th>Primary End Point</th>
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</thead>
<tbody>
<tr>
<td>Time to CV death or first HF hospitalization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to all-cause mortality</td>
</tr>
<tr>
<td>Days alive and not hospitalized for CV reasons</td>
</tr>
<tr>
<td>Recurrent hospitalizations</td>
</tr>
<tr>
<td>Time to CV death</td>
</tr>
<tr>
<td>Time to first HF hospitalization</td>
</tr>
<tr>
<td>HRQOL</td>
</tr>
<tr>
<td>Resource utilization, cost and cost effectiveness</td>
</tr>
</tbody>
</table>

| Safety                                                 |

CV indicates cardiovascular; HF, HF; HRQOL, health related quality of life.