

10-1-2014


Rationale and design of the GUIDE-IT study: Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure.

G. Michael Felker
Duke University Medical Center

Tariq Ahmad
Duke University Medical Center

Kevin J. Anstrom
Duke University Medical Center

Kirkwood F. Adams
University of North Carolina
Follow this and additional works at: <https://jdc.jefferson.edu/cardiologyfp>

 Lawton S. Cooper
Part of the [Cardiology Commons](#)
National Heart, Lung, and Blood Institute

[Let us know how access to this document benefits you](#)

See next page for additional authors

Recommended Citation

Felker, G. Michael; Ahmad, Tariq; Anstrom, Kevin J.; Adams, Kirkwood F.; Cooper, Lawton S.; Ezekowitz, Justin A.; Fiuzat, Mona; Houston-Miller, Nancy; Januzzi, James L.; Leifer, Eric S.; Mark, Daniel B.; Desvigne-Nickens, Patrice; Paynter, Gayle; Piña, Ileana L.; Whellan, David J.; and O'Connor, Christopher M., "Rationale and design of the GUIDE-IT study: Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure." (2014). *Division of Cardiology Faculty Papers*. Paper 61.
<https://jdc.jefferson.edu/cardiologyfp/61>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Division of Cardiology Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: JeffersonDigitalCommons@jefferson.edu.

Authors

G. Michael Felker, Tariq Ahmad, Kevin J. Anstrom, Kirkwood F. Adams, Lawton S. Cooper, Justin A. Ezekowitz, Mona Fiazat, Nancy Houston-Miller, James L. Januzzi, Eric S. Leifer, Daniel B. Mark, Patrice Desvigne-Nickens, Gayle Paynter, Ileana L. Piña, David J. Whellan, and Christopher M. O'Connor



Published in final edited form as:

JACC Heart Fail. 2014 October ; 2(5): 457–465. doi:10.1016/j.jchf.2014.05.007.

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

G. Michael Felker, MD, MHS^{1,2}, Tariq Ahmad, MD, MPH^{1,2}, Kevin J. Anstrom, PhD², Kirkwood F. Adams, MD³, Lawton S. Cooper, MD, MPH⁴, Justin Ezekowitz, MBBCh, MSc⁵, Mona Fiuzat, Pharm.D^{1,2}, Nancy Houston-Miller, RN, BSN⁶, James L. Januzzi, MD⁷, Eric Leifer, PhD⁴, Daniel Mark, MD, MPH^{1,2}, Patrice Desvigne-Nickens, MD⁴, Gayle Paynter, BS, RN², Ileana L. Piña, MD, MPH⁸, David J. Whellan, MD, MHS⁹, and Christopher M. O'Connor, MD^{1,2}

¹Division of Cardiology, Duke University Medical Center, Durham, NC

²Duke Clinical Research Institute, Duke University Medical Center, Durham, NC

³University of North Carolina, Chapel Hill, NC

⁴National Heart, Lung, and Blood Institute, Bethesda, MD

⁵University of Alberta, Alberta, Canada

⁶Stanford University, Palo Alto, CA

⁷Massachusetts General Hospital, Boston, MA

⁸Montefiore-Einstein Medical Center, Bronx, NY

⁹Thomas Jefferson University, Philadelphia, PA, NY

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

© 2014 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Address for correspondence: G. Michael Felker, MD, MHS, Duke Clinical Research Institute, DUMC Box 3850, Durham, NC 27710, Phone: 919-668-8919, Fax: 919-668-7063, michael.felker@duke.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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] \leq 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 \leq 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 \leq 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 rationale 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 or 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 (HFpEF), 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.

Relevant Disclosures: Dr Felker has received research funding from Roche Diagnostics, BG Medicine, and Critical Diagnostics, and has served as a consultant for Roche Diagnostics, Singulex, and HDL. Dr Ahmad received support from the Daland Fellowship in Clinical Investigation. Dr Adams has received research funding from and served as a consultant to Roche Diagnostics. Dr Fiuzat has received research funding from Roche Diagnostics, BG Medicine, and Critical Diagnostics. Dr. Dr. Januzzi has served as a consultant for Critical Diagnostics and Novartis, and has research funding from Critical Diagnostics, Roche Diagnostics, Seimens, Singulex, and Thermo-Fisher. Dr O'Connor has received research funding from Roche Diagnostics, BG Medicine, and Critical Diagnostics.

References

1. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. *Circulation*. 2008; 117:2544–65. [PubMed: 18391114]
2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013; 62:e147–239. [PubMed: 23747642]
3. Lee DS, Mamdani MM, Austin PC, et al. Trends in heart failure outcomes and pharmacotherapy: 1992 to 2000. *Am J Med*. 2004; 116:581–9. [PubMed: 15093753]
4. Stafford RS, Radley DC. The underutilization of cardiac medications of proven benefit, 1990 to 2002. *J Am Coll Cardiol*. 2003; 41:56–61. [PubMed: 12570945]
5. 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; 60:208–15. [PubMed: 22560018]
6. Fonarow GC, Yancy CW, Albert NM, et al. Heart failure care in the outpatient cardiology practice setting: findings from IMPROVE HF. *Circ Heart Fail*. 2008; 1:98–106. [PubMed: 19808279]
7. Fonarow GC, Albert NM, Curtis AB, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation*. 2010; 122:585–96. [PubMed: 20660805]
8. Desai AS. Home monitoring heart failure care does not improve patient outcomes: looking beyond telephone-based disease management. *Circulation*. 2012; 125:828–36. [PubMed: 22331920]
9. Fuat A, Hungin AP, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. *BMJ*. 2003; 326:196. [PubMed: 12543836]
10. Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol*. 2005; 45:1654–64. [PubMed: 15893183]
11. Whellan DJ, Hasselblad V, Peterson E, O'Connor CM, Schulman KA. Metaanalysis and review of heart failure disease management randomized controlled clinical trials. *American Heart Journal*. 2005; 149:722–729. [PubMed: 15990759]
12. Bourge RC, Abraham WT, Adamson PB, et al. Randomized Controlled Trial of an Implantable Continuous Hemodynamic Monitor in Patients With Advanced Heart Failure: The COMPASS-HF Study. *J Am Coll Cardiol*. 2008; 51:1073–1079. [PubMed: 18342224]
13. Fonarow GC. Heart failure disease management programs: not a class effect. *Circulation*. 2004; 110:3506–8. [PubMed: 15583088]
14. Januzzi JL Jr, Sakhuja R, O'Donoghue M, et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. *Arch Intern Med*. 2006; 166:315–320. [PubMed: 16476871]
15. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M. Admission B-Type Natriuretic Peptide Levels and In-Hospital Mortality in Acute Decompensated Heart Failure. *J Am Coll Cardiol*. 2007; 49:1943–1950. [PubMed: 17498579]
16. Cleland JG, McMurray JJ, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J Am Coll Cardiol*. 2009; 54:1850–9. [PubMed: 19892235]
17. Anand IS, Fisher LD, Chiang YT, et al. Changes in Brain Natriuretic Peptide and Norepinephrine Over Time and Mortality and Morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation*. 2003; 107:1278–1283. [PubMed: 12628948]

18. McKelvie RS, Yusuf S, Pericak D, et al. Comparison of Candesartan, Enalapril, and Their Combination in Congestive Heart Failure : Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study: The RESOLVD Pilot Study Investigators. *Circulation*. 1999; 100:1056–1064. [PubMed: 10477530]
19. Frantz RP, Olson LJ, Grill D, et al. Carvedilol therapy is associated with a sustained decline in brain natriuretic peptide levels in patients with congestive heart failure. *Am Heart J*. 2005; 149:541–547. [PubMed: 15864245]
20. Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol*. 2001; 37:1228–1233. [PubMed: 11300427]
21. Fruhwald FM, Fahrleitner-Pammer A, Berger R, et al. Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony. *Eur Heart J*. 2007; 28:1592–1597. [PubMed: 17298973]
22. Masson S, Latini R, Anand IS, et al. Prognostic value of changes in N-terminal pro-brain natriuretic peptide in Val-HeFT (Valsartan Heart Failure Trial). *J Am Coll Cardiol*. 2008; 52:997–1003. [PubMed: 18786480]
23. Eurlings LWM, van Pol PEJ, Kok WE, et al. Management of Chronic Heart Failure Guided by Individual N-Terminal Pro-B-Type Natriuretic Peptide Targets: Results of the PRIMA (Can Pro-brain-natriuretic peptide guided therapy of chronic heart failure IMprove heart fAilure morbidity and mortality?) Study. *Journal of the American College of Cardiology*. 2010; 56:2090–2100. [PubMed: 21144969]
24. Shah MR, Califf RM, Nohria A, et al. The STARBRITE trial: a randomized, pilot study of B-type natriuretic peptide-guided therapy in patients with advanced heart failure. *J Card Fail*. 2011; 17:613–21. [PubMed: 21807321]
25. Troughton RW, Frampton CW, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet*. 2000; 355:1126–1130. [PubMed: 10791374]
26. 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; 55:53–60. [PubMed: 20117364]
27. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. *Jama*. 2009; 301:383–92. [PubMed: 19176440]
28. 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; 58:1881–9. [PubMed: 22018299]
29. Berger R, Moertl D, Peter S, et al. N-Terminal Pro-B-Type Natriuretic Peptide-Guided, Intensive Patient Management in Addition to Multidisciplinary Care in Chronic Heart Failure: A 3-Arm, Prospective, Randomized Pilot Study. *J Am Coll Cardiol*. 2010; 55:645–653. [PubMed: 20170790]
30. Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007; 49:1733–9. [PubMed: 17448376]
31. Berger R, Moertl D, Peter S, et al. N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study. *J Am Coll Cardiol*. 2010; 55:645–53. [PubMed: 20170790]
32. Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlstrom U. Improved pharmacological therapy of chronic heart failure in primary care: a randomized Study of NT-proBNP Guided Management of Heart Failure--SIGNAL-HF (Swedish Intervention study--Guidelines and NT-proBNP AnaLysis in Heart Failure). *Eur J Heart Fail*. 2010; 12:1300–8. [PubMed: 20876734]

33. 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; 158:422–30. [PubMed: 19699866]
34. Januzzi JL Jr. The role of natriuretic peptide testing in guiding chronic heart failure management: review of available data and recommendations for use. *Archives of cardiovascular diseases.* 2012; 105:40–50. [PubMed: 22369917]
35. Masson S, Latini R, Anand IS, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem.* 2006; 52:1528–38. [PubMed: 16777915]
36. Masson S, Latini R, Carbonieri E, et al. The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. *Eur J Heart Fail.* 12:338–47. [PubMed: 20097683]
37. Hauck WW, Anderson S, Marcus SM. Should we adjust for covariates in nonlinear regression analyses of randomized trials? *Control Clin Trials.* 1998; 19:249–56. [PubMed: 9620808]
38. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Medical care.* 2007; 45:S103–7. [PubMed: 17909367]
39. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *Jama.* 2007; 297:1319–31. [PubMed: 17384437]
40. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials.* 2010; 7:197–208. [PubMed: 20423925]
41. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. *Br J Radiol.* 1971; 44:793–7. [PubMed: 4940475]
42. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer.* 1976; 34:585–612. [PubMed: 795448]
43. Januzzi JL, Troughton R. Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are useful in heart failure management. *Circulation.* 2013; 127:500–7. discussion 508. [PubMed: 23357662]
44. Porapakham P, Zimmet H, Billah B, Krum H. B-type natriuretic peptide-guided heart failure therapy: A meta-analysis. *Arch Intern Med.* 2010; 170:507–14. [PubMed: 20308637]
45. Savarese G, Trimarco B, Dellegrottaglie S, et al. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. *PloS one.* 2013; 8:e58287. [PubMed: 23472172]
46. Gaggin HK, Truong QA, Rehman SU, et al. Characterization and prediction of natriuretic peptide “nonresponse” during heart failure management: results from the ProBNP Outpatient Tailored Chronic Heart Failure (PROTECT) and the NT-proBNP-Assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) study. *Congest Heart Fail.* 2013; 19:135–42. [PubMed: 23279139]

Abbreviation List

HF	Heart Failure
NP	Natriuretic Peptides
BNP	B-type natriuretic peptide
NT-proBNP	Amino terminal pro-B-type natriuretic peptide
RASS	Renin-angiotensin-aldosterone system
EQOL	Economic and Quality of Life

CCC Clinical Coordinating Center
DCC Data Coordinating Center

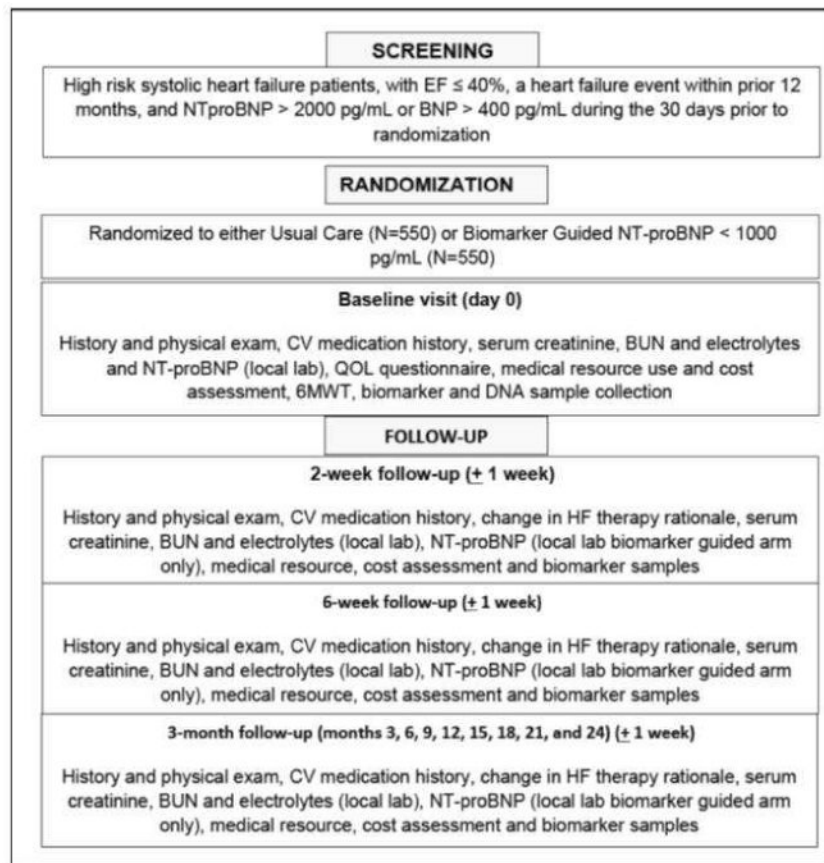


Figure 1. Schematic diagram for the GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in HF (GUIDE-IT) trial

GUIDE-IT aims to randomize approximately 1100 high risk chronic heart failure patients with left ventricular ejection fraction \leq 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.

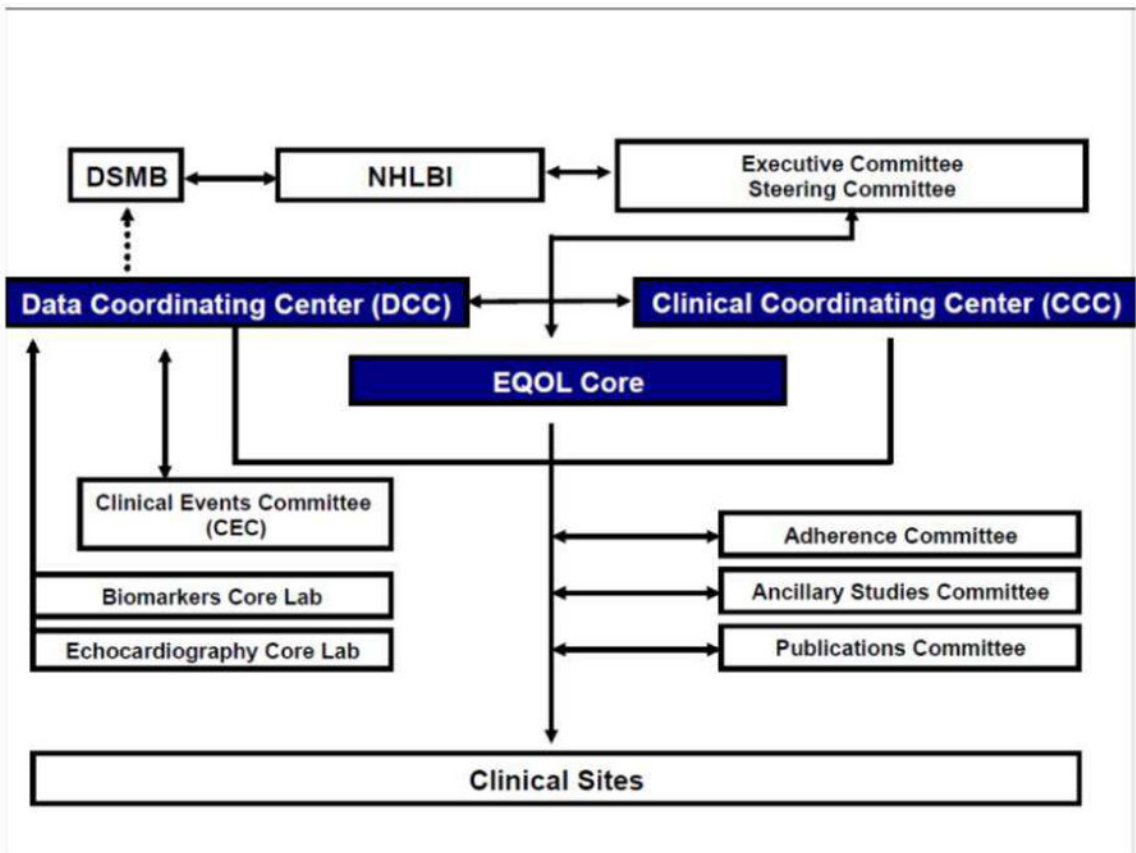


Figure 2. Trial Organization

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

Diuresis (loop or thiazide)	↓
Angiotensin-converting enzyme inhibitors	↓
Angiotensin receptor blockers	↓
β-Blockers	Transient ↑, mostly ↓
Mineralocorticoid receptor antagonists	↓
Cardiac resynchronization therapy	↓
Exercise	↓
Rate control of atrial arrhythmia	↓

Table 2

Design of Selected RCTs of Biomarker-Guided Therapy in HF

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

* 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

Inclusion Criteria
Age ≥ 18 years
HF event in Prior 12 months*
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

* 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, orthotopic heart transplantation; VAD, ventricular assist device; ESRD, end stage renal disease.

Table 4
Potential Interventions to Decrease NT-proBNP Levels

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

Primary End Point
Time to CV death or first HF hospitalization
Secondary End Points
Time to all-cause mortality
Days alive and not hospitalized for CV reasons
Recurrent hospitalizations
Time to CV death
Time to first HF hospitalization
HRQOL
Resource utilization, cost and cost effectiveness
Safety

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