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Biomarkers

Use of Amino-Terminal Pro–B-Type Natriuretic Peptide to Guide Outpatient Therapy of Patients With Chronic Left Ventricular Systolic Dysfunction

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Objectives The aim of this study was to evaluate whether chronic heart failure (HF) therapy guided by concentrations of amino-terminal pro–B-type natriuretic peptide (NT-proBNP) is superior to standard of care (SOC) management.

Background It is unclear whether standard HF treatment plus a goal of reducing NT-proBNP concentrations improves outcomes compared with standard management alone.

Methods In a prospective single-center trial, 151 subjects with HF due to left ventricular (LV) systolic dysfunction were randomized to receive either standard HF care plus a goal to reduce NT-proBNP concentrations ≤1,000 pg/ml or SOC management. The primary endpoint was total cardiovascular events between groups compared using generalized estimating equations. Secondary endpoints included effects of NT-proBNP–guided care on patient quality of life as well as cardiac structure and function, assessed with echocardiography.

Results Through a mean follow-up period of 10 ± 3 months, a significant reduction in the primary endpoint of total cardiovascular events was seen in the NT-proBNP arm compared with SOC (58 events vs. 100 events, $p = 0.009$; logistic odds for events 0.44, $p = 0.02$); Kaplan-Meier curves demonstrated significant differences in time to first event, favoring NT-proBNP–guided care ($p = 0.03$). No age interaction was found, with elderly patients benefitting similarly from NT-proBNP–guided care as younger subjects. Compared with SOC, NT-proBNP–guided patients had greater improvements in quality of life, demonstrated greater relative improvements in LV ejection fraction, and had more significant improvements in both LV end-systolic and -diastolic volume indexes.

Conclusions In patients with HF due to LV systolic dysfunction, NT-proBNP–guided therapy was superior to SOC, with reduced event rates, improved quality of life, and favorable effects on cardiac remodeling. (Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting; NCT00351390) (J Am Coll Cardiol 2011;58:1881–9)

The rising incidence and prevalence of chronic heart failure (HF) constitutes a major health care burden in both developed and developing countries (1). In addition, HF is accompanied by significant morbidity and mortality, and although evidence-based therapy for HF has improved prognosis, rates of adverse outcomes in patients with HF remain high, with considerable impairment in quality of life (QOL) for those afflicted. Thus, significant opportunities exist for the improvement in the evaluation and management of patients with HF.

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The standard of care (SOC) for outpatient pharmacologic management of subjects with chronic HF due to left ventricular systolic dysfunction (LVSD) includes the introduc-

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Abbreviations and Acronyms

GEE = generalized estimating equations
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
LV = left ventricular
LVSD = left ventricular systolic dysfunction
NT-proBNP = amino-terminal pro–B-type natriuretic peptide
QOL = quality of life
SOC = standard of care

tion and adjustment of beta-adrenergic blockers and vasodilators to achieve clinical trial–based targets, with the addition of aldosterone blockade or cardiac resynchronization therapy reserved for those with persistent symptoms (2). In addition, although loop diuretic agents are supported to reduce symptoms in chronic HF, minimization of doses of these agents is recommended. However, ascertainment of clinical stability and volume status in chronic HF can be challenging in inexperienced hands (3). Also, up-titration of beneficial HF medications in clinical practice is often suboptimal (4), with achieved doses lower than in prospective trials (4). In this regard, an objective biochemical marker for HF stability would be invaluable to physicians, particularly if it could be used as an adjunctive "guide" to standard HF care.

Trends of amino-terminal pro–B-type natriuretic peptide (NT-proBNP) predict prognosis in chronic HF (5), often declining after HF therapy with agents such as vasodilators, beta-adrenergic blockers, and aldosterone antagonists (6–10), while persistently elevated (or rising) levels of NT-proBNP are predictive of poor outcomes (5). However, it remains unclear whether adjusting medications on the basis of standard HF care plus the goal to reduce NT-proBNP values improves patient outcomes. Previous clinical trials of various designs have examined this question, returning mixed results (11–18). We therefore wished to clarify the potential role of NT-proBNP–guided HF care.

Methods

The rationale and methods of the PROTECT (Use of NT-proBNP Testing to Guide Heart Failure Therapy in the Outpatient Setting) study were recently published (19). Briefly, PROTECT was a single-center, investigator-initiated, randomized controlled trial with a primary hypothesis that standard guideline-compliant HF care with an adjunctive goal to lower and sustain NT-proBNP concentrations ≤1,000 pg/ml would be superior to SOC treatment for patients with HF due to LVSD (left ventricular [LV] ejection fraction ≤40%). Inclusion and exclusion criteria for the trial are detailed in Online Table 1. The Partners Healthcare Institutional Review Board approved all study procedures.

After providing consent, patients were block-randomized on the basis of their New York Heart Association functional class symptom severity. The study was a prospective, randomized, open-label, blinded endpoint trial, with endpoints adjudicated blinded to treatment allocation or biomarker level in the office. Patients were free to withdraw from the trial at any time, but outcomes were analyzed per intent to treat.

Study procedures. After randomization, a subject was assessed at scheduled clinic visits in the Massachusetts General Hospital Heart Center quarterly, to a maximum of 12 months, or until the last subject was randomized and completed a 6-month follow-up visit. For both treatment arms, a sample of blood for standard laboratory testing and NT-proBNP measurement (Roche Diagnostics, Inc., Indianapolis, Indiana) was obtained. The Minnesota Living With Heart Failure Questionnaire was administered at each clinic visit, and 2-dimensional echocardiography was performed at baseline and (when possible) at the completion of study procedures; performance and interpretation of the echocardiograms were blinded to NT-proBNP results.

Patient management. Patients were managed by physicians skilled in HF care, according to consensus guidelines (2), with the goal of a maximally tolerated neurohormonal antagonist or beta-adrenergic blocker medication program and concomitant efforts to minimize loop diuretic doses when possible. For the NT-proBNP arm, those with NT-proBNP concentrations above 1,000 pg/ml (a threshold associated with increased risk in HF [5,20–22]) were considered for drug therapy intensification and/or careful reassessment of their medical programs irrespective of clinical status or perception of the presence of an optimal medical program. In the NT-proBNP arm, neither caregivers nor patients were blinded to the NT-proBNP results. As noted in our methods report (19), although clinicians were reminded of the sequence and goal doses for the therapies applied in the PROTECT study, no algorithm for drug therapy introduction or intensification was used, as it was believed that such an approach would confound the concept of standard HF management, which does not typically rely on such algorithmic care.

If adjustment of medical therapy was deemed necessary for either treatment arm, the choice of medication was made by the clinician, and follow-up visits were made until optimal medical therapy was achieved, a clear therapeutic limit was reached, or the subject required hospitalization.

Primary endpoint. The primary clinical endpoint of the PROTECT study was total cardiovascular events, a composite of the following: worsening HF (defined as new or worsening symptoms or signs of HF requiring unplanned intensification of decongestive therapy), hospitalization for HF (including treatment with intravenous diuretic agent in the emergency department setting without hospitalization), clinically significant ventricular arrhythmia, acute coronary syndromes, cerebral ischemia, and cardiac death; specific definitions of endpoints are described elsewhere (19).

Sample size. An initial goal enrollment of 300 subjects was estimated on the basis of effect sizes and outcomes of previous studies (19). To minimize the type I error rate, only 1 interim analysis was planned and was performed upon enrollment of 151 subjects. As reported (19), the interim analysis indicated a statistically significant reduction in the

primary endpoint of total cardiovascular events, favoring the NT-proBNP arm. On the basis of the magnitude of reduction in events related to NT-proBNP allocation and the results of recent trials, a decision was made to suspend active enrollment, with planned 6-month follow-up for the remaining active patients.

Statistical analysis. Differences in characteristics between subjects in each arm were assessed using chi-square tests for categorical variables and Student *t* tests or Wilcoxon rank sum tests for continuous variables, as appropriate. For the primary endpoint, comparison of event rates between study arms was performed using generalized estimating equations (GEE), a method used to correct for multiple events within some subjects (23); from the GEE, a logistic beta coefficient was calculated for the differential effect of adding NT-proBNP results to clinical management of HF, after adjusting for age, LV ejection fraction, New York Heart Association functional class, and estimated glomerular filtration rate; from this beta coefficient, logistic odds and 95% confidence intervals were estimated. Hosmer-Lemeshow testing was applied to assess model fit. Time-to-first-event analyses were performed using the Kaplan-Meier method, and groups were compared using the log-rank test.

Associations between treatment strategy and treatment-related serious adverse events were examined, after adjustment for relevant baseline covariates, such as estimated glomerular filtration rate, potassium, and blood pressure. Parametric and nonparametric tests were used to examine therapy changes between treatment groups; all subjects completing at least 1 follow up visit were included in the analysis of therapy changes as a function of treatment allocation. Additionally, we examined the effects of NT-proBNP–guided HF care on QOL, as well as echocardiographic parameters. A 2-tailed p value <0.05 was considered to indicate statistical significance. All analyses were performed using Stata version 9.2 (StataCorp LP, College Station, Texas) or PASW version 17 (SPSS, Inc., Chicago, Illinois).

Results

Patient demographics, study visits, and therapeutic interventions. Figure 1 details the study flow; of 151 randomized patients, there were 6 withdrawals in each arm. Table 1 details baseline patient characteristics for the trial. The mean age of the study population was 63.3 ± 13.9 years; 21.9% were ≥75 years of age.

Over a mean follow-up period of 10 ± 3 months, study subjects made 908 visits, with a median number of 5.0 visits (interquartile range: 4.0 to 8.0 visits); those in the NT-proBNP arm were seen a median of 6.0 times, while those in the SOC arm were seen a median of 5.0 times ($p = 0.05$). Subjects age ≥75 years were seen a median of 7.5 times, compared with 5.0 times in those age <75 years ($p < 0.001$).

Tables 2 and 3 depict HF therapies at baseline and at the completion of the study. The majority of patients in both arms entered the study on guideline-based medical regimens

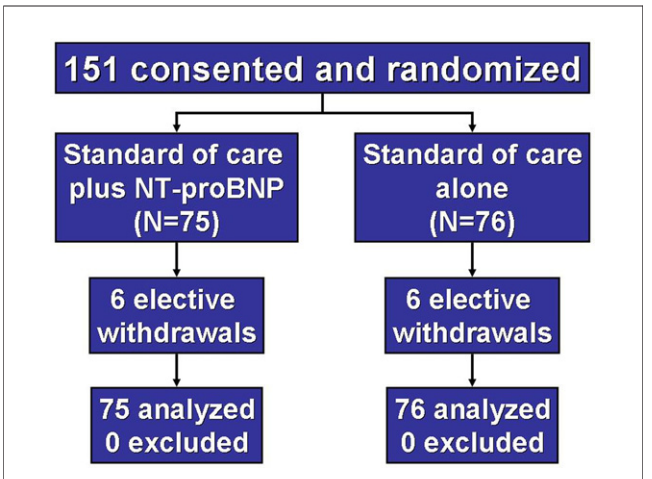

Figure 1 Study Flow

Patients were block-randomized on the basis of heart failure symptom severity into 1 of 2 treatment strategies; withdrawals were balanced between the 2 arms and analyzed per intent to treat. NT-proBNP = amino-terminal pro–B-type natriuretic peptide.

(Table 2). During study procedures, patients in the NT-proBNP arm had an average of 7 therapy adjustments compared with SOC-managed patients, who had 6 ($p = 0.23$ for difference), although dosing changes were typically more aggressive in the NT-proBNP arm (Table 3). The proportion achieving ≥50% goal doses (2) for their therapies was consistently numerically (but not statistically) higher in the NT-proBNP arm; this included angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (56.5% vs. 50.8%), as well as beta-blockers (53.4% vs. 41.9%). Notably, at the completion of the study (Table 2), compared with SOC, patients in the NT-proBNP arm were more likely to be taking aldosterone blockers (62.7% vs. 44.7%, $p < 0.001$) and less likely to be taking loop diuretic agents (85.3% vs. 96.1%, $p = 0.05$).

NT-proBNP concentrations. At baseline, the median NT-proBNP concentration for the group as a whole was 2,118 pg/ml (interquartile range: 1,122 to 3,831 pg/ml); there was no difference between the NT-proBNP and SOC arms with respect to NT-proBNP concentrations at baseline (2,344 pg/ml vs. 1,946 pg/ml, $p = 0.40$). After the study procedures, the median NT-proBNP concentration for the group as a whole fell to 1,321 pg/ml ($p = 0.02$ vs. baseline); a significant reduction was seen only in the NT-proBNP arm (to 1,125 pg/ml, $p = 0.01$ vs. baseline), while the SOC arm had no significant decrease (1,844 pg/ml, $p = 0.61$ vs. baseline and $p = 0.03$ vs. NT-proBNP arm in follow-up). At the end of the study procedures, 44.3% of the NT-proBNP arm and 35.6% of the SOC arm had NT-proBNP values below 1,000 pg/ml; similar distributions of subjects were below 2,000 pg/ml (68.6% vs. 57.5%) and 3,000 pg/ml (80.0% vs. 69.9%).

Outcomes. Over the follow-up period of the study, a total of 158 events were registered. The mean number of events

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Table 1 Baseline Characteristics of the Study Cohort as a Function of Randomization

Characteristic	NT-proBNP (n = 75)	SOC (n = 76)	p Value
Age (yrs)	63.0 ± 14.5	63.5 ± 13.5	0.41
NYHA functional class II or III	65 (85.5%)	64 (84.2%)	0.46
LV ejection fraction	28.0 ± 8.7%	25.9 ± 8.3%	0.52
Men	67 (88.2%)	61 (81.3%)	0.24
Caucasians	65 (85.5%)	66 (88.0%)	0.65
Cause of HF			0.17
Ischemic	40 (53.3%)	45 (60.0%)	
Nonischemic	25 (33.3%)	18 (24.0%)	
Other	10 (13.3%)	12 (16.0%)	
Medical history			
Hypertension	40 (52.6%)	39 (52.0%)	0.94
Coronary artery disease	42 (55.3%)	50 (66.7%)	0.09
Myocardial infarction	28 (36.8%)	30 (40.0%)	0.69
Atrial fibrillation	31 (40.8%)	30 (40.0%)	0.92
Ventricular tachycardia	23 (30.3%)	21 (28.0%)	0.76
Obstructive airways disease	15 (19.7%)	16 (21.3%)	0.81
Diabetes mellitus	30 (39.5%)	32 (42.7%)	0.19
Implanted devices			
Cardioverter-defibrillator	52 (69.3%)	50 (65.8%)	0.32
Biventricular pacemaker	30 (40.0%)	30 (39.4%)	0.68
Tobacco use			0.94
Active smokers	5 (6.6%)	6 (8.0%)	
Never smokers	47 (61.8%)	45 (60.0%)	
Ex-smokers	24 (31.6%)	24 (32.0%)	
Physical examination			
Body mass index (kg/m^2)	28.8 ± 6.4	28.5 ± 6.1	0.63
Heart rate (beats/min)	73 ± 13	73 ± 12	0.48
Systolic blood pressure (mm Hg)	108 ± 15	112 ± 16	0.07
Diastolic blood pressure (mm Hg)	64 ± 9	67 ± 9	0.05
Jugular venous distension	24 (31.6%)	30 (40.0%)	0.28
Pulmonary rales	8 (10.5%)	11 (14.7%)	0.44
S4 gallop	6 (7.9%)	9 (12.0%)	0.40
S3 gallop	20 (26.3%)	23 (30.7%)	0.55
Murmur	51 (67.1%)	48 (64.0%)	0.69
Lower extremity edema	26 (34.2%)	21 (28.0%)	0.41
QRS duration (ms)	140 ± 35	137 ± 37	0.70
Laboratory results			
Sodium (mmol/l)	138 ± 3.5	138.6 ± 2.6	0.07
Potassium (mg/dl)	4.3 ± 0.4	4.2 ± 0.4	0.71
Blood urea nitrogen (mg/dl)	31.5 ± 16.8	29.6 ± 14.4	0.78
Creatinine (mg/dl)	1.46 ± 0.5	1.49 ± 0.43	0.39

Values are mean ± SD or n (%).
HF = heart failure; LV = left ventricular; NT-proBNP = amino-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; SOC = standard of care.

was 1.06, with a median of 0 events (interquartile range: 0 to 2), the latter because the majority of subjects (60.9%) had no events registered during the study. Of those with events, 72% had 3 or fewer events.

Lower achieved NT-proBNP concentrations were correlated with lower event rates: those below 1,000 pg/ml had the lowest frequency of events (0.45 events) compared with those between 1,000 and 2,000 pg/ml (1.1 events), between 2,000 and 3,000 pg/ml (1.25 events), and above 3,000 pg/ml (2.0 events) ($p < 0.001$ for trend) (Online Fig. 1).

With respect to the primary endpoint, those in the NT-proBNP arm had fewer total cardiovascular events, compared with the SOC arm (58 events vs. 100 events; $p = 0.009$). The adjusted logistic odds for NT-proBNP–guided management on cardiovascular events were 0.44 (95% confidence interval: 0.22 to 0.84; $p = 0.02$). Sensitivity analyses with removal of events related to acute coronary syndromes or cerebral ischemia had no effect on the benefits of NT-proBNP–guided care.

Considered as a function of treatment allocation, those in the NT-proBNP arm had fewer events per patient (0.77 events vs. 1.3 events, $p = 0.03$), and fewer patients in the NT-proBNP arm had a single event, compared with the SOC arm (29.3% vs. 48.6%, $p = 0.04$). Discrete outcome measures are noted in Table 4. No significant effect on cardiovascular death was noted associated with NT-proBNP–guided HF care; notably, 3 of the 4 decedents in the NT-proBNP had withdrawn from the study before their deaths.

Kaplan-Meier curves depicting time-to-first-event analyses for the primary endpoint demonstrate a significant event rate reduction for those in the NT-proBNP arm (log-rank $p = 0.03$) (Fig. 2).

No interaction between NT-proBNP–guided care and age was found ($p = 0.11$). NT-proBNP–guided HF management reduced total cardiovascular events in elderly patients (age ≥75 years) in a comparable manner as the trial as a whole (0.71 events vs. 1.71 events, $p = 0.01$; adjusted logistic odds 0.48, $p = 0.005$).

Safety. No significant difference in serious adverse events between treatment arms was noted (Table 5).

QOL. Those in the NT-proBNP arm had a larger improvement in QOL compared with SOC-treated patients, with a significantly larger median improvement (−10.0 vs. −5.0, $p = 0.05$); NT-proBNP–treated patients were also more likely to demonstrate large (≥10-point) improvements in QOL scores (61.2% vs. 38.8%, $p = 0.03$).

Echocardiographic parameters of LV remodeling. A total of 116 study participants (60 in the NT-proBNP arm and 56 in the SOC arm) underwent both baseline and follow-up echocardiographic studies (Fig. 3). During the study period, absolute LV ejection fraction improved by a median of 6.0% (relative change 14.0%). Compared with SOC, those in the NT-proBNP arm demonstrated greater absolute (8.3% vs. 4.0%, $p = 0.06$) and relative (18.0% vs. 8.0%, $p = 0.01$) improvements in LV ejection fraction. Those in the NT-proBNP arm demonstrated greater improvement in LV end-systolic volume index (from 65.0 to 48.5 ml/m^2, median change −15.6%) compared with SOC patients (from 55.5 to 48.5 ml/m^2, median change −6.7%) ($p < 0.001$). Similarly, NT-proBNP patients also had more significant improvements in LV end-diastolic volume index (from 85.0 to 77.5 ml/m^2, median change −8.8%) compared with SOC patients (from 77.0 to 75.0 ml/m^2, median change −2.5%) ($p = 0.008$).

Table 2 Medication Use at Baseline and After Completion of Study Procedures

Medication	Baseline			Final		
	NT-proBNP (n = 75)	SOC (n = 76)	p Value	NT-proBNP (n = 75)	SOC (n = 76)	p Value
ACE inhibitors	53 (70.7%)	47 (61.8%)	.21	56 (74.7%)	46 (60.5)	0.20
Angiotensin receptor blocker	8 (10.7%)	15 (19.7%)	.11	9 (12.0%)	17 (22.4%)	0.05
Beta-blockers	74 (98.7%)	71 (93.4%)	.19	73 (97.3%)	73 (96.1%)	0.56
Aldosterone antagonists	37 (49.3%)	26 (34.2%)	.10	47 (62.7%)	34 (44.7%)	0.001
Loop diuretic agents	67 (89.3%)	71 (93.4%)	.27	64 (85.3%)	73 (96.1%)	0.05
Thiazide diuretic agents	5 (6.7%)	3 (4.0%)	.48	5 (6.7%)	3 (3.9%)	0.42
Digoxin	22 (29.3%)	25 (32.9%)	.89	23 (30.7%)	23 (30.3%)	0.90
Hydralazine	4 (5.3%)	4 (5.3%)	.89	2 (2.7%)	4 (5.3%)	0.12
Nitrates	8 (10.7%)	16 (21.1%)	.07	7 (9.3%)	14 (18.4%)	0.06

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

Discussion

Despite the establishment of optimal therapeutic strategies in chronic HF management, clinical outcomes for affected patients remain poor, with frequently inadequate application of HF therapies in the highest-risk patients. Attempts have been made to close the existing treatment gap in HF while improving clinicians' ability to more accurately identify and treat patients with HF at risk for impending complications. Elevated values of natriuretic peptides are powerfully predictive of adverse outcomes in a manner additive and/or superior to most traditional prognostic measures in HF (24), while rising values identify a rising risk for adverse outcome (5). After initial landmark results from Troughton et al. (11) from New Zealand establishing the concept of biomarker-guided care, several studies have examined this approach; some have shown benefits of guided therapy (11,14,16), whereas in others, the benefit was less obvious, with either mixed or totally negative results (13,15,17,18). Thus, as noted by thought leaders in the field, an answer regarding this approach is still awaited (25).

In the PROTECT study, against a background of excellent HF care, the addition of NT-proBNP guidance significantly improved the primary endpoint of total cardiovascular events for patients with LVSD and was well tolerated, with favorable effects on QOL and significant improvements in LV volumes on echocardiography. Our results thus suggest that in patients with HF due to LVSD, NT-proBNP monitoring with aggressive care to lower concentrations below a threshold value may be a useful tool to assist in standard HF care.

Understanding differences among published studies in this area and their occasionally conflicting results is important. Explanations may include heterogeneity in design, the inclusion of difficult-to-treat populations in HF (such as those with heart failure with preserved ejection fraction [HFpEF]), as well as heterogeneity of aggressiveness in attempts to lower natriuretic peptide concentrations compared with control management.

In our study, we focused solely on LVSD, because the treatment approach to patients so afflicted is very clearly defined (26). This is in contrast to HFpEF, for which less clearly defined treatment options exist to clearly reduce adverse outcomes. Indeed, HFpEF is widely recognized to be caused by a heterogeneous group of disease states, without defined, accepted drug therapies as for LVSD (27); thus, guided drug therapy may be less useful in this type of patient. Indeed, a prior study of guided therapy including a mixture of patients with LVSD and HFpEF (15) suggested that a trend toward more benefit in those with LVSD was

Table 3 Medication Use as Mean Changes in Dosages During the Course of the Study

Medication	NT-proBNP (n = 75)	SOC (n = 76)	p Value
ACE inhibitors	+25.4%	+18.1%	0.15
Angiotensin receptor blockers	+5.8%	+22.3%	0.01
Beta-blockers	+46.0%	+34.5%	0.05
Aldosterone antagonists	+22.7%	+5.8%	<0.001
Loop diuretic agents	+23.7%	+25.6%	0.65
Thiazide diuretic agents*	−16.7%	−12.5%	0.88
Digoxin*	−10.9%	+2.0%	0.78
Hydralazine*	+27.5%	−50.0%	0.20
Nitrates*	+59.4%	−3.7%	0.08

*Limited number of observations
Abbreviations as in Tables 1 and 2.

Table 4 Outcomes in the PROTECT Study

Outcome Measure	NT-proBNP (n = 75)	SOC (n = 76)	p Value
Total cardiovascular events	58	100	0.009
Discrete outcome measures			
Worsening heart failure	27	54	0.001
HF hospitalization	11	27	0.002
Acute coronary syndromes	9	9	0.72
Significant ventricular arrhythmia	7	4	0.41
Cerebral ischemia	0	0	0.98
Cardiovascular death	4	6	0.52
Subjects with at least 1 event	28.3%	48.6%	0.04

A significant reduction in the primary endpoint of total cardiovascular events was driven by improvements in rates of worsening HF and reduced HF hospitalizations.
Abbreviations as in Table 1.

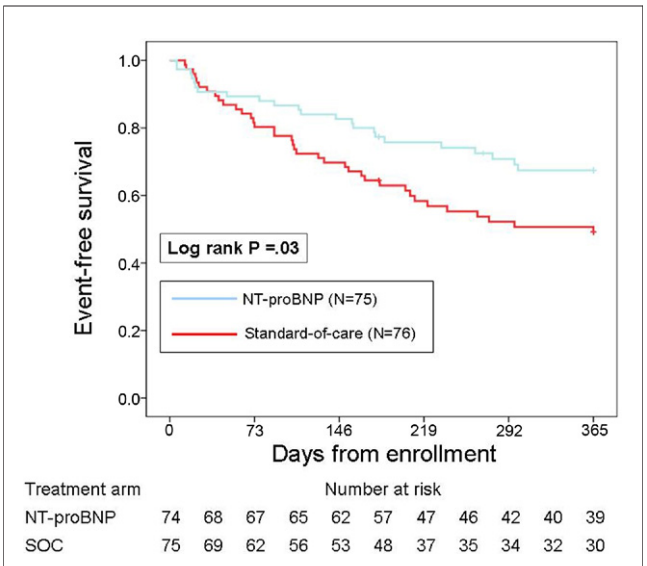

Figure 2 **Kaplan-Meier Curves Depicting Outcomes as a Function of Treatment Assignment**

As a function of time to first event, a significant reduction in adverse outcome was noted in those patients treated with a strategy guided by amino-terminal pro–B-type natriuretic peptide. SOC = standard of care.

present, while in another trial including patients with HFpEF (17), no mention was made. Thus, it remains speculative.

Another difference compared with prior studies was the goal NT-proBNP value of 1,000 pg/ml selected in this study, as well as, and perhaps most important, the assiduousness of the care given to achieve this goal. Our goal NT-proBNP value of 1,000 pg/ml was selected on the basis of clinical trials defining an inflection point of risk at this concentration (5,20–22); indeed, the results of the PROTECT study validate this goal value, demonstrating a clear gradient of risk in subjects with NT-proBNP concentrations above 1,000 pg/ml. In trials with higher target values for NT-proBNP (15), rates of adverse outcome were, not surprisingly, high, with negative results overall. In some other studies, the goal NT-proBNP values were similar to ours, but rates of achievement of these goal concentrations were very low (13,18). For example, in the report of Persson et al. (18), NT-proBNP concentrations were lowered by approximately 10% from baseline (to approximately 2,360 pg/ml), a reduction less than biological variability for the biomarker; thus, the benefit of NT-proBNP lowering was not adequately assessed in that study. In another negative study that included a large number of elderly subjects, goal NT-proBNP values were rarely met, despite more drug titration in the NT-proBNP arm (13); thus, above and beyond simply triggering drug titration, the available data would suggest that efforts to lower of NT-proBNP values below a target value are crucial to reduce risk.

In testing the hypothesis that improved outcomes would follow reduction of NT-proBNP, we carefully managed patients with the objective of significant NT-proBNP lowering and achieved this goal in the highest percent of subjects in any guided therapy trial reported to date. In doing so, although both arms of the trial received aggressive care, we titrated therapies such as aldosterone antagonists and beta-blockers more aggressively in the NT-proBNP–guided arm; in addition, NT-proBNP patients were less likely to be taking loop diuretic agents at the completion of the study. Given associations between loop diuretic agents, neurohormonal activation, and adverse outcome in HF (28), the reduction in use of this class of drugs after NT-proBNP guidance is an important finding. In comparison, studies finding no difference between guided therapy and standard management often reported no significant difference in drug titrations between the biomarker arm and control groups (17,18) or mainly up-titrated loop diuretic agents (15). Overall, however, in our study and others, achievement of "goal" doses of drug was a challenge, even when guided by

Table 5 **Serious Adverse Events During the Study as a Function of Treatment Allocation**

	NT-proBNP (n = 75)		SOC (n = 76)		
Adverse Event	Total Events	% With 1 Event	Total Events	% With 1 Event	p Value for Difference (in % With 1 Event)
Abdominal pain	1	1.3%	1	1.3%	0.90
Acute renal failure	4	5.3%	3	3.9%	0.72
Anemia	1	1.3%	0	0%	0.90
Atrial fibrillation	2	2.7%	5	6.6%	0.42
Cough	2	2.7%	1	1.3%	0.41
Diarrhea	2	2.7%	1	1.3%	0.65
Dizziness	5	6.7%	4	5.3%	0.70
Fever	1	1.3%	1	1.3%	0.89
Gastrointestinal bleeding	1	1.3%	1	1.3%	0.78
Hyperkalemia/hypokalemia	3	2.7%	1	1.3%	0.32
Hypotension	4	5.3%	0	0%	0.08
Respiratory infection	2	2.7%	4	5.3%	0.25
Syncope	2	2.7%	1	1.3%	0.70

Abbreviations as in Table 1.

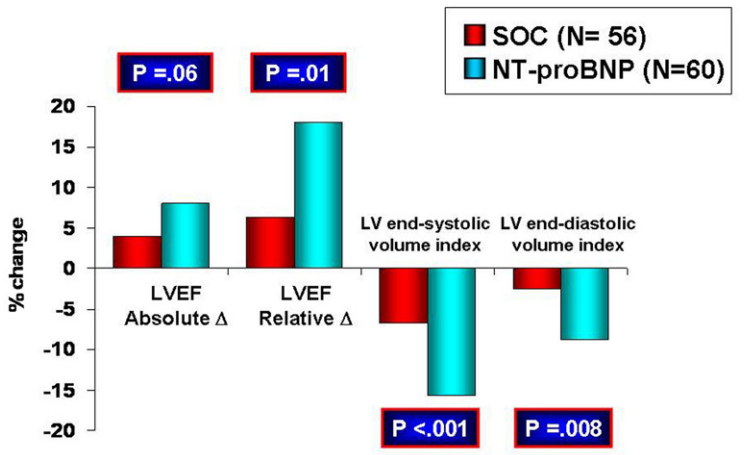

Figure 3 Echocardiographic Results Among Patients as a Function of NT-proBNP Versus SOC Management

Those with heart failure management guided by NT-proBNP had greater improvement in ventricular function and more favorable reverse remodeling.
LV = left ventricular; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 2.

NT-proBNP concentrations, illustrating the challenge of managing these complex patients well.

The elderly population is at highest risk in chronic HF, more often demonstrating suboptimal responses to therapy and greater intolerance to medication titration (13) compared with younger patients; thus, it is not a stretch to assert that any modality to guide HF care is likely to be more challenged in the elderly, and biomarker-guided care is no exception (13,17). However, drug therapy titration in elderly patients with HF, although more gradual, may often be comparably successful with that in younger patients (29). In our study, we found no clear interaction with age (modeled as a continuous variable), and subjects ≥75 years of age seemed to significantly benefit from NT-proBNP–guided care, albeit in the context of a relatively limited number of patients in this age range. It remains speculative why our results contrast those of other trials, but it may be due to the larger number of visits in the elderly population of the PROTECT study, allowing for more gradual, but ultimately successful, up-titration of therapies. The elderly are also more likely to have HFpEF, with attendant limitations as mentioned previously.

The more significant improvement in LV ejection fraction and end-systolic and -diastolic volume indexes associated with NT-proBNP–guided HF care is of great interest, lending mechanistic support to the event rate reductions associated with the approach. Therapies that lead to improved remodeling in chronic HF not only have a direct impact on nonfatal HF events but also typically reduce mortality (30). Recent meta-analyses suggest a potential mortality reduction from natriuretic peptide–guided care (31,32); our results suggest that favorable effects on remodeling may in part explain this finding. More in-depth analyses of extensive echocardiographic results from the PROTECT study are forthcoming.

Study limitations. Limitations of our study include that it was relatively small (although robust) and was performed at a tertiary care teaching hospital. In addition, the PROTECT study was a single-center trial; although potentially limiting generalizability, the single-center nature of the study may be a strength in a way, because it allowed for strong adherence to study protocol with maintenance of efforts at NT-proBNP lowering, something particularly feasible in a single-center design. Our study design and findings should be replicated in larger, multicenter analyses, which are planned. Although outcomes favored NT-proBNP guidance, a primary endpoint of total cardiovascular events may also be a limitation. However, patients with chronic HF are a clinically recidivistic population, and use of the GEE approach allows comparison of the impact of HF therapy guided by NT-proBNP on these high rates of recurrent events. In this, we found that NT-proBNP guidance not only reduced overall event rates but also reduced the risk for a first event, as evidenced in Kaplan-Meier analysis. Also, the use of the GEE approach minimizes the risk that a few patients with a large number of events will influence the outcome analysis. Although the GEE analysis has value in this context, we concede that the adjustments applied within the equations used did include potentially relevant covariates (such as duration of HF diagnosis, achieved drug doses, and ischemic vs. nonischemic HF etiology, as well as many other potential choices), the inclusion of which may have rendered the model unstable. However, the benefits of guided therapy were significant in Kaplan-Meier analyses, as well as in our echocardiographic data, which lends support to the primary endpoint. The benefits of guided therapy in the elderly subjects of the PROTECT study may

be questioned, given the limited number of patients in this age range, which reduces our statistical power compared with larger landmark studies (13,17); although our mean age is younger than those of many guided therapy trials, it is very comparable with the mean ages in clinical trials of drugs applied to treat HF due to LVSD, which allows examination of the approach of guided therapy in a patient population that is consistent with the clinical trials of drug therapy in HF represented in consensus guidelines. In addition, as noted, it is unclear if negative results regarding age and natriuretic peptide–guided HF therapy have to do with a universal futility of HF therapy in the elderly, or whether a different approach for such patients compared with younger patients is needed. Another potential limitation is the use of an unblinded trial design; this could lead to bias, as managing physicians would be aware of treatment allocation. Nonetheless, this design has been used in similar "guided therapy" trials (16), patients in the SOC arm received excellent, aggressive care, all endpoints were adjudicated blinded to treatment allocation, and both QOL and echocardiographic improvement was seen in parallel with better outcomes in these subjects.

Conclusions

Against a backdrop of standard HF care, the addition of a strategy to suppress NT-proBNP values led to significant reductions in adverse outcomes in a population of patients with chronic HF. If confirmed, the addition of natriuretic peptide–guided therapy to standard care may represent a new paradigm for HF practice.

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Key Words: heart failure ■ natriuretic peptides ■ outcomes.

APPENDIX

For supplementary tables and figures, please see the online version of this article.