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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