Natriuretic peptides in heart failure: should therapy be guided by BNP levels?

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Abstract | Heart failure (HF) is a leading cause of morbidity and mortality worldwide. Testing for natriuretic peptide markers, such as B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), has emerged as an important tool for the diagnosis and risk stratification of patients with HF. However, questions remain regarding the potential role for natriuretic peptides to guide therapy in patients with HF. In this Review, we address the underlying assumptions and the existing evidence supporting a natriuretic-peptide-guided approach to the outpatient management of HF.

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Introduction

Heart failure (HF) is a leading cause of morbidity and mortality and accounts for an estimated annual expenditure of more than $20 billion in the US alone.[1] HF is the only cardiovascular disorder that continues to increase in both incidence and prevalence and, as the population ages, the prevalence of this disease is expected to continue to rise. Although the armamentarium of medications that reduce mortality among patients with HF has grown, the relative number of eligible patients receiving these therapies remains low.[2,3]

Testing for natriuretic peptide markers, such as B-type natriuretic peptide (BNP), or its amino-terminal fragment N-terminal proBNP (NT-proBNP), has emerged as an important tool for the diagnosis and risk stratification of patients with HF. However, questions remain regarding the use of natriuretic peptides to help guide therapy in patients with HF. In this Review, we discuss the evidence supporting a natriuretic-peptide-guided approach to the outpatient management of patients with HF.

Physiology of natriuretic peptides

The concept of the heart as an endocrine organ was first introduced more than 40 years ago;[4] however, the clinical relevance of this discovery has only become apparent in the past 15–20 years. Experimental studies, conducted in the mid 1950s, revealed that dilatation of the cardiac atria could induce natriuresis.[5] In 1964, electron microscopy revealed the presence of secretory granules in the atrial myocyte.[6] Not until nearly 20 years later was the importance of these granules revealed, when de Bold and colleagues demonstrated that extracts from atrial myocytes injected into rats led to brisk natriuresis and diuresis.[7] These atrial hormones were subsequently named atrial natriuretic peptides.

In 1988, another natriuretic peptide was isolated from porcine brain and was named brain natriuretic peptide, now more commonly referred to as BNP.[8] This peptide and its amino-terminal fragment, NT-proBNP, are both derived from a single 108 amino acid polypeptide, proBNP, which is synthesized by myocytes and fibroblasts in the atria and ventricles in response to left ventricular filling pressures and wall stress.[9–11] This prohormone is subsequently cleaved into the 32 amino acid peptide BNP and the 76 amino acid amino-terminal fragment, NT-proBNP by the myocyte. ProBNP or proBNP-derived products may also be released into the circulation and

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The authors, the journal Editor B. Mearns and the CME questions author D. Lie declare no competing interests.

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Key points

- Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), are useful for risk stratification in patients with heart failure
- Several established heart failure therapies have been shown to significantly reduce the concentration of natriuretic peptides
- Limited evidence exists that patients with higher concentrations of natriuretic peptides derive a greater benefit from established heart failure therapies than patients with lower concentrations of natriuretic peptides
- More research is required before a natriuretic peptide-guided approach to the outpatient management of heart failure can be endorsed in all patients

Box 1 | A natriuretic-peptide-guided approach to heart failure therapy

- Assumption 1: Natriuretic peptides help to identify patients at increased risk of adverse outcomes
- Assumption 2: A reduction in natriuretic peptide concentration is associated with improved clinical outcomes
- Assumption 3: Therapies with established benefit in the management of hear failure lower natriuretic peptide concentrations
- Assumption 4: Elevated natriuretic peptide levels help to identify patients who derive greater benefit from these therapies in the management of heart failure

can crossreact with commercial BNP assays. As such, alternative forms of proBNP-derived fragments, with lower biological activity than the 32 amino acid form of BNP, could constitute a substantial portion of the BNP that is detected in the plasma with available assays.[12]

Although BNP and NT-proBNP levels are closely correlated, the two hormones have different ranges, proposed cut points,[13] and physiological differences. BNP is a biologically active neurohormone that targets many of the mechanisms central to the pathophysiology of HF. BNP has sympathoinhibitory effects and reduces secretion of renin, angiotensin II, and aldosterone and also leads to vasodilation, decreased blood pressure, and increased sodium and water excretion. By contrast, NT-proBNP circulates as a biologically inert substance. The clearance mechanisms and half-lives of BNP and NT-proBNP are also different. BNP is degraded by endopeptidases and has a half-life of 5–10 min, whereas NT-proBNP is cleared passively primarily by the kidney and has a longer half-life of 25–120 min.[14,15] Despite these notable differences, the two hormones share many similarities in terms of their utility for diagnosis and risk stratification and can be considered largely interchangeable from the perspective of their potential role for tailoring therapy for HF.

Natriuretic peptide levels have been shown to fluctuate on a day-to-day basis and are correlated with a variety of characteristics including the individual's age, sex,[16,17] BMI,[18] and renal function.[19] Common genetic polymorphisms in the promoter region of the BNP gene have also been shown to be associated with increased levels of circulating BNP.[20–22] These factors contribute to the observed inter-patient and intra-patient variability in natriuretic peptide levels, which in turn have clinical relevance for the interpretation of assay results and the utility of natriuretic peptide levels for guiding HF therapy.

Natriuretic peptides in HF management

The results of several trials demonstrate that natriuretic peptides, including BNP and NT-proBNP, are useful for diagnosis and risk stratification of patients with HF.[23] As a consequence, interest in the potential utility of natriuretic peptides to guide the management of HF has grown over the past decade. Point-of-care assays are readily available for both BNP and NT-proBNP, thereby making measurement of these hormones easy in both the inpatient and outpatient settings. In addition, clinicians are familiar with the concept of treating to prespecified targets for several common diseases. For example, the management of hyperlipidemia, hypertension, and diabetes mellitus involves monitoring the results of routine laboratory tests to guide treatment.

However, the argument for the use of a common prespecified target natriuretic peptide concentration to guide HF therapy relies on the validity of four key assumptions, which are listed in Box 1. In the following sections, we address the validity of these assumptions, and discuss the existing clinical trial data examining a natriuretic peptide-guided approach to the management of HF.

Risk stratification

The value of BNP and NT-proBNP for risk stratification in patients with HF in both the inpatient and outpatient settings is well established. Measuring levels of these peptides provides incremental information beyond that offered by other biomarkers.[23] A systematic review that included 19 studies of patients with HF showed that for every 100 ng/l rise in BNP concentration, there was a corresponding 35% increase in the relative risk of death.[24]

Moreover, a growing number of studies indicate that changes in natriuretic peptide concentrations over time are correlated with risk of adverse outcomes. In Val-HeFT,[25] 5,010 patients with symptomatic HF were enrolled and randomly assigned to receive valsartan or placebo. Plasma levels of BNP were measured in approximately 4,300 patients at baseline and again at 4 and 12 months follow-up. Patients with a BNP level greater than the median at baseline had a more than twofold higher risk of death or morbidity during long-term follow-up than did those with a BNP level below the median.[25] Importantly, the study demonstrated that the percentage change in BNP levels during follow-up was an important determinant of clinical outcome. Patients with the largest relative reductions in BNP levels 4 months after randomization had the most favorable outcomes, whereas patients with the greatest percentage increase in BNP were observed to have the highest event rates.

Similarly, the relative changes in natriuretic peptide levels during acute care hospitalization for HF have been shown to be useful for risk stratification. Bettencourt and colleagues measured NT-proBNP levels in 182 patients admitted to the hospital with decompensated HF and classified them into three groups depending on whether NT-proBNP levels decreased by at least 30%, did not significantly change, or significantly increased by at least 30% between hospital admission and discharge.[26] The change in NT-proBNP levels during hospitalization was found to

be the strongest independent predictor of death or hospital readmission during 6 months of follow-up (Figure 1).

Logeart *et al.* also evaluated the prognostic utility of serial BNP levels in 105 patients hospitalized with decompensated HF.[27] The investigators observed that an elevated BNP level at admission, an elevated BNP level at discharge, and a small relative change in BNP level during hospitalization were associated with poor outcomes following hospital discharge. After multivariate analysis, the relative change in BNP level during hospitalization and BNP level at the time of hospital admission were no longer significantly associated with outcomes, and BNP concentration at the time of hospital discharge was the sole independent predictor of death or rehospitalization.

Response to HF therapies

We should emphasize that natriuretic peptides, in and of themselves, are not believed to play a pathological role in the response to HF. In fact, animal models indicate that natriuretic peptides could play a protective role by promoting diuresis and by possibly preventing maladaptive forms of hypertrophy and fibrosis.[28,29]As such, a reduction in natriuretic peptide concentration over time, or in response to established therapies, is believed to reflect primarily amelioration of the underlying stress placed on the ventricle. Several therapies with proven benefit in patients with HF—such as angiotensin-converting-enzyme (ACE) inhibitors,[30] angiotensin-receptor blockers,[31] spironolactone,[32] and cardiac resynchronization therapy[33]—have also been shown to significantly reduce natriuretic peptide concentration in parallel with the improvements in outcomes attributed to these established therapies. However, the natriuretic peptide response to the initiation of β-blocker therapy appears to follow a more biphasic pattern; concentrations rise soon after treatment is commenced, and then fall to below baseline levels after several months of therapy.[34,35]

Benefit of HF therapies

Many evidence-based therapies for HF have been shown to reduce natriuretic peptide levels. However, there are limited data to indicate that patients with higher BNP or NT-proBNP levels obtain a greater benefit from these therapies than patients with lower natriuretic peptide concentrations.[36] These observations underlie one of the key assumptions for targeting a prespecified BNP or NT-proBNP concentration in the management of HF. Critics of a natriuretic peptide-guided approach to HF management assert that the strategy is primarily useful because it leads to more frequent and aggressive uptitration of therapies with established benefit in HF. However, if patients with lower levels of BNP and NT-proBNP derive at least as much benefit from established HF therapies as do patients with higher levels of natriuretic peptides, one could argue that the majority of patients with HF would benefit from intensive use of evidence-based therapies regardless of their natriuretic peptide levels. Furthermore, dose selection for many HF therapies, including ACE inhibitors, angiotensin-receptor blockers, and β-blockers (but not diuretics), is based on maximum tolerability rather than on physical function or volume status.

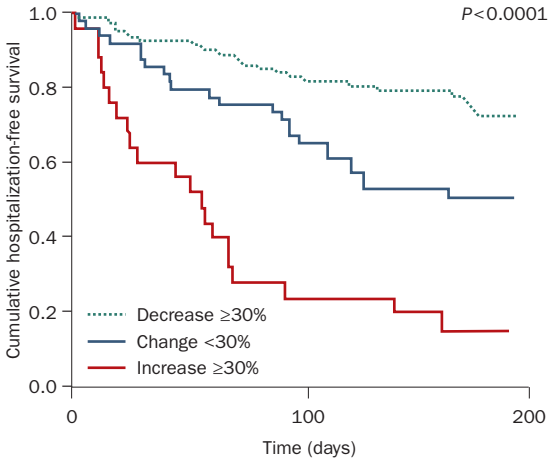


Figure 1 | Cumulative hospitalization-free survival following hospital discharge stratified by the change in NT-proBNP concentration during HF hospitalization. Change in NT-proBNP levels during hospitalization was the strongest independent predictor of death or hospital readmission. Abbreviations: HF, heart failure; NT-proBNP, N-terminal proB-type natriuretic peptide. Permission obtained from Wolters Kluwer Health © Bettencourt P. *et al.* N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation* **110**, 2168–2174 (2004).

Richards and colleagues reported a possible interaction between NT-proBNP concentration and the benefit of carvedilol in trials of patients with ischemic left ventricular dysfunction who were randomly assigned to receive carvedilol or placebo.[36,37] They observed that only patients with NT-proBNP (combined with norepinephrine or adrenomedullin) levels greater than the median appeared to benefit from treatment with carvedilol. By contrast, there appeared to be no appreciable benefit from carvedilol in patients with NT-proBNP levels below the median. However, subsequent studies have failed to confirm these findings. In the larger COPERNICUS trial,[38] all patients appeared to benefit from carvedilol therapy regardless of baseline NT-proBNP concentration. Similarly, analyses from randomized trials of other HF therapies, including ACE inhibitors[39] and cardiac resynchronization,[40] have not observed a significant interaction between natriuretic peptide concentration and treatment benefit.

Clinical trials

The completed trials that have examined a natriuretic-peptide-guided approach to the outpatient management of patients with HF are summarized in Table 1.

The Christchurch New Zealand pilot trial

A natriuretic-peptide-guided approach to the management of HF was first tested in a pilot study of 69 patients in Christchurch, New Zealand by Troughton and colleagues.[41] In this study, outpatients with symptomatic HF (NYHA class II–IV) and impaired systolic function (left ventricular ejection fraction [LVEF] <40%) were enrolled and randomly assigned to receive therapeutic strategies guided either by NT-proBNP levels or by a clinical score based on signs and symptoms of HF. For patients in the

Table 1 | Design of trials investigating a natriuretic peptide-guided approach to outpatient HF therapy

Trial name and reference	*n*	Study population	Natriuretic peptide target	Control group(s)	Follow-up	Primary endpoint(s)
The Christchurch New Zealand pilot trial[41]	69	Enrolled at hospital discharge LVEF <40% NYHA class III–IV	NT-proBNP <1,691 ng/l	Framingham HF score <2	9.5 months (median)	Cardiovascular death or hospitalization
STARS-BNP[42]	220	Stable outpatients Optimal background therapy LVEF <45% NYHA class II–III	BNP <100 ng/l for first 3 months after randomization	Clinical judgment	15 months (months)	Unplanned HF hospitalization or HF death
STARBRITE[43]	130	Enrolled at hospital discharge LVEF ≤35% NYHA class III–IV	BNP<2x hospital discharge	Standardized congestion score	90 days	Hospitalization-free survival
TIME-CHF[45]	499	Age ≥60 years LVEF ≤45% NYHA class II–IV Hospitalized with HF in past year NT-proBNP >2x upper limit of normal	NT-proBNP <400 ng/l if <75 years old or <800 ng/l if ≥75 years old	NYHA class I or II	18 months	Hospitalization-free survival and quality of life
BATTLESCARRED[46]	364	Symptomatic HF with preserved or reduced LVEF Recent hospitalization with HF (<2 weeks) NT-proBNP >400 ng/l	NT-proBNP <1,300 ng/l	Standardized HF score or standard care	2.8 years (median)	Total mortality and death or HF hospitalization
PRIMA[47]	345	Hospitalized with HF Preserved or reduced LVEF NT-proBNP >1,700 ng/l at hospital admission NT-proBNP drop by >10% before hospital discharge	NT-proBNP at discharge or at 2 weeks' follow-up	Clinical judgment	1.9 years (median)	Hospitalization-free survival

Abbreviations: BNP, B-type natriuretic peptide; HF, heart failure;' LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal B-type natriuretic peptide.

natriuretic peptide arm, therapy was increased in a stepwise fashion according to a predetermined algorithm until NT-proBNP targets were met (<1,691 ng/l).

At the end of the study (median follow-up 9.5 months), the incidence of the composite primary end point of cardiovascular death, hospital admission, or HF decompensation was significantly reduced in the group guided by NT-proBNP levels compared with the group guided by standardized clinical assessment (19 versus 54 events, $P = 0.02$; Figure 2). However, there were no observed differences between the two groups in terms of quality of life, renal function, or HF symptoms. Therapy changes were more frequently undertaken in the NT-proBNP-guided group, including uptitration of ACE inhibitors and initiation of spironolactone. For patients in the NT-proBNP arm, the improvement in clinical outcomes was accompanied by a significant reduction in NT-proBNP levels, which was not observed in patients who were clinically managed.

A key limitation of the Christchurch study was that very few patients received optimum background medical therapy for HF, such as β-blockers or spironolactone. Despite this limitation and the relatively small sample size, the Christchurch experience sparked great interest in a natriuretic peptide-guided approach to HF management and paved the way for subsequent trials.

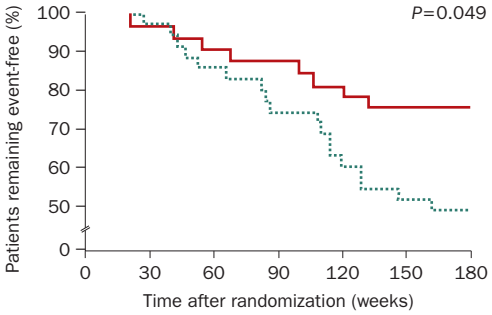
The STARS-BNP trial

The STARS-BNP trial[42] was the first large trial to demonstrate improved outcomes using a natriuretic peptide-guided approach in patients with HF. The investigators enrolled 220 participants with LVEF <45% and NYHA class II or III from 17 hospitals in France. These individuals were randomly assigned to standard care (according to established guidelines) or standard care plus BNP reduction to <100 ng/l. Patients were required to be receiving optimum background therapy, unless not tolerated, and to have been on stable doses of HF medications for 1 month before enrollment. Titration of medication in both treatment arms was left to the physician's discretion.

During follow-up (median 15 months), the BNP-guided strategy was associated with a greater than 50% reduction in the incidence of HF-related death or hospitalization for HF when compared with standard care (24% vs 52%, $P < 0.001$). This difference was driven primarily by a reduction in the number of hospitalizations for HF. Notably, patients in the BNP-guided arm were seen by their physician more than twice as frequently, and had the medication changed more frequently, during the initial 3-month titration phase than were patients whose treatment was not guided by BNP. The mean doses of ACE inhibitors and β-blockers were significantly higher in the BNP group than the standard-care group, whereas the mean increase in furosemide dose was similar in both treatment arms during the first 3 months after randomization (Figure 3). Although mean BNP levels were significantly reduced in the BNP-guided arm, only 33% of participants in the trial achieved their target BNP value of <100 ng/l.

The STARBRITE trial

Although the Christchurch[41] and STARS-BNP[42] trials yielded promising results, subsequent studies have not



Number at risk							
BNP guided	33	31	29	28	26	25	24
Clinically guided	36	34	31	27	23	21	17

Figure 2 | The primary outcome of the pilot trial in Christchurch, New Zealand. These curves shows survival free from death or HF among patients randomly assigned to therapy guided by serial NT-proBNP levels (solid red line) versus standard clinical decision-making (dashed line). Abbreviations: HF, heart failure; NT-proBNP, N-terminal proB-type natriuretic peptide. Reprinted from *The Lancet* **355**, Troughton R. W. *et al.* Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Pages 1126–1130, Copyright (2000), with permission from Elsevier.

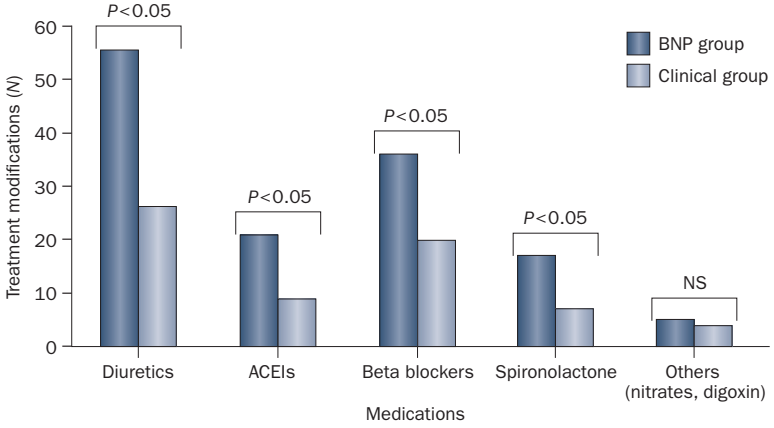


Figure 3 | Treatment modifications in the STARS-BNP trial. Diuretics, ACE inhibitors, β-blockers and spironolactone were all modified more frequently in the BNP-guided treatment arm than in the clinically managed group. Abbreviations: ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide. Reprinted from the *Journal of the American College of Cardiology* **49**, Jourdain P. *et al.* Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. Pages 1733–1739, Copyright (2007), with permission from Elsevier.

demonstrated such a clear benefit from a natriuretic-peptide-guided approach to HF management. The investigators of the STARBRITE trial[43] enrolled 130 patients who had been hospitalized with HF at three centers in the US. Patients with systolic dysfunction (LVEF ≤35%) and symptomatic HF (NYHA class III–IV) were randomly assigned to therapy guided by a standardized congestion score versus guidance by BNP levels. For patients in the BNP-guided arm, clinicians were instructed to titrate diuretics to target a BNP less than twice the value obtained at the time of hospital discharge or an alternate BNP target if deemed appropriate by the clinician.[44]

After 90 days of follow-up, patients randomly assigned to the BNP-guided arm had longer hospitalization-free survival, although this finding was not statistically significant (hazard ratio [HR] 0.72, 95% CI 0.41–1.25, $P=0.25$). ACE inhibitor use was significantly more common in the BNP-guided arm ($P=0.03$). Perhaps surprisingly, there were numerically more frequent uptitrations of diuretics in the arm guided by clinical assessment alone, although not statistically significant ($P=0.11$). Renal function and blood pressure were similar between groups.[43]

Notably, there were important differences between the STARS-BNP[42] and STARBRITE[43] studies. Patients enrolled in the STARBRITE trial had been discharged less than 72 h after an HF hospitalization and all were severely symptomatic (NYHA class III or IV). By contrast, patients enrolled in the STARS-BNP trial were outpatients receiving a stable dosage of HF medications for 1 month before enrollment. Moreover, the target BNP level in the STARS-BNP trial (<100 ng/l) was arguably more aggressive than in STARBRITE (less than twice the BNP level at hospital discharge). Finally, the sample size was smaller and the duration of follow-up much shorter (90 days versus 15 months) for the STARBRITE trial than in the STARS-BNP study and the former might, therefore, have been underpowered to test its primary hypothesis.

TIME-CHF

TIME-CHF[45] was designed to evaluate an NT-proBNP-guided strategy versus symptom-guided therapy in patients with HF aged 60 years or older. A total of 499 patients with symptomatic HF (NYHA class II–IV), a history of HF hospitalization during the preceding year, and a baseline NT-proBNP level ≥400 pg/ml (for patients younger than 75 years) or ≥800 pg/ml (for patients 75 years or older) were enrolled from 15 centers in Switzerland and Germany. Patients in the study could have either a preserved or reduced LVEF. Clinicians managing patients in the symptom-guided therapy arm were instructed to uptitrate therapy to reduce symptoms to NYHA class I or II. For patients in the NT-proBNP-guided arm, however, clinicians uptitrated therapy to target an NT-proBNP level less than two times the upper limit of normal (NT-proBNP <400 ng/l if <75 years old, or NT-proBNP < 800 ng/l if ≥75 years old), in addition to a NYHA class of II or less.

The two primary end points of the trial were survival free of all-cause hospitalization and quality of life. After 18 months of follow-up, survival free of all-cause hospitalization was not significantly different between the two groups (HR 0.91, 95% CI 0.72–1.14, $P=0.39$). Although quality of life improved significantly in both groups, this difference was not statistically different between treatment arms. Furthermore, as in the STARS-BNP trial,[42] patients randomly assigned to the NT-proBNP-guided group had significantly fewer hospitalizations for heart failure (HR 0.68, 95% CI 0.50–0.92, $P=0.01$), which was a key secondary end point. In addition, the investigators observed an apparent interaction between patient age and the benefit of a BNP-guided strategy, such that an NT-proBNP-guided strategy reduced HF hospitalizations only in patients younger than 75 years (P for interaction = 0.02). The

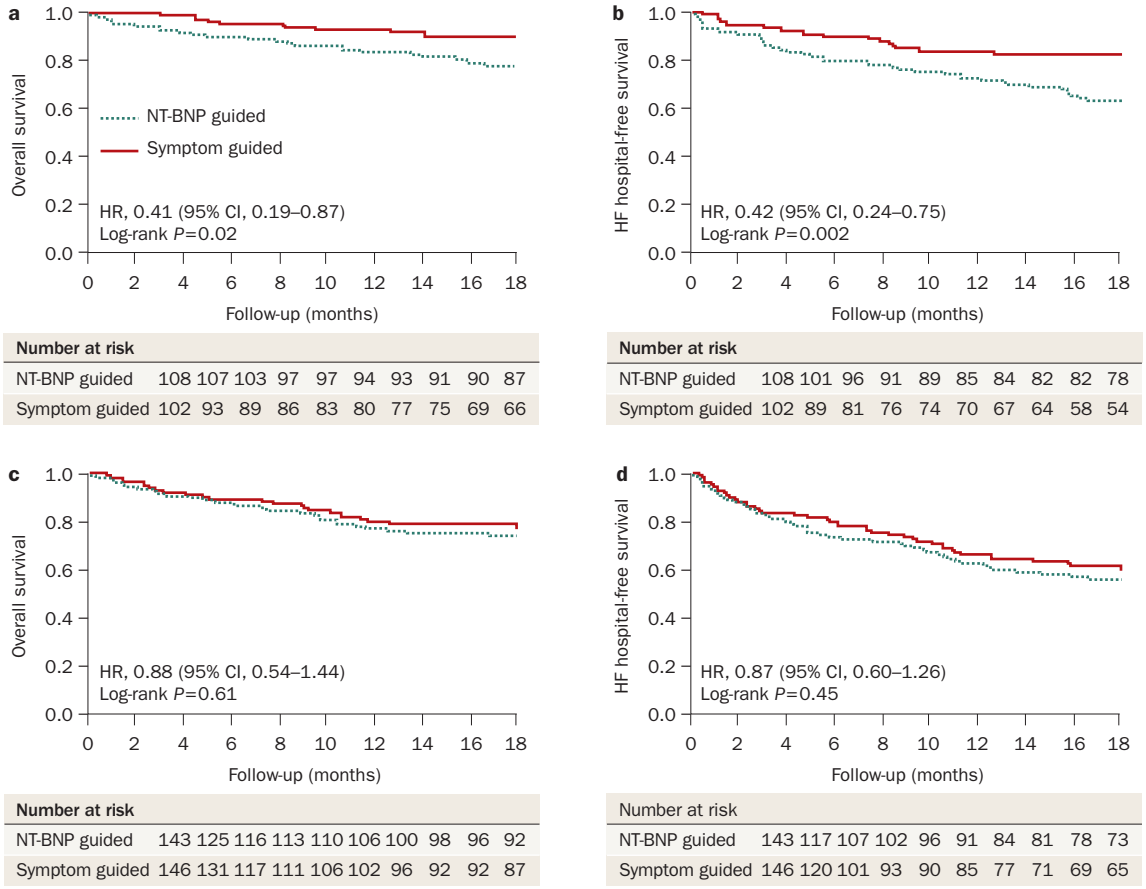


Figure 4 | Clinical outcomes stratified by treatment arm and patient age in the TIME-CHF trial. In patients younger than 75 years (**a**, **b**), a strategy guided by NT-proBNP level reduced hospitalization for heart failure and mortality. This benefit was not observed in patients older than 75 years (**c**, **d**). Abbreviation: NT-proBNP, N-terminal proB-type natriuretic peptide. Reprinted from *JAMA*, January 28 2009, **301**, 383–392. Copyright © (2009) American Medical Association. All rights reserved.

NT-proBNP-guided strategy was also associated with significant reductions in mortality (HR 0.41, 95% CI 0.19–0.87, log rank $P=0.02$) and HF hospitalizations (HR 0.42, 95% CI 0.24–0.75, log rank $P=0.002$) in this younger subset of patients. By contrast, participants aged 75 years or older did not appear to benefit from a NT-proBNP-guided strategy and were more frequently observed to have serious adverse events (Figure 4).

This observed discrepancy in outcomes for older versus younger patients could, in part, be explained by differences in baseline characteristics. Patients aged 75 years or older were more likely to be women, have a history of hypertension, stroke or atrial fibrillation, and to have impaired renal function than their younger counterparts. Older patients were also more likely to have a higher LVEF than those aged younger than 75 years, which could further explain the lack of an apparent benefit from uptitration of therapy, since there are fewer therapies with established benefit in the management of patients with HF with preserved systolic function.

Although individuals in the NT-proBNP-guided arm were more likely to receive higher doses of ACE inhibitors and β-blockers, or to be treated with spironolactone or eplerenone, the relative decrease in NT-proBNP levels after 6 months was similar between treatment arms. Thus, despite greater intensification of therapies and fewer HF hospitalizations in the NT-proBNP-guided arm, the reduction in NT-proBNP levels did not differ between groups. Therefore, the correlation between prognosis and a reduction in natriuretic peptide concentration might not be as strong as previously believed. To that end, natriuretic peptide concentration might not always decrease in response to therapy intensification; this finding is relevant to physicians who use natriuretic peptide levels to titrate therapy.

The BATTLESCARRED trial

The results of the BATTLESCARRED trial[46] were presented at the AHA Scientific Sessions in 2008. The investigators enrolled 364 patients, who had been hospitalized with HF at a single center in Christchurch, New Zealand, and randomly assigned them to one of three treatment arms—usual care, intensive clinical management, or NT-proBNP-guided therapy. Patients enrolled in the trial could have either a preserved or depressed LVEF. After 12 months of follow-up, all-cause mortality was reduced by 50% in patients assigned to intensive clinical management or NT-proBNP-guided therapy ($P=0.028$ for both), as compared with usual care. Mortality was identical in the NT-proBNP and intensively managed groups. After 2 and

3 years of follow-up, however, the two intensive management treatment strategies were no longer significantly better than usual care in terms of mortality.

As was observed in TIME-CHF,[45] there appeared to be a significant interaction between patient age and the benefit of an NT-proBNP-guided approach in the BATTLESCARRED trial. In patients aged younger than 75 years, mortality was consistently lower in the NT-proBNP-guided group after 1, 2, and 3 years follow-up, as compared with the usual-care arm. There was no apparent benefit with any strategy in patients aged over 75 years. In addition, 3-year mortality was significantly reduced in the NT-proBNP guided group in patients younger than 75 years, as compared with intensive clinical management ($P = 0.048$); however, this finding should be considered in the context of testing multiple hypotheses and the risk of detecting a false positive.

The BATTLESCARRED trial is notable because two intensive-management treatment strategies were compared with usual care. This type of trial design provides insight into whether NT-proBNP guidance is primarily useful for encouraging more frequent uptitation of HF medications or whether it provides unique information for optimizing HF therapy in a given individual. Although there was a trend toward fewer adverse events with NT-proBNP-guided therapy, there was no clear advantage with this approach over more intensive clinical management. Further trials will be needed to establish the superiority of natriuretic peptide-guided approach in patients under the age of 75 years.

The PRIMA Trial

The results of the PRIMA trial[47] were presented at the ACC Scientific Session in 2009. This study included 345 patients who were hospitalized with HF and had elevated NT-proBNP levels (≥1,700 ng/l). By contrast to many other trials, patients with renal dysfunction were eligible for enrollment. After NT-proBNP levels had decreased by ≥10% (>850 ng/l) in response to treatment for HF, patients were randomly assigned to undergo NT-proBNP-guided or clinically guided therapy. Rather than using a common NT-proBNP target for all patients in the natriuretic peptide arm, clinicians were asked to target an NT-proBNP concentration from the time of hospital discharge or after 2 weeks follow-up, whichever value was lower.

During follow-up (median 23 months), the number of days that patients were alive and not hospitalized did not differ significantly between treatment arms (685 vs 664, $P = 0.49$). Neither did mortality differ significantly between the two groups (26.5% vs 33.3%, $P = 0.20$). The only medication that was titrated significantly more frequently in the NT-proBNP-guided arm was diuretics. The prespecified, individualized NT-proBNP target level was achieved in 80% of patients in the NT-proBNP arm, far more than in the STARS-BNP trial[42] or the TIME-CHF,[45] which used a common natriuretic peptide target for all participants.

As with the STARBRITE trial,[43] the PRIMA study[47] is notable for individualizing the target natriuretic peptide range for each patient. Given the known interindividual variability in natriuretic peptide levels, it is intuitive that a single natriuretic peptide target level might not be appropriate for all patients. However, there seemed to be less frequent intensification of therapies in the natriuretic-peptide-guided arms of the STARBRITE and PRIMA trials, which could indicate that clinicians should be targeting a more aggressive natriuretic peptide concentration than the concentration at the time of discharge after hospitalization for HF. The optimum target range for individual-specific BNP or NT-proBNP levels will need to be evaluated in future trials.

Conclusions

During the past several years, the measurement of natriuretic peptides has rapidly moved from virtual obscurity to widespread use. Natriuretic peptides are now recognized as a valuable tool in the evaluation of dyspnea, as well as for risk stratification in patients with HF. As a consequence, many clinicians have adopted the routine measurement of natriuretic peptides in the outpatient setting to assist with the management of HF. However, the randomized trials that have evaluated this approach have thus far yielded inconsistent results. Synthesizing the data across existing trials is difficult because of variations in study populations, interventions, duration of follow-up, and primary end points. The generalizability of these results to patients with HF in general remains unclear, since most of the trials excluded patients with renal failure or hypotension, and those who could not tolerate dose escalation of medications. The trials are also limited by relatively small sample sizes and observed trends cannot, therefore, be demonstrated with statistical certainty. Furthermore, the nature of the interventions makes incorporation of a double-blind design complicated, which in turn introduces the possibility of bias.

Despite these limitations, the weight of the available evidence suggests that a natriuretic-peptide-guided approach could reduce hospitalizations for HF in patients under the age of 75, as compared with usual therapy. Much of the benefit from this approach is likely to be explained by improved adherence to medication and uptitration of therapies with established value in patients with HF. However, at this time, there is no evidence to support the routine measurement of natriuretic peptides in the outpatient setting for patients over the age of 75 years. Additional well-powered trials will be important for further establishing natriuretic peptide goals and the clinical benefit of a natriuretic-peptide-guided approach to HF management.

Review criteria

This article is based on a comprehensive search of papers in the PubMed database. Search terms included "natriuretic peptides", "heart failure", and "clinical trials". The reference lists of the articles identified during this search were checked for additional publications. Abstracts presented at major scientific cardiovascular meetings since January 2005 were also reviewed.

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