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

Michelle O’Donoghue and Eugene Braunwald

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.


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. 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. 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; 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. In 1964, electron microscopy revealed the presence of secretory granules in the atrial myocyte. 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. 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. 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. 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 so be measured in plasma as NT-proBNP.

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

**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. 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. 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.

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, 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. 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 decompenated 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. 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. They 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.\(^{23,25}\) 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 underline 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 titration 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
Despite this limitation and the relatively small sample size, therapy for HF, such as β-blockers or spironolactone, very few patients received optimum background medical therapy changes were more frequently undertaken in the NT-proBNP-guided arm, 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 was the first large trial to demonstrate improved outcomes using a natriuretic peptide-guided approach to HF management. Although the Christchurch41 and STARS-BNP42 trials yielded promising results, subsequent studies have not

<table>
<thead>
<tr>
<th>Trial name and reference</th>
<th>n</th>
<th>Study population</th>
<th>Natriuretic peptide target</th>
<th>Control group(s)</th>
<th>Follow-up</th>
<th>Primary endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Christchurch New Zealand pilot trial41</td>
<td>69</td>
<td>Enrolled at hospital discharge LVEF &lt;40% NYHA class III–IV</td>
<td>NT-proBNP &lt;1,691 ng/l</td>
<td>Framingham HF score &lt;2</td>
<td>9.5 months (median)</td>
<td>Cardiovascular death or hospitalization</td>
</tr>
<tr>
<td>STARS-BNP42</td>
<td>220</td>
<td>Stable outpatients Optimal background therapy LVEF &lt;45% NYHA class II–III</td>
<td>BNP &lt;100 ng/l for first 3 months after randomization</td>
<td>Clinical judgment</td>
<td>15 months (months)</td>
<td>Unplanned HF hospitalization or HF death</td>
</tr>
<tr>
<td>STARBRITE43</td>
<td>130</td>
<td>Enrolled at hospital discharge LVEF ≤35% NYHA class III–IV</td>
<td>BNP &lt;2x hospital discharge</td>
<td>Standardized congestion score</td>
<td>90 days</td>
<td>Hospitalization-free survival</td>
</tr>
<tr>
<td>TIME-CHF45</td>
<td>499</td>
<td>Age ≥60 years LVEF ≤45% NYHA class II–IV Hospitalized with HF in past year NT-proBNP &gt;2x upper limit of normal</td>
<td>NT-proBNP &lt;400 ng/l if &lt;75 years old or &lt;800 ng/l if ≥75 years old NYHA class I or II</td>
<td>18 months</td>
<td>Hospitalization-free survival and quality of life</td>
<td></td>
</tr>
<tr>
<td>BATTLESCARRED46</td>
<td>364</td>
<td>Symptomatic HF with preserved or reduced LVEF Recent hospitalization with HF (&lt;2 weeks) NT-proBNP &gt;400 ng/l</td>
<td>NT-proBNP &lt;1,300 ng/l</td>
<td>Standardized HF score or standard care</td>
<td>2.8 years (median)</td>
<td>Total mortality and death or HF hospitalization</td>
</tr>
<tr>
<td>PRIMA47</td>
<td>345</td>
<td>Hospitalized with HF Preserved or reduced LVEF NT-proBNP &gt;1,700 ng/l at hospital admission NT-proBNP drop by &gt;10% before hospital discharge</td>
<td>NT-proBNP at discharge or at 2 weeks’ follow-up</td>
<td>Clinical judgment</td>
<td>1.9 years (median)</td>
<td>Hospitalization-free survival</td>
</tr>
</tbody>
</table>

Abbreviations: BNP, B-type natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal B-type natriuretic peptide.
Other
Spironolactone
Beta block
A
150
180
120
30

Figure 2 | The primary outcome of the pilot trial in Christchurch, New Zealand. These curves show 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.

demonstrated such a clear benefit from a natriuretic-peptide-guided approach to HF management. The investigators of the STARBRITE trial43 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.

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.

Notably, there were important differences between the STARS-BNP42 and STARBRITE43 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-CHF45 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
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 up titration 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 BATTELESARRED trial

The results of the BATTELESARRED trial 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 ejection fraction, and to have impaired renal function than their younger counterparts.

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.

**Figure 4** | Clinical outcomes stratified by treatment arm and patient age in the TIME-CF 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.
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, 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 up titration 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 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, $P=0.499$). 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 or the TIME-CHF, which used a common natriuretic peptide target for all participants.

As with the STARBRUTE trial, the PRIMA study 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 STARBRUTE 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 up titration 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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