Natriuretic peptides in heart failure

Congestive heart failure (CHF) is the leading cause of adult hospitalization in the USA, and despite advancements in treatment, the disease remains a major clinical challenge. The primary symptom of CHF is dyspnea; however, it is often difficult to distinguish between cardiac and other unrelated causes of this symptom. The synthesis, storage and release of B-type natriuretic peptide (BNP) from the ventricular myocytes is strongly induced during acute episodes of ventricular-wall tension or stretch. Thus, BNP levels can be easily measured and have proven extremely useful at the point of care and can be used to differentiate cardiac from pulmonary etiologies of dyspnea. In addition to its diagnostic utility, it also has prognostic value and may help guide the treatment of patients with CHF. For these reasons, natriuretic peptides have established themselves in recent years as cornerstones in the diagnosis, treatment and prognosis of patients with heart failure, and it is likely that future algorithms will incorporate BNP levels and other clinical indicators to guide critical-care physicians in making management decisions for their CHF patients.

KEYWORDS: B-type natriuretic peptide ■ cardiac troponin ■ cardiovascular biomarker ■ heart failure ■ mid-region biomarkers

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Heart failure (HF) is a rising epidemic in the USA currently affecting 5.7 million Americans [1]. More than 3 million hospital admissions per year are HF-related, and of these patients, approximately 35% will suffer HF-related readmissions or death within 60 days [1]. HF is divided into systolic HF and diastolic HF (DHF). DHF incorporates approximately 30–50% of patients with clinical signs and symptoms of congestive heart failure (CHF). The estimated direct and indirect cost of HF in the USA for 2009 is US$37.2 billion [1], and as the leading cause of hospital admission among patients over the age of 65 years [2], it is clear that this growing public health concern holds significant health and financial consequences for our nation.

Physicians have traditionally relied upon clinical assessment of symptoms and hemodynamics in the management of HF; however, this approach is often limited by several factors, including the individual skill of the clinician, the variability and nonspecificity of symptoms, and the costly and time-consuming nature of conventional tests for cardiac function [3,4]. For these reasons, natriuretic peptides (NPs) have established themselves in recent years as cornerstones in the diagnosis, treatment and prognosis of patients with HF [5–7]. This article serves to summarize the current clinical use and research in the field of NPs and HF, as well as shed light on the future and how we might continue to further our understanding of NPs and other biomarkers to improve patient care.

Natriuretic peptides: the basics

The NPs are a family of structurally and functionally related peptide hormones targeted at protecting the cardiovascular system from the effects of fluid overload. The three major NPs, atrial NP (ANP), B-type NP (BNP) and C-type NP, share a common 17-amino acid ring structure and are released by cardiomyocytes in response to mechanical wall stretch, ventricular dilation and/or increased filling pressures caused by fluid overload. ANP is synthesized and released preferentially by the atria, while C-type NP is secreted predominantly by the myocardial endothelial cells [8]. BNP is primarily synthesized and released by the ventricles; however both ANP and BNP can be synthesized by either chamber under pathologic conditions [9]. Over the years, BNP has emerged as the superior marker for HF, thus, the focus here will be on BNP. However, it should be noted that many of BNP's effects are common to NPs.

In the setting of volume overload or increased filling pressures, the mechanical stretch on the ventricular walls induces the synthesis of pre-proBNP$_{1–134}$, which is subsequently cleaved to the prohormone proBNP$_{1–108}$, and finally into the biologically active peptide BNP$_{1–32}$

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and its inactive N-terminal (NT) fragment, NT-proBNP. Once released, BNP circulates to target sites where it binds preferentially to the membrane-bound NP receptor (NPR)-A. This binding triggers a cGMP signaling cascade, and works to dramatically reduce volume overload and hypertension in patients. BNP is then quickly removed from circulation (half-life of 18–22 min) by both NPR-mediated endocytosis and endopeptidase degradation [10]. By contrast, NT-proBNP is cleared from circulation predominantly by renal excretion, rendering NT-proBNP less susceptible to fluctuations in circulating levels as well as a markedly longer half-life of 60–120 min [10]. In general, BNP and NT-proBNP levels are reasonably correlated, and while their values are not interchangeable, either can be used in patient-care settings.

NPs in HF diagnosis

The clinical diagnosis of HF can be challenging as clinical symptoms, such as dyspnea, are often nonspecific, and accurate histories are difficult to obtain from an acutely distressed patient. In addition, routine laboratory values, electrocardiograms and x-rays are often inadequate to make an appropriate diagnosis [11], while echocardiography is limited in acute settings.

The landmark Breathing Not Properly Multinational Study was a seven-center, prospective study irrefutably establishing BNP as an invaluable addition to clinical judgment in the acute diagnosis of HF in dyspneic patients [5]. A total of 1586 dyspneic patients presenting to the emergency department (ED) had their BNP levels measured upon arrival. BNP levels were found to be more accurate in diagnosing HF than clinical exam alone (area under the curve [AUC]: 0.91). Using a BNP cutoff point of 100 pg/ml, 90% sensitivity and 76% specificity in the diagnosis of HF was achieved.

In the ProBNP Investigation of Dyspnea in the ED (PRIDE) study, NT-proBNP levels were measured upon the arrival of 599 dyspneic patients to the ED [12]. Patients with acute HF had a median NT-proBNP level greater than 4000 pg/ml in comparison to the median NT-proBNP level of 130 pg/ml in patients without HF. An NT-proBNP cutoff point of 300 pg/ml was deemed sufficient to exclude HF, thereby introducing a cost-effective measure to screen patients before further costly exam. In order to 'rule in' HF, the PRIDE investigators used two age-dependent cutoff points, and demonstrated that, alongside clinical assessment, these NT-proBNP cutoff points were diagnostically superior to clinical judgment or NT-proBNP alone (AUC: 0.94 vs 0.90, respectively).

These findings present important cost-saving implications for the reduction of rates of readmission, hospital-stay duration and direct costs of HF events. The BNP Peptide for Acute Shortness of Breath Evaluation (BASEL) study randomized 425 patients to a single BNP measurement in the ED [13]. BNP measurements were associated with a 10% decrease in both hospital and intensive care unit admissions, and admitted patients had a 3-day decreased median length of stay without any increase in deaths or rehospitalizations. Perhaps most notably, the use of BNP led to a total cost reduction of 26%, which could represent hundreds of millions in savings if applied nationwide. Similar improvements in diagnoses and cost savings were observed in the Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) study, in which 500 dyspneic patients presenting to the seven different EDs had their NT-proBNP levels measured upon arrival [14].

Biomarkers have also been studied in the setting of HF with preserved ejection fraction. In a study by Grewal *et al.*, the Candesartan in HF: Assessment of Reduction in Mortality and Morbidity (CHARM) trial, NP values were used in conjunction with clinical parameters to predict the severity of diastolic dysfunction [15]. Using echocardiographic indices, investigators grouped 181 patients into normal/mild versus moderate/severe diastolic dysfunction cohorts. Elevated NP levels (NT-proBNP and BNP above 600 and 100 pg/ml, respectively) were demonstrated to be predictive of moderate/severe diastolic dysfunction.

Caveats

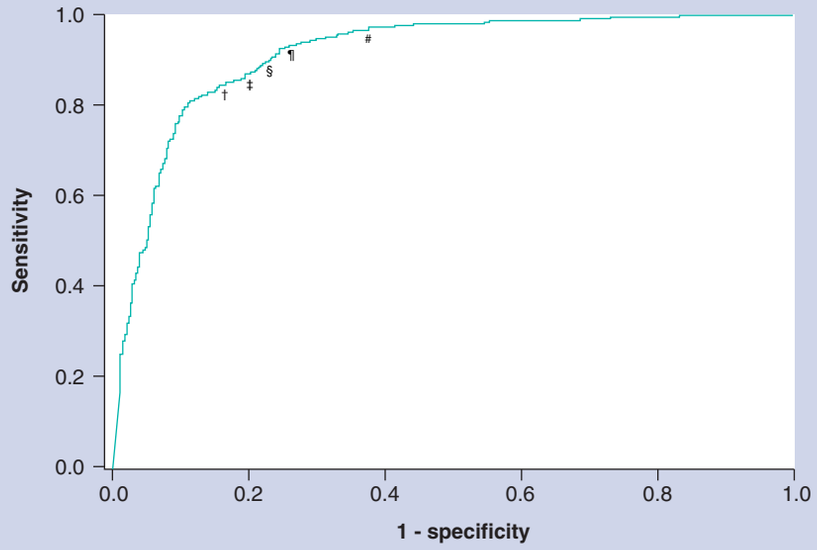
Of note, there are several clinical settings apart from the typical acute HF scenario in which BNP levels may be elevated or lower than expected, as listed in Figure 1. NP levels are known to be higher in older patients and in women [16,17]. Investigators have suggested that age-related decline in myocardial function and NP clearance mechanisms, as well as estrogen in women, might be partly responsible for these elevated NP levels. BNP levels have also been observed to be elevated in dyspneic patients with a history of HF, but without an acute HF decompensation. These patients' BNP levels tended to be intermediate, in between those of patients without a HF diagnosis and those of HF patients in an acutely decompensated state [5].

Renal impairment

Higher NP levels have been consistently observed in HF patients with chronic kidney disease (CKD) [18,19]. Some investigators have stipulated that the higher prevalence of concomitant cardiac abnormalities in CKD patients cause the ventricles to release more NPs into the bloodstream, while others cite reduced renal clearance of the NPs by injured nephrons [5]. This phenomenon of concomitant cardiac and renal dysfunction has become known as cardiorenal syndrome [20]. While the exact mechanism of cardiorenal syndrome is not yet understood, it is believed that acute or chronic dysfunction in either the heart or kidneys induces dysfunction in the other organ. Thus, while the reason for higher circulating NP levels in CKD patients is still under investigation, cardiorenal syndrome has been largely implicated. The interaction between NT-proBNP levels and CKD was evaluated in a secondary analysis of the previously described PRIDE study [18]. Patients with CKD had a higher prevalence of CHF, and renal insufficiency was closely related to risk factors for CHF. NT-proBNP values and glomerular filtration rate were found to be inversely and independently related and, accordingly, worsening renal function was associated with cardiac abnormalities found on echocardiography. Although a higher NT-proBNP cutoff point was used in patients with impaired renal function (glomerular filtration rate <60 ml/min/1.73 m^2) versus those with normal renal function, the NT-proBNP test was still extremely sensitive and specific to HF diagnosis. In addition, NT-proBNP remained the strongest independent predictor of mortality, irrespective of renal function. McCullough *et al.* reported a similar interaction between BNP and glomerular filtration rate in an analysis from the Breathing Not Properly Multinational Study [19]. These results suggest that in the case of CHF and CKD coincidence, classic NP-guided algorithms may still be appropriate, but they must be readjusted for renal function.

Obesity

It is well-documented that NP values are markedly lower in obese HF patients than in nonobese patients [21]; however, the implications of such an interaction between NPs and obesity are not yet well understood. In the Breathing Not Properly Multinational Study, there was an almost threefold difference in BNP levels across the study population's BMI extremes [5]. In another study, Mehra *et al.* divided 318 CHF patients into three BMI cohorts: lean, overweight and obese (BMI <25, 25–29 and ≥30 kg/m^2, respectively) [21]. BNP values trended downwards across all three groups, and were significantly lower in obese patients than in nonobese patients.



BNP (pg/ml)	Sensitivity	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Accuracy
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

Figure 1. Receiver-operating-characteristic curve for various cutoff levels of B-type natriuretic peptide in differentiating between dyspnea due to congestive heart failure and dyspnea due to other causes. Area under the receiver-operating-characteristic curve: 0.91 (95% CI: 0.90–0.93).
†BNP: 150 pg/ml; ‡BNP: 125 pg/ml; §BNP: 100 pg/ml; ¶BNP: 80 pg/ml; #BNP: 50 pg/ml.
BNP: B-type natriuretic peptide; CI: Confidence interval.
Reproduced with permission from [5].

Despite the distinct disparity in BNP levels across BMI groups, the event rate among Mehra *et al.*'s obese patients (25%) was found to be lower than that of the nonobese patients (29%) through 1 year. This finding, also documented in other studies, has become widely known as 'the obesity paradox.' It appears that although obesity is a known risk factor for cardiovascular disease, obese HF patients have equal or better rates of survival than nonobese patients.

Recent studies suggest that the suppression of the BNP response and the early manifestation of HF in obese patients may be accounted for, in part, by increased NPR-mediated BNP clearance in adipose tissue, as well as an intimate relationship between BNP and lipolysis [21]. Indeed, the mice studies by Miyashita *et al.* suggest that NP signaling cascades can promote muscle mitochondrial proliferation, as well as increased fat oxidation to

protect against diet-induced obesity and insulin resistance [22]. However, upon multivariate analysis of the Breathing Not Properly Multinational Study population, adjusting for gender, renal function, race, CHF severity and abnormal S3 sounds, no independent correlation between BNP and BMI could be found. Therefore, investigators concluded that much of the inverse relationship between BNP and BMI might, in fact, be caused by these clinical confounders and not by any specific NP–obesity interaction [5].

Gray zone

In many clinical settings, investigators have not been able to identify a single cutoff point to empirically rule in or rule out every patient with HF. This observation is in keeping with clinically guided, often nonspecific algorithms in which binary 'black or white' diagnoses are customarily inappropriate. It appears that two cutoff points are necessary to adequately screen patients and reduce costs: one to effectively rule out HF in mildly dyspneic patients and eliminate unneeded hospitalizations, and another to rule in diagnosis and trigger prompt, appropriate treatment. The problem arises in the gray zone between these two cutoff points in which NP levels cannot be used as consistently to guide management decisions.

Van Kimmenade *et al.* studied 215 patients with intermediate NT-proBNP concentrations, approximately half of whom were diagnosed with HF [23]. Irrespective of their final diagnosis, subjects with 'gray zone' NT-proBNP values were found to have intermediate mortality rates between the high mortality rates of patients with HF and diagnostically high NT-proBNP levels, and the low mortality rates of those without HF and NT-proBNP concentrations less than 300 ng/l. In addition, investigators found that adding specific clinical information to intermediate NT-proBNP values increased diagnostic accuracy, suggesting the inherent utility of a gray zone NT-proBNP value as a signal for further exam.

Investigators documented similar findings in the 153 patients of the Rapid ED Heart Failure Outpatient Trial (REDHOT) study presenting with intermediate BNP values of 100–500 pg/ml [6]. While there was no difference in the perceived New York Heart Association (NYHA) class or rates of admission of these patients, they were found to have fewer events than the diagnostically high BNP cohort, suggesting that irrespective of clinical symptoms, patients with gray zone BNP values have a better prognosis than those in the high level composite.

These two studies demonstrate that a gray zone in patients presenting with acute dyspnea is a major limitation of NPs in daily practice. In this setting, radiographic evidence of pulmonary congestion [24], history of HF [25] and comprehensive Doppler echocardiography at bedside [26] are all extremely useful in patient diagnosis and prognosis.

Almost all of the studies previously described addressed the diagnostic relevance of NPs in patients presenting with acute dyspnea in EDs (i.e., decompensated state). Such results are not relevant in stable patients, and very few data are available in patients with isolated exertional symptoms, which offer evidence that cutoff values for the diagnosis are lower than expected [27–29].

The gray zone for stable patients with exertional symptoms has not yet been clearly defined. In addition, NPs have not yet been proven to be of significant clinical value in screening for CHF in the general population. Therefore, BNP has limited diagnostic value in stable patients with suspected HF, and general practitioners should be cautious in using BNP and NT-proBNP in outpatient settings. An echocardiography remains the gold standard for diagnosing unexplained dyspnea.

NPs in HF prognosis

The prognostic utility of BNP measurements was demonstrated in the multicenter REDHOT study in which BNP levels were demonstrated to be very strong predictors of 90-day outcomes [6]. Among the 464 patients enrolled, patients admitted with BNP levels over 200 pg/ml were at a markedly higher risk for future HF events and mortality in comparison to those with lower BNP levels. ED physician assessment had a poor predictive value, and investigators observed a striking disparity between the ED physicians' perception of CHF severity and the severity determined by BNP levels.

The International Collaborative of NT-proBNP (ICON) study pooled the NT-proBNP results from 1256 subjects recruited from multiple medical centers worldwide, to evaluate the prognostic potential of NT-proBNP in AHF [30]. Similar to BNP, patients with marked elevations in NT-proBNP concentrations had a more than fivefold increase in mortality risk through 76 days.

Continuing data suggest that patients with preserved ejection fraction HF have an associated significant mortality. In patients discharged following DHF exacerbation, Feola *et al.*

demonstrated that higher mean BNP levels (833 ± 604 vs 397 ± 396 pg/ml; p = 0.01) were associated with increased 6-month death and readmission for CHF [31].

Natriuretic peptide levels are equally effective in predicting outcomes for patients with chronic HF. In an analysis of the 4300 stable HF outpatients enrolled in the Valsartan HF (Val-HeFT) trial, patients with the greatest increase in BNP levels had the greatest risk of HF events and mortality, irrespective of treatment [32]. In a substudy of Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), NT-proBNP levels above the median were consistently associated with an increased risk for all-cause mortality or hospitalization for HF in patients with severe CHF, even in those who were clinically euvolemic [33].

As discussed previously, while NPs have been demonstrated to be effective in risk stratification, Doppler echocardiography remains the single most useful diagnostic tool in assessing left ventricular ejection fraction and cardiac abnormalities in patients with the clinical syndrome of HF [34,35]. Therefore, a multiparametric approach based on NPs and comprehensive Doppler echocardiography in this clinical setting is of major importance [36]. Investigators found that tissue Doppler imaging and BNP were powerful and incremental predictors of CHF-related rehospitalizations and deaths, and other conventional predictors did not add further predictive value.

Inpatient management of acute HF

In inpatient settings, NPs have emerged as superior, objective indices of HF severity and treatment adequacy. A patient's circulating NP levels may be thought to consist of two components: a 'dry' baseline component, as well as a 'wet' component, in which increased mechanical pressure and stretching of the ventricles during decompensation causes NP levels to rise [37]. Empirical NP targets have been suggested to optimize diagnosis and prognosis; however, dry NP levels are known to vary appreciably within individuals over time [38], as well as between individuals owing to clinical confounders such as gender, age, BMI and renal function [39]. Thus, universal cutoff points and targets may not always be appropriate.

In practice, a patient's median dry NP value and NP changes during decompensation, treatment and post-treatment may provide the most useful information in making clinical decisions. BNP circulating levels correlate strongly with left ventricle end-diastolic wall stress [15]; therefore, with validated automated and point-of-care assays widely available, NP measurements provide a quick and convenient surrogate measure of HF severity, irrespective of clinical symptoms [40]. In addition, NP values have been demonstrated to fall across diuretic, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, spironolactone and nesiritide-induced cardiac improvements [41], suggesting that NP guidance may prove extremely effective in determining the method and adequacy of HF treatment. As described previously, baseline NP values also offer significant prognostic information, with follow-up NP measurement offering perhaps even more significance. Patients with the greatest fall in plasma NP concentrations have been demonstrated to have the most favorable outcomes [39].

In support of these assertions, Bettencourt *et al.* demonstrated in 50 decompensated HF patients that when comparing between those with either more or less than 30% decrease in NT-proBNP concentrations, those with the greatest decrease had superior outcomes [42]. The investigators also demonstrated that patients discharged with a BNP value less than 250 pg/ml had a very strong prognosis for event-free survival, while failure of BNP levels to decline over hospitalization was a very strong predictor of death and/or readmission. In addition, Bayés-Genís *et al.* demonstrated in 100 HF patients with NT-proBNP measurements over 7 days of hospitalization, that those with a NT-proBNP drop of 50% or less had the highest survival rates, while those with a 15% or more drop were most likely to have future complications [43]. Notably, the NT-proBNP percent change post-treatment was superior to initial NT-proBNP values in the prognostication of patients.

To aid clinicians, Rehman and colleagues have proposed the following algorithm for NP-guided management of AHF patients: NP baseline values should be obtained upon presentation for diagnosis, treatment guidance and in-hospital prognosis [39]. After treatment, a follow-up NP value should be obtained before discharge in order to determine adequacy of treatment and long-term prognosis. For the best outcomes, the investigators proposed the empirical targets of a 30% or less decrease in NP levels over the duration of the hospitalization, with a discharge BNP target of less than 350 ng/l and/or NT-proBNP target of less than 4000 ng/l.

Outpatient management of HF

It has been well documented that NPs can be used in outpatient settings as an important prognostic indicator in outpatients with stable HF [32,44–46], with follow-up BNP measurements sometimes

being even more prognostic than those taken during hospitalization. In the same way that blood pressure is used to guide hypertension management and cholesterol levels for hypercholesterolemia, NP levels, as surrogate for left ventricular function and pulmonary capillary wedge pressure [47], may be used to monitor patients and optimize the complex pharmacotherapy of CHF [37] to reduce the risk of new cardiac events and death.

The STARS-BNP study randomized 220 HF patients to clinically- or BNP-guided treatment with a BNP target of less than 100 ng/l [48]. At 3 months, the BNP cohort was seen twice as often with more changes to their HF medications; however, they were also found to be less likely to decompensate, and had far less HF-related readmissions and deaths through 15 months of follow-up. Troughton and colleagues randomized 69 stable HF patients to NT-proBNP-guided treatment (target <1700 ng/l) and observed similar reductions in HF-related events [49]. In Strategies for Tailoring Advanced HF Regimens in the Outpatient Setting: BNP Versus the Clinical Congestion Score (STARBRITE) study [50], investigators did not find an improvement in outcomes in the BNP-guided cohort, although some have suggested that this difference may stem from the study's use of a higher BNP target and enrolling sicker patients. The BATTLESCARRED [51] and Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) [52] studies produced similarly mixed results, with the NT-proBNP-guided strategies of the BATTLESCARRED trial improving outcomes, while no improvements were observed among the NT-proBNP-guided arm of the TIME-CHF study.

Despite the conflicting findings of these various studies, in a recent meta-analysis of the 918 patients enrolled in the TIME-CHF, STARS-BNP and STARBRIGHT studies, NP-guided medication strategies significantly reduced all-cause mortality, suggesting that overall, NP-guided therapy does appear to improve outcomes among stable HF outpatients [53].

Since there is a considerable amount of intra-individual variation in NP levels depending on how the measurement is made (i.e., point-of-care vs central laboratory), as well as the time frame of the serial measurements, the optimal frequency and time frame in which to monitor NP levels is still under rigorous investigation. Since BNP has a half-life of only minutes, it has been suggested that outpatient NP measurements on a monthly time scale may miss key biological indicators of disease progression. To address this question, the pioneer HF Assessment with BNP in the Home (HABIT) trial will enroll stable HF patients upon discharge from the hospital, and will follow their daily home testing of BNP levels for 60 days. HABIT began enrollment in the summer of 2009 [54].

In patients with advanced HF and ventricular dyssynchrony, several recent trials have shown improvement in quality of life and overall reduction in left ventricular volume indices with resultant increase in left ventricular ejection fraction with the use of cardiac resynchronization therapy (CRT). Outside of quality of life measures and echocardiographic parameters, it can sometimes be difficult to assess the efficacy of CRT with biventricular pacing. Investigators have shown both short- and long-term reductions in serum BNP levels with the use of CRT. This information can be used to help correlate the degree of ventricular reverse remodeling with BNP concentrations demonstrating the effectiveness of these devices [55,56].

The future of biomarkers in HF: a multimarker approach?

Troponin

The cardiac troponins (cTns), cTnT and cTnI, are proteins located in skeletal and cardiac muscle that are responsible for regulating actin and myosin interactions during muscle contraction. Elevated levels of cTns in the serum, described as a 'positive' troponin, suggest myocardial injury or loss of cell membrane integrity. Reversible injury [57], frank myocyte necrosis [58–60] and apoptosis [61–63] have all been described as possible contributing processes; however, further experimental studies are necessary to clearly elucidate the mechanism of troponin release during HF.

Cardiac troponin is well established as a diagnostic and prognostic indicator in patients with acute coronary syndromes; however, its role in acute decompensated HF (ADHF) is still under investigation. In a landmark study, Peacock *et al.* evaluated 84,872 patients with recorded troponin measurements on admission from the Acute Decompensated HF National Registry (ADHERE) to investigate the association between elevated cTn levels and adverse events in hospitalized ADHF patients [64]. Overall, 4240 of these patients were positive for troponin (defined as cTnI ≥1.0 µg/l or cTnT ≥0.1 µg/l), and had an almost fourfold increase in in-hospital mortality when compared with those who were negative for troponin, conclusively demonstrating that independent of other predictive variables, a positive cTn test is associated with higher in-hospital

mortality. Since BNP is also known to be a significant prognostic indicator in HF, Fonarow *et al.* combined the two indices in evaluating 42,636 hospitalized ADHF patients from the ADHERE Registry with recorded BNP and Tn measurements upon admission [65]. The investigators found that using a multimarker strategy for assessing hospitalized ADHF patients added prognostic information to using either marker alone. BNP levels above the median and positive Tn laws were associated with a significantly increased risk of in-hospital mortality. Mortality was 10.2% in patients with BNPs of 840 or less and increased Tn in comparison to 2.2% mortality in those with BNPs less than 840 and Tn not increased, demonstrating that admission BNP and cTn levels are significant, independent predictors of in-hospital mortality in ADHF.

ST2

The novel ST2 marker, a member of the IL-1 receptor family, has generated a great deal of interest as a powerful, independent, as well as complementary, prognostic marker in patients with HF. The *ST2* gene is markedly upregulated in an experimental model of HF [66], and circulating ST2 concentrations are thought to be prognostically meaningful in patients with chronic severe HF [67]. To evaluate the relationship between ST2 levels and outcomes in HF, samples from the 593 dyspneic patients of the PRIDE study were evaluated with ST2 and NT-proBNP measurements [68]. While NT-proBNP was better than ST2 in diagnosing AHF, median concentrations of ST2 upon arrival to the ED were markedly higher among decedents than in survivors at 1 year, as shown in Figure 2. In this study, ST2 augmented the prognostic capability of NT-proBNP and, using a multimarker strategy of both markers, identified subjects with the highest risk for death. Rehman *et al.* found similar results when using both ST2 and BNP levels to identify subjects with the highest risk of mortality [69]. They also found that ST2 has strong biochemical and clinical correlates in patients with acute HF. Specifically, ST2 levels correlated with HF severity, ejection fraction and NP levels.

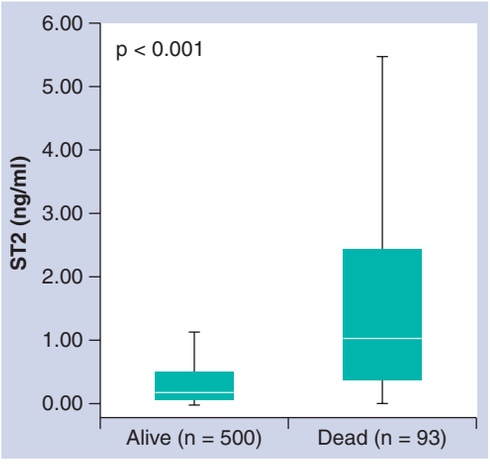


Figure 2. ST2 concentrations at presentation as a function of survival at 1 year. Medians are depicted; boxes represent the 25th and 75th percentile, whereas whiskers represent the 5th and 95th percentile. Reproduced with permission from [68].

Mid-region biomarkers

The mid-regional markers, mid-regional pro-ANP (MR-proANP) and mid-regional proadrenomedullin (MR-proADM), are derived from precursor active peptides (ANP and ADM), which are released into circulation in response to cardiovascular fluid imbalance, as seen with BNP and NT-proBNP. These mid-regional markers are much more stable than their active peptide counterparts, and are easily measured by standard sandwich immunoassay technology, making them incredibly well adapted to clinical settings as surrogate markers for their respective mature hormones.

The Biomarkers in Assessment of CHF (BACH) multinational study evaluated 1636 dyspneic patients presenting to the ED for the diagnostic and prognostic capability of these two markers in comparison to NPs [70].

Mid-regional proANP was found to be non-inferior to BNP in HF diagnosis. Furthermore, when used in a multimarker approach, MR-proANP added significantly to the diagnostic performance of BNP (irrespective of clinical confounders). When used in conjunction with clinical assessment, MR-proANP reduced physician diagnosis indecision by 29%.

Prognostically, MR-proADM was superior to both BNP and NT-proBNP in predicting 90-day mortality in short-of-breath patients arriving to the ED and diagnosed with HF. MR-proADM added significantly to both BNP and NT-proBNP in HF prognosis, and was particularly strong in predicting 30-day survival, as indicated by the area under the receiver-operating curves of MR-proADM, BNP and NT-proBNP (0.739, 0.555 and 0.641, respectively). The BACH investigators concluded that the use of mid-region biomarkers could add significantly to existing diagnostic and prognostic biomarkers, as well as help identify patients who should receive higher priority in the ED.

Future perspective

Despite extensive advances in the understanding and treatment of HF in the last 50 years, HF remains a major health concern with a poor prognosis. The complex etiology and nonspecific symptoms of HF make diagnosis incredibly difficult, and researchers have abandoned the idea of finding a single diagnostic test for HF. However, the continued discovery and refinement of novel biomarker assays, combined with advances in genomics and proteomics promise to transform biomarker research, in which the major challenge will not be the individual discovery of new markers, but rather the optimal combination of markers and other diagnostic tools that will prove most clinically useful. Further studies are needed to test the efficacy of these new markers within a multiparameter strategy in order to develop algorithms for patient diagnosis, treatment, prognosis, and management in daily clinical practice.

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Executive summary

- Within the congestive heart failure (HF) setting, the primary objectives of biomarker testing include: diagnosis, treatment, prognosis and management.
- The natriuretic peptides (NPs) are a family of structurally and functionally related peptide hormones targeted at protecting the cardiovascular system from the effects of fluid overload.
- In the setting of volume overload or increased filling pressures, the mechanical stretch on the ventricular walls triggers B-type NP (BNP) synthesis, which works to dramatically reduce volume overload and hypertension in patients.
- Clinical diagnosis of HF can be challenging owing to nonspecific clinical symptoms, such as dyspnea and lack of efficient, cost-effective tests.
- The landmark Breathing Not Properly Multinational Study irrefutably established BNP as an invaluable adjunct to clinical judgment in the acute diagnosis of HF in dyspneic patients.
- The BNP for Acute Shortness of Breath Evaluation (BASEL) study showed that BNP measurements were associated with decreased hospital admissions and decreased lengths of stay, representing a simple, efficient way to dramatically reduce HF-related hospitalizations and costs.
- NP concentrations are known to be higher in older patients and in women, and BNP levels tend to be elevated in dyspneic patients with a history of HF.
- Higher NP levels have been consistently observed in HF patients with chronic kidney disease, while NP levels are markedly lower in obese HF patients. The implications of these observations are not yet fully understood.
- An intermediate NP value is not entirely uninformative, and should signal further exam, as it may still aid in patient prognosis.
- The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) demonstrated the prognostic utility of BNP measurements as very strong predictors of 90-day outcomes. A BNP-adjudicated prognosis had better predictive value than the emergency department (ED) physician's assessment, which reveals the striking disparity between the ED physicians' perception of congestive HF severity and the severity determined by BNP levels.
- In both inpatient and outpatient settings, NPs have emerged as superior, objective indices of HF severity and treatment adequacy, irrespective of clinical symptoms. However, due to inter-individual variation and various clinical confounders, universal cutoff points and targets may not always be appropriate.
- The future of HF treatment may include using multimarker strategies to diagnose, treat and manage HF patients.
- Cardiac troponin is well established as a diagnostic and prognostic indicator in patients with acute coronary syndromes; however, its role in acute decompensated HF is still under investigation. Peacock *et al.* demonstrated that elevated BNP and troponin levels were associated with a significantly increased risk of in-hospital mortality.
- Circulating ST2 concentrations are thought to be prognostically meaningful in patients with chronic severe HF. Using samples from the ProBNP Investigation of Dyspnea in the ED (PRIDE) study, ST2 augmented the prognostic capability of N-terminal (NT)-proBNP, and using a multimarker strategy of both markers identified subjects with the highest risk for death. Specifically, ST2 levels correlated with HF severity, ejection fraction and NP levels.
- The mid-regional markers, mid-regional pro-atrial NP (MR-proANP) and mid-regional pro-adrenomedullin (MR-proADM) are more stable and easily measured than their precursor active peptides (ANP and ADM), rendering them incredibly well suited to clinical settings as surrogate markers for their respective mature hormones.
- In the multinational Biomarkers in Assessment of Congestive HF (BACH) study, MR-proANP added significantly to the diagnostic performance of BNP (irrespective of clinical confounders). When used in conjunction with clinical assessment, MR-proANP reduced physician diagnosis indecision by 29%.
- Prognostically, MR-proADM was superior to both BNP and NT-proBNP in predicting 90-day mortality in short of breath patients arriving to the ED and diagnosed with HF. MR-proADM added significantly to both BNP and NT-proBNP in HF prognosis, and was particularly strong in predicting 30-day survival.
- The BACH investigators concluded that the use of mid-region biomarkers could add significantly to existing diagnostic and prognostic biomarkers, as well as help identify patients who should receive higher priority in the ED.

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