

Novel Applications of Cardiac Biomarkers in Heart Failure

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Abstract

Cardiac biomarkers, both established and emerging ones, have various novel applications in heart failure. The role of established biomarkers such as natriuretic peptides—both B-type natriuretic peptide (BNP) and N-terminal prohormone brain natriuretic peptide (NT-proBNP)—in acute heart failure has been well studied. The role of natriuretic peptides in the primary care setting and utilization of natriuretic peptides along with clinical evaluation in the treatment of patients with chronic heart failure are promising. In addition, other markers such as cardiac-specific troponins or C-reactive protein (CRP), as well as more emerging markers of matrix remodeling such as matrix metalloproteinases, tissue inhibitors of metalloproteinases, galectin-3, and ST2, may have a role not only for prognostication of patients with heart failure but also in the optimal management of these patients.

Keywords

Biomarkers, natriuretic peptides, BNP, NT-proBNP, novel cardiac biomarkers, galectin-3, ST2

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Several cardiac biomarkers may aid in the diagnostic and prognostic evaluation of acute and chronic heart failure. In this article we discuss more novel and emerging applications of such established cardiac biomarkers in heart failure and review emerging data for several other promising markers.

Novel Applications of Established Cardiac Biomarkers—Natriuretic Peptides

B-type natriuretic peptide (BNP) and its amino-terminal cleavage equivalent N-terminal prohormone brain natriuretic peptide (NT-proBNP) originate from a pre-proBNP hormone of 134 residues that is cleaved to yield a 108 amino acid intracellular pro-hormone, proBNP108; from proBNP108, BNP and NT-proBNP are liberated in varying amounts.¹ The utility of BNP and NT-proBNP for the diagnostic evaluation of suspected acute heart failure in patients presenting with acute dyspnea has been well studied and previously reviewed.²⁻⁵ Emerging applications of BNP and NT-proBNP include their application in primary care, as well as their use in better managing patients with heart disease besides acute heart failure.

Natriuretic Peptides and Evaluation of Dyspnea in the Primary Care Setting

The emerging utilities of BNP and NT-proBNP levels in the primary care setting include evaluation of patients with dyspnea as well as screening for asymptomatic left ventricular (LV) dysfunction. As both BNP and NT-proBNP are greatly affected by hemodynamic stress, it is well accepted

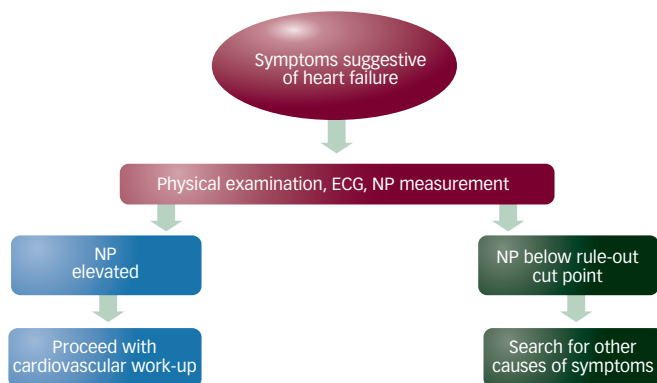
that the optimal cut-off values for both BNP and NT-proBNP levels are lower in primary care patients than seen in patients with acute dyspnea presenting to the emergency room. Tang et al.⁶ demonstrated that the use of a BNP cut-point of 100ng/l was associated with a disastrously low sensitivity among symptomatic heart failure patients in a heart failure clinic. Given this fact, lower BNP cut-points than those applied for acute heart failure screening are clearly necessary; in this context, the primary care application for BNP and NT-proBNP is best considered as a 'rule-out' rather than 'rule-in' tool. In other words, the choice of cut-off for these markers should be made based on the ability of the marker to exclude heart failure in a symptomatic patient rather than to identify it. This requires good understanding of the negative predictive value (NPV) for BNP and NT-proBNP in primary care and the factors that affect the peptides. Important physiological variables to consider when interpreting natriuretic peptides are detailed in *Table 1*.

In the primary care setting, it has been suggested that the NPV optimal cut-off for BNP would be 20–30ng/l, although there are relatively few data prospectively supporting this cut-point. NT-proBNP has been studied and validated in the primary care setting; for this use, an optimal NPV value of 125ng/l for ruling out heart failure among patients <75 years of age is useful;⁷ as the median value of NT-proBNP among those ≥75 years of age has been shown to be 150ng/l, a higher cut-point is necessary for the elderly. While 450ng/l has been advocated, a lower value of 300ng/l may have slightly better NPV for those >75 years of age.⁸⁻¹²

Table 1: Causes of Increased and Relatively Decreased Natriuretic Peptides

Increased Natriuretic Peptide Levels (Besides Heart Muscle Disease)	
Cardiac Causes	
Valvular heart disease	
Arrhythmia	
Ischemic heart disease	
Non-cardiac Causes	
Pulmonary hypertension	
Renal insufficiency	
Age	
Relatively Decreased Natriuretic Peptide Levels	
Obesity	
Cardiac medicines	

Figure 1: Suggested Application of Natriuretic Peptides for Primary Care Diagnostic Evaluation



With the proper application of BNP or NT-proBNP in primary care (see *Figure 1*), one can expect cost-effective exclusion of heart failure.¹³ Indeed, Heidenreich and colleagues suggested that use of natriuretic peptides for excluding the need for echocardiography was associated with cost-effective care.¹⁴ Furthermore, as echocardiography is costly and not always immediately available, the use of a biomarker to act as a gatekeeper for use of cardiac ultrasound is intuitively attractive. This leads to another potential application: specifically, detecting asymptomatic LV dysfunction.

It is important to emphasize that this application is somewhat less supported by the data. Since the prevalence of asymptomatic LV dysfunction is variable,¹⁵ the widespread use of BNP or NT-proBNP (and the use of a single cut-off value for 'abnormal') is somewhat challenging. Nonetheless, some clarity may be gained when examining the results of available studies. In one study,¹⁶ the use of a BNP value of 75ng/l to detect abnormal echocardiographic findings has a sensitivity and a specificity of 85 and 97%, respectively. Vasan et al.¹⁷ and Redfield et al.¹⁸ found BNP levels were suboptimal to screen patients with asymptomatic systolic or diastolic dysfunction. In contrast, Galasko et al.¹⁹ demonstrated that NT-proBNP levels >80th percentile (greater than two times normal value) were associated with an approximate two-fold increase in the risk for mortality and a 3.24-fold increase for the first major cardiovascular events associated with LV dysfunction. In another study,²⁰ NT-proBNP and BNP were directly compared for detecting LV systolic dysfunction, and

NT-proBNP performed better than BNP in predicting death in the general population. Given these results, it is reasonable to assert that while both BNP and NT-proBNP have a clear role for evaluation of dyspnea in primary care and both predict outcomes in apparently well patients, their widespread routine use for identification of asymptomatic structural heart disease is not yet defined. As these BNP and NT-proBNP appear to offer superior predictive ability for identifying structural heart disease in those at a higher risk, such as those with diabetes or hypertension with LV hypertrophy on electrocardiography, such patients may represent the first area of application for natriuretic peptide testing for screening out asymptomatic structural heart disease.

Management of Heart Failure

An area of great interest in modern medicine is whether either BNP or NT-proBNP would be useful for the management of heart failure. Conceptually, the use of a biomarker that independently associates with cardiac structure and function as well as prognosis for guidance of medical treatment of heart failure is attractive. Furthermore, natriuretic peptides tend to 'respond' to therapeutic interventions for heart failure (such as diuretics, angiotensin-converting enzyme or angiotensin receptor inhibitors, β -blockers, aldosterone blockers, or biventricular pacing), especially when prognosis is favorably affected by such interventions. Accordingly, the use of either BNP or NT-proBNP added to clinical assessment for management of heart failure appears promising. A pre-requisite for the use of these markers for optimal management in heart failure is a clear understanding of the prognostic value of either BNP and NT-proBNP, target/goal values for both markers and their optimal modes of measurement (i.e. timing-wise).

Acute Heart Failure

BNP and NT-proBNP levels at presentation predict both long- and short-term mortality in hospitalized patients with acutely destabilized heart failure;²¹ a follow-up post-treatment value may be more important. Logeart et al.²² demonstrated that the strongest predictor of adverse outcome following therapy for acute heart failure was the discharge BNP value; in a similar fashion, Bayes-Genis et al.²³ established that trans-hospital (days one to seven) change in values of NT-proBNP among hospitalized patients with acute heart failure who suffered complications had a smaller drop in NT-proBNP values (15% or less) than those who survived (50% or greater); NT-proBNP reduction percentage during admission for acute heart failure was superior to the presenting NT-proBNP concentration for prognosis. Knebel et al.²⁴ showed similar findings despite poor correlation between single hemodynamic parameters and NT-proBNP levels.

In other studies,^{22-23,25} it has been demonstrated that no change in BNP/NT-proBNP concentrations, irrespective of heart failure symptom improvement, is also associated with increased morbidity and mortality. In the most significant fashion study, Bettencourt and colleagues demonstrated that an admission-to-discharge fall of >30% in NT-proBNP values provided reassurance for a favorable short-term prognosis, while those who had a less robust fall (or a rise) in NT-proBNP had worse outcomes, with a readmission hazard ratio (HR) of 5.96 and a death HR of 3.67.²⁵ Hence, a suggested algorithm would be to obtain a BNP or NT-proBNP value at baseline for a patient with acute heart failure, treat the patient using standard heart failure management guidelines, and at the time of perceived 're-compensation' re-measure BNP or

NT-proBNP. If a robust decrease is not observed, intensification of heart failure treatment would be indicated.

Chronic Heart Failure

In patients with chronic heart failure, both natriuretic peptides have shown to remain prognostically meaningful despite available results from other measures of prognostication such as LV function, signs and symptoms, and even peak oxygen consumption (VO_2).^{26,27} Similar to acute heart failure, patterns of BNP or NT-proBNP over time are more indicative of risk than are single measurements;²⁸ changes in natriuretic peptides appear to parallel the benefit of therapeutic interventions for chronic heart failure, with a gradual change in response to therapy most apparent approximately two weeks following treatment changes.²⁹

Given these facts, the use of BNP or NT-proBNP as an adjunct to management in chronic heart failure appears logical. Troughton et al.³⁰ first demonstrated that an NT-proBNP level below approximately 1,700ng/l was associated with fewer combined events of heart failure decompensation, hospitalization, and mortality (19 versus 54; $p=0.02$) during a median 9.5 months of follow-up. Importantly, this study was small and the medical management was not optimal with regard to β -blockers. The Systolic Heart Failure Treatment Supported by BNP (STARS-BNP)³¹ study further explored the concept of BNP-guided heart failure management among 220 patients with class II–IV symptoms who were randomized to BNP (target value $<100\text{ng/l}$) and clinically guided treatment. In this study with 15 months of follow-up, primary end-points (unplanned hospital stays for heart failure or death related to heart failure) were observed in 24% of the BNP group versus 52% of the clinical group.

Several larger randomized trials are ongoing to examine NT-proBNP guidance for heart failure therapy as outpatients. Method papers have been published for the BNP-Assisted Treatment To Lessen Serial Cardiovascular Readmissions and Death (BATTLE-SCARRED)³² and Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) studies,³³ and both trials have been presented. In both, the use of NT-proBNP guidance for heart failure management was associated with significant improvements in mortality (BATTLESCARRED) or heart-failure-free survival (TIME-CHF); however, these benefits were most obvious among those <75 years of age. Accordingly, more information is necessary regarding the specific benefits of natriuretic-peptide-guided heart failure management before it becomes standard of care in heart failure.

Novel Applications of Established Cardiac Biomarkers—Markers of Myocyte Injury

The utility of markers of cardiomyocyte injury or necrosis in heart failure remain unclear, but preliminary data in this area are compelling. It is well known that cardiac-specific troponin (cTn) levels may be elevated in patients with heart failure without overt ischemia.^{34–35} Elevated cTnI and cTnT levels among patients with both acute and chronic heart failure have been associated with both short- and long-term adverse outcomes.

In the context of acute decompensated heart failure, Del Carlo et al.³⁶ demonstrated that persistently measurable levels of cTnT by day seven

among patients admitted with acute decompensated heart failure were associated with adverse outcomes. In a similar fashion, Sakhujia and colleagues showed that cTnT was prognostic for short-term mortality, and was additive to results for either BNP or NT-proBNP for this application.³⁷ Recently, Peacock et al.³⁸ analyzed the Acute Decompensated Heart

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Failure National Registry (ADHERE) and found the adjusted odds ratio for in-hospital death associated with a measurable cTnI was 2.33 (95% confidence interval [CI] 1.98–2.75; $p<0.001$).

Hudson et al.³⁹ analyzed cTnT levels on 136 ambulatory patients with chronic stable heart failure and found that elevated cTnT levels $>0.02\text{ng/ml}$ were associated with increased relative risks (RR) of death or heart failure hospitalization (RR 2.7, 95% CI 1.7–4.3, $p<0.001$) and death alone (RR 4.2, 95% CI 1.8–9.5; $p<0.001$) during a median follow-up of 14 months. Similarly, Sato et al.⁴⁰ observed that persistently elevated cTnT levels $>0.02\text{ng/ml}$ had deterioration of left ventricular ejection fraction (LVEF). Lastly, Miller and colleagues showed that serial sampling of cTnT provided superior prognostication for adverse outcome, with a rising pattern associated with the greatest risk; this risk was independent of that of BNP and was superior to this latter marker for prognosis.⁴¹ Thus, available data support the use of cTn methods for risk assessment in acute and chronic heart failure; what remains less clear is the therapeutic imperative associated with an elevated cTn value in this setting.

Novel Applications of Established Cardiac Biomarkers—Inflammatory Markers

Inflammation plays a pivotal role in heart failure, and there is an emerging appreciation for the role of inflammatory marker measurement for risk assessment in heart failure patients.

C-reactive Protein

C-reactive protein (CRP) is a member of the pentraxin family of inflammatory markers, and represents the prototypical biomarker of inflammation.⁴² Synthesized by the liver in response to numerous stimuli, CRP has been shown to be powerfully prognostic for the development of heart failure and is also predictive of risk across the spectrum of heart failure.

In the Framingham Heart Study, Vasan et al.⁴³ reported that elevated CRP (5mg/dl) had near-tripling of heart failure risk, while Anand et al.⁴⁴ demonstrated that chronic stable heart failure patients with CRP above the median value of 3.23mg/l had features of more severe heart failure than those with CRP levels below the median. Multivariate analysis also indicated that increased CRP was an independent

Figure 2: Value of ST2 as an Additive Marker of Risk in Heart Failure Relative to NT-proBNP⁶⁰

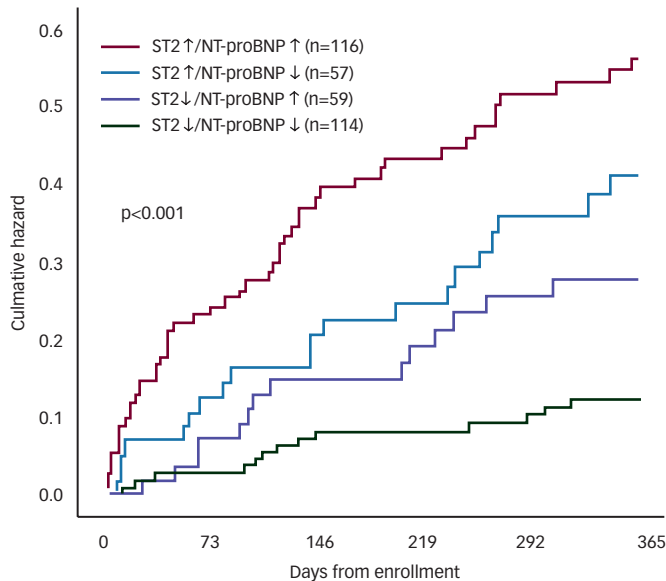
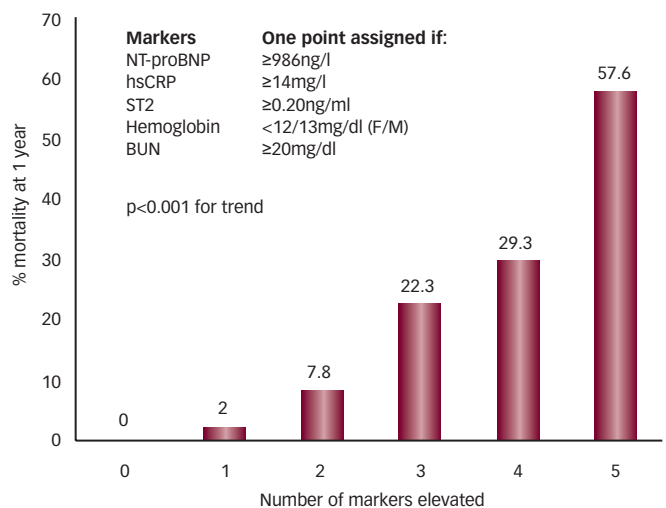


Figure 3: Multimarker Approach for Risk Stratification in Acute Heart Failure Evaluation⁶²



predictor of adverse outcomes in patients with acute or chronic heart failure. Furthermore, Rehman and colleagues demonstrated a potent association between CRP concentrations and risk for death in acute heart failure, independent of NT-proBNP or other biochemical predictors of risk.⁴⁵

The mechanistic relationships between inflammation (as reflected by elevated CRP concentrations) and outcomes in heart failure are complex and include associations with coronary artery disease, cardiac injury, and fibrosis/remodeling, as well as risk factor status (such as metabolic syndrome). Although inflammation is potentially prognostic in heart failure, therapeutic trials to reduce it have thus far failed in patients suffering from advanced symptoms.⁴⁶ Currently, specific therapeutic interventions based on CRP concentrations (for example) remain unclear.

Novel Markers in Heart Failure

Biomarkers of Matrix Remodeling

Ventricular remodeling plays an important role in the progression of heart failure;⁴⁷ remodeling represents a balance between matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMPs). An imbalance between MMP and TIMPs occurs during ventricular dilatation and remodeling, with relatively increased levels of MMP. Sundstrom et al., the Framingham Heart Study investigators,⁴⁸ demonstrated that detectable levels of MMP-9 among community-dwelling individuals were associated with increased LV end-diastolic diameter, LV wall thickness, and LV mass. In another study,⁴⁹ levels of MMP-9 and TIMP among patients after myocardial infarction were compared with NT-proBNP; while MMP-9 was inferior to NT-proBNP for predicting outcomes related to heart failure, patients with tissue inhibitor of metalloproteinases-1 (TIMP-1) >135ng/ml ($p < 0.001$) or NT-proBNP >1,472ng/l ($p < 0.001$) had increased risk.

During the matrix remodeling process, type III procollagen is cleaved to form type III collagen and its amino terminal propeptide of type III procollagen (PIIINP). Rossi et al.⁵⁰ reported that a higher concentration of PIIINP is associated with restrictive mitral filling patterns and worsened survival in patients with dilated cardiomyopathy. Ciccoira et al.⁵¹ also observed that the level of plasma procollagen type III is an independent predictor of adverse outcomes among patient with heart failure.

Galectin-3

Galectin-3 is a protein secreted by activated macrophages, and has a role in development of fibrosis in injured tissues.⁵² Galectin-3 has been shown to be secreted in the context of LV hypertrophy, and galectin exposure results in heart failure in experimental models.⁵² Van Kimmenade and colleagues demonstrated that concentrations of galectin-3 were prognostically meaningful in acute heart failure, with superior area under the receiver operator characteristic curve for predicting death at 60 days compared with NT-proBNP; the odds ratio for elevated galectin-3 was 10.3 ($p = 0.007$) for this indication.⁵³ Importantly, the combination of elevated NT-proBNP plus elevated galectin-3 provided superior prognostication.

In a similar fashion, Lok and colleagues⁵⁴ showed that galectin-3 values during heart failure treatment for those with chronic stable symptoms were prognostically meaningful on top of natriuretic peptide values. These results suggest that a 'multimarker' approach with galectin-3 (or a similar marker) together with a natriuretic peptide is a sound approach for enhanced risk stratification.

ST2

ST2 is a member of the interleukin-1 receptor family, and is secreted by both fibroblasts and cardiomyocytes in response to strain.⁵⁵ ST2 exists in two forms: a membrane-bound receptor and a truncated soluble form (sST2), detectable in the peripheral blood of patients after myocardial infarction and in those with heart failure.⁵⁶ The ligand for ST2 was recently reported to be interleukin-33; together with intact and normal ST2 signaling, interleukin-33 reduces cardiac fibrosis and hypertrophy.^{57,58} When the ST2 receptor is interrupted or large amounts of sST2 are administered in an animal model, severe

myocardial dysfunction, hypertrophy, fibrosis, and death occur.^{57,58} Thus, ST2 appears to play a pivotal role in the process and complications of heart failure.

Clinically, Januzzi et al.⁵⁹ demonstrated sST2 values to be powerfully predictive of death among patients presenting to the emergency department with dyspnea. In a follow-up study Rehman and colleagues⁶⁰ showed that sST2 values were additively valuable for prognosis in patients with acute heart failure (see *Figure 2*); these results were expanded upon in another study,⁶¹ where serial sampling of sST2 among patients admitted with acutely destabilized heart failure better predicted 90-day mortality than did single measurement. Patients who did not have a decrease of 15% in sST2 levels during the hospital stay had a 33% risk of 90-day mortality, and among those patients with a fall in NT-proBNP values, a persistently elevated sST2 concentration was still associated with risk. Thus, similar to natriuretic peptides, the role of sST2 as a potential cardiac biomarker in the diagnosis, prognostication, and management of heart failure is strongly possible pending further large randomized trials.

Conclusion

The field of biomarker testing in heart failure has evolved dramatically over the past several years. In addition to expanded diagnostic

applications of natriuretic peptides (such as primary care use or heart failure management), a wide array of biomarkers now exist for prognostication in heart failure. We have reviewed several of these in the foregoing discussion. Ultimately, a ‘multimarker’ strategy using multiple different markers reflective of differential pathologies in heart failure (see *Figure 3*) may be the best way to titrate therapeutic intervention and reduce the considerable risk of patients with elevations in these powerfully predictive markers. ■



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