# Natriuretic Peptides in Heart Failure

## Atrial and B-type Natriuretic Peptides

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**KEYWORDS**

• B-type natriuretic peptide • N-terminal B-type natriuretic peptide
• Midregional pro–atrial natriuretic peptide • Heart failure • Diagnosis • Prognosis

**KEY POINTS**

- The natriuretic peptides are important biomarkers for diagnosing and risk stratifying patients with heart failure.
- B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) can help optimize therapy in patients with chronic heart failure.
- The natriuretic peptides also have an important use for prognostication in other cardiovascular diseases.
- Further research is needed to understand how to interpret BNP and NT-proBNP in the setting of new neprilysin inhibitors.

## INTRODUCTION

The natriuretic peptides (NPs) play a critical role in maintaining homeostasis in the cardiovascular system, serving as counter-regulatory hormones for volume and pressure overload. It was recognized early that measurement of NPs might serve as useful surrogates for patient status and pathophysiology. With more than 3 decades of research, NPs are now vital tools in the diagnosis of heart failure (HF), can also aid in prognosis, and can sometimes help with guiding therapy. Their utility also extends beyond HF into other cardiovascular and noncardiovascular conditions. However, with the introduction of neprilysin inhibitors that alter the physiology of the NP system, a new avenue of research has opened to better understand the changes that occur in clinical assessment of NPs. This article discusses the history and uses of NP assessment in HF and other cardiovascular diseases.

### *Physiologic Production of the Natriuretic Peptides*

The existence of atrial NP (ANP), also known as atrial natriuretic factor, was first recognized in 1981 when homogenized atrial tissues were injected into rats and resulted in a reduction of blood pressure, diuresis, and natriuresis.[1] Subsequent research led to a further understanding of the NP system and the discovery of B-type natriuretic peptide (BNP), also known as brain-type natriuretic peptide, and C-type natriuretic peptide

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(CNP). At present, clinical assays for ANP and BNP are most widely used in cardiovascular disease and are discussed here.

ANP is encoded by the *NPAA* gene on chromosome 1. It is translated into a 151-amino-acid preprohormone (preproANP) that is cleaved in the sarcoplasmic reticulum to a 126-amino-acid prohormone (proANP), which is stored in intracellular granules.[2] When stimulated and released, proANP is further cleaved into a 28-amino-acid bioactive form (ANP) and a 98-amino-acid N-terminal fragment (NT-proANP).[2] The half-life of ANP is approximately 2 minutes, whereas NT-proANP half-life is variable depending on the fragment measured.[2]

ANP is predominantly produced in the atria of the heart and to a lesser extent the ventricles and extracardiac tissues, such as the kidney.[3] Unlike BNP, which has minimal preformed and stored hormone, most proANP is stored in intracellular granules of the atria and released on stimulation, whereas further production of ANP involves the slower process of transcription and translation.[4] The major stimulus for ANP release is increased atrial wall stretch reflecting increased intravascular volume. Other stimuli for release include catecholamines, arginine vasopressin, and endothelin.[3] These stimuli reflect the counter-regulatory role ANP plays against volume overload and hypertension.

BNP was first described in 1988 after isolation from porcine brain tissues (hence its original name of brain-type natriuretic peptide) with subsequent studies finding it produced in the cardiac ventricles.[5] As with ANP, BNP is a peptide neurohormone synthesized by cardiac ventricular myocytes in response to mechanical stretch.[6,7] During periods of volume overload, mechanical stretch on cardiomyocyte membranes activates signal transduction leading to downstream transcription and translation of preproBNP, a 134 amino acid precursor peptide.[8] PreproBNP undergoes a 2-step enzymatic cleavage to produce the biologically active product. The first cleavage occurs in the sarcoplasmic reticulum during translation, removing a 26-amino-acid signaling peptide and producing $proBNP_{1\text{-}108}$.[9,10] ProBNP subsequently undergoes a second cleavage by prohormone convertases (including the enzymes corin and furin) to produce the biologically active C-terminal peptide, $BNP_{1\text{-}32}$, and an inactive N-terminal fragment, NT-proBNP.[9] BNP and NT-proBNP peptides are secreted in equal concentrations into the circulation.[11–13] As discussed earlier, ANP is predominantly stored preformed in intracellular granules, but BNP is minimally stored and is mostly produced and secreted directly in large bursts following stimulation.[14] BNP has a serum half-life of 20 minutes, whereas NT-proBNP has a half-life of 120 minutes (**Fig. 1**).[11,15]

ANP and BNP interact with 3 NP receptors (NPRs; A, B, and C) with their main physiologic effects exerted through the NPR-A receptor. The NPR-A receptor is the predominant form on blood vessels, with a smaller amount of NPR-B receptor, and both receptors are found in the kidneys and adrenal glands.[3] ANP and BNP binding to NPR-A and NPR-B leads to activation of guanylyl cyclase and downstream signaling through cyclic guanosine monophosphate (cGMP).[3] NPR-C clears ANP, and, to a lesser extent, BNP by binding and internalizing the receptor, and degrading the hormone. ANP is also inactivated and cleared by neutral endopeptidases (see **Fig. 1**).[2]

ANP signaling leads to a reduction in blood pressure, natriuresis, and diuresis. These actions are predominantly performed via effects on the kidneys. ANP increases renal blood flow, dilates afferent arterioles, and constricts efferent arterioles, leading to increased glomerular filtration.[16] It inhibits angiotensin II–mediated sodium and water reabsorption in the proximal tubule, inhibits sodium reabsorption in the inner medullary ducts, and antagonizes vasopressin, leading to decreased water reabsorption in the collecting duct.[17–20] These effects lead to a potent diuresis and natriuresis. Outside of the kidney, ANP reduces blood pressure by decreasing sympathetic output, increasing venous capacitance, and increasing vascular permeability.[21–23] These actions seem to be mediated by ANP inhibiting catecholamines, renin, angiotensin II, aldosterone, and endothelin.[24–28] ANP also directly affects the heart, preventing hypertrophy.[2]

When BNP circulates and binds NPRs on target tissues, it triggers increased intracellular cGMP signaling cascades, inducing actions that reduce cardiac preload and afterload to counteract the detrimental effects of pressure and volume overload, as seen in HF (see **Fig. 1**).[29] This process includes vasodilation, diuresis, natriuresis, and inhibition of the renin-angiotensin-aldosterone system (RAAS).[11] BNP is primarily cleared through degradation by circulating neutral endopeptidases and, to a lesser extent, through uptake by NPR-C in peripheral tissues and minimally through renal excretion (see **Fig. 1**).[11,29] These physiologic processes are counter-regulatory to the detrimental neurohormonal activation of the sympathetic nervous system and RAAS in HF and are why ANP and BNP levels reflect HF severity.

## *Clinical Assessment of the Natriuretic Peptides*

BNP and NT-proBNP are measured using standard immunoassays that are now widely available;

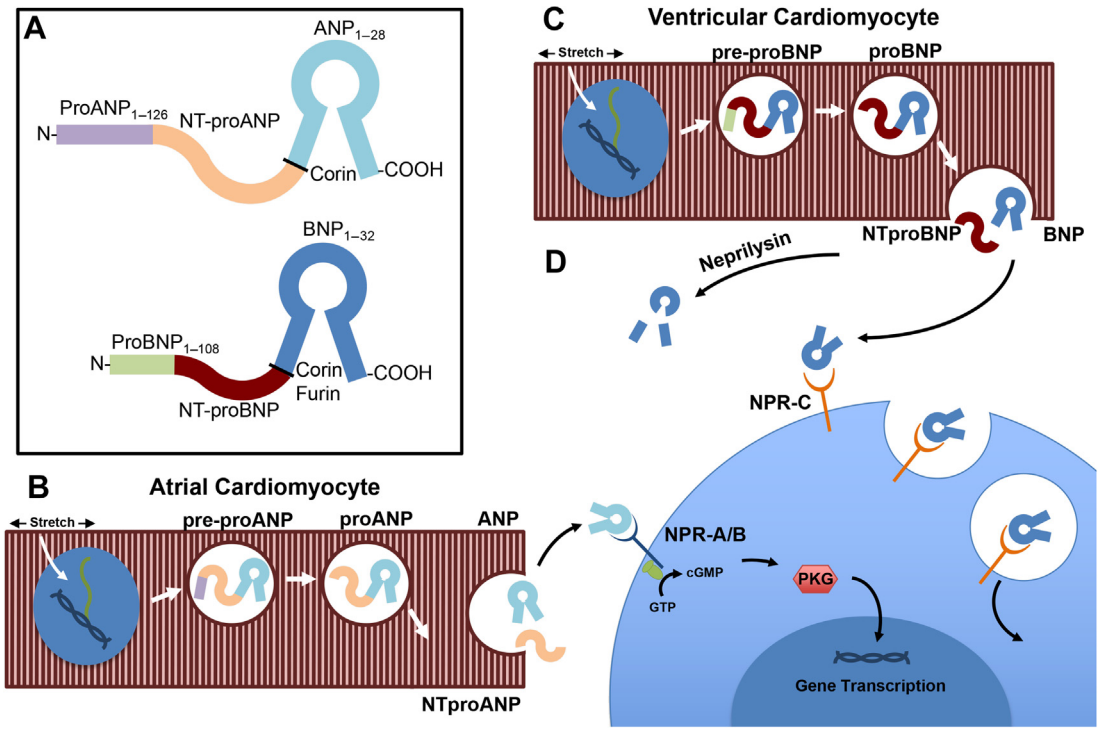


**Fig. 1.** ANP and BNP physiology. (*A*) Molecular structure of ANP (*top*) and BNP (*bottom*) showing enzymatic cleavage sites and end-product fragments. (*B*) Production and processing of ANP by atrial cardiac myocyte in response to mechanical stretch stimulus. (*C*) Production and processing of BNP by ventricular cardiac myocyte in response to mechanical stimulus. (*D*) Effects of ANP and BNP on target tissues. Both ANP and BNP bind NP receptor (NPR)A and NPR-B on target cells, inducing cleavage of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) by cytoplasmic G proteins, initiating an intracellular cGMP signaling cascade involving protein kinase G (PKG), ultimately leading to downstream transcription of genes involving smooth muscle cell relaxation, diuresis and natriuresis (depending on target tissue). Both ANP and BNP are broken down in serum by circulating endogenous peptidases, including neprilysin. ANP and BNP are also degraded (to a lesser extent) by cellular uptake through binding NPR-C, undergoing receptor-mediated endocytosis and intracellular breakdown by lysosomes.

however, they are controversial. The assays for detection of BNP rely on antibodies that have minimal cross-reactivity with NT-proBNP and vice versa.[30] The available BNP immunoassay relies on 2 monoclonal antibodies, recognizing the BNP ring structure and the C-terminal tail,[31] and these antibodies have significant cross-reactivity with portions of pro-$BNP_{1\text{-}108}$. Thus the available immunoassays measure total circulating BNP, including the biologically active $BNP_{1\text{-}32}$ and the inactive pro-$BNP_{1\text{-}108}$. The exact clinical significance of measuring the non–biologically active pro-$BNP_{1\text{-}108}$ remains unclear. Novel assays are now being developed that allow for differential measurement of $BNP_{1\text{-}32}$ and pro-$BNP_{1\text{-}108}$ isoforms.[32]

As mentioned, the bioactive form of ANP is labile with a very short half-life; thus, it is difficult to accurately measure the bioactive form in clinical practice.[33–35] As a result, the N-terminal prohormone fragment (NT-proANP) was subsequently measured, which is more chemically stable in serum, but its concentrations may be higher than the bioactive isoform.[33] A variety of clinical assays, most often immunoassays, were developed to measure NT-proANP, but subsequently it was found that even the NT-proANP portion underwent further degradation.[33] In 2004, an assay was developed focusing on the midregion of NT-proANP (MR-proANP), because little proteolytic degradation occurs in this region.[33,36] MR-proANP is now the primary biomarker measured in clinical assays. Aside from MR-proANP, newer research has shown that fragments of the preprohormone may remain stable after cleavage and could be quantified, suggesting that assays could be developed to explore this marker of ANP physiology.[33] Further research is needed to establish whether this is a clinically useful marker.

### *Diagnostic Utility of B-type Natriuretic Peptide and N-terminal pro–B-type Natriuretic Peptide in Acute Heart Failure*

Although the molecular structure and cellular production of BNP was first described in the late 1980s, its clinical significance was not fully elucidated until the early 2000s. The evidence is now overwhelming that early measurement of serum BNP levels should be used to diagnose acute heart failure (AHF), and it is a class I indication in the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of HF that BNP levels should be measured in all hospital admissions for AHF.[37] Cardiac-specific biomarkers are particularly useful in the emergency department (ED) setting when evaluating dyspneic patients, because it is difficult to distinguish between shortness of breath caused by HF versus that caused by pulmonary disease.

The Breathing Not Properly Multinational Study published in 2002 was the first large study to evaluate the efficacy of BNP as a cardiac biomarker for diagnosis of HF in the ED setting.[14] This study evaluated 1586 patients presenting to EDs with the chief complaint of dyspnea at 7 different medical centers around the world. Serum BNP levels were higher in patients presenting with dyspnea caused by AHF than in dyspnea from a noncardiac cause. Serum BNP levels were positively correlated with severity of HF using the New York Heart Association (NYHA) classification. Using a BNP cutoff of 100 pg/mL, serum BNP level was 90% sensitive and 76% specific for HF. Using a cutoff of 50 pg/mL, BNP had a negative predictive value of 96%.[14] The Pro-BNP Investigation of Acute Dyspnea in the Emergency Department (PRIDE) study published similar findings using NT-proBNP in 2005.[38] NT-proBNP level was highly sensitive and specific at diagnosing AHF among 600 patients presenting to the ED with dyspnea using a cutoff level of 300 pg/mL, and NT-proBNP was 90% sensitive and 85% specific for diagnosis of AHF.[38] Numerous studies have subsequently confirmed the excellent predictive value as assessed by the area under the receiver operator characteristic curve (AUC) of BNP and NT-proBNP (**Figs. 2** and **3**).

Because of the speed and ease of measuring serum biomarkers, use of BNP in EDs has the potential to greatly reduce hospital stay and overall treatment costs associated with HF. A 2004 study by Mueller and colleagues[39] evaluated 452 patients presenting to the ED with acute dyspnea and found that measurement of BNP led to more rapid HF diagnosis, which reduced time to discharge and decreased overall cost of treatment associated with the ED visit. The Canadian Multicenter Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) study showed similar findings using NT-proBNP in a population of 500 patients presenting to 7 different EDs in Canada. Measurement of serum NT-proBNP level to aid in the diagnosis of HF reduced duration of ED visits by 21%, reduced the rate of rehospitalization after 60 days by 45%, and similarly reduced the overall cost of treatment of these patients.[40]

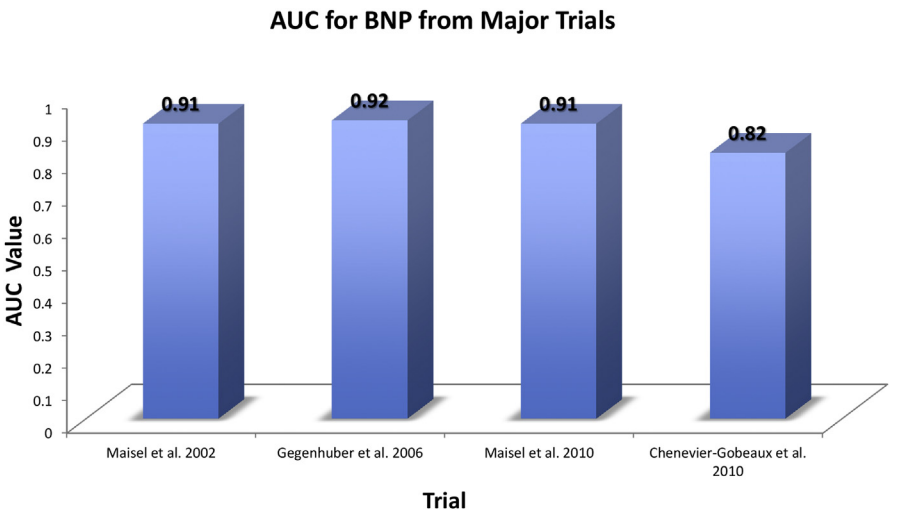


**Fig. 2.** Values for AUCs from major trials evaluating the predictive value of BNP, which show the excellent predictive value of BNP.

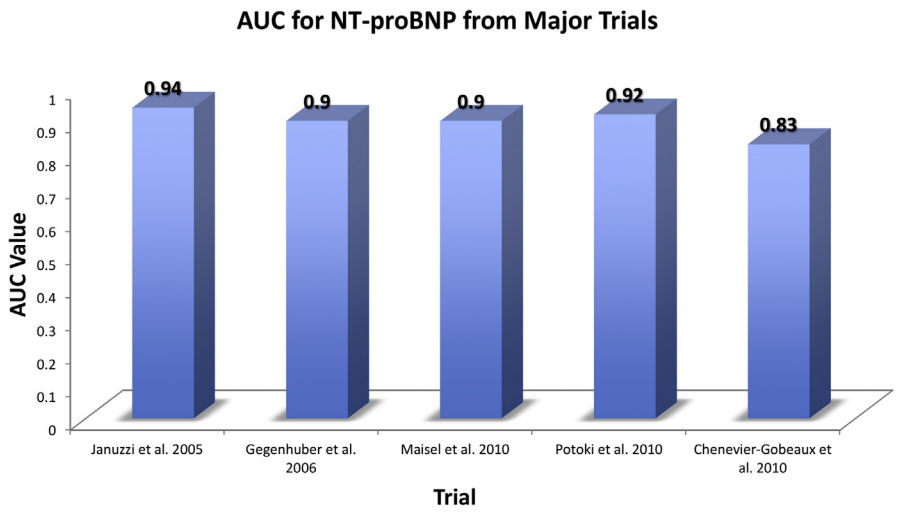


**Fig. 3.** Values for AUCs from major trials evaluating the predictive value of NT-proBNP, which show an excellent predictive value similar to BNP.

### *Diagnostic Utility Midregion Pro–Atrial Natriuretic Peptide in Acute Heart Failure*

The largest study to evaluate MR-proANP for the diagnosis of AHF, the Biomarkers in Acute Heart Failure (BACH) study was a multisite international trial enrolling 1641 patients presenting with acute dyspnea, of whom 568 patients were diagnosed with AHF.[41] MR-proANP was noninferior to BNP and NT-proBNP with a sensitivity of 97.0%, a negative predictive value of 97.4% at a cutoff of 120 pmol/L, and an excellent AUC of 0.90.[41] Furthermore, the addition of MR-proANP to BNP improved the diagnostic performance of BNP with the C-statistic increasing from 0.787 to 0.816, and it had an incremental benefit in diagnosing AHF in patients with BNP and NT-proBNP values in the gray zone as well as in obese patients.[41] Other studies have shown similar findings and furthered the evidence for MR-proANP for AHF (**Fig. 4**).[42–45] Similar improvements in the diagnosis of patients with AHF with BNP or NT-proBNP levels in the gray zone by MR-proANP have been found.[43] MR-proANP and BNP diagnosed AHF better than 8 other biomarkers.[42] The investigators of the PRIDE study explored different age-based cutoffs for MR-proANP (similar to NT-proBNP), which improved specificity

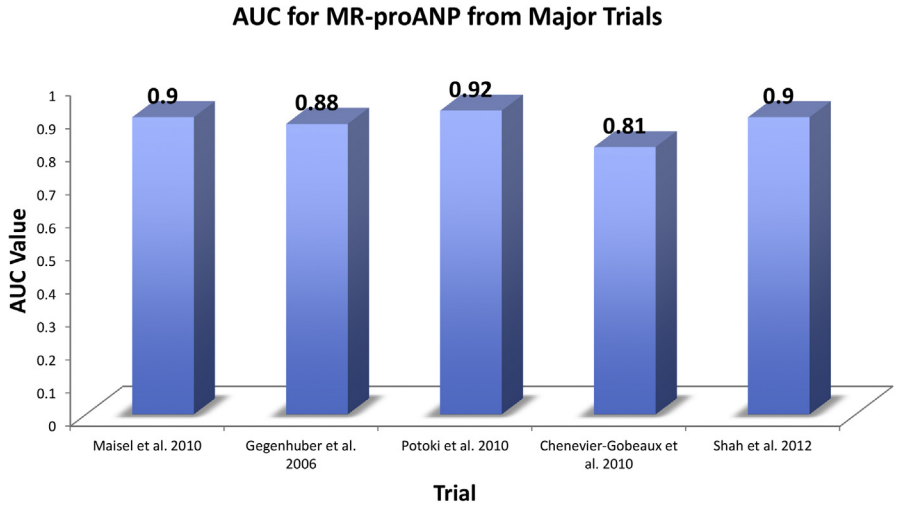


**Fig. 4.** Values for AUCs from major trials evaluating the predictive value of MR-proANP, again showing an excellent predictive value, as with BNP and NT-proBNP.

but decreased sensitivity.[44] Further study is needed to establish whether age-based cutoffs are indicated.

### *Prognostic Utility of B-type Natriuretic Peptide in Heart Failure*

In addition to its diagnostic value, many studies have now shown the utility of BNP levels for prognostication. In 2002, Berger and colleagues[46] evaluated 452 ambulatory patients to determine whether serum BNP levels were predictive of future sudden cardiac death (SCD) in patients with a left ventricular ejection fraction (LVEF) less than 35% within a 3-year follow-up period. Patients with a baseline serum BNP level greater than 130 pg/mL had higher rates of SCD, and the investigators suggested that patients with an increased BNP level at baseline should be evaluated for implantable cardiac defibrillator therapy.[46] A substudy of the A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure (Val-HeFT) trial also evaluated the prognostic value of BNP.[47] This analysis was of 4300 patients who had serial serum BNP levels drawn at baseline, 4 months, and 12 months after enrollment. Patients with the largest percentage decline in BNP level from baseline during follow-up had the lowest morbidity and mortality. In contrast, patients with the highest percentage increase in BNP from baseline had the worst morbidity and mortality using a Cox proportional hazard model.[47]

The 2004 Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT) trial evaluated 464 patients presenting to the ED with dyspnea and with NYHA class II to IV HF with baseline BNP greater than 100 pg/mL. The investigators found that baseline BNP levels greater than 200 pg/mL were strongly predictive of 90-day outcomes (combined HF visits, admissions, and mortality).[48] An analysis of the PRIDE trial examined 1-year outcomes of patients presenting to the ED with acute dyspnea. NT-proBNP levels greater than 986 pg/mL at baseline were associated with more severe HF, and a single baseline NT-proBNP level increased above this cutoff was the strongest individual predictor of death at 1 year.[49] In a meta-analysis of 19 prospective randomized controlled clinical trials, Doust and colleagues[50] found that, for every 100-pg/mL increase in serum BNP, there was a 35% increased risk of death for patients with both acute and chronic HF.

Failure of NP levels to decrease during an HF hospitalization while undergoing treatment is associated with worse prognosis and suggests a potential role for serial BNP measurement during HF hospitalization.[51,52] Cheng and colleagues[52] evaluated 72 male veterans admitted with decompensated NYHA class III to IV HF and followed them for 30 days after discharge. Serial BNP levels were followed, starting with baseline values drawn within 24 hours of admission. Of these patients, 13 died and 9 were readmitted during the study period. Patients who died or were readmitted had increasing BNP levels during hospitalization. Patients who survived and were not readmitted showed decreasing BNP levels during admission. In a study of 50 patients admitted for AHF, Bettencourt and colleagues[51] measured BNP levels at admission and then serially throughout hospitalization. Patients were followed for 6 months after discharge to determine whether BNP trends during the index hospitalization were predictive of end points including readmission for cardiovascular causes and death. Patients who died or were readmitted had less marked decline in BNP levels during hospitalization (770 $\pm$ 608 pg/mL to 643 $\pm$ 465 pg/mL; $P$ = .08), whereas increasing BNP levels during hospitalization were associated with increased event rate (hazard ratio = 3.3; 95% confidence interval, 1.3–8.8).

Several large clinical databases have also been evaluated to determine the prognostic value of BNP in treatment of HF. In the Acute Decompensated Heart Failure National Registry (ADHERE) database of 65,275 patients with AHF, increased serum BNP levels at time of admission for HF exacerbation correlated with an increased risk of in-hospital mortality.[53] In a study of the Get With the Guidelines Heart Failure Registry, 99,930 patients with AHF were stratified into subgroups based on gender and LVEF (reduced, <40%; borderline, 40%–49%; preserved, $\geq$50%). Regardless of gender or LVEF, patients with BNP levels greater than the median had a higher mortality than those less than the median serum BNP level.[54] A substudy of the Framingham Offspring Study evaluated 3346 asymptomatic patients in the ambulatory setting and measured their serum BNP values over time. An increased BNP level greater than the 80th percentile was associated with an increased risk of death, first major cardiovascular event, atrial fibrillation (AF), stroke or transient ischemic attack, and HF.[55] In sum, these studies show the powerful prognostic ability of BNP and NT-proBNP.

### *Prognostic Utility of Midregion Pro–Atrial Natriuretic Peptide in Heart Failure*

MR-proANP has shown significant prognostic utility for morbidity and mortality in acute and chronic

HF. Multiple studies have shown that increasing levels of MR-proANP are associated with increasing mortality in patients with AHF up to 4 years from presentation.[44,45,56] Findings are similar in chronic HF, with MR-proANP predictive of mortality more than 5 years after initial assessment.[45,57–59] Some studies have shown that serial monitoring of MR-proANP in chronic HF improves mortality prediction.[58,60] MR-proANP levels are also associated with risk of cardiovascular admission.[58]

MR-proANP has prognostic utility in non-HF cardiovascular conditions as well. In acute coronary syndrome, MR-proANP was highly predictive for mortality to the same degree as NT-proBNP, and combining both biomarkers captured more patients at risk for mortality.[61] In patients with stable coronary artery disease in the Prevention of Events With Angiotensin Converting Enzyme (PEACE) trial, MR-proANP levels were shown to risk stratify for the development of cardiovascular death and incident HF.[62] A biomarker substudy of the Rule Out Myocardial Infarction Using Computer Assisted Tomography (ROMICAT) trial showed that MR-proANP correlated with left atrial volume measured by cardiac computed tomography, suggesting MR-proANP can potentially screen for structural heart disease.[63] An analysis of the PRIDE study examining all patients presenting with dyspnea showed that MR-proANP had good prognostic utility for mortality up to 4 years from presentation.[44]

Some studies have also suggested that MR-proANP can serve as a screening tool in asymptomatic at-risk patients. In a large community-based population from Sweden, MR-proANP predicted incident HF and AF.[64] Although NT-proBNP and MR-proANP both predicted incident HF, only MR-proANP predicted incident AF.[64] In a study of men in Italy without known cardiovascular disease, NT-proANP (note: not MR-proANP assay) correlated better with risk prediction scores for cardiovascular outcomes than NT-proBNP because increasing tertiles of NT-proANP correlated with higher risk scores.[65] However, a limitation of this study was the use NT-proANP and not the more stable isoform MR-proANP, and levels were compared with risk scores rather than cardiovascular outcomes.

### *Using Serum Natriuretic Peptides to Guide Heart Failure Treatment*

Whenever a patient is admitted for an HF exacerbation, the patient should have serum BNP level measured in the ED on admission, and this value should be compared with the baseline outpatient serum BNP level from when the patient was euvolemic, if available.[66] Several studies (as mentioned earlier) have suggested that BNP should then be trended during the course of hospitalization to help guide clinical management. In 2001, Kazanegra and colleagues[67] measured serial serum BNP levels and pulmonary capillary wedge pressures using Swan-Ganz catheters in patients admitted to the hospital for an AHF exacerbation. Treatment-related decreases in pulmonary capillary wedge pressures corresponded with declining serum BNP levels, suggesting that BNP levels should decline with diuresis. Although it may not be necessary to trend BNP levels daily in admitted patients, serial measurements should be considered in patients without clinical improvement to help guide therapy.

Several studies have shown that using a BNP-guided treatment strategy in outpatients with chronic HF translates into improved patient outcomes. The Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure (STARS-BNP) trial published in 2007 evaluated the use of BNP-guided treatment strategies compared with standard clinical therapy in 220 patients with NYHA class II to III HF who were taking optimal medical management (angiotensin-converting enzyme [ACE] inhibitors, β-blockers, and diuretics).[68] Patients were randomized to receive BNP-guided treatment with a goal BNP level of less than 100 pg/mL or treatment guided by clinical and symptomatic improvement. By 15-month follow-up, patients in the BNP-guided treatment arm had a significantly lower primary outcome of HF-related death or readmission (24% vs 52%; $P<.001$).[68] The 2009 NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) trial found similar results using NT-proBNP–guided clinical management.[69] In this trial, 364 patients admitted for HF exacerbation were assigned to NT-proBNP–guided therapy, intensive clinical management (using aggressive uptitration of HF medications to optimal clinical trial doses), or usual care using symptom-guided management. At 1-year follow-up, mortality was significantly lower in the NT-proBNP–guided treatment arm versus usual care (9.1% vs 18.9%; $P = .03$). By 3-year follow-up, mortality was significantly lower in the NT-proBNP–guided group (15.5%) compared with the intensive clinical management group (30.9%; $P = .048$) and usual-care group (31.3%; $P = .021$).[69] The 2009 Trial of Intensified versus Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) study also evaluated NT-proBNP–guided therapy.[70] This trial included 499 patients with chronic HF

who were older than 60 years, NYHA class greater than II, hospitalized for HF within the last year, and had a baseline NT-proBNP level greater than twice the upper limit of normal. These patients were followed for 18 months after initial admission, and the NT-proBNP–guided therapy arm had higher rates of survival and lower rates of all-cause hospitalizations in patients aged 60 to 75 years ($P<.02$) but not in patients older than 75 years ($P<.02$).[70] In addition, a 2014 meta-analysis by Troughton and colleagues[71] evaluated BNP-guided treatment in 2000 patients with HF and confirmed that BNP-guided treatment reduced all-cause mortality in patients less than 75 years old. Furthermore, BNP-guided treatment reduced hospitalizations caused by HF and cardiovascular disorders in all patients regardless of age or LVEF.[71]

MR-proANP has not been studied to the same extent as BNP or NT-proBNP for guiding therapy in HF or other conditions; however, some studies have suggested that it could be as useful. In a biomarker substudy of the PEACE trial, MR-proANP was one of 3 biomarkers showing an association between biomarkers levels and response to therapy with trandolapril.[62] If subjects had 2 or more of the biomarkers at increased levels, patients had an almost 50% reduction in cardiovascular death and incident HF with trandolapril, whereas subjects with none or 1 increased biomarker level did not derive benefit.[62] Another small study has suggested that MR-proANP can predict responsiveness to cardiac resynchronization therapy (CRT).[72] Patients who responded to CRT had lower MR-proANP levels at device insertion and levels decreased at 6 months compared with increased levels in nonresponders. Comparatively, midregional proadrenomedullin levels were lower at baseline in responders versus nonresponders, but levels did not change based on response at 6-month follow-up. NT-proBNP levels showed a trend to lower levels in responders versus nonresponders at baseline but decreased in both groups at 6-month follow-up. Increased levels of all 3 biomarkers were associated with higher rates of major adverse cardiovascular events at 2 years. Further studies are needed to establish whether MR-proANP can reproduce or enhance the findings that BNP and NT-proBNP have had at guiding treatment in HF.

### *Limitations of Natriuretic Peptide Measurement*

There are several factors that can increase baseline serum NP levels, including age, female gender, and renal dysfunction. Higher baseline levels of BNP have been observed with increasing age; however, the exact mechanism is unknown.[73] This age-related increase was independent of age-related diastolic dysfunction. Some investigators have hypothesized that this is caused by reduced expression of NPRs with age, which could result in decreased clearance of circulating BNPs in older patients.[11] Several studies have shown that women have higher levels of BNP and NT-proBNP.[73,74] These studies evaluated age-matched cohorts in which serum BNP and NT-proBNP levels were higher in women than in men at any age, although the reason for this finding was not clear.[73,74] Some have proposed that estrogen levels may play a role in this observation, because women on hormone replacement therapy had higher baseline serum BNP levels than those not taking hormone therapy.[73] However, NT-proBNP levels were not increased in women on hormone replacement, making the role of estrogen in NP levels less clear. In addition, renal dysfunction may cause increases in baseline serum NP levels, but the reason for this is not clearly understood. BNP is primarily cleared from circulation through degradation by circulating endogenous peptidases rather than by renal clearance.[75] The mechanism behind this observation is probably multifactorial, considering that patients with renal dysfunction tend to be older and less healthy, with higher intravascular volume and ventricular strain contributing to increased baseline BNP levels independently of renal function.

In contrast, several factors may decrease baseline serum BNP levels, including obesity and flash pulmonary edema. Although obesity is a well-documented factor that can decrease baseline serum BNP level, the exact mechanism behind this remains unclear.[74,76–78] Adipocytes are known to have increased concentration of NPRs, thus obese patients may have greater clearance of BNP by adipocytes.[79] However, other studies have shown a correlation between BNP levels and lean mass rather than fat, which contradicts this hypothesis.[80] It is less clear whether serum NT-proBNP level is similarly decreased in obese patients, and, unlike BNP, NT-proBNP is not cleared by NPRs (natriuretic peptide receptors). Regardless, NT-proBNP retains its diagnostic value in obese patients as long as it is measured against a known baseline value.[80] In addition, patients with early flash pulmonary edema may have lower than expected serum BNP levels. As discussed earlier, volume overload produces mechanical stretch on cardiomyocyte cell membranes, leading to downstream transcription and translation of BNP. Flash pulmonary edema occurs so rapidly that BNP is

not translated rapidly enough to be detected early in the disease course of these patients, making serum BNP less useful in this setting.[7]

Similar to BNP and NT-proBNP, certain caveats to MR-proANP interpretation should be noted. An analysis of the BACH study examined the influences of age, sex, race, and body mass index (BMI) on the diagnostic utility of MR-proANP and showed that it retained a high sensitivity regardless of these factors.[81] MR-proANP levels were noted to increase with age, decrease with BMI, and vary with race; however, a lower cutoff was only suggested for white patients younger than 50 years.[81] Other studies have confirmed the influence of BMI on MR-proANP levels.[58,82] In addition, levels go up with decreasing glomerular filtration rate (GFR), with one study suggesting potential adjustment in cutoffs based on GFR.[57,58,82,83] Overall, there are fewer studies evaluating factors influencing MR-proANP levels compared with studies for BNP and NT-proBNP, thus further study is needed to confirm these findings.

### *Measurement of B-type Natriuretic Peptide in Patients Taking Neprilysin Inhibitors*

The 2014 Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF) trial compared the novel neprilysin-angiotensin inhibitor LCZ696, a combination of the salt form of valsartan combined with sacubitril, with the ACE inhibitor enalapril and showed a dramatic improvement in the primary outcome of mortality and HF hospitalization with LCZ696.[84] Sacubitril is an inhibitor of neprilysin, a circulating neutral endopeptidase involved in the degradation of NPs.[85] As the clinical use of sacubitril-valsartan becomes more widespread, there is a growing concern that the measurement of serum NP levels in patients taking this drug may be problematic. In patients taking the neprilysin inhibitor, levels of BNP, which is broken down by neprilysin among other enzymes, may be increased because of decreased serum breakdown rather than because of change in underlying disease state (such as volume overload in AHF), potentially interfering with the prognostic and diagnostic utility of BNP.[86]

Results from the PARADIGM-HF trial did show that plasma BNP concentrations were significantly increased in patients taking sacubitril-valsartan versus enalapril, whereas NT-proBNP levels were significantly lower in the sacubitril-valsartan group.[87] However, the decreases were only modest and, although significantly different between the two treatment arms, the mean serum values in each group decreased to well within the anticipated variation of these biomarkers.[88,89] Neprilysin primarily breaks down ANP and CNP, whereas BNP may be more resistant to neprilysin cleavage.[90] As such, serum BNP levels may be less affected by neprilysin inhibition, as implied by initial interpretations of the PARADIGM-HF trial results.

Although more studies will be needed to determine the exact effect of neprilysin inhibition on BNP, there are some data to support that NT-proBNP may be more reliable in patients taking sacubitril.[86] The earlier Angiotensin Receptor Neprilysin Inhibitor LCZ696 in Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial examined effects of sacubitril-valsartan compared with valsartan alone in patients with chronic HF with preserved ejection fraction. Although significant early declines in NT-proBNP were observed at 12 weeks, NT-proBNP levels were no longer significantly different between the two groups after 36 weeks. Serum BNP was not measured in this trial.[91,92] At present, there are no published data on MR-proANP levels in patients taking sacubitril-valsartan.

## SUMMARY

Since their discovery in the 1980s, extensive research has shown the important physiologic actions NPs play in regulating the detrimental neurohormonal effects occurring in patients with HF. Thus, they serve as an appropriate and excellent surrogate marker for assessing HF. A summary of the clinical applications of the NPs discussed is shown in **Table 1**. Ample evidence has shown

**Table 1**
**Comparison of midregion of N-terminal Pro–atrial natriuretic peptide, B-type natriuretic peptide, and N-terminal pro–B-type natriuretic peptide in the management of heart failure**

| | MR-proANP | BNP | NT-proBNP |
|---|---|---|---|
| Diagnostic of HF? | +++ | +++ | +++ |
| Prognostic of HF? | ++ | ++ | ++ |
| Levels Change with treatment | +/– | +++ | ++ |
| Evidence for Guided Therapy | +/? | +/? | +/? |
| Levels affected by Entresto | ? | +/? | — |
| Useful for outpatient screening? | + | + | + |

the utility of BNP, NT-proBNP, and MR-proANP in the diagnosis of HF, leading to the ACC/AHA heart failure guidelines to give a class I recommendation to measurement of BNP or NT-proBNP in patients with AHF. Furthermore, there is considerable evidence showing the usefulness of NP for prognostication and guiding therapy. Also, the roles of NP assessment extend beyond HF to many other cardiovascular conditions. Although numerous clinical uses have been described for NPs, further roles are being explored in the prevention of HF and other cardiovascular and noncardiovascular conditions. Further research will surely expand the roles of NPs in the management of HF and other conditions.

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