Introduction

Natriuretic peptides (NP) have been the center of particular focus and discussion in the last several years. Their impact in cardiovascular and non cardiovascular medicine is persistently growing as we slowly begin to understand that their value may be beyond what we ever imagined. The discovery and isolation of atrial natriuretic peptide (ANP), a polypeptide hormone, secreted by the heart is credited to de Bold in 1979, although the secretory granules were first recognized in 1956 (1, 2). Natriuretic polypeptides hormones (NP) circulate and are stored in several forms namely ANP, brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). More recently, the fourth discovered NP was dendroapsis naturietic peptide, a D-type NP found in the green mamba that remains of unknown significance in humans. There has been extensive research on the role of NPs in cardiovascular disease state, and more specifically BNP and pro-BNP have become the center of attention to guide medical care in patients with congestive heart failure (CHF), coronary artery disease, and valvular heart disease (3). The purpose of this article is to provide an overview of the role of NPs in the pathogenesis of cardiovascular disease. We also discuss the diagnostic and prognostic utilities of NPs and their therapeutic roles in cardiovascular medicine. It is important to recognize that NPs have been linked to many noncardiovascular disease processes and may prove beneficial in their outcome, but the discussions of such studies are beyond the scope of this article.

Role of NPs in Pathogenesis of Cardiovascular Disease

BNP and ANP have a number of clinical effect including diuresis, natriuresis, direct vasodialation, inhibition of the renin–angiotensin system, and inhibition of cardiac hypertrophy (3, 4). ANP, BNP, and CNP all have a typical 17 amino acid ring structure formed by an intramolecular disulfide bridge. They all exist as prohormone which is further cleaved into N-terminal peptide and C-terminal (5). Figure 1 shows the structures of NPs.

There are three important NP receptors—NPR-A, NPR-B, and NPR-C. NPR-A and B are guanylyl cyclase receptors, acting through cyclic guanosine monophosphate as the second messenger, mediating all known effects of NPs (5). NPR-C acts in plasma clearance of NP along with renal excretion and plasma neutral endopeptidase to clear NPs from the body (5).

ANP is a 28 amino acid polypeptide mainly produced in the atrial myocytes. The prohormone is 126 amino acid polypeptide with the first 30 amino acids from the N-terminal end of the prohormone being long-acting NP, amino acids 31–67 from the N-terminal end being...
the vessel dilator, the amino acids 79–98 the kaliuretic peptide, and the amino acids 99–126 being ANP (6). The ANP prohormone in the kidney has additional four amino acids for urodilitan and present only intrarenally (6). ANP’s action consists of vasodilation, naturiesis, kaliuresis, inhibition of renin–aldosterone–angiotensin system and sympathetic nervous system through the NPR-A receptor (5). It has also been shown to be synthesized and secreted in the ventricles of patients with CHF (7).

BNP is a 32 amino acid polypeptide, first discovered from the brain, but then found to be mainly produced and secreted by the ventricle myocytes and to a lesser extent from the atria (6). Pro-BNP is a 108 amino acid polypeptide with the first 76 amino acids from the N terminal being pro-BNP, and 77–108 amino acids from the N terminal being BNP – both of which circulate in plasma of humans (6). BNP is produced by direct synthesis in response to the degree of ventricular stretch, and also upregulated in failing ventricular myocardium. The messenger RNA for pro-BNP is unstable, so there is active regulation of BNP levels according to ventricular wall tension. Hence, BNP acts as a reliable biomarker of ventricular dilatation (6). Like ANP, BNP action consists of vasodilation, naturiesis, kaliuresis, inhibition of renin–aldosterone–angiotensin system and sympathetic nervous system through the NPR-A receptor (5). Both NPs also use this same NPR-A receptor for antiproliferative effects on cardiac myocyte growth (8).

CNP exists as two polypeptides – one a 22 amino acid polypeptide and the other the 53 polypeptide amino acid. The 22 amino acid polypeptide is more potent of the two (6). Pro-CNP is the 126 amino acid precursor of CNP and is found in the central nervous system, vascular endothelium, and bones (6). It preferentially binds NPR-B. CNP plays a role in vascular tone (9), paracrine and autocrine function in the ossification process (10). CNP may also have neurotransmitter roles (10), and may provide protection against remodeling effects post MI (11, 12).

**Regulation and Induction of NPs in Heart Failure**

BNP is primarily controlled by the stretch of the atria and the ventricle and to a lesser degree by tachycardia and glucocorticoids (13). The release of BNP is modulated by both pressure and volume overload, therefore both left-ventricular chamber size and left-ventricular (LV) end diastolic pressure play a role in plasma concentration of BNP (13,14). ANP is released in response to increased transmural pressure (14). ANP gene regulation occurs slowly days after cardiac overload occurs but ANP is mainly stored in granules and can be secreted when stimulated with small changes like in exercise or in compensated heart failure even with normal LV end diastolic pressure (12,13). In contrast, BNP gene is activated within hours of myocardial stretch and due to high turnover is secreted in bursts; BNP is secreted in heart failure when the LV end diastolic pressure increases (12,13,15). BNP therefore has become pivotal in the acute setting for the diagnosis of decompensated heart failure (13). In a landmark study, Maisel et al. in 2001 showed that bedside BNP measurement can predict if diastolic and/or systolic dysfunction exists (16).

BNP and NT-pro-BNP both exist in plasma but have different half-life in plasma. BNP has a half-life of 20 minutes while NT-pro-BNP has a half-life of about 2 hours which leads to higher concentration and less fluctuation in plasma concentration compared to BNP (12). BNP and NT-pro-BNP are comparable but absolute levels are not the same (12). The choice of BNP versus NT-pro-BNP use is institutional but it is imperative to understand the difference between the two including that of renal function especially on NT-pro-BNP concentrations (12).

Table 1 compares BNP and NT-pro-BNP.

It is important to also note that there are additional factors that have been shown to affect BNP levels. In practice it is important to be aware of these pathological and physiological factors which will influence BNP levels. Table 2 lists factors that influence plasma BNP levels.

**Natriuretic Peptides: Diagnostic, Prognostic, and Therapeutic Recommendations**

**Diagnostic utilities**

**Heart failure**

The most extensively studied utility and most applicable use of BNP is in the setting of evaluation of patient with complaint of dyspnea or suspected heart failure in the emergency room (3).

- In the Breathing not Properly study, Maisel et al. found of 1586 patients in the emergency room
Table 1.
Distinguishing characteristics of BNP and NT-pro-BNP in diagnosing congestive HF.

<table>
<thead>
<tr>
<th></th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>32 amino acid peptide</td>
<td>76 amino acid peptide</td>
</tr>
<tr>
<td><strong>Half-life (mins)</strong></td>
<td>20</td>
<td>120</td>
</tr>
<tr>
<td><strong>Biological activity</strong></td>
<td>Active</td>
<td>Inactive</td>
</tr>
<tr>
<td><strong>Factors affecting NP levels:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary disease*</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Renal disease†</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Diastolic dysfunction‡</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Obesity§</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Flash pulmonary edema║</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Other causes#</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Diagnostic cut-off</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF present (pg/ml):</td>
<td>&gt;400</td>
<td>&lt;50 years: &gt;450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–75 years: &gt;900</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;75 years: &gt;1800</td>
</tr>
<tr>
<td>HF absent (pg/ml):</td>
<td>&lt; 100</td>
<td>&lt;75 years: 125</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;75 years: 450</td>
</tr>
<tr>
<td>Grey-zone (pg/ml)</td>
<td>100–400</td>
<td>&lt;50 years: 300–450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50–75 years: 300–900</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;75 years: 300–1800</td>
</tr>
</tbody>
</table>

* Pulmonary conditions (COPD, pneumonia, etc.) causing right ventricular dysfunction and pulmonary hypertension result in elevated NP levels in HF patients.
† HF patients with renal insufficiency often have elevated NP levels due to decreased glomerular filtration of peptides.
‡ Although NPs are unable to distinguish between systolic and diastolic HF, their high negative predictive values make them an effective screening tool in such patients.
§ In HF patients with BMI >35 kg/m² low NP levels are possibly due to increased clearance via adipocytes, thus using low cut-off values may improve diagnostic accuracy in such patients.
║ In the acute setting, NP levels may be deceivingly low, thus care should be taken to serially monitor NP levels in these patients.
# Patients with HF resulting from causes such as mitral incompetence, pericardial tamponade/constriction, which are upstream from the left ventricle, may also exhibit low NP levels.

BNP, B-type natriuretic peptide; NT-pro-BNP, amino-terminal B-type natriuretic peptide.

Table 2.
Pathologic and physiologic factors that result in the rise of BNP/NT-pro-BNP levels.

<table>
<thead>
<tr>
<th>Expected Rise</th>
<th>Unexpected Rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure Volume Overload</td>
<td>Increasing age</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Female Sex</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>Obesity</td>
</tr>
<tr>
<td>Systolic/diastolic dysfunction</td>
<td>Renal implant</td>
</tr>
<tr>
<td></td>
<td>Sleep apnea</td>
</tr>
<tr>
<td></td>
<td>Primary or secondary pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
</tbody>
</table>

who presented with acute dyspnea, 1538 (97%) had clinical certainty of CHF determined by the attending physician in the emergency department. Participants had BNP measured in a blinded manner and underwent routine care. Two independent, blinded, cardiologists determined the BNP reference for CHF. At 100 pg/mL BNP had a sensitivity of 90% and specificity of 73%. Also adding BNP to clinical judgment of CHF versus no CHF enhanced diagnostic accuracy from 74% to 81%. In those participants with an intermediate (21–79%) probability of CHF, BNP at a cutoff of 100 pg/mL accurately classified 74% of the cases. Maisel et al. also found that BNP alone for heart failure had a better predictive accuracy than the widely used NHANES and Framingham criteria of diagnosis of heart failure (83% vs 67% and 73%, respectively) (17).

The PRIDE study looked at the NT-pro-BNP in 600 patients who presented with dyspnea in the emergency department. The median NT-pro-BNP level among 209 patients (35%) who had acute CHF was 4054 pg/mL versus 131 pg/mL among 390 patients (65%) who did not (p <0.001). NT-pro-BNP values >450 pg/mL for patients <50 years of age and >900 pg/mL for patients ≥50 years of age were highly sensitive and specific for the diagnosis of acute CHF (p <0.001). Data also showed that NT-pro-BNP <300 pg/mL was most effective in “ruling out” CHF as a possible diagnosis with a negative predictive value of 99%. The study showed NT-pro-BNP as more accurate than clinical judgment alone for diagnosis of CHF (p=0.006) and also showed that NT-pro-BNP with clinical judgment proved more accurate than either alone (18).

In 2005, Wang et al. conducted a meta-analysis of 22 studies to distinguish heart failure from other causes of dyspnea in the emergency room based on history, symptoms, and routine diagnostic studies (chest radiograph, electrocardiogram, and serum BNP). The study showed that low serum BNP (BNP<100) proved to be the most useful test (negative LR = 0.11; 95% CI, 0.07–0.16) to rule out acute exacerbation of CHF (19).

These studies like others have time and time again showed the remarkable strength of NPs, specifically BNP and NT-pro-BNP, to be used in the diagnosis of acute decompensating heart failure. The efficiency of BNP and NT-pro-BNP in this setting was the starting point of their clinical use and has now dramatically progressed for further utility.

Recent studies have not only shown that baseline BNP is a great tool for efficiently triaging patients in the emergency room, they have also shown BNP to help in the decision to admit or discharge patients (3).

- The REDHOT study by Maisel et al. showed that the 90-day event rate in patients with baseline BNP <200 pg/mL was 9% and those with BNP>200 pg/mL with event rate of 29% (20).

Furthermore in diastolic dysfunction, plasma BNP was found to be of strong diagnostic utility and BNP correlated with LV end diastolic wall stress (21,22).

- Hitoshi et al. found that despite a similar distribution of LV mass index, the BNP level was higher in the diastolic dysfunction group than in the control group (149 ± 38 vs. 31 ± 5 pg/mL, p<0.01) (21).
- Iwanaga et al. found that plasma BNP levels reflect LV end diastolic wall stress more than any other parameter previously reported in patients with diastolic dysfunction (22).

**Acute Coronary Syndrome**

BNPs have naturally also been studied in other cardiovascular diseases and studies suggest that they may have a diagnostic role in acute coronary disease and atrial fibrillation. In acute coronary artery disease NP has been associated with an elevation in concentration in the absence of LV dysfunction (23).

- Lemos et al. found that BNP result in the first few days of ischemic symptoms had predictive value for use in risk stratification for all acute coronary syndromes (24).

**Atrial Fibrillation**

Data with atrial fibrillation and NP is limited, but BNP and NT-pro-BNP may have some diagnostic utility in atrial fibrillation.

- Patrick et al. found that in 150 patients with lone atrial fibrillation median levels of NT-pro-BNP were significantly elevated in subjects with lone AF as compared with control subjects (166 vs.133 fmol/
mL, \( p=0.0003 \). No such difference was found in pro-ANP (25).

- Kudsen et al. found similar findings with BNP, in which patients with Atrial Fibrillation without heart failure had significantly higher BNP levels \( (p=0.001) \) than those with heart failure with or without Atrial Fibrillation (26).

## Prognostic Utilities

### Heart Failure:

Plasma BNP has been evaluated as a predictor of outcome in both acute and chronic heart failure. In acute and chronic heart failure plasma BNP has been shown to be a strong indicator of death or cardiovascular events and seems to be a great marker for foreseeing patient outcome and for tailoring management particularly in those with high risk.

- Doust et al. did a systematic review of 19 studies, which used BNP to estimate the relative risk of death or cardiovascular events in heart failure patients, and five studies, which used BNP to estimate the relative risk of death or cardiovascular events in asymptomatic patients. The results showed that each 100 pg/mL increase in BNP in heart failure patients was associated with a 35% increase in relative risk of death. The study further showed that no variable was as significant as BNP in prognostic information for risk and may be a better predictor of survival than factors like left ventricular ejection fraction or NYHA (3,27).

- In the Valsartan Heart Failure Trial, plasma BNP and norepinephrine were measured before randomization and during follow-up in approximately 4300 patients. Those with baseline plasma BNP concentration in the highest quartile \( (\geq 238 \text{ pg/mL}) \) had significantly higher mortality at 2 years than those with BNP in the lowest quartile \( (<41 \text{ pg/mL}) \) (32.4 % versus 9.7%) (28).

- In the Acute Decompensated Heart Failure (ADHF) study, serial BNP was shown to have significant prognostic predictive value. The study included 300 patients admitted for acute de-compensated heart failure and underwent serial BNP and body water assessment with BIVA. Undesirable events included death and re-hospitalization which was monitored with a 6-month follow-up. On discharge, the group with BNP \( \leq 250 \text{ pg/mL} \) led to a 25% event rate within 6 months versus those in group with BNP \( >250 \text{ pg/mL} \) was associated with a 37% event rate (29).

From these studies it is conceivable that tailoring heart failure management to BNP levels during an acute exacerbation along with conventional therapy of managing body fluid levels could be predictive of upcoming admissions and important in lowering ill outcomes (28).

- In the Italian RED study, 287 patients with acute decompensated heart failure had BNP measurements at admission, at 24 hours, and at discharge. Follow-up was performed 180 days after hospital discharge. Data showed a BNP reduction of >46% at discharge had an area under curve (AUC) of 0.70 \( (p=0.001) \) for predicting future adverse events. Also, patient whose BNP level at discharge was >300 pg/mL and whose percentage decrease at discharge was <46% versus patients whose BNP level at discharge was <300 pg/mL and whose percentage decrease at discharge was >46% had an odds ratio of 9.614 \( (p<0.001) \). Patients with BNP at discharge <300 pg/mL and percentage change <46% versus those with BNP <300 pg/mL and percentage change >46% during hospitalization had odds ratio of 4.775 (95% CI 1.76–12.83, \( p<0.002 \)) for future adverse events (30).

This study showed that there is a strong negative predictive value with BNP reduction >46% during hospitalization and BNP levels of <300 pg/mL at discharge could be quite useful in stratifying patient risk in acute decompensated heart failure.

Additionally, recent studies have compared the utility of BNP versus NT-pro-BNP and their predictive outcomes.

- Noveanu et al. found that BNP and NT-pro-BNP levels did predict mortality at 30 days or 1 year, although neither proved accurate in predicting 1-year heart failure readmission. In those that passed away, the BNP did not change significantly during the hospitalization. Their multivariate analysis showed BNP at 24 h \( (1.02 \text{ HR [1.01–1.04 95% CI], } p=0.003) \), 48 h \( (1.04 \text{ HR [1.02–1.06 95% CI], } p<0.001) \), and discharge \( (1.02 \text{ HR [1.01–1.03 95% CI], } p<0.001) \) independently predicted 1-year mortality. Only predischarge NT-pro-BNP was
predictive of 1-year mortality (1.07 HR [1.01–1.13 95% CI], \( p=0.016 \)) (31).

The study emphasized the prognostic value of serial BNP levels and predictive capacity of predischarge NT-pro-BNP. The potential for serial NPs and mortality benefit further suggests that tailoring management with biomarkers would likely lessen morbidity and mortality in heart failure patients.

**Acute coronary syndrome**

In recent studies NPs have shown prognostic value in stable angina.

- Schnabel et al. conducted a study that compared 12 biomarkers in 1781 stable angina patients in relation to nonfatal myocardial infarction (MI) and cardiovascular death for 3.6 years. C-reactive protein, growth-differentiation factor (GDF)-15, neopterin, apolipoproteins AI, B100, cystatin C, serum creatinine, copeptin, C-terminal-pro-endothelin-1, mid-regional-pro-adrenomedullin (MR-pro-ADM), mid-regional-pro-atrial NP (MR-pro-ANP), NT-pro-BNP were investigated. Of these, NT-pro-BNP, GDF-15, MR-pro-ANP, cystatin C, and MR-pro-ADM were the strongest predictors of cardiovascular outcome in stable angina. Each marker had predictive value separately over established risk factors (32).

- Similar results were found in CLARICOR trial, where NT-pro-BNP was a stronger marker for MI, cardiovascular, and noncardiovascular death compared to HS-CRP in patients with stable CAD (33).

- Additionally, Shahabi et al. conducted a study of 92 patients who came in with the appearance of stable angina and were candidate for coronary angiography. Patients had NT-pro-BNP drawn prior to left heart catheterization from coronary blood sample. The study confirmed that plasma BNP level was a strong predictor for CAD severity (\( p=0.009 \)) (31). Also with all the patients with LV ejection fraction <40 the BNP was above 100 (34).

These studies have indicated that NT-pro-BNP may be beneficial in categorizing patients with stable angina in the outpatient setting for risks and prognosis of poor outcome.

In unstable angina and MI, BNP seems to also show prognostic utility in risk stratification of undesirable outcome.

- In the PROVE IT-TIMI22 trial, 3501 patients were involved in a study to assess growth differentiation factor 15 and association with mortality, MI, or heart failure in patients with acute coronary syndrome. After adjustment for risk factors BNP, growth factor 15, and HS-CRP was found to have significant association with death, MI, and CHF (35). Although, the trial was not specifically geared as a trial for BNP, the results reaffirm multiple past studies showing the prognostic value of BNP in ACS patients (36).

- In the AGUSTO-IV Substudy, elevation of troponin-T or NT-pro-BNP was associated with a significantly high mortality in NSTEMI patients. When NT-pro-BNP and troponin-T markers were elevated, a lower mortality status postrevascularization was seen. In patients without an elevation of NT-pro-BNP or Troponin-T, low mortality at 1 year remained without any reduction status postrevascularization. Further, the study showed that patients with normal levels of both troponin-T and NT-pro-BNP had a significant increase in 1-year mortality after revascularization (37).

The results of the GUSTO trial are indicative of the strength of NP for risk stratification in ACS and may even indicate the patients who would not benefit, or have worsened prognosis, from early revascularization.

- Ahmed et al. found similar findings in patients with unstable angina, non-ST elevation MI, and ST elevation MI. Their study showed that patients with BNP >80 had significantly more episodes of new heart failure, MI, or death than those with BNP <80. Also revascularization or coronary artery bypass in those with elevated BNP showed significantly improved outcomes versus those with low BNP (38).

The role of NPs in ACS is still not clearly determined and underutilized. The future of NPs in ACS is promising as more studies focus attention on this subject.

**Sudden cardiac death**

Several studies have shown that NP levels can be useful in sudden cardiac death as well (39,40).
Tapanainen et al. followed 521 post-MI patients and found that after adjustment for other variables, BNP (HR 3.9, 95% CI 1.2–12.3, \( p = 0.02 \)) and ejection fraction (40%) (\( p = 0.03 \)) were significant predictors of sudden cardiac death during 56 months follow-up, while ANP and NT-ANP did not meet significance (41).

**Valvular disease**

In valvular disease NPs show potential benefit due to known pressure and volume changes.

**Aortic stenosis**

- Rosca et al. recently found in a study with 48 patients with severe aortic stenosis (AS) (<0.6 cm²/m²) and preserved LV ejection fraction (≥50%) that the aortic stiffness or beta index (calculated with aortic diameters measured with echo and blood pressure) was significantly and independently correlated to BNP levels (\( r = 0.45, p = 0.001 \)) (42). The prognostic correlation may allow for tailoring treatment to use BNP along with usual guidelines for treatment (42).

There also have been studies that have shown that NT-pro-BNP is independently higher in patients who have symptomatic AS than those with asymptomatic AS (43). NT-pro-BNP was also shown to be higher with increase in NYHA class and decreasing LV function (43). And with severe AS, NT-pro-BNP independently predicted postoperative outcome in terms of survival (43).

**Aortic regurgitation**

- In chronic asymptomatic aortic regurgitation and normal ejection fraction, Pizarro et al. recommended that BNP be used routinely due to its incremental prognostic value. BNP was the strongest independent predictor by multivariate analysis of CHF, LV dysfunction, or death at follow-up (44).

- Similarly, other studies have shown that there is correlation of NT-pro-BNP with severity in patients with chronic aortic regurgitation (45).

It is understandable that the ventricle wall stretch owing to chronic aortic regurgitation could lead to BNP secretions and therefore its prognostic capabilities have been the focus of several studies.

**Mitral stenosis**

In patients with mitral stenosis, LV stretch is limited and therefore one might think that NP would be of limited use, but BNP has shown to improve risk stratification.

- Sharma et al. showed in a recent study of 30 patients with moderate to severe mitral stenosis that BNP had significant correlation with severity of disease. The study showed that increase in BNP associated with lower treadmill exercise capacity (AUC = 0.82 [95% CI 0.67, 0.97], \( p = 0.004 \)), associated with guidelines for intervention (AUC = 0.87 [95% CI 0.74, 0.99], \( p = 0.006 \)), and adverse events during follow-up (AUC = 0.81 [95% CI 0.64, 0.99], \( p = 0.03 \)). ANP did not have any additional predictive value (45). Also, an increased BNP was noted with larger left atrial area index, reduced mitral valve area, and higher resting pulmonary artery pressure (46).

**Mitral regurgitation**

- Magne et al. recently showed that in asymptomatic patients with mitral regurgitation, BNP had a strong graded relationship to adverse event (46). Left atrial volume and LV strain correlated with BNP levels and are likely the etiology behind the elevation of BNP in mitral regurgitation (47).

Similar findings have been seen in other studies as well (48).

The role of NP in valvular disease still needs further discussion and no clear guidelines exist for their use. However, many studies are suggesting their guidance as a powerful tool for patient prognosis.

**Therapeutic Role of NPs**

Given the predictive capacity of NPs in cardiovascular disease it is only natural that many studies have focused their attention on their therapeutic use in hopes of reducing risk of poor outcome.

- In the ADHF study, patients’ treatment was guided whenever possible to BNP <250 pg/mL and the combination of BNP and BIVA (used for fluid status) was used to tailor therapy and showed that BNP/BIVA could be used to adequately achieve fluid balance (29). The hope would be that using NPs in this capacity would decrease the burden of morbidity and mortality especially if high-risk patients can be identified and treated aggressively with a biomarker-tailored plan in a time-efficient manner (49).
In the TIME-CHF trial, Busser et al. treated heart failure guided by N-terminal BNP versus symptom-guided therapy. Heart failure guided therapy did not show improvement in overall clinical outcomes or quality of life compared with symptom-guided treatment. But interestingly, therapy guided by NT-BNP improved outcomes in patients aged 60–75 years but not in those patients who were older (P<0.02 for interaction) (50).

In recent Pro-BNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study, patients treated with biomarker-guided care was shown to have improved quality of life and significantly better reverse remodeling on echocardiography compared with patients with standard care (BNP, 100 pg/mL; NT-pro-BNP, 1000 pg/mL) (51).

NP-guided therapy also showed mortality benefit in the BATTLESCARRED study, where >300 chronic heart failure patients underwent treatment based on NT-pro-BNP, or intensive clinical management, or usual care. At 1 year, mortality was 9.1% in both NP-guided and intensive clinical management groups, but higher at 18.9% (p=0.03) for the usual management group. At 3 years follow-up, mortality for those patients <72 years was much less at 15.5% for those in the hormone-guided treatment, compared with patients in intensive clinically managed treatment (30.9%; p=0.048) or usual care (31.3%; p=0.021) (52).

There have been several studies mainly in heart failure for tailored treatment guide using NPs and although there are promising results in some studies as mentioned above, others have been equivocal (53). Nevertheless, there seems to be a sway toward the fact that NPs, specifically BNP/NT-pro-BNP, confer an outcome benefit when treated to lower levels in heart failure patients. This seems to be particularly true in patients under 72 years old.

### NPs in Eastern Indians

The role of NPs in cardiovascular disease in the east Indian population has not been specifically studied (54). With the ongoing studies on NP-guided therapy around the world and their suggested prognostic and therapeutic roles, it would only be reasonable to conduct studies in the Indian population. Studies like BASEL (BNP for Acute Shortness of breath EvalUation) and IMPROVE-CHF (Improved Management of Patients with Congestive Heart Failure) have also shown cost-saving benefit and effectiveness of BNP in the diagnosis of heart failure (55, 56). From the data seen it is likely that NP will help in the diagnosis and management of heart failure in Indians but to what extent still remains an unknown and can only be discovered by further study. It would also be interesting to do substudies in Indians abroad and compare NP utilities to those in India.

### Conclusion

NPs have become the center of immense discussion and curiosity during the last several years due to the growing discovery of their utility. They were landmark in heart failure diagnostics and eventually found to be of prognostic value and growingly felt to be of therapeutic value in treatment of heart failure by experts. Studies are also showing that NPs can be an immense source of diagnostic, prognostic, and likely therapeutic influence in coronary artery disease and other cardiovascular diseases. Our knowledge is still growing when it comes to these biomarkers and we remain very limited in research of NPs in certain populations including Indians. Given the recent studies that have been discussed about NPs in this article, it would be crucial to further study these biomarkers in Indians in hopes of better prognostic, diagnostic, and therapeutic measures in cardiovascular diseases in Indians.

### Conflict of Interest

Alan Maisel – Consultant: Alere, Critical Diagnostics, EFG

Research support: Alere, Abbott, Nanosphere, Brahms-Thermofisher, Novartis

### References


