Natriuretic Peptides in Heart Failure and Acute Coronary Syndrome

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KEYWORDS

• Laboratory medicine • Cardiac markers • Biomarkers • BNP • NT-proBNP
• Heart failure • Acute coronary syndrome • Natriuretic peptides

KEY POINTS

- B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are the gold standard biomarkers in determining diagnosis and prognosis in patients with heart failure (HF).
- BNP and NT-proBNP may be useful in guiding HF management, but further studies are needed before natriuretic peptide-guided HF care can be routinely recommended.
- Midregional pro-atrial natriuretic peptide shows promise in determining diagnosis and prognosis in HF patients.
- Although the pathophysiology behind elevated BNP or NT-proBNP levels in patients with acute coronary syndrome remains elusive, BNP or NT-proBNP may be of use for excluding myocardial infarction and are independently predictive of risk following acute myocardial infarction. Therapeutic implications of natriuretic peptides in patients with acute myocardial infarction are unclear.

The number of patients affected by cardiovascular (CV) disease, such as heart failure (HF) and coronary heart disease (CHD), is growing at an alarming pace. Fortunately, the science supporting the evaluation and management of these diseases is advancing rapidly; the use of biomarkers has added valuable biologic information to the understanding of disease processes and in certain circumstances has added considerably to standard clinical assessment of patients affected by heart disease.

Funding Sources: Dr H.K. Gaggin is supported in part by the Ruth and James Clark Fund for Cardiac Research Innovation, and Dr J.L. Januzzi is supported in part by the Roman W. DeSanctis Clinical Scholar Endowment.
Disclosures: Dr J.L. Januzzi reports research grants from Roche Diagnostics, Siemens Diagnostics, Critical Diagnostics, and BRAHMS. Dr H.K. Gaggin does not have any disclosures.
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Clin Lab Med 34 (2014) 43–58
http://dx.doi.org/10.1016/j.cll.2013.11.007 **labmed.theclinics.com**
0272-2712/14/$ – see front matter

Natriuretic peptides (NP), in particular, have played an important role in the evaluation and management of CV disease, including HF and CHD.

NP

The history of the NP class of biomarkers dates back to 1950s when early electron microscopy studies reported dense granules in the atrial myocardium similar to glandular tissue from endocrine organs.[1] Soon, the close interplay between atria and intravascular volume was revealed; stretching of canine left atrium increased urine output[2] and injection of atrial tissue into rats caused diuresis and natriuresis.[3] Atrial natriuretic peptide (ANP) was subsequently purified, sequenced, and reproduced. A homologous peptide named B-type natriuretic peptide (BNP) was discovered in porcine brain and was shown to have similar biologic activity as ANP.[4] Other NPs that share a common biochemical structural feature, a 17-amino-acid ring and a disulfide bridge between 2 cysteine molecules, have been discovered since: urodilantin (an isoform of ANP), C-type natriuretic peptide, and Dendroaspis natriuretic peptide.[5]

Of these, there is a large body of evidence supporting the use of BNP and its biologically inert counterpart, N-terminal B-type natriuretic peptide (NT-proBNP); these peptides will be the major focus of this article. It is now widely known that BNP and NT-proBNP are both elevated in other CV disorders including CHD.

Physiology

Unlike ANP, which is presynthesized and stored in granules before being released by a stimulus, the B-type peptides' release into circulation is largely regulated at the level of the BNP gene expression. The BNP gene is strongly induced in response to myocardial stretch, predominantly from elevated left ventricular (LV) volume or pressures, and the stretch is thought to be the principal stimulus for BNP production.[6] However, other processes also contribute to the activation of the BNP gene, such as inflammation, activation of the sympathetic nervous system, and the renin-angiotensin-aldosterone system as well as myocardial ischemia.[7–9] Some suggest that there may be an alternative mechanism of rapid BNP release because BNP levels can increase faster than expected from the gene induction pathway in the setting of acute coronary syndrome (ACS), but the exact mechanism remains elusive.

Transcription of the BNP gene first results in a 134-amino-acid intracellular pre-pro-peptide, which is rapidly processed to a 108-amino-acid precursor peptide, $proBNP_{1\text{-}108}$. This peptide is cleaved into the biologically active 32-amino-acid BNP and a biologically inert 76-amino-acid, NT-proBNP, before being released into circulation within minutes of their production (**Fig. 1**). The degree of peripheral conversion of $proBNP_{1\text{-}108}$ is not known, but it is clear that a certain percentage of uncleaved pro-peptide is also released, particularly in those with more advanced HF.

BNP binds to membrane-bound natriuretic peptide receptors (NPR) type A and B, activating intracellular cyclic guanosine monophosphate and starting a cascade of events that attempt to compensate for the unhinged hemodynamics in HF patients, including natriuresis, diuresis, vasodilation, inhibition of renin and aldosterone, and inhibition of fibrosis.[10–13] BNP is removed from circulation by both receptor-mediated mechanisms (NPR type C) and enzymatic processes (neutral endopeptidases, meprin-A, and dipeptidylpeptidase-IV present in various tissues).

On the other hand, NT-proBNP is passively cleared by multiple organs with high blood flows, including the kidneys. About a quarter of both BNP and NT-proBNP are cleared by renal mechanisms, down to an estimated glomerular filtration rate of less than 15 mL/min/1.73 m^2.[14] Because of the above-mentioned differences in the

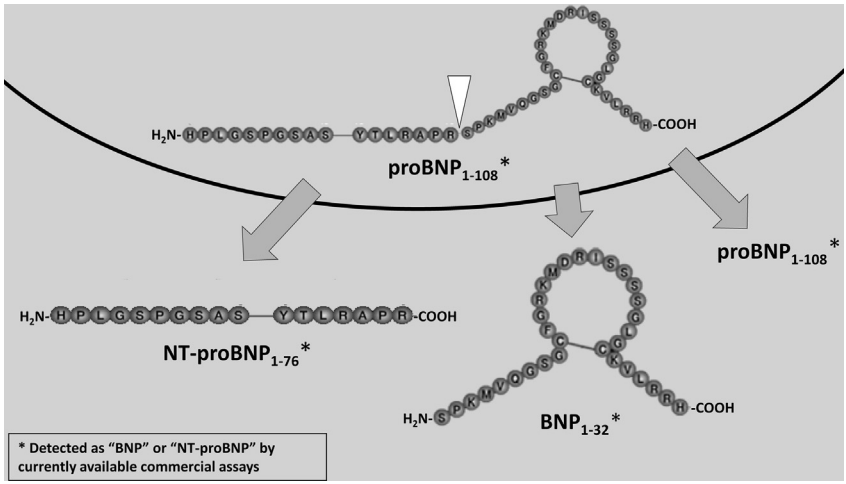

Fig. 1. BNP and NT-proBNP formation (Arrowhead: cleavage site, Arrows: movement out of the cell).

mechanism of clearance, the circulating half-life of BNP is much shorter at about 20 minutes, whereas that for NT-proBNP is longer at about 70 minutes (**Table 1**).[15,16]

Analytical Properties

Preanalytically, NT-proBNP is accepted to be more biochemically stable than BNP. BNP, when left at room temperature or when without a protease inhibitor such as ethylenediaminetetraacetic acid (EDTA) added, is prone to degradation, with rapid loss of immunoreactive peptide. BNP should be drawn into plastic rather than glass tubes because of degradation. NT-proBNP, on the other hand, is much more flexible; it can be drawn into glass or plastic tubes and does not require an addition of protease inhibitors such as EDTA. NT-proBNP can be drawn into serum, heparin plasma, or EDTA. The intra-individual, day-to-day biologic variation in stable HF patients is about 38% for BNP and 28% for NT-proBNP[17]; in patients without HF, these figures are considerably larger, but it is worth noting that substantially higher biologic variation in patients with extremely low concentrations is rarely of clinical importance.

Analytically, most of the commercially available assays for BNP and NT-proBNP are sandwich immunoassays, which considerably improved the specificity as well as sensitivity of enzyme-linked immunosorbent assays. Although there is no cross-reactivity between BNP and NT-proBNP assays, recent evidence suggests that a substantial percentage of what is detected as "BNP" or "NT-proBNP" by available immunoassays for each may in fact be a mixture of the targeted protein as well as (as noted above) uncleaved $proBNP_{1\text{-}108}$; in the case of BNP, various degraded fragments are also detected.[18] The mechanism explaining the release of $proBNP_{1\text{-}108}$ is not known, but studies have shown that circulating $proBNP_{1\text{-}108}$ concentrations are elevated in patients with more advanced HF. Importantly, $proBNP_{1\text{-}108}$ has reduced or absent biologic activity relative to BNP[19]; the lack of a diuretic and natriuretic effect is clearly deleterious to the patient with HF and implies a potential therapeutic target for future therapies that may address the handicap in cleavage of this important cardiac hormone.

Table 1
Biochemical properties of prominent NP

	Size (kDa)	Half-Life (min)	Normal Ranges Male (pg/mL)	Normal Ranges Female (pg/mL)	Clearance	Biologic Activity	In Vitro Stability at Room Temperature	Biologic Variability (%)[a]
BNP	3.5	21	8.0	13.9	NPR type C, neutral endopeptidases, meprin-A, and dipeptidylpeptidase-IV	Active	6 h	38
NT-proBNP	8.5	60–120	46.9	64.3	Passively cleared through multiple organs	Inactive	>3 d	28

[a] Intra-individual, day-to-day biologic variation in patients with established HF.

With fully automated immunoassays, the turn-around time for BNP and NT-proBNP are acceptable, and precision is excellent. Whole-blood point-of-care assays for BNP or NT-proBNP are available, providing much more rapid turn-around time than automated assays, but with considerably greater costs and analytic performance is not as precise.

Postanalytically, for BNP, reference ranges have to be separately determined for each assay and the resulting BNP values cannot easily be compared between different assays. On the other hand, NT-proBNP values across different assays can be compared with only modest differences in results as the methods are based on the same antibodies.

HEART FAILURE

BNP and NT-proBNP

The introduction of BNP and NT-proBNP has considerably altered the evaluation of patients with HF in the recent decades; these biomarkers have been established as the gold standard for biomarker-driven diagnosis and prognostication. Despite recent revelation that conventional assays may measure a combination of the "target" peptide, they were designed to detect variable amounts of $proBNP_{1\text{-}108}$,[19] concentrations of BNP or NT-proBNP as measured by commercially available assays that nonetheless have an established track record of utility and accuracy for the diagnosis and prognostication in HF.[20] In addition, these NPs may have therapeutic application in guiding HF therapy.

Diagnosis: acute setting

In a seminal trial of 1586 patients presenting with acute dyspnea to the emergency department, the Breathing Not Properly Study Multinational Study[21] showed that patients with acute decompensated HF (ADHF) had significantly higher BNP concentrations compared with patients without HF (mean 675 $\pm$ 450 vs 110 $\pm$ 225 pg/mL, $P<.001$). In addition, BNP concentrations were directly associated with increasing severity of HF symptoms. The diagnostic accuracy of a BNP measurement greater than 100 pg/mL surpassed any other single findings from routine evaluation including history and physical examination, chest x-ray, or laboratory tests in identifying HF as the cause of dyspnea (sensitivity of 90%, specificity of 76%, and accuracy of 85%). BNP performed better than established clinical HF criteria such as the National Health and Nutrition Examination Survey criteria (accuracy = 67%) or the Framingham criteria for the diagnosis of HF (accuracy = 73%) and added independent information to the traditional evaluation of these patients. The diagnostic performance of BNP for ADHF can be summarized by its receiver operating characteristic curve area under the curve (AUC) of 0.91 (95% confidence interval [CI] = 0.90–0.93; $P<.001$).

Excellent diagnostic performance has also been established for NT-proBNP. In a cohort of patients presenting with dyspnea to the emergency department, the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study[22] showed that patients with ADHF had much higher NT-proBNP concentrations compared with patients without HF (median 4054 vs 131 pg/mL, $P<.001$) and higher NT-proBNP concentrations were also directly associated with increasing severity of HF ($P = .001$). Of all single traditional HF evaluation techniques, NT-proBNP was the strongest predictor of the diagnosis of ADHF (**Table 2**). The diagnostic accuracy of NT-proBNP was stronger than that of clinical judgment alone (AUC of 0.94 vs 0.90), but the best way to accurately diagnose ADHF was by using a combination of NT-proBNP and clinical judgment (AUC 0.96). A single NT-proBNP cutoff value of 900 pg/mL provided identical performance to that reported for a BNP value of 100 pg/mL. In subsequent

Table 2
Multivariable predictors of acute decompensated HF

Predictor	Odds Ratio	95% CI	*P* Value
NT-proBNP	44.0	21.0–91.0	<.0001
Interstitial edema on CXR	11.0	4.5–26.0	<.0001
Orthopnea	9.6	4.0–23.0	<.0001
Loop diuretic use	3.4	1.8–6.6	.01
Rales	2.4	1.2–5.2	.05
Age	1.03 (per year)	1.01–1.05	.01
Cough	0.43	0.23–0.83	.05
Fever	0.17	0.05–0.50	.03

Data from Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005;95:948–54.

studies, a 3-tiered age-stratification approach for upper reference limits was found to be superior to a single cutoff (**Fig. 2**; recommended cutoffs: ≥450 for ages <50 years, ≥900 for ages 50–75 years, and ≥1800 pg/mL for ages >75 years).[23] An NT-proBNP cutoff point of less than 300 pg/mL was especially useful in excluding ADHF with near 100% negative predictive value.

The addition of BNP and NT-proBNP to traditional evaluation of HF patients has been particularly valuable in patients with increased diagnostic uncertainty as determined by traditional assessment. Diagnostic uncertainty, seen in up to 30% of patients presenting with dyspnea, is associated with increased short-term risk.[24] Investigators from the Improved Management of Patients With Congestive Heart Failure (IMPROVE-CHF) study showed that NT-proBNP was particularly useful in correctly reclassifying patients with increased diagnostic uncertainty.[25]

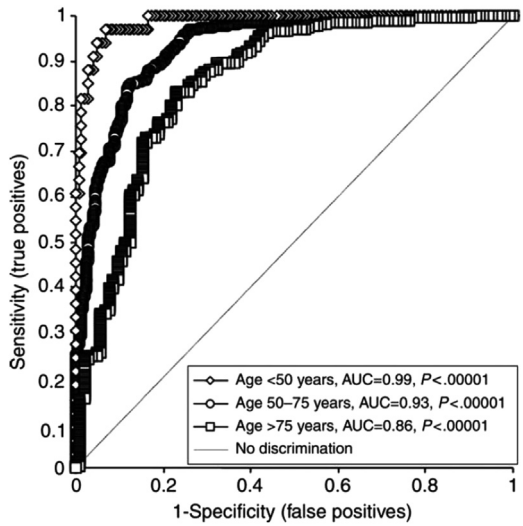

Fig. 2. Receiver operating curve for the diagnosis of acute heart failure by age-stratified NT-proBNP cutoff points. (*From* Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27:330–7; with permission.)

Beyond an improvement in diagnostic performance, adding information derived from these NP measurements appears to improve cost-effectiveness and resources utilization. Several studies including the B-type natriuretic peptide for Acute Shortness of breath EvaLuation (BASEL) study,[26] the IMPROVE-CHF,[25] study and the PRIDE study,[27] all showed cost savings with a diagnostic evaluation that included BNP or NT-proBNP measurement. The BASEL study showed that the group with a diagnostic strategy involving BNP measurement had a decreased need for hospitalization and intensive care without excess hazard. In the IMPROVE-CHF study, NT-proBNP supplemented evaluation strategy was associated with better clinical outcomes as well.

Notably, both BNP and NT-proBNP concentrations are typically lower in HF patients with preserved ejection fraction (EF) or HFpEF compared with HF patients with reduced EF (HFrEF), but the same respective cutoff points for BNP and NT-proBNP have been shown to diagnose ADHF accurately regardless of EF, albeit with a slightly reduced sensitivity for HFpEF.[28,29] Clinicians should be aware of the potential for a "false negative" result for both peptides in this setting, therefore.

Approximately 20% of patients tested with BNP or NT-proBNP will have values in between the cutoff point optimized to exclude HF and the cutoff point optimized to diagnose HF; this is known as a result in the "gray zone." With NP values that fall in the gray zone, clinical evaluation becomes even more important. More importantly, gray zone values are associated with a risk higher than those not in the gray zone.[30]

Diagnosis: outpatient setting

Most studies evaluating the use of BNP and NT-proBNP in the outpatient setting have focused on the negative predictive value of either peptide to exclude HF. Using lower optimal cutoff points of less than 40 pg/mL for BNP, and less than 50 pg/mL for age less than 50 years, less than 75 pg/mL for ages 50–75 years, and less than 250 pg/mL for age greater than 75 years for NT-proBNP, negative predictive values approach 95% to 99%.[31] In those with elevated values, to determine a diagnosis of HF, however, further evaluation such as echocardiography is needed. In patients without any symptoms, BNP or NT-proBNP may potentially be used for the purpose of screening at-risk patients for the presence of underlying structural heart disease; they have been found to be useful for both reduced LV function and diastolic ventricular dysfunction.[32]

Factors that influence NP values

There are some important caveats to be cognizant of when interpreting BNP or NT-proBNP results; both advanced age and male sex can lead to higher than expected BNP or NT-proBNP values, for example, whereas other factors can lead to lower than expected results. Clinicians should have a good understanding of the broad factors that may influence both peptides either upwards or downwards.

First, BNP or NT-proBNP values are often elevated in patients with significant CV disorders without HF, many of them associated with elevated filling pressures such as apical ballooning syndrome, myocarditis, ACS (more details in the later section titled "CHD Including ACS"), valvular heart disease (either stenotic or regurgitant), arrhythmias such as atrial fibrillation or flutter, as well as cardiotoxic drugs such as anthracycline chemotherapy.

Not surprisingly, many pulmonary disorders that result in elevated right ventricular pressures are also associated with elevated levels of these NPs: pulmonary embolism, pulmonary hypertension, congenital heart disease, and sleep apnea. In addition, most critical illnesses are associated with increased NP levels, although the exact mechanism is less clear: acute stroke, severe anemia, bacterial sepsis, severe burn, and acute respiratory distress syndrome. In most of these cases, the extent of BNP or

NT-proBNP elevation is not quite as high as the cutoff points used to diagnose ADHF, but clinical judgment is crucial in correctly interpreting NP concentrations in such patients. In addition, even in these "non-HF" causes of BNP or NT-proBNP elevation, the prognostic value of the peptides hold.

There is an intimate relationship between renal function and BNP or NT-proBNP values; patients with chronic kidney disease typically have higher NP concentrations in parallel with the severity of renal disease. As the clearance of both BNP and NT-proBNP is partially dependent on the kidneys, there is no doubt of an amount of peptide accumulation with renal dysfunction. In addition, patients with renal dysfunction tend to have comorbid CV disorders that are associated with elevated BNP or NT-proBNP values including LV hypertrophy and chronic volume overload state. In patients with renal dysfunction, a slightly higher BNP cutoff of 200 pg/mL or NT-proBNP of 1200 pg/mL can be used with a good accuracy. Alternatively, the age-stratified NT-proBNP values, as used in patients without renal dysfunction, can be used as the cutoff with similar results.

On the other hand, certain states are associated with lower than expected BNP or NT-proBNP concentrations. Patients with elevated body mass index (BMI) tend to have lower BNP or NT-proBNP values compared with leaner counterparts. This occurrence is thought to be due to suppression of synthesis or release of NPs in obese patients. Nevertheless, the diagnostic accuracy of NP cutoff points (age-stratified cutoff points for NT-proBNP) used to diagnose ADHF remained acceptable regardless of BMI (AUC of 0.94 for lean, 0.95 for overweight, and 0.94 for obese patients),[33] although BNP shows slightly lower sensitivity in those with high BMI and lower cut-offs have been advocated.

Prognosis in HF

Concentrations of BNP or NT-proBNP have been shown to be strongly predictive of clinical outcomes in a wide range of populations including healthy subjects, patients at high risk for developing HF, asymptomatic patients with LV dysfunction, and symptomatic and/or advanced HF patients. Doust and colleagues[34] polled data from 19 HF studies in a systematic review including 5 studies with patients with asymptomatic LV dysfunction. They showed that each 100 pg/mL increase in BNP was associated with a 35% increase in relative risk of death.

In patients with symptomatic HF, studies have consistently demonstrated the prognostic significance of elevated BNP or NT-proBNP. In 48,629 patients hospitalized for acute exacerbation of HFpEF or HFrEF,[35] a single elevated BNP value was robustly associated with increased in-hospital mortality; in addition, there was a direct relationship between quartiles of BNP concentration and mortality even after adjusting for multiple confounders including age, gender, vital signs, renal function, and sodium. Similarly, NT-proBNP values at the time of admission also strongly predict short- and long-term clinical outcomes.[23,36] For example, Januzzi and colleagues[36] showed that the optimal NT-proBNP cutoff point for 1-year mortality was 986 pg/mL (sensitivity = 79% and specificity = 68%, $P<.001$). In a multivariable model that included traditional risk factors for HF outcomes, NT-proBNP greater than 986 pg/mL was the strongest predictor with a hazard ratio of 2.88 (95% CI 1.64–5.06, $P<.001$).

In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure trial, BNP values taken at admission and discharge were examined; the median admission BNP value was 832 pg/mL and discharge BNP value was 534 pg/mL. Although admission, discharge, and a change in BNP value from admission to discharge all added incremental prognostic information to the base clinical

model, the best predictor was the discharge BNP value obtained after inpatient therapy for ADHF. Similar results were reported by Bettencourt and colleagues[37] whereby a lack of reduction in NT-proBNP was associated with greater risk. In aggregate, it would appear that while a baseline measurement for BNP or NT-proBNP in ADHF is prognostic, a follow-up, posttreatment measurement adds incremental prognostic value.

Relative to chronic HF, similar findings have been found. In a large analysis of patients with chronic HF from the Valsartan Heart Failure Trial (Val-HeFT) trial,[38] similar to findings from a study of patients with ADHF, BNP was the single strongest predictor of mortality among traditional risk factors; a single plasma BNP value $\geq$238 pg/mL predicted mortality at 2 years (**Fig. 3**) better than a low BNP value less than 41 pg/mL (32.4 vs 9.7%). Similar findings are seen with NT-proBNP. As a matter of fact, investigators from the same group[39] showed that BNP and NT-proBNP performed almost identically in predicting all-cause mortality in chronic HF (AUC was 0.665 for BNP vs 0.679 for NT-proBNP, $P = .07$). NT-proBNP was superior to BNP for predicting mortality and morbidity ($P = .03$) or hospitalization for HF ($P = .01$).

In analogy to patients with ADHF, serial assessment with BNP or NT-proBNP for prognosis in chronic HF has revealed that changes in NP concentrations over time with medical therapy can predict clinical outcomes; again, in the Val-HeFT study, when NT-proBNP was measured at baseline and at 4 months, the change in NT-proBNP concentrations was superior to a single baseline value for predicting all-cause mortality.[40]

Management

Shortly after studies reported that change in BNP or NT-proBNP was associated with a change in prognosis and that therapies for HF may lower NP concentrations, it was not long before investigators began to examine the role of NP-guided HF management. Conceptually, the use of either peptide to guide therapy is based on the concept that BNP and NT-proBNP inform a broad array of pathophysiology and do so in a manner that augments clinical judgment. That therapies with salutary effects in HF

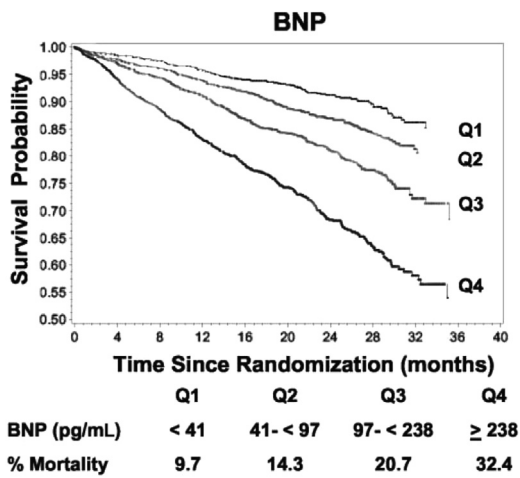

Fig. 3. All-cause mortality and first morbid event by BNP quartiles. (*Reproduced from* Anand IS, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;107:1280; with permission.)

(such as β-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, as well as cardiac resynchronization therapy) all reduce NP concentrations[41] has given further enthusiasm to explore this strategy in depth.

A pilot study[42] from the Christchurch Cardioendocrine Group first randomized patients with chronic HF to standard of care only, or standard of care plus NT-proBNP-guided HF therapy and showed promising results in improving clinical outcomes with guided care. Since then, several studies have evaluated the role of BNP or NT-proBNP-guided HF management with mixed results.[43] However, there was great heterogeneity in study designs (in particular, target biomarker concentrations, study population characteristics, and resulting biomarker changes with biomarker-guided care) and many of the studies were underpowered. When results from available randomized trials were pooled, a 20% to 30% mortality reduction with biomarker-guided HF management over standard HF care has been observed.[44,45] A large prospective randomized trial based on the successful ProBNP Outpatient Tailored Chronic HF Therapy study[46] is now underway.

ANP

Circulating concentrations of ANP increase dramatically and rapidly with myocardial stretch. ANP's rapid response to changing hemodynamics is because it is premade and stored in the myocardium, which contrasts to the B-type peptides. However, the half-life of ANP is extremely short at 2 to 5 minutes, which makes its reliable detection difficult and dilutes its clinical value. Recently, a renewed focus has been placed on ANP as its immediate precursor protein, proANP, appears to have a longer half-life. A novel assay that detects the midregion of proANP (MR-proANP) has been developed and evaluated for its role in HF.

Measurement of MR-proANP was noninferior to BNP or NT-proBNP for diagnosing ADHF and, in combination with established NPs, appeared to improve on the diagnostic performance. In 1641 patients with acute dyspnea in the Biomarkers in the Acute Heart Failure trial,[47] MR-proBNP $\geq$120 pmol/L had a sensitivity of 97%, specificity of 60% with accuracy of 74% for the diagnosis of ADHF. In the PRIDE study,[48] MR-proANP was inferior to NT-proBNP in the diagnosis of ADHF (AUC of 0.90 for MR-proANP vs 0.94 for NT-proBNP, $P = .001$ for difference), but MR-proBNP added independent and additive information beyond NT-proBNP in a multivariable analysis (odds ratio = 4.34, 95% CI = 2.11–8.92, $P<.001$). Furthermore, MR-proANP correctly reclassified patients who had false negative and false positive results by NT-proBNP testing alone. MR-proANP appears to be similarly affected by covariates that also reduce diagnostic accuracy of BNP or NT-proBNP such as age, renal function or obesity.[48]

MR-proANP has been shown to predict clinical outcomes in both acute and chronic HF patients as well. In the PRIDE study, MR-proANP concentrations independently predicted 1- and 4-year mortality in acute HF patients in a model that included NT-proBNP and showed promise as a part of a multimarker strategy. Similar findings were found in patients with chronic HF; in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure (GISSI-HF) study,[49] MR-proANP $\geq$278 pmol/L strongly predicted 4-year mortality, beating out other novel and established biomarkers such as NT-proBNP, midregional proadrenomedullin, C-terminal provasopressin (copeptin), and C-terminal proendothelin-1. In the GISSI-HF study, a change in MR-proANP over 3 months also predicted mortality, but no studies have evaluated the possibility of MR-proANP-guided HF management to date.

CHD INCLUDING ACS

Disruption of the normal cardiomyocyte membrane results in release of inner contents of the cell into extracellular space, with detectable increase of such contents in peripheral blood; these include cellular and structural proteins such as troponin, creatine kinase, myoglobin, and cardiac fatty acid binding protein. Of these, cardiac troponins have been established as the gold standard biomarker in diagnosing myocardial infarction (MI).[50] Intriguingly, elevated levels of BNP and NT-proBNP, traditionally thought of as HF biomarkers, have been detected in patients with ACS.[51] Most studies for NP in ACS have been with regards to risk stratification, whereas few studies have evaluated its role in diagnosis of ACS in combination with the standard of care biomarker, cardiac troponins.

Diagnosis in ACS

Morita and colleagues[51] examined BNP levels in patients presenting with suspected ACS and found that BNP concentrations were elevated in patients with MI compared with those without (mean 92 vs 5.2 pg/mL on presentation, $P<.01$) and peaking at a mean level of 319 pg/mL about 16 hours after admission. The extent of BNP or NT-proBNP elevation seemed to be related to the degree of infarct size and myocardial dysfunction.[52] The widely accepted reason behind NP elevation is increased wall tension due to LV systolic or diastolic dysfunction caused by myocardial ischemia through rapid induction of BNP gene expression.[9] However, there are data to suggest that BNP and NT-proBNP may be directly released from cardiomyocytes in response to myocardial ischemia regardless of ventricular wall stress.[53] Theories abound regarding cause, including the activation of the inflammatory pathway; BNP's structure is thought to be similar to some of the acute phase reactants.

The diagnostic use of BNP or NT-proBNP in patients presenting with acute chest pain was evaluated in 328 patients from the Rule Out Myocardial Infarction using Computer Assisted Tomography trial.[54] Patients with ACS had higher concentrations of NT-proBNP, conventional cardiac troponin T (cTnT), highly sensitive cardiac troponin T (hsTnT), and MR-proANP; adding NT-proBNP to either cardiac troponin improved diagnostic performance for ACS by correctly reclassifying events. The best approach was in a dual-negative marker strategy with improved sensitivity and negative predictive value for ACS on presentation with a single time measurement (sensitivity: cTnT from 38% to 83%–86%, hsTnT from 59% to 86%–90%; all $P<.01$ and negative predictive value: cTnT from 94% to 97%–98%, hsTnT from 96% to 97%–98%). Similar findings were reported by another study of patients presenting with acute chest pain; NT-proBNP had comparable sensitivity and negative predictive value compared with cTnT, with the best strategy being a combination of the 2 markers.[55]

Prognosis and Therapeutic Intervention in ACS

Several large, clinical trials have measured BNP or NT-proBNP in patients presenting with ACS and either non-ST elevation MI or ST-elevation MI and consistently found that elevated NP values revealed important prognostic information.[56,57] Both BNP and NT-proBNP have been shown to be predictive of future adverse outcomes independent of other biomarkers, including and especially the cardiac troponins. On a more detailed examination, it should be noted that elevated BNP or NT-proBNP values typically predict future onset of HF or death, rather than ischemic events, whereas troponins typically predict recurrent ischemic events.

There are a limited number of studies that evaluated the role of serial assessment of BNP or NT-proBNP in patients with ACS; the optimal time to reassess BNP or

NT-proBNP values after the first admission measurement also remains elusive. Two studies[56,58] did not show any advantages in remeasuring NT-proBNP at 6 and 48 hours after admission, whereas other studies[57,58] reported an improvement in prediction of adverse events at longer time frames of 72 hours, 3 and 6 months after admission.

Some investigators have examined whether elevated BNP or NT-proBNP value may help identify patients who would benefit from a specific therapeutic intervention, but with inconsistent results. In a substudy of the Fragmin and fast revascularization during InStability in Coronary artery disease trial,[59] 2-year mortality was reduced by 7.3% in patients with elevated NT-proBNP and interleukin-6 levels at admission who underwent an early invasive strategy (risk ratio 0.46, 95% confidence interval 0.21–1.00). However, only elevated cTnT was independently associated with a reduction of MI by means of an invasive strategy. Another study[57] did not find any significant interaction between NT-proBNP values and clinical benefit of tirofiban treatment. Unifying conclusions regarding the role of NPs in guiding ACS management are difficult to make as these studies are limited by the heterogeneity of NP cutoff points used for the trials. More studies are needed before NP measurement for this purpose can be recommended.

FUTURE DIRECTIONS

The best evidence for the use of BNP or NT-proBNP exists for HF diagnosis and prognosis and has established these NPs as the gold standard biomarker in HF. However, the role of novel biomarkers as well as the novel use of established biomarkers including the use of BNP or NT-proBNP in guiding HF management, MR-proANP in HF diagnosis and prognosis, and BNP or NT-proBNP in ACS diagnosis, prognosis, and management may expand in the near future as more studies come forth. Together with these and other potently prognostic biomarkers, the future direction of this space appears to be heading toward a multimarker approach, with the promise of more individualized characterization of patients and derivation of marker-specific therapy strategies.

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