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STATE-OF-THE-ART PAPER

Natriuretic Peptides

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Natriuretic peptides (NPs) are released from the heart in response to pressure and volume overload. B-type natriuretic peptide (BNP) and N-terminal-proBNP have become important diagnostic tools for assessing patients who present acutely with dyspnea. The NP level reflects a compilation of systolic and diastolic function as well as right ventricular and valvular function. Studies suggest that using NPs in the emergency department can reduce the consumption of hospital resources and can lower costs by either eliminating the need for other, more expensive tests or by establishing an alternative diagnosis that does not require hospital stay. Caveats such as body mass index and renal function must be taken into account when analyzing NP levels. Natriuretic peptide levels have important prognostic value in multiple clinical settings, including in patients with stable coronary artery disease and with acute coronary syndromes. In patients with decompensated heart failure due to volume overload, a treatment-induced drop in wedge pressure is often accompanied by a rapid drop in NP levels. Knowing a patient's NP levels might thus assist with hemodynamic assessment and subsequent treatment titration. Monitoring NP levels in the outpatient setting might also improve patient care and outcomes. (J Am Coll Cardiol 2007;50:2357–68) © 2007 by the American College of Cardiology Foundation

The Basics

Physiology of natriuretic peptides (NPs). There are 3 major NPs, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type NP, all of which share a common 17-amino-acid ring structure and have actions that are targeted at protecting the cardiovascular system from the effects of volume overload. The ANP and BNP are released primarily from the heart but circulate as hormones to act in various tissues in the body and induce vasodilation, natriuresis, and diuresis (1). Although ANP is preferentially synthesized and secreted from the atria and BNP from the ventricles, both can be synthesized in either chamber under pathologic conditions (2). Unlike ANP, which is stored in granules and thus released with even minor triggers such as exercise, BNP has minimal storage in granules; rather, it is synthesized and secreted in bursts (3). C-type NP, derived primarily from endothelial cells, is also synthesized in myocardial tissue and might protect against remodeling effects in the post-myocardial infarction (MI) setting (4).

In the setting of volume expansion or pressure overload, the resulting wall stress initiates synthesis of pre–proBNP in the ventricular myocardium. Subsequently, the peptide is cleaved first to $proBNP_{1\text{-}108}$, then to the biologically active $BNP_{1\text{-}32}$ and the inactive amino-terminal fragment (NTproBNP). The release of BNP results in improved myocardial relaxation and serves an important regulatory role in response to acute increases in ventricular volume by opposing the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin-angiotensin-aldosterone system (5). The biological actions of NPs are mediated through membrane-bound natriuretic peptide receptors (NPRs) that are linked to a cyclic guanosine monophosphate-dependent signaling cascade, including NPR-A, which preferentially binds ANP and BNP, and NPR-B, which preferentially binds C-type NP. Clearance of NPs from the blood is mediated by NPR-C. In addition, BNP is degraded by neutral endopeptidase, which opens the ring structure and inactivates the peptide. Direct renal filtration and passive excretion might be responsible for some BNP clearance as well.

Circulating forms of NPs in heart failure (HF). Although blood levels of NPs rise to very high levels in the setting of acute HF, recent studies support the notion that HF patients actually manifest a state of BNP insufficiency, due to both a deficiency of biologically active $BNP_{1\text{-}32}$ and resistance to its effects (6). Evidence for a state of deficiency comes from molecular analysis of BNP in subjects with acute HF, which reveals 2 distinct circulating forms of BNP: a high-molecular weight form, thought to be $proBNP_{1\text{-}108}$, and a low-molecular weight form, the 32-amino acid active $BNP_{1\text{-}32}$ (7). Instead of recognizing $BNP_{1\text{-}32}$ or NTproBNP alone, recent studies

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Abbreviations and Acronyms

AF = atrial fibrillation
ANP = atrial natriuretic peptide
AUC = area under the receiver-operating characteristic curve
BNP = B-type natriuretic peptide
CAD = coronary artery disease
CHF = congestive heart failure
ED = emergency department
GFR = glomerular filtration rate
HF = heart failure
LV = left ventricle/ventricular
MI = myocardial infarction
NP = natriuretic peptide
NPR = natriuretic peptide receptor
NTproBNP = amino-terminal fragment of B-type natriuretic peptide
NYHA = New York Heart Association

have shown that the standard NP assays also recognize the high-molecular weight proBNP$_{1\text{-}108}$, which comprises a significant percentage of immunoreactive BNP in HF patients yet seems to have less biologic activity than BNP$_{1\text{-}32}$, thus explaining the paradox of HF as an NP-deficient state despite high levels of these biomarkers (8,9). Abnormal processing of proBNP into less active forms might also factor into the state of relative BNP insufficiency (10).

In addition, HF patients seem to suffer some degree of BNP resistance. Animal studies have implicated an up-regulation of phosphodiesterase in HF, causing impaired cyclic-GMP activity despite high stimulation of the NPRs by NPs (11). Taken together, these studies help explain the paradox of high measurable BNP and NTproBNP levels in HF patients who nonetheless suffer physiologically from a state of BNP deficiency and its attendant fluid and salt retention.

NTproBNP versus BNP. Performance characteristics for BNP and NTproBNP are similar in many clinical scenarios. In general, BNP and NTproBNP levels are reasonably correlated, and either can be used in patient care, although clinicians must understand their differences and that absolute levels are not interchangeable (Table 1). The choice of which NP to use often comes down to an institutional decision.

The BNP has a half-life of approximately 20 min and is quickly cleared via several mechanisms as described in the previous text. The NTproBNP, in contrast, has a longer half-life of approximately 1 to 2 h, leading to higher circulating levels and slower fluctuations compared with BNP, despite the 1:1 secretion. Both peptides are influenced by renal function, but the effect seems to be greater for NTproBNP (12); however, the clinical implications of this seem to be modest, especially in patients with HF.

Table 1 BNP Versus NTproBNP

	BNP	NTproBNP
Amino acids	32	76
Molecular weight (kd)	3.5	8.5
Half-life (min)	22	60–120
Clearance		
Primary mechanism	Neutral endopeptidase	Renal
Clearance receptor	NPR-C	Renal
Hemodialysis	No	No
Point-of-care	Yes	Pending
Correlation with GFR	Moderate	Strong
Biologically active	Yes	No
Clinical range (pg/ml)	0–5,000	0–35,000

BNP = B-type natriuretic peptide; GFR = glomerular filtration rate; NPR-C = natriuretic peptide receptor-C; NTproBNP = amino-terminal fragment of B-type natriuretic peptide.

What is a "normal" value? The definition of a "normal" NP level depends upon the clinical feature being detected (i.e., severe, symptomatic left ventricular [LV] dysfunction versus subclinical disease) and the prevalence of that condition in the population being tested, because different thresholds will be needed in different clinical settings. In addition, the specific assay used can affect NP levels, particularly when screening the general population, in which NP levels will tend to fall toward the lower end of the spectrum.

Natriuretic peptide levels are clearly age- and gender-specific. Two studies looked at BNP levels in normal subjects without cardiovascular disease or ventricular (systolic or diastolic) dysfunction and found increased levels with age and in women (13,14). Therefore, "normal" values vary.

As a general guideline, in young, healthy adults, 90% will have BNP <25 pg/ml and NTproBNP ≤70 pg/ml (15). For acutely dyspneic patients, some have suggested cutoffs of BNP <100 pg/ml and NTproBNP <300 pg/ml to rule out HF (Fig. 1) (16,17).

Diagnosis With NPs

NPs in dyspnea. The BNP and NTproBNP have become important diagnostic tools for assessing patients who present acutely with dyspnea. In the Breathing Not Properly Multinational Study, BNP levels measured on arrival in 1,586 emergency department (ED) patients presenting with acute shortness of breath had higher diagnostic accuracy that did the ED physician in diagnosing HF, with an area under the receiver-operating characteristic curve (AUC) of 0.91 (16). A BNP cut-point of 100 pg/ml was 90% sensitive and 76% specific for diagnosing HF as the cause of dyspnea.

The PRIDE (ProBNP Investigation of Dyspnea in the ED) study was a similar study performed with NTproBNP, measured in 600 patients who presented to a single ED with dyspnea. In this study, NTproBNP was sensitive and specific for the diagnosis of congestive heart failure (CHF) (AUC = 0.94). Patients with acute HF had a median NTproBNP over 4,000 pg/ml, compared with 130 pg/ml in those without acute HF. An NTproBNP cut-point of 300 pg/ml was proposed to "rule-out" a diagnosis of HF, whereas higher age-dependent cut-points were suggested to "rule-in" HF (AUC = 0.94) (17).

The cost-effectiveness of using BNP to aid in the emergency diagnosis of HF was shown in the BASEL (BNP for Acute Shortness of breath EvaLuation) study, in which 452 patients presenting to the ED with acute dyspnea were randomized to undergo either a single measurement of BNP

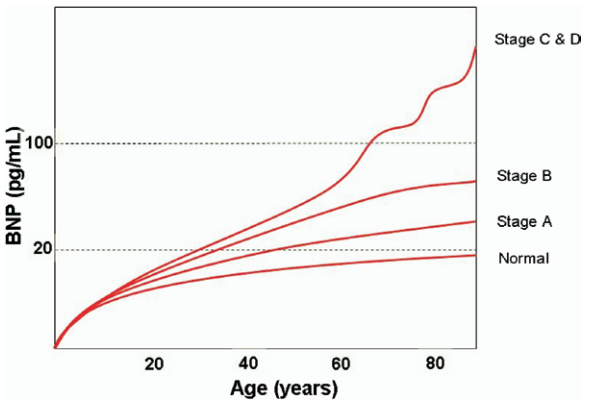

Figure 1 **BNP Levels by ACC/AHA Heart Failure Stages**

B-type natriuretic peptide (BNP) rises with age over the course of a lifetime but generally stays under 20 pg/ml in the absence of left ventricular dysfunction or structural heart disease. B-type natriuretic peptide >100 pg/ml is the cutoff for diagnosing congestive heart failure in symptomatic patients. Stage A = risk factors; Stage B = asymptomatic structural heart disease; Stage C = symptomatic heart failure; Stage D = refractory heart failure. ACC = American College of Cardiology; AHA = American Heart Association.

or no such measurement (18). Measurement and use of BNP levels by ED physicians was associated with a 10% decrease in the rate of hospital admission and a 3-day decrease in the median length of stay, at a total cost savings of approximately $1,800/patient without increased mortality or repeat hospital stays. Similar improvements in diagnosis and cost savings were seen in the IMPROVE-CHF (Improved Management of Patients With Congestive Heart Failure) study of NTproBNP use in the ED (19).

DIASTOLIC HF. The BNP levels are also useful in establishing a diagnosis of diastolic dysfunction in acute HF patients (20). As diastolic dysfunction increases in severity as assessed by Doppler filling patterns of mitral inflow and pulmonary venous flow, BNP levels rise accordingly (21) as a reflection of LV end-diastolic wall stress (22).

NPs in other clinical scenarios. Several clinical scenarios exist that can cause NP levels to rise, apart from the typical acute HF setting. Acknowledging these other etiologies for elevated NP levels might help clarify what might otherwise seem to be a discordant clinical picture (Table 2).

PREVIOUS HF. The Breathing Not Properly trial demonstrated that NP levels can be elevated in patients with a history of HF who present with dyspnea but without an acute HF exacerbation. In this setting, patients' BNP levels tend to be intermediate, in between those without HF and those with an acute HF diagnosis (16).

ACUTE CORONARY SYNDROME. Acute coronary syndrome is associated with a rise in NP levels even in the absence of concomitant HF. The degree of elevation might reflect the severity of LV dysfunction (23). Some have suggested using NP levels as a guide to institute more aggressive treatments aimed at reducing ventricular wall stress (24).

PULMONARY DISEASE. Differentiating between patients with a pulmonary etiology for their dyspnea and a cardiac etiology can be clinically challenging at times, and the fact that NP levels can be elevated in both settings might confound the picture. However, although patients with pulmonary disease can have elevated NP levels, their elevations often fall within the gray zone and are not usually as high as in patients with CHF (25). Natriuretic peptide levels can still be useful in diagnosing HF in patients with a history of lung disease, such as chronic obstructive pulmonary disease or asthma, because levels will often be higher in patients with both HF and pulmonary disease than in pulmonary disease alone (BNP levels 587 vs. 109 pg/ml, respectively, in the 417 patients from the Breathing Not Properly study with a history of pulmonary disease [asthma or chronic obstructive pulmonary disease] plus a new diagnosis of HF versus those with a history of pulmonary disease without HF) (26).

Elevated NP levels can also be seen in the setting of an acute, hemodynamically significant pulmonary embolism, likely reflecting right heart strain (27). In fact, right heart dysfunction due to severe lung disease from a variety of etiologies can cause elevated NP levels. The mechanism is likely due to release of peptide from the right ventricular myocardium (28), although decreased lung expression of the NPR-C clearance receptor in response to hypoxia has been demonstrated in animal models (29). This scenario can be seen in severe chronic obstructive pulmonary disease, primary pulmonary hypertension, and other causes of pulmonary hypertension (28,30,31). Because of this, when evaluating acutely dyspneic patients, it is important to note that

Table 2 **Interpretation of NP Levels in Special Situations**

Causes of elevated NP levels other than CHF
LV dysfunction
Previous heart failure
Advanced age
Renal dysfunction
Acute coronary syndromes
Pulmonary disease (e.g., acute respiratory distress syndrome, lung disease with right heart failure)
Pulmonary embolism
High output states (e.g., sepsis, cirrhosis, hyperthyroidism)
Atrial fibrillation
NP levels lower than expected
Obesity
Flash pulmonary edema
Heart failure etiology upstream from LV (e.g., acute mitral regurgitation, mitral stenosis)
Cardiac tamponade
Pericardial constriction

Adapted from Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. Rev Cardiovasc Med 2002;3 Suppl 4:S10–7.
CHF = congestive heart failure; LV = left ventricle; NP = natriuretic peptide.

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elevated NP levels are not pathognomonic for CHF, and other potentially life-threatening etiologies including pulmonary embolism must still be excluded, especially when NP levels fall within the "gray zone" (BNP 100 to 500 pg/ml; NTproBNP 300 to 900 pg/ml for 50- to 75-year-olds) (32,33).

HIGH-OUTPUT STATES. Several conditions that cause high cardiac outputs, including sepsis, cirrhosis, and hyperthyroidism, can contribute to elevated NP levels. Although the mechanisms are unclear, patients with severe sepsis or shock might have markedly elevated NP levels (34), possibly due to induction by endotoxin or other inflammatory mediators (35) or due to underlying myocardial dysfunction (36). Values are higher in nonsurvivors than in survivors (37). Similarly, hyperthyroid patients might have higher NP levels than euthyroid patients, and although the levels typically do not exceed diagnostic thresholds, they do tend to decrease with treatment of the hyperthyroid state (38). Elevated NP levels are also seen in patients with cirrhosis and likely reflect cardiac dysfunction or a hyperdynamic circulatory state (39).

ATRIAL FIBRILLATION (AF). Natriuretic peptide levels seem to rise in the setting of AF, including lone AF (40). However, in an analysis of the Breathing Not Properly study, Knudsen et al. (41) showed that this pattern was present in patients without but not with HF and that BNP still performed well in patients with AF, with an AUC of 0.84, which was only slightly lower than the AUC of 0.91 for the overall cohort. In patients with AF, a cutoff of 200 pg/ml resulted in a marked improvement in specificity and positive likelihood ratio for diagnosing HF, compared with the conventional cutoff of 100 pg/ml, with little loss of sensitivity.

Caveats: high levels of NPs. A number of factors have been associated with higher NP levels in addition to ventricular wall stress.

ADVANCED AGE. Both BNP and NTproBNP levels increase with age (14,42), and the increased prevalence of diastolic dysfunction alone does not seem to account for the entire increase. A study by Redfield et al. (13), which excluded patients with "age-related" diastolic dysfunction, nonetheless found an association between age and elevated levels of BNP. Other possible explanations include altered renal function, production, secretion, or metabolism. One study has suggested that there is a reduction in the NPR-C clearance receptor with aging (43).

FEMALE GENDER. B-type natriuretic peptide and NT-proBNP are higher in women than in men at any age (13,14). Although the reason for the higher levels in women is unknown, estrogen might play a role, because 1 study showed that older women on hormone replacement therapy had higher BNP levels than women not on therapy (13). However, use of estrogen had only a minimal effect on NTproBNP levels in the same community cohort (42), and other data suggest that an inverse relationship between free testosterone levels and NPs and not estrogen levels might be responsible (44).

RENAL DISEASE. The association between NP levels and renal function is complex. Patients with chronic renal dysfunction tend to have higher atrial pressure, systemic pressure, and ventricular mass, all of which could lead to higher "true" physiologic NP levels; or, they might have increased levels due to decreased renal filtration, decreased clearance by NPR-C and endopeptidases within renal tissue, or decreased renal responsiveness to BNP.

Multiple studies have found that BNP levels begin to rise at a threshold of estimated glomerular filtration rate (GFR) of 60 ml/min/1.7 m^2 (45), which is approximately the same level where increased rates of both systolic and diastolic HF are seen. The NP elevations in patients with chronic renal disease might reflect concurrent LV hypertrophy or coronary disease (46). Because the majority of BNP is not renally cleared, the mechanism of elevated BNP levels in renal failure is likely multifactorial, representing in part a true counter-regulatory response from the heart to the kidney, and not simply decreased passive renal clearance. The Breathing Not Properly study found a weak but significant correlation between GFR and BNP and suggested that higher cut-points are reasonable for those with GFR <60 ml/min/1.7 m^2 (47).

Clearance of NTproBNP, which is not mediated by the NPR-C receptor or neutral endopeptidase, might be more sensitive than BNP to reduced renal filtration and clearance (48). In a study of breathless patients, there was a stronger relationship between GFR and NTproBNP levels ($r = -0.55$) than BNP levels, although the relationship was somewhat attenuated among patients with acute CHF ($r = -0.33$ for NTproBNP and $r = -0.18$ for BNP) (49). Because of this renal influence, interpretation of NTproBNP levels might be more difficult in patients with a GFR <60 ml/min/1.7 m^2 (50,51). However, an analysis from the PRIDE study showed that NTproBNP levels in patients with GFR <60 ml/min/1.7 m^2 were still the strongest independent predictor of outcome and suggested the higher cut-point of NTproBNP >1,200 pg/ml for diagnosing HF in such patients (49). In relatively healthy subjects with only mild renal impairment, in contrast, there seems to be no significant relationship between NTproBNP levels and GFR (42). Thus, NTproBNP might have additional as yet undiscovered modes of clearance, such as degradation by nonspecific peptidases.

Although neither BNP nor NTproBNP are cleared by hemodialysis, BNP levels do rise along with volume status in the days leading up to hemodialysis and then drop by approximately 15% to 30% after a routine hemodialysis session (52).

Caveats: low levels of NPs. OBESITY. Several studies have documented lower BNP levels in obese compared with nonobese patients (14,53–55). This inverse relationship

between BMI and BNP has been observed in patients both with and without HF. Although the reason for the relationship is unknown, the increased concentration of the NPR-C clearance receptor on adipocyte cells has led some to postulate that increased clearance is the reason for lower BNP levels in obese patients (56). However, evidence against this hypothesis comes from Das et al. (57), who found that BNP was correlated with greater lean mass but not greater fat mass.

Whether a similar negative correlation is seen with NTproBNP is controversial; some have found that NT-proBNP levels might be lower in obese patients, despite the fact that NTproBNP is not believed to be cleared by NPR-C (57,58). Others, however, have found that the degree of impact of body mass index on NTproBNP was minimal (42). A recent study of post-bariatric surgery patients hypothesized that, because both BNP and NT-proBNP levels increased after weight loss, decreased NP production and not increased clearance might be the responsible mechanism (59).

Despite the lower circulating levels, NPs retain their prognostic capacity in obese patients (60), although lower NP cut-points are needed for diagnosing HF in patients with a high body mass index (Fig. 2) (55).

FLASH PULMONARY EDEMA. Natriuretic peptide levels might seem discordantly low in patients presenting early with HF symptoms that developed precipitously, in under approximately 1 h. In this setting, BNP gene expression has had insufficient time, between the initial trigger of increased ventricular wall stress and the measurement of NP levels, to up-regulate peptide production. Because only small amounts of BNP are stored in secretory granules, the development of elevated NP levels in flash pulmonary edema is dependent upon the de novo synthesis and secretion of the peptide (3).

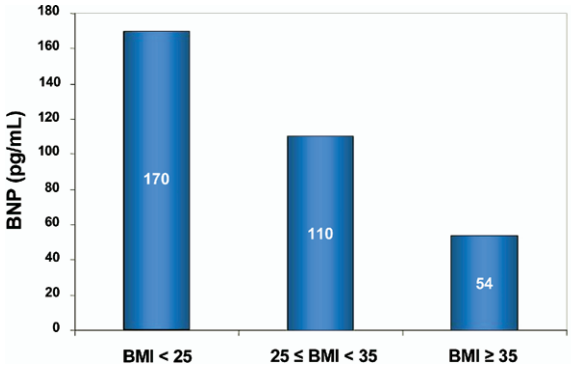

Figure 2 **BNP Cut-Points for 90% Sensitivity**

B-type natriuretic peptide (BNP) cut-points for 90% sensitivity in diagnosing congestive heart failure in patients with dyspnea, on the basis of body mass index (BMI) subgroup. Specificity at the 90% sensitivity level shown was at least 70% for all 3 groups. Data from the Breathing Not Properly Multinational Study; figure adapted from Daniels et al. (55).

CHF DUE TO CAUSES UPSTREAM FROM THE LV. When CHF is due to a cause upstream from the LV—as in acute mitral regurgitation or mitral stenosis, for example—NP levels might be relatively low despite impressive symptoms. The absence of significant LV wall stress in these acute settings explains the lack of marked BNP production, and although NP levels might still be higher than normal, they will not rise to the same degree as when the CHF occurs with a concomitant overload on the LV. Similarly, pericardial constriction can sometimes cause symptoms of CHF; however, because the myocardium is prevented from stretching by the confines of the pericardium, NP levels are typically normal or only minimally elevated in this setting (61).

Prognosis

Evidence continues to mount showing that NP levels measured in various settings are highly predictive of subsequent cardiac events (Table 3) (62–70).

CHF. Several studies have shown that NP levels in patients presenting with HF are predictive of future outcomes. In both acute and chronic HF, BNP provides important prognostic information, with every 100-pg/ml increase associated with a 35% increase in the risk of death (71). The prospective, multicenter REDHOT (Rapid ED Heart Failure Outpatient Trial) of 464 patients presenting to the ED with HF showed that BNP provides prognostic value in the acute ED setting (72). B-type natriuretic peptide was predictive of future HF events and mortality and outperformed ED physician assessment, which had poor predictive value.

In chronic HF patients too, NP levels provide powerful prognostic information about survival and are predictors of functional status deterioration (73,74). In an evaluation of Val-HeFT (Valsartan Heart Failure Trial) comprising 4,300 outpatients with chronic HF, those with the greatest increase in BNP despite therapy had the highest morbidity and mortality (74).

Coronary artery disease (CAD)/acute coronary syndrome/sudden cardiac death. STABLE ANGINA. Both BNP and NTproBNP have strong prognostic value in patients with stable CAD and display nearly identical test performance in predicting all-cause mortality or HF (75). In a study of 1,085 patients with stable CAD followed for an average of 2.5 years, BNP and LV ejection fraction were the strongest predictors of future cardiovascular events, independent of known risk factors. B-type natriuretic peptide had the highest prognostic accuracy and was complementary to the angiographically defined extent of CAD and to LV systolic function (76). Similar prognostic utility has been demonstrated for NTproBNP, which improved prediction of all-cause mortality above and beyond the predictive ability from conventional cardiovascular risk factors (77,78).

UNSTABLE ANGINA AND MI. Natriuretic peptide levels obtained in patients with unstable angina and MI also play a

Table 3 Summary of Selected Studies Evaluating Prognostic Abilities of Natriuretic Peptides

Condition	Study Population	n	Cutoff Value	End Points	Change in Risk	Follow-Up	Ref. #
HF	Meta-analysis of 4 HF studies	652	Every 100-pg/ml increase in BNP	All-cause mortality	35% increased RR of death	1.4 to 2 yrs	62
	Admitted with HF, REDHOT study	317	BNP <200 pg/ml	All-cause mortality, CHF visit or admission	9%, 90-day event rate (CHF visit/admission, all-cause death) versus 29%		63
	Admitted with HF, ADHERE study	48,629	BNP 4th quartile (≥1,730 pg/ml) versus 1st quartile (<430 pg/ml)	In-hospital mortality	Adjusted odds ratio for mortality 2.2	In-hospital	112
	ED with dyspnea, pooled analysis of 4 studies, ICON	1,256	NTproBNP >5,180 pg/ml	All-cause mortality	RR 5.2 for in-hospital mortality	76 days	113
	Chronic HF, COPERNICUS study	1,011	NTproBNP > versus < median (1,767 pg/ml)	All-cause mortality	RR 2.7 for all-cause mortality	Up to 29 months	114
Stable CAD	Stable coronary heart disease, Heart and Soul Study	987	1 SD increase in logNT-proBNP; NTproBNP >100 pg/ml	All-cause death or hospitalization for MI, HF, or stroke	2.3× increased risk of adverse cardiovascular outcome; 3× increased risk above cutoff level	Mean 3.7 yrs	69
	Stable CAD, AtheroGene Study	1,085	BNP >100 pg/ml	MI and cardiovascular death	4.4× increased risk	2.5 yrs	67
ACS	ACS, TIMI 16 study	2,525	BNP >80 pg/ml	All-cause mortality	Increased risk OR 5.8 for 4th (≥138 pg/ml) versus 1st (<44 pg/ml) quartile	10 months	70
	ACS, BNP measured at entry and 4 and 12 months; A to Z trial	4,487	BNP >80 pg/ml	Death or new-onset HF	2.5× increased risk: 3.9× at 4 months, 4.7× at 12 months	1 yr	115
SCD	Ejection fraction ≤35%	452	BNP ≥130 pg/ml	SCD	SCD in 19% of patients above cutoff versus 1% below cutoff	Mean 1.6 yrs	64
CRT	NYHA functional class III/IV HF, undergoing CRT; retrospective	154	BNP ≥447 pg/ml	CRT response (No HF hospitalization and ≥1 NYHA functional class improvement)	62% sensitive, 79% specific in identifying CRT response at 6 months (no HF hospitalization and ≥1 NYHA functional class improvement)	6 months	77
Cardiac and vascular surgery	Male veterans undergoing open-heart surgery	98	BNP >385 pg/ml	All-cause mortality and post-operative complications	Increased risk: 90% specific, 93% NPV	1 yr	87
	Major vascular surgery	335	NTproBNP ≥319 pg/ml	All-cause mortality	HR 4.0 for all-cause mortality (10.9 for MACE)	Mean 1.2 yrs	88
PE	Acute PE, consecutive	73	BNP >90 pg/ml; NTproBNP ≥500 pg/ml	MACE	OR 8.0 for BNP, 14.6 for NTproBNP; BNP <50 pg/ml, NTproBNP <500 pg/ml predictive of benign clinical course	In-hospital	27,90
Pulmonary hypertension	Primary pulmonary hypertension	60	BNP ≥180 pg/ml	All-cause mortality	Increased risk	Mean 2 yrs	31
	Pulmonary hypertension (35 idiopathic), consecutive	55	NTproBNP ≥1,400 pg/ml	All-cause mortality	5.5× increased risk of death: 91% NPV for death if < cutoff	Mean 2.1 yrs	116
Renal dysfunction	End-stage renal disease on dialysis, without HF	246	BNP tertiles: 3rd (>125 pg/ml) versus 1st (<49 pg/ml)	All-cause mortality	RR 7.1	Mean 2.2 yrs	117
Atrial fibrillation	NYHA functional class III/IV HF (76 with atrial fibrillation)	354	NTproBNP >449 pg/ml	Cardiovascular mortality	HR 5.8 in multivariate model (HR 10.3 univariate)	Mean 3.2 yrs	118
Stroke	Acute ischemic stroke	250	NTproBNP ≥615 pg/ml on day 2	All-cause mortality	Increased risk	6 months	119
Septic shock	Prospective case series study: 22 with shock, 11 with severe sepsis, 20 healthy control subjects	53	BNP >650 pg/ml on day 2	All-cause mortality	Increased risk, 92% sensitivity	1 month	120

ACS = acute coronary syndrome; ADHERE = Acutely Decompensated Heart Failure National Registry; A to Z = Aggrastat to Zocor; CAD = coronary artery disease; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; CRT = cardiac resynchronization therapy; ED = emergency department; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrilator; MACE = major adverse cardiac event; NPV = negative predictive value; NYHA = New York Heart Association; PE = pulmonary embolism; REDHOT = Rapid Emergency Department Heart Failure Outpatient Trial; RR = relative risk; SCD = sudden cardiac death; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Tables 1 and 2.

prognostic role, which is incremental and in some instances superior to the prognostic value of troponins (79–82). Persistent elevation of NTproBNP 3 to 6 months after an acute coronary syndrome is associated with chronically impaired LV function (80). Some have recommended, on the basis of these data, careful re-evaluation for risk-reducing interventions when NP levels remain elevated 3 months after an acute coronary syndrome (83).

SUDDEN CARDIAC DEATH. Several studies have shown that NPs might be useful in predicting who is at risk for sudden cardiac death (73,84). In 452 ambulatory patients with HF and LV ejection fraction <35%, BNP levels independently predicted sudden cardiac death (73). In this study, only 1% of patients with BNP <130 pg/ml died suddenly, compared with 19% of patients with BNP ≥130 pg/ml. Natriuretic peptides might help predict sudden cardiac death after acute MI as well. A study of 521 acute MI patients found that BNP predicted sudden cardiac death (but not other deaths) and was the strongest predictor even after adjusting for clinical variables, including ejection fraction (84).

In cardiomyopathy patients undergoing cardioverter-defibrillator implantation, a single pre-implantation BNP level is independently predictive of future appropriate defibrillator therapies (85). Although decisions to implant a defibrillator should not be made solely on the basis of NP levels, future research might find that NP levels can help guide our choices more wisely.

CARDIAC RESYNCHRONIZATION THERAPY. In patients with New York Heart Association (NYHA) functional class III or IV HF, BNP ≥447 pg/ml can help predict cardiac resynchronization therapy response at 6 months, defined as absence of hospital stays for HF and improvement by at least 1 NYHA functional class (86). Cardiac resynchronization therapy induces an early and sustained reduction in NP levels, which might reflect the efficacy of the therapy (87). Future large studies will determine whether NP levels are helpful in targeting candidates for cardiac resynchronization and for monitoring those already with the devices.

Valvular disease. In the setting of cardiac valvular disorders, NPs are becoming a useful clinical tool for monitoring patients' pre- and post-valvular surgery. In general, NP levels tend to rise with increasing severity of the valvular abnormality and with the resulting cardiac remodeling. Natriuretic peptide levels can also provide important prognostic information and might assist with risk stratification and timing for surgery.

MITRAL VALVE. Natriuretic peptide levels increase with increasing severity of mitral regurgitation (88). Recently, BNP was shown to be a marker of poor outcome in a study of 124 patients with organic mitral regurgitation, where levels were independently predictive of death (89).

Owing to underfilling of the LV, NP levels might not rise as high in mitral stenosis as they might in other causes of HF; however, NP levels do increase in this setting and decrease after balloon valvotomy (90). Natriuretic peptide levels are correlated with echocardiographic findings, including mitral valve area and mean mitral gradient, as well as NYHA functional class (91).

AORTIC VALVE. In the setting of aortic stenosis, NP levels are associated with severity of stenosis, might predict development of symptom onset, and increase progressively with worsening NYHA functional class (92). Levels might also predict survival in patients with stenosis who are treated without surgery (93). In patients who do undergo valve replacement, NP levels might predict survival and post-operative LV function (94).

In chronic aortic regurgitation, NP levels are also associated with severity of regurgitation even in asymptomatic individuals (95), although levels tend to rise less than in aortic stenosis even when LV dilation has occurred. Thus, measurement of NP levels might complement clinical and echocardiographic evaluation, particularly when symptoms are unclear or when valvular function is difficult to interpret on echocardiography.

Cardiac and vascular surgery. Natriuretic peptide levels measured pre-operatively can help predict post-operative outcomes such as mortality and major adverse cardiac events among patients undergoing cardiac or vascular surgery (96,97). Levels can also help predict which patients are at increased risk of developing post-operative AF (98).

Pulmonary embolism. Patients with pulmonary embolism and other pulmonary diseases can also have elevated levels of NPs, although not usually to the same extent as in CHF. In the setting of acute pulmonary embolism, BNP levels <50 pg/ml or NTproBNP levels <500 pg/ml might help predict a benign outcome (27,99), although some have suggested lower cut-points for improved negative predictive values.

Monitoring Therapy

Because NP levels fluctuate with changes in myocardial filling pressures, monitoring levels might be helpful in evaluating the progress of patients receiving therapies aimed at reducing this wall stress.

Biologic variability of NP levels. Several studies have shown considerable intraindividual variation of NP levels in both normal individuals and in apparently stable HF patients (100,101). These studies suggest that serial BNP levels need to change by a minimum of approximately 70% to constitute a significant change over 1 week in stable HF patients and NTproBNP levels must change by at least 50% (100,101). The degree of biologic variability in acutely decompensated patients is more difficult to ascertain, but in general, because clinical improvement should be associated with large changes in NP levels, the degree of intraindividual variability might be less important than in the outpatient arena of stable patients.

Inpatients. Several studies have evaluated the relationship between NP levels and pulmonary capillary wedge pressure measurements derived from invasive hemodynamic catheters. Not all patients with elevated NP levels will have high wedge pressures; as detailed earlier, there are many clinical situations in which NP levels can seem discordant with the clinical picture. Thus, in a given patient, the NP level does not always correlate to wedge pressure (102). However, in patients with decompensated HF due to volume overload, a treatment-induced drop in wedge pressure will almost always be accompanied by a rapid drop in NP levels, especially during the first 24 h of treatment, as long as adequate urine output is maintained (103).

In patients with decompensated HF, the NP level can hypothetically be thought of as consisting of 2 components: the "dry weight" component, which reflects the patient's compensated NP level, plus the additional NP level due to the acute pressure or volume overload.

Natriuretic peptide levels do not need to be measured each hospital day; however, the failure of NP levels to decrease during hospital stay is a poor prognostic sign (104,105). More important than repeated measurements of NP levels in inpatients is obtaining a level immediately before discharge. A single pre-discharge BNP level is strongly predictive of early and later outcome, regardless of the initial BNP level or echocardiographic findings (106). In a study of 114 patients admitted with CHF, those with a pre-discharge BNP level >700 pg/ml were over 15 times more likely to die or get readmitted within 6 months compared with those with BNP <350 pg/ml at discharge (107).

A reasonable approach to monitoring inpatients with decompensated HF would be to obtain an NP level on admission and just before discharge when the patient is presumed to be euvolemic, both for prognostic purposes and to aid in tailoring the intensity of post-discharge care (108); it might also help to establish the patient's "dry weight" NP level, although patients often need additional diuresis after discharge, leading ultimately to a dry weight NP level lower than the discharge level. Additional measurement of NP levels in inpatients might be appropriate if the patient experiences a significant change in status during the hospital stay, although the benefit of this has not been tested.

Outpatients. Monitoring NP levels in the outpatient setting might improve patient care and outcomes, although prospective studies of this have shown conflicting results. In the STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) study of 220 patients with HF and LV dysfunction who were randomized to receive therapy guided by NP levels or standard care, NP-guided treatment targeting a BNP level <100 pg/ml significantly reduced HF deaths and hospital stays for HF (109). However, the smaller STARBRITE (Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: BRain NatrIuretic Peptide Versus the Clinical CongesTion ScorE) study (n = 130) failed to show a significant improvement in the primary outcome of nonhospital days alive in patients whose treatment was guided by BNP levels, although STARBRITE enrolled sicker patients and used a higher BNP target than STARS-BNP (110). In both STARS-BNP and STARBRITE, clinicians who adjusted treatments based on BNP levels prescribed higher doses of angiotensin-converting enzyme (ACE) inhibitors and beta blockers, compared with those whose treatment was guided by clinical signs and symptoms alone.

For patients regularly followed in clinic, it might be beneficial to establish their "steady state" NP level, that is, the BNP or NTproBNP level that corresponds to their optimized fluid status. Knowing a patient's steady state NP level might be helpful for management in both the inpatient and outpatient settings, because baseline NP levels can vary on the basis of the patient's underlying severity of disease and NYHA functional class (111). Significant deviations above this steady state value might prove more helpful than traditional cut-points for diagnosing HF exacerbations in those individuals who are closely followed as outpatients and whose NP levels tend to stay elevated, whereas values much lower than their steady state level might signal a patient who is over-diuresed or intravascularly depleted.

A post-discharge rise in NP level can be an important marker for repeat hospital stay. How high an NP level must rise over baseline before a patient is deemed "decompensated" is unknown, because as noted previously, there is a certain amount of intraindividual variation in NP levels, and certainly the clinical picture is important in this regard. However, an increase by at least 50% over one's steady state NP level might be a reasonable benchmark for triggering an evaluation for confirmatory signs and symptoms followed by more aggressive treatment.

Toward the Future—Screening for Subclinical Disease

Up to one-half of individuals with LV dysfunction might be asymptomatic and unaware of their condition (112,113). Because NPs are elevated in the setting of LV dysfunction, their use as a screening test for this condition has aroused much interest. Although echocardiography is the current gold standard for detection of LV dysfunction and many other structural cardiac abnormalities, its cost and limited availability make it an impractical choice for mass screening.

Several studies have evaluated the use of NPs to identify asymptomatic subjects with poor ventricular function. Most concluded that, owing to the relatively low prevalence of disease, the best potential use for NPs was to use the high negative predictive value for "ruling out" disease (114,115). Other studies looking to screen for a broader range of subclinical cardiovascular disorders also found excellent negative predictive value (116).

The diagnostic value of NPs in community screening depends largely on the prevalence of disease. As such, NPs might be most useful for detecting a range of clinical

disorders. In the Framingham Offspring Study of 3,346 asymptomatic middle-age subjects, for example, Wang et al. (117) prospectively examined BNP and NT-proANP levels and found that BNP levels were independently predictive of the risk of death, HF, stroke or transient ischemic attack, and AF, even after adjusting for traditional risk factors. The BNP levels above the 80th percentile (approximately 20 pg/ml) carried a 62% increased risk of death and a 76% increased risk of a first major cardiovascular event. With each increment of 1 SD in log BNP levels, there was a 27% increase in risk of death, a 77% increase in risk of HF, a 66% increase in the risk of AF, and a 53% increase in the risk of stroke or transient ischemic attack, all of which were statistically significant. Another study in nonhospitalized individuals ages 50 to 89 years showed that NTproBNP provides prognostic information of mortality and first major cardiovascular events beyond traditional risk factors (118). Thus even small elevations of NP levels (e.g., in the BNP 20- to 100-pg/ml range), significantly less than traditional cut-points for acutely dyspneic patients, might serve as an early warning sign, aiding in the timely detection of cardiovascular disease.

An intriguing future use of NPs might be as an adjunct to the athletic pre-participation screening exam. A preliminary study of college athletes showed that most have low levels of NPs (15); on the basis of what is known about NPs, athletes with the highest NP levels might have a physiologic basis for the elevation and might represent a higher-risk subgroup that warrants closer evaluation. However, large-scale studies are needed to evaluate the incremental value and cost-effectiveness of using NPs in this setting.

Cost-effectiveness. Screening populations at high risk for development of HF, such as diabetic and elderly patients, and referring those with elevated NP levels for echocardiogram might in fact prove cost-effective despite the higher prevalence of elevated NP levels in these populations (119,120). Heidenreich et al. (120) recently found that using a BNP cutoff level of 24 pg/ml for echocardiogram referral was a cost-effective means of screening for LV dysfunction in populations (such as men over age 60 years and possibly women over age 60 years) with a prevalence of LV systolic dysfunction of at least 1%.

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