N-Terminal B-type Natriuretic Peptide in Heart Failure

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KEYWORDS

• NT-proBNP • Heart failure • Diagnosis • Prognosis • Monitoring

KEY POINTS

- Amino-terminal pro–B-type natriuretic peptide (NT-proBNP) is an excellent rule out test in the dyspneic patient with suspected acute decompensated heart failure.
- Factors partially confounding of the test, especially in nonacute settings, include advancing age, preserved ejection fraction, renal dysfunction, obesity, and atrial fibrillation.
- NT-proBNP adds strong prognostic information at all grades of heart failure independent of standard clinical predictors.
- Serial measurement of NT-proBNP in chronic heart failure provides ongoing risk stratification and a guide to titration of treatment.
- NT-proBNP is the marker of choice in assessing possible acute decompensation and for serial monitoring in patients receiving combination angiotensin 2 type 1 receptor blockade-neprilysin inhibition therapy.

INTRODUCTION

B-Type natriuretic peptide was discovered in 1988.[1] Proof of the existence of amino-terminal pro–B-type natriuretic peptide (NT-proBNP) in the human circulation and its relationship to cardiac function were first reported by Hunt and colleagues[2,3] in 1995. The B-type natriuretic peptides (BNP) are predominantly synthesized and released constitutively from ventricular cardiac myocytes. A proportion of proBNP 108 is also stored in, and released (alongside atrial natriuretic peptide [ANP]) from, perinuclear granules in cardiac atrial myocytes. The prime stimulus for synthesis and release of BNP is myocyte stretch secondary to transmural distending pressure. On cleavage of proBNP 108; NT-proBNP 1–76 is released in a 1:1 ratio with its carboxy-terminal congener BNP 1-32 (**Fig. 1**). The biological actions of the cardiac natriuretic peptides (NP) indicate they constitute an endogenous compensatory system that acts to counter excess cardiac load and volume expansion. Actions include natriuresis, diuresis, vasodilation, and lusitropism, plus direct suppression of volume-retaining, vasoconstricting systems including the renin–angiotensin–aldosterone and sympathetic nervous systems. NP also have trophic actions opposing cardiac hypertrophy and fibrosis.[4] It is the relationship between intracardiac pressures and plasma concentrations of BNP and NT-proBNP that underpin their value as biomarkers in HF as now

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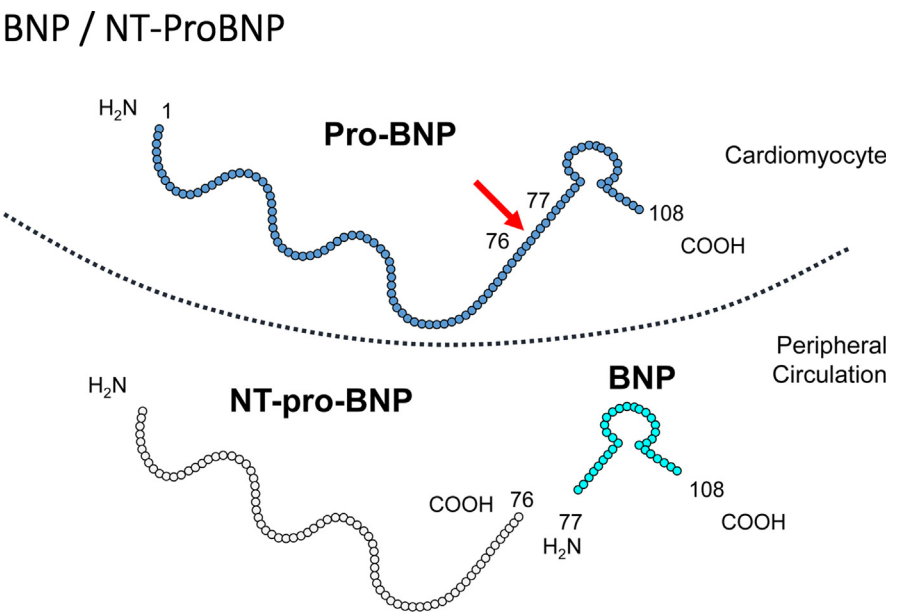

Fig. 1. Processing of pro–B-type natriuretic peptide (proBNP) to amino-terminal proBNP (NT-proBNP) and BNP. Alternative forms with cleavage by alternative dipeptidases: 3 to 32 (22%), 3 to 108 (60%). Commercial assays may not be specific for peptide (cross-react with other congeners or forms). BNP assay may measure 1-32, 3-32. Commercial assays validated for heart failure diagnosis, but may not reflect endogenous activity. (*Adapted from* Lam CS, Burnett JC Jr, Costello-Boerrigter L, et al. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. J Am Coll Cardiol. 2007;49(11):1193–202; with permission.)

mandated by authoritative international guidelines for the diagnosis and management of HF.

Amino-Terminal Pro–B-Type Natriuretic Peptide and Measures of Cardiac Structure and Function

Cardiac chamber wall stress, the prime driver of NP synthesis and release, in accord with the law of Laplace, is directly related to intrachamber pressure and chamber radius and inversely related to wall thickness. In concentrically hypertrophied hearts, as commonly observed in patients with HF with preserved ejection fraction (HFpEF), unit wall stress is less than in those patients with HF with reduced ejection fraction (HFrEF) and dilated left ventricles. Accordingly, plasma NP in acute decompensated HF (ADHF) are lower in HFpEF compared with HFrEF.[5,6]

NT-proBNP is correlated with several echocardiographic indicators of cardiac structure and function including:

- Left ventricular (LV) end-diastolic wall stress;
- LV ejection fraction (LVEF);
- E/e';
- LV longitudinal strain;
- LV circumferential strain;
- Left atrial dimensions;
- Right ventricular ejection fraction; and
- Right ventricular pressures.

Plasma NT-proBNP concentrations are related to a number of echocardiographically determined measures of cardiac structure and function in HF.[5–9] Iwanaga and colleagues[10] measured systolic and diastolic wall stress by echocardiography and cardiac catheterization, and related this key measurement to plasma concentrations of NP in patients with HF. A striking correlation between plasma BNP with end-diastolic wall stress (r^2 = 0.887; P<.001) seemed to be far stronger than the correlation with LV end-diastolic pressure (r^2 = 0.296; P<.001). NP levels seem to reflect LV wall stress more closely than other ventricular parameters in HF, and this relationship may better account for interindividual differences in plasma NP values than other measures.

Plasma NP concentrations reflect aspects of diastolic dysfunction independent of age, sex, renal function, body mass index, and LVEF. Plasma NT-proBNP (>600 pg/mL) and BNP (>100 pg/mL) are strong, albeit relatively nonspecific, independent predictors of restrictive filling the most severe grade diastolic dysfunction. In HF, plasma NT-proBNP correlates with E/e', a

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well-validated index of LV filling pressures, in addition to measures of LV compliance, myocardial relaxation, and left atrial dimensions. With respect to right heart function, plasma concentrations of B-type NPs are inversely related to right ventricular ejection fraction and directly related to right ventricular dimensions and estimated intraventricular pressures.[9]

An echocardiographic substudy of the phase II PARAMOUNT trial (LCZ696 Compared to Valsartan in Patients With Chronic Heart Failure and Preserved Left-ventricular Ejection Fraction) of valsartan-sacubitril therapy in HFpEF, demonstrated decreases in LV systolic longitudinal and circumferential strain that were significantly related to plasma NT-proBNP independent of age, sex, systolic and diastolic blood pressures, body mass index, LVEF, left atrial volume index, E/E', atrial fibrillation (AF), or renal function.[11]

Amino-Terminal Pro–B-Type Natriuretic Peptide in the Diagnosis of Acute Heart Failure

The relationship between cardiac structure and function and associated cardiac transmural distending pressures and myocyte stretch on the one hand with cardiac release and plasma concentrations of NT-proBNP on the other underpins the strength of NT-proBNP as a biomarker in HF. NT-proBNP has good diagnostic performance for discrimination of acute heart failure among patients presenting with new-onset dyspnea. Key publications include a report generated though data pooling from emergency department studies undertaken in New Zealand, the United States, Spain, and the Netherlands.[12] The ICON study (International Collaboration on NT-proBNP) included data on 1256 patients presenting with new-onset shortness of breath. ICON data defined the sensitivity, specificity, negative predictive value, positive predictive value, and overall accuracy of NT-proBNP for the diagnosis of acute HF in acutely symptomatic patients, and these data have informed international guidelines for the diagnosis and management of heart failure.[13,14] Plasma NT-proBNP of 300 pg/mL acts as an excellent rule-out threshold with a sensitivity for ADHF consistently greater than 90%. A plasma NT-proBNP of less than this threshold indicates symptoms are highly unlikely to be due to acute heart failure. Acutely symptomatic patients with a NT-proBNP of less than 300 pg/mL are very unlikely to have acute heart failure. Specificity is improved by using age-specific cutpoints with 450, 900, and 1800 pg/mL performing well for age groups less than 50, 50 to 75, and greater than 75 years, respectively (**Table 1**).[12] The 2016 European Society of Cardiology guidelines for the diagnosis and management of heart failure strongly mandate measurement of NT-proBNP in the diagnostic workup for suspected acute heart failure emphasizing a rule out threshold of 300 pg/mL.[14]

Therapy with combined angiotensin 2 type1 receptor blockade and neprilysin inhibition (ARNI) has recently been shown to be superior to treatment with angiotensin-converting enzyme inhibition in chronic heart failure, offering an approximate 20% improvement in all key important clinical endpoints.[15] The new therapy has already entered authoritative guidelines and

Table 1
Optimal NT-proBNP cutpoints for the diagnosis or exclusion of acute heart failure among dyspneic patients

Category	Optimal Cutpoint (pg/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Exclusionary "rule out" cut point all patients (n = 1256)	300	99	60	77	99	83
Confirmatory ("rule-in") cutpoints						
<50 y (n = 184)	450	97	93	76	99	94
50–75 y (n = 537)	900	90	82	83	88	85
>75 y (n = 535)	1800	85	73	92	55	83
Rule-in, overall (n = 1256)	—	90	84	88	66	85

Abbreviations: NT-proBNP, amino-terminal pro–B-type natriuretic peptide; NPV, negative predictive value; PPV, positive predictive value.

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.

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its use is likely to become very widespread.[14,16] Neprilysin mediates cleavage of the biologically active carboxy terminals of ANP, BNP, and C-type NP, and prolongation of the circulating and tissue half-lives of these powerful effectors is presumed to underlie a significant proportion of the benefit offered by ARNI.[17] Accordingly, prescription of ARNI in chronic HF resulted in sustained elevations in plasma BNP, whereas NT-proBNP (which is not cleaved by neprilysin) decreased, reflecting impaired metabolism of carboxy terminal BNP and decreased cardiac release of NP, respectively (**Fig. 2**).[18] In this setting the relationship of NT-proBNP to intracardiac pressures and HF status, plasma is undistorted, whereas BNP is no longer a reliable marker. NT-proBNP but not BNP remains a valid marker during ARNI therapy. Where ARNI therapy is contemplated or already in place, NT-proBNP is the marker of choice in assessment of possible incident ADHF and for serial monitoring.

Amino-Terminal Pro–B-Type Natriuretic Peptide for the Diagnosis of Early Heart Failure in the Community

For the nonacute case with early or incipient decompensation, the much lower threshold of NT-proBNP of 125 pg/mL is recommended.[14] Diagnostic performance at this level in the nonacute setting is not as well-defined as it is for the case with severe acute symptoms. However, NT-proBNP at about this level does aid in identification (area under the curve [AUC] > 0.9) of asymptomatic or minimally symptomatic LV dysfunction with an LVEF of less than 40% in community-dwelling patients as demonstrated by reports from the Olmsted County studies and from the ICON Primary Care study of approximately 5000 participants in an array of screening cohorts (**Fig. 3**).[19,20] NT-proBNP is also the only marker to have undergone a randomized, controlled trial to ascertain the additional diagnostic benefit it confers for the diagnosis of HF in primary care.[21] In a study of 305 patients assessed by 92 family doctors for suspected incipient heart failure (on the basis of exertional dyspnea and/or peripheral edema), the addition of plasma NT-proBNP measurements to clinical history and examination, significantly improved diagnostic accuracy by 10 patients per 100 assessed.

Modifiers of the Diagnostic Performance of Amino-Terminal Pro–B-Type Natriuretic Peptide

The typical elevation of plasma NT-proBNP in the setting of severe symptomatic ADHF is so pronounced (median values are >5000 pg/mL and are typically >40-fold greater than the levels observed in controls without HF) that this marker achieves an excellent "signal-to-noise ratio" for ADHF.[12] However, elevation of plasma NT-proBNP is not specific for ADHF. AF, renal failure,

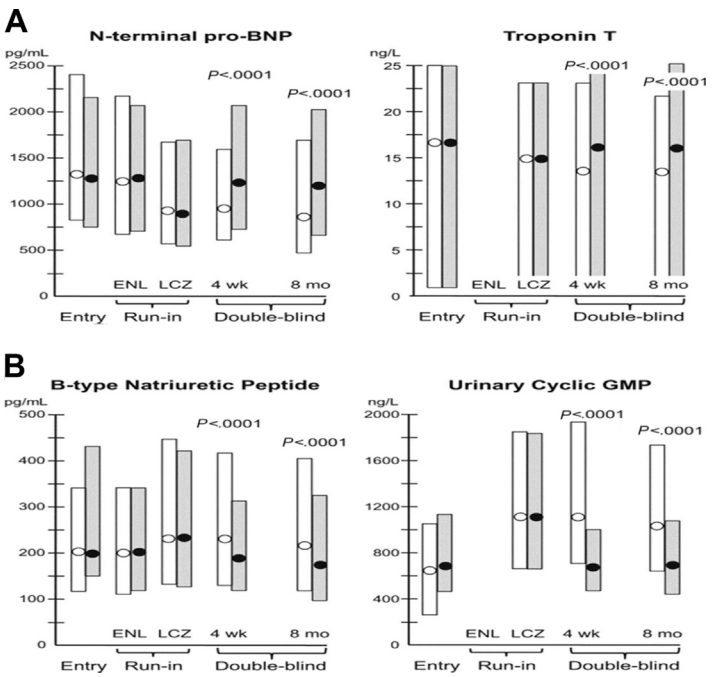

Fig. 2. (*A*) Median amino-terminal pro–B-type natriuretic peptide (NT-pro-BNP) and troponin T at entry and during single-blind run-in and double-blind periods. Medians are shown in circles, and 25%–75% interquartile ranges are shown in bars, where patients in the LCZ696 group are shown in white circles and bars and patients in the enalapril group are shown in black circles and bars. (*B*) Median values for BNP and urinary cyclic GMP according to same format as in (*A*). ENL, end of the enalapril phase of the run-in period; LCZ, end of the LCZ696 phase of the run-in period. *P* values give significance of difference between the 2 treatment groups. (*From* Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54–61; with permission.)

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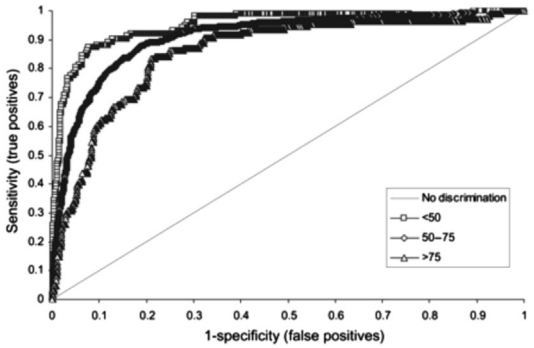

Fig. 3. Receiver operating characteristic curves for discrimination of a left ventricular ejection fraction of less than 40% among community dwelling asymptomatic or minimally symptomatic subjects according to age (<50, 50–75, and >75 years). (*From* Hildebrandt P, Collinson P, Fuat A, et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care: the International Collaborative study of Natriuretic peptides in Primary Care (ICON-PC). Eur Heart J 2010;31(15);1881–9; with permission.)

pulmonary embolism, and a number of other causes increase NT-proBNP (**Box 1**). NT-proBNP level should be considered in concert with the clinical history, examination findings, and data from other tests, including a standard laboratory workup and cardiac imaging. Age, obesity, preserved ejection fraction, renal dysfunction, and AF may affect the diagnostic performance of NT-proBNP.

Consideration of confounding influences on NP plasma concentrations is necessary for interpretation of plasma NT-proBNP results in those with mild or early decompensated HF, or in epidemiologic settings where elevation of median plasma concentrations is not profound and background confounders become more intrusive.

Age is a strong determinant of NT-proBNP. This relationship is independent of kidney and cardiac function, and the exact underlying mechanisms remain unclear. Age-adjusted values enhance the specificity and accuracy of NT-proBNP in diagnosis of ADHF at the cost of some loss of sensitivity (**Fig. 4**; see **Table 1**).[12] An NT-proBNP level of 450 pg/mL or more in the presence of new onset dyspnea is highly discriminating for ADHF (AUC, 0.99) in those less than 50 years of age. Most HF patients are older and the AUC falls progressively to 0.93 and then 0.86 in patients aged 50 to 75 years (optimal threshold of 900 pg/mL) and those older than 75 years (1800 pg/mL), respectively. Age-adjusted values have been calculated for NT-proBNP but not BNP.[12]

Box 1
Causes of elevated plasma amino-terminal pro–B-type natriuretic peptide

Cardiac

- Heart failure, acute and chronic
- Acute coronary syndromes
- Atrial fibrillation
- Valvular heart disease
- Cardiomyopathies
- Myocarditis
- Cardioversion
- Left ventricular hypertrophy

Noncardiac

- Age
- Renal impairment
- Pulmonary embolism
- Pneumonia (severe)
- Obstructive sleep apnea
- Critical Illness
- Bacterial sepsis
- Severe burns
- Cancer chemotherapy
- Toxic and metabolic insults

LV structure and function influence plasma NT-proBNP. Specifically, plasma NT-proBNP plasma concentrations in HFpEF are approximately half those observed in HFrEF (**Table 2**) in both acute and chronic HF.[6,7,22] This reflects the integrated influence of ventricular internal dimensions, wall thickness, and intraventricular pressures (embodied in the law of Laplace) on unit wall stress and cardiomyocyte stretch, the primary driver of NP synthesis and release. In the event, the diagnostic performance of NT-proBNP in HFpEF is only marginally impaired in view of the high signal-to-noise ratio in acute HF, as discussed elsewhere in this article. In contrast, in the setting of incipient or treated HF, NP values often fall into the subdiagnostic range and this is particularly so in HFpEF.[23] This emphasizes the need to apply the recommended cutpoint values for acute HF in the appropriate setting; that is, with new onset of distressing breathlessness where acute HF is likely. When NPs fall into the "gray zone" between rule out and rule in values for acute HF (eg, NT-proBNP between 300 and 450 pg/mL <50 years of age; 300 and 900 pg/mL in those 50–75 years of age; and 300 and 1800 pg/mL in those >75 years of age), echocardiography is an invaluable diagnostic adjunct with

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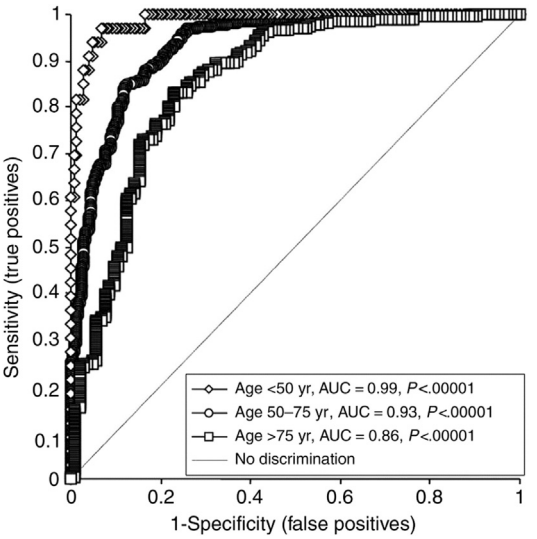

Fig. 4. Receiver operator characteristic curves for discrimination by amino-terminal pro–B-type natriuretic peptide of acute heart failure among dyspneic patients according to age. (*From* Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006;27(3):330–7; with permission.)

elevated E/e' and/or the presence of a restrictive filling pattern helping securing the diagnosis of HF.[24]

AF increases plasma NT-proBNP whether HF is present or not.[25–28] AF is a common complication of HF, and occurs in approximately 30% of populations with ADHF. AF reduces the discriminative performance NT-proBNP for newly symptomatic ADHF, reducing the AUC on receiver operator analysis to approximately 0.7, which is well below the approximately 0.9 observed in HF cases with preserved sinus rhythm (**Fig. 5**).[28] The sensitivity of the standard thresholds of NT-proBNP are preserved in the face of overall increases in plasma peptide concentrations, but specificity and accuracy are clearly reduced and cannot be improved solely by selection of an alternative cut point. Empirical observation indicates that between 65% and 85% of acutely breathless patients with AF and NT-proBNP levels of greater than 300 pg/mL will receive a final diagnosis of acute HF and they should be managed as such until an alternative diagnosis is proven.[25–28]

Obesity lowers plasma NP concentrations through poorly understood mechanisms. Body mass index is actually inversely related to plasma NT-proBNP concentrations in both health and HF.[29–31] Unlike renal impairment or AF, which irretrievably impair the specificity and accuracy of plasma NT-proBNP, obesity shifts the optimal threshold but preserves discriminatory performance. The effect on the diagnostic performance of BNP at 100 pg/mL is pronounced, with a clear loss of sensitivity that has led to the recommendation to reduce the cutpoint to 50 pg/mL for those with a BMI greater than of 30 kg/m^2.[31] However, the test performance of age-specific thresholds of NT-proBNP seem to be less affected (**Fig. 6**).[30]

Plasma NT-proBNP increases as renal function decreases. Estimated glomerular filtration fraction rate are inversely related to plasma concentrations of BNP and NT-proBNP.[12,32,33] For BNP, this has led to the recommendation that the BNP threshold be increased to 200 pg/mL for an estimated glomerular filtration rate of less than 60 mL/min/1.73 m.[34] No specific corresponding change in cutpoint is generally applied to NT-proBNP values and the performance of age-specific NT-proBNP diagnostic thresholds seem to be less affected (**Table 3**).[34] The diagnostic specificity and accuracy of NT-proBNP are somewhat reduced in the presence of impaired renal function at any selected cutpoint.

Table 2
Median plasma concentrations of NT-proBNP in acute and chronic HFrEF and HFpEF

Category of Heart Failure	NT-proBNP Median (pg/mL)	N	Study/Trial	Ref
Acute decompensated heart failure				
HFrEF	6356	358	ICON	Januzzi et al,[12] 2006
HFpEF	3070	295	ICON	Januzzi et al,[12] 2006
Chronic heart failure				
HFrEF	895	3916	ValHeFT	Masson et al,[40] 2006
HFpEF	339	3480	I-PRESERVE	Komajda et al,[23] 2011

Abbreviations: HFpEF, heart failure with preserved left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; NT-proBNP, amino-terminal pro–B-type natriuretic peptide.

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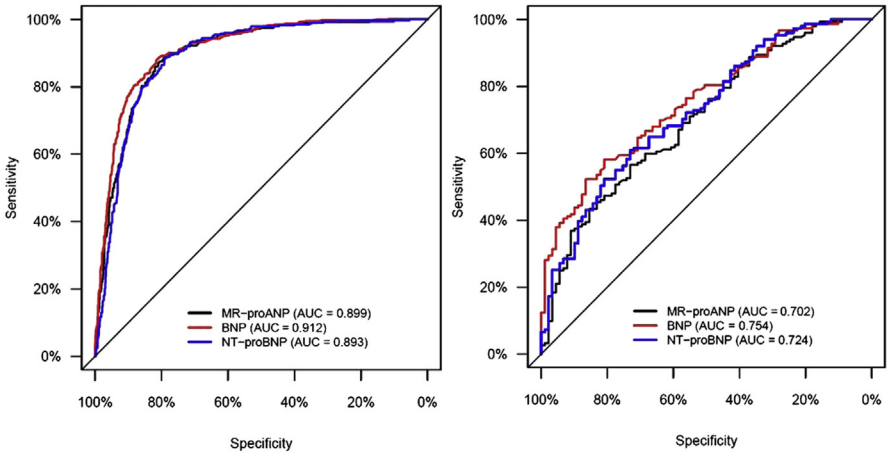

Fig. 5. Receiver operator curves for discrimination by amino-terminal pro–B-type natriuretic peptide (NT-proBNP; *blue*), BNP (*red*) or midregion amino terminal atrial natriuretic peptide (*blue*) of a diagnosis acute heart failure among breathless patients in (*left*) normal sinus rhythm or in (*right*) atrial fibrillation. (*From* Richards AM, Di Somma S, Mueller C, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the Biomarkers in Acute Heart Failure (BACH) Study. JACC Heart Fail 2013;1:192–9; with permission.)

Amino-Terminal Pro–B-Type Natriuretic Peptide and Prognosis in Heart Failure

Along with BNP and mid-region amino terminal pro-ANP, NT-proBNP is endorsed as an independent prognostic marker in acute and chronic HF and is endorsed for these indications in authoritative international guidelines on the diagnosis and management of HF.[13,14] Both single and serial measurements of NT-proBNP offer prognostic information in acute and chronic HF.[12,22,23,33,35–38]

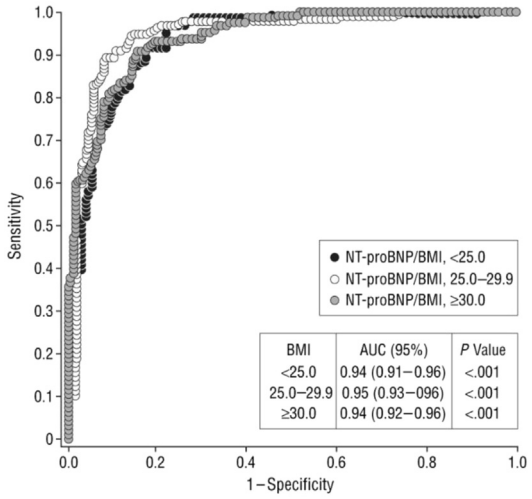

Fig. 6. Receiver operating characteristic curves for discrimination of acute heart failure amino-terminal pro–B-type natriuretic peptide (NT-proBNP) across 3 categories of body mass index (BMI; kg/m^2). AUC, area under the curve. (*From* Bayes-Genis A, Barallat J, Richards AM. A test in context. neprilysin: function, inhibition and biomarker. J Am Coll Cardiol 2016;68:639–53; with permission; and *Data from* Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. Arch Intern Med 2007;167(4):400–7.)

Amino-terminal pro–B-type natriuretic peptide and early mortality in acute decompensated heart failure

The ICON study, although primarily aimed at assessing the diagnostic value of markers, also indicated NPs measured at admission for ADHF

Table 3
Impact of renal disease on the diagnosis of acute decompensated heart failure in patients presenting with dyspnea

	GFR (mL/min per 173 m^2)	Area Under the Curve	Cutpoint (ng/L)
BNP	>90	0.91	70.7
	60–90	0.90	104.3
	30–59	0.81	201.2
	<30	0.86	225
NT-proBNP	≥60	0.95	900/450
	<60	0.88	1200

Abbreviations: BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, amino-terminal pro–B-type natriuretic peptide.

From DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. Am J Cardiol 2008;101:82–8; with permission.

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provided indications of longer term prognosis (Fig. 7).[12] Notably, the BACH study (Biomarkers in Acute Heart Failure) demonstrated midregion amino terminal adrenomedullin to be clearly superior to NP in predicting mortality over the first 30 days after admission for ADHF.[39]

Amino-terminal pro–B-type natriuretic peptide and prognosis in chronic heart failure

The ValHeFT therapeutic trial (Valsartan Heart Failure Trial) in chronic HFrEF generated a large neurohormonal substudy providing excellent data on the prognostic performance of both NT-proBNP and BNP in chronic heart failure with reduced LVEF.[40,41] After comprehensive adjustment for demographic, biochemical, clinical, and imaging predictors, NT-proBNP remained an independent predictor of all-cause death and of readmission for HF. NT-proBNP performed more strongly than endothelin, aldosterone, or norepinephrine.[41] Median plasma NT-proBNP concentrations of 895 pg/mL corresponded with an unadjusted crude annual mortality of approximately 10.1%. Increments of 500 pg/mL in NT-proBNP conferred a 3.0% to 3.8% increment in risk of all-cause death or HF readmission. From first to tenth deciles of NT-proBNP, the ValHeFT population exhibited a 10-fold range in risk of all-cause death, HF readmission and the composite endpoint.

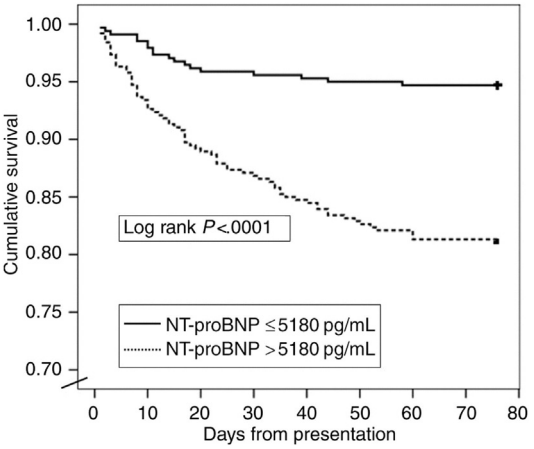

Fig. 7. Kaplan–Meier curves demonstrating survival rates of patients with acute heart failure (n = 720) during the first 76 days after presentation, expressed as a function of amino-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration (log-rank test, *P*<.001). (*From* Januzzi JL, van Kimmenade 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.)

A large number of HF patients (n = 4128) participated in the marker substudy from the I-PRESERVE therapeutic trial (Irbesartan in Heart Failure With Preserved Systolic Function) of irbesartan in HFpEF. Plasma NT-proBNP concentrations were related to outcomes, including 1515 episodes of all-cause death/cardiovascular admission, 881 deaths, and 716 HF deaths/HF admissions.[23] A median NT-proBNP of 339 pg/mL conferred a crude unadjusted annual mortality of 5.1%. In comprehensive multivariate modeling, NT-proBNP was the strongest independent predictor of outcomes at 3 years of follow-up. Across septiles of NT-proBNP, risk extended over 7- to 20-fold ranges from 8.1% to 59.9% for the primary endpoint, 2.7% to 36.5% for death and 2.1% to 38.9% for HF death/HF admission. NT-proBNP, independent of multiple other accepted predictors, provided fine-grained prediction of clinical outcomes from low to very high risk. Findings from I-PRESERVE were also assessed by Anand and colleagues.[42] An additional report from I-PRESERVE displayed a 4- to 6-fold range of risk of these endpoints from the first to the fourth to quartiles of NT-proBNP.

Plasma NP criteria enrich trial populations for events, thus rendering sample sizes more manageable and providing greater certainty that the condition of interest, HF, is indeed present. The TOPCAT trial (Therapy for Adults with HFPEF) tested the efficacy of spironolactone in HFpEF in 3445 patients aged more than 50 years with signs and symptoms of HF and either a history of hospitalization with HF in the past 12 months or a NT-proBNP of greater than 360 pg/mL. Notably, outcomes were clearly improved by spironolactone in the subset of patients selected according to NT-proBNP.[43]

In the landmark PARADIGM trial (A Multicenter, Randomized, Double-blind, Parallel Group, Active-controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction) comparing sacubitril and valsartan with enalapril in the treatment of HFrEF, plasma NT-proBNP was measured in a subgroup (n = 2080) of participants.[44] Those with baseline levels of greater than 1000 pg/mL (n = 1292) who achieved a decreases in NT-proBNP to less than 1000 pg/mL at 1 month (24%) after randomization incurred 59% fewer deaths or admissions with HF compared with patients with NT-proBNP remaining above this concentration (Fig. 8).

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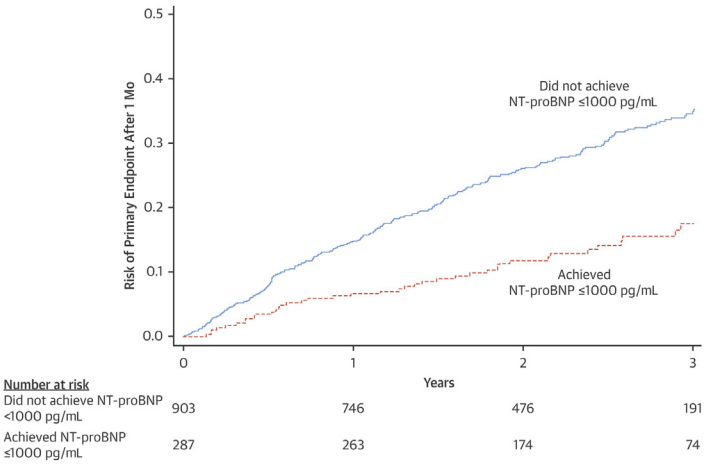

Fig. 8. Risk of primary endpoint after 1 month of randomization in patients with a baseline amino-terminal pro–B-type natriuretic peptide (NT-proBNP) of greater than 1000 pg/mL. The risk at 3 years of follow-up was 50% less in those who achieved an NT-proBNP of less than 1000 pg/mL than in those who did not. (*From* Zile MR, Claggert BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol 2016;68:2425–36; with permission.)

Markers to Replace or to Complement Amino-Terminal Pro–B-Type Natriuretic Peptide

Myriad additional candidate markers for HF have been reported. These include galectin 3, midregion proadrenomedullin, GDF 15, and ST-2.[45–47] NT-proBNP may combine with other markers including ST2, GDF15, galectin 3, midregion amino terminal adrenomedullin, and others to further refine risk stratification. Some are recommended within clinical guidelines as markers providing additional prognostic information in acute and chronic HF.[13,14] Many offer refinement of risk stratification when combined with NT-proBNP (**Fig. 9**).[14,45,46]

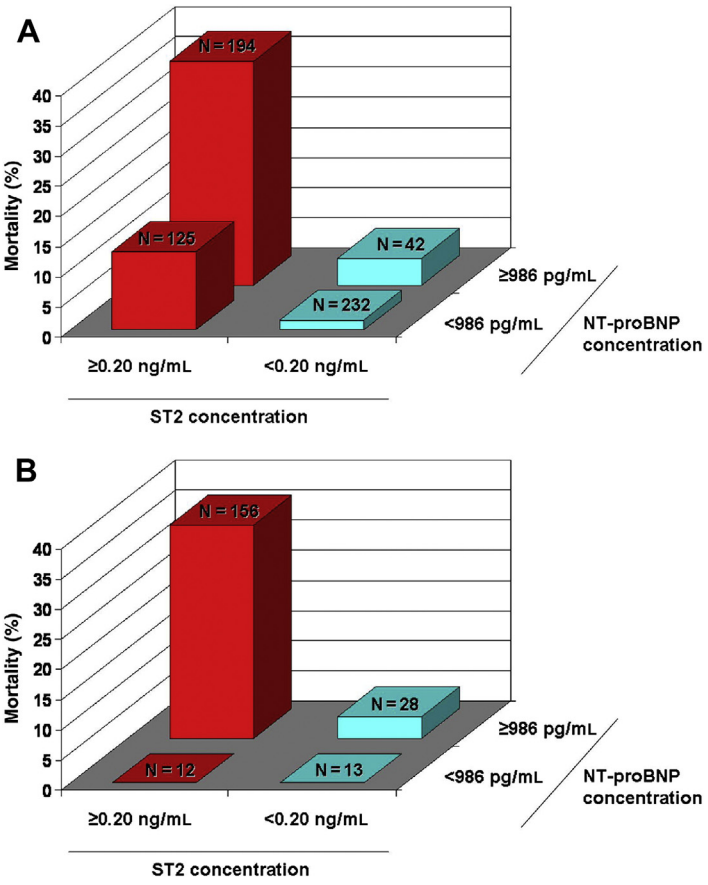

Fig. 9. Mortality rates at 1 year as a function of ST2 and amino-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations among (*A*) all patients with dyspnea (n = 593) and in (*B*) the subgroup with acute heart failure (n = 208). (*From* Januzzi JL, Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. J Am Coll Cardiol 2007;50:607–13; with permission.)

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Although a number of markers provide comparable or complementary prognostic information to NT-proBNP, at our present state of knowledge, no marker is superior to NT-proBNP in the diagnosis of HF.

Marker-Guided Therapy in Chronic Heart Failure

The associations between plasma BNPs and prognosis has provided the rationale for a series of controlled trials of hormone-guided therapy in chronic HF.[35–38] Although individual trials have variously yielded positive or neutral results, serial metaanalyses have consistently indicated benefit from guided therapy with greater than 20% reductions in total mortality and HF hospitalizations (**Fig. 10**)[37,38] Metaanalyses of trials of NT-proBNP–guided therapy in chronic heart failure suggest improved outcomes and confirm achievement of NT-proBNP of less than 1000 pg/mL confers a better prognosis. All trials of marker-guided therapy have consistently confirmed the strong association between achieved plasma B-type peptide levels and outcome regardless of allocated treatment strategy. The GUIDE-IT trial (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) (ClinicalTrials.gov NCT01685840) was intended to provide definitive answers with respect to guided therapy in HFrEF.[48] However, it has been halted early reflecting full and effective therapy, which unprecedentedly reduced average levels of NT-proBNP to less than 1000 pg/mL in both limbs of the trial. This finding left no possibility for the marker to trigger meaningful intergroup differences in management because the 2 groups both received maximal therapy. Event rates were low in the well-treated GUIDE-IT trial population, again reinforcing the very consistent message that attaining low plasma NT-proBNP (ie, <1000 pg/mL) is associated with improved outcomes.

Biomarkers and Heart Failure Risk Scores

Although guidelines recommend the use of risk calculators to inform management decisions on advanced therapies such as ventricular assist

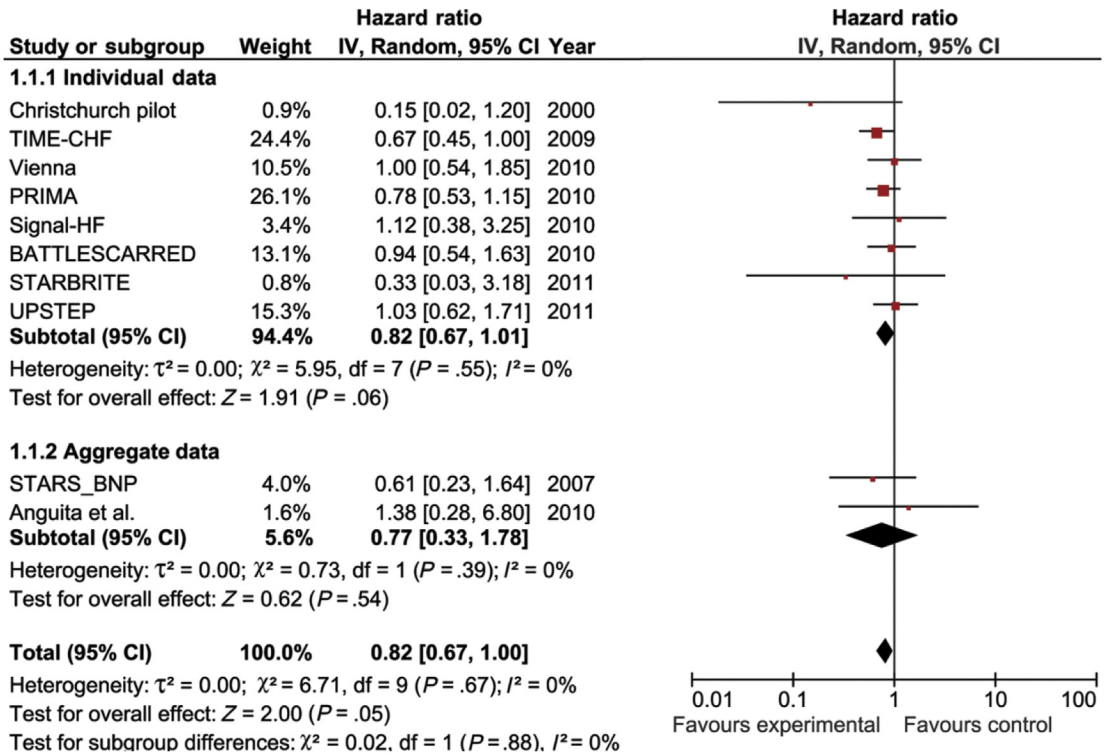

Fig. 10. Forest plot of mortality among participants in trials of marker-guided treatment of chronic heart failure showing unadjusted individual and mean hazards ratios with 95% confidence intervals (CIs) for 8 studies providing individual patient data and 2 studies providing aggregate data. (*From* Troughton RW, Frampton CM, Brunner-La Rocca HP, et al. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur Heart J 2014;35(3):1559–67; with permission.)

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devices and cardiac transplantation, the performance of such risk engines in individual patient management has been challenged.[14,49]

Risk calculators would likely be improved by incorporation of markers such as NT-proBNP. May and colleagues[50] assessed the performance of the Seattle Heart Failure Model in ambulant chronic heart failure and found, in a subgroup of 544 out of 4077 registered patients with BNP results available, that the marker modestly augmented the *c*-statistic for prediction of the composite endpoint of survival free from death, transplantation, or LV assist device implantation from 0.73 to 0.78 for events at 1 year. In the CORONA trial (Controlled Rosuvastatin Multinational Trial in Heart Failure) of rosuvastatin in HF, Wedel and colleagues[51] reported the *c*-statistic for prediction of all-cause mortality improved from 0.667 to 0.719 when NT-proBNP and high-sensitivity C-reactive protein were added to a clinical model. For predicting death specifically owing to heart failure, the *c*-statistic increased from 0.742 to 0.800.

SUMMARY

Plasma NT-proBNP is a powerful marker in heart failure. Its usefulness is best proven as an adjunctive rule-out test in the diagnosis of acute heart failure among patients with new-onset dyspnea. Guidelines recommend NT-proBNP be measured in all acutely symptomatic patients in whom the differential diagnosis includes acute heart failure. It is also a useful screening tool in the nonacute and primary care settings for identification of incipient HF and asymptomatic LV dysfunction (LVEF < 40%). Plasma NT-proBNP results are affected by age, preserved ejection fraction, renal dysfunction, obesity, and AF. Although these factors have little impact on the sensitivity and negative predictive value of B-NT-proBNP in the acute setting, they may reduce specificity and overall accuracy of the test and certainly require consideration when the test is turned to nonacute settings and use as an epidemiologic tool. NT-proBNP adds prognostic information at all stages of acute and chronic heart failure with a more than 10-fold gradation of risk of key adverse outcomes from first to tenth decile of plasma NT-proBNP concentrations. Serial measurements provide a tool to monitor HF status and prognosis and to facilitate titration of therapy. Achieving plasma NT-proBNP concentrations of less than 1000 pg/mL is associated with lower rates of death and hospital readmission. A range of more recently discovered markers rival NT-proBNP as indicators of prognosis, but none outperform NT-proBNP as diagnostic test. Risk stratification can be refined by combining NT-proBNP with another marker and multimarker strategies may come into use when they can be shown to enhance management and outcomes. Current HF risk calculators incorporating a selection of acknowledged clinical predictors are not reliable in the prediction of key outcomes in individual patients and are likely to be improved by the incorporation of data on markers like NT-proBNP.

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