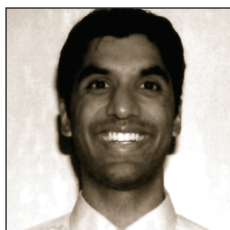# NT-proBNP – A New Test for Diagnosis, Prognosis and Management of Congestive Heart Failure

a report by
Drs Rahul Sakhuja *and* **James L Januzzi**

Cardiology Division and Department of Medicine, Massachusetts General Hospital, Harvard Medical School

Dr Rahul Sakhuja

Dr James L Januzzi

Dr Rahul Sakhuja is currently a second-year resident in Internal Medicine at Massachusetts General Hospital. He received an MD from Harvard Medical School and a Master of Public Policy from the John F Kennedy School of Government at Harvard University. He plans to pursue a career in cardiology.

Dr James Januzzi is an Assistant Professor of Medicine at Harvard Medical School, and a Cardiologist in the Division of Cardiology of Massachusetts General Hospital in Boston. He has won numerous academic honors and awards, and is on several editorial boards for peer-reviewed journals. After completing internal medicine training, Dr Januzzi began a fellowship in cardiology at Massachusetts General Hospital, after which he remained on staff. Dr Januzzi was the top-ranked graduate of the New York Medical College in 1994, after which he did his internal medicine training at the Brigham and Women's Hospital in Boston.

Introduction

With nearly 500,000 new cases per year and direct costs estimated as high as US$38 billion annually, congestive heart failure (CHF) has become a major priority in modern medicine. This crisis will continue to grow as the population ages, thus the discernment of new diagnostic and therapeutic strategies to improve prognosis and reduce costs is critical.[1]

The irony is that therapies with great benefit for patients with CHF exist, such as angiotensin converting enzyme (ACE) inhibitors and beta-blockers. However, these agents are under-utilized, and when employed may be dosed inadequately.[2,3] Accordingly, a widely available and accurate diagnostic tool to identify those with CHF would be essential in order to identify those patients eligible for proven therapies in CHF. Such a diagnostic tool for early diagnosis would theoretically lead to earlier initiation of these beneficial medicines while potentially assisting in chronic out-patient management of such patients. As CHF is the leading cause of hospitalization in adults over 65, achieving such early diagnosis and initiation of therapy would thus prevent hospitalizations and reduce the considerable costs of CHF.[4]

Markers of cardiac neurohormonal activation, particularly B-type natriuretic peptides, have been identified as possible tools to identify and treat patients with CHF. While most studies to date have focused on the diagnostic utility of B-type natriuretic peptide (BNP), more recent research has revealed that the amino-terminal fragment of the BNP molecule (NT-proBNP), a marker with great diagnostic and prognostic power, is a marker for CHF. Recently, a new automated immunoassay has made NT-proBNP testing a reality for diagnostic, prognostic, and possibly therapeutic, purposes in CHF.[5] This paper reviews some of the growing evidence behind the use of NT-proBNP in patients with CHF.

Biology of Natriuretic Peptides

The natriuretic peptides are a family of molecules consisting of several structurally-related hormones. At present, the natriuretic peptide family includes atrial natriuretic peptide (ANP), B-type (or brain) natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP).

In particular, the B-type natriuretic peptide family has gained popularity as candidate markers for CHF. Biologically, these neurohormones affect body fluid homeostasis (through natriuresis and diuresis) and vascular tone (through decreased angiotensin II, norepinephrine synthesis), both essential components in the pathophysiology of CHF.[6]

B-type natriuretic peptides are produced initially as a 134 amino acid pre-pro-peptide, which is cleaved into proBNP108, a precursor molecule stored in secretory granules in myocytes (see *Figure 1*). Upon release, proBNP108 is cleaved by a protease known as furin into N-terminal (NT)-proBNP (a 76 amino acid biologically-inert portion), and BNP (which is biologically active). In humans, NT-proBNP and BNP are found in largest concentration in the left ventricular (LV) myocardium, but are also detectable in atrial tissue as well as in the myocardium of the right ventricle.

Among the many signals for B-type natriuretic peptide release is myocardial stretch. From animal studies, myocardial induction and secretion of B-type natriuretic peptides in such situations is rapid, with detectable levels in the blood soon thereafter, making it a candidate tool for the recognition of CHF.[7–9]

Although derived from a common precursor, BNP and NT-proBNP are considerably different in many ways. As a biologically active compound, BNP is actively cleared from the circulation via natriuretic peptide receptors, as well as by degradation by neutral endopeptidases in the blood stream. Accordingly, the half-life of BNP is only 18 minutes. Additionally, once drawn, BNP levels are not stable *in vitro* for long periods, dropping significantly over the first 24 hours following collection.[10] Also, if blood is collected into glass tubes, BNP levels may fall, due to activation of the kallikrein system. NT-proBNP is not biologically active, and as such does not have active clearance mechanisms. Therefore, the half-life of NT-proBNP is approximately 60–120 minutes. In

humans, a renal route of clearance is suspected as a partial mechanism for NT-proBNP metabolism. NT-proBNP is dramatically more stable than BNP, with very little variation in the level of the marker after collection for at least 72 hours, and probably longer. In addition, NT-proBNP may be collected into glass tubes without any issues.

As noted above, sensitive assays now exist for both markers, though the NT-proBNP assay may be more sensitive than BNP in certain scenarios. Recent data has grown demonstrating the value of NT-proBNP testing for a wide variety of uses for patients with CHF.

Uses of NT-proBNP in CHF

A significant body of evidence has developed to demonstrate that NT-proBNP levels correlate with diagnosis, clinical status and prognosis in congestive heart failure, and may be useful for the longitudinal management of patients with CHF.

Diagnosis of CHF

Bay and colleagues published one of the first large studies revealing the utility of NT-proBNP in predicting LV dysfunction. From 3,236 hospitalized patients with symptomatic and asymptomatic CHF, NT-proBNP had a sensitivity of 73%, specificity of 82%, and, most impressively, a negative predictive value of 98%. The diagnostic value to predict a left ventricular ejection fraction (LVEF) <40% as represented by the area under the receiver operating characteristic curve (AUC) was 0.85. As compared with BNP, NT-proBNP was an equivalent predictor of LVEF <30% as reflected by an AUC of 0.88 versus 0.85. Overall, the study revealed that NT-proBNP added significantly more diagnostic power to the clinical history.[11] Subsequently, other studies revealed that not only was NT-proBNP elevated in CHF from LV dysfunction, but was also in forms of CHF with normal LV function (diastolic dysfunction), although the levels of NT-proBNP among patients with non–systolic CHF are typically lower than those with systolic dysfunction and CHF.[9]

Following such large-scale studies demonstrating the feasibility of detection of LV abnormalities, the use of NT-proBNP for the acute evaluation of dyspneic patients with possible CHF was then explored in three recent studies. In the first such study, Lainchbury and colleagues demonstrated NT-proBNP to be of value in the evaluation of patients with dyspnea and suspected acute CHF in the emergency department (ED).[12] Subsequently, Bayes-Genis and colleagues found that NT-proBNP levels were significantly higher in patients with decompensated CHF, and also demonstrated the value of the marker for identifying

Figure 1: Biology of NT-proBNP and BNP
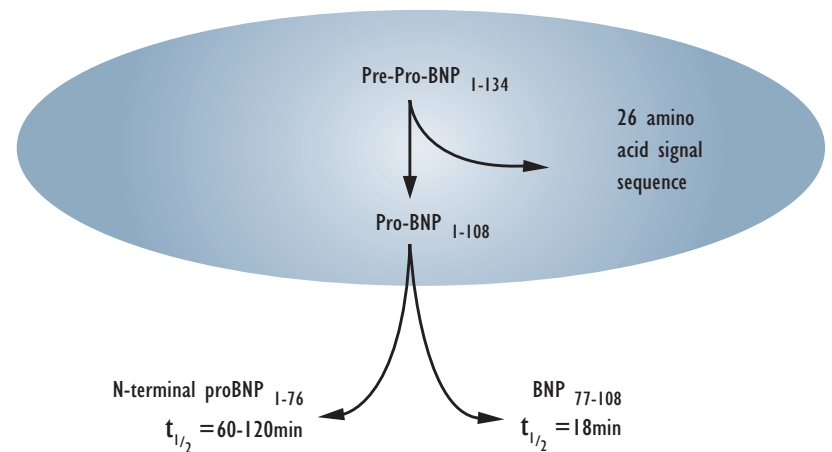
Both NT-proBNP and BNP are derived from a common intracellular 108 amino acid precursor, which is cleaved into the two circulating fragments (NT-proBNP and BNP), as depicted.

those patients with 'masked' heart failure, defined as those patients with LV dysfunction and concomitant pulmonary disease. Furthermore, Bayes-Genis and others demonstrated as the heart failure was treated, NT-proBNP levels fell in tandem.[13,14]

Most recently, more definitive data supporting the use of NT-proBNP in the ED were reported. In a blinded prospective analysis of 600 patients presenting with acute dyspnea, the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study investigators demonstrated NT-proBNP levels to be markedly elevated among patients with decompensated CHF (see *Figure 2*).[15] NT-proBNP was highly sensitive and specific for the diagnosis of acute CHF, and correlated with the severity of CHF symptoms. Among all the factors evaluated, an elevated NT-proBNP proved to be the single strongest independent predictor for the final diagnosis of acute CHF. Lastly, in the PRIDE Study, NT-proBNP was superior to clinical assessment for the identification of acute CHF. However, the combination of NT-proBNP testing plus clinical assessment was the most superior tool for patient evaluation.

Limited head-to-head data exist comparing NT-proBNP to BNP for patients with suspected or confirmed CHF. As a general rule, BNP is used for the detection of acute CHF, but exceptions may exist and, in many studies, NT-proBNP was the more sensitive marker.[12] Among patients with acute CHF in the PRIDE Study, NT-proBNP was more sensitive than BNP (90% versus 80% overall), a finding demonstrated in several other studies.[16–19] In most of these studies, NT-proBNP was particularly superior to BNP when evaluating patients with mild–to–moderate structural heart disease, diastolic CHF, or chronic relatively compensated CHF. Indeed, relevant to the last category of patients, Tang and colleagues demonstrated that more

than 20% of symptomatic out-patients with chronic CHF may have BNP levels in the normal range, a finding not frequently demonstrated with NT-proBNP.[20] Thus, in certain scenarios, NT-proBNP may be more sensitive than BNP.

Prognosis in CHF

With a five-year mortality of 50% and a 10-year mortality nearing 90%, a marker that correlates with prognosis would be helpful in risk stratification, particularly if such a marker was also useful for patient management.[21]

Fisher and colleagues measured the concentration of NT-proBNP in 87 patients emergently admitted with CHF caused by LV dysfunction and found that NT-proBNP levels were a strong predictor of both death and CHF hospitalization.[22] A larger follow-up study validated these findings in 650 ambulatory patients, among whom NT-proBNP was the strongest independent predictor of mortality (hazard ratio=5.70, p <0.0001), hospital admissions for CHF (hazard ratio=13.83, p <0.0001), and other cardiac admissions.[23]

Interestingly, in addition to predicting prognosis and risk for decompensated CHF after MI, NT-proBNP recently also predicted mortality and urgent transplantation among patients with advanced heart failure from all etiologies awaiting transplant.[24–26] Among a study of patients with severe advanced LV dysfunction, NT-proBNP was the strongest predictor of adverse outcome, more so than LV ejection fraction, heart failure survival scores, and the usual 'gold standard' for predicting mortality in chronic CHF, maximal oxygen extraction.[26] These exciting studies have led to the concept that NT-proBNP testing may be the new 'gold standard' for predicting long-term outcomes in CHF.

Management of CHF

NT-proBNP is clearly useful for diagnosis and prognosis of CHF, and may be useful for monitoring and guiding therapy to improve such potential risk. Bettencourt and colleagues observed in 176 hospitalized patients that plasma NT-proBNP levels decreased significantly in patients whose New York Heart Association (NYHA) classification improved.[14] Moreover, aggressive employment of therapies of proven value in CHF such as ACE inhibitors or beta-blockers decreased NT-proBNP levels, paralleled by improved outcomes including fewer total cardiovascular events, and delayed times to first event (see *Figure 3*).[27]

In addition to guiding therapy with agents such as ACE-inhibitors, NT-proBNP may be of particular use in the guidance of CHF therapy with nesiritide, a synthetic BNP analogue with vasodilator and natriuretic effects.

Figure 2: Median Levels of NT-proBNP Among Patients Presenting with Dyspnea Due to Acute CHF Versus Other Causes
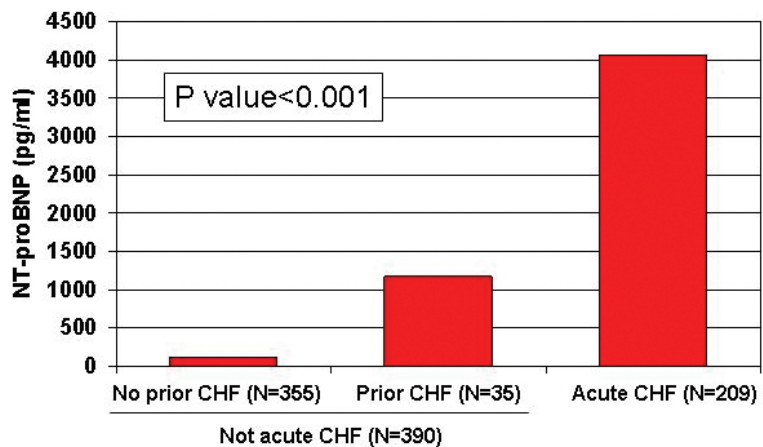
Data from the PRIDE study.[15]

Figure 3: Outcomes of Patients Treated with NT-proBNP Guided Therapy Versus Standard Clinical Judgment. NT-proBNP guided therapy was associated with fewer clinical events
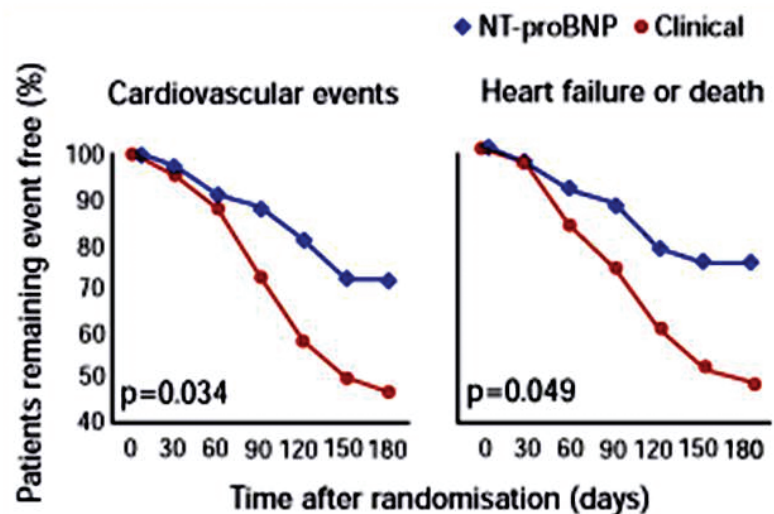
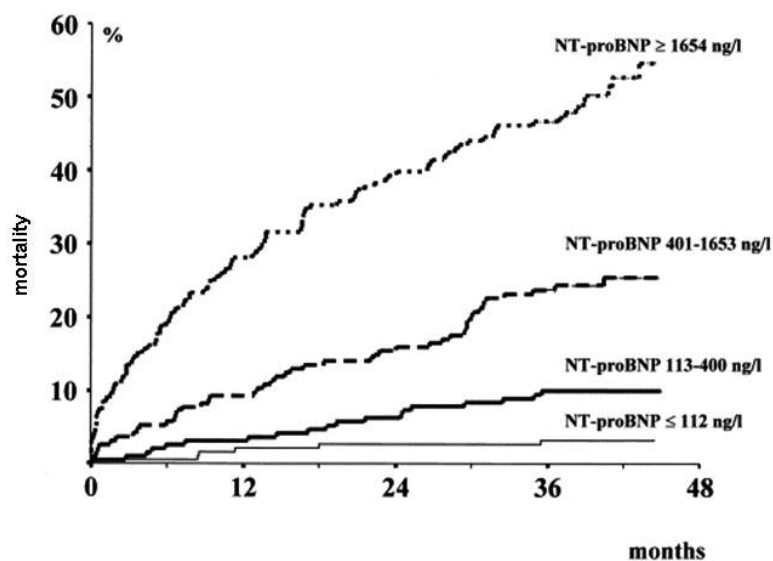*Reproduced with permission from Troughton et al.[28]*

As nesiritide is 100% homologous to endogenous BNP, use of this agent understandably alters assayed levels of BNP rendering biomarker-guided therapy with BNP useless. However, NT-proBNP measurement is not affected by nesiritide. Therefore, in the settings of nesiritide therapy, NT-proBNP proves more useful in monitoring therapy and managing heart failure.

Other Uses of NT-proBNP

While much of the literature has focused on the natriuretic peptides in CHF, it is necessary to point out that NT-proBNP may be elevated in states other than CHF, such as acute coronary syndromes (ACS) as well as pulmonary thromboembolism (PE).

Similar to CHF, ACS patients constitute a large, high-risk population, for which an early diagnostic and

Figure 4: Adverse Prognosis Associated with Elevated NT-proBNP Levels in the Setting of Acute Coronary Syndrome

Reproduced with permission from Jernberg et al[30]

study demonstrated that NT-proBNP also identified those most likely to benefit from early invasive strategies for the management of their ACS.[30]

In addition to CHF and ACS, elevations of NT-proBNP may be powerfully prognostic among patients with acute PE. In 73 patients with acute PE, elevated NT-proBNP levels predicted in-hospital complications (including death) compared with patients with low NT-proBNP levels. In this study, the negative predictive value of NT-proBNP was 97%, similar to that of d-dimer.[31]

Conclusion

Aggregate data now point to the exceptional value of NT-proBNP for the diagnosis, prognosis, and management of patients with acute CHF. While many studies suggest that NT-proBNP and BNP are similar in their potential as a marker for heart failure, some recent studies conclude that NT-proBNP is a more discerning marker in many common clinical scenarios, such as diastolic CHF. In addition, the value of NT-proBNP for diagnosis and prognosis extends to other cardiovascular disease states such as ACS and PE. This versatile marker should help to optimize the care of a wide range of patients with prevalent cardiovascular illnesses. ■

prognostic marker would prove useful. Multiple studies of patients with ACS now demonstrate that NT-proBNP levels are the most powerful predictor of mortality at presentation (see *Figure 4*), superior to troponins for this purpose.[28,29] Interestingly, a follow-up

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