

NT-BNP in Stable Coronary Artery Disease

a report by

Venu Menon

Staff Physician, Department of Cardiovascular Medicine,
Cleveland Clinic

Background

The management of patients with stable coronary artery disease (CAD) is characterised by the utilisation of proven medical therapy and on-going effective risk stratification. Periodic assessment of patient symptomatology and functionality; evaluation and control of traditional risk factors; presence and extent of ischaemia; extent of CAD and left ventricular (LV) function; and referral to revascularisation when indicated all play an important role in delivering optimal care. There remain significant clinical limitations to this treatment strategy. A reliable biomarker or group of markers that would provide incremental data to predict risk for cardiovascular morbidity and death would certainly enhance clinical care in the out-patient setting. An enhanced appreciation of risk may lead to adequate up-titration of medical therapy and improve patient compliance in high-risk subsets. The biomarker would be most useful if it further guided targeted treatment strategies that would in turn optimise patient outcome.

The role of natriuretic peptides has evolved rapidly since their original discovery approximately a quarter of a century ago.¹ An understanding of this complex homeostatic system has led to rapid advances that have been quickly translated from the basic laboratory to practical usage by the patients' bedside.² Brain natriuretic peptide (BNP) and N-terminal (NT)-BNP have emerged as promising molecules for assay and are now available for routine clinical use. The negative predictive value of NT-BNP in ruling out a cardiac aetiology of shortness of breath is now established in current clinical practice.^{3,4} The utility of NT-BNP in risk stratification of subjects with S-acetylated (AcS);⁵ and as a screening tool for occult LV dysfunction has been documented. The role of NT-BNP in guiding the titration of medical therapy is actively being explored.⁶ This manuscript will review the potential of the NT-BNP assay in the setting of stable CAD.

Lessons from the Prior Index Event

A large proportion of patients with stable coronary artery disease have had a prior index myocardial

infarction (MI) or non-ST elevation MI (NSTEMI). Baseline NT-BNP measurements; regardless of the sample timing (on presentation; early 12–24 hours and sub-acute >three days); during the index clinical presentation have consistently been shown to be of utility as a predictive marker for short- and long-term mortality. The discriminating power of the assay is noted even when analysis is limited to patients without any clinical evidence of heart failure (HF). NT-BNP has been shown to be an independent predictor of mortality in these studies. However, a significant proportion of the predictive ability of increasing levels of NT-BNP in the acute setting is due to its association with other well established clinical risk factors: age, female gender, diabetes mellitus, hypertension, previous MI, HF, resting heart rate, and ST-segment depression; renal dysfunction and inflammatory markers, like C-reactive protein (CRP).^{7,8} NT-BNP measurements have also been correlated with myocardium at risk, infarct size and extent and complexity of CAD.^{9–11} The assay may thus be best appreciated as a non-specific marker that appears to provide the clinician with an overall cross-sectional risk estimate. The clinician taking care of the stable patient with CAD should utilise this information in the downstream assessment of patients in an out-patient setting. A number of clinical observations support the utility of NT-BNP as a biomarker in the setting of an acute coronary syndrome. For the benefit of readers; some of the studies focussing in this area are summarised below.

In a small nested case control study from the Thrombolysis in Myocardial Infarction (TIMI) 11B trial, Omland and colleagues observed an increase in baseline NT-BNP measurements obtained 12–24 hours post-presentation in patients meeting the end-point of death (n =22) within 43 days of study entry compared with matched controls (299 ± 65 versus 138 ± 31 pmol/L; p=0.039).¹² Jernberg and colleagues showed the ability of an admission NT-BNP measurement to predict death during a median follow-up of 40 months in the universe of patients admitted with chest discomfort without STEMI on presenting electrocardiogram (ECG).¹³ The median

NT-BNP for the overall population on admission in this study was 400pg/mL (range 111–1,646pg/mL). The median values in the 407 patients with unstable angina and NSTEMI were 409 and 1,089pg/mL, respectively. NT-BNP was an independent predictor of death but as a critique LV ejection fraction (LVEF) was not included as a variable in this analysis. When compared with subjects in the lowest quartile, patients in the second, third and fourth quartiles had a relative risk of subsequent death of 4.2, 10.7 and 26.6, respectively. This utility of NT-BNP in a broad population with chest pain was also noted in studies restricted to patients with ACS.¹⁴ A consecutive Scandinavian series of patients with STEMI (n=204), NSTEMI (n=220) and unstable angina (n=185), were followed for a median 51 months during which 86 patients died. In this study, NT-BNP measurements on samples obtained at a median of three days following clinical presentation NT-BNP levels were found to be significantly higher in patients dying during follow-up (1,306 versus 442pmol/L; P=0.0001). The NT-BNP measurements were found to be an independent predictor of death in this patient population (RR 2.1 [95% confidence interval (CI) 1.1–3.9]) even with the inclusion of LVEF into the multivariate Cox regression model. NT-BNP also remained strongly predictive in this population when the analysis was restricted to patients without overt clinical HF (RR 2.4 [95% CI, 1.1 to 5.4]).

The largest study with NT-BNP in the acute setting was the GUSTO-IV sub-study.⁷ In this study, 6,809/7,800 ACS patients enrolled in the trial had NT-BNP measurements performed on a sample collected at a 9.5 median hours after symptom onset. A continuous increase in risk of death with increasing NT-BNP levels was observed. At one year, mortality rates in the four quartiles increased from 1.8% in the lowest quartile to 3.9%; 7.7% and 19.2% in the second, third and highest quartiles, respectively. In this sub-study, NT-BNP was shown to be the most potent biomarker predicting death and when utilised in combination with creatinine clearance was able to discriminate groups of patient ranging in one-year mortality from 0.3–25.7%. In the Fagmin and Fast Revascularisation During Instability in Coronary Artery Disease (FRISC-II) study, NT-BNP measured at a median of 39 hours in 2,019 patients continued to show the consistent independent association with mortality reported above.⁸ Over two years of follow-up, patients in the highest NT-BNP tertile had a 4.1-fold (95% CI 2.4–7.2) and 3.5-fold (95% CI 1.8–6.8) increased mortality in the non-invasive and invasive groups, respectively. Galvani and colleagues reported on the utility of NT-BNP drawn at a median of three hours after clinical presentation amongst 1,756 patients

with symptoms and ECG evidence of ischaemia in the Early Prognostic Value of Biochemical Markers of Myocardial Damage, Activation of Hemostatic Mechanism and Inflammation in Acute Ischemic Syndromes Study (EMAI).¹⁵ Using the lowest quartile as baseline, patients in the second, third and fourth quartiles had a relative risk of subsequent death at 30 days of 2.94 (95% CI, 1.15–7.52), 5.32 (95% CI, 2.19–12.91) and 11.5 (95% CI, 4.90–26.87), respectively. NT-BNP was independently associated with death in this study, regardless of baseline troponin status. The odds ratio (OR) for death in the highest quartile when compared with the lowest was 7.0 (95%CI, 1.9–25.6) and 4.1 (95% CI, 1.1–14.6) in troponin-positive and -negative groups. In this study, NT-BNP was also an independent predictor of severe HF. Its incidence increased with increasing NT-BNP quartiles and ranged from 2.1% in the lowest to 9%, in the highest quartile (P=0.0001).

NT-BNP in the Non-acute Setting

Does the predictive value of NT-BNP continue to exist when measured in a more stable setting? A significant proportion of the 2,019 FRISC II patients with baseline NT-BNP measurement at randomisation also had serial evaluation at 48 hours, six weeks, three months and six months following the index clinical event.¹⁶ The median NT-BNP levels in this population gradually declined over time from 529ng/L at baseline, 345ng/L at six weeks, 253ng/L at three months to 238ng/L at six months in the 961 patients with complete serial sampling. This decline appears to reflect a reversible component in the rise noted during the index ACS presentation. Despite the fall in NT-BNP the assay remained a predictor of death at all measurement time-points and the adjusted OR for death was noted to increase over time. The FRISC II study thus provides support for the utility of NT-BNP measurements in patients with stable CAD. Further, it highlights the importance of sampling time and the needed multiple time-dependent cut-offs. In FRISC II, the specificity of subsequent death with a baseline cut-off of 722ng/L had the same performance characteristic as a cut-off 264ng/L with a sample obtained at six months.

All patients with late samples in FRISC II had a documented recent prior ACS by study design. Would there be a utility for NT-BNP in more stable patients with CAD? Kragelund and colleagues evaluated the value of measuring NT-BNP in 1,034 patients referred for angiography to evaluate symptoms or signs of suspected CAD.¹⁷ Patients were followed-up for a median of nine years, during which time 288 deaths occurred. The median NT-pro-BNP levels at baseline were noted to be

significantly less among survivors than among those who died during follow-up (120pg/mL versus 386pg/mL). Similar to prior observations in ACS; NT-BNP levels at baseline increased with increasing age, reduced creatinine clearance, extent of CAD, severity of angina, prior MI, left ventricular (LV) dysfunction and other important prognostic variables. In a Cox regression analysis, the unadjusted hazard ratio (HR) for death for patients in the second, third and highest quartiles of NT-BNP were 2.1 (95%; CI: 1.3–3.3; P=0.002), 3.5 (95%; CI: 2.3–5.4; P<0.001), and 6.1 (95%; CI: 4.0–9.2; P<0.001), respectively. After adjustment, NT-BNP was found to add incremental prognostic value, independent of routine clinical variables, creatinine clearance; lipid levels; LVEF; and the presence of epicardial CAD.

In a more contemporary population, Ndrepepa and colleagues measured NT-BNP in baseline samples collected in 1,059 patients with chronic stable angina prior to coronary angiography.¹⁸ Patients were followed-up for a median of 3.6 years. Subjects were divided into four quartiles based on baseline NT-BNP values and the primary endpoint of the study was all-cause mortality. The mortality rates were noted to increase with increasing NT-BNP measurements at baseline. There were 106 deaths during follow-up and the KM estimates of five-year mortality were 4.7% and 7.8% in the lowest two quartiles. Mortality in the third and fourth quartiles were 11.4% and 32.7% in respectively confirming graded risk with increasing NT-BNP values. A Cox proportional hazards model showed that NT-BNP was the strongest correlate of mortality with an adjusted HR 5.83 [95%, CI: 2.07–16.44] for the fourth versus the first quartile. A similar prognostic value of NT-BNP was demonstrated for cardiovascular mortality (HR, 5.98 [95%, CI: 1.55–23.13] for the fourth versus the first quartile) and for patients with New York Heart Association (NYHA) class I and II with a HR, 6.03 [95%, CI: 2.07–17.52] for the highest versus lowest quartile.

NT-BNP in the General Population

The potential utility of NT-BNP in patients with stable CAD is further supported by studies in the general population. The prospective Danish study evaluated the utility of NT-BNP in 764 patients in an age range of 50–89 years.¹⁹ The majority of patients enrolled had no prior history of documented CAD (n=537). During the five years of clinical follow-up; 94 participants died and 65 developed a first major cardiovascular event. After adjustment for the cardiovascular risk factors the HR of mortality for values above the 80th

percentile of NT-BNP was 1.96 (95%, CI: 1.21–3.19). The absolute unadjusted increase in mortality risk for participants with values above the 80th percentile compared with below the 80th percentile was 24.5% for NT-BNP, which was greater than the 7.8% observed for CRP and 19.5% noted using the urinary albumin/creatinine ratio. Similarly, the Belgian Job Stress Project (BELSTRESS) was designed to evaluate the utility of NT-BNP sampling in 10,000 middle-aged male workers.²⁰ During the 2.66 years of clinical follow-up, 66 patients developed coronary events. When compared with matched controls, subjects with events were noted to have higher median baseline NT-BNP levels (median 48.5pg/mL versus 30pg/mL). Following multivariable conditional logistic regression analysis, NT-BNP was strongly associated with risk for coronary events. Similar predictive ability was also noted in the 6,105-patient Perindopril Protection Against Recurrent Stroke Study²¹ as well as the Life sub-study²² featuring patients with cerebrovascular events and hypertension, respectively.

Conclusions

This review of the literature clearly indicates the remarkable ability of NT-BNP to predict adverse clinical events, particularly death in a large spectrum of patients. It appears to be effective in patients with an ACS, in stable CAD and in populations at risk from CAD. Its value appears to be incremental to that obtained from standard clinical variables. In addition, it seems to integrate risk from an array of clinical variables that may be relatively easy to comprehend.

However, implementation of these findings into clinical practice will require substantial further research. The mechanism of incremental benefit appears uncertain, although its role as a marker for ischaemia/CAD burden is strongly implicated. The cost implications for NT-BNP assay in the large population with stable CAD are tremendous and cost-effectiveness data are lacking. Numerous questions continue to linger. When and how often should an assay be performed; what cut-off should be utilised? How should NT-BNP be integrated with other biomarkers? Can we translate the heightened appreciation of risk into improved clinical outcome? While there is a suggestion that patients with raised NT-BNP benefit from an early revascularisation strategy,^{23,24} how should clinicians respond therapeutically to values in the stable CAD and general population. Will there be specific therapeutic strategies to lower NT-BNP levels and will reduction in NT-BNP levels mitigate cardiovascular risk? ■

References

1. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H, "A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats", *Life Sci* (1981);28: pp. 89–94.
2. Levin ER, Gardner DG, Samson WK, "Natriuretic peptides", *N Engl J Med* (1998);339: pp. 321–328.
3. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al., "The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study", *Am J Cardiol* (2005);95: pp. 948–954.
4. 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: pp. 330–337.
5. Jernberg T, James SA, Lindahl BA, et al., "Natriuretic peptides in unstable coronary artery disease", *European Heart Journal* (2004);25: pp. 1486–1493.
6. Lainchbury JG, Troughton RW, Frampton CM, et al., "NTproBNP-guided drug treatment for chronic heart failure: design and methods in the "BATTLESCARRED" trial", *Eur J Heart Fail* (2006);5: pp. 532–538.
7. James SK, Lindahl B, Siegbahn A, et al., "N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy", *Circulation* (2003);108: pp. 275–281.
8. Jernberg T, Lindahl B, Siegbahn A, et al., "N-terminal pro brain natriuretic peptide in relation to inflammation, myocardial necrosis and the effect of an invasive strategy in unstable coronary artery disease", *J Am Coll Cardiol* (2003);42: pp. 1909–1916.
9. Ndrepepa G, Braun S, Mehilli J, von Beckerath N, et al., "N-terminal pro-brain natriuretic peptide on admission in patients with acute myocardial infarction and correlation with scintigraphic infarct size, efficacy of reperfusion, and prognosis", *Am J Cardiol* (2006);97: pp. 1151–1156.
10. Ezekowitz JA, Theroux P, Chang W, et al., "N-terminal pro-brain natriuretic peptide and the timing, extent and mortality in ST elevation myocardial infarction", *Can J Cardiol* (2006);22: pp. 393–397.
11. Navarro Estrada JL, Rubinstein F, Bahit MC, et al., "PACS Investigators. NT-probrain natriuretic peptide predicts complexity and severity of the coronary lesions in patients with non-ST-elevation acute coronary syndromes", *Am Heart J* (2006);151: pp. 1093.e1–7.
12. Omland T, de Lemos JA, Morrow DA, et al., "Prognostic value of N-terminal pro-atrial and pro-brain natriuretic peptide in patients with acute coronary syndromes", *Am J Cardiol* (2002);89: pp. 463–465.
13. Jernberg T, Stridsberg M, Venge P, Lindahl B, "N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation", *J Am Coll Cardiol* (2002);40: pp. 437–445.
14. Omland T, Persson A, Ng L, et al., "N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes", *Circulation* (2002);106: pp. 2913–2918.
15. Galvani M, Ottani F, Oltrona L, et al., "Italian Working Group on Atherosclerosis, Thrombosis, and Vascular Biology and the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO). N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes", *Circulation* (2004);110: pp. 128–134.
16. Lindahl B, Lindback J, Jernberg T, et al., "Serial analyses of N-terminal pro-B-type natriuretic peptide in patients with non-ST-segment elevation acute coronary syndromes: a Fragmin and fast Revascularisation during In Stability in Coronary artery disease (FRISC)-II substudy", *J Am Coll Cardiol* (2005);45: pp. 533–541.
17. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R, "N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease", *N Engl J Med* (2005);352: pp. 666–675.
18. Ndrepepa G, Braun S, Niemoller K, et al., "Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina", *Circulation* (2005);4: pp. 2102–2107.
19. Kistorp C, Raymond I, Pedersen F, et al., "N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults", *JAMA* (2005);293: pp. 1609–1616.
20. De Sutter J, De Bacquer D, Cuypers S, et al., "Plasma N-terminal pro-brain natriuretic peptide concentration predicts coronary events in men at work: a report from the BELSTRESS study", *Eur Heart J* (2005);26: pp. 2644–2649.
21. Campbell DJ, Woodward M, Chalmers JP, et al., "Prediction of myocardial infarction by N-terminal-pro-B-type natriuretic peptide, C-reactive protein, and renin in subjects with cerebrovascular disease", *Circulation* (2005);112: pp. 9–11.
22. Olsen MH, Wachtell K, Tuxen C, et al., "N-terminal pro-brain natriuretic peptide predicts cardiovascular events in patients with hypertension and left ventricular hypertrophy: a LIFE study", *J Hypertens* (2004);22: pp. 1597–1604.
23. Jernberg T, Lindahl B, Siegbahn A, et al., "N-terminal pro-brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effect of an invasive strategy in unstable coronary artery disease", *J Am Coll Cardiol* (2003);42: pp. 1909–1916.
24. James SK, Lindback J, Tilly J, et al., "Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy", *J Am Coll Cardiol* (2006) 19(48): pp. 1146–1154.