Brain Natriuretic Peptide as a Predictor of Prognosis in Patients with Unstable Angina/Non ST Elevation Myocardial Infarction

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Abbreviations

ACS, acute coronary syndrome

ANP, atrial natriuretic peptide

BNP, brain (B-type) natriuretic peptide

CNH, cardiac natriuretic hormones

CNP, C-type natriuretic peptide

DNP, dendroaspis (D-type) natriuretic peptide

ECG, electrocardiogram

ECLIA, electro-chemi-luminescence-immuno-assay

EF, ejection fraction

EIA, enzyme-immuno-assay

GATA, zinc-finger proteins binding consensus sequence (A/T)GATA(A/G)

GC, guanylate cyclase

Gi protein, inhibitory guanine nucleodite regulatory (Gi) protein

HF, heart failure

HPLC, high pressure (performance) liquid chromatography

IL, interleukin

IRMA, immuno-radio-metric-assay

KO mice, knockout mice for some genes

NEP, neutral endopeptidase

NPPA, human coding gene for ANP

NPPB, human coding gene for BNP

NPV, negative predictive value

NRP, natriuretic receptor peptide

NT-proANP, N-terminal fragment of proANP

NT-proBNP, N-terminal fragment of proBNP

NT-proCNP, N-terminal fragment of proCNP

NYHA, New York Heart Association

POCT, point-of-care testing

PPV, positive predictive value

ET-1, endothelin 1

PKG, cGMP-dependent protein kinase

RIA, radio-immuno-assay

VNP, ventricular natriuretic peptide

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Introduction

Discovery of the cardiac peptides in the 1980s renewed our appreciation of the heart as an endocrine organ. The natriuretic peptide family comprises atrial natriuretic peptide (ANP), BNP, C-type natriuretic peptide (CNP), and D-type natriuretic peptide. ANP and BNP are synthesized in the heart, CNP is produced mainly in vessels, and D-type natriuretic peptide has been isolated in plasma and atrial myocardium. The precursor prohormone of each natriuretic peptide is encoded by a separate gene. BNP is a 108 amino acid pro-hormone that, after cleavage by the proteolytic enzyme furin, is separated into a 32 amino acid carboxi-terminal biologically active portion (BNP) and a 76 amino acid amino terminal part without biological activity (NT-proBNP).

ANP and BNP exert their effects through interaction with specific high affinity receptors on the target cells. Three effective receptors have been identified at target sites and kidneys. These receptors, located on cell membranes, although not reflecting their affinity for the different peptides, are termed: natriuretic receptors type A, natriuretic receptor type B, and type C—a clearance receptor. Most cardiovascular and renal effects of ANP and BNP result from cyclic guanyl monophosphate formation which acts as a second messenger responsible for the cellular physiological responses to natriuretic peptide stimulation. Natriuretic peptides are cleared from plasma by binding to natriuretic peptide receptors and through proteolysis by peptidases. NT-proBNP has a longer half life than BNP (118 v 18 minutes).Renal excretion is currently regarded as the main clearance mechanism of NT-proBNP.

Elevated plasma brain natriuretic (BNP) concentrations correlate with increased cardiac filling pressures. Therefore, increased BNP has been proposed as a marker for asymptomatic ventricular dysfunction, as an aid in the diagnosis of cardiac dyspnea, as an end point to assess the efficacy of heart failure therapy, and as a prognostic marker in heart failure. Both ANP and BNP were determined to have potent natriuretic, diuretic, vasodilator, and antimitotic properties that served to counterbalance the volume retaining, vasoconstrictive, and ventricular remodeling effects of renin angiotensin- aldosterone system activation. The natriuretic peptides are coun-

ter-regulatory hormones that are thought to play a role in the stabilization of circulatory function during the early stages of the progression of ventricular dysfunction.

Clinicians have become increasingly sophisticated in their application of cardiac biomarkers in the management of acute coronary syndromes (ACS). In the 1950s, clinical investigators first reported that proteins released from necrotic cardiac myocytes could be detected in the serum and could aid in the diagnosis of acute myocardial infarction.[2] The ensuing 40 years witnessed progressive improvement in the cardiac tissue-specificity of biomarkers of myocardial necrosis and a corresponding enhancement in the clinical sensitivity and specificity of their use for establishing the diagnosis of acute myocardial infarction. Over the past decade, the emergence of convincing evidence for the value of cardiac troponin in guiding therapy has dramatically accelerated the integration of cardiac biomarkers into clinical decision-making for patients with ACS.[3] Concurrently, advances in our understanding of the pathogenesis and consequences of acute coronary atherothrombosis have stimulated the development of new biomarkers and created the opportunity for an expanded role of multiple biomarkers, some old and others new, in the classification and individualization of treatment for ACS.[4,5] There is accumulating evidence that a multimarker strategy, employing a pathobiologically diverse set of biomarkers,[4] is likely to add importantly to cardiac-specific troponin alone in the risk assessment of patients with ACS.

At least 5 studies have now demonstrated a robust association between BNP or NT-proBNP and the short- and long-term risk of death across the spectrum of non-ST-elevation ACS,[5,6,7–9] including patients without myocardial necrosis or clinical evidence of heart failure.[4] In some patients with ACS, elevated levels of BNP directly reflect the degree of left ventricular dysfunction resulting from acute myocardial infarction. However, the strong association between levels of BNP/NT-proBNP and mortality among patients without measurable myocyte necrosis (i.e., release of cardiac troponin) indicate that the level of BNP may reflect the extent or severity of the ischemic insult, even when irreversible injury has not occurred. Several additional observations support this hypothesis.[10] Specifically, levels of BNP increase transiently after uncomplicated coronary angioplasty in the presence of stable intracardiac filling

pressure, as well as after exercise-induced ischemia in patients with stable coronary artery disease.[10] Together, these findings suggest that transient ischemia may induce BNP synthesis and release in proportion to the severity of myocardial ischemia. As such, BNP adds a new dimension to our ability to quantify the consequences of acute myocardial ischemia.

Patients presenting with chest pain or other symptoms suggestive of an acute coronary syndrome amount today to about 20% of all visits to the medical emergency department [11]. Of the two-thirds who will be admitted, about 90% will have an electrocardiogram (ECG) nondiagnostic of acute myocardial infarction (AMI) and, thereby, constitute a heterogeneous group concerning both the underlying pathophysiology and future risk of cardiac events [12]. An early risk stratification of these patients is important for several reasons. Those identified as being high-risk patients might need a more intense pharmacologic treatment and be considered for intervention early [13]. Patients with a low risk, in contrast, may benefit more from conservative management with a low risk of side effects. Moreover, considerable economic gains may be achieved by early identification of patients who are at sufficiently low risk for early transfer to a lower level of care and early discharge.

Substudies of large scaled clinical trials (OPUS-TIMI 16, TACTICS-TIMI 18, FRISC II, GUSTO IV, PRISM) [14,15] have evaluated the prognostic value of BNP and NT-proBNP in patients presenting with non-ST elevation acute coronary syndromes (NSTE-ACS). In all studies elevated values of BNP and NT-proBNP have consistently been found. Furthermore, both markers were highly predictive for an adverse outcome independently of other biomarkers, especially troponins and C reactive protein (CRP). However, it must be emphasised that BNP and NT-proBNP were predictive for mortality and heart failure after an ACS but not for recurrent ischaemic events. Similar results were reported for the predictive value of BNP and NT-proBNP after ST elevation myocardial infarction (STEMI).[16] Different studies evaluated whether serial assessment of NT-proBNP is superior to a one time point assessment at admission. Jernberg et al studied 755 patients with an ACS and observed no difference in the predictive value as indicated by the AUC of the ROC curve for NT-proBNP on admission and after 6 h. [14] In a substudy of the PRISM trial Heeschen et al demonstrated an incre-

mental prognostic value of serial NT-proBNP assessment on admission and a second measurement 72 h later. In the FRISC-II trial serial NT-proBNP analyses were evaluated during the acute and the chronic phase of ACS and disclosed that the predictive value of NT-proBNP value measured three and six months after the index event is a better predictor for two year mortality than early NT-proBNP determination at admission or at 48 h after the acute event. However, the best time to take a sample for BNP or NT-proBNP assessment still remains to be fully established.

In addition, the therapeutic benefits that can be derived from BNP and NT-proBNP assessment in ACS are not clear. The only published study to date which investigated the usefulness of NT-proBNP for identifying patients who might benefit from an early invasive strategy is a substudy of the FRISC-II trial. In this study a trend towards a better outcome of patients with NT-proBNP values in the highest tertile was observed. However, in combination with elevated interleukin (IL)-6 concentrations, NT-proBNP values in the third tertile indicated a significant treatment benefit from early invasive therapy.[16] In the substudy of the PRISM trial, Heeschen et al analysed the effect of glycoprotein IIb/IIIa inhibition with tirofiban with respect to NT-proBNP values.[15] Even though they found that patients with high NT-proBNP values had a lower event rate with tirofiban treatment compared to placebo at 48 h, they found no significant interaction between NT-proBNP values and the clinical benefit of tirofiban treatment at 30 days.

Several matters need to be addressed before BNP and NT-proBNP can be recommended for application in clinical routine in patients with ACS. Different cut-off values have been applied in the various studies, but to date no clearly defined cut-off value has been established. Moreover, further studies are needed to assess the therapeutic benefits that can be derived from BNP and NT-proBNP assessment.

For a cardiac biomarker to be clinically useful, it must help clinicians select an appropriate therapeutic regimen. For example, patients who have an elevation in troponin T or I levels after acute coronary syndromes appear to derive specific benefit from an early, aggressive strategy that includes potent antiplatelet[17] and antithrombotic[18] therapy and early revascularization.[19] In addition, patients who have elevated C-reactive protein levels after myocardial infarction appear to benefit from statin

therapy.[20] Patients with elevated levels of B-type natriuretic peptide after an acute coronary syndrome are at high risk for death, a new myocardial infarction, and heart failure and may benefit from intensive antiplatelet and antithrombotic therapies, neurohormonal antagonism with agents such as beta-blockers and angiotensin-converting–enzyme inhibitors, and early revascularization. Equally important, patients who have normal levels of B-type natriuretic peptide after an acute coronary event appear to have a particularly low long-term risk of death and heart failure. In this group of patients, a less intensive management approach may be appropriate, in order to avoid the cost and risk associated with potentially unnecessary therapies. Future studies should directly assess the role of B-type natriuretic peptide in identifying patients who would benefit from various treatment strategies.

At present, there are four BNP assays commercially available for routine clinical practice. BNP can be assayed by a rapid fluorescence immunoassay (Biosite Diagnostic), an enzyme immunoassay (Abbott Laboratories), or a chemiluminescent immunoassay (Bayer Healthcare), and NT-proBNP can be measured by an electrochemiluminescent assay (Roche Diagnostics). Although initial efforts focused on ANP and N-terminal ANP as markers for ventricular dysfunction, BNP was eventually shown to have greater sensitivity and specificity for both systolic and diastolic dysfunction. Consequently, most recent studies have used BNP or NTproBNP. [1]

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