Natriuretic Peptides in the Prognosis and Management of Acute Coronary Syndromes

James A. de Lemos, MD, FACC,[1] W. Frank Peacock, MD, FACEP,[2]
Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA[3]

[1]Donald W. Reynolds Cardiovascular Research Center and Division of Cardiology, University of Texas Southwestern Medical Center, Dallas TX; [2]Cleveland Clinic Foundation, Cleveland, OH; [3]Department of Medicine, Divisions of Cardiology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI

Over the past decade, an evidence base has accumulated to support natriuretic peptide (NP) testing for diagnosis, risk assessment, and therapeutic monitoring and guidance of patients with heart failure. Investigators have also explored multiple other potential uses for these tests, including risk assessment of patients with suspected acute coronary syndromes (ACS). This article discusses the utility of NPs in the diagnosis and management of patients with ACS.
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Over the past decade, an evidence base has accumulated to support natriuretic peptide (NP) testing for diagnosis, risk assessment, and therapeutic monitoring and guidance of patients with heart failure (HF). Paralleling the emergence of B-type natriuretic peptide (BNP) and N-terminal prohormone BNP (NT-proBNP) as routine tests in patients with congestive heart failure (CHF), investigators have explored multiple other potential uses for these tests, including risk assessment of patients with suspected acute coronary syndromes (ACS).

Rationale for NP Testing in ACS

BNP is synthesized as a 132-amino acid prepro hormone, from which a 24-amino acid signaling sequence is rapidly removed, and the remaining 1-108 proBNP peptide is then cleaved by a number of proteases at the time of release from the cardiomyocyte to the active 32-amino acid hormone (BNP) and a 76-amino acid inactive fragment (N-terminal prohormone BNP [NT-proBNP]). Moreover, some unprocessed 1-108 proBNP is also released, with the proportion of processed/unprocessed BNP fragments varying between individuals based on factors such as the severity and time course of disease,[1] as well as genetic and environmental influences on corin, which is the primary enzyme responsible for processing proBNP.[2] Unlike atrial natriuretic peptide (ANP), which is synthesized and then stored in granules, BNP is regulated primarily at the level of gene transcription and can be synthesized very rapidly. However, under certain circumstances BNP may be costored with ANP in storage granules. The very rapid increase in BNP levels reported after induced ischemia suggests that some BNP is released from stored pools, rather than synthesized on demand.[3]

BNP gene transcription is rapidly induced in response to increases in myocardial wall stress. Thus, it is not surprising that myocardial ischemia, which may rapidly increase left ventricular (LV) wall stress, can trigger the release of NPs. Indeed, multiple components of the pathophysiology of acute and chronic myocardial ischemia may contribute directly or indirectly to release of BNP and NT-proBNP (Figure 1). For example, in vitro studies and in vivo studies using animal models suggest that hypoxia and tissue ischemia may directly lead to synthesis and secretion of NPs, before changes in LV hemodynamics occur.[4-7] Several lines of human evidence also support a direct role for cardiac ischemia, including studies in which myocardial biopsies obtained during coronary artery bypass graft surgery identified higher BNP expression in ischemic versus nonischemic segments.[8] Observational analyses of patients undergoing coronary angiography for non–ST-elevation ACS (NSTE-ACS) have shown that angiographic severity of coronary disease, as demonstrated by Gensini score, correlates with BNP levels independent of LV ejection fraction (LVEF), wall motion, and LV mass.[9] Finally, atherosclerosis itself, even in the absence of ischemia, may contribute to higher circulating levels of BNP and NT-proBNP. For example, in a population study of US adults, a higher coronary calcium score (a marker of subclinical atherosclerosis burden) was associated with higher NT-proBNP levels even among individuals with normal cardiac structure and function, no symptoms of cardiac ischemia, and normal renal function.[10] Interestingly, direct NP expression within the human coronary arterial wall has been reported, with greater expression in atherosclerotic regions compared with normal segments.[11]

Important insights have been gained from several human studies that have induced ischemia in the experimental design. For example, balloon inflation for percutaneous coronary intervention (PCI) briefly causes transmural ischemia, and leads to a transient increase in BNP levels not seen with coronary angiography alone (Figure 2, panel A). Similarly, exercise-induced ischemia measured using nuclear scintigraphy is associated with modest transient increases in BNP levels (Figure 2, panel B). The magnitude of BNP elevation in these studies is proportional to the size and severity of the ischemic insult. In patients with ACS, location of a stenosis more proximally in the coronary tree, or in the left anterior descending artery, compared with other vessels, is associated with higher BNP levels—a finding that further supports the hypothesis that the magnitude of ischemic burden is a determinant of BNP levels.[12]

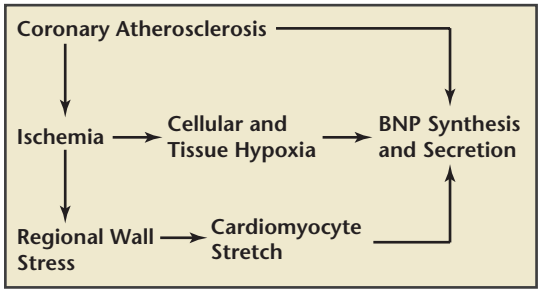

Figure 1. *Mechanisms of natriuretic peptide release in coronary artery disease. BNP, B-type natriuretic peptide.*

Can BNP or NT-proBNP Be Used to Diagnose ACS?

Although both BNP and NT-proBNP are released in response to cardiac ischemia, neither peptide offers sufficient sensitivity or specificity to be useful for the diagnosis of ACS. It is important to note that the etiologies leading to NP release are "promiscuous" and many pathologic conditions other than cardiac ischemia lead to similar modest elevations in BNP and NT-proBNP (Table 1). Moreover, the magnitude of BNP

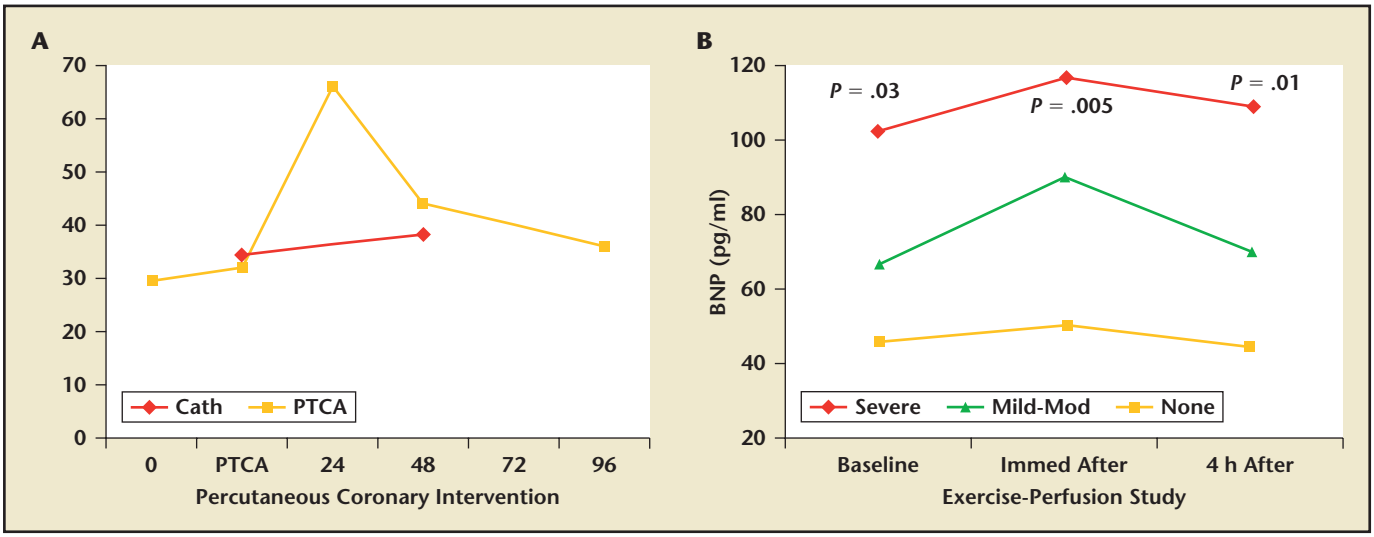

Figure 2. *Transient BNP elevation following induced ischemia in humans following balloon occlusion during coronary angioplasty (**A**) or treadmill exercise (**B**). In panel B, the severity of ischemia was defined using exercise nuclear imaging. BNP, B-type natriuretic peptide; PTCA, percutaneous transluminal coronary angioplasty. Adapted with permission from Tateishi J et al.[46] and Sabatine MS et al.[47]*

Table 1
Conditions Other Than Ischemia Causing Modest BNP or NT-proBNP Elevation

- Asymptomatic LV systolic or diastolic dysfunction
- Valvular heart disease, including aortic stenosis and mitral regurgitation
- Pulmonary embolism
- Sepsis
- Right HF
- Severe hypertension
- Advanced age
- Chronic kidney disease

BNP, B-type natriuretic peptide; HF, heart failure; LV, left ventricular; NT-proBNP, N-terminal prohormone BNP.

elevation in patients with ischemia or ACS is typically modest compared with that of HF, and levels fall within the normal range in many patients with clearly diagnosed ACS. Thus, NP testing does not have utility for ACS diagnosis.

Factors Influencing BNP and NT-proBNP Levels in Patients With ACS

Just as the disease states leading to modest BNP elevation are diverse, so are the pathophysiologic factors influencing BNP levels in an individual or population with ACS. Preexisting cardiac factors such as LV systolic or diastolic function, LV mass, and extent of coronary disease; acute factors such as the size and severity of the ischemic insult, changes to LV function and hemodynamics; and noncardiac factors such as renal function and body mass all influence NP levels in a patient with ACS. This diversity may contribute to difficulty in determining the etiology of modest elevations in BNP and NT-proBNP and for guiding a specific therapeutic response, as the level reflects cardiac neurohormonal stress but not the cause of that stress. On the other hand, because all of the factors influencing BNP levels contribute to adverse outcomes, BNP and NT-proBNP may integrate these multiple pathophysiologic insults into a single prognostic variable. Indeed, the powerful prognostic utility of BNP and NT-proBNP in both CHF and ACS is likely due to their ability to integrate multiple interrelated pathophysiologic processes.[13]

In patients with ST-segment elevation myocardial infarction (STEMI), BNP levels rise gradually, peaking at 24 to 48 hours after myocardial infarction (MI). In patients with a large anterior MI, a second peak may be observed around days 5 to 7, likely reflecting the beginning of adverse ventricular remodeling processes.

BNP and NT-proBNP Measurement for Prognostic Assessment in ACS

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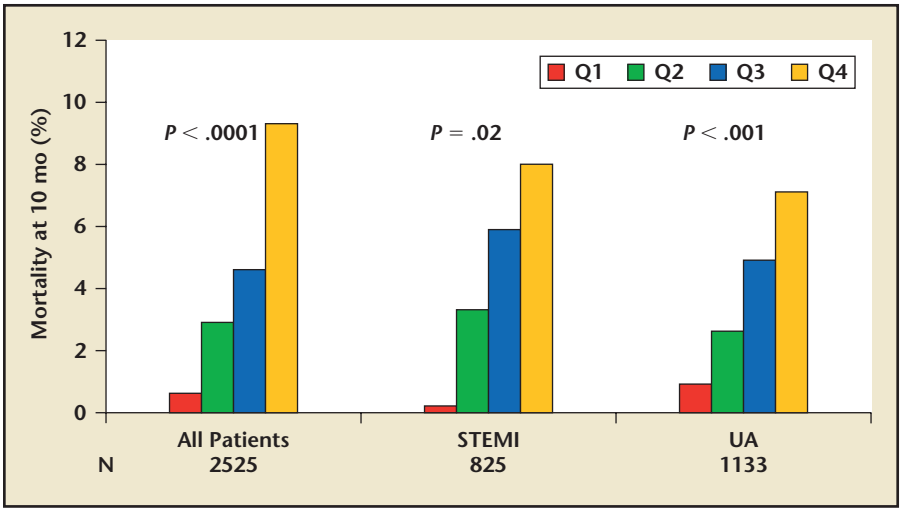
reflecting the beginning of adverse ventricular remodeling processes. Indeed, higher BNP or NT-proBNP levels after acute MI may help to identify patients at high risk for adverse ventricular remodeling.[14] Moreover, multiple studies have reported a strong association between higher BNP or NT-proBNP levels and death or HF outcomes in patients with STEMI.[15-17] These associations are independent of measures of infarct size and LVEF[15,16] as described in the Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy-Thrombolysis in Myocardial Infarction 23 (ENTIRE-TIMI 23) trial that studied the prognostic value of BNP measurements within 6 hours of symptom onset in patients with STEMI.[18] In this analysis, a BNP > 80 pg/mL was associated with a 7-fold higher mortality than levels below this threshold in multivariable models adjusting for other prognostic indicators. In this and other studies, BNP and NT-proBNP elevation have also been associated with measures of inadequate reperfusion including failure to resolve ST-elevation after fibrinolytic therapy and angiographic no-reflow after primary PCI.[18,19]

It is not surprising that neurohormonal activation would occur after STEMI, given the high ventricular wall stress seen in this condition. As such, the associations of BNP and NT-proBNP with "pump failure" events such as death and HF are not unexpected. However, similar associations with death and MI have also been observed in patients with non-STEMI (NSTEMI), even occurring in those with unstable angina and no demonstrable myocardial necrosis. Indeed, BNP and NT-proBNP predict mortality risk across the full spectrum of ACS, suggesting that neurohormonal activation is an important marker of risk, regardless of ACS type.

Most early studies evaluated relatively selected patients enrolled in clinical trials. A substudy of the Oral Glycoprotein IIb/IIIa Inhibition With Orbofiban in Patients With Unstable Coronary Syndromes-TIMI 16 (OPUS-TIMI 16) trial was one of the first to assess BNP in a large population of patients with ACS.[17] In this study, BNP was measured an average of 40 hours after presentation in 2525 patients with ACS, including large numbers with STEMI, NSTEMI, and unstable angina. Older age, hypertension, abnormal renal function, peripheral vascular disease, more severe coronary artery disease, prior history or current evidence of CHF, electrocardiographic changes, and elevated creatine kinase-myocardial band were all associated with higher BNP levels. Mortality and HF events increased in a stepwise fashion across increasing quartiles of plasma BNP levels, with similar associations seen in the groups with unstable angina, NSTEMI, and STEMI (Figure 3). In multivariable models adjusting for other important prognostic factors, BNP levels remained the most powerful predictor of long-term mortality. Conversely, an underappreciated finding in this and other studies was the very low risk for mortality for ACS patients who have low BNP levels. For example, mortality at 10 months after a confirmed ACS event was < 1% among the 25% of subjects with BNP levels < 40 pg/mL.

In a study involving 1676 patients enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-TIMI 18 (TACTICS-TIMI 18) trial,[20] differences in risk prediction between troponin (Tn) and BNP were explored in more depth. BNP was a much more powerful predictor of death and HF than Tn, but Tn was a much stronger predictor of nonfatal recurrent ischemic events than BNP (Figure 4). Almost all other studies have confirmed the role of BNP as a very powerful "pump failure" marker, robustly and independently predicting death and HF, but providing weak prediction of recurrent MI and unstable angina. In fact, in most studies, if associations between NPs

Figure 3. *Association between BNP levels at baseline and the risk of death at 10 months in the OPUS-TIMI 16 study. BNP, B-type natriuretic peptide; OPUS-TIMI, Oral Glycoprotein IIb/IIIa Inhibition With Orbofiban in Patients With Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction; Q, quartile of baseline; STEMI, ST-elevation myocardial infarction; UA, unstable angina. Adapted with permission from de Lemos JA et al.[17]*



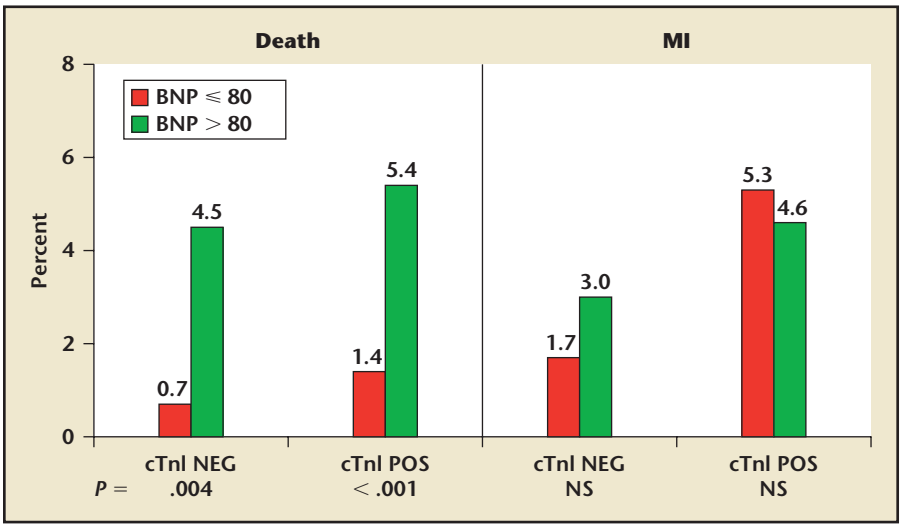


Figure 4. *Differential associations of cTnI and BNP with death and MI outcomes in the TACTICS-TIMI 18 Study. BNP, B-type natriuretic peptide; cTnI, cardiac troponin-I; MI, myocardial infarction; NEG, negative; NS, not significant; POS, positive; TACTICS-TIMI, Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction. Adapted with permission from Morrow DA et al.*[20]

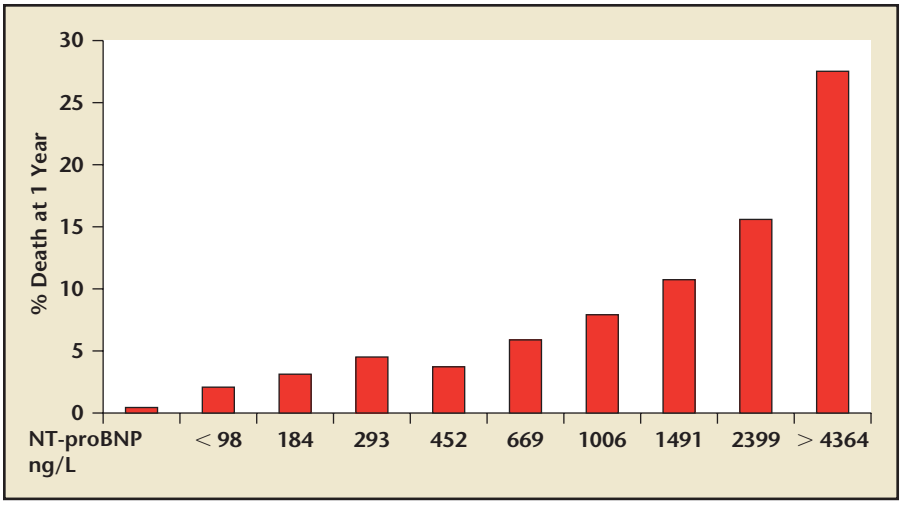
and nonfatal ischemic events are seen, they typically do not persist after adjustment for other predictive variables.

Similar findings have been reported using NT-proBNP. In a substudy of the Global Utilization of Strategies To open Occluded arteries (GUSTO)-IV trial, involving 6809 patients, NT-proBNP measurements at baseline were robustly associated with mortality (Figure 5) and outperformed Tn T, creatinine clearance, and ST-segment depression for prediction of death and HF. Consistent with other studies, NT-proBNP was not independently associated with recurrent MI after adjustment for other variables.[21]

These studies using clinical trial databases have several limitations, including the selected patient populations enrolled, and the absence of routine collection of data on LVEF. More recent studies have addressed these limitations, including an important study by Omland and colleagues[22] that confirmed the powerful associations of NT-proBNP levels for all-cause mortality across all types of ACS after fully accounting for LVEF and other potential confounders.

The prognostic value of BNP and NT-proBNP should be considered in the context of existing global risk assessment algorithms. For example, adding NT-proBNP to the TIMI risk score or the American College of Cardiology/American Heart Association (ACC/AHA) risk classification algorithm improved their predictive capacity for death.[23] For each TIMI and ACC/AHA risk category, patients with NT-proBNP > 586 pg/mL had significantly higher probability of death (Figure 6). Similarly, in a study of 449 consecutive patients with ACS, increasing BNP tertiles remained associated with cardiovascular events even after adjustment for and stratification by the Global Registry of Acute Coronary Event (GRACE) risk score.[24] These findings suggest that NP measurements augment existing global risk assessment algorithms, and future work should focus on full integration of BNP and NT-proBNP into these algorithms.

Figure 5. *Association between deciles of baseline NT-proBNP and 1-year mortality in the GUSTO-IV trial. GUSTO, Global Utilization of Strategies To open Occluded arteries; NT-proBNP, N-terminal prohormone B-type natriuretic peptide. Adapted with permission from James SK et al.*[21]



Decision Limits for Clinical Use

The TACTICS-TIMI 18 analysis described prospectively validated the BNP decision-limit of 80 pg/mL that was identified in the original OPUS-TIMI 16 study. In this study, the 80 pg/mL threshold performed better than other prespecified cutpoints.[20] With NT-proBNP, reported thresholds have varied more between studies, and fewer validation studies of

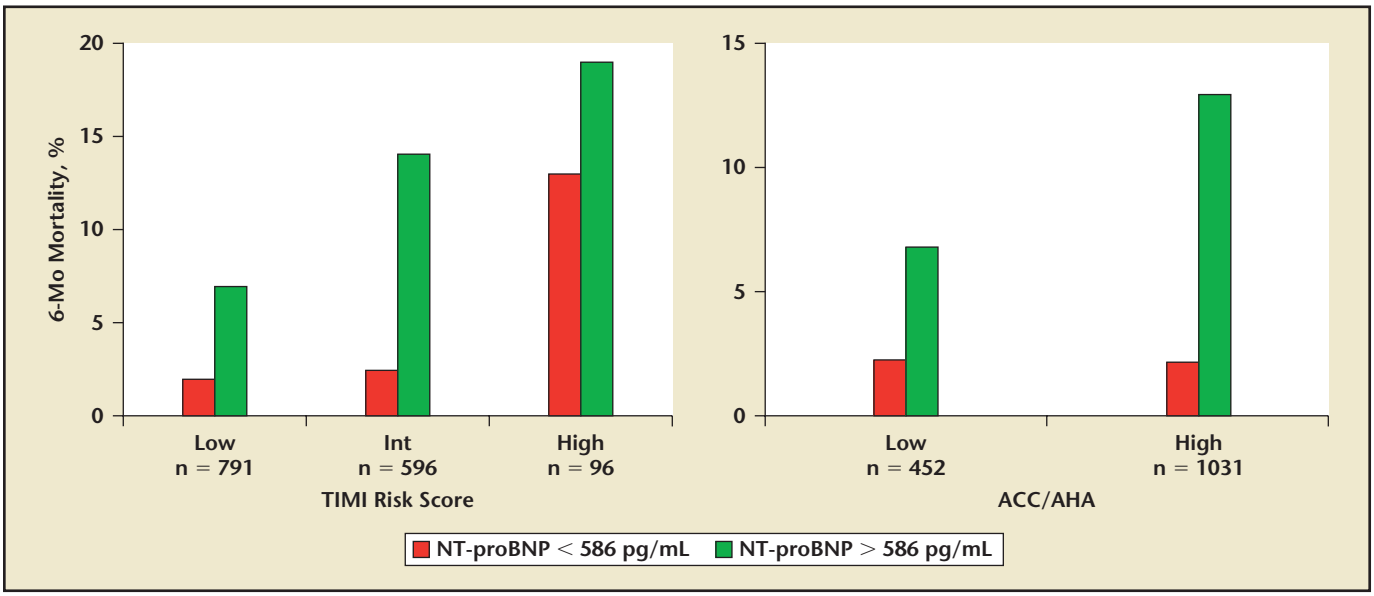


Figure 6. *NT-proBNP improves global risk assessment based on the TIMI Risk Score and ACC/AHA Risk Assessment Algorithm. ACC/AHA, American College of Cardiology/American Heart Association; Int, intermediate; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; TIMI, Thrombolysis In Myocardial Infarction. Adapted with permission from Bazzino O et al.*[23]

the suggested thresholds have been performed. Although the 80 pg/mL threshold has been prospectively used for BNP, and shown to stratify death and HF risk in several ACS populations, it must be emphasized that the associations between BNP (and NT-proBNP) and death and HF are continuous with linear or even exponential associations with outcomes. Thus, attempts to simplify risk stratification using dichotomous cutpoints may diminish the prognostic information obtained from these tests.

Timing and Frequency of Measurements

Studies reporting associations between BNP or NT-proBNP and outcomes after ACS have included widely varying times for the baseline measurement, from within several hours of admission to 4 days or later. At 1 end of the extreme, the Fast Assessment in Thoracic Pain (FAST) study[25] measured NT-proBNP levels on admission in 755 patients, who were subsequently followed for > 3 years. Long-term risk of mortality increased with higher NT-proBNP independently of cardiac Tn T (cTnT) and electrocardiographic changes. Similarly, in another study, measurements of NT-proBNP an average of 3 hours after onset of symptoms predicted a 12-fold range of death and HF risk independent of other factors, including Tn T.[26] At the other extreme, BNP levels measured as late as 3 to 4 weeks after MI also demonstrate powerful prognostic capacity.[27]

Several studies have evaluated serial measurements of NPs after ACS. In a substudy of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial, NT-proBNP assessed at 48 and 72 hours after ACS provided additional risk stratification information compared with baseline measurement only.[28] Compared with patients with persistently low NT-proBNP levels (≤ 250 mg/dL), those with persistent elevation > 250 mg/dL at 72 hours were at markedly increased risk for death or MI (odds ratio [OR] 33.7; 95% confidence interval [CI], 8.2-138.8; $P < .001$), as were those who had initially low values but developed new elevation in NT-proBNP > 250 mg/dL after hospitalization (OR, 24.0; 95% CI, 8.4 to 68.5; $P < .001$). In contrast, a single-center study serially measured BNP and NT-proBNP levels in 276 patients over 5 time points within the first 24 hours after emergency department presentation for chest pain. In this study, NPs were useful for a CHF diagnosis but not for an ACS diagnosis. With regard to prognostic assessment, baseline BNP and NT-proBNP measurements predicted 30- and 90-day adverse events, but serial measurements over this short time period did not provide incremental prognostic information over the baseline measurement alone.[29]

Although the data supporting serial NP measurement in the hospital after ACS are conflicting, a more compelling case can be made for serial measurements over longer-term outpatient follow-up. In an analysis from the Fragmin and fast Revascularization during InStability in

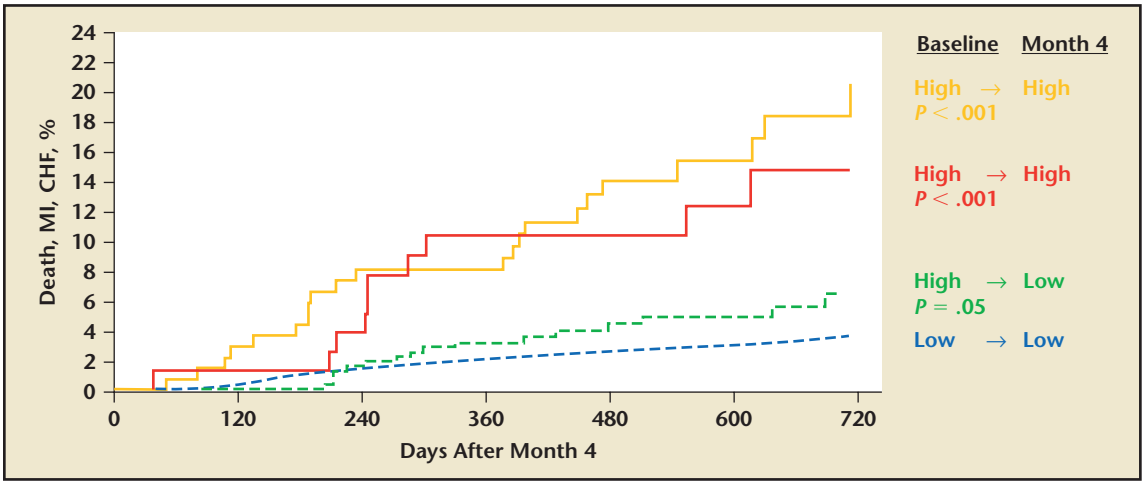
Coronary artery disease (FRISC) II trial, in which NT-proBNP was measured at randomization, 48 hours, 6 weeks, and 3 and 6 months after ACS,[30] NT-proBNP levels fell steadily by about 50% to 60% over long-term follow-up, with smaller reductions seen in patients with higher risk profiles and in particular larger MIs. At each time point NT-proBNP predicted increased mortality, but the odds for death were greater with each successive measurement, suggesting that later measurements provide even more powerful mortality prediction than those performed during the hospital phase, when elevations may be reversible.[30]

In the Aggrastat to Zocor (A to Z) trial, BNP was measured during the index hospitalization for ACS in 4266 patients and then again at 4 (n = 3618) and 12 months (n = 2966) during the outpatient follow-up phase.[31] The 4- and 12-month measurements provided clear incremental prognostic information over the baseline measurement alone. For example, the multivariable-adjusted ORs for the primary endpoint of subsequent death and HF associated with BNP elevation > 80 pg/mL were 2.5 at baseline, 3.9 at 4 months, and 4.7 at 12 months. Patients were divided into 4 groups on the basis of the baseline and follow-up BNP levels: those with persistently low BNP levels (≤ 80 pg/mL); those with persistently elevated levels (> 80 pg/mL); those with newly elevated levels at 4 months; and those that fell from high to low values. Patients in whom BNP increased during outpatient follow-up were at significantly higher risk for the combined outcome of death and HF between 4 months and the end of the study than the group in whom it remained low; additionally, the group in whom BNP fell from high to low over follow-up was at significantly lower risk than the group in whom it remained elevated (Figure 7). These associations persisted in a multivariable analysis adjusting for interval clinical changes,[31] suggesting that serial BNP measurement may provide novel information about changes in risk status over long-term follow-up in patients stabilized following an ACS episode.

Using BNP and NT-proBNP to Guide Clinical Decision-Making in ACS

Despite the robust evidence base just discussed supporting the role of NP testing to identify patients at risk for death and HF following ACS, few data are available regarding the therapeutic implications of these findings. Given the consistent associations observed between BNP and NT-proBNP and the extent and severity of coronary artery disease as well as LVEF, it might be anticipated that a more aggressive use of coronary revascularization would mitigate risk associate with elevated BNP or NT-proBNP levels. However, studies evaluating NP testing to select patients for an invasive management strategy have shown contradictory results. In the substudy of TACTICS-TIMI 18 described in detail earlier, no interaction of invasive therapy based on BNP levels was seen; despite robust associations with mortality and HF after ACS, elevated BNP levels did not identify patients who derived incremental benefit from randomization to the early invasive management strategy.[20] Similarly, in the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial, no benefit of the early invasive strategy was seen in non-ST-segment elevation (NSTE)-ACS patients with elevated Tn and NT-proBNP.[32] Compared with patients

Figure 7. *Changes in BNP from baseline (in hospital) to 4 months (outpatient phase) and the risk for death, MI, and CHF in the A to Z trial. High BNP levels are defined as > 80 pg/mL and low as ≤ 80 pg/mL. A to Z, Aggrastat to Zocor; BNP, B-type natriuretic peptide; CHF, congestive heart failure; MI, myocardial infarction. Adapted with permission from Morrow DA et al.*[31]



with NT-proBNP levels in the first 3 quartiles, those with levels in the fourth quartile (≥ 1170 ng/L for men, ≥ 2150 ng/L for women) were at increased risk for mortality at 1 year (hazard ratio [HR] 5.0; 95% CI, 2.1-11.6; $P < .0002$), but no interaction was detected based on assignment to the invasive or conservative arm.

In contrast, in a substudy of the FRISC II trial, patients with elevated NT-proBNP and interleukin (IL)-6 had a survival benefit when assigned to an early invasive strategy as opposed to an early conservative strategy.[33] Because the benefit was restricted to the highly selected subgroup with concomitant elevation in both NT-proBNP and IL-6, the above findings should be interpreted with caution. An observational analysis from the GUSTO IV trial also provides some support for a more aggressive use of revascularization for patients with elevated NT-proBNP. In analyses adjusted for the propensity to perform coronary revascularization, patients with NT-proBNP > 237 ng/L who underwent revascularization had lower mortality compared with those treated without revascularization (relative risk [RR] 0.63; 95% CI, 0.5-0.8). In contrast, among patients with BNP ≤ 237 ng/L, revascularization was associated with an increase in mortality (RR 1.91; 95% CI, 0.7-5.3). When Tn and NT-proBNP were considered together, patients with either or both biomarkers elevated had lower mortality following revascularization, whereas those with neither elevated had higher mortality with revascularization.[34] This study is limited by the observational design and the fact that invasive therapy was not randomized.

The discrepancy in the results of these substudies may reflect differences in the design of the parent clinical trials.[35-37] In TACTICS-TIMI 18 and ICTUS, the requirements for "crossover" to angiography and revascularization for patients randomized to an initial conservative strategy were much more lenient than in the FRISC II study. As a result, revascularization was performed during the initial hospitalization in 36% of patients randomized to the conservative arm in TACTICS-TIMI 18 and 40% in ICTUS, compared with only 9% within the first 10 days in FRISC II. The higher crossover rates in TACTICS-TIMI 18 and ICTUS likely diminished differences in mortality between the conservative and invasive groups: in TACTICS-TIMI 18 and ICTUS no difference in mortality was seen between groups, whereas in FRISC II, 1-year mortality was reduced by 43% in the invasive arm. As highlighted above, BNP and NT-proBNP are markers of fatal "pump failure" events rather than nonfatal ischemic events; thus, it is not surprising that they would perform better for selecting therapy in studies in which the active therapy lowered mortality.

Several other therapies have been evaluated for an interaction with BNP or NT-proBNP levels in patients with ACS or stable ischemic heart disease, including intensive statin therapy,[31,38] angiotensin-converting enzyme (ACE) inhibitors,[39] and ranolazine.[40] Although each of these studies confirmed the prognostic role of NPs, they failed to identify a clear therapeutic response for patients with BNP or NT-proBNP elevation post-ACS. In the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes-TIMI 36 (MERLIN-TIMI 36) study,[40] ranolazine reduced the primary endpoint of death, MI, and recurrent ischemia among patients with BNP > 80 pg/mL (HR 0.79; 95% CI, 0.66-0.94), but not among patients with BNP levels ≤ 80 pg/mL (HR 1.01; 95% CI, 0.85-1.20). Although this interaction was nominally statistically significant ($P = .05$), the clinical relevance of this observation is modest, given the limited role for ranolazine after ACS, the exploratory nature of the analyses, and the absence of a mechanism to clearly explain the observation. The most surprising and disappointing results were from the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial, in which no interaction was observed for therapy with the ACE inhibitor trandalopril based on BNP or NT-proBNP levels. Many experts predicted that ACE inhibitors would reduce risk among patients with chronic coronary disease and elevated NP levels, but no benefit of trandalopril over placebo was seen, even for patients with high levels of BNP or NT-proBNP.[39]

ACS exists on a continuum that in many individuals culminates in the development of HF. Although targeting therapy based on BNP and NT-proBNP is still in its infancy in the ACS field, in patients with CHF, a series of randomized controlled trials have been performed evaluating various biomarker-guided treatment strategies using BNP or NT-proBNP. It is plausible that lessons learned from these studies may help to pave the way for biomarker-guided treatment strategies in ACS. Moreover, some of the elevations in BNP or NT-proBNP detected during outpatient follow-up after ACS will be due to newly diagnosed or progressive HF.

Although the studies performed to date have differed in many aspects of trial design, they have all performed serial measurements of BNP or NT-proBNP in the biomarker-guided arm, titrating HF therapies to lower the NP level in addition to improving signs and symptoms of CHF. Rather than initiating novel therapies, the studies have intensified existing evidence-based therapies to achieve lower NP levels, and consis-

tently NP-guided therapy has resulted in more patients being treated with higher dosages of guideline-based medications.[41,42] In a meta-analysis of 6 randomized controlled trials in patients with HF, NP-guided therapy reduced mortality significantly versus usual care (HR 0.69; 95% CI, 0.55-0.86) (Figure 8).[43] A persistently elevated NP level may serve as a reminder to intensify therapy in a patient who otherwise feels well, in much the same way therapy is intensified to lower lipid and blood pressure values in asymptomatic individuals. The biomarker-guided strategy merits prospective evaluation among patients stabilized following an ACS event.

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Current Status and Recommendations for NP Testing in ACS

As just described, the evidence base linking elevated BNP and NT-proBNP levels after ACS with higher rates of death and HF, although very robust and consistent, has been limited because to date studies have not identified therapies that can mitigate risk associated with NP elevation. For this reason, BNP or NT-proBNP measurement for risk stratification in ACS has been given only a qualified recommendation (Class IIb, level of evidence: B) in the most recent ACC/AHA guidelines for unstable angina/NSTEMI.[44] In guidelines from the National Association of Clinical Biochemistry, the recommendation is stronger (Class IIa, level of evidence: A), although it is acknowledged that the benefits of therapy based on NP levels remains uncertain.[45] Interestingly, in both guidelines the recommendation is the same as that for C-reactive protein (CRP) measurement, despite the much stronger and consistent evidence base supporting the prognostic value for BNP and NT-proBNP compared with CRP after ACS.

Conclusions

BNP and NT-proBNP testing are now firmly established as powerful tools to augment risk assessment after ACS. However, given the conflicting data from existing studies, additional research is needed to clarify the potential role of NP testing to identify patients who otherwise appear to be at low risk but who may benefit from a more aggressive use of coronary revascularization after ACS. Moreover, "outside the box" thinking will be required to identify novel treatment strategies and study designs to mitigate risk associated with BNP and NT-proBNP elevation in patients with ACS. ■

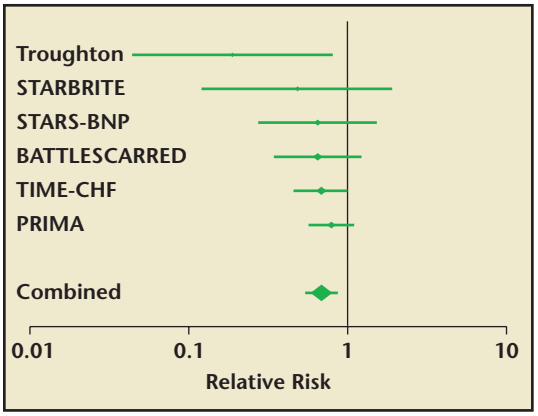

Figure 8. *Meta-analysis of trials comparing BNP- or NT-proBNP–guided therapy versus usual care in patients with heart failure. Shown is a forest plot for all-cause mortality. BATTLESCARRED, NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PRIMA, Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?; STARBRITE, Pilot Trial of BNP-Guided Therapy in Patients With Advanced Heart Failure; STARS-BNP, Systolic Heart Failure Treatment Supported by BNP; TIME-CHF, Trial of Intensified (BNP-guided) versus standard (symptom-guided) Medical therapy in Elderly patients with Congestive Heart Failure. Adapted with permission from Felker GM et al.*[43]

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Main Points

- Although both B-type natriuretic peptide (BNP) and N-terminal prohormone BNP (NT-proBNP) are released in response to cardiac ischemia, neither peptide offers sufficient sensitivity or specificity to be useful for the diagnosis of acute coronary syndromes (ACS).
- Natriuretic peptide (NP) levels reflect cardiac neurohormonal stress but not the cause of that stress.
- Although the data supporting serial NP measurement in the hospital after ACS are conflicting, a more compelling case can be made for serial measurements over longer-term outpatient follow-up.
- The evidence base linking elevated BNP and NT-proBNP levels after ACS with higher rates of death and heart failure, although very robust and consistent, has been limited because to date studies have not identified therapies that can mitigate risk associated with NP elevation.
- BNP and NT-proBNP testing are now firmly established as powerful tools to augment risk assessment after ACS. However, given the conflicting data from existing studies, additional research is needed to clarify the potential role of NP testing to identify patients who may benefit from a more aggressive use of coronary revascularization after ACS.

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