# Time to Treatment and Acute Coronary Syndromes: Bridging the Gap in Rapid Decision Making

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*The role of cardiac biomarkers in the diagnosis, risk stratification, and treatment of patients with chest pain and suspected acute coronary syndromes (ACS) has continued to evolve. Although it is clear that troponin (Tn) measurement provides independent prognostic information in patients with suspected ACS, it is less well established that early B-type natriuretic peptide (BNP) measurement provides additional incremental prognostic information above and beyond electrocardiography and Tn measurement. It is useful to identify patients at high risk for adverse events through measurement of Tn and BNP levels so that timely treatment decisions can be made.*
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**Key words:** Acute coronary syndromes • B-type natriuretic peptide • Cardiac troponin

Measurement of cardiac troponin (Tn) represents the standard for the definition of myocardial infarction (MI).[1,2] Although it is clear that Tn measurement provides independent prognostic information in patients with suspected acute coronary syndromes (ACS)[3-9] it is less well established that early B-type natriuretic peptide (BNP) measurement provides additional incremental prognostic information above and beyond electrocardiography and Tn measurement in the acute evaluation of suspected ACS.[10-13] BNP, a unique neurohormonal indicator that is released in the setting of elevated intracardiac pressure or strain,[14-16] provides an index to hemodynamic abnormalities and cardiac wall stress. In selected studies among patients with non–ST-segment elevation and ACS (NSTE-ACS), an elevated BNP has been shown to be associated with a higher risk of mortality.[10-13] Further, clinical trial

database analyses suggest an increased BNP is associated with a higher risk of mortality compared with an elevated Tn level.[11] Thus, the accuracy of early risk stratification in suspected ACS may be improved by combining a marker of necrosis with a neurohormonal marker of myocardial stress.

## Clinical Data

Although large prospective datasets evaluating outcomes associated with BNP measurement in non-ST segment elevation myocardial infarction and ACS (NSTEMI-ACS) are lacking, the CRUSADE (Can Rapid Risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative has evaluated the use of the combination of BNP and Tn for predicting in-hospital mortality. CRUSADE collected data on patients presenting to hospitals with NSTE-ACS if they reported ischemic symptoms at rest within 24 hours of presentation that were also accompanied by high-risk features that included transient electrocardiographic changes or positive cardiac markers (elevated Tn-I, Tn-T, or creatine kinase-myocardial band [CK-MB]) exceeding the upper limit of normal (ULN) for the local laboratory assay. Using the first serum sample drawn for cardiac markers after hospital presentation, researchers performed analyses by dividing each biomarker result into 5 a priori defined groups. Because these data were obtained from 293 hospitals using different nonstandardized laboratory platforms (from 2003 to 2004), baseline and maximum Tn concentrations measured within 24 hours of presentation were then transformed into ratios of each institution's ULN. These ranges were defined as $\leq$ 1, $>$ 1-2, $>$ 2-5, $>$ 5-10, and $>$ 10 times the ULN. Because at the time of this analysis only a single standardized BNP laboratory platform was available, result ranges were defined as $\leq$ 100 pg/mL, $>$ 100-500 pg/mL, $>$ 500-1000 pg/mL, $>$ 1000-2500 pg/mL, and $>$ 2500 pg/mL. Applying these ranges, and after excluding transfer patients and those with missing markers to the CRUSADE database, yielded a final analysis population of 5325 patients.

The results of this CRUSADE analysis reported that increasing BNP in patients presenting with NSTEMI-ACS was associated with a greater severity of illness. In-hospital adverse events, stratified by BNP group, increased proportionately to BNP level, and were associated with greater mortality, higher rates of cardiogenic shock and cerebrovascular accidents, and more erythrocyte transfusion (Table 1). Additionally, the probability of death increased directly with BNP concentration (Figure 1). Figure 2 shows the distribution of mortality by ranges of BNP and Tn. Not unexpectedly, as BNP concentrations were increased across the groups, there were associated increases in patients' age, length of hospitalization, and prior rates of cardiovascular disease (MI, heart failure, and stroke) (Table 1). There were also proportionally fewer males, less obesity, and a declining rate of self-reported smoking.

When considering this analysis of outcomes by levels of Tn or BNP individually, researchers found that in-hospital mortality roughly doubled from the lowest to the highest Tn ratio; from 4.5% to 8.2% (Figure 2). Increasing BNP concentration was associated with greater relative increases in mortality across groups than the mortality increase across the ranges of Tn. From the lowest to highest BNP group, mortality increased from 1.1% to 17.2%. The significant increase in mortality with increasing BNP remained even after risk adjustment. The mortality odds

**Table 1**
**Rate of Unadjusted In-Hospital Clinical Outcomes Stratified by BNP Group**

| | BNP $\leq$ 100 n = 799 | BNP $>$ 100-500 n = 1943 | BNP $>$ 500-1000 n = 1129 | BNP $>$ 1000-2500 n = 966 | BNP $>$ 2500 n = 488 | *P* value |
|---|---|---|---|---|---|---|
| Cardiogenic shock | 1.0 | 3.0 | 3.1 | 6.4 | 5.9 | $<$ .0001 |
| Congestive heart failure | 3.0 | 11.3 | 20.5 | 22.7 | 26.8 | $<$ .0001 |
| Stroke | 0.4 | 0.8 | 1.4 | 1.0 | 2.5 | .0008 |
| Death[a] | 1.1 | 4.2 | 7.6 | 11.6 | 17.2 | $<$ .0001 |

Data presented as percentages.
[a]Predicted risk of in-hospital mortality from hospital presentation variables based on CRUSADE Mortality Model.
BNP, B-type natriuretic peptide; CRUSADE, Can Rapid Risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines.

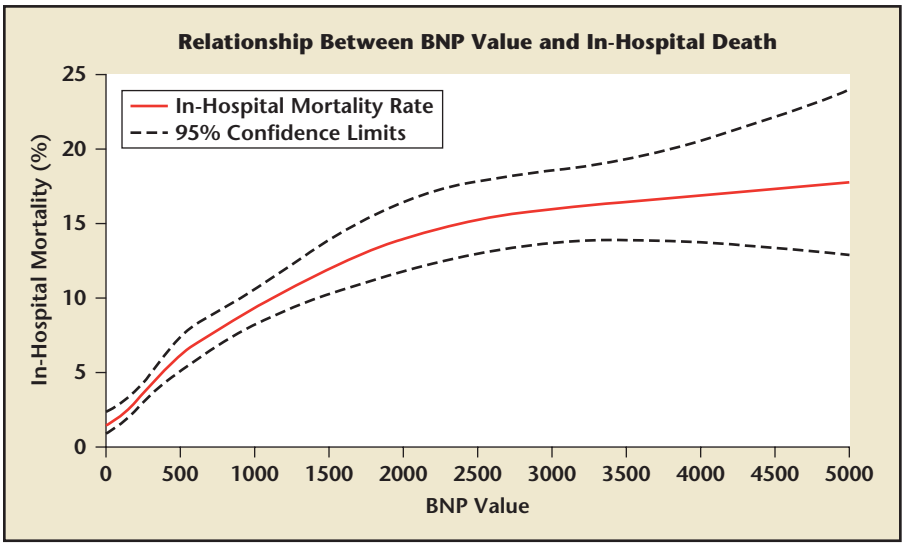
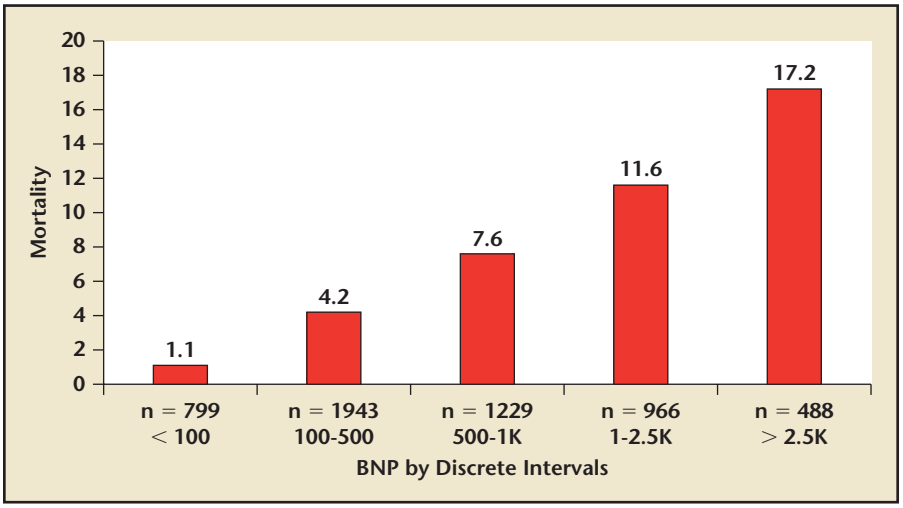



**Figure 1.** *Continuous distribution of BNP levels with unadjusted in-hospital mortality. BNP, B-type natriuretic peptide.*



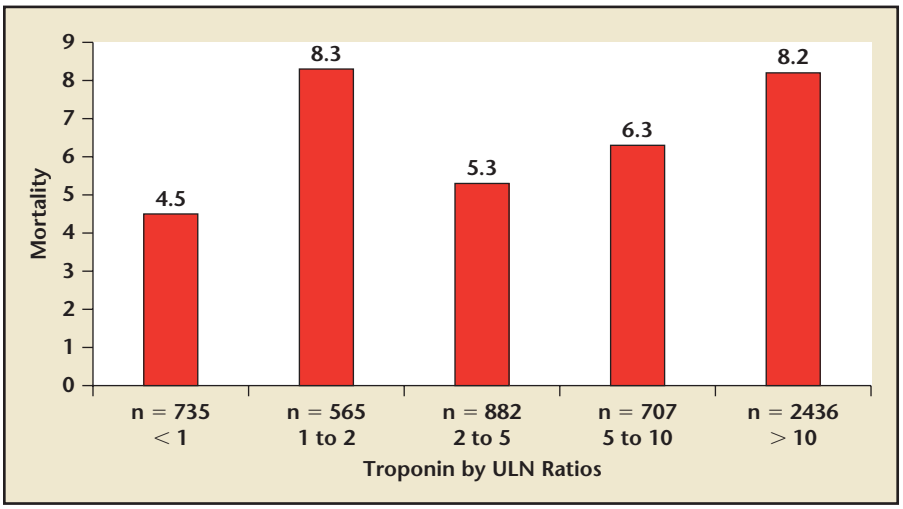




**Figure 2.** *Frequency of in-hospital mortality versus marker range. BNP, B-type natriuretic peptide; ULN, upper limit of normal.*

ratios for each increasing BNP group, compared with normal defined as a BNP ≤ 100, were 2.8 (95% confidence interval [CI], 1.6-5.0), 4.2 (95% CI, 2.2-7.9), 6.3 (95% CI, 3.2-12.4), and 9.3 (95% CI, 4.5-19.2), respectively.

This CRUSADE analysis indicates that BNP may be an important prognostic marker in patients presenting to the hospital with NSTE-ACS. In this population, an elevated BNP portends a marked increase of in-hospital mortality, with the odds of short-term death for patients with a BNP > 2500 pg/mL increased nearly 10-fold compared with patients with a BNP < 100 pg/mL.

Surprisingly, BNP was a better predictor of in-hospital mortality than Tn, and the increase in mortality associated with increasing the absolute marker value was greater for BNP than Tn (Figure 3). Although there was an association between higher Tn and in-hospital mortality, the absolute increase in mortality rate from the lowest to the highest Tn group was only 0.7% in the normal BNP cohort, and 4% when the BNP exceeded 2500 pg/mL. Comparatively, a higher BNP value within a Tn stratum was associated with much greater in-hospital mortality. As BNP increased from the lowest to the highest range, mortality increased by an absolute 13.9% in the group with normal Tn levels; and in the group with the highest Tn levels, the highest BNP level was associated with an absolute mortality increase of 17.2% higher than the lowest BNP level.

The fact that there is a 15% mortality rate associated with an elevated BNP level in the setting of ACS with a Tn below the institutional ULN is an important finding. This has clinical ramifications because measuring BNP in patients with suspected NSTE-ACS is not currently standard practice. It is well known that at presentation many patients ultimately diagnosed as having an NSTE-ACS or STEMI may

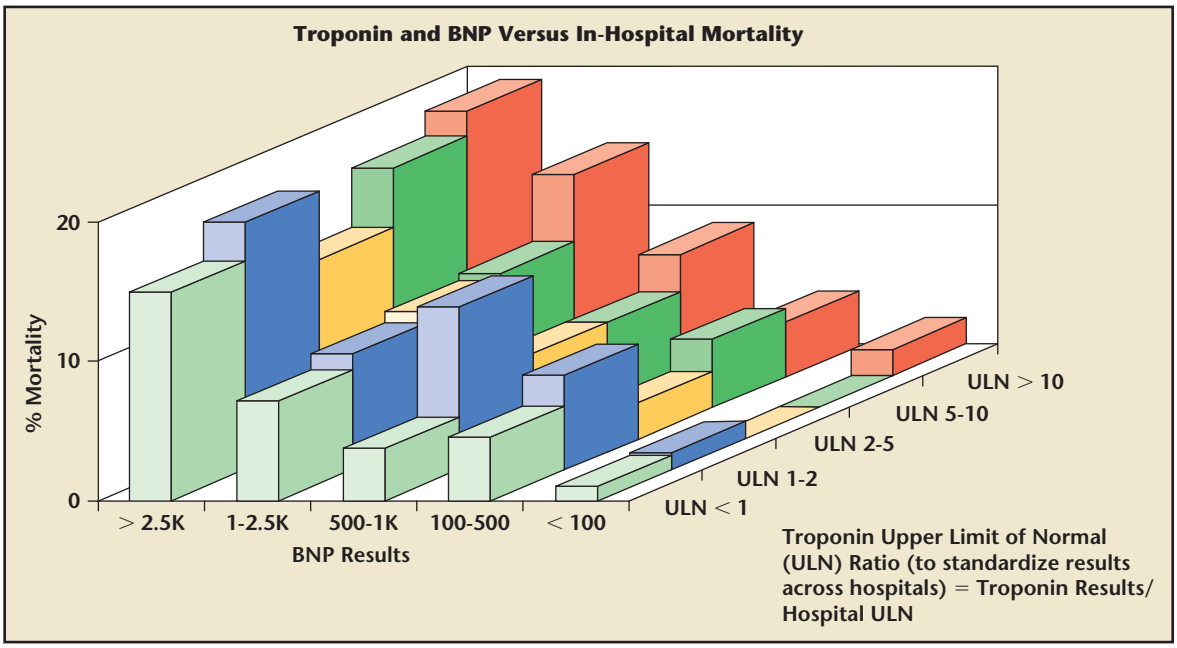



**Figure 3.** *The interaction among troponin, BNP, and in-hospital mortality. BNP, B-type natriuretic peptide.*

have an initially nondiagnostic Tn. An elevated BNP in this scenario suggests neurohormonal activation and should raise concern for adverse outcomes. It does seem clear that in the setting of ACS there is an increased risk of adverse outcome associated with an elevated BNP even with a nondiagnostic Tn concentration.

Other data support the association of elevated BNP and adverse outcomes in the setting of myocardial ischemia. Morrow and colleagues,[13] in an analysis of 1676 patients enrolled in Thrombolysis In Myocardial Infarction (TIMI)-18, found that 1-week NSTEMI mortality more than tripled if the baseline BNP exceeded 80 pg/mL. de Lemos and coauthors,[10] in an analysis of 2525 TIMI-16 patients undergoing BNP measurement within 40 hours of presentation, reported an increase in long-term mortality and heart failure risk with higher BNP levels.

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Stress test investigations have supported the underlying physiologic mechanism by which acute myocardial ischemia could be associated with a rising BNP. In a study of 256 patients by Staub and associates,[17] those with the highest quartile of BNP elevation as a result of peak exercise stress testing had a 3-fold increase in the risk of inducible myocardial ischemia. In this same study, a postexercise BNP elevation more accurately distinguished between ischemic and nonischemic patients than did exercise testing.

In a second stress test study, Sabatine and colleagues[12] reported that transient myocardial ischemia was associated with an immediate rise in circulating BNP levels, and the magnitude of the rise was proportional to the severity of the ischemia. If BNP elevation is related to the relative amount of myocardial ischemia, then an elevated BNP in the setting of an acute ischemic syndrome would be physiologically consistent with the suggestion that the higher the BNP levels are, the greater the risk of associated adverse outcomes.

Ultimately, BNP is a neurohormonal marker of cardiac stress, and irrespective of the etiology of its elevation, patients with a higher BNP concentration have worse outcomes than those without an increase. Whether an aggressive management strategy is beneficial in the cohort of NSTE-ACS patients with elevated BNP is currently unclear due to a lack of prospective, randomized research.

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Interestingly, and defying our current physiologic understanding of the pathophysiology of ACS, most large prospective studies have not been able to identify a clearly time-dependent association between therapy and outcomes in ACS. One postulate is that inaccurate risk stratification, from using Tn alone to identify interventional necessity, has resulted in a heterogeneous population in which the inclusion of relatively low-risk patients results in an erosion of the ability to demonstrate a time-dependent outcome benefit. If BNP could further identify higher risk patients in an NSTEMI-ACS population that was Tn negative, the importance of early intervention may be discernable.

Although the current literature suggests that BNP may help guide the risk stratification process in patients with suspected ACS, it does not currently define what treatment modalities are appropriate and it is unclear how these data should influence treatment strategies. One study suggested that coronary interventional procedures may reduce mortality outcomes when BNP is elevated,[18] but others have not duplicated this finding.[13,19] Regardless, it is still useful to identify patients at high risk for adverse events so that accurate triage and disposition decisions can be made.

Other investigators have evaluated the NSTE-ACS population using N-terminal prohormone BNP (NT-proBNP).[20] In a retrospective analysis of the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial, Heeschen and colleagues[20] demonstrated that NT-proBNP increases predicted death and recurrent MI in ACS patients. Overall outcomes were similar to BNP, in that the lowest rate of death or MI occurred if both Tn and NT-proBNP were low, were highest when both were elevated, and were midrange when only a single marker was elevated. However, NT-proBNP is not as effective an early or initial risk stratification tool as BNP. Although the finding of an initial BNP elevation in the setting of ACS is associated with increased mortality, Heeschen and colleagues[20] reported that NT-proBNP does not predict increased adverse events until 48 hours after presentation. The possibility that the different half-lives of these markers (BNP half-life = 20 minutes, NT-proBNP half life = 2 hours) may impact their performance should be considered. Evaluation of the relative use of these 2 markers in risk assessment requires a direct head-to-head comparison. Ultimately, regardless of which natriuretic peptide marker is used, evidence of neurohormonal activation in the setting of ACS suggests a bad short-term prognosis.

Finally, other authors[21,22] have reported that early declines in serially measured BNP or NT-pro BNP levels, as compared with later declines, are associated with improved prognosis following an ischemic event. How this should impact therapy and the implications for risk stratification are less clear. Irrespective, an elevated BNP level at any time during the course of NSTEMI-ACS management is a poor prognostic indicator.

Currently, the majority of available data regarding the use of BNP in the setting of NSTEMI-ACS are registry derived. This limitation prevents determining the actual sensitivity and specificity of BNP for predicting adverse outcomes in NSTEMI-ACS because by their very definition registries do not gather data on an "all-comers" population. However, an emergency department study[11] provided insight into this information. In an analysis of 631 patients—72 of whom were ultimately diagnosed with NSTEMI—it was found that the initial BNP had a higher sensitivity and specificity for predicting an ultimate MI diagnosis as compared with either CK-MB or Tn-I.

Finally, although patients with elevated BNP have greater risk for adverse outcomes, and patients with lower BNP values have better outcomes, we cannot suggest that a BNP below a given cutpoint should be used as a risk stratification tool for disposition decisions. Further research will be required to delineate the utility of a negative BNP as a risk exclusion parameter in the suspected ACS population.

## Implications for Clinical Practice

There is reasonable evidence to suggest that BNP elevations are independently and incrementally associated with in-hospital mortality in patients with NSTE-ACS. Furthermore, in patients in whom both BNP and Tn levels are measured at hospital admission, BNP provides incremental information for in-hospital risk stratification above and beyond that of Tn.

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It also seems that the presence of an elevated BNP in patients undergoing an evaluation for suspected ACS would identify individuals at higher risk for short-term adverse outcomes. For example, in the patient with chest pain, a negative Tn test result, and an elevated BNP level, appropriate testing may require serial Tn measures. However, consideration for a higher-risk presentation should be entertained. This suggests that myocardial perfusion and structural cardiac evaluation are warranted, as opposed to

an outpatient evaluation, if results of all serial Tn tests were negative. Whether that is accomplished by stress echocardiography or computed coronary angiogram with a myocardial function evaluation is at the discretion of the treating physician. However, because of the risk that an elevated BNP portends in the setting of NSTEMI-ACS, a more rapid investigation strategy is probably indicated.

## Conclusions

In the setting of a patient presenting with a suspected NSTEMI-ACS, BNP levels obtained at the time of Tn measurement can provide incremental prognostic information, above and beyond that suggested by the Tn concentration, to identify patients at increased risk of short- and long-term adverse outcomes. Although the lack of a BNP elevation in the setting of suspected NSTEMI-ACS does not identify a low-risk cohort in whom hospital discharge is acceptable, a BNP elevation suggests that a more aggressive evaluation of the potential for high-risk ACS is warranted. ■

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## Main Points

- Measurement of cardiac troponin (Tn) is the gold standard used to define myocardial infarction; Tn measurement provides independent prognostic information in patients with suspected acute coronary syndromes (ACS).
- B-type natriuretic peptide (BNP) is released in the setting of elevated intracardiac pressure or strain. Early BNP measurement provides additional incremental prognostic information above and beyond electrocardiography and Tn measurement.
- There is reasonable evidence to suggest that BNP elevations are independently and incrementally associated with in-hospital mortality in patients with non–ST-elevation ACS.
- It is useful to identify patients at high risk for adverse events through measurement of Tn and BNP levels so that timely treatment decisions can be made.