**Prognostic Value of Serial B-Type Natriuretic Peptide Testing During Follow-up of Patients With Unstable Coronary Artery Disease**

David A. Morrow, MD, MPH
James A. de Lemos, MD
Michael A. Blazing, MD
Marc S. Sabatine, MD, MPH
Sabina A. Murphy, MPH
Petr Jarolim, MD, PhD
Harvey D. White, DSc
Keith A. A. Fox, MB, ChB
Robert M. Califf, MD
Eugene Braunwald, MD
for the A to Z Investigators

**B-Type Natriuretic Peptide (BNP)** is released from cardiac myocytes in response to increased wall stress, and is elevated in settings in which myocardial ischemia occurs. B-type natriuretic peptide is released during ischemia provoked by exercise testing and after acute myocardial infarction (MI), with some patients exhibiting a late increase, possibly related to adverse remodeling. When measured at the time of presentation, up to 7 days after onset of acute coronary syndrome (ACS), blood concentrations of BNP and N-amino terminal fragment of the prohormone BNP (NT-proBNP) are strongly associated with the short-term and long-term risk of death and new congestive heart failure (CHF). These data have led to approval for use of BNP and NT-proBNP levels for risk stratification in ACS, and to the proposal that serial determinations during follow-up may be associated with long-term clinical outcomes and may provide a basis for enhanced clinical decision making in patients after onset of ACS.

**Context** Elevated concentrations of B-type natriuretic peptide (BNP) at presentation in patients with acute coronary syndrome (ACS) are associated with long-term mortality. Few data exist regarding serial assessment of BNP levels during follow-up.

**Objective** To determine whether concentrations of BNP at study entry (prior to hospital discharge for ACS) and at outpatient follow-up at 4 months and 12 months are associated with subsequent clinical outcomes.

**Design, Setting, and Patients** Prospective observational substudy of 4497 patients with non-ST-elevation or ST-elevation ACS who were enrolled in phase Z of the A to Z trial, which was conducted in 41 countries at 322 acute care hospitals between 1999 and 2003.

**Main Outcome Measure** Death from any cause or new onset of congestive heart failure (CHF) through 2 years.

**Results** Levels of BNP were available in 4266 patients at study entry (prior to hospital discharge), 3618 patients at 4 months, and 2966 patients at 12 months. During follow-up there were 230 deaths and 163 incident cases of CHF. Adjusting for age, sex, index event, renal function, hypertension, prior heart failure, and diabetes, elevated levels of BNP (>80 pg/mL) were associated with subsequent death or new CHF when measured at study entry (111 [21%] vs 246 [7%]; adjusted hazard ratio [HR], 2.5; 95% confidence interval [CI], 2.0-3.3), at 4 months (34 [19%] vs 125 [4%]; adjusted HR, 3.9; 95% CI, 2.6-6.0), and at 12 months (19 [11%] vs 37 [1%]; adjusted HR, 4.7; 95% CI, 2.5-8.9). Patients with newly elevated levels of BNP at 4 months were at increased risk of death or new CHF (10 [15%] vs 105 [3%]; HR, 4.5; 95% CI, 2.3-8.6). Patients with elevated levels of BNP at study entry and with BNP levels lower than 80 pg/mL at 4 months tended to have only modestly increased risk (HR, 1.7; 95% CI, 1.0-2.9) compared with patients with BNP levels lower than 80 pg/mL at both visits.

**Conclusions** Serial determinations of BNP levels during outpatient follow-up after ACS predict the risk of death or new CHF. Changes in BNP levels over time are associated with long-term clinical outcomes and may provide a basis for enhanced clinical decision making in patients after onset of ACS.

**Clinical Trials Registration** ClinicalTrials.gov Identifier: NCT00251576
useful both for additional prognostic assessment as well as monitoring response to therapy. However, few studies have evaluated serial measurements of BNP during extended follow-up of patients after ACS. Therefore, we investigated the prognostic value of BNP and changes in its concentration in patients with ACS prior to hospital discharge (study entry), at 4 months, and at 12 months in the A to Z trial.

METHODS

Study Population

Between 1999 and 2003, patients with non-ST-elevation or ST-elevation ACS were enrolled in phase Z of the A to Z trial and followed up for a median of 2 years. The study design, entry criteria, and primary results have been published previously. In phase Z, an early intensive statin strategy was compared with a less aggressive statin strategy in patients with ACS that was stabilized after initial presentation. The protocol was approved by the ethics committee at each of the 322 acute care hospitals and written informed consent was provided by all 4497 participants. All participants in phase Z who had plasma samples available for measurement of BNP were eligible for this substudy. Exclusion criteria for the A to Z trial relevant to this substudy included age older than 80 years, renal dysfunction (serum creatinine level $>2.0$ mg/dL [176.8 pmol/L]), acute pulmonary edema requiring intubation, or plans for coronary revascularization.

BNP Testing

Samples of EDTA-anticoagulated plasma were obtained prior to randomization into phase Z (median [range] of 84 [62-107] hours after symptom onset) and at outpatient follow-up at 4 months and 12 months and were shipped on ice overnight in plastic tubes for storage. Aliquots were then shipped on dry ice to the TIMI Biomarker Laboratory at Brigham and Women’s Hospital (Boston, Mass) where they were analyzed by batch. B-type natriuretic peptide was measured using the ADVIA Centaur (Bayer HealthCare Diagnostics, Tarrytown, NY). All testing was performed by personnel blinded to clinical outcomes and treatment allocation.

Statistical Methods

The prespecified primary end point for this substudy was the composite of death from any cause or new onset of CHF (requiring admission or initiation of medications). The major secondary end point was death from any cause. The concentration of BNP at each time point was described by the median (25th and 75th percentiles). The results of BNP testing were considered as a dichotomous variable using a prespecified level of 80 pg/mL based on prior research on ACS. Baseline characteristics were compared using the Wilcoxon rank sum test for continuous variables and the $\chi^2$ test for categorical variables. Event rates for clinical outcomes were determined using the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses of the association between BNP levels and clinical outcomes were performed using the Cox proportional hazards regression model to adjust for the effects of other major clinical predictors of mortality (age, sex, index event [non-ST-elevation vs ST-elevation ACS], deviation in ST-segment depression, creatinine clearance at the time of the visit, hypertension at study entry, history of CHF, and diabetes). Creatinine clearance was estimated using the Cockroft-Gault formula. The proportional hazards assumption was validated. Assessment of an expanded model in the subset of patients with data available for C-reactive protein (study entry [baseline] and at 4 months), local troponin level from the index event, glucose level, and treatment with blockers of the renin-angiotensin-aldosterone pathway and $\beta$-blockers revealed no significant confounding (<10% change in the adjusted hazard ratio [HR]), with the exception of the assessment of BNP level and C-reactive protein at entry to phase Z (reported in "Results"). Formal testing for an interaction with prior CHF revealed none (at each time point, $P > .20$ for interaction).

Testing was performed for an association between the concentration of BNP at 4 months and at 12 months with subsequent clinical outcome by time-to-event (landmark) analysis beginning at the time of sampling and including all patients with an available BNP result from the relevant visit. Confirmatory analyses excluding patients with nonfatal ischemic and CHF events prior to the visit also were performed to eliminate possible confounding by recent cardiac events resulting in an increase in BNP level. All analyses were performed by the Thrombolysis in Myocardial Infarction study group using STATA Intercooled software version 8.2 (STATA Corp, College Station, Tex). $P < .05$ (2-tailed) was considered to indicate statistical significance.

RESULTS

Changes in BNP Level During Long-term Follow-up After ACS

The distribution of BNP concentrations at each visit are reported in Table 1. There were no significant differences between the study population and patients with missing BNP values at outpatient follow-up at 4 months and 12 months with respect to variables associated with BNP (age, presentation with ST-elevation, history of CHF, creatinine clearance). However, there was a greater proportion of women with missing plasma samples at 4 months (missing vs nonmissing: 31% vs 23%; $P = .001$) and at 12 months (28% vs 23%; $P = .002$).

Among the 3493 patients with measurements at baseline and at 4 months, 473 (13.3%) had BNP concentrations higher than 80 pg/mL at baseline; of these 473 patients, 140 (29.6%) had levels that remained elevated at 4 months, while the remainder (n = 333; 70.4%) had levels that were lower than 80 pg/mL. There were 77 (2.5%) patients who had a newly elevated concentration of BNP at 4 months. Among the 2901 patients with plasma samples at 4 months and at 12 months, 173 (6.0%) had levels of BNP that were higher than 80 pg/mL at 4 months; of these 173 patients, 85
Table 1. Univariate Associations With Elevated Levels of B-Type Natriuretic Peptide (BNP)*

<table>
<thead>
<tr>
<th>BNP Level</th>
<th>&lt;80 (n = 3657)</th>
<th>&gt;80 (n = 609)</th>
<th>P Value</th>
<th>&lt;80 (n = 2374)</th>
<th>&gt;80 (n = 218)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>60 (52-69)</td>
<td>65 (55-72)</td>
<td>&lt;.001</td>
<td>60 (52-68)</td>
<td>67 (60-74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Women</td>
<td>867 (23.7)</td>
<td>172 (28.2)</td>
<td>.02</td>
<td>761 (22.4)</td>
<td>73 (32.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1708 (49.2)</td>
<td>337 (55.3)</td>
<td>.005</td>
<td>1642 (48.4)</td>
<td>137 (61.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>1493 (40.9)</td>
<td>231 (37.9)</td>
<td>.12</td>
<td>1424 (42.0)</td>
<td>55 (24.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>748 (20.3)</td>
<td>154 (25.3)</td>
<td>.007</td>
<td>672 (19.8)</td>
<td>65 (29.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>170 (4.7)</td>
<td>42 (6.9)</td>
<td>.02</td>
<td>152 (4.5)</td>
<td>23 (10.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Presenting characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>1304 (35.7)</td>
<td>398 (65.4)</td>
<td>&lt;.001</td>
<td>1289 (38.0)</td>
<td>143 (64.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Creatinine clearance, median (range), mL/min</td>
<td>76.8 (61.6-94.4)</td>
<td>66.8 (52.1-86.4)</td>
<td>&lt;.001</td>
<td>76.8 (61.7-94.1)</td>
<td>61.0 (47.9-76.4)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; STEMI, ST-elevation myocardial infarction. SI conversion factor: To convert creatinine clearance to mL/s, multiply by 0.0167.

*Values are expressed as number (percentage) unless otherwise indicated.
†The median (range) BNP level was 11.5 (5-45) pg/mL.
‡The median (range) BNP level was 5.2 (5-23) pg/mL.

Table 2. Risk of Death or Congestive Heart Failure (Kaplan-Meier Estimated Rates) Stratified by B-Type Natriuretic Peptide (BNP) Results*

<table>
<thead>
<tr>
<th>BNP Threshold</th>
<th>&lt;80 (n = 3396)</th>
<th>&gt;80 (n = 222)</th>
<th>P Value</th>
<th>&lt;80 (n = 2748)</th>
<th>&gt;80 (n = 218)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 pg/mL Baseline</td>
<td>1741 (41)</td>
<td>158 (6.5)</td>
<td>199 (12.7)</td>
<td>1.6 (1.3-2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td>1027 (29)</td>
<td>88 (3.3)</td>
<td>71 (8.1)</td>
<td>2.9 (2.0-4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>1021 (35)</td>
<td>24 (1.1)</td>
<td>32 (3.3)</td>
<td>2.0 (1.1-3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 pg/mL Baseline</td>
<td>1149 (27)</td>
<td>198 (6.6)</td>
<td>159 (15.6)</td>
<td>1.9 (1.5-2.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td>540 (15)</td>
<td>105 (3.4)</td>
<td>54 (12.0)</td>
<td>2.9 (2.0-4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>535 (18)</td>
<td>30 (1.2)</td>
<td>26 (5.7)</td>
<td>3.0 (1.7-5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 pg/mL Baseline</td>
<td>609 (14)</td>
<td>246 (7.0)</td>
<td>111 (21.0)</td>
<td>2.5 (2.0-3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td>219 (6)</td>
<td>125 (3.7)</td>
<td>34 (19.4)</td>
<td>3.9 (2.6-6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>215 (7)</td>
<td>37 (1.4)</td>
<td>19 (10.7)</td>
<td>4.7 (2.5-8.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>160 pg/mL Baseline</td>
<td>216 (5)</td>
<td>297 (7.7)</td>
<td>60 (32.2)</td>
<td>3.2 (2.3-4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td>76 (2)</td>
<td>140 (4.0)</td>
<td>19 (33.1)</td>
<td>5.4 (3.2-9.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>62 (2)</td>
<td>46 (1.7)</td>
<td>10 (17.9)</td>
<td>5.7 (2.5-13.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio.
*The additional prognostic information obtained from a BNP result was maximal (using the likelihood ratio test in the adjusted model) at 80 pg/mL for each of the time points.

(49%) had levels that remained elevated at 12 months. At 12 months, 125 (4.6%) patients had a newly elevated concentration of BNP. Relationship Between BNP Level and Clinical Outcome During 2 years of follow-up, there were 230 deaths and 163 cases of incident CHF (Table 2). Patients with a BNP level higher than 80 pg/mL at entry to phase Z were at significantly higher risk of death or new CHF through 2 years. After adjustment for other clinical predictors, a baseline BNP level higher than 80 pg/mL was associated with a 2-fold higher long-term risk of death (adjusted HR, 2.1; 95% confidence interval [CI], 1.5-3.0) and death or new CHF (adjusted HR, 2.5; 95% CI, 2.0-3.3). Addition of C-reactive protein to the model for those with data available partially attenuated the relationship with death or new CHF (adjusted HR, 1.9; 95% CI, 1.5-2.5). B-type natriuretic peptide was not associated with the risk of MI (47 [8.4%] vs 243 [6.9%]; adjusted HR, 1.2; 95% CI, 0.9-1.7) or readmission for ACS (36 [0.7%] vs 167 [4.7%]; adjusted HR, 1.1; 95% CI, 0.7-1.7). Stratification by index presentation (ST-elevation vs non–ST-elevation ACS) revealed no heterogeneity with regard to the relationship between BNP level and death (P = .32 for interaction) or the risk of death or new CHF (P = .55 for interaction).

When measured at 4 months, BNP level remained strongly associated with
subsequent survival (adjusted HR, 3.6; 95% CI, 2.2-6.2), as well as the risk of death or new CHF (adjusted HR, 3.9; 95% CI, 2.6-6.0; Figure 1). Moreover, when patients with CHF or ischemic events that might contribute to increases in BNP level prior to outpatient follow-up at 4 months were excluded, an elevated level of BNP remained associated with a significantly higher risk of death (adjusted HR, 3.0; 95% CI, 1.7-5.6) and death or new CHF (adjusted HR, 3.5; 95% CI, 2.2-5.6).

Results at outpatient follow-up at 12 months were similar with respect to survival (adjusted HR, 3.9; 95% CI, 1.9-8.5) and death or new CHF (adjusted HR, 4.7; 95% CI, 2.5-8.9). The absolute and relative risk relationships for BNP level applied at a range of possible decision limits at each time point appear in Table 2.

Value of Serial Determination of BNP Level

Patients with a persistently elevated level of BNP were at highest risk of death or new CHF (HR, 4.5; 95% CI, 2.3-8.6). In contrast, patients with elevated BNP levels at baseline who returned with BNP levels lower than 80 pg/mL at 4 months tended to have only a modestly increased risk compared with patients with BNP levels lower than 80 pg/mL at both visits (HR, 1.7; 95% CI, 1.0-2.9). These observations were not altered by excluding patients with intercurrent ischemic or CHF events between visits. Similarly, compared with patients who had BNP levels lower than 80 pg/mL at 12 months (death or new CHF, n=2592; 1.4%), patients with either persistently (n=85; 16.0% [P<.001]) or newly (n=125; 8.2% [P<.001]) elevated levels of BNP at 12 months were at increased risk of death or new CHF.
No difference in the concentration of BNP or change in BNP level was observed at 4 months or 12 months between the randomized statin groups in phase Z.

**COMMENT**

This evaluation of BNP levels obtained early and during long-term follow-up after presentation in patients with ACS supports the value of serial determinations of BNP concentration for refining risk assessment and providing data to create a secondary prevention strategy in this population.

**Serial Determination of BNP Level in Patients With ACS**

Emerging evidence suggests that ascertainment of changes in BNP level over time may be useful in risk assessment, as well as for monitoring and directing therapy in patients with CHF, and has stimulated interest in whether a similar approach may be valuable in patients with ACS. A study of 1791 ACS patients showed that persistent or new increases in NT-proBNP levels at 72 hours were associated with significantly higher risk of subsequent cardiovascular events through 30 days. Lindahl et al23 found that levels of NT-proBNP declined substantially over time following onset of ACS and identified left ventricular dysfunction as a major predictor of persistent elevation of NT-proBNP level. Notably, while they found that NT-proBNP level was associated with mortality when tested at 6 weeks to 6 months after presentation, these investigators did not detect a relationship between changes in NT-proBNP concentration and clinical outcome.

Our observations indicate that the achieved concentration of BNP during ambulatory follow-up after recent ACS is predictive of long-term clinical outcomes and that changes in the results of BNP testing are associated with subsequent survival without CHF. These findings have important clinical implications for the care of patients with ACS. Unlike traditional biomarkers used for risk stratification (cardiac troponin and creatine kinase-MB), BNP has potential clinical applications both during the acute phase and for monitoring the longitudinal course after ACS. While we found no influence of the intensity of statin therapy on the levels of BNP, other treatments, such as angiotensin II receptor blockers and β-blockers, have been shown to lower levels of natriuretic peptides in patients with CHF26 and to improve clinical outcomes in high-risk patients with atherosclerotic vascular disease.27,28

**Contemporary Application of BNP Level for Risk Stratification in Patients With ACS**

Formal guidelines regarding the use of BNP level as a biomarker for risk stratification in patients with ischemic heart disease are under development.29 By virtue of its robust sample size, almost equal to the aggregate of previously available data for measurement of BNP levels in ACS (approximately 4300 patients), this study adds to the cumulative evidence for the prognostic value of BNP concentration measured during the initial hospitalization,30 and points toward novel applications for monitoring and guiding therapy. Nevertheless, recommendations for routine measurement of BNP levels in patients with ACS are not likely to emerge unless additional criteria are satisfied. Foremost, data supporting the benefit of specific therapeutic interventions to modify the risk associated with neurohormonal activation must be available before determination of BNP concentration is integrated into standard risk assessment strategies. At present, it seems reasonable to selectively apply BNP and NT-proBNP testing in patients for whom a more complete assessment of the absolute risk of death and/or CHF is desired by the clinician.

**Limitations**

We studied the use of BNP levels for risk assessment in patients with a high clinical probability of ACS. The results regarding in-hospital testing of BNP concentration may not apply to patients presenting with chest pain and low probability of ACS. Levels of BNP are increased in a variety of other conditions,30 and thus must be integrated with findings from the clinical examination to arrive at an overall diagnostic and prognostic assessment. Moreover, patients enrolled in the A to Z trial did not have significant renal insufficiency and were younger than 80 years. Application of the specific decision limits evaluated in this study may not be appropriate for patients with more advanced age or renal dysfunction. The analysis at each time point was by necessity limited to survivors with available samples that may have some impact on the generalizability of the findings.

**CONCLUSIONS**

Serial determination of BNP concentration prior to hospital discharge and during outpatient follow-up of patients with ACS provides significant independent prognostic information with respect to the risk of death or new heart failure. Changes in BNP level over time are associated with long-term clinical outcome and may provide a basis for enhanced clinical decision making in patients recovering from ACS.
for speaking from Biosite and Roche. Dr Blazing has received honoraria from Merck and Pfizer.

**Funding/Support:** This study was supported by Merck and Co and Bayer Healthcare Diagnostics Division.

**Role of the Sponsor:** Staff from Merck assisted in monitoring the progress and conduct of the A to Z trial. Bayer Healthcare provided reagents for B-type natriuretic peptide testing. The sponsors were not involved in the biomarker testing, analysis, or interpretation of the data, or in preparation of the manuscript for this substudy. Medical specialists employed by the sponsors reviewed the manuscript prior to submission.

**REFERENCES**


