Association of Elevated B-Type Natriuretic Peptide Levels With Angiographic Findings Among Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

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OBJECTIVES
We hypothesized that elevated B-type natriuretic peptide (BNP) levels would be associated with a greater severity of angiographic disease and a greater extent of myocardium at risk.

BACKGROUND
Elevations of BNP have been associated with increased risk of adverse outcomes in patients with unstable angina and non–ST-segment elevation myocardial infarction (UA/NSTEMI).

METHODS
Of the 2,220 patients with UA/NSTEMI enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction-18 (TACTICS–TIMI-18) trial, 276 randomized to the invasive arm had both baseline BNP levels and angiographic core laboratory data. Patients were categorized according to their baseline BNP levels as ≤80 or >80 pg/ml.

RESULTS
A total of 233 patients (84%) had BNP levels ≤80 pg/ml, and 43 (16%) had admission BNP levels >80 pg/ml. Patients with BNP >80 pg/ml had tighter culprit vessel stenosis on quantitative coronary angiography (median stenosis 76% vs. 67%, p = 0.004) and a higher (slower) corrected TIMI frame count (median CTFC 43 vs. 30, p = 0.018) in the culprit vessel. The median BNP level was higher in patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit lesion location (median BNP level 40 vs. 24 pg/ml, p = 0.005), and the culprit artery was more often the LAD in patients with BNP >80 pg/ml compared with ≤80 pg/ml (44% vs. 30%, p = 0.06).

CONCLUSIONS
Among patients with UA/NSTEMI, elevated BNP levels are associated with tighter culprit stenosis, higher CTFC, and LAD involvement. These findings suggest that elevated BNP may be associated with a greater severity and extent of myocardial ischemic territory during the index event and may partly explain the association between elevated BNP and adverse outcomes. (J Am Coll Cardiol 2004;44:564–8) © 2004 by the American College of Cardiology Foundation

B-type natriuretic peptide (BNP) is a peptide hormone released from cardiac ventricles in response to myocardial stretch or increased wall tension (1). The diagnostic and prognostic significance of elevated BNP in patients with heart failure has been well studied (2,3). In patients with ST-segment elevation myocardial infarction (STEMI), elevated levels of BNP are associated with a larger infarct size, progressive left ventricular (LV) remodeling, and increased mortality (4–9). Several studies have also demonstrated a strong association between elevated BNP levels and an increased incidence of adverse outcomes in patients with unstable angina and non–ST-elevation myocardial infarction (UA/NSTEMI) (10–16). This association was incremental to the prognostic information provided by elevated cardiac troponin levels (13). However, the underlying pathophysiologic mechanisms responsible for this association between BNP and outcome have not been well defined. We tested the hypothesis that elevated BNP levels in patients with UA/NSTEMI would be associated with more severe coronary vascular disease and greater abnormalities in coronary blood flow.

METHODS

Study population. The study population was derived from the UA/NSTEMI patients enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction-18 (TACTICS–TIMI-18) trial, the results of which have been previously published (17). A total of 2,220 patients with UA/NSTEMI were randomly as-
samples were collected at the time of enrollment, according
to the protocol, in citrate-anticoagulated tubes and plasma
isolated within 60 min of sample collection. Aliquots of the
samples were shipped frozen to Biosite Inc. (San Diego,
California), where they were thawed and analyzed using an
established immunoassay by personnel blinded to the study
details. The primary decision limit of 80 pg/ml was pre-
specified based on previous work with this assay (12,13).

Angiographic analysis. At centers participating in the
angiographic substudy, all coronary angiograms of patients
undergoing cardiac catheterization and/or percutaneous
coronary intervention were evaluated at the TIMI angiogra-
phic core laboratory by physicians who were blinded to the
patient’s clinical or BNP status. Coronary stenoses were
quantified using validated quantitative coronary angiogra-
phy. Assessment of epicardial coronary flow was done using
the TIMI flow grade and corrected TIMI frame count (CTFC),
according to previously described methods (18,19). The presence of thrombus was assessed by visual
estimation.

Statistical methods. Variables were compared using the
chi-square test for categorical data. Continuous data are
reported as the median value and interquartile range. The
nonparametric Wilcoxon rank-sum test was used for the
analysis of continuous variables.

RESULTS

Of the 2,220 patients from the TACTICS–TIMI-18
trial, 1,114 were randomized to early invasive strategy.
Overall, 276 patients had both core laboratory angiogra-
phic data and BNP levels at randomization. Of these,
233 patients (84%) had BNP levels >80 pg/ml and 43
patients (16%) had BNP level >80 pg/ml. The median
(25th, 75th percentile) BNP levels of the two groups were
22 (3, 41) and 137 (95, 173) pg/ml, respectively. The
baseline clinical characteristics of the patients in both
groups are shown in Table 1. Patients with BNP >80
pg/ml were older (median age 67 [60, 73] vs. 61 [53, 70]
years, p = 0.007) and were more likely to have NSTEMI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BNP ≤80 pg/ml* (n = 233)</th>
<th>BNP &gt;80 pg/ml† (n = 43)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs)</td>
<td>61 (53, 70)</td>
<td>67 (60, 73)</td>
<td>0.007</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>67</td>
<td>56</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>63</td>
<td>74</td>
<td>0.15</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22</td>
<td>28</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>30</td>
<td>21</td>
<td>0.22</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>65</td>
<td>47</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>37</td>
<td>47</td>
<td>0.26</td>
</tr>
<tr>
<td>Previous PTCA (%)</td>
<td>33</td>
<td>30</td>
<td>0.68</td>
</tr>
<tr>
<td>History of previous angina (%)</td>
<td>15</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>ST-segment deviation ≥0.5 mm (%)</td>
<td>36</td>
<td>42</td>
<td>0.43</td>
</tr>
<tr>
<td>T-wave changes (%)</td>
<td>32</td>
<td>44</td>
<td>0.11</td>
</tr>
<tr>
<td>Index event NSTEMI (%)</td>
<td>39</td>
<td>60</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Median 22 (25th, 75th percentiles of 3, 41) pg/ml. †Median 137 (95, 173) pg/ml.
BNP = B-type natriuretic peptide; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial
infarction; PTCA = percutaneous transluminal coronary angioplasty.
as the index event at randomization (60% vs. 39%, p = 0.008). They also had a lower prevalence of hyperlipidemia (47% vs. 65%, p = 0.02), but the populations were otherwise similar.

A BNP level >80 pg/ml was associated with tighter culprit vessel diameter stenoses (median stenosis 76% vs. 68%, p = 0.004) and higher CTFCs (i.e., slower flow in the culprit artery) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2). The median BNP level was higher among patients with a left anterior descending coronary artery (LAD) versus non-LAD culprit artery (%) (median CTFC 43 vs. 30, p = 0.018) (Table 2).

**DISCUSSION**

Among patients with UA/NSTEMI, elevated BNP is associated with tighter culprit lesion diameter stenoses, a higher CTFC (slower flow in culprit artery), and an LAD and more proximal culprit lesion location.

Several studies have evaluated the clinical significance of elevated BNP in patients with UA/NSTEMI (12–16). In the Oral Glycoprotein IIb/IIIa Inhibition with Orbofibin in Patients with Unstable Coronary Syndromes–Thrombolysis In Myocardial Infarction-16 (OPUS–TIMI-16) trial, elevated BNP measured at a mean time of 40 ± 20 h after the onset of symptoms was associated with a high risk of death, myocardial infarction, and heart failure at 30 days and 10 months. This association remained significant for the subgroup of patients with UA/NSTEMI. Furthermore, after adjustment for other independent predictors of the long-term risk of death, BNP >80 pg/ml was significantly associated with increased mortality at 10 months. Moreover, patients with BNP >80 pg/ml were also at a high risk of new or progressive heart failure, as compared with patients with BNP ≤80 pg/ml. In the TACTICS–TIMI-18 trial, UA/NSTEMI patients with BNP >80 pg/ml at enrollment had a higher mortality at seven days and six months. The association between elevated BNP and increased mortality was independent of other important clinical predictors, including elevated troponin I and heart failure (13). N-terminal pro-BNP (the amino terminal portion of the pro-hormone pro-BNP) has also been shown to have similar prognostic significance in patients with UA/NSTEMI (14–16). Jernberg et al. (14) studied 755 patients with UA/NSTEMI who had N-terminal pro-BNP measured on admission. During a median follow-up of 40 months, patients with elevated N-terminal pro-BNP had a higher mortality independent of clinical features, electrocardiographic changes, and troponin levels. Similar results were obtained by Omland et al. (15), who showed that elevated N-terminal pro-BNP was a powerful indicator of long-term mortality independent of age, Killip class, and LV ejection fraction. James et al. (16) studied 6,809 patients withUA/NSTEMI enrolled in the Global Utilization of Strategies To Open occluded arteries IV (GUSTO-IV) trial, who had N-terminal pro-BNP measured at a median time of 9.5 h after symptom onset. In this study, increasing
quartiles of N-terminal pro-BNP were independently associated with both short- and long-term mortality.

Despite the growing body of evidence demonstrating a strong association between elevated BNP in patients with UA/NSTEMI and increased risk of adverse outcomes, the underlying pathophysiologic mechanisms responsible for this adverse association are not well defined. Because BNP is released in response to increased intraventricular pressure or wall tension, in UA/NSTEMI patients with manifest heart failure or a decreased LV ejection fraction, elevated BNP reflects a greater degree of myocardial dysfunction and hence, not surprisingly, is associated with a greater risk of death and recurrent congestive heart failure. However, the association between elevated BNP and increased risk of adverse outcomes appears to be independent of heart failure or LV ejection fraction (12,13,15). Thus, mechanisms other than LV dysfunction may also play a role (20,21).

Several observations have suggested that elevated BNP may be a marker of the extent and severity of ischemia. Patients with proven coronary artery disease (CAD) have elevated BNP levels during dynamic exercise, as compared with patients without CAD (22). In a study of 35 patients with stable angina and CAD documented on coronary angiography and 35 control subjects with normal angiograms, plasma levels of BNP increased during thallium exercise testing in patients with angina and CAD, but did not change significantly in the control group. Further, a greater severity of myocardial perfusion defect on the thallium perfusion scans correlated with greater plasma levels of BNP. It has also been demonstrated that transient ischemia induced by percutaneous transluminal coronary angioplasty can lead to elevation of BNP even in the absence of demonstrable changes in LV systolic function or LV end-diastolic pressure (23,24). It has been speculated that ischemia may lead to altered regional myocardial stretch, causing active secretion of BNP (1).

We have previously shown that elevated BNP levels are associated with multi-vessel CAD (13). The results of this extended analysis demonstrate that UA/NSTEMI patients with elevated BNP have tighter culprit artery diameter stenoses, a higher CTFC, and a more LAD and proximal culprit lesion location. The tighter stenosis would predispose to more severe ischemia, and the association with a proximal/mid-LAD culprit lesion location suggests a larger extent of ischemia. The higher CTFC in patients with elevated BNP levels is most likely related to the severity of epicardial stenosis. The association of elevations of BNP with a greater severity and extent of ischemia may explain, at least in part, the adverse clinical outcomes of such elevation.

**Study limitations.** This is a retrospective subgroup analysis. The study population was small; hence, the data should be interpreted with caution. Assessment of LV function was not routinely available. Some of the angiographic findings may have been rendered nonsignificant because of the size of the study population. A prospective study of a larger population is desirable.

**Conclusions.** Elevated BNP in patients with UA/NSTEMI is associated with tighter culprit lesion diameter stenosis, higher (slower) CTFC, as well as an LAD and proximal culprit lesion location. These results suggest that elevated BNP may be associated with a greater severity and extent of myocardial ischemic territory during the index event.

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**REFERENCES**


