N-Terminal Pro–B-Type Natriuretic Peptide Levels for Dynamic Risk Stratification of Patients With Acute Coronary Syndromes

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Background—Elevated baseline levels of B-type natriuretic peptide (BNP) and the N-terminal fragments of its prohormone, N-terminal-pro-BNP (NT-proBNP), have been associated with adverse long-term outcome in patients with acute coronary syndromes, whereas the prognostic implications of serial NT-proBNP measurements have not been investigated to date.

Methods and Results—NT-proBNP, troponin T, and C-reactive protein were measured at baseline and at 48 and 72 hours in 1791 patients with non–ST-elevation acute coronary syndromes. Death and myocardial infarction were recorded during 30 days of follow-up. After adjustment for independent predictors of cardiac risk, baseline NT-proBNP levels >250 ng/L were associated with higher event rates (adjusted OR, 3.7; 95% CI, 2.3 to 5.7; P < 0.001). In troponin T–negative patients, NT-proBNP identified a subgroup of high-risk patients (OR, 5.9; 95% CI, 2.6 to 13.3; P < 0.001). The risk in those patients (7.2%) did not significantly differ from that in troponin T–positive patients (9.8%; P = 0.25).

Importantly, clinical stabilization without refractory ischemia was associated with a rapid (as soon as 48 hours after onset of symptoms) and significant (48 hours; −24%; 72 hours, −49%; both P < 0.001) decline in NT-proBNP levels. In patients with high NT-proBNP baseline levels, lack of a rapid decline in NT-proBNP levels (≤250 ng/L) was linked to an adverse short-term prognosis (OR, 33.7; 95% CI, 8.2 to 138.8; P < 0.001). In patients with low NT-proBNP baseline levels, a rise in NT-proBNP levels over 72 hours to >250 ng/L was also linked to an adverse 30-day prognosis (OR, 24.0; 95% CI, 8.4 to 68.5; P < 0.001).

Conclusions—Neurohumoral activation as evidenced by NT-proBNP appears as a unifying feature that is independent of other biochemical markers (myocardial necrosis, inflammation) and is a powerful and independent determinant of the short-term cardiac risk in patients with acute coronary syndromes. Whether serial measurements of NT-proBNP in patients with ACS may be used to more rapidly identify patients suitable for early discharge or more intensive therapy deserves future prospective studies. (Circulation. 2004;110:3206-3212.)

Key Words: peptides □ coronary disease □ risk factors □ ischemia □ prognosis

A cute coronary syndromes (ACS) encompass a continuum of cardiac ischemic events, ranging from unstable angina pectoris with no biochemical evidence of myocardial necrosis to ST-elevation acute myocardial infarction. The prognosis of patients with ACS varies widely, and clinical, ECG, and biochemical markers of adverse prognosis are used to identify patients who are at risk of developing a life-threatening cardiac event and who have predominant benefit from intensive antithrombotic and antiplatelet medical and interventional strategies.

In this regard, markers of myocardial cell necrosis, most notably cardiac troponin T (TnT) and troponin I, have become valuable tools in the evaluation of patients with ACS and have been implemented into the new guidelines as part of the risk stratification in patients with ACS. Recently, B-type natriuretic peptide (BNP) has been shown to provide significant prognostic information in patients with ACS. Increasing evidence suggests that the N-terminal fragment of the BNP prohormone (NT-proBNP) may also provide prognostic information in patients with ACS. It is unknown, however, whether serial NT-proBNP measurements provide additive prognostic information for the short-term clinical course and may predict clinical stabilization of the individual patient. Accordingly, we investigated the predictive value of...
NT-proBNP levels for short-term cardiac events in patients with ACS enrolled in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial.13

Methods

Patients

The study population of the PRISM trial was composed of patients with chest pain at rest or accelerating chest pain within the previous 24 hours. All patients had evidence of coronary artery disease as described previously.13 All patients received aspirin before randomization and were randomized to treatment with either tirofiban or heparin for 48 hours. Angiography and revascularization during 48 hours of infusion therapy were discouraged. The primary end point of the present study was a composite of mortality and myocardial infarction during 30 days of follow-up.13 Refractory ischemia was defined as recurrent anginal chest pain with ischemic ST-T-segment changes despite full medical therapy.13

Biochemical Analysis

In the 3232 patients enrolled in the PRISM trial, plasma samples for the determination of the cardiac markers were collected at baseline (n=1791), 48 hours (n=1401), and 72 hours (n=1401). TnT and NT-proBNP were quantified by use of a 1-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010, Roche Diagnostics).14 C-reactive protein (CRP) was determined with assay based on electrochemiluminescence technology (Elecsys 2010, Roche Diagnostics).14 C-reactive protein (CRP) was determined with the Hitachi 717 system (Roche Diagnostics).15 All samples were stored at −80°C before analysis, and the biomarker measurements were performed in samples that underwent only a single thaw cycle.

Statistical Analysis

Logistic regression analysis was used to estimate the relative risk for cardiovascular events, and patients were categorized into quartiles of NT-proBNP levels.16 Post hoc analysis of NT-proBNP quartiles was performed by use of the logistic regression model, with NT-proBNP quartiles as categorical variables and the first quartile serving as the reference group. Receiver-operating characteristics curve analysis over the dynamic range of the NT-proBNP assay was used to identify the threshold level for NT-proBNP providing the highest predictive value. The effect of baseline characteristics and other biochemical markers on any observed associations between NT-proBNP levels and cardiovascular events was analyzed with stepwise logistic regression models. Continuous variables are expressed as mean±SD. Comparisons between groups were analyzed by t test (2 sided). Comparison of categorical variables was generated by the Pearson χ² test. Values of P<.05 were considered statistically significant. All analyses were performed with SPSS 11.5 (SPSS Inc).

Results

Baseline blood samples were available for 1791 patients (55.4% of the entire study population); serial blood samples were available for 1401 patients (43.3% of the entire study population).13 The baseline characteristics of the substudy population were not different from those of the total study population with respect to age, gender, cardiovascular risk profile, and concomitant treatment before and after randomization. The reduction in cardiac events in the tirofiban group of the substudy populations was comparable to that of the entire PRISM study population.13

Baseline NT-proBNP Levels in Relation to Short-Term Cardiovascular Risk

All substudy patients were stratified into quartiles according to their measured baseline NT-proBNP levels (Figure 1). For the initial 48-hour period, the combined end points—death and myocardial infarction—did not significantly differ between the NT-proBNP quartiles (first quartile, 0.2%; second quartile, 0.7%; third quartile, 1.4%; fourth quartile, 1.6%). For the later follow-up time points (7 and 30 days, respectively), event rates were significantly higher in both the third (P=0.008 and P=0.002, respectively) and fourth (P=0.006 and P<.001, respectively) quartiles. Consistent with these results, receiver-operating characteristics curve analysis indicated a threshold level of 246 ng/L NT-proBNP for maximized predictive value. Accordingly, the patient sample was dichotomized with this calculated threshold level. There were significant differences for several baseline characteristics between patients with high and low baseline NT-proBNP levels (Table 1). The incidence of death or myocardial infarction was significantly higher in patients with elevated baseline NT-proBNP levels after 48 hours (1.5% versus 0.4%; P=0.029), after 7 days (5.3% versus 1.6%; P<.001), and after 30 days (9.8% versus 2.9%; P<.001). The predictive value of baseline NT-proBNP was maintained after adjustment for observed differences in baseline characteristics (adjusted OR, 3.7; 95% CI, 2.3 to 5.7; P<.001) and other biochemical markers including CRP and TnT (adjusted OR, 2.7; 95% CI, 1.7 to 4.3; P<.001) (Table 2). Most notably, the predictive value of baseline NT-proBNP was not restricted to the single end point of mortality (Figure 2, left). A similar difference was observed for the end point of nonfatal myocardial infarction (Figure 2, right). In patients without myocardial necrosis as evidenced by low TnT levels (<0.01 μg/L), NT-proBNP identified a group of patients with increased cardiac risk (crude event rates, 7.2% versus 1.3% for NT-proBNP−negative patients; OR, 5.9; 95% CI, 2.6 to 13.3; P<.001) (Figure 3). Even in patients with low TnT levels (0.01 to 0.1 μg/L), NT-proBNP identified a group of patients with increased cardiac risk (crude event rates, 15.1% versus 5.6% for NT-proBNP−negative patients; OR, 3.0; 95% CI, 1.4 to 6.5; P=.004) The data remained consistent even

![Figure 1. Association between baseline NT-proBNP and cardiac event rate during 30 days of follow-up (n=1791). Kaplan-Meier event rate curves showing cumulative incidence of death or nonfatal myocardial infarction according to baseline NT-proBNP quartiles. Range of baseline NT-proBNP levels was as follows: <75 ng/L for first quartile (n=461), 75 to 250 ng/L for second quartile (n=441), 251 to 759 ng/L for third quartile (n=442), and >759 ng/L for fourth quartile (n=447). Upper 2 NT-proBNP quartiles significantly differed from first NT-proBNP quartile (P<0.01).


after exclusion of patients with ST-segment depression. Patients who were negative for both biomarkers were at remarkably low risk (0.6% event rate at 30 days of follow-up). In contrast, in patients with high TnT levels (<0.1 µg/L), NT-proBNP did not serve as a significant predictor for patient outcome (P=0.58).

Effect of Tirofiban in Relation to Baseline NT-proBNP Levels

In patients with low baseline NT-proBNP levels, no difference in the rate of death or myocardial infarction was observed between patients randomized to tirofiban or control (48 hours, 0.2% versus 0.6%; P=0.63; 7 days, 2.7% versus 1.5%; P=1.00; 30 days, 2.8% versus 2.9%; P=1.00). In contrast, event rates were significantly higher in patients with high baseline NT-proBNP levels randomized to control and tended to be reduced by treatment with tirofiban at 48 hours (0.5% versus 2.5%; P=0.02) and at 7 days (3.4% versus 7.2%; P=0.09) of follow-up. This absolute difference in event rates of 3.8% between the 2 treatment groups was mostly maintained during the 30 days of follow-up (8.3% versus 11.2%; adjusted OR, 0.7; 95% CI, 0.5 to 1.1; P=0.18) (Figure 4). In TnT-negative patients (<0.1 µg/L), baseline NT-proBNP identified a subgroup of patients who suffered from increased cardiac risk (9.9% event rate at 30 days of follow-up). However, this subgroup of high-risk patients did not derive any clinical benefit from tirofiban treatment (adjusted OR, 1.1; 95% CI, 0.6 to 1.9; P=0.89) (Figure 4). Placebo patients negative for both TnT and NT-proBNP were at lowest risk (1.4% event rate at 30 days of follow-up). Although we observed a trend to a higher event rate if these patients were randomized to tirofiban treatment (adjusted OR, 2.2; 95% CI, 0.8 to 6.1; P=0.15), the present study was not powered to demonstrate a significant difference for such a low event rate.

### TABLE 1. Baseline Characteristics According to Baseline NT-proBNP Status

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th>Male gender, %</th>
<th>Age, y</th>
<th>Transient ST elevation</th>
<th>ST depression</th>
<th>T-wave inversion</th>
<th>Diabetes</th>
<th>Hypercholesterolemia</th>
<th>Hypertension</th>
<th>Smoking</th>
<th>History of CHF</th>
<th>History of CHD</th>
<th>Medication before enrollment, %</th>
<th>Aspirin</th>
<th>Heparin</th>
<th>Nitrates</th>
<th>β-Blockers</th>
<th>ACE inhibitors</th>
<th>Calcium antagonists</th>
<th>Statins</th>
<th>Biomedical markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤250 ng/L</td>
<td>68.4</td>
<td>59.9±10.9</td>
<td>6.9</td>
<td>22.1</td>
<td>40.5</td>
<td>22.3</td>
<td>49.6</td>
<td>57.0</td>
<td>70.6</td>
<td>6.1</td>
<td>43.5</td>
<td>93.6</td>
<td>20.2</td>
<td>75.7</td>
<td>47.7</td>
<td>21.3</td>
<td>48.1</td>
<td>14.7</td>
<td>0.09±0.29</td>
<td>0.04±1.61</td>
</tr>
<tr>
<td>&gt;250 ng/L</td>
<td>64.8</td>
<td>64.1±10.8</td>
<td>7.2</td>
<td>35.3</td>
<td>54.0</td>
<td>21.5</td>
<td>44.0</td>
<td>54.3</td>
<td>68.5</td>
<td>16.6</td>
<td>49.7</td>
<td>94.7</td>
<td>22.2</td>
<td>74.6</td>
<td>51.9</td>
<td>22.3</td>
<td>43.6</td>
<td>10.7</td>
<td>0.40±1.61</td>
<td>0.20±2.0</td>
</tr>
</tbody>
</table>

P < 0.001

CHF indicates congestive heart failure; CHD, coronary heart disease.

### TABLE 2. Multivariable Logistic Regression Model for Death or Nonfatal Myocardial Infarction During 30 Days of Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment depression</td>
<td>2.25</td>
<td>1.51–3.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TnT &gt;0.01 µg/L</td>
<td>2.03</td>
<td>1.29–3.20</td>
<td>0.002</td>
</tr>
<tr>
<td>NT-proBNP &gt;250 ng/L</td>
<td>2.68</td>
<td>1.66–4.34</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 2. Elevated levels of NT-proBNP at baseline were associated with both increased mortality (left) and increased incidence of myocardial infarction (right).

Figure 3. Predictive value of baseline NT-proBNP in relation to presence or absence of myocardial necrosis as evidenced by elevated levels of TnT (n=1791). *P<0.01 vs NT-proBNP ≤250 ng/L.
Severe Patients (n = 1401), biomarker levels were determined at baseline and at 48 and 72 hours. In this subset of patients, the predictive value of baseline NT-proBNP was similar to the predictive value observed for all patients with available baseline samples (adjusted OR, 3.7; 95% CI, 2.2 to 5.8; P < 0.001). Patients without major adverse cardiac events (death, nonfatal myocardial infarction) during the initial 72 hours (n = 1392) were divided into patients with refractory ischemia (n = 91) and those without refractory ischemia during the initial 72 hours (n = 1301). Patients without refractory ischemia showed a significant reduction in NT-proBNP levels at both 48 hours and 72 hours, respectively, whereas patients with refractory ischemia showed no significant change in NT-proBNP levels (Figure 5). In contrast, for TnT and CRP, no such pattern was observed (data not shown). When the NT-proBNP status of the patients was reevaluated after 72 hours, a marked improvement in the prediction of short-term cardiovascular risk was obtained. In patients with low NT-proBNP values at baseline, a second blood sample at 72 hours identified an additional set of patients (n = 85) at high risk for cardiovascular event during the subsequent 27 days of follow-up (NT-proBNP positive versus NT-proBNP negative, 16.5% versus 0.8%; P < 0.001) (Figure 6, left). On the other hand, in patients with high NT-proBNP levels at baseline, a low NT-proBNP level in the blood sample at 72 hours identified about half of the patients (n = 327) as being at low risk during the subsequent 27 days, whereas those patients who remained with a high NT-proBNP level at 72 hours (n = 367) were at strikingly high risk for cardiac events after 27 days of follow-up (NT-proBNP positive versus NT-proBNP negative, 17.2% versus 0.6%; P < 0.001) (Figure 6, right).

The predictive value of a second NT-proBNP sample collected after 72 hours was consistent for the separate end points of death or myocardial infarction. In patients with high NT-proBNP at baseline, mortality was 9.3% for patients who remained positive for NT-proBNP on day 3 compared with 0.6% for NT-proBNP negative patients on day 3 (P < 0.001). The crude event rates for the end point of nonfatal myocardial infarction were 10.1% and 0.3% (P < 0.001). In patients with low NT-proBNP at baseline, mortality was 7.1% for NT-proBNP–positive patients on day 3 compared with no death for NT-proBNP–negative patients on day 3 (P < 0.001). The crude event rates for the end point of nonfatal myocardial infarction were 10.6% and 0.8% (P < 0.001).

Discussion

Here, we demonstrate in a heterogeneous population of patients with non–ST-elevation ACS that serial measurements of NT-proBNP, a marker for neurohumoral activation, significantly enhance the predictive value compared with a single baseline NT-proBNP measurement. In addition to the baseline NT-proBNP sample, a second blood sample drawn up to 72 hours after the onset of symptoms provides important information about the further clinical course of the patients. Importantly, the predictive value of NT-proBNP was not restricted to the single end point of mortality but also predicted nonfatal myocardial infarctions during 30 days of follow-up. A rapid decline in NT-proBNP levels may indicate responsiveness to the therapeutic regimen that was chosen for the individual patient and thus may explain the reduced event rates observed in patients with declining NT-proBNP levels during the first days after symptom onset. None of the other investigated biomarkers (TnT and CRP) demonstrated a similar pattern during clinical stabilization of the patients. These data suggest for the first time that serial measurements of NT-proBNP in patients with ACS can be used for dynamic risk assessment and may be helpful for rapidly identifying patients who are suitable for early discharge or who may need
more intensive therapy, including intervention, although the data at present are contraindicating.17,18

After the description of elevated levels of BNP and NT-proBNP in patients with congestive heart failure, several investigations focused on the prognostic value of neurohormonal activation in the setting of acute myocardial infarction. More recently, however, the prognostic implications of BNP and NT-proBNP have also been extended to patients with non–ST-elevation ACS. In a first small case-control study of patients with non–ST-elevation ACS, NT-proBNP levels were higher among patients who died than those who survived.19 In the Orbofiban in Patients With Unstable Coronary Syndromes (OPUS)-TIMI 16 trial in which BNP was measured at the time of arrival in the emergency room were strongly associated with long-term mortality, again independently of the index diagnosis.10 A more recent study in patients with stable coronary heart disease demonstrated that elevated levels of BNP are independently associated with inducible ischemia.20 Data from the present analysis of the PRISM population are consistent in that we also found that NT-proBNP levels related to effects of any treatment initiated after the onset of ACS.

BNP and NT-proBNP also did not provide any prognostic information. These data appear to be in contrast to our findings from the present study indicating that serial NT-proBNP measurements are superior to a single NT-proBNP value obtained at baseline. However, it is important to note that the serial blood samples in the PRISM trial were collected at far later time points of up to 72 hours compared with the 6-hour values in the study by Jernberg and coworkers.10 Most likely, the 6-hour time period was too short to monitor changes in NT-proBNP levels related to effects of any treatment initiated after the onset of ACS.

Figure 6. Dynamic risk assessment in patients with ACS using serial NT-proBNP measurements (n = 1392 patients without death or nonfatal myocardial infarction during initial 72 hours). Despite NT-proBNP levels ≤250 ng/L at baseline, an increase in NT-proBNP levels during the following 72 hours indicated an adverse clinical course for these patients (left). In contrast, in patients with NT-proBNP levels >250 ng/L at baseline, rapid decline over the following 72 hours indicated low cardiac risk during the subsequent 27 days, whereas patients with consistently high NT-proBNP levels continued to be at increased cardiac risk (right). Dotted lines indicate event rate curves based on baseline NT-proBNP levels. Only patients with available serial blood samples were considered for this analysis.
In patients with suspected ACS, BNP and NT-proBNP clearly add important and unique prognostic information, but to date we do not know how this information should be translated into clinical practice because no therapeutic strategy for these high-risk patients with elevated levels of BNP and NT-proBNP has been developed. Because BNP levels are associated with left ventricular dysfunction and the extent of coronary disease, one might expect that patients presenting with non-ST-elevation ACS and elevated levels of BNP and NT-proBNP may derive incremental benefit from an early invasive strategy, as has been demonstrated for troponins.2,3,24 However, a report from the Treat Angina With Aggrastat and Determine Costs of Therapy With Invasive or Conservative Strategies (TACTICS–TIMI 18) study does not support this hypothesis. There was no difference in the benefit of the early invasive strategy on mortality between patients with and without BNP elevation.17,25 However, this study had no overall effect on mortality. In contrast, a sub-study of the FRISC II study (which did show an overall benefit of intervention on mortality) showed that intervention reduced mortality outcomes in patients with elevated BNP but not in patients without elevated BNP.18 In the present study, we did not find a significant interaction between NT-proBNP levels and the clinical benefit of glycoprotein IIb/IIIa inhibition by tirofiban. Whereas the prognostic association between BNP and NT-proBNP and subsequent myocardial infarction, heart failure, and death has clearly been demonstrated, directed efforts with prospective randomized trials are now needed to address the therapeutic implications of neurohumoral activation in patients with ACS.


In conclusion, we demonstrate that neurohumoral activation as evidenced by NT-proBNP elevation is an independent and powerful determinant of the short-term cardiac risk in patients with ACS. Serial measurements of NT-proBNP in patients with ACS may be used for monitoring the clinical course of the patients. If future prospective studies confirm that those patients are indeed at very low risk for cardiovascular events during short-term follow-up, serial NT-proBNP levels may be helpful for rapidly identifying patients who are suitable for early discharge.

Acknowledgments

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References


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