N-Terminal Pro-Brain Natriuretic Peptide on Admission Has Prognostic Value Across the Whole Spectrum of Acute Coronary Syndromes

Marcello Galvani, MD; Filippo Ottani, MD; Luigi Oltrona, MD; Diego Ardissino, MD; Gian Franco Gensini, MD; Aldo P. Maggioni, MD; Pier Mannuccio Mannucci, MD; Nicola Mininni, MD; Maria Domenica Prando, MD; Marco Tubaro, MD; Aialdo Vernocchi, PhD; Carlo Vecchio, MD; on behalf of the Italian Working Group on Atherosclerosis, Thrombosis, and Vascular Biology and the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)

Background—The prognostic value of natriuretic peptide elevations in patients with acute coronary syndromes (ACS) is still incompletely defined. We measured N-terminal pro-brain natriuretic peptide (NT-proBNP) on admission in patients with ACS and ECG evidence of myocardial ischemia.

Methods and Results—The NT-proBNP was measured at a median time of 3 hours after symptom onset in 1756 patients. The outcome measure was death at 30 days, which occurred in 113 patients (6.4%). The median NT-proBNP level was 353 ng/L (107 to 1357 ng/L). Compared with the lowest quartile, patients in the second, third, and fourth quartiles had a relative risk of subsequent death of 2.94 (95% CI, 1.15 to 7.52), 5.32 (95% CI, 2.19 to 12.91), and 11.5 (95% CI, 4.90 to 26.87), respectively. The NT-proBNP was independently associated with death in a logistic regression model, which included clinical variables, ECG, and troponin T in patients either with (OR of highest versus lowest quartile, 7.0; 95% CI, 1.9 to 25.6) or without (OR of highest versus lowest quartile, 4.1; 95% CI, 1.1 to 14.6) persistent ST-segment elevation. NT-proBNP was also an independent predictor of severe heart failure.

Conclusions—The measurement of NT-proBNP on admission improves the early risk stratification of patients with ACS, suggesting the need for the development of targeted therapeutic strategies. (Circulation. 2004;110:128-134.)

Key Words: natriuretic peptides ■ myocardial infarction ■ prognosis

Optimal risk stratification of patients with acute coronary syndromes (ACS) is of paramount importance to deliver appropriate care according to risk categories in patients both with and without persistent ST-segment elevation.1,2 Risk prediction based on clinical, ECG, and biochemical, ie, cardiac troponin, markers, however, is relatively inaccurate.3 B-type natriuretic peptide (BNP) is a circulating cardiac hormone released mainly from the ventricles in response to increased wall stretch.4 The BNP is produced as a prohormone, proBNP, which on secretion is split into BNP and N-terminal BNP (NT-proBNP). In patients, the proportional and absolute increases of NT-proBNP exceed those of BNP, suggesting that NT-proBNP may be a more sensitive marker of left ventricular (LV) dysfunction.5

The measurement of both BNP and NT-proBNP has been shown to be useful in detecting LV dysfunction,6,7 particularly after acute myocardial infarction (AMI), and to be related to poor outcome.8 It was recently shown that BNP and NT-proBNP also provide important prognostic information in patients with non–ST-segment elevation AMI or unstable angina pectoris.9–11

In the present study, we evaluated the short-term prognostic value of the early measurement of NT-proBNP in a wide cohort of patients encompassing the whole spectrum of ACS.

Methods

Study Population
We studied patients included in the EMAI study (The Early prognostic value of biochemical markers of Myocardial damage, Activation of hemostatic mechanism and Inflammation in acute ischemic syndromes study), a multicenter, nationwide study on biomarkers in ACS. We enrolled patients admitted to 31 Italian coronary care units with rest anginal pain lasting more than 10 minutes and occurring within 24 hours before admission, and associated with ischemic ECG changes.
Patient enrollment started March 1, 1998, and ended June 30, 1999. The study protocol was approved by the institutional ethics committees, and all patients gave written informed consent to participate.

Resting ECG
The patients were divided into 4 mutually exclusive groups based on the ECG findings at presentation: (1) isolated T-wave inversions of more than 0.1 mV; (2) ST-segment depression ≥0.05 mV; (3) transient (less than 30 minutes) ST-segment elevation of at least 0.05 mV in at least 2 contiguous leads; and (4) persistent (more than 30 minutes) ST-segment elevation. Patients with left bundle-branch block were included in the group with persistent ST-segment elevation.

Definitions
Myocardial infarction (MI) as the index event was defined as creatine kinase (CK)-MB levels twice the upper reference limit in at least 2 blood samples collected within 16 hours after arrival. Subsequent MI was considered to be present in the case of recurrence of symptoms associated with new ST-T abnormalities and CK-MB levels twice the upper reference limit. Recurrent ischemic events were the combination of subsequent MI and recurrent angina (defined as recurrent chest pain associated with ST-T changes not satisfying the biochemical criteria for MI).

Severe heart failure was defined as the occurrence of acute pulmonary edema or cardiogenic shock.

Renal insufficiency was defined as a baseline creatinine value ≥2 mg/dL.

Laboratory Analysis
Blood samples were collected in tubes without anticoagulant. The samples were then centrifuged, and serum was stored frozen in aliquots at −70°C within 30 minutes. Serum cardiac troponin T (cTnT) (third-generation assay) and serum NT-proBNP (proBNP Sandwich immunoassay) were determined on an Elecsys 2010 (Roche Diagnostics). The analytical range of NT-proBNP assay extends from 5 to 35 000 ng/L. At our laboratory, the total coefficient of variation was 4.1% (n = 15) at a level of 140 ng/L and 5.8% (n = 18) at a level of 2700 ng/L.

CK-MB measurements were performed by local laboratories in each participating center, using commercial assays, at baseline and at 8, 16, and 24 hours after admission.

Study End Points and Follow-Up
The study end point was the occurrence of death at 30 days. Secondary end points were recurrent ischemic events and severe heart failure.

Follow-up was performed by outpatient visit in 97% of surviving patients and by telephone interview in the remaining 3%. Events were adjudicated by a clinical event committee unaware of results of the biochemical markers under study.

Statistical Analysis
Data analysis was performed using the Statistical Package for Social Sciences (SPSS 10.1) software (SPSS Inc). Patients were divided into quartiles on the basis of their NT-proBNP level. Differences in proportions were judged by χ² analysis. If not stated otherwise, continuous data are given as median value (25th to 75th percentile).

TABLE 1. Baseline Clinical Characteristics According to the Quartile of NT-proBNP

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NT-proBNP ≤107 ng/L (n = 441)</th>
<th>NT-proBNP 108–353 ng/L (n = 437)</th>
<th>NT-proBNP 354–1357 ng/L (n = 439)</th>
<th>NT-proBNP ≥1358 ng/L (n = 439)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>59 ± 11</td>
<td>65 ± 11</td>
<td>68 ± 11</td>
<td>73 ± 10</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>79 (18%)</td>
<td>103 (24%)</td>
<td>143 (33%)</td>
<td>183 (42%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>63 (14%)</td>
<td>69 (16%)</td>
<td>109 (25%)</td>
<td>117 (27%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>180 (41%)</td>
<td>207 (48%)</td>
<td>239 (54%)</td>
<td>277 (63%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>121 (27%)</td>
<td>155 (36%)</td>
<td>205 (47%)</td>
<td>240 (45%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>46 (10.4%)</td>
<td>91 (21%)</td>
<td>124 (28%)</td>
<td>130 (30%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous PCI/CABG, n (%)</td>
<td>24 (6%)</td>
<td>44 (19%)</td>
<td>65 (15%)</td>
<td>35 (8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous CHF, n (%)</td>
<td>3 (1%)</td>
<td>9 (2%)</td>
<td>15 (3%)</td>
<td>43 (10%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Kilip class &gt; 1</td>
<td>28 (6%)</td>
<td>41 (9%)</td>
<td>62 (14%)</td>
<td>112 (26%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>SBP &lt;100 mm Hg</td>
<td>38 (8.7%)</td>
<td>26 (6.1%)</td>
<td>22 (5.9%)</td>
<td>38 (8.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>HR ≥100 bpm</td>
<td>21 (1.2%)</td>
<td>17 (1.0%)</td>
<td>33 (1.9%)</td>
<td>84 (4.8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Laboratory findings, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB &gt; URL</td>
<td>117 (27%)</td>
<td>136 (31%)</td>
<td>177 (40%)</td>
<td>218 (50%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>cTnT ≥0.1 μg/L</td>
<td>74 (17%)</td>
<td>124 (29%)</td>
<td>193 (44%)</td>
<td>280 (64%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>5 (1%)</td>
<td>9 (2%)</td>
<td>24 (6%)</td>
<td>62 (14%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>39 (9%)</td>
<td>42 (10%)</td>
<td>47 (11%)</td>
<td>48 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Transient ST-segment elevation</td>
<td>63 (14%)</td>
<td>60 (14%)</td>
<td>73 (17%)</td>
<td>74 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>ST-segment depression ≥0.05 mV</td>
<td>110 (25%)</td>
<td>131 (30%)</td>
<td>173 (39%)</td>
<td>196 (45%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Persistent ST-segment elevation</td>
<td>229 (33%)</td>
<td>204 (29%)</td>
<td>146 (21%)</td>
<td>121 (17%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Index diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>207 (34%)</td>
<td>183 (30%)</td>
<td>128 (21%)</td>
<td>97 (16%)</td>
<td></td>
</tr>
<tr>
<td>NSTE-ACS, n (%)</td>
<td>234 (21%)</td>
<td>254 (22%)</td>
<td>309 (27%)</td>
<td>341 (30%)</td>
<td></td>
</tr>
<tr>
<td>Time from pain onset to blood sampling, mean (interquartile range)</td>
<td>135 (150)</td>
<td>150 (182)</td>
<td>220 (330)</td>
<td>270 (403)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CK-MB, creatine kinase myocardial isoenzyme; cTnT, cardiac troponin T; HR, heart rate; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and URL, upper reference limit.
Comparison of continuous data in 2 or more independent groups was performed with the Mann-Whitney U test and Kruskal-Wallis ANOVA, respectively. NT-proBNP and different variables were correlated with the Spearman rank-correlation coefficient. The Kaplan-Meier method was used to analyze the timing of events with log-rank test comparisons.

To assess the predictive value of NT-proBNP and TnT, receiver operating characteristic (ROC) curves were generated, and the area under the curves (AUC) was calculated. Optimal discrimination limits were identified at the cutpoint that maximizes sensitivity and specificity.

To identify independent predictors of outcome, all variables with a value of $P<0.10$ were tested in a multivariate logistic regression analysis using backward stepwise selection. Variables were entered if $P<0.05$ and removed if $P>0.10$.

**Results**

One thousand nine hundred seventy-one patients were enrolled in the EMAI study. Serum samples for determination of NT-proBNP were available in 1756 patients (89.1%); their clinical characteristics and 30-day outcomes were similar to those of the 206 patients excluded.

Six hundred fifteen patients (35.0%) had ST-segment elevation MI (STEMI), and 1138 patients (64.8%) had no ST-segment elevation ACS (NSTE-ACS). In 3 patients (0.2%), the index diagnosis was not specified.

The NT-proBNP ranged from 5 to >35 000 ng/L, with a median of 354 ng/L (107 to 1358 ng/L); the median time from symptom onset to blood sampling was 3.0 hours (1.8 to 6.0 hours). In patients with STEMI, the median NT-proBNP was 201 ng/L (80 to 741 ng/L); the median time from symptom onset to blood sampling was 2.5 hours (1.5 to 4.0 hours). In patients with NSTE-ACS, the median NT-proBNP was 506 ng/L (144 to 1801 ng/L); the median time from symptom onset to blood sampling was 3.5 hours (2.0 to 7.5 hours).

One hundred thirteen patients (6.4%) died within 30 days. Two hundred thirty-seven patients (13.5%) had recurrent ischemic events (51 subsequent MI, 213 recurrent angina), and 67 (3.8%) had severe heart failure.

**Association With Baseline Clinical Variables**

Table 1 shows the univariate association of NT-proBNP with clinical, ECG, and biochemical variables. In addition, there was a weak relation between NT-proBNP and time from symptom onset to blood sampling (Spearman $\rho=0.28$; 2-tailed $P=0.01$) and between NT-proBNP and creatinine (Spearman $\rho=0.23$; 2-tailed $P=0.01$).
Clinical Outcomes

Mortality
The unadjusted mortality rate increased directly across quartiles of NT-proBNP ($P<0.0001$) (Figure 1). This association was also highly significant in subgroups of patients who had STEMI and patients who had NSTE-ACS (Figure 2A). The same relationship was observed in the 1464 patients without a history of heart failure and in Killip class 1 at presentation (Figure 2B).

When stratification was based on the level of TnT, NT-proBNP remained associated with a higher 30-day mortality in both STEMI and NSTE-ACS patients, particularly among the 1077 patients with TnT <0.1 µg/L ($P=0.0001$) (Figure 3).

Table 2 shows the univariate and multivariate predictors of 30-day death. In the logistic regression model, in which we adjusted for the other independent predictors, NT-proBNP remained associated with an increased risk. No interaction was found between NT-proBNP and treatment options (including thrombolytic therapy, performed in 61% of patients with STEMI, and in-hospital revascularization, performed in 16.2% of the study population). In addition, there was no significant interaction between NT-proBNP and creatinine. When age, systolic blood pressure, TnT, and NT-proBNP were entered into the logistic regression model as continuous variables, NT-proBNP was still an independent predictor of death ($Wald 8.09; P=0.0044$). Furthermore, NT-proBNP was independently associated with death in patients with both STEMI and NSTE-ACS (Figure 4).

Ischemic Events
The incidence of subsequent MI and recurrent ischemic events increased according to NT-proBNP quartiles (from 2.3% to 3.6%, $P=NS$, and from 10.6% to 18.6%, $P=0.005$, respectively). The risk of subsequent MI was not independently predicted by any variable. Previous MI, age $\geq 70$
years, systolic blood pressure <100 mm Hg, troponin-T quartiles, and ST-segment depression, but not NT-proBNP quartiles, constituted independent predictors of recurrent ischemic events. The results were unchanged with NT-proBNP as a continuous variable.

**Severe Heart Failure**
The incidence of severe heart failure increased according to NT-proBNP quartiles (from 2.1% to 9.0%, P<0.0001). Previous MI, previous heart failure, Killip class >1, systolic blood pressure <100 mm Hg, age ≥70 years, the diagnosis of STEMI rather than NSTE-ACS, and NT-proBNP quartiles (Wald=11.552, P=0.009) were independent predictors of severe heart failure. The results were similar with NT-proBNP as a continuous variable (Wald=5.572, P=0.018).

**Prognostic Accuracy of NT-proBNP**
The AUC of NT-proBNP (0.727; 95% CI, 0.680 to 0.775) was significantly higher than that of cTnT (0.658; 95% CI, 0.604 to 0.712) (P=0.01) (Figure 5A). The NT-proBNP value yielding maximal sensitivity (78.9%) and specificity (56.7%) was 437 ng/L. The AUC of NT-proBNP for patients without a history of previous heart failure in Killip class 1 at presentation (n=1468) was similar to that of the general population (0.719; 95% CI, 0.653 to 0.766). The prognostic accuracy of NT-proBNP was similar in patients with STEMI (0.747; 95% CI, 0.680 to 0.814) and NSTE-ACS (0.735; 95% CI, 0.674 to 0.797) (Figure 5B). In patients with STEMI, the NT-proBNP value associated with maximal sensitivity (70.8%) and specificity (69.0%) was 437 ng/L; in patients with NSTE-ACS, it was 794 ng/L (sensitivity, 76.9%; specificity, 61.9%).

**Discussion**
In this study, we have demonstrated that the early measurement of NT-proBNP provides important and independent information for risk stratification across the entire spectrum of ACS. To the best of our knowledge, this is the first time that elevations of NT-proBNP early after symptom onset are shown to have a profound and independent impact on short-term mortality and severe heart failure in STEMI.
patients. Such findings may have important implications for immediate management of high-risk patients with ACS.

Prognostic Value of Natriuretic Peptides in ACS

Previous studies had shown the prognostic value of natriuretic peptides, measured in the subacute phase, on mortality of patients with ACS ranging from STEMI to unstable angina. The value of early measurement of BNP and NT-proBNP has been less extensively studied.

Our results, obtained at the earliest time from symptom onset, are in keeping with previous studies. In particular, they confirm the prognostic value of natriuretic peptides even in patients without heart failure as detected by patient history or at initial evaluation, the additional prognostic accuracy with respect to cardiac troponin, and the absence of predictive value for recurrent ischemic events. In addition to previous studies, however, we showed that NT-proBNP was an independent predictor of the short-term occurrence of severe heart failure and that it had independent prognostic value in patients with STEMI, with a prognostic accuracy similar to that observed in NSTE-ACS.

Significance of Early Measurement of NT-proBNP

The mechanisms potentially responsible for the strong association between NT-proBNP elevations and short-term mortality cannot be ascertained by the present study. However, BNP and NT-proBNP release may be triggered by transient or permanent ventricular dysfunction induced by myocardial ischemia. Moreover, the magnitude of the increase may reflect the extent of the ischemic injury, elevations being detected soon after the onset of myocardial ischemia. We measured NT-proBNP at a median time of 3 hours after the onset of ischemic symptoms. Such early increases may reflect the amount of the ischemic insult to the myocardium rather than the actual extent of myocardial necrosis. Accordingly, the prognostic accuracy of NT-proBNP was greater than that of TnT, suggesting that NT-proBNP may be considered as an early ischemic marker. Conversely, it is also possible that early NT-proBNP elevations reflect the consequences of repeated episodes of myocardial ischemia occurring in the past several hours or days.

Partially in contrast to cardiac troponin, NT-proBNP and BNP elevation is associated with several other risk factors for adverse outcome, including age, renal impairment, hypertension, and previous heart failure. As suggested by others, BNP and NT-proBNP may therefore also be considered a general marker for cardiac dysfunction.

It should be acknowledged that the prognostic value of NT-proBNP may be limited by the occurrence of elevations in clinical contexts different from myocardial ischemia, particularly in renal insufficiency. However, we were not able to show any significant interaction between NT-proBNP and creatinine.

NT-proBNP Prognostic Accuracy

The cutoff point derived from ROC analysis was very close to the median NT-proBNP level detected in our population, suggesting its use in clinical practice. However, because levels of NT-proBNP (and BNP) vary considerably according to index diagnosis and rise continuously during the first 24 hours, it is likely that prognostic cutoffs differ markedly according to these factors. We showed that patients with STEMI, having been admitted earlier, had lower NT-proBNP than patients with NSTE-ACS. Accordingly, the NT-proBNP cutoff in patients with STEMI was 1.8 times lower. Furthermore, it must be acknowledged that BNP and NT-proBNP concentrations differ by age, sex, and assay system.

Study Limitations

We measured NT-proBNP in preserved samples obtained in a large fraction (89%) of patients initially enrolled in our prospective study; this is an accepted methodology, which, however, has inherent limitations. Because we measured NT-proBNP only once, we cannot exclude that elevations preceded the index event. However, even after adjustment for variables such as the presence or absence of a history of hypertension, heart failure, and renal insufficiency, the level of NT-proBNP remained predictive of the short-term risk of death. Furthermore, the lack of LV function data is an objective limitation of our study.

Conclusions

Our data suggest that NT-proBNP levels, measured at admission early after the onset of the ischemic episode, are strongly predictive of short-term mortality in patients with ACS. Our results have practical implications, because the electrochemiluminescence immunoassay we used has become commercially available. It is necessary, however, to wait for the results of future studies addressing the value of NT-proBNP measurements as a guide to different therapeutic strategies in patients with ACS to definitely establish the clinical value of NT-proBNP in acute myocardial ischemia. Such evidence is, at the present time, still conflicting.

Appendix

Study Chairmen
M. Galvani and L. Oltrona.

Steering Committee

Coordinating Center
Fondazione Sacco, Forlì: D. Ferrini, C. Nanni, A. Ramberti; Executive Center: Centro Studi ANMCO, Firenze: D. Lucci; Clinical Events Committee: M. Carli, R. Puggioni; Statistics: A. Morabito, Milano; Monitoring Center: Innovex, Monza: R. Candiani.

Participants
Acknowledgments
The authors thank Roche Diagnostics for having provided the kits for NT-proBNP and TnT measurement.

References
N-Terminal Pro-Brain Natriuretic Peptide on Admission Has Prognostic Value Across the Whole Spectrum of Acute Coronary Syndromes

Marcello Galvani, Filippo Ottani, Luigi Oltrona, Diego Ardissino, Gian Franco Gensini, Aldo P. Maggioni, Pier Mannuccio Mannucci, Nicola Mininni, Maria Domenica Prando, Marco Tubaro, Atrialdo Vernocchi and Carlo Vecchio on behalf of the Italian Working Group on Atherosclerosis, Thrombosis, and Vascular Biology and the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)

_Circulation_. 2004;110:128-134; originally published online June 14, 2004;
doi: 10.1161/01.CIR.0000134480.06723.D8

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/110/2/128

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/