Natriuretic Peptides as Predictors of Non-Sudden and Sudden Cardiac Death After Acute Myocardial Infarction in the Beta-Blocking Era

Jari M. Tapanainen, MD,* Kai S. Lindgren, MD,* Timo H. Mäkikallio, MD,* Olli Vuolteenaho, MD,† Juhani Leppäläuoto, MD,‡ Heikki V. Huikuri, MD, FACC*

Oulu, Finland

OBJECTIVES This prospective study tested whether the natriuretic peptides predict cardiac death among patients using beta-blocking therapy after an acute myocardial infarction (AMI).

BACKGROUND Natriuretic peptides have provided prognostic information after AMI, but their predictive value has not been well established in the era of beta-blocker use.

METHODS A series of 521 patients (mean age 61 ± 10 years) with AMI was included in the study. The end points were total mortality and non-sudden and sudden cardiac death (SCD). Plasma concentrations of atrial natriuretic peptide (ANP), N-terminal atrial natriuretic propeptide (N-ANP), brain natriuretic peptide (BNP), and ejection fraction (EF) were analyzed before hospital discharge. The cardiac medication was optimized (e.g., adherence to beta-blocking therapy was 97% at discharge and 95% at one year after AMI).

RESULTS During a mean follow-up of 43 ± 13 months, total mortality was 11.5% (60/521), cardiac mortality was 6.3% (33/521), and 3.1% (16/521) experienced SCD. On univariate analysis, high levels of all measured peptides and low EF predicted the occurrence of non-SCD (p < 0.001 for all). Peptides and EF also predicted the occurrence of SCD (p < 0.05), with elevated BNP (>23.0 pmol/l) being the most powerful predictor (hazard ratio [HR] 4.4, 95% confidence interval [CI] 1.4 to 13.8; p = 0.01). After adjusting for clinical variables, only elevated BNP (HR 3.9, 95% CI 1.2 to 12.3, p = 0.02) and low EF (<40%) (p = 0.03) remained as significant predictors of SCD.

CONCLUSIONS Natriuretic peptides retain their prognostic value in the beta-blocking era among survivors of AMI. Elevated BNP provides information on the risk of subsequent SCD, independent of clinical variables and left ventricular EF. (J Am Coll Cardiol 2004;43:757–63) © 2004 by the American College of Cardiology Foundation

Changes in the neuroendocrine system and various neurohormonal markers, such as natriuretic peptides, have been shown to provide prognostic information among patients surviving an acute myocardial infarction (AMI). Concentrations of atrial (A-type) natriuretic peptide (ANP), N-terminal pro-ANP (N-ANP), brain (B-type) natriuretic peptide (BNP), and N-terminal pro-BNP (N-BNP) have been shown to predict both total and cardiac mortality when measured after AMI (1–9). However, a majority of the studies assessing the prognostic power of vasoactive peptides were performed in the era before the introduction of optimal medical therapy (e.g., beta-blocking therapy), which has major influences on the outcome of post-AMI patients, particularly on the incidence of sudden cardiac death (SCD) (10–13). Therefore, their prognostic significance among patients treated with contemporary guidelines is not well established.

From the *Division of Cardiology, Department of Internal Medicine, Oulu University Hospital, Oulu; and †Department of Physiology, Oulu University, Oulu, Finland. This study was supported by grants from Aarne and Aili Turunen's Foundation, the Finnish Foundation for Cardiovascular Research, and the Medical Council of the Finnish Academy of Science, Helsinki, Finland. Melvin D. Cheitlin, MD, acted as Guest Editor of this paper.

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METHODS

Patients. A single-center prospective study—the Multiple Risk Factor Analysis Trial (MRFAT)—was started in 1996 at the Division of Cardiology, University of Oulu, aiming to determine the prognostic power of several noninvasive risk
markers of mortality in patients who had survived an AMI. The results of the predictive power of specific arrhythmia risk variables in the same population have been reported earlier (21,22). The patients were recruited to participate during the first seven days after AMI. The qualifying diagnosis and inclusion and exclusion criteria have been described in detail in previous reports (21,22). The present study describes the results of patients who consented to a substudy assessing the prognostic power of natriuretic peptides.

To optimize treatment, aspirin (or warfarin) and beta-blocking drugs were given to all patients, angiotensin-converting enzyme inhibitors to patients with a left ventricular ejection fraction (EF) below 40%, and lipid-lowering agents to patients with increased levels of total cholesterol, whenever no contraindications for such medications existed and the patients consented to start the medication. The dose of beta-blocking therapy was adjusted to achieve a resting heart rate between 50 and 60 beats/min. Special emphasis was paid to long-term adherence to the beta-blocking medication. All patients had a telephone contact at 6, 24, 36, 48, and 60 months after the AMI and a clinical visit at the outpatient clinic 12 months after AMI. During these contacts, the medication and symptoms of the patients were checked. All patients were required to give written, informed consent, and the study was approved by the Ethical Committee of the institution.

**Blood sampling and assay for natriuretic peptides.** The blood sample for natriuretic peptides was taken 7 ± 2 days after AMI through an intravenous cannula into EDTA vacuum tubes. The samples were placed on ice and centrifuged at 4°C for 10 min, and the plasma was stored at −70°C. The assay was performed as previously described (23,24).

**Left ventricular function.** Left ventricular systolic function was measured with two-dimensional echocardiography, using wall motion index analysis at three to seven days after AMI. A rough estimate of LVEF can be calculated by multiplying the wall motion index by 30. Details of this method and its use have been described earlier (21,25,26).

**End points.** The survival status was checked during the follow-up from the National Register of Mortality if the patient could not be contacted. In cases of death, the reasons for death were verified by hospital and autopsy records and by either relatives or the primary physicians who had witnessed the death. The mode of death was classified as cardiac or noncardiac, with cardiac mortality being the primary end point. The cardiac deaths were defined as sudden or non-sudden deaths by two independent investigators. Cardiac death was defined as “sudden” if it was: 1) a witnessed death occurring within 60 min from the onset of new symptoms, unless a cause other than cardiac was obvious; 2) an unwitnessed death (<24 h) in the absence of pre-existing progressive circulatory failure or other causes of death; or 3) a death during attempted resuscitation (25,26).

**Statistical analysis.** The data were analyzed using SPSS software (SPSS version 10.0, SPSS Inc., Chicago, Illinois). Univariate comparisons of the baseline characteristics between the deceased and survivors were performed with the chi-square test for categorical variables. For continuous variables, one-way analysis of variance was used with either the Bonferroni multiple comparison test or Tamhane’s T² test (27), depending on Levene’s statistic for homogeneity of variance (28). As for the Bonferroni test, up to four comparisons were included in

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**Table 1. Clinical Features of the Patients**

<table>
<thead>
<tr>
<th>Males/females</th>
<th>403/118 (77%/23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, mean ± SD)</td>
<td>61.1 ± 10.0</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>249 (48%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>108 (21%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>105 (20%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>29 (6%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>51 (10%)</td>
</tr>
<tr>
<td>COPD</td>
<td>39 (8%)</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>51 (10%)</td>
</tr>
<tr>
<td>Smoking (current or former)</td>
<td>359 (69%)</td>
</tr>
<tr>
<td>Features before discharge</td>
<td></td>
</tr>
<tr>
<td>Type of infarction</td>
<td></td>
</tr>
<tr>
<td>Q-wave</td>
<td>267 (51%)</td>
</tr>
<tr>
<td>Non-Q-wave</td>
<td>230 (44%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>Site of infarction</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>243 (47%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>234 (45%)</td>
</tr>
<tr>
<td>Indeterminate/other</td>
<td>44 (8%)</td>
</tr>
<tr>
<td>Thrombolytic therapy or primary PTCA</td>
<td>245 (47%)</td>
</tr>
<tr>
<td>NYHA class at discharge</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>455 (88%)</td>
</tr>
<tr>
<td>III/IV</td>
<td>62 (12%)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>504 (97%)</td>
</tr>
<tr>
<td>ACE inhibitors or AT II receptor antagonists</td>
<td>227 (44%)</td>
</tr>
<tr>
<td>In patients with EF &lt;40%</td>
<td>69 (84%)</td>
</tr>
<tr>
<td>ASA or warfarin</td>
<td>495 (95%)</td>
</tr>
<tr>
<td>Statins</td>
<td>235 (45%)</td>
</tr>
<tr>
<td>In patients with LDL cholesterol &gt;3.0 mmol/l</td>
<td>106 (72%)</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; AT II = angiotensinogen II; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; LDL = low-density lipoprotein; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack.
hazard regression analyses. Kaplan-Meier estimates of the

calculated for each categorical variable as a predictor of
groups.

ded from studies on diverse patient materials, and their

size. We did not use previously de

quartile of EF was chosen as another cut-off point for the

this, the highest quartile of vasoactive peptides

median value for EF. The value that resulted in

median value for vasoactive peptides and in fifth-percentile

steps up to the median value for EF. The value that resulted in

validity has not been proved in current post-AMI patient

vasoactive peptides, because these cut-off points have been

of SCD and non-SCD are shown in Table 3. Reduced EF

cardiac and sudden arrhythmic mortality in the Cox regres-

the analysis. The optimal cut-off points for all predictive

variables were determined as follows: various cut-off points

were tested in Cox regression analysis using cardiac death as

the end point. This was done in fifth-percentile steps above the

median value for vasoactive peptides and in fifth-percentile

steps up to the median value for EF. The value that resulted in

the statistically most significant hazard ratio (HR) in the Cox

analysis was chosen as the “best” cut-off value. In addition to

this, the highest quartile of vasoactive peptide—or the lowest

quartile of EF—was chosen as another cut-off point for the

survival analyses in order to generate subgroups of comparable

sizes. We did not use previously defined cut-off points for

vasoactive peptides, because these cut-off points have been
deducted from studies on diverse patient materials, and their

validity has not been proved in current post-AMI patient

groups.

The relative risk and 95% confidence interval (CI) were

calculated for each categorical variable as a predictor of

cardiac and sudden arrhythmic mortality in the Cox regres-

sion model. To estimate the independent power of the

variables in predicting cardiac and sudden arrhythmic mor-

tality, age, diabetes, and New York Heart Association

functional class were included in the Cox proportional

hazards regression analyses. Kaplan-Meier estimates of the
distribution of times from baseline to the end point were

computed, and log-rank analysis was performed to compare

the survival curves between the groups. A value p < 0.05

was considered significant.

RESULTS

A sample of 521 patients was included in the study. The

majority of them (97%) were receiving beta-blockers at

discharge, and 95% had continued receiving beta-blocking

therapy at one year after AMI. Other clinical characteristics

of the patients are shown in Table 1. Total mortality was

11.5% (60 of 521 patients) after the mean follow-up of 43 ±

13 months (range 12 to 60 months). Cardiac mortality was

6.3% (33 of 521 patients). The incidence of SCD during

this period was 3.1% (16 of 521 patients).

Univariate predictors of mortality. The mean values of

vasoactive peptides were significantly higher and EF was

lower among those who died from a cardiac cause, as

compared with survivors (Table 2). In general, peptides

were elevated among those who experienced either non-

SCD or SCD. However, the BNP level was not significantly

higher among those with non-SCD than among survivors.
The univariate relative risks of the test results as predictors of

SCD and non-SCD are shown in Table 3. Reduced EF

Table 3. Predictors of Sudden Cardiac Deaths and Non-Sudden Cardiac Deaths in Univariate and Multivariate Analyses (Adjusted for Age, Diabetes, and New York Heart Association Class)

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Sudden Cardiac Deaths</th>
<th>Non-Sudden Cardiac Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>ANP ≥67.5 pmol/l (highest quartile)</td>
<td>2.06</td>
<td>0.77–5.57</td>
</tr>
<tr>
<td>ANP ≥37.6 pmol/l (best cut-off)</td>
<td>4.12</td>
<td>1.33–12.82</td>
</tr>
<tr>
<td>N-ANP ≥786 pmol/l (highest quartile)</td>
<td>2.36</td>
<td>0.88–6.33</td>
</tr>
<tr>
<td>N-ANP ≥973 pmol/l (best cut-off)</td>
<td>3.39</td>
<td>1.23–9.32</td>
</tr>
<tr>
<td>BNP ≥33.9 pmol/l (highest quartile)</td>
<td>3.74</td>
<td>1.35–10.32</td>
</tr>
<tr>
<td>BNP ≥23.0 pmol/l (best cut-off)</td>
<td>4.38</td>
<td>1.39–13.77</td>
</tr>
<tr>
<td>EF &lt;40% (lowest quartile)</td>
<td>3.45</td>
<td>1.30–9.20</td>
</tr>
<tr>
<td>EF &lt;30% (best cut-off)</td>
<td>4.94</td>
<td>1.40–17.36</td>
</tr>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>RR</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>ANP ≥67.5 pmol/l (highest quartile)</td>
<td>1.76</td>
<td>0.64–4.81</td>
</tr>
<tr>
<td>ANP ≥37.6 pmol/l (best cut-off)</td>
<td>3.65</td>
<td>1.17–11.42</td>
</tr>
<tr>
<td>N-ANP ≥786 pmol/l (highest quartile)</td>
<td>1.80</td>
<td>0.63–5.09</td>
</tr>
<tr>
<td>BNP ≥33.9 pmol/l (highest quartile)</td>
<td>3.39</td>
<td>1.22–9.45</td>
</tr>
<tr>
<td>BNP ≥23.0 pmol/l (best cut-off)</td>
<td>3.89</td>
<td>1.23–12.33</td>
</tr>
<tr>
<td>EF &lt;40% (lowest quartile)</td>
<td>3.05</td>
<td>1.13–8.21</td>
</tr>
<tr>
<td>EF &lt;30% (best cut-off)</td>
<td>3.68</td>
<td>1.02–13.29</td>
</tr>
</tbody>
</table>

CI = confidence interval; RR = relative risk; other abbreviations as in Tables 1 and 2.
and high levels of all natriuretic peptides predicted both non-SCD and SCD during the follow-up period at the cut-off points tested.

**Multivariate predictors of mortality.** After adjusting for clinical variables, high levels of vasoactive peptides and reduced EF remained as independent predictors of cardiac mortality at all cut-off points tested (Table 3). Non-SCD was predicted by elevated ANP and N-ANP at both cut-off point levels. Elevated BNP was not a significant predictor of non-SCD. However, elevated BNP (at both cut-off point levels) predicted the occurrence of SCD, whereas elevated ANP and N-ANP were not as powerful predictors of SCD than non-SCD. Reduced EF similarly predicted both SCD and non-SCD (Table 3).

The levels of all measured natriuretic peptides had a significant inverse correlation (ANP: $r = -0.123$, $p < 0.01$; N-ANP: $r = -0.351$, $p < 0.001$; and BNP: $r = -0.370$, $p < 0.001$) to LVEF, but they still provided independent prognostic information after adding EF into the Cox regression model (e.g., elevated BNP at the best cut-off point predicted cardiac death [HR 2.97, 95% CI 1.29 to 6.83; $p = 0.01$] and SCD [HR 3.86, 95% CI 1.22 to 12.23; $p = 0.02$]).

The Kaplan–Meier survival curves for peptides and EF are shown in Figure 1. The cardiac mortality curves start to diverge already during the first months after discharge, and the difference between the patient groups remains throughout the follow-up time. In contrast, the SCD curves among the patients with and without elevated BNP levels start to diverge relatively late (>20 months) after AMI, the divergence becoming larger during longer follow-up (Fig. 2). Sensitivity, specificity, and negative and positive predictive accuracy of BNP, LVEF, and their combination as predictors of SCD are shown in Table 4.

![Figure 1](image-url)
Figure 2. Kaplan-Meier survival curves among patients with and without elevated brain natriuretic peptide (BNP).

DISCUSSION

The main findings of this study are that plasma levels of natriuretic peptides still retain their prognostic power among patients who are receiving beta-blocking medication. Furthermore, BNP also predicts the occurrence of SCD, independent of clinical variables and LVEF.

Natriuretic peptides as predictors of mortality. Natriuretic peptides have been shown to be strong predictors of cardiac and all-cause mortality after AMI (1–9,29,30). In most of the previous reports comparing the predictive accuracy between the different natriuretic peptides, BNP has been shown to be superior to N-ANP and ANP as a prognostic marker (2,8). Also, BNP has been shown to be more stable than ANP, with a longer half-life (31), and its reliability in indicating LV dysfunction after AMI is not as dependent on the time point of measurement as that of ANP or N-ANP (4).

In the present study, ANP and BNP performed somewhat better than N-ANP in predicting cardiac mortality. Of the three, BNP seemed to be the most specific in predicting SCD, but it was clearly inferior to ANP and N-ANP in predicting non-SCD. The time point of making the peptide measurement certainly has some effect on the predictive accuracy of vasoactive peptides because the secretion of natriuretic peptides varies with changes in hemodynamics in the immediate post-AMI period (4). Despite the relatively long time period between AMI and the taking of blood samples, the present results confirm the previous observation that vasoactive peptides provide prognostic information among post-AMI patients even when medical therapy is optimized according to current guidelines.

Prediction of SCD after AMI. Several risk markers, such as autonomic markers, the signal-averaged electrocardiogram (ECG), and T-wave alternans, have been extensively studied as predictors of SCD after AMI (14–16,21,22,32). Most of the studies have suggested that these variables provide information on the risk of subsequent SCD and arrhythmia events (14–16,32). However, the majority of these observational studies have been performed in the era without optimized medical therapy. For example, in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study, showing that autonomic markers predict subsequent sudden death, only ~20% of patients were receiving beta-blocking therapy (14). Similarly, only 13% of patients were receiving beta-blocking medication in studies showing that T-wave alternans after AMI predicts SCD (16,32). Our previous analyses of the same population as in the current study suggested that the arrhythmia risk variables, such as autonomic markers, signal-averaged ECG, and T-wave alternans, lose some of their predictive power among post-AMI patients with optimized beta-blocking therapy (21,22). In the light of these findings, the present observations suggest that elevated BNP may have some potential value in the prediction of SCD among the current post-AMI populations.

Elevated BNP and risk of SCD. A recent study including patients with chronic HF also showed that elevated BNP predicts the occurrence of SCD (20). There are some important differences between the previous and the present study. Patients with symptoms of HF and LVEF <35% were included in the previous study, and only 30% of the patients were using beta-blocking medication. The present study confirms that BNP also predicts SCD—indeed, of clinical HF and reduced EF—among the post-AMI patients.

There may be several reasons why BNP provides more specific information on the risk of SCD than the other peptides, or even measurement of LV systolic function. Both ANP and N-ANP are more closely related to atrial...

Table 4. Sensitivity, Specificity, and Positive, Negative, and Overall Predictive Accuracies of Brain Natriuretic Peptide and Left Ventricular Systolic Function for Prediction of Sudden Cardiac Death at Different Cut Points

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>Positive Predictive Accuracy (%)</th>
<th>Negative Predictive Accuracy (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP ≥23.0 pmol/l (60th percentile)</td>
<td>61.3</td>
<td>73.3</td>
<td>5.4</td>
<td>98.7</td>
<td>61.6</td>
</tr>
<tr>
<td>BNP ≥33.9 pmol/l (highest quartile)</td>
<td>75.8</td>
<td>53.3</td>
<td>6.2</td>
<td>98.2</td>
<td>75.2</td>
</tr>
<tr>
<td>EF &lt;40% (lowest quartile)</td>
<td>76.8</td>
<td>50.0</td>
<td>6.4</td>
<td>98.0</td>
<td>76.0</td>
</tr>
<tr>
<td>EF &lt;30% (5th percentile)</td>
<td>95.0</td>
<td>18.8</td>
<td>10.7</td>
<td>97.4</td>
<td>92.7</td>
</tr>
<tr>
<td>Combination of BNP ≥23.0 pmol/l and EF &lt;40%</td>
<td>85.2</td>
<td>40.0</td>
<td>7.5</td>
<td>97.9</td>
<td>83.9</td>
</tr>
<tr>
<td>Combination of BNP ≥23.0 pmol/l and EF &lt;30%</td>
<td>96.4</td>
<td>20.0</td>
<td>14.3</td>
<td>97.6</td>
<td>94.1</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 2.
volume loading, whereas BNP secretion from the ventricles is increased during progressing HF (33,34) and is released from the ventricles in response to increased pressure, stretch, and hypertrophy (35). Ventricular stretch, hypertrophy, and fibrosis can have significant influences on cardiac electrophysiologic properties via mechano-electrical feedback (36–39). Thereby, BNP may be an indirect marker of the mechanical factors predisposing to the onset and perpetuation of life-threatening arrhythmias. This is also supported by an observation that BNP specifically predicted the occurrence of SCD late after the index event. It is possible that elevated BNP is a marker of LV remodeling occurring late after AMI, which then predisposes to sudden arrhythmic death.

Clinical implications. A significant proportion of post-AMI patients, even with adequate treatment, are still at high risk of dying during the first few years after AMI. The prediction and prevention of SCD is of particular importance because recent large-scale randomized trials have documented the mortality benefit from prophylactic ICD therapy in certain high-risk subgroups of patients (19). Recently, Berger et al. (20) proposed the use of BNP measurements for determining which patients might benefit from ICD placement in chronic HF. The positive predictive accuracy of elevated BNP alone in our post-AMI population remained relatively low, preventing the recommendations for widespread screening of the candidacy for ICD therapy based only on the measurement of BNP. Furthermore, the accuracy of a low BNP plasma concentration as a predictor of survival with low risk of SCD was excellent, suggesting that this simple measurement could be used for screening purposes to exclude the risk of future SCD and the need for further risk stratification. The present data suggest that BNP should also be included as one of the risk variables in future studies comparing the various indexes as predictors of SCD.

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Reprint requests and correspondence: Dr. Heikki V. Huikuri, Professor of Medicine, Division of Cardiology, Department of Internal Medicine, Oulu University Hospital, Kajaanintie 50, 90220 Oulu, Finland. E-mail: heikki.huikuri@oulu.fi.

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