B-Type Natriuretic Peptides and Ejection Fraction for Prognosis After Myocardial Infarction

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Background—A recent landmark report has demonstrated that plasma B-type natriuretic peptide (BNP) measured in acute coronary syndromes independently predicts mortality, heart failure, and new myocardial infarction. After acute cardiac injury, left ventricular ejection fraction (LVEF) is also of prognostic significance and plays a major role in determining the therapeutic response.

Methods and Results—The present report is the first from a substantial (n=666) cohort of patients with acute myocardial infarction to test the prognostic utility of concurrent measurements of BNP, amino-terminal BNP (N-BNP), norepinephrine, and radionuclide LVEF. The B-type peptides and LVEF were predictors of death, heart failure, and new myocardial infarction (all P<0.001) independent of patient age, gender, previous myocardial infarction, antecedent hypertension or diabetes, previous heart failure, plasma norepinephrine, creatinine, cholesterol, drug therapy, and coronary revascularization procedures. The combination of N-BNP (or BNP) with LVEF substantially improved risk stratification beyond that provided by either alone. Elevated N-BNP (or BNP) predicted new myocardial infarction only in patients with LVEF ≤40%. LVEF ≤40% coupled to N-BNP over the group median conferred substantial 3-year risks of death, heart failure, and new myocardial infarction of 37%, 18%, and 26%, respectively. N-BNP and BNP were equivalent prognostic markers for these clinical outcomes.

Conclusions—Plasma N-BNP (or BNP) and LVEF are complementary independent predictors of major adverse events on follow-up after myocardial infarction. Combined measurement provides risk stratification substantially better than that provided by either alone. (Circulation. 2003;107:2786-2792.)

Key Words: coronary disease • natriuretic peptides • heart failure

Plasma hormones, particularly the cardiac natriuretic peptides, reflect ventricular impairment and the severity of hemodynamic decompensation in heart disease.1–12 They also have prognostic significance,1,2,5,6,9,11 may indicate likelihood of benefit from antifailure therapy,2,6,7 and may be useful in titrating pharmacotherapy in heart failure.13 De Lemos et al14 demonstrated the ability of plasma B-type natriuretic peptide (BNP), measured within a few days of acute coronary syndromes, to predict risk of mortality, clinical heart failure, and new myocardial infarction. The authors suggest that “cardiac neurohormonal activation may be the unifying feature among patients at high risk for death after acute coronary syndromes” (De Lemos et al,14 p 1018). These findings have been corroborated by two more recent reports in a cohort covering the range of acute coronary syndromes15 and a non–ST-elevation chest pain population.16

Landmark trials of treatment in heart failure and after myocardial infarction have established the prognostic significance of asymptomatic as well as symptomatic left ventricular systolic impairment and have demonstrated the value of converting enzyme inhibitor and β-blocker therapy.17–23 These studies have used reduced left ventricular ejection fraction (LVEF) as a cardinal criterion for randomization with threshold LVEF of 35% to 45%,18–20,22–26 and it is now widespread practice to introduce anti–heart failure therapy when LVEF is reduced. However, it is not clear that LVEF is the best indicator of prognosis or an appropriate sole trigger for initiation of treatment. A significant proportion of clinical heart failure occurs in the presence of preserved ejection fraction.24–26 Recent reports14–16 indicating the prognostic value of BNP in patients with chest pain and acute coronary syndromes have not included measurement of LVEF, either amino-terminal pro-BNP or BNP, or measurements of other neurohormones such as plasma norepinephrine (NE).1

The comparability or complementarity of the two (carboxy terminal and amino-terminal) plasma BNP measurements in contrast to, or together with, each other, plasma NE, or left ventricular imaging for prognosis after cardiac injury and
whether such profiling offers improved risk stratification are unknown.

Since our original demonstration of the presence of the amino-terminal fragment of BNP (N-BNP) in the human circulation, we and others have confirmed that plasma N-BNP reflects the degree of left ventricular dysfunction and has prognostic significance after acute myocardial infarction and in chronic heart failure.27–31

The present report assesses the prognostic value of plasma N-BNP in comparison with BNP and in concert with LVEF (by radionuclide ventriculography) measured 1 to 4 days after myocardial infarction and extends our initial findings in 121 patients followed for 1 year to an expanded cohort of 666 patients with a mean 3-year follow-up.

Methods

We studied 666 patients (Table 1) with acute myocardial infarction (MI) admitted to the Christchurch Hospital Coronary Care Unit (CCU) between November 1994 and September 1998. Patients provided written informed consent for their participation. The protocol was approved by the Health Funding Authority Ethics Committee (Canterbury). MI was defined by typical ischemic symptoms, ischemic change (including ST elevation or depression or dynamic T-wave changes; ie, includes ST-elevation, non–ST-elevation, Q-wave, and non–Q-wave infarcts) in 2 or more ECG leads and peak elevation of plasma creatine kinase to at least twice the upper limit of normal. Inclusion criteria included age <80 years, absence of immediate heart failure or cardiogenic shock, and survival for at least 24 hours after onset of MI. The study population included 64% of all patients with acute MI and elevation of creatine kinase beyond 400 IU/L admitted to the CCU over the recruitment period. All were also troponin T positive (ie, peak TNT >0.1 pg/mL), although this was not a stipulated entry criterion at the launch of the study.

Blood samples were taken 24 to 96 hours after the onset of symptoms through an intravenous cannula placed at least 30 minutes before sampling, with the patient resting quietly while semirecumbent. Samples in chilled EDTA vacutainers were placed on ice and centrifuged within 20 minutes at 4°C, and the plasma was stored at −80°C before assay for N-BNP, BNP, and NE according to our published methods.24,32,33 Interassay and intra-assay coefficients of variation all fell below 8.5%. Radionuclide ventriculography was performed within 24 hours of blood sampling, with a General Electric 400 AC gamma camera interfaced to a General Electric 3000f computer system after standard in vivo technetium 99 mol/L red blood cell labeling.

Events, including death, readmission to hospital with heart failure (defined by the presence of new symptoms of dyspnea or edema with one or more concurrent signs, including ventricular gallop rhythm, pulmonary crepitations, elevated venous pressure, or radiologic evidence of left ventricular failure) and new acute coronary syndromes leading to hospital admission were recorded for a mean period of 3 years. Outpatient review occurred at 4 and 12 months after infarction, and clinical questionnaires were distributed (with telephone follow-up) annually. Deaths were confirmed with hospital medical staff or the family physician.

Statistical Analysis

Data are expressed as mean ± SD or SEM. Mean neurohumoral scan variables were compared between groups incurring and spared clinical end points by independent t test. Event rates were compared by Kaplan-Meier curves calculated for hormone levels above compared with below the median and LVEF <40% versus ≥40%. The predictive characteristics of neurohormones were assessed by receiver-operator analysis to give sensitivity, specificity, positive and negative predictive values, and area under the curve of optimal threshold hormone values for the specified clinical end points. The independent predictive power of N-BNP, BNP, NE, LVEF, and other

<table>
<thead>
<tr>
<th>TABLE 1. Plasma Hormone Concentrations and Radionuclide Ventriculography Data According to Clinical Events After Acute MI (n=666)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong> (n=95)</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>N-BNP, pmol/L (normal, 5 to 50 pmol/L)</td>
</tr>
<tr>
<td>Y 286±23*</td>
</tr>
<tr>
<td>N 144±5</td>
</tr>
<tr>
<td>BNP, pmol/L (normal, 2 to 12 pmol/L)</td>
</tr>
<tr>
<td>Y 41±3‡</td>
</tr>
<tr>
<td>N 24±1</td>
</tr>
<tr>
<td>NE, pmol/L (normal, 470 to 3800 pmol/L)</td>
</tr>
<tr>
<td>Y 3167±217‡</td>
</tr>
<tr>
<td>N 2682±62</td>
</tr>
<tr>
<td>LVEF, %</td>
</tr>
<tr>
<td>Y 37±1*</td>
</tr>
<tr>
<td>N 49±0.5</td>
</tr>
<tr>
<td>LVEDV, mL</td>
</tr>
<tr>
<td>Y 190±8*</td>
</tr>
<tr>
<td>N 153±2</td>
</tr>
<tr>
<td>LVESV, mL</td>
</tr>
<tr>
<td>Y 124±8*</td>
</tr>
<tr>
<td>N 82±2</td>
</tr>
</tbody>
</table>

Y indicates yes, incurred event; N, no, spared event; NS, not significant; LVEDV, left ventricular end-diastolic volume; and LVESV, left ventricular end-systolic volume.

*P < 0.001; ‡ P < 0.01; † P < 0.05.
TABLE 2. Clinical Events According to LVEF and Plasma N-BNP

<table>
<thead>
<tr>
<th></th>
<th>LVEF</th>
<th>N-BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40% (n=177)</td>
<td></td>
<td>&gt;Median (n=332)</td>
</tr>
<tr>
<td>Death</td>
<td>95</td>
<td>79 (24)†</td>
</tr>
<tr>
<td>HF readmit</td>
<td>48</td>
<td>41 (12)†</td>
</tr>
<tr>
<td>Death/HF</td>
<td>126</td>
<td>104 (31)†</td>
</tr>
<tr>
<td>MI</td>
<td>118</td>
<td>67 (20)*‡</td>
</tr>
<tr>
<td>ACS</td>
<td>235</td>
<td>132 (40)‡</td>
</tr>
<tr>
<td>n ( % of Subgroup)</td>
<td>(57)</td>
<td>(83)</td>
</tr>
<tr>
<td>n ( % of Subgroup)</td>
<td>(43)</td>
<td>(15)</td>
</tr>
<tr>
<td>n ( % of Events)</td>
<td>(25)</td>
<td>(54)</td>
</tr>
<tr>
<td>n ( % of Events)</td>
<td>(70)</td>
<td>(43)</td>
</tr>
<tr>
<td>n ( % of Subgroup)</td>
<td>(30)</td>
<td>(56)</td>
</tr>
<tr>
<td>n ( % of Subgroup)</td>
<td>(40)</td>
<td>(31)</td>
</tr>
<tr>
<td>n ( % of Events)</td>
<td>(31)</td>
<td>(44)</td>
</tr>
</tbody>
</table>

**Statistical significance of Kaplan-Meier event-free curve separation for each clinical end point (comparing those with LVEF < vs ≥40% and those with plasma N-BNP > vs ≤ median)**

*P<0.05; †P<0.001; ‡P<0.01.

Results

Patient Population
The study population consisted of 666 patients (78.2% male) aged 62.4±10.4 years (range, 26 to 80 years). Thirty-eight percent of AMI was anterior, 53% inferior, and 9% of lateral or indeterminate location. Peak creatine kinase was 2156±2068 U/L (range, 404 to 2330), and peak Troponin T levels were 12.9±12.5 μg/L (range, 0.13 to 24.2). Known antecedent coronary disease was present as a history of angina in 38%, and 18.3% had documented previous MI. Thirty-seven percent had known essential hypertension, and 11.4% had diabetes. Previous heart failure, stroke, or peripheral vascular disease had been documented in 4.4%, 8%, and 6.8%, respectively. Total cholesterol averaged 6.1±1.2 mmol/L (range, 2.2 to 11.8 mmol/L). Twenty-nine percent were current smokers, and 36% were past smokers.

Treatment included primary PTCA in 10% and thrombolytic therapy in 62% of cases, predischARGE coronary artery bypass grafting was undertaken in 5.5%, and rates of discharge prescription of ACE inhibitor, β-blocker, aspirin, and statins were 46%, 78%, 90%, and 36%, respectively.

Cumulative event rates over the mean 3-year follow-up period (Table 2) were as follows: death, 14% (n=95); readmission to hospital with heart failure, 7% (n=48); new myocardial infarction, 18% (n=118); and all recurrent acute coronary syndromes, 35% (n=235).

Association of Hormones and LVEF With Outcomes
Plasma levels of N-BNP and BNP were higher in those incurring death, heart failure, MI, or other new acute coronary syndrome than in those spared these events (Table 1). NE was higher in those who died compared with survivors but was not significantly elevated in those incurring the other clinical end points. LVEF was less, and left ventricular systolic and diastolic volumes significantly greater, in those incurring death, heart failure, or MI. The proportional increase in plasma N-BNP in those with an event relative to those without exceeded that observed for BNP, NE, LVEF, or LV volumes for all end points (Table 1).

Kaplan-Meier analysis (Figure 1, Table 2) indicated differences in event-free survival for mortality (Figure 1), readmission with heart failure, the composite of death or heart failure, MI, or all new acute coronary syndromes when the group was divided according to median levels of N-BNP or BNP. In contrast, analysis by median levels of NE indicated no significant separation for any of these events. Event rates in those with LVEF below compared with above (or equal to) 40% were significantly higher for death, heart failure, and MI but not total acute coronary syndromes. Table 2 gives cumulative clinical events according to LVEF and plasma N-BNP. Those with LVEF <40% included 57% and 63% of fatal and heart failure events, respectively (with associated individual 3-year risks of 31% and 17%). In comparison, those with above-median levels of N-BNP included 83% and 85% of cases of death and heart failure readmissions (corresponding individual risks of 24% and 12%, respectively). For all acute coronary syndromes, LVEF <40% conferred an individual 3-year risk of 40%, but this subgroup incurred only 30% of such events. In contrast, plasma N-BNP above median levels conferred the same individual risk (40%), but this subgroup suffered the majority of such events (56%).

Comparison of BNP and N-BNP
Table 3 gives receiver-operator characteristics for the 3 hormones and LVEF as predictors of a composite end point of death or heart failure. N-BNP and BNP were closely comparable and superior to NE. Similar numerical values were obtained for prediction of death and heart failure separately. Weaker values were observed for prediction of new acute coronary syndrome (AUC for N-BNP and BNP 0.57 and 0.56, respectively).

In univariate and multivariate analyses including ejection fraction and N-BNP or BNP as continuous or binary (N-BNP greater or less than gender-specific median and LVEF <40% or ≥40%) terms, both indicators remained independent predictors of death and the composite end point of death or heart failure readmission. Univariate risk ratios (RR [95% confidence interval]) for death were 3.6 (2.5 to 53) and 4.9 (2.9 to 8.2) (both P<0.001) for LVEF (<40% or ≥40%) and
N-BNP (less than or greater than median), respectively. Corresponding univariate risk ratios for heart failure readmission were 4.6 (2.6 to 8.1) and 5.8 (2.7 to 12.8) (both \( P < 0.001 \)) and for the composite end point of death or heart failure readmission 3.7 (2.7 to 5.0) and 4.7 (3.0 to 7.3) (both \( P < 0.001 \)).

Multivariate analysis (Table 4) by stepwise Cox proportional hazards regression analysis (incorporating as putative predictors age, gender, previous MI, antecedent hypertension, diabetes, heart failure, plasma NE, creatinine, total cholesterol, and presence versus absence of specific treatments, including discharge prescription of converting enzyme inhibitor, \( \beta \)-blocker, diuretic, anti-\( \beta \)-blocker, angiotensin II receptor blockers, or coronary bypass graft surgery) confirmed N-BNP remained independently predictive of death 6.63 (3.72 to 11.79), and a significant interaction between LVEF (above versus below 40%) and N-BNP (above versus below median) was observed (Table 4; Figure 2; \( P < 0.0001 \)). An elevated N-BNP level together with LVEF <40% conferred a 3-year mortality risk of 37%, clearly a more than additive risk compared with those patients who had only 1 adverse marker (ie, LVEF <40% alone was associated with 6% mortality, an elevated N-BNP with LVEF ≥40% with a 14% risk). LVEF and N-BNP also interacted significantly in the independent prediction of myocardial infarction (Table 4, Figure 2). The interaction for prediction of MI is illustrated in the bottom of Figure 2. Supramedian N-BNP was associated with increased risk of MI only when ejection fraction was reduced (conferring a 26% 3-year risk). The 2 markers conferred additive risk for heart failure (Figure 2, middle). LVEF <40% without increased N-BNP was associated with 11% risk of this event; a raised N-BNP with LVEF ≥40% was associated with an 8% risk; and when both markers were present, the risk was 18%.

For the composite end point of death or heart failure readmission, both N-BNP and LVEF remained independent predictors (\( P < 0.0001 \) for both, Table 4).

For the entire study population, the goodness of fit of the final model from stepwise Cox proportional regression analysis for the composite of death, heart failure, or acute coronary syndrome was assessed by operating characteristic analysis and yielded an area under the curve of 0.74.

**TABLE 3. N-BNP, BNP, and NE as Predictors of Death/Heart Failure (n=126 events)**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>AUC (0 to 1.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-BNP (162 pmol/L)</td>
<td>80</td>
<td>72</td>
<td>25</td>
<td>97</td>
<td>0.81</td>
</tr>
<tr>
<td>BNP (30 pmol/L)</td>
<td>71</td>
<td>76</td>
<td>25</td>
<td>96</td>
<td>0.81</td>
</tr>
<tr>
<td>NE (2670 pmol/L)</td>
<td>57</td>
<td>57</td>
<td>13</td>
<td>92</td>
<td>0.55</td>
</tr>
<tr>
<td>LVEF (40%)</td>
<td>78</td>
<td>64</td>
<td>25</td>
<td>95</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Values in parentheses are the optimum, ie, nearest Euclidean distance from perfect sensitivity and specificity. PPV indicates positive predictive value; NPV, negative predictive value; and AUC, area under the curve.
Additional multivariate analyses (same predictors) were conducted following grouping according to ejection fractions <40% (n=177) or ≥40% (n=489). In the subgroup with reduced LVEF, N-BNP remained independently predictive of death (p<0.01) and heart failure (p<0.01). Furthermore, N-BNP was the single most powerful independent predictor in those with reduced LVEF of MI (p<0.001). In contrast, within the low EF group, LVEF itself remained indepen-
dently predictive for mortality only. In the larger subgroup with preserved ejection fraction (ie, ≥40%), N-BNP re-
ained predictive of death (p<0.05) or heart failure (p<0.05) whereas LVEF did not predict either. Neither

N-BNP nor LVEF was independently predictive of MI in patients with LVEF ≥40%.

For all of the univariate and multivariate tests described, plasma BNP (analyzed both as a continuous variable and in binary fashion, ie, above versus below median levels) performed similarly to N-BNP when substituted in analyses.
**Discussion**

This is the first report to include measurement of all of N-BNP, BNP, NE, and left ventricular function assessment by radionuclide scanning in a substantial cohort of patients with MI. In 666 patients, measurement of N-BNP (or BNP) together with radionuclide LVEF improved risk stratification beyond and independent of other indicators. LVEF and the B-type natriuretic peptides proved to be powerful independent predictors of death, heart failure, recurrent MI, and overall acute coronary syndromes. The combination of N-BNP (or BNP) with LVEF substantially improved risk stratification for mortality, heart failure, and new ischemic events.

These data provide the first opportunity to compare N-BNP with N-BNP as prognostic markers in a substantial cohort with MI and prolonged follow-up. Both can now be measured using commercialized, automated rapid-turnaround assays, and their relative performance is therefore of some interest. Notably, compared with BNP or left ventricular imaging variables, N-BNP exhibits a greater proportional and absolute increase in values observed in patients incurring death, heart failure, or myocardial infarction (Table 1). However, by other tests in the present report, both N-BNP and BNP perform very similarly as exemplified by Kaplan-Meier analysis (Figure 1) and receiver-operator curve analysis (Table 3). When substituted for one another in the multivariate analyses, the results were very similar. Therefore, both B-type peptides have similar utility as prognostic markers when measured early in the course of a broad spectrum of acute coronary syndromes. Plasma NE did not provide useful additional information for independent prediction of these important clinical end points in this heterogeneous group of people experiencing acute myocardial infarction.

Notably, raised plasma N-BNP/BNP is of adverse prognostic significance even when LVEF is preserved. However, although plasma N-BNP (or BNP) is the more powerful single marker, peptide levels and left ventricular imaging are complementary and interactive prognostic indicators. Together they offer practical early postmyocardial infarction risk stratification, which is more precise than either used alone. Concurrent elevation of plasma N-BNP/BNP and reduction of ejection fraction in the early postinfarction period defines a group at increased risk of death, heart failure, or MI and should trigger closer surveillance and more aggressive therapy.

These data extend existing knowledge provided by the recent reports in groups with chest pain and acute coronary syndromes in which BNP (or N-BNP) data were available but concurrent measurement of both was not performed. Furthermore, these existing reports did not provide data on LVEF or NE. The present report extends our earlier publication, which was confined to short-term follow-up on only 121 post-MI patients.

The prime stimulus for release of the cardiac natriuretic peptides is atrial and ventricular transmural distending pressure, which is related to ventricular filling pressures, the prime hemodynamic indicator of the severity of cardiac compromise. Higher levels of plasma N-BNP/BNP reflect greater degrees of cardiac hemodynamic dysfunction, and therefore it is not surprising that they are associated with greater risk of decompensated heart failure and death. The mechanisms underlying the association of raised plasma natriuretic peptides with increased risk of new ischemic events are less intuitively obvious and cannot be fully elucidated from the present report. It is possible that plaque rupture and partial thrombus formation in coronary arteries may more readily progress to full-blown infarction when coronary flow (which occurs in diastole) is already compromised by high intraventricular end-diastolic pressures. When myocytes are already metabolically challenged by adverse ventricular remodeling and the potentially toxic effects of high circulating levels of angiotensin II, endothelin-1, and catecholamines (all of which are activated in heart failure), they may be more vulnerable to necrosis at any given reduction of coronary flow.

Plasma NE concentrations are a long-recognized prognostic marker in established heart failure. However, early after MI in a group incurring a broad spectrum of cardiac injury, we found NE has no independent prognostic power for clinical outcomes. This may reflect the heterogeneous response of NE in the early postinfarction period in which pain, anxiety, and multiple drugs may acutely modify plasma catecholamine levels in addition to the extent of cardiac injury.

In conclusion, plasma N-BNP and BNP levels measured within a few days of acute MI independently predict death and heart failure in the presence or absence of preserved ejection fraction and are related to the risk of new ischemic events specifically in those with impaired systolic function. Measurements of the plasma B-type natriuretic peptides together with measures of left ventricular contractile function allow useful refinement of risk stratification beyond that provided by either marker alone.

**Acknowledgments**

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**References**


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