Comparison of B-Type Natriuretic Peptides for Assessment of Cardiac Function and Prognosis in Stable Ischemic Heart Disease

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OBJECTIVES
The aim of this work was to test B-type natriuretic peptides for assessment of function and prognosis in stable ischemic heart disease (IHD) and to compare brain natriuretic peptide (BNP) with amino terminal pro-brain natriuretic peptide (NTproBNP), including the relative effects of age and renal function on test performance.

BACKGROUND
Brain natriuretic peptide and NTproBNP are emerging diagnostic and prognostic markers in heart failure and acute coronary syndromes. Their performance in assessing function and prognosis in stable IHD is unknown. Whether one marker is superior and the relative effects of age and renal function on test performance are uncertain.

METHODS
In 1,049 patients with stable IHD, left ventricular ejection fraction (LVEF) was measured by radionuclide scanning and creatinine clearance estimated by the Cockcroft-Gault equation. Age, gender, and body mass index were recorded. Twelve-month all-cause mortality or admission with heart failure was prospectively recorded; BNP and NTproBNP were measured by radioimmunoassay.

RESULTS
Brain natriuretic peptide and NTproBNP correlated closely (r = 0.90, p < 0.001) and had similar relationships to LVEF (r = −0.50 and −0.46, respectively, both p < 0.001), age (0.44 and 0.47, both p < 0.001), and creatinine clearance (−0.51 and −0.51, both p < 0.001). Areas under receiver-operating characteristic curves for detection of LVEF <30% were similar (0.83 and 0.80, both p < 0.001) with strong negative predictive values for both (95% and 94%). Both markers independently predicted the clinical end point with closely overlapping event-free survival curves.

CONCLUSIONS
In stable IHD, BNP and NTproBNP display strong and near-identical test performance in ruling out severely reduced LVEF and in prediction of all-cause mortality or heart failure despite significant effects of age, gender, and renal function on levels of both markers. (J Am Coll Cardiol 2006;47:52–60) © 2006 by the American College of Cardiology Foundation

The B-type natriuretic peptides (i.e., brain natriuretic peptide [BNP] and amino terminal pro-brain natriuretic peptide [NTproBNP]) are acknowledged biomarkers of cardiac function and prognosis. Clinical applications under ongoing investigation include their use as a diagnostic test for the presence of heart failure in the newly symptomatic (most commonly dyspneic) patient (1–5); risk stratification for prognosis after recent cardiac decompensation, in chronic heart failure, or after acute coronary events (6–17); monitoring and adjustment of therapy in chronic heart failure (18,19); and screening of asymptomatic at-risk populations for significant cardiac impairment (20–25). Studies in cardiovascular patients have been confined to those with acute heart failure, chronic heart failure, and acute coronary syndromes (1–17). There is little information on the utility of B-type natriuretic peptides across the spectrum of stable chronic ischemic heart disease (IHD), although such patients generate a large proportion of cardiological practice.

Whether BNP or NTproBNP measurements offer any advantage over the other in any clinical setting is controversial (26–32). Initial reports from Hunt et al. (26,27) demonstrating NTproBNP was present in human plasma (with increased levels in heart failure) also suggested NTproBNP may detect earlier, asymptomatic cardiac impairment with greater sensitivity than BNP (27). Some subsequent reports have corroborated this suggestion (28–30), although counterclaims have also been made (31,32). Notably, in several reports the pur-
portrayed differences in test performance have not attained statistical significance (29–31).

Gender, age, renal function, and body mass index (BMI) all influence plasma B-type natriuretic peptide levels (13,15,21, 25,33,34). In severe, recent-onset symptomatic heart failure, plasma BNP is typically elevated many times above normal, and the influence of acute heart failure on BNP generally far outweighs that of these other factors, which do not alter peptide levels sufficiently to substantially abrogate the diagnostic utility of BNP in distinguishing dyspnea due to acute heart failure from that due to other causes (1–5,33). However, in stable IHD less profound elevation of BNP or NTproBNP may be anticipated, and the potential employment of peptide levels to reflect cardiac function and to assist in risk stratification of stable patients may be more vulnerable to confounding by these factors. Some authors also assert that age and renal function have a greater effect on levels of one peptide marker (implying a more potentially confounding influence on test performance) than the other (32). However, consensus on such questions has yet to be reached.

This report provides a comparison of BNP with NT-proBNP and assesses their performance in over 1,000 patients with stable IHD. The ability of both peptides to detect left ventricular ejection fraction (LVEF) reduced below pre-set thresholds is tested in both symptomatic and asymptomatic patients, and the relative effects of age, gender, and renal function and BMI on plasma peptide levels are also assessed. Finally, we compare the prognostic performance of both peptides in predicting death and/or admission with decompensated heart failure over 12 months’ follow-up.

METHODS

Study population. Patients were included from both the Australia-New Zealand (ANZ) Heart Failure trial (8,9,35) and the Christchurch Cardioendocrine post-myocardial infarction (PMI) cohort (11,36).

The ANZ heart failure patients (n = 292) participated in a randomized trial of carvedilol with results as previously published. Recruited from 20 hospitals in ANZ, they had chronic stable IHD (defined as a documented history of myocardial infarction, typical angina, exercise test positive for ischemia, or angiographic evidence of coronary disease) and LVEF by radionuclide ventriculography of <45%. At recruitment they were of New York Heart Association (NYHA) functional class II or III. Exclusion criteria included coronary events or procedures within the previous four weeks and primary myocardial or valvular disease. Cases selected (292 of 415 within the original study) were those for whom all of the required variables were available for analysis. Originally, all 415 ANZ heart failure subjects were sampled pre-randomization, and BNP was assayed in all (8). Residual plasma sample number and volumes permitted additional assay for NTproBNP (9) in the 292 patients included in this report. As previously reported, the 292 cases included in the current analyses did not differ significantly in any measured variable from the remaining 123 ANZ trial patients (9). Christchurch PMI patients (n = 757) were admitted to the Christchurch Hospital coronary care unit between November 1994 and November 1999. Myocardial infarction was defined by typical ischemic symptoms, ischemic changes (including ST-segment elevation or depression or dynamic T-wave changes, i.e., includes ST-segment elevation and non-ST-segment elevation infarcts) in two or more electrocardiogram leads and peak elevation of creatine kinase to at least twice upper limit of normal. All were troponin-positive. Patients included in this report were all those surviving at least four months after myocardial infarction, free of coronary events or interventions for at least one month, and clinically stable. Although early post-infarction levels of BNP and NTproBNP have been related to function and prognosis in subgroups of this cohort in previous publications (8,11,36), this is the first report relating late post-infarction (>4 months) peptide levels to concurrent left ventricular function and subsequent clinical events.

The two subgroups totaled 1,049 patients with the common characteristics of proven IHD and clinical stability.

Measurements. Left ventricular ejection fraction was assessed by equilibrium-gated radionuclide ventriculography (coefficients of variation ≤5.3%) (37). Renal function was calculated as creatinine clearance according to the Cockcroft-Gault equation (38). Plasma NTproBNP and BNP concentrations were ascertainied by previously well-validated and widely published radioimmunoassays (26,27,39). Normal ranges (from measurements in over 200 healthy men and women randomly selected from the Christchurch electoral role) for BNP and NTproBNP (up to 97.5 percentile of normal subjects) were <40 and <425 pg/ml, respectively.

Clinical outcome. The composite end point employed in the current report for analysis of the prognostic performance of both peptides was 12-month all-cause mortality and/or hospital admission with heart failure.

Statistical analysis. Data are given as arithmetic mean values ± SD. Peptide levels were log transformed to normalize the distributions, before all analyses. The normality of the log-transformed levels was confirmed by statistical tests of the skewness and kurtosis of the resultant distributions. In no instance did these indicate significant departures from normality. Peptide levels were compared between genders using
unpaired t tests. Pearson’s product moment correlation coefficients were used to test the strength of the associations of variables of interest with both BNP and NTproBNP values. Correlations (standardized slopes, $\beta$) were compared using a $z$ test. The potential independent influences of age, renal function, gender, BMI, and LVEF on peptide levels were tested by multiple linear regression including all five variables with BNP or NTproBNP as the dependent variable.

The ability of the peptides to detect LVEF $<30\%$, $<40\%$, and $<50\%$ was assessed using receiver-operating characteristic (ROC) curves to provide optimal peptide values and areas under curves (AUC), which were compared by the method of Hanley and McNeil (40). The rates of all-cause mortality and/or readmission with heart failure were calculated using Kaplan-Meier survival curves and compared above and below median peptide level groups, using the log-rank test. The independent predictive power of both peptides was tested by Cox proportional hazards multivariate analysis; the model incorporating age, recruitment from ANZ heart failure, or PMI cohorts; creatinine clearance; gender; LVEF; prescription of angiotensin-converting enzyme inhibitors, beta-blockers, diuretics; past history of documented myocardial infarction, hypertension, or diabetes.

**RESULTS**

The study population included 1,049 patients with stable coronary heart disease (with the expected gender distribution: 827 men and 222 [21%] women) encompassing a wide range of age, renal function, BMI, and LVEF (Table 1). Distribution among NYHA functional classes I, II, III, and IV was 63%, 30.4%, 6.2%, and 0.4%, respectively. In 588 (56%) of the group, LVEF fell below 50%, in 330 (32%) below 40%, and in 141 (13%) below 30%. The proportions of the group with previous myocardial infarction, hypertension, and diabetes were 97%, 39%, and 15%, respectively. Percentages prescribed beta-blockers, angiotensin-converting enzyme inhibitors, diuretics; past history of documented myocardial infarction, hypertension, or diabetes.

Table 1. Age, LVEF, Renal Function, and B-Type Natriuretic Peptides in 1,049 Patients With Stable Ischemic Heart Disease

<table>
<thead>
<tr>
<th></th>
<th>Age (yrs)</th>
<th>BMI (kg/m²)</th>
<th>LVEF (%)</th>
<th>Creatinine Clearance (ml/min)</th>
<th>BNP (pg/ml)</th>
<th>NTproBNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>63.4</td>
<td>26.7</td>
<td>46</td>
<td>80.6</td>
<td>69</td>
<td>820</td>
</tr>
<tr>
<td>SD</td>
<td>10.0</td>
<td>4.1</td>
<td>14</td>
<td>32.9</td>
<td>69</td>
<td>863</td>
</tr>
<tr>
<td>Min</td>
<td>25.8</td>
<td>16.5</td>
<td>10</td>
<td>16</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Max</td>
<td>87.6</td>
<td>45.4</td>
<td>95</td>
<td>270</td>
<td>887</td>
<td>9,523</td>
</tr>
</tbody>
</table>

BMI = body mass index (weight[kg]/height[m]²); BNP = brain natriuretic peptide; LVEF = left ventricular ejection fraction; Max = maximum; Min = minimum; NTproBNP = amino terminal pro-brain natriuretic peptide.

Figure 1. Plasma brain natriuretic peptide (BNP) plotted against plasma amino terminal pro-brain natriuretic peptide (NTproBNP) in 1,049 patients with stable ischemic heart disease.
in LVEF, 40% and 60% increases with each 10-year increase in age, and 80% and 120% increments for each halving of renal function (serial 30 ml/min decrements in creatinine clearance from 150 ml/min down to 120, 90, 60, and 30 ml/min were associated with serial increments in BNP of 21%, 29%, 45%, and 86% and in NTproBNP of 32%, 38%, 60%, and 123%, respectively). Brain natriuretic peptide and NTproBNP fell 15% and 22%, respectively, with each 5-U increment in BMI. When appropriately adjusted (for concurrent change in the other four variables), a 10% decrement in LVEF corresponded to 21% and 24% increases in BNP and NTproBNP, respectively, a 10-year increment in age to 18% and 30% increments, and serial 30 ml/min decrements in creatinine clearance from 150 ml/min down to 30 ml/min corresponded to increments in BNP of 9%, 22%, 44%, and 89% and in NTproBNP of 9%, 24%, 46%, and 95%. Each 5-U increment in BMI was associated with adjusted 3% and 9% decreases in BNP and NT-proBNP, respectively.

Test performance of both peptides was conducted in the total study group and separately in the 649 asymptomatic patients (NYHA functional class I). Compared with symptomatic patients, NYHA functional class I patients averaged 2.5 years younger (62.4 ± 10.4 years vs. 65.1 ± 9.1 years, p < 0.001), were less likely to have a previous history of hypertension (37% vs. 43%, p = 0.047) or diabetes (13% vs. 18%, p = 0.015), had better creatinine clearance (86 ± 33 ml/min vs. 72 ± 32 ml/min, p < 0.001), better LVEF (49 ± 13% vs. 41 ± 13%, p < 0.001), and had a lower proportion of women (17% vs. 28%, p < 0.001).

Receiver-operator characteristic curves indicated both peptides had similar ability to detect LVEF below thresholds of 30%, 40%, and 50% in the total study group (Fig. 5) and in the asymptomatic (NYHA functional class I; n = 649) subgroup (Fig. 6). For both peptides, the AUC was significantly less for detection of LVEF below 50% (AUCs 0.75 and 0.73 for BNP and NTproBNP, respectively) than below 30% (AUCs 0.83 and 0.80, respectively; p < 0.01 for
both comparisons within the total study group). Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for the optimal levels of each peptide lying on each of the ROC curves are shown in Table 3. Values for these test performance characteristics were similar for both peptides in the total group and asymmetric subgroup and at all three LVEF thresholds. At an LVEF threshold of 30%, consistently high negative predictive values (94% or higher) were observed for optimal levels of both peptides in both subgroups; ROC curves and test performance characteristics were also significant and similar for men and women analyzed separately (data not shown).

Seventy-nine patients (7.5%) died and/or were readmitted to hospital for heart failure. Brain natriuretic peptide and NTproBNP were higher (double) in those incurring, compared with those spared, these adverse outcomes (129 ± 14 pg/ml vs. 65 ± 2 pg/ml and 1,591 ± 156 pg/ml vs. 757 ± 25 pg/ml for BNP and NTproBNP, respectively; p < 0.001 for both). Event-free survival curves for the two peptide markers were closely overlapped with greater risk of adverse outcomes in those with peptide levels above compared with below the median (Fig. 7, cumulative event rates of 12% vs. 3% for both peptides). Unadjusted risk ratios (95% confidence intervals) were 4.07 (2.38 to 6.94) and 4.15 (2.40 to 7.19) for BNP and NTproBNP, respectively (p < 0.001 for both). On Cox proportional hazards multivariate analysis, both BNP and NTproBNP remained independently predictive with adjusted risk ratios of 1.89 (1.02 to 3.52) and 2.08 (1.12 to 3.89), respectively (p < 0.05 for both).

**DISCUSSION**

In patients with stable IHD, BNP and NTproBNP were closely correlated and exhibited parallel changes across a broad range of age, renal function, and LVEF. The two markers performed similarly in the detection of LVEF reduced below 30%, 40%, or 50%, in symptomatic and asymptomatic patients, and were indistinguishable in their ability to predict 12-month all-cause mortality and/or readmission with heart failure.

Existing studies in cardiac clinical cohorts have examined situations in which B-type peptides are generally higher than in stable IHD and rapidly changing in an evolving response to recent clinical instability (1–17). This report provides new information on the test performance of BNP and NTproBNP across a broad spectrum of stable IHD.

The group studied is representative of the ambulant IHD population, which generates a large part of cardiac practice. We confirm previously described relationships of the two peptides to one another and to cardiac function and prognosis (1,4,7,11,36). In this stable group, mean BNP and NTproBNP levels were raised to approximately twice the upper limits of normal, comparable to levels in chronic stable heart failure, and lower than observed in acute heart failure or in the early PMI period (1–5,9–11,36).

By ROC analysis, both peptides had good power to detect LVEF <30% with AUC of 0.80 to 0.85 for both peptides in the group overall, with similar performance in the asymptomatic subgroup (Fig. 2). As noted previously in many settings, the negative predictive value of both peptides in ruling out severe systolic ventricular dysfunction (LVEF <30%) was consistently high in these stable patients (94% or higher) whether or not symptoms were present.

The ability of both peptides to predict 12-month all-cause mortality and/or admission with heart failure was clear-cut and comparable to the prognostic strength exhibited by both peptides in both acute coronary or established heart failure cohorts (6–8,10–13,15).

Our results do not support previous claims that the test performance of one or other of the two markers is more influenced by gender, age, or renal function, or that one of the two markers is superior in detecting milder degrees of left ventricular dysfunction in asymptomatic patients (27–32). Age and renal function both independently influenced both BNP and NTproBNP levels to an important degree with absolute and proportional changes in NTproBNP generally more pronounced than concurrent shifts in BNP, consistent with an analyte with mean levels 10-fold higher than the comparator peptide and in which slower metabolic clearance will ensure greater increments in plasma levels for any disturbance generating increased secretion. However, any differences in absolute or proportional shifts of BNP compared to NTproBNP did not result in differences in test performance. The close match of ROC curves for selected LVEF threshold values (Fig. 2) and overlapping event-free survival curves (Fig. 3) confirm these background factors influence the test performance of one peptide no more than the other.

The effects of gender, age, and renal function suggest the use of these markers for follow-up of ventricular function and for risk stratification in individual patients with stable IHD may require adjustment for these variables. In such
patients, an additional decade of life, a 10% decrement in LVEF (e.g., a fall from 40% to 30%), and a 30 ml/min fall in creatinine clearance (i.e., from 120 to 90 ml/min) are associated with similar increments (20% to 30%) in plasma BNP and NTproBNP. A doubling in mean peptide levels is associated with an approximate doubling in 12-month risk (adjusted) of death or decompensated heart failure. Brain natriuretic peptide and NTproBNP levels in those presenting with dyspnea due to heart failure are, respectively, 6- and 12-fold those observed in patients with a non-cardiac cause (3,4). Hence, the “signal-to-noise” ratio in the latter application is far more robust than in the assessment of function and prognosis in stable IHD. Despite these reservations, the current data still indicate that both peptides retain high negative predictive value for ruling out severe reduction in LVEF even without adjustment for potential confounders.

**Figure 5.** Receiver–operating characteristic curves for detection of left ventricular ejection fraction (LVEF) <30% (top), 40% (middle), or 50% (bottom) by brain natriuretic peptide (BNP) (solid lines) and amino terminal pro-brain natriuretic peptide (NTproBNP) (dotted lines) in 1,049 patients with stable ischemic heart disease. Curves do not significantly differ for any level of LVEF. AUC = area under the curve.

**Figure 6.** Receiver–operating characteristic curves for detection of left ventricular ejection fraction (LVEF) <30% (top), 40% (middle), and 50% (bottom) by brain natriuretic peptide (BNP) (solid lines) or amino terminal pro-brain natriuretic peptide (NTproBNP) (dotted lines) in 1,049 patients with asymptomatic stable ischemic heart disease. AUC = area under the curve.
The current analyses apply to patients with stable IHD. In this group, a broad spectrum of age, renal function, and cardiac function is represented. The population studied in the current study is representative of much of the commonplace workload of cardiology throughout the Western world.

It remains possible subtle differences between BNP and NTproBNP in test performance may be observed when comparing their ability to distinguish truly normal subjects from those with asymptomatic or early heart disease, or that in other forms of heart disease the two may perform somewhat differently. Differences in peptide plasma half-life may enable BNP to more rapidly reflect evolving changes in hemodynamic status occurring over short periods of time as in the setting of introduction of intensive parenteral therapy in decompensated heart failure; NTproBNP may prove a more reliable indicator of cardiac status when BNP itself is administered as therapy or in the presence of other treatments that modify plasma clearance of BNP. However, these considerations in no way refute the evident interchangeability of these two markers in the assessment of cardiac function and prognosis in stable IHD.

The analyses were conducted with radioimmunoassays, validated in the course of multiple publications (1,4,8,9,11,19,26,27,39), which correlate closely with currently available widely used commercial assays for both NTproBNP and BNP (r \( \approx 0.91 \) for relationships of both assays to both BIOSITE point of care BNP assays [BIOSITE Inc., San Diego, California] and the Roche Diagnostics NTproBNP assay [Roche Diagnostics, Indianapolis, Indiana]). Both assays exhibit near-identical ROC curves and test performance characteristics to the two commercially available assays when used to diagnose heart failure in dyspneic patients (4).

Across the broad spectrum of stable IHD plasma BNP and NTproBNP are powerful indicators of ventricular function and independent predictors of clinical outcome. They are similarly and independently influenced by gender, age, and renal function and have indistinguishable performance in detection of left ventricular dysfunction and as prognostic markers.

Figure 7. Kaplan-Meier event-free survival curves for death or heart failure admission for those with brain natriuretic peptide (BNP) (solid lines) and amino terminal pro-brain natriuretic peptide (NTproBNP) (dotted lines) above (lower two lines) or below (upper two lines) the median level for the group. For both peptides, the separation of survival curves was highly significant (p < 0.001). CHF = congestive heart failure.

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<tr>
<th>Peptide Test Performance in Detection of Selected LVEF Thresholds in Patients With Stable Ischemic Heart Disease</th>
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<tr>
<td><strong>Optimal Value</strong></td>
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<tr>
<td><strong>BNP</strong></td>
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<tr>
<td>All (n = 1,049)</td>
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<tr>
<td>LVEF &lt;30%</td>
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<td>LVEF &lt;40%</td>
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<td>LVEF &lt;50%</td>
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<tr>
<td>NYHA functional class I (n = 649)</td>
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<td>LVEF &lt;30%</td>
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<tr>
<td>LVEF &lt;40%</td>
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<td>LVEF &lt;50%</td>
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<td><strong>NTproBNP</strong></td>
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<td>All (n = 1,049)</td>
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<td>LVEF &lt;30%</td>
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<td>LVEF &lt;40%</td>
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<td>LVEF &lt;50%</td>
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</tbody>
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NPV = negative predictive value; NYHA = New York Heart Association; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; other abbreviations as in Table 1.
REFERENCES


APPENDIX

For a list of investigators who participated in the Australia-New Zealand Heart Failure Research Collaborative Group, please see the online version of this article.