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Pro-B-Type Natriuretic Peptide Levels in Acute Decompensated Heart Failure

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Objectives The present study sought to evaluate the clinical utility of pro-B-type natriuretic peptides (proBNP) in patients admitted with acute decompensated heart failure.

Background Plasma natriuretic peptides ($BNP_{1–32}$, N-terminal [NT]-$proBNP_{1–76}$) have been demonstrated to assist in the diagnosis of patients with heart failure. However, the precursor to these polypeptides ($proBNP_{1–108}$) circulates in plasma and may interfere with the measurement of currently used biomarkers.

Methods Plasma natriuretic peptides were assessed in 164 individuals (99% men) hospitalized with decompensated heart failure. The B-type natriuretic peptide (BNP), NT-proBNP, and proBNP levels at hospital admission and discharge were compared with the incidence of cardiac death and all-cause mortality within 90 days post-discharge.

Results Pro-B-type natriuretic peptides demonstrated a high degree of correlation with both BNP ($R = 0.924$, $p < 0.001$) and NT-proBNP ($R = 0.802$, $p < 0.001$) at admission. Further characterization of proBNP demonstrated little variation with changes in age, body mass index, creatinine, or systolic dysfunction. All 3 plasma natriuretic peptides were significantly elevated at admission in patients suffering a cardiac death or all-cause mortality ($p < 0.05$). Receiver-operating characteristic curves demonstrated that admission and discharge NT-proBNP (area under the curve [AUC] 0.788 and AUC 0.834) had superior prognostic power for all-cause mortality when compared with BNP (AUC 0.644, $p < 0.01$ and AUC 0.709, $p < 0.01$) and proBNP (AUC 0.653, $p < 0.01$ and AUC 0.666, $p < 0.01$) at the same time points.

Conclusions Admission values of all natriuretic peptides can be used to predict cardiac death and all-cause mortality. A preliminary comparison suggests that discharge values of NT-proBNP have the greatest diagnostic yield for predicting these end points. Further studies should explore the synergistic prognostic potential of all natriuretic peptides. (J Am Coll Cardiol 2008;51:1874–82) © 2008 by the American College of Cardiology Foundation

Congestive heart failure is the leading cause of hospital admission among patients over the age of 65 years (1). Five percent of the total national health care budget is spent on the treatment and hospitalization of patients suffering from heart failure (1). Despite advances in treatment modalities, patients admitted with decompensated heart failure have significant hospital mortality and considerable readmission rates (2). The lack of an effective method to assess treatment efficacy in heart failure patients may contribute to these problems. A simple diagnostic protocol capable of measuring inpatient treatment efficacy would be invaluable in guiding clinical decision making.

B-type natriuretic peptide (BNP) is a cardiac hormone secreted from membrane granules of the ventricles in response to volume expansion and pressure overload (3). Unlike other natriuretic peptides, the precursor to BNP is translated from an inherently unstable messenger ribonucleic acid (mRNA) sequence containing the bases TATTTAT (4). The inherent instability of the BNP precursor sequence leads to the rapid turnover of its mRNA resulting in bursts of peptide release temporally corresponding to increases in ventricular volume and pressure (5). The expression and translation of the BNP precursor sequence results in a 134-amino-acid peptide denoted as preproBNP that is subsequently cleaved to a 108-amino-acid sequence denoted as $proBNP_{1–108}$ (3,6). Further proteolytic processing cleaves a mature 32-amino-acid peptide from pro-B-type natriuretic peptides (proBNPs), designated $BNP_{1–32}$, that produces vaso-

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dilation and increased urinary salt clearance (6). The N-terminal peptide fragment (NT-proBNP$_{1–76}$) released from this proteolytic modification also circulates in plasma without known physiological activity (3). Research suggests that each of these peptides can be used in the evaluation of patients with heart failure.

A number of studies have demonstrated the clinical utility of natriuretic peptides in the diagnosis and treatment of heart failure. Initial work demonstrated that circulating BNP levels correspond to pulmonary capillary wedge pressure and clinical symptoms measured by the New York Heart Association functional classification (7,8). Subsequent research has proven that changes in BNP levels during inpatient treatment are strong predictors for subsequent hospitalization and eventual mortality (9,10). The NT-proBNP, like its active analogue BNP, can also aid in the diagnosis of heart failure in asymptomatic patients presenting with acute dyspnea (11). Research has suggested that NT-proBNP levels during hospitalization are strong predictors for hospital readmission and mortality (12,13). The utility of NT-proBNP in predicting subsequent cardiac events has been confirmed in patients with renal insufficiency in spite of its renal clearance (14,15). Despite the intensive investigations of BNP and NT-proBNP in heart failure patients, little data have been presented regarding other natriuretic peptide metabolites or precursor compounds.

Research has demonstrated that the intact precursor to both BNP and NT-proBNP circulates in the blood stream of patients with heart failure (16). Some have suggested that current assays for both BNP and NT-proBNP may be influenced by the presence of proBNP in serum (17). This has prompted the development of a specific assay for proBNP (18). However, prospective studies evaluating the clinical utility of proBNP have not yet been performed. The present study characterizes proBNP in patients hospitalized with acute decompensated heart failure.

Methods

Population. The study design was reviewed and approved by the University of California at San Diego Institutional Review Board. Patients admitted to the San Diego Veterans Affairs Medical Center with a clinical diagnosis of acute decompensated heart failure between July 2002 and December 2005 were eligible for enrollment in the study and inclusion in the Veterans' Administration Effective Therapy cohort. Patients under the age of 18 years or unable to provide informed consent were excluded from participation. Of the eligible patients, 192 unique individuals agreed to participate, and 164 individuals provided sufficient blood samples for analysis of all natriuretic peptides. A sufficient blood sample was defined as a volume sufficient for biochemical analysis within 24 h of hospital admission and a separate sample within 24 h of in-hospital death or discharge. After obtaining written informed consent, data were obtained from verbal conversations with the patient and a review of the electronic medical record. Blood samples from venipuncture were immediately frozen and stored at admission and during each subsequent hospital day until discharge for further analysis. After discharge from the hospital, the patient was re-evaluated through a review of the electronic medical record or via telephone conversation to evaluate for the primary and secondary end points. The pre-specified primary end point was cardiac death within 90 days post-discharge. The secondary end point was all-cause mortality during the same follow-up period. In-hospital mortality was considered a death on the day of discharge. For comparison, proBNP levels were also assessed in a group of 50 normal male volunteers (age 54 ± 3 years) without known cardiac disease.

Abbreviations and Acronyms

AUC = area under the curve
BMI = body mass index
BNP = B-type natriuretic peptide
NT-proBNP = N-terminal pro-B-type natriuretic peptide
proBNP = pro-B-type natriuretic peptide
ROC = receiver-operating characteristic

Biochemical assays. Approximately 5 ml of blood from venipuncture was collected into a tube containing potassium ethylenediamine tetra-acetic acid (1 mg/ml) at each time point. The samples were subsequently frozen at −70°C until further analysis without undergoing any additional freeze–thaw cycles. B-type natriuretic peptide was measured using the Triage B-Type Natriuretic Peptide Assay (Biosite, San Diego, California) as previously described (19,20). The NT-proBNP was assessed using the Elecsys ProBNP assay (Roche Diagnostics, Indianapolis, Indiana) as outlined in prior publications (20,21). It is important to note that current assays for BNP and NT-proBNP do not use specific antibodies against the cleavage products and thus recognize both the proBNP precursor as well as their intended target (22,23).

Pro-B-type natriuretic peptide was determined using an improved version of the Bio-Rad proBNP assay (Research Use Only, Bio-Rad, Hercules, California) initially described by Giuliani et al. (18). This assay utilizes an immobilized antibody targeted toward the hinge region (residues 75 to 80) of the proBNP precursor that is not present on subsequent natriuretic peptides. Consequently, there is minimal cross reactivity (<1.5%) of this assay with BNP and NT-proBNP. The method described by Giuliani et al. (18) was improved in the present study by using a monoclonal murine secondary antibody specifically targeting the BNP ring, resulting in a significant reduction in background signal. This proBNP assay is characterized by excellent linearity with recombinant proBNP (Hytest Ltd., Turku, Finland) with concentrations ranging from 10 to 10,000 ng/l. The detection limit, calculated as the mean ± 3 standard deviations, was computed as 4 ng/l with an intra-assay coefficient of variation of <5%.

Statistics. The correlation of natriuretic peptides was computed with a Spearman correlation coefficient. Box and

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whisker plots were created such that a box contained the 25th to 75th percentiles and the whiskers contained the 10th to 90th percentiles. Mann-Whitney *U* tests were utilized to determine statistical differences in natriuretic peptides among patients reaching the primary or secondary end point. These statistics were computed using SPSS statistical software (SPSS Inc., Chicago, Illinois). Receiver-operating characteristic (ROC) curves were created to identify the prognostic utility of each assay. Statistical comparisons of the area under the curves (AUCs) were computed based on a previously described model using SAS statistical software (SAS Institute, Cary, North Carolina) (24). For all comparisons, a p value ≤0.05 was considered statistically significant.

Table 1 Demographic Data

	n	%
Age (yrs)	68 ± 13	
Gender		
Male	162	99
Female	2	1
Race		
Caucasian	124	76
African American	24	15
Hispanic	12	7
Other	4	3
Past medical history		
Hypertension	123	75
Coronary artery disease	104	63
Diabetes	87	53
Myocardial infarction	59	36
Atrial fibrillation	58	35
Chronic renal insufficiency	49	30
Chronic obstructive pulmonary disease	44	27
Admission diagnosis		
Congestive heart failure (exacerbation)	118	72
Congestive heart failure (new onset)	17	10
NYHA functional classification	3.4 ± 0.6	
Admission etiology		
Ischemic	107	65
Hypertensive	34	21
Idiopathic	9	5
Alcohol abuse	6	4
Valvular	4	2
Admission medications		
Diuretic	109	66
Beta-blocker	85	52
ACE inhibitor	82	50
Digoxin	38	23
Calcium-channel blocker	34	21
Angiotensin receptor blocker	16	10
Spironolactone	11	7
Admission vitals		
Weight (lbs)	212 ± 56	
Systolic blood pressure	135 ± 26	
Diastolic blood pressure	74 ± 19	
Admission labs		
Serum sodium (mEq)	138 ± 4	
Serum creatinine (mg/dl)	1.7 ± 1.0	

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

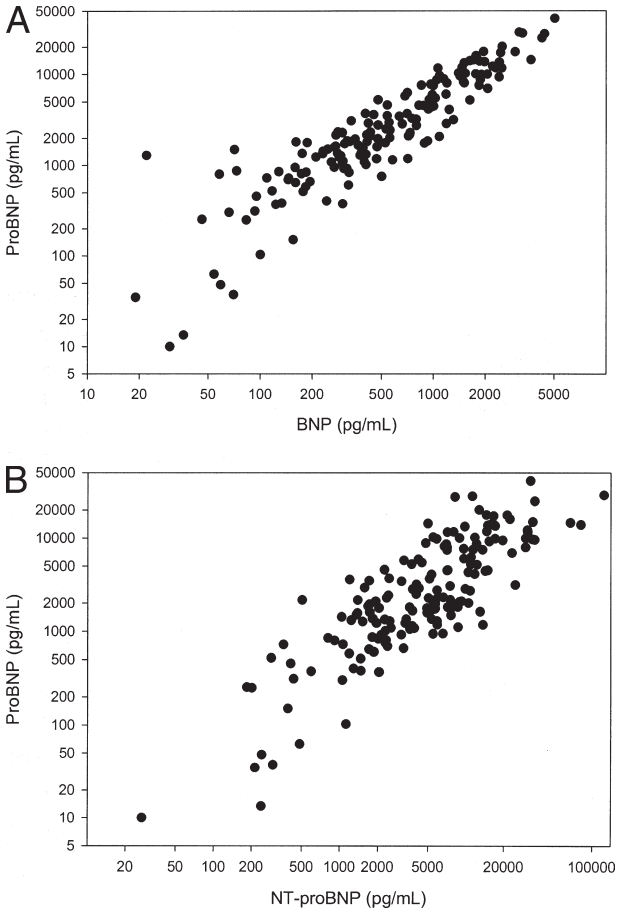

Figure 1 Natriuretic Peptide Correlation

Plasma natriuretic peptides were assessed in 164 unique individuals admitted for decompensated congestive heart failure. The scatter plots above demonstrate that pro-B-type natriuretic peptide (proBNP) at admission is highly correlated with both B-type natriuretic peptide ($R = 0.924$, $p < 0.001$) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) ($R = 0.802$, $p < 0.001$) at the same time point. This correlation was consistent at all time points assessed during a mean hospital stay of 5.5 ± 7.1 days (data not shown).

Results

Demographic data. The demographic characteristics of the 164 patients that provided blood samples for all natriuretic peptide analyses are summarized in Table 1. The majority of participants were men (99%) with a predominance of ischemic cardiomyopathy (65%). In accordance with the study inclusion criteria, these patients were hospitalized with a median New York Heart Association functional classification of III. The majority of participants were also previously diagnosed with significant comorbid conditions including hypertension (75%), coronary artery disease (63%), and diabetes mellitus (53%).

Natriuretic peptide correlation. The correlation between natriuretic peptides was calculated from a total of 539 samples taken from 164 unique individuals over an average of 5.5 ± 7.1 hospital days. As a representative example, Figure 1 summarizes the correlation for each pair of natriuretic peptides at admission. The measurements of proBNP demonstrate a high correlation with both BNP ($R = 0.924$, $p < 0.001$) and NT-proBNP ($R = 0.802$, $p < 0.001$) at this time point. This high degree of correlation was consistent at all time points assessed throughout hospitalization (data not shown).

Natriuretic peptide characterization. The admission values of natriuretic peptides were compared with the characteristics of the 164 unique individuals hospitalized for heart failure. Figures 2A and 2B demonstrate that proBNP is independent of age and body mass index (BMI). As shown in Figure 2C, proBNP levels are also independent of serum creatinine and corresponding renal insufficiency. Figure 2D demonstrates that proBNP levels are similar in patients with systolic or diastolic dysfunction as determined by transthoracic echocardiography. It is important to note that BNP and NT-proBNP were also not affected by these parameters in our limited patient population (data not shown). For comparison, a group of 50 normal male volunteers without known cardiac disease age 54 ± 3 years had a mean proBNP level of 223 ± 570 pg/ml.

Natriuretic peptides and cardiac death. The plasma natriuretic peptide levels at admission and discharge were compared among the 13 patients that met the primary end point. As shown in Figure 3A, all 3 natriuretic peptides were significantly increased at admission in patients that suffered a cardiac death within 90 days of hospital discharge ($p < 0.05$). As shown in Figure 3B, patients with a cardiac death had a decrease in proBNP levels during their hospital course that made the discharge value statistically similar to patients without a subsequent cardiac death ($p = 0.13$). The level of decline in proBNP during hospitalization had little relation to ultimate events.

Natriuretic peptides and all-cause mortality. The plasma natriuretic peptide levels obtained at admission and discharge were compared among the 22 patients that met the secondary end point. As shown in Figure 4A, all 3 natriuretic peptides were significantly increased at admission in patients that suffered all-cause mortality within 90 days of hospital discharge ($p < 0.05$). Figure 4B demonstrates that these peptides were also significantly increased at discharge

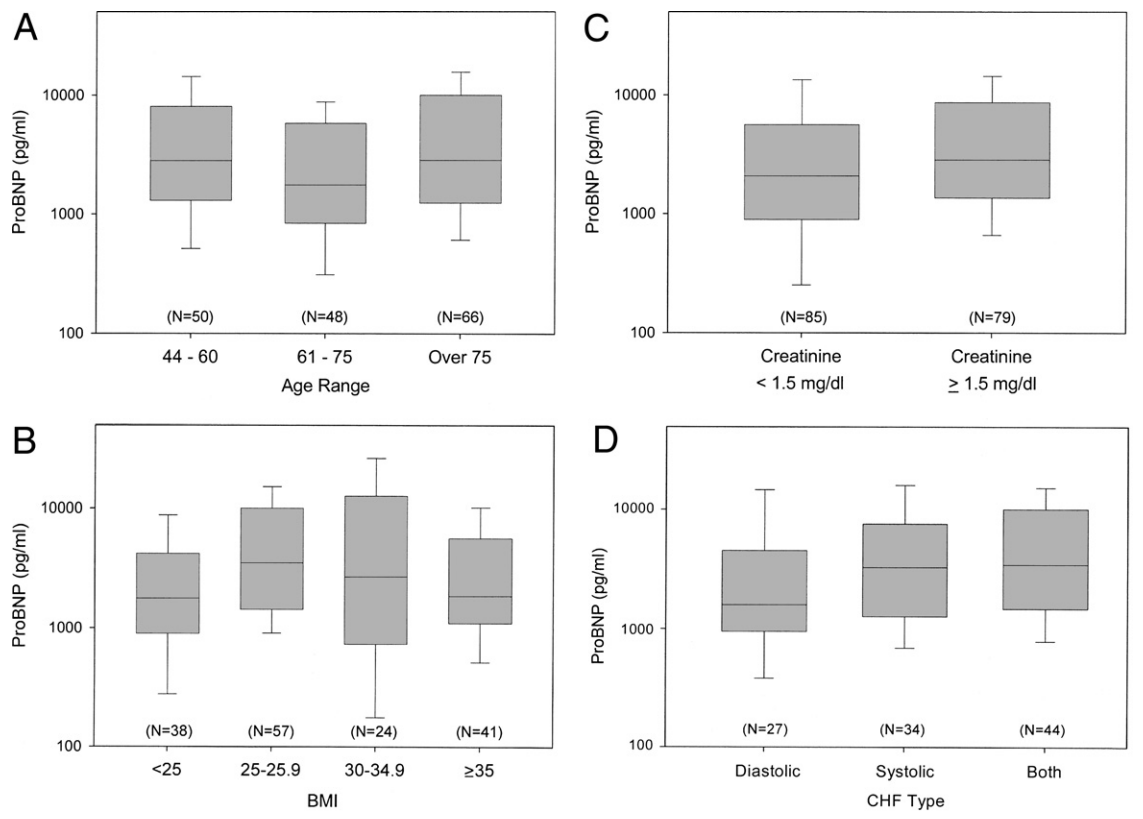

Figure 2 Natriuretic Peptide Characterization

Plasma B-type natriuretic peptides were compared with the characteristics of the 164 unique individuals hospitalized for congestive heart failure (CHF). The **box and whisker plots in A and B** demonstrate that pro-B-type natriuretic peptide (proBNP) is independent of age and body mass index (BMI). **Panel C** suggests that proBNP levels are also independent of serum creatinine and corresponding renal insufficiency. **Panel D** demonstrates that proBNP levels are unchanged in patients with systolic or diastolic dysfunction.

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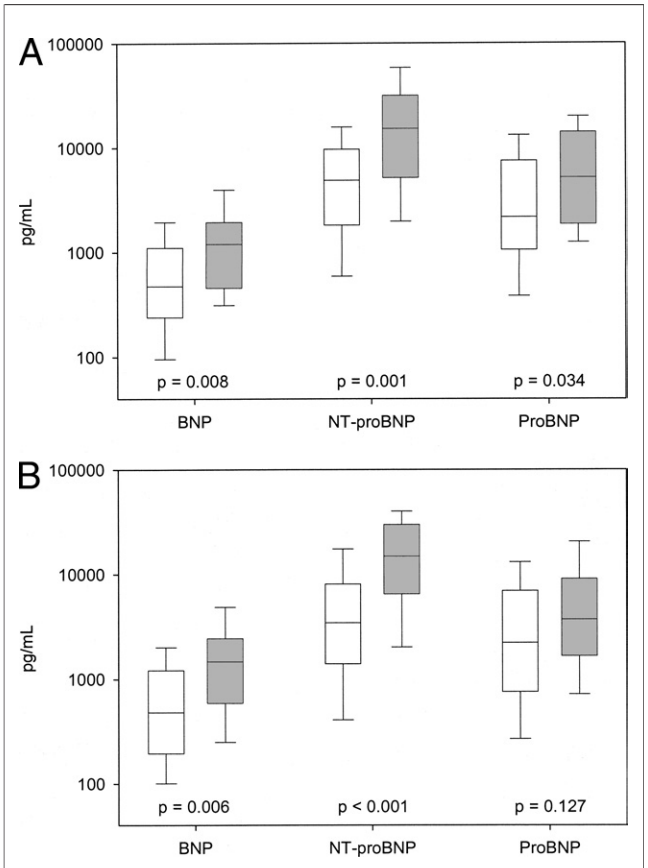


Figure 3 Natriuretic Peptides and Cardiac Death

Admission and discharge plasma natriuretic peptide levels were evaluated in patients that met the primary end point. The **box and whisker plots in A** demonstrate that patients that suffered a cardiac death **(gray boxes)** had significantly higher plasma natriuretic peptide levels at admission compared with those that did not have an event **(open boxes)** within 90 days of hospital discharge. **Panel B** demonstrates that B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptides (NT-proBNP) levels were also significantly elevated at discharge in patients suffering a cardiac death **(gray boxes)** when compared with those that did not **(open boxes)**.

in patients that met the secondary end point ($p < 0.05$). Once again, changes in levels during hospitalization had no bearing on ultimate outcomes.

Natriuretic peptides and prognosis. The differences in admission levels of proBNP among the patients that met the primary or secondary end point prompted investigation of absolute proBNP values that could be used for prognosis. The plasma levels of proBNP at admission were thus divided into tertiles and compared with the incidence of the primary and secondary end points. Figure 5A demonstrates that patients admitted with a proBNP level less than 1,400 pg/ml regardless of BNP level had significantly fewer cardiac deaths ($n = 0$) within the follow-up period than those with an admission proBNP value of 1,400 to 4,550 pg/ml ($p < 0.05$) or >4,550 pg/ml ($p < 0.001$). Figure 4B demonstrates that patients admitted with a proBNP level <1,400 pg/ml had significantly fewer all-cause deaths ($n = 3$) within the follow-up period than those with an admission proBNP value >4,550 pg/ml ($p < 0.05$). The middle tertile of admission proBNP levels (1,400 to 4,550 pg/ml) did not have a significantly different outcome from the other tertiles in terms of all-cause mortality.

Comparing natriuretic peptides for cardiac death prognosis. The admission and discharge values of the natriuretic peptides were compared for their ability to predict the incidence of the primary end point. A series of ROC curves were created for each of the natriuretic peptides at admission and discharge as related to the incidence of cardiac death (Fig. 6A). Each natriuretic peptide at admission demonstrated an AUC exceeding 0.71 that statistically differed from the null hypothesis ($p < 0.02$). The AUC for predicting cardiac death was not statistically different among the natriuretic peptides at admission. At discharge, BNP and NT-proBNP demonstrated an AUC exceeding 0.73 that statistically differed from the null hypothesis ($p < 0.01$). A statistical comparison of the

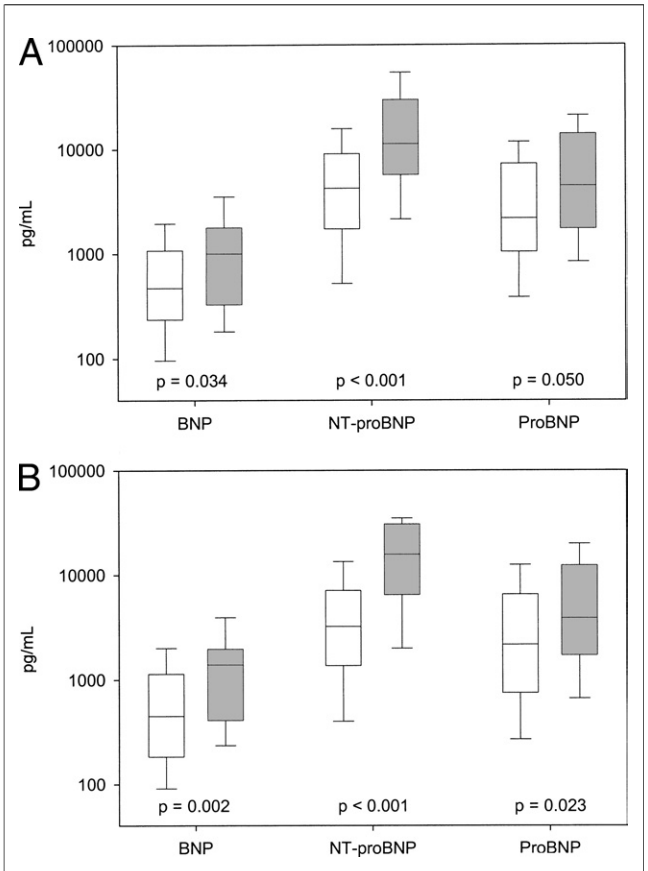


Figure 4 Natriuretic Peptides and All-Cause Mortality

Admission and discharge proBNP levels were evaluated in patients that met the secondary end point. The **box and whisker plots in A** demonstrate that patients that suffered all-cause mortality **(gray boxes)** within 90 days of hospital discharge had significantly higher natriuretic peptide levels at admission compared with those that survived **(open boxes)**. **Panel B** demonstrates that all 3 natriuretic peptides were also significantly elevated at discharge in patients suffering all-cause mortality **(gray boxes)** when compared with those that did not meet the secondary end point **(open boxes)**. BNP = B-type natriuretic peptide; other abbreviations as in Figure 1.

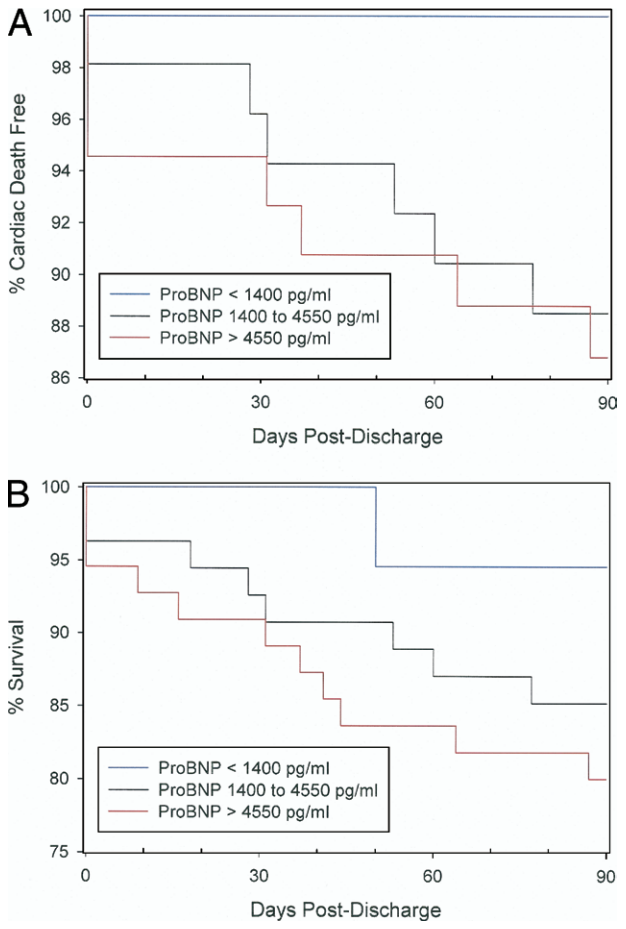


Figure 5 **Natriuretic Peptides and Prognosis**

The plasma natriuretic peptide levels at admission were divided into tertiles and compared with the primary and secondary end points. The Kaplan-Meyer curve in **panel A** demonstrates that patients admitted with a pro-B-type natriuretic peptide (proBNP) level <1,400 pg/ml had significantly fewer cardiac deaths compared with patients in the other tertiles within the follow-up period ($p < 0.05$). **Panel B** demonstrates that patients admitted with a proBNP level <1,400 pg/ml had significantly fewer all-cause deaths within the follow-up period than those with an admission proBNP value >4,550 pg/ml ($p < 0.05$).

AUC suggests that NT-proBNP and BNP at discharge has superior prognostic power for cardiac death compared with proBNP ($p < 0.05$). As shown in the figure, the change in all natriuretic peptides during hospitalization did not predict outcome.

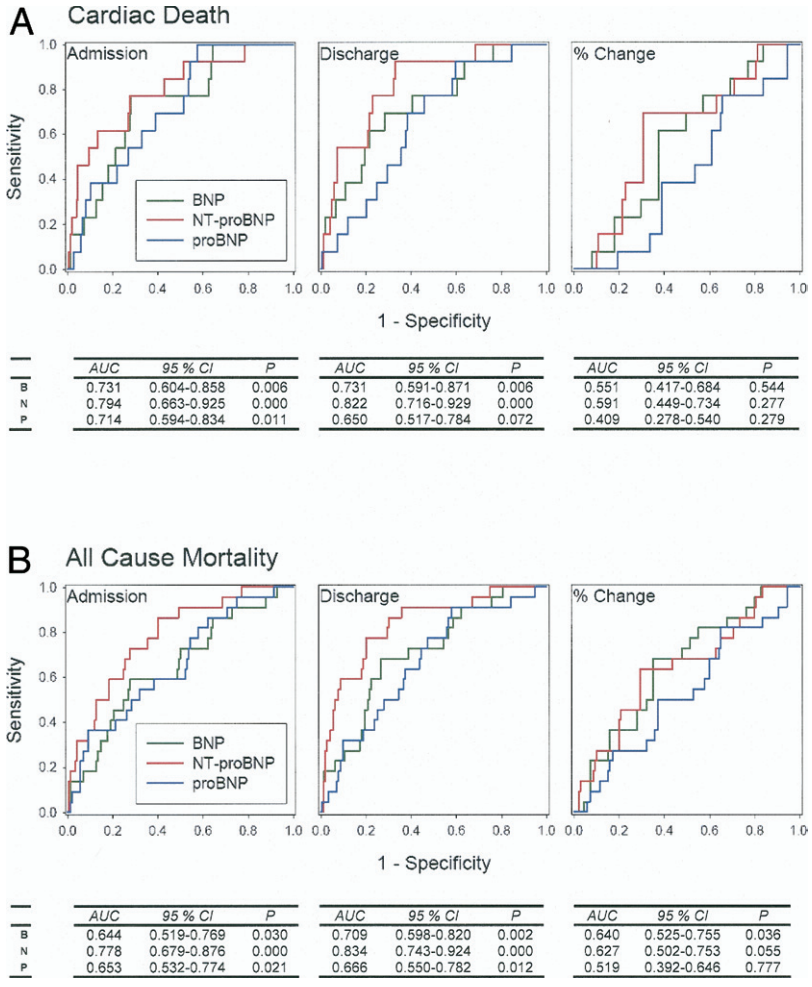
Comparing natriuretic peptides for all-cause mortality prognosis. The admission and discharge values of the natriuretic peptides were compared for their ability to predict the incidence of the secondary end point. A series of ROC curves were created for each of the natriuretic peptides at admission and discharge as related to all-cause mortality (Fig. 6B). All natriuretic peptides at admission exhibited an AUC exceeding 0.64 that statistically differed from the null hypothesis ($p < 0.05$). Comparison of the AUC demonstrated that admission values of NT-proBNP had significantly greater prognostic power for all-cause mortality when compared with BNP ($p < 0.01$) and proBNP ($p < 0.01$). At discharge, each natriuretic peptide demonstrated an AUC exceeding 0.66 that statistically differed from the null hypothesis ($p < 0.02$).

Comparison of the AUC demonstrated that discharge values of NT-proBNP had significantly greater prognostic power for all-cause mortality when compared with BNP ($p < 0.01$) and proBNP ($p < 0.01$). The percent change in BNP during hospitalization produced an AUC of 0.64 ($p < 0.05$). Thus, the admission and discharge values of NT-proBNP had superior prognostic power for all-cause mortality when compared with the other natriuretic peptides assessed at the same time point.

Discussion

Congestive heart failure is a leading cause of morbidity and mortality with significant rates of treatment failure. Research has demonstrated that metabolites of natriuretic peptides may assist in the diagnosis and treatment of this disease. Numerous studies have demonstrated that BNP and NT-proBNP are capable of predicting hospital readmission and eventual mortality in patients suffering from heart failure (9,10,12–14,25). However, it is now apparent that the current assays for both BNP and NT-proBNP may be influenced by other circulating forms of BNP (17). This hypothesis is supported by recent work utilizing mass spectroscopy that failed to identify any circulating BNP in patients with class IV heart failure despite significant elevations on point-of-care BNP testing (26). The present study provides the first prospective evaluation of proBNP in patients hospitalized with acute decompensated heart failure.

The initial characterization of proBNP in the present study suggests that it has significantly different pharmacokinetics from its cleavage products. Previous work has suggested that BNP and NT-proBNP levels increase with age even after excluding patients with "age-related diastolic dysfunction" (27,28). In the present study, our data indicate similar proBNP levels in heart failure patients throughout all age groups. Previous research has also demonstrated that BNP and NT-proBNP levels are inversely related to obesity (29–32). Investigators have hypothesized that there may be a BMI-related defect in natriuretic peptide secretion (29). In the present study, measurements of proBNP were consistent across all degrees of obesity suggesting that the secretion is constant but the subsequent metabolism of the natriuretic peptides may be altered in the setting of increased BMI. Additional studies have suggested that both BNP and NT-proBNP levels are elevated in patients with end-stage renal disease (15,25). The present study demonstrates that proBNP levels are not significantly elevated in heart failure patients with renal insufficiency possibly suggesting a more accurate representation of isolated cardiac dysfunction. It is important to note that others have observed differences in proBNP levels with regard to age, obesity, and renal function among nonhospitalized patients



	AUC	95 % CI	P	AUC	95 % CI	P	AUC	95 % CI	P
B	0.731	0.604-0.858	0.006	0.731	0.591-0.871	0.006	0.551	0.417-0.684	0.544
N	0.794	0.663-0.925	0.000	0.822	0.716-0.929	0.000	0.591	0.449-0.734	0.277
P	0.714	0.594-0.834	0.011	0.650	0.517-0.784	0.072	0.409	0.278-0.540	0.279

	AUC	95 % CI	P	AUC	95 % CI	P	AUC	95 % CI	P
B	0.644	0.519-0.769	0.030	0.709	0.598-0.820	0.002	0.640	0.525-0.755	0.036
N	0.778	0.679-0.876	0.000	0.834	0.743-0.924	0.000	0.627	0.502-0.753	0.055
P	0.653	0.532-0.774	0.021	0.666	0.550-0.782	0.012	0.519	0.392-0.646	0.777

Figure 6 **Natriuretic Peptides and Prognosis of All-Cause Mortality**

The admission and discharge natriuretic peptides were assessed for their ability to predict the incidence of the primary end point and secondary end points. **Panel A** summarizes the relationship between all natriuretic peptides and cardiac death. As demonstrated in the figure, discharge values of NT-proBNP and proBNP had the greatest prognostic potential ($p < 0.05$). **Panel B** summarizes the relationship between natriuretic peptides and all-cause mortality. Once again, the admission and discharge values of NT-proBNP had the greatest prognostic potential ($p < 0.01$). AUC = area under the curve; BNP = B-type natriuretic peptide; CI = confidence interval; other abbreviations as in Figure 1.

(33). The different findings in the present study may be related to our relatively selective patient population. Regardless, the pharmacokinetics of proBNP may have implications for its clinical utility.

The present study confirms the role of natriuretic peptides in the diagnosis and treatment of congestive heart failure. These findings parallel studies that suggest that plasma BNP and NT-proBNP levels are independent predictors of cardiovascular events in populations with heart failure or acute coronary syndromes (9,10,12–14,25,34,35). The precursor to these natriuretic peptides, proBNP, also demonstrated clinical utility with significantly elevated levels at admission in patients ultimately suffering a cardiac death or all-cause mortality. The present data suggest that an admission proBNP level <1,400 pg/ml regardless of BNP level predicts excellent outcomes. The utility of this finding is particularly important in patients with "gray-zone" BNP levels (100 to 500 pg/ml). Dyspneic patients in the emergency department with "gray-zone" BNP levels have better outcomes than those with BNP levels above the "gray zone," despite being perceived as having more severe decompensation (36). If the results of the present study are validated in other patient populations, patients presenting to the emergency department with proBNP levels under 1,400 pg/ml would be considered to be at very low risk. Further studies powered to detect this interaction with larger patient cohorts should evaluate the ability of proBNP to triage patients in combination with existing biomarkers.

The prognostic potential of proBNP may reflect its role in the pathophysiology of decompensated heart failure. A number of studies now suggest that the major circulating natriuretic peptide in patients with decompensated heart

failure is proBNP (22,26). However, proBNP has been demonstrated to have significantly lower biological activity than its active metabolite BNP (22). Because of this, there may be discordance between the high level of circulating natriuretic peptide metabolites and their physiological activity, thus resulting in a functional deficiency in the decompensated state. Some have suggested that a further investigation into the biochemistry behind natriuretic peptide metabolism may provide insight into this paradox (37,38). Unfortunately, available assays for BNP and NT-proBNP also detect proBNP, making it impossible to currently construct meaningful ratios of the known natriuretic peptides. Elucidating the role of the individual natriuretic peptides in the neuroendocrine mechanisms of decompensated heart failure will aid in prognosis.

The present study sought to provide an initial comparison of the prognostic potential of the available natriuretic peptides. The data presented suggest that discharge values of NT-proBNP have the greatest diagnostic yield in predicting patients that will suffer a cardiac death or all-cause mortality within the follow-up period. In concordance with this finding, pilot studies that utilize serial measurements of NT-proBNP to guide management in heart failure patients have demonstrated fewer cardiovascular events (39). Large clinical trials assessing NT-proBNP for monitoring treatment efficacy are currently underway (40). Previous studies have suggested that the ability of NT-proBNP to predict all-cause mortality may be related to its association with renal disease and the resulting cardiorenal syndrome (25). Further studies may illuminate the molecular mechanisms accounting for increased NT-proBNP in excess of other natriuretic peptides in patients eventually suffering cardiac death and all-cause mortality. Perhaps, more importantly, additional studies with larger patient cohorts producing greater statistical power could explore the synergistic potential of combining existing natriuretic peptides with the proven benefit of proBNP measurement.

Study limitations. The present study is hindered by a few unavoidable limitations. The number of patients in the study population was relatively small, making some comparisons difficult without adequate statistical power. The study population was a convenience sample recruited from a single Veterans' Administration Medical Center with a predominantly male patient base. This population also had a high incidence of cardiac disease with other significant comorbidities. Because of this, the results presented may not be applicable to other community settings. Assessment for subsequent cardiac events was largely performed on the electronic medical record. Because of this, it is possible that certain events were not included in our analysis. However, the number of events missed is likely to be negligible, as all study participants have primary care physicians within the Veterans' Administration Medical Center system and most obtain their care solely through the same center. It is important to note that all of the events recorded from telephone follow-up were consistent with the electronic medical record. Despite these limitations, though, the present study does provide the first prospective evidence for the clinical utility of proBNP in patients hospitalized with congestive heart failure.

Conclusions

Our findings provide an initial characterization of proBNP in patients admitted with acute decompensated heart failure. Furthermore, these data demonstrate that all 3 natriuretic peptides are significantly increased at hospital admission in patients ultimately suffering a cardiac death or all-cause mortality. An initial comparison of the natriuretic peptides suggests that discharge values of NT-proBNP have the greatest collective prognostic utility for reaching these end points. It is possible, though, that the assay for NT-proBNP cross reacts with proBNP mitigating some of its benefit. Further studies with larger cohorts producing greater statistical power should explore the role of combining natriuretic peptides to enhance their prognostic potential.

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