Correlation and Prognostic Utility of B-Type Natriuretic Peptide and Its Amino-Terminal Fragment in Patients With Chronic Kidney Disease

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Key Words: Chronic kidney disease; B-type natriuretic peptide; Left ventricular dysfunction

DOI: 10.1309/M7AAXA0J1THMNCDF

Abstract

This study compared the correlation and prognostic utility of B-type natriuretic peptide (BNP) and the N-terminal fragment of proBNP (NT-proBNP) in 171 outpatients with renal dysfunction. The NT-proBNP correlated well with BNP in all cases (r = 0.911; P ≤ .01), regardless of degree of renal impairment or type of left ventricular dysfunction. BNP and NT-proBNP concentrations (P < .005) and their ratios (P ≤ .01) increased as the glomerular filtration rate (GFR) declined, indicating a greater effect of GFR on NT-proBNP levels. Both natriuretic peptide levels were higher in patients with systolic dysfunction (P < .05) compared with patients with normal echocardiograms. In contrast, BNP and NT-proBNP levels were below the diagnostic cutoffs for congestive heart failure exacerbations in patients with normal heart function or diastolic dysfunction, with no statistical difference between these groups (P = .99). Both peptides are useful prognostic tools for predicting mortality and cardiac hospitalization in renal patients.

Cardiovascular disease accounts for half of all deaths in the developed world. Among people with cardiovascular disease, there are 4.7 million Americans with symptomatic heart failure and many more with asymptomatic disease.[1]

More than 9 million Americans have the diagnosis of chronic kidney disease (CKD).[2,3] In an aging population with increasingly prevalent comorbid risk factors such as hypertension and diabetes mellitus, the incidence of patients with both congestive heart failure (CHF) and renal disease will continue to rise, especially given the availability of dialysis and increasing survival rates following myocardial insult. The cardiorenal syndrome is an active area of investigation in which, as kidney function worsens, there is an increased incidence of CHF and decreased survival. CKD is a major predictor of increased cardiovascular events, including cardiac and all-cause mortality.[4-7]

The cardiac ventricles release B-type natriuretic peptide (BNP), a bioactive cardiac neurohormone, and its inactive amino-terminal fragment, NT-proBNP, in response to volume expansion and pressure overload.[8] The physiologic functions of BNP counteract many detrimental neurohormonal pathways involved in the perpetuation of CHF. These functions include natriuresis, diuresis, vasodilation, inhibition of sympathetic tone, inhibition of the renin-angiotensin-aldosterone axis, and inhibition of endothelin-1.[8] BNP concentrations, which are elevated in patients with left ventricular dysfunction, correlate with New York Heart Association functional class,[9] pulmonary capillary wedge pressure,[10] systolic and diastolic left ventricular dysfunction echocardiographic findings,[11-13] and prognosis.[14,15] The availability of BNP measurements, in conjunction with history and physical examination findings, increases the diagnostic accuracy of CHF in patients admitted to an emergency department with shortness of

breath.[9] BNP also is validated as a biomarker of decompensated heart failure in patients with renal disease.[16] Like its active counterpart, NT-proBNP diagnoses CHF and predicts subsequent cardiac outcomes.[17-19]

It has been suggested that due to its increased reliance on renal clearance, NT-proBNP is a less reliable biomarker in patients with renal disease.[20] The goal of the present study was to evaluate the correlation of BNP and NT-proBNP in stable patients with renal dysfunction. Furthermore, we analyzed the prognostic usefulness of these biomarkers in this high-risk patient population.

Materials and Methods

Study Design and Population

The University of California San Diego Institutional Review Board approved the study. All patients admitted to the San Diego Veteran Affairs (VA) Medical Center renal clinic between June 2003 and April 2004 with an established diagnosis of CKD were eligible to participate in this study. Patients receiving dialysis were excluded. Of the eligible patients, 171 were enrolled and 29 declined. After obtaining signed, written consent, data were obtained from the electronic medical record, including medical history, physical examination, laboratory tests, and echocardiograms. If the enrolled patient did not have an echocardiogram within 6 months before enrollment, every effort was made to obtain one. We obtained echocardiograms on 78 of 171 patients. The primary end point for our prognostic analysis was defined as all-cause mortality or cardiac hospitalization (hospitalization for acute coronary syndrome or CHF). Patients were followed up prospectively through medical record chart review and a 6-month phone conversation to obtain data on this end point.

Biochemical Analysis

At enrollment, a 5-mL blood sample was collected into a plastic tube containing potassium EDTA (1 mg/mL blood). Within 5 hours, samples were centrifuged at 1,000 relative centrifugal force for 15 minutes at 4°C, and plasma samples then were stored at –70°C in plastic vials. Samples were stored for a maximum of 3 months before analysis. There were no freeze-thaw cycles. BNP was measured using the Triage B-Type Natriuretic Peptide test (Biosite, San Diego, CA)[21] and ADVIA Centaur BNP assay (Bayer Diagnostics, Tarrytown, NY).[22] The reference interval for both BNP assays is less than 100 pg/mL.[21,22] NT-proBNP was measured using the Elecsys ProBNP assay (Roche Diagnostics, Indianapolis, IN).[23] The NT-proBNP reference interval is less than 125 pg/mL for people younger than 75 years and less than 450 pg/mL for people 75 years or older.[23] The coefficients of variation for commercially prepared quality control materials are approximately 12%, 5%, and 5% for the Biosite, Bayer, and Roche assays, respectively.

Creatinine was measured using the Jaffe rate reaction with conventional calibration in a College of American Pathologists certified laboratory. The glomerular filtration rate (GFR) then was calculated based on the conventional Modification of Diet in Renal Disease equation.[24]

Statistical Analysis

Descriptive statistics were computed for all subjects. Parametric analyses using BNP and NT-proBNP were computed with log-transformed values. All results are expressed in mean values (antilogs of means of log-transformed values) and standard errors in the figures. For subgroup analysis, the patient population was divided by GFR and type of left ventricular dysfunction. Differences among subgroups were tested with analysis of variance followed by Tukey post hoc tests. Correlations with natriuretic peptides were computed using Pearson correlations. In addition, receiver operating characteristic (ROC) curves were calculated to predict cumulative events (mortality or hospitalization for cardiac events). Sensitivity, specificity, and negative predictive value were computed for BNP and NT-proBNP at selected cut points. Kaplan-Meier survival analyses with log-rank tests were used to evaluate the significance of BNP and NT-proBNP cut points in determining our primary outcome. These cutoff values were chosen based on ROC curve data to yield equal sensitivities. Cox regression analyses based on a multivariable approach were performed on each of our natriuretic peptide assays to analyze the influence of other variables on the prediction of death or cardiac events requiring hospitalization. The association of NT-proBNP/BNP ratios with GFR was assessed by using the Spearman correlation.

Results

The baseline characteristics of all 171 patients are shown in **Table 1**. NT-proBNP correlated well with BNP in all cases, with the Biosite and Bayer BNP assays providing comparable results (r = 0.911 and 0.912, respectively, $P < .01$) **Figure 1**.

Effect of CKD Stage on Natriuretic Peptide Concentrations

The National Kidney Foundation recommends that CKD be divided into 5 stages based on GFR: I, GFR 90 or more (CKD risk factors); II, GFR 60 to 89 (mild renal insufficiency); III, GFR 30 to 59 (moderate renal insufficiency); IV, GFR 15 to 29 (severe renal insufficiency); and V, GFR less than 15 (end-stage renal disease).[25] With the exception of stage I,

DOI: 10.1309/M7AAXA0J1THMNCDF

which had a small sample size, BNP correlated well with NT-proBNP across all stages of CKD **Table 2**. Owing to insufficient blood sampling, both natriuretic peptides were not measured for 5 of 171 patients. Therefore, the numbers of patients used to assess each correlation also are noted in Table 2. Creatinine levels ranged from 0.8 to 8.1 mg/dL (71-716 μmol/L). GFR correlated weakly with BNP (Biosite, r = 0.362; $P \leq .01$; Bayer, $r = 0.333$; $P \leq .01$) and NT-proBNP (r = 0.458; $P \leq .01$). BNP and NT-proBNP levels increased progressively as GFR declined ($P < .005$) **Figure 2**. The NT-proBNP/BNP ratio also increased as GFR declined (Biosite, r = –0.429; $P \leq .001$; Bayer, $r = –0.496$; $P \leq .001$), indicating a greater rise in NT-proBNP relative to BNP.

Effect of Left Ventricular Dysfunction Type on Natriuretic Peptide Concentrations

When analyzed by the type of left ventricular dysfunction as determined from echocardiographic data, the correlation between BNP and NT-proBNP remained strong **Table 3**. The only exception was with systolic-only dysfunction, which had a small sample size and did not reach statistical significance. Creatinine was similar in these left ventricular dysfunction groups ($P = .606$). BNP (Biosite and Bayer) and NT-proBNP concentrations were significantly higher in patients with systolic left ventricular dysfunction (464, 363, and 3,773 pg/mL, respectively) and combined systolic and diastolic dysfunction (242, 197, and 1,671 pg/mL, respectively) compared with patients with normal echocardiograms (81, 58, and 348 pg/mL, respectively), $P < .05$ **Figure 3**. However, there was no statistically significant difference between patients with normal echocardiograms and patients with diastolic dysfunction (71, 63, and 376 pg/mL, respectively; $P = .99$ for each).

Table 1
Characteristics of 171 Patients*

Characteristic	Value
Age, mean, y	65
Male sex	167 (98.2)
Caucasian	114 (66.7)
African American	22 (12.9)
Mean body mass index, kg/m^2	30
Mean blood pressure, mm Hg	
Systolic	149
Diastolic	71
Medical history	
Coronary artery disease	55 (32.2)
Myocardial infarction	19 (11.1)
Coronary artery bypass graft	18 (10.5)
Percutaneous coronary intervention	11 (6.4)
Diabetes mellitus	85 (49.7)
Hypertension	149 (87.1)
Hyperlipidemia	97 (56.7)
Renal transplantation	15 (8.8)
Medications	
Angiotensin-converting enzyme inhibitor	78 (45.6)
Angiotensin receptor blocker	32 (18.7)
Beta blocker	96 (56.1)
Calcium channel antagonist	58 (33.9)
Diuretic	111 (64.9)
Mean laboratory data	
Creatinine, mg/dL (μmol/L)	2.3 (203)
Glomerular filtration rate, mL/min/1.73m^2	41
Serum urea nitrogen, mg/dL (mmol/L)	35.2 (12.6)

* Data are given as number (percentage) unless otherwise indicated.

Prognostic Utility of Natriuretic Peptides in Renal Disease

The primary end point was defined as mortality or a cardiac event requiring hospitalization. Patients were followed up for a mean of 268 days (100-473 days). During follow-up, 7 deaths (4.1%) and 15 cardiac events (8.8%) requiring hospitalization occurred. BNP (Biosite), BNP (Bayer), and NT-proBNP levels were significantly higher in patients who had a

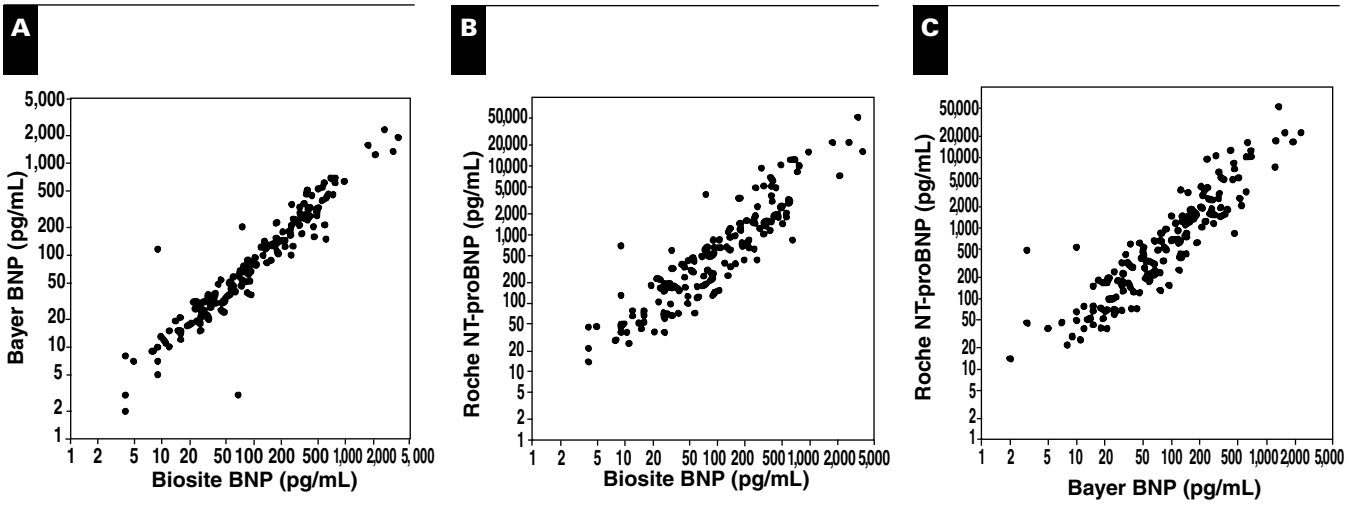

Figure 1 Natriuretic peptides in 171 patients with chronic kidney disease. BNP, B-type natriuretic peptide; NT-proBNP, N-terminal fragment of proBNP.

DOI: 10.1309/M7AAXA0J1THMNCDF

Table 2
Correlation of BNP and NT-proBNP Across the GFR Spectrum*

	Correlation	*P*
Stage I (GFR, ≥90)		
Bayer vs Biosite BNP assay (n = 6)	0.851	.032
Bayer BNP vs Roche NT-proBNP assay (n = 6)	0.431	.394
Biosite BNP vs Roche NT-proBNP assay (n = 6)	0.797	.058
Stage II (GFR, 60-89)		
Bayer vs Biosite BNP assay (n = 13)	0.974	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 12)	0.928	<.01
Biosite BNP vs Roche NT-proBNP assay (n = 12)	0.934	<.01
Stage III (GFR, 30-59)		
Bayer vs Biosite BNP assay (n = 88)	0.960	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 92)	0.926	<.01
Biosite BNP vs Roche NT-proBNP assay (n = 89)	0.900	<.01
Stage IV (GFR, 15-29)		
Bayer vs Biosite BNP assay (n = 42)	0.950	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 42)	0.923	<.01
Biosite BNP vs Roche NT-pro BNP assay (n = 42)	0.906	<.01
Stage V (GFR, <15)		
Bayer vs Biosite BNP assay (n = 12)	0.893	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 12)	0.881	<.01
Biosite BNP vs Roche NT-proBNP assay (n = 12)	0.954	<.01

BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, N-terminal fragment of proBNP.
* The GFR unit is mL/min/1.73 m^2.

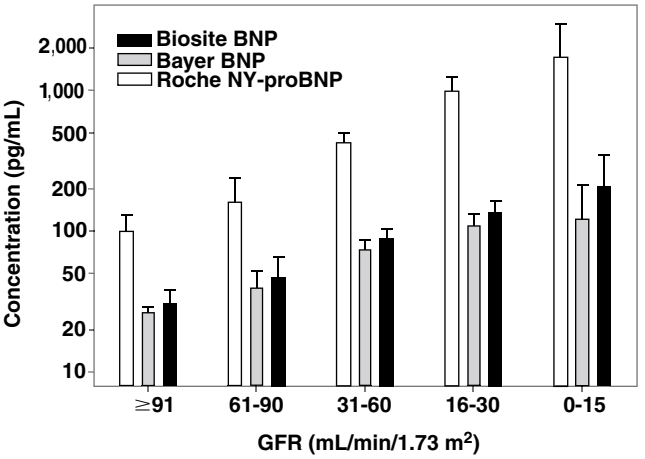

Figure 2 B-type natriuretic peptide (BNP) and N-terminal fragment of proBNP (NT-proBNP) concentrations based on stage of chronic kidney disease. Values are expressed as mean ± SE. $P < .005$ between groups.

primary event (266, 217, and 1,774 pg/mL, respectively) compared with those for patients who remained event-free (84, 68, and 438 pg/mL, respectively; $P \leq .001$) **Figure 4**. When BNP (Biosite and Bayer) and NT-proBNP were used to predict the endpoint, the areas under the ROC curve were 0.711 ($P = .002$), 0.729 ($P = .001$), and 0.705 ($P = .003$), respectively. Cut points were chosen based on ROC curve data to yield equivalent sensitivities: Biosite BNP, 175 pg/mL (65% sensitivity and 66% specificity); Bayer BNP, 175 pg/mL (65% sensitivity and 74% specificity); and Roche Diagnostics NT-proBNP, 1,250 pg/mL (65% sensitivity and 74% specificity). The negative predictive value was 93% for both BNP assays and 94% for the NT-proBNP.

Kaplan-Meier curves, based on these cut points, displayed a statistically significant difference in mortality or hospitalization for cardiac event **Figure 5**.

Cox regression analyses indicated that age, race, weight, hypertension, diabetes mellitus, and, most notably, GFR were not independent predictors of our end point. In contrast, a history of coronary artery disease had a statistically significant influence

Table 3
Correlation of BNP and NT-proBNP by Type of Left Ventricular Dysfunction

	Correlation	*P*
Normal		
Bayer vs Biosite BNP assay (n = 14)	0.973	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 14)	0.960	<.01
Biosite BNP vs Roche NT-proBNP assay (n = 14)	0.952	<.01
Systolic dysfunction		
Bayer vs Biosite BNP assay (n = 6)	0.986	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 6)	0.799	.57
Biosite BNP vs Roche NT-proBNP assay (n = 6)	0.828	.04
Diastolic dysfunction (n = 35)		
Bayer vs Biosite BNP assay (n = 34)	0.916	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 35)	0.902	<.01
Biosite BNP vs Roche NT-proBNP assay (n = 35)	0.847	<.01
Combined systolic and diastolic dysfunction (n = 23)		
Bayer vs Biosite BNP assay (n = 23)	0.867	<.01
Bayer BNP vs Roche NT-proBNP assay (n = 24)	0.785	<.01
Biosite BNP vs Roche NT-proBNP assay (n = 23)	0.874	<.01

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal fragment of proBNP.

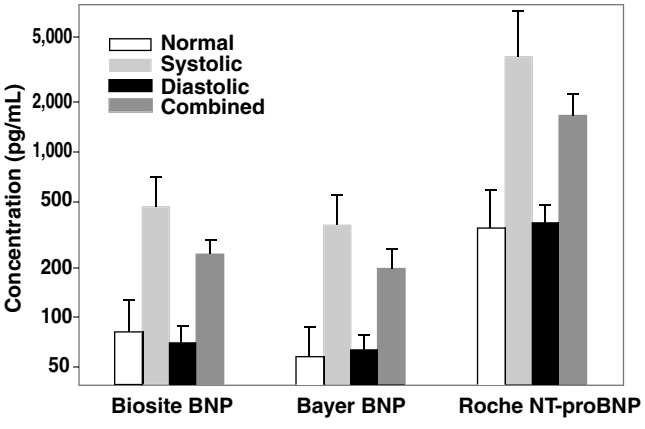

Figure 3 B-type natriuretic peptide (BNP) and N-terminal fragment of proBNP (NT-proBNP) concentrations based on type of left ventricular dysfunction. Values are expressed as mean ± SE.

DOI: 10.1309/M7AAXA0J1THMNCDF

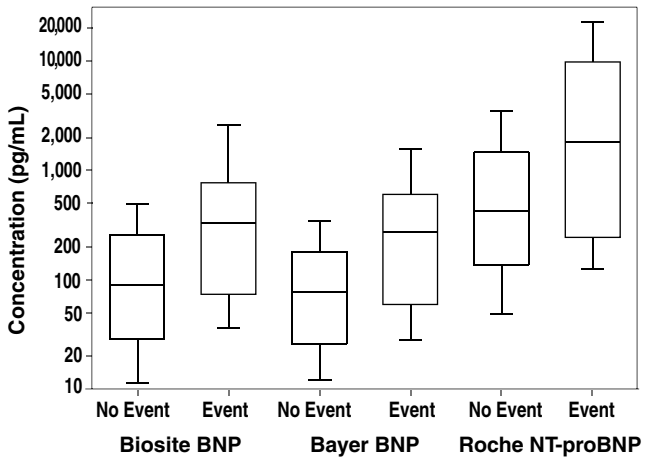

Figure 4 B-type natriuretic peptide (BNP) and N-terminal fragment of proBNP (NT-proBNP) concentrations in patients who did and did not reach the clinical endpoint of mortality or hospitalization for cardiac event. The line represents the median; box ends, the 25th and 75th percentiles; and whiskers, the 10th and 90th percentiles.

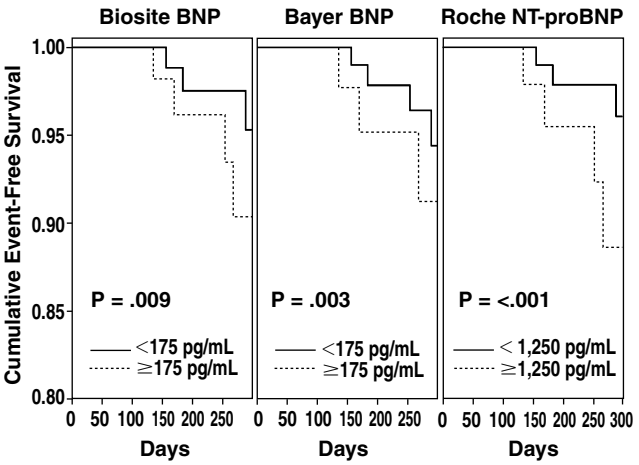

Figure 5 Kaplan-Meier curves showing a B-type natriuretic peptide (BNP) cutoff of 175 pg/mL and an N-terminal fragment of proBNP (NT-proBNP) cutoff of 1,250 pg/mL to predict our combined end point of mortality and cardiac hospitalization.

on end point prediction (P = .009, P = .012, and P = .006 for multivariate analysis including Biosite BNP, Bayer BNP, and NT-proBNP, respectively). After adjustment for coronary artery disease history, both BNP assays retained their independent prognostic ability (Biosite, P = .027 and Bayer, P = .041), with NT-proBNP on the border of statistical significance (P = .051).

Discussion

Patients with both CHF and renal disease are at higher risk for premature death and hospitalization for cardiac events. An assay to assist in the diagnosis of decompensated CHF and risk stratification should lead to more aggressive medical therapy and lifestyle modification, with the intent of altering the rate of disease progression. The interpretation of BNP and NT-proBNP levels in patients with renal disease requires an understanding of how these biomarkers compare in the compensated state and how they are altered based on the degree of renal impairment and type of left ventricular dysfunction.

The results of our study indicate that BNP and NT-proBNP correlate well in a stable outpatient population with renal disease irrespective of CKD stage. Similar results were seen in a patient population with stable ischemic heart disease, in which BNP and NT-proBNP also correlated well regardless of renal function.[26] BNP and NT-proBNP concentrations, as well as the BNP/NT-proBNP ratio, increase as the GFR declines. This increasing ratio of NT-proBNP/BNP with decreasing GFR indicates that NT-proBNP is influenced to a greater degree by renal function. In our study, this divergence of natriuretic peptide concentrations does not alter their correlation and, thus, does not seem to be clinically significant in the compensated state.

Our correlations of GFR with BNP (Biosite, r = 0.362 and Bayer r = 0.333) and NT-proBNP (r = 0.458) are consistent with trends observed in several other recent articles.[26-29] There remains, however, conflicting data about the independent influence of renal function on natriuretic peptide concentrations.[26,27,29,30] DeFilippi et al[28] found that the incidence of coronary artery disease increased with declining GFR. It is possible that the increased incidence of heart disease in patients with renal failure, rather than the renal failure itself, is the major determinant of elevated BNP and NT-proBNP concentrations in this patient population. In our patients with CKD with no evidence of structural heart disease, BNP and NT-proBNP concentrations were in the normal range. This finding is in agreement with that of Takami et al,[27] who found that without evidence of fluid overload, there was no creatinine-driven elevation of BNP, even in patients with severe renal disease.

Our echocardiographic data indicate a strong correlation between BNP and NT-proBNP regardless of type of left ventricular dysfunction. It is interesting that there is no detectable BNP or NT-proBNP difference between patients with normal echocardiograms and those with diastolic dysfunction in the compensated state. Therefore, normal levels of these biomarkers do not necessarily indicate that the patient is free of underlying heart disease.

DOI: 10.1309/M7AAXA0J1THMNCDF

Patients with both renal disease and compensated systolic dysfunction had mean BNP (Biosite and Bayer) and NT-proBNP levels of 464, 363, and 3,773 pg/mL, respectively. These natriuretic peptide concentrations are significantly higher than the currently recommended diagnostic cutoffs for CHF, even when incorporating recently suggested increases to the NT-proBNP cutoff.[31-33] This discrepancy highlights the importance of establishing adjusted diagnostic cut points for BNP and NT-proBNP for the diagnosis of CHF exacerbation in patients with both systolic dysfunction and renal impairment.

To the best of our knowledge, this is the first prospective study to show that both BNP and NT-proBNP are strong prognostic indicators of mortality or cardiac hospitalization in patients with renal failure. Another recent study also found levels of both natriuretic peptides to be significantly elevated in patients with stable ischemic heart disease who reached the composite end point of 12-month all-cause mortality and/or hospitalization for heart failure.[26] Their analyses were carried out with mean peptide levels as cut points, whereas our cut points were optimized using ROC curve data to yield equivalent sensitivities and are most useful for their very high negative predictive values.

There are several limitations to the present study. Because it was conducted at a single veteran's hospital with a patient population consisting predominantly of older men with a high prevalence of cardiac disease, one must be careful about generalizing these results to a broader population. Also, because we relied on VA electronic medical records for outcome adjudication, there exists the potential of missed outcomes. This risk is minimal, however, because all of our study patients have VA primary care physicians and most obtain their care solely through the VA San Diego medical system. Notably, all of the events recorded from our 6-month phone follow-up were represented in the electronic chart review. Finally, because we restricted our echocardiographic data analysis to less than half of our patient population, the correlation of natriuretic peptides based on type of left ventricular dysfunction might be biased by a small sample.

There is a strong correlation between BNP and NT-proBNP in patients with renal disease regardless of the degree of renal insufficiency or type of left ventricular dysfunction. From our ROC curve analysis, a BNP level of 175 pg/mL and an NT-proBNP level of 1,250 pg/mL clearly identify renal patients at high risk for mortality or cardiac hospitalization. Further studies are needed to determine why BNP and, to a greater effect, NT-proBNP are elevated in patients with renal failure and whether these elevations are clinically important in the decompensated state.

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DOI: 10.1309/M7AAXA0J1THMNCDF