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Impact of Renal Disease on Natriuretic Peptide Testing for Diagnosing Decompensated Heart Failure and Predicting Mortality

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Background: **Concomitant occurrence of kidney disease (KD) and heart failure (HF) is common and associated with poor outcomes. Natriuretic peptide studies have typically excluded many individuals with KD. We compared the accuracy of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) for diagnosing decompensated HF and predicting mortality across the spectrum of renal function.**

Methods: **BNP and NT-proBNP were prospectively measured in a cohort of 831 dyspnea patients. KD was defined as an estimated glomerular filtration rate $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. The accuracy and predictive value of each test for diagnosing decompensated HF and predicting all-cause 1-year mortality were assessed by ROC area under the curve (AUC) and multivariate regression analysis.**

Results: **Among the 831 dyspnea patients, 393 (47%) had KD. The diagnostic accuracies of BNP and NT-proBNP in detecting decompensated HF were similar to each other in patients without KD (AUC 0.75 vs 0.74, respectively; $P = 0.60$) and in patients with KD (AUC 0.68 vs 0.66; $P = 0.10$). One-year mortality rates were 36.3% and 19.0% in those with and without KD, respectively ($P < 0.001$). Progressively higher BNP and NT-proBNP concentrations remained predictive of increased mortality in KD patients. Compared with the lowest quartile, quartile 4 of BNP had an adjusted hazards ratio (HR) of 2.6 (95% CI 1.4–4.8; $P = 0.004$ for trend) and NT-proBNP quartile 4 had an HR of 4.5 (95% CI 2.0–10.2; $P < 0.001$ for trend). Only NT-proBNP remained a predictor of death after adjustment for clinical confounders and the other natriuretic peptide marker.**

Conclusions: **NT-proBNP and BNP are equivalent predictors of decompensated HF across a spectrum of renal function, but NT-proBNP is a superior predictor of mortality.**

B-type natriuretic peptide (BNP)[3] and N-terminal proBNP (NT-proBNP) are established markers for decompensated heart failure (HF) in patients with dyspnea *(1–6)*. In the setting of impaired renal function the accuracy of BNP and NT-proBNP concentrations for predicting decompensated HF are reported as reduced *(7, 8)*. Prior reports of diagnostic accuracy are derived from prospectively performed studies that enrolled a majority of patients with either a high or low pretest likelihood of decompensated HF and only a small minority of patients with impaired renal function, as defined by chronic kidney disease (CKD) stage 3 [estimated glomerular filtration rate (eGFR) 30–59 $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ (calculated by the abbreviated Modification of Diet in Renal Disease formula)] or greater *(5, 6, 9)*. Few patients studied to date have an eGFR $<30\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ (stage 4–5). Lastly, little is known about the prognostic accuracy for mortality of either assay in the CKD population and how prognosis compares with the ability of the assays to diagnose decompensated HF in a population who also carry a high burden of coronary disease and other comorbid condi-

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[3] Nonstandard abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; HF, heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ED, emergency department; AMR, analytical measurement range; LVEF, left ventricular ejection fraction; AUC, area under the curve; PRIDE, Pro-BNP Investigation of Dyspnea in the Emergency Department.

tions that may increase natriuretic peptide concentrations in the absence of HF *(10)*.

The objectives of this study were 2-fold. First, we compared the diagnostic accuracies of NT-proBNP and BNP for diagnosing decompensated HF and predicting 1-year all cause mortality in a large cohort of patients with a full spectrum of impaired renal function who presented to a community hospital. Second, we determined whether the natriuretic peptide cutoffs derived from previously published studies of prospectively recruited all-comers cohorts remained optimal in this clinician-selected cohort.

Materials and Methods

PATIENT POPULATION

We included 831 consecutive patients with the complaint of dyspnea who presented to the Carolinas Medical Center emergency department (ED) from June 2003 to June 2004 and who underwent measurement of a natriuretic at presentation. Patients younger than 18 years or in whom there was inadequate clinical information recorded to assess the etiology of dyspnea were excluded from the analysis. For patients with multiple admissions, the first admission was reviewed. This protocol was approved by the Institutional Review Boards of the University of Maryland and the Carolinas Medical Center.

NATRIURETIC PEPTIDE MEASUREMENT

Blood samples were anticoagulanted with EDTA and sent immediately to the clinical laboratory. For BNP measurements (Triage, Biosite) whole blood was used. For NT-proBNP measurements (Elecsys 2010, Roche Diagnostics) plasma was used. All measurements were performed within 4 h of specimen collection. Total imprecision values for BNP were 10%–15% at 115 ng/L and for NT-proBNP were 2%–5% at 175 and 4550 ng/L. The analytical measurement range (AMR) for NT-proBNP was 5–35 000 ng/L. A BNP range of 5–1150 ng/L was maintained throughout the study, although the manufacturer's AMR was extended above 1150 ng/L. No sample dilutions were performed; NT-proBNP values exceeding AMR were reported as >35 000 ng/L; all BNP values >1150 ng/L were reported as >1150 ng/L. Thirty-five (3.9%) of the patients had an NT-proBNP value above the AMR and 165 (18.3%) had a BNP value above the AMR.

DATA COLLECTION AND HF ADJUDICATION

This study was prospectively designed to simultaneously measure both NT-proBNP and BNP and review medical records to identify potential factors that influenced each biomarker's accuracy for diagnosing decompensated HF. All patient charts were reviewed and demographics, height, weight, serum creatinine, cardiovascular risk factors, cardiovascular history, cardiovascular test results, medications, and discharge ICD-9 codes were abstracted into a case report form. eGFR was estimated using the abbreviated (4-variable) Modification of Diet in Renal Disease formula *(9)*. Renal functional impairment was defined as an eGFR $<60\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ based on criteria established by the National Kidney Foundation *(9)*. Severe renal impairment was characterized by an eGFR $<30\ mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$. Prior coronary artery disease was defined as a history of myocardial infarction or revascularization or an ischemic cardiomyopathy (a history of coronary disease or myocardial infarction with a left ventricular ejection fraction [LVEF] ≤40%). A history of HF was defined by a prior diagnosis, or if uncertain, by the use of loop diuretics in the setting of a known LVEF ≤40%. Atrial fibrillation was defined as a current or prior diagnosis of the arrhythmia. In addition we used disposition within the hospital as a surrogate for the clinician's opinion of illness severity (i.e., emergency room discharge, admission to hospital wards, or admission to an intensive care unit). When NT-proBNP and BNP values were available at more than one time point, the first set drawn was used for the analysis. Case report forms were reviewed by a cardiologist blind to the natriuretic peptide results for a final diagnosis of decompensated HF. To determine whether interobserver agreement would be comparable to prior studies that used 2 adjudicators, a 2nd cardiologist reviewed 50 randomly selected cases. Agreement between the reviewers was 84%, comparable to the agreement between reviewers in a multicenter study *(7)*. Factors influencing the adjudicated diagnosis of the cardiologist included the clinicians' diagnosis, presenting symptoms, presenting laboratory results other than natriuretic peptides, hospital course (particularly use of medications such as loop diuretics, ionotropes such as dobutamine, or vasodilators such as neseritide), diagnostic test results during hospitalization, prior history of HF or cardiomyopathy, and absence of alternative explanations for dyspnea. The diagnosis of decompensated HF was confirmed by the adjudicator when this was a primary discharge diagnosis, when other causes of dyspnea were absent, and when the treatment plan was consistent with decompensated HF. In the setting of multiple diagnoses to potentially explain dyspnea, the adjudicator evaluated the medical record to determine whether decompensated HF was an active problem or of primarily historical importance. In the absence of a clinical diagnosis of decompensated HF the adjudicator would contradict the clinician diagnosis only in the presence of documented treatment and test results consistent with decompensated HF.

FOLLOW-UP

The Social Security Death Index database was reviewed through April 2005 for all-cause mortality with a median follow-up of 400 days (interquartile range 300–475). Mortality status could be determined in 816 (98%) of patients.

STATISTICAL ANALYSIS

Baseline characteristics were compared among patients with and without impaired eGFR using the χ^2 or the *t*-test for categorical or gaussian distributed continuous covari-

ates, respectively; the Wilcoxon rank-sum test was used to compare continuous covariates with nongaussian distributions. Correlation between each natriuretic peptide and eGFR was estimated with the Spearman rank correlation coefficient. The diagnostic accuracy of each natriuretic peptide for decompensated HF was first examined using ROC plots. For the purposes of these ROC analyses, we redefined those measurements that were above the upper limit of the analytic measurement range to be 1 ng/L greater than this upper limit. Areas under the curve (AUC) of ROC plots for BNP and NT-proBNP were estimated and compared using the method of DeLong et al. *(11)*. For each biomarker we selected optimal cutoff values at which disease status was correctly identified for the greatest percentage of individuals (i.e., where accuracy was maximized). Where accuracy was maximized at more than one cut-point, the cut-point with the highest accuracy and sensitivity was selected. These cutoff values were compared with those derived from prospective trials *(7, 8)*. Overall accuracy of diagnosis of decompensated HF for the internally derived cutoff values was nearly identical to the accuracy for the cutoff values derived from the prospective trials. For BNP accuracy was 71.0% vs 70.7%, respectively, and for NT-proBNP accuracy was 69.0% vs 68.5%, respectively. Therefore, for consistency, performance characteristics are reported only for cutoff values derived from prospective trials.

Multivariate logistic regression was used to determine the association between each natriuretic peptide and decompensated HF, adjusted for potential confounders. Adjustment covariates were selected a priori on the basis of a plausible causal relationship with both natriuretic peptides and risk of decompensated HF, and included age, sex, race, renal function, history of dialysis treatment, diabetes, atrial fibrillation, hypertension, coronary artery disease, prior history of HF, and patient disposition from ED (home, ward admission, or intensive care unit admission—a marker of acuity of illness). Quartiles of either BNP or NT-proBNP were entered into these models as the primary predictor variables of interest; likelihood ratio testing of these quartiles was used to determine their statistical significance. Goodness of fit of the logistic models was determined by the Hosmer–Lemeshow test; all final multivariate models showed reasonable goodness of fit ($P > 0.3$).

For analysis of natriuretic peptides and 1-year all-cause survival, Kaplan–Meier estimates of cumulative survival were compared across the highest and lowest quartiles of BNP and NT-proBNP. The log rank test was used to test for significance between highest and lowest quartiles of each biomarker. ROC curves for 1-year mortality were generated and compared between BNP and NT-proBNP as described for the analysis of decompensated HF. Cox proportional hazard regression was used to estimate the association between quartiles of BNP and NT-proBNP with all-cause mortality, with participants censored at 1 year of follow-up. Adjustment was made for the same set of potential confounders as in the analysis of decompensated HF, with additional adjustment for the presence of decompensated HF. Statistical significance of the natriuetic peptide variables in predicting all-cause mortality was determined with the likelihood ratio test. Interactions between quartiles of natriuretic peptides and eGFR were examined through likelihood ratio testing of multiplicative interaction terms. Tests for violations of the proportional hazards assumption were performed, and no such violations were identified. All statistical analyses were preformed using Intercooled Stata version 8.2 (StataCorp).

Results

A total of 831 patients who had undergone simultaneous measurement of BNP and NT-proBNP concentrations had adequate information recorded to calculate eGFR and to determine the presence or absence of HF. Impaired renal function [eGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$] was present in 393 (47%) of these patients, of whom 139 had an eGFR <30 mL · min^{-1} · (1.73 m^2)$^{-1}$ and 20 were receiving maintenance dialysis treatment. Baseline characteristics of patients with moderate to severely impaired renal function vs those with normal to mildly impaired renal function are shown in Table 1. Patients with impaired renal function were older, more frequently white, and had a greater prevalence of cardiovascular risk factors, history of HF, and coronary artery disease. LVEF tended to be lower, and both NT-proBNP and BNP were significantly higher in patients with impaired renal function. The correlation between NT-proBNP and BNP concentrations and eGFR was modest but significant (NT-proBNP vs eGFR, $\rho = -0.42$, $P < 0.01$, and BNP vs eGFR, $\rho = -0.34$, $P < 0.01$). NT-proBNP and BNP were highly correlated among individuals with impaired renal function ($\rho = 0.87$; $P < 0.0001$) and those with eGFR $\geq$ 60 mL · min^{-1} · (1.73 m^2)$^{-1}$ ($\rho = 0.90$; $P < 0.0001$).

DECOMPENSATED HF DIAGNOSIS

The diagnosis of decompensated HF was present in 437 (53%) patients. The diagnosis was more common in patients with impaired renal function (61%) vs patients with more preserved renal function (45%; $P < 0.01$). Among patients with impaired renal function and an adjudicated diagnosis of decompensated HF, 42% had no prior history of HF, and 36% (of the 186 with measured LVEF and decompensated HF) had an LVEF $\geq$50%. In patients with more preserved renal function, 40% of the 152 with measured LVEF and decompensated HF had an LVEF $\geq$50%, and 52% with decompensated HF had no prior history of HF. In patients diagnosed with decompensated HF, values of both BNP and NT-proBNP were significantly higher in patients with moderately to severely impaired renal function ($P < 0.01$ for both comparisons; Fig. 1).

Median values of BNP augment comparably in HF vs non-HF patients with impaired renal function (688 ng/L vs 180 ng/L; $P < 0.001$) and in those with an eGFR $\geq$60

Table 1. Characteristics of study population, by eGFR.

Characteristic	eGFR<60 mL · min^{-1} · (1.73 m^2)$^{-1}$ (n = 393)[a]	eGFR≥60 mL · min^{-1} · (1.73 m^2)$^{-1}$ (n = 438)[a]	*P* value
Age	69.3 (13.1)	63.5 (16.0)	<0.001
Male	188 (47.8)	192 (43.8)	0.3
African-American	133 (33.8)	185 (42.2)	0.04
Hypertension	286 (72.8)	269 (61.4)	0.001
Diabetes	181 (46.1)	124 (28.3)	<0.001
Prior HF	164 (41.7)	123 (28.1)	<0.001
Atrial fibrillation	91 (23.2)	84 (19.2)	0.16
Coronary disease	147 (37.4%)	116 (26.5)	0.001
BNP, ng/L	534 [123, 1150]	215 [63, 546]	<0.001
NT-proBNP, ng/L	3961 [863, 12407]	1058 [296, 3288]	<0.001
Creatinine, mg/L	18.0 [14.0, 26.0]	9.0 [8.0, 11.0]	<0.001
Disposition from ED			
Home	12 (3.1)	26 (6.0)	
Ward	292 (74.9)	325 (74.5)	0.1
ICU[b]	86 (22.1)	85 (19.5)	
LVEF (n = 564, 68%)	45 [28, 58]	52 [33,58]	0.052
BMI (n = 619, 74%)	28.8 [23.8, 34.6]	27.9 [23.1, 34.4]	0.3

[a] Percentages are shown in parentheses and interquartile ranges in brackets. Values are n (%) or mean (SD) or median [interquartile range], as appropriate.
[b] ICU, Intensive care unit; BMI, body mass index.

mL · min^{-1} · (1.73 m^2)$^{-1}$ (435 ng/L vs 107 ng/L; P <0.001). Comparable to BNP, similar proportional augmentation of median NT-proBNP values are seen in HF vs non-HF patients with impaired renal function (5305 ng/L vs 1331 ng/L; P <0.001) and in those with an eGFR ≥60 mL · min^{-1} · (1.73 m^2)$^{-1}$ (2916 ng/L vs 451 ng/L; P <0.001).

NT-proBNP and BNP had a similar accuracy for the diagnosis of decompensated HF within each category of renal function. For patients with an eGFR ≥60 mL · min^{-1} · (1.73 m^2)$^{-1}$ the AUC for BNP = 0.75 (95% CI 0.70–0.79) vs an AUC for NT-proBNP = 0.74 (95% CI 0.70–0.79; P = 0.6 comparing AUC between biomarkers). For patients with an eGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ the AUC for BNP = 0.68 (95% CI 0.63–0.74) vs an AUC for NT-proBNP = 0.66 (95% CI 0.60–0.71; P = 0.1 comparing AUC between biomarkers). For patients with moderate to severely impaired renal function [eGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$] the cut-point of 1200 ng/L to diagnose decompensated HF for NT-proBNP had an 81% sensitivity and a 49% specificity, a 71% positive predictive value, a 63% negative predictive value, and a 68.5% overall accuracy. The cut-point of 200 ng/L for BNP had an 82% sensitivity, a 53% specificity, a 73% positive predictive value, a 65% negative predictive value, and a 70.3% overall accuracy. For patients with an eGFR ≥60 mL · min^{-1} · (1.73 m^2)$^{-1}$ the cut-points of 900 ng/L (for age ≥50 years) and 450 ng/L for (for age <50 years) to diagnose decompensated HF for NT-proBNP had an 81.0% sensitivity and a 52.3% specificity, a 65.3% positive predictive value, a 71.3% negative predictive value, and a 67.4% overall accuracy. The cut-point of 100 ng/L for BNP had an 89.9% sensitivity, a 36.8% specificity, a 69.0% positive predictive value, a 71% negative predictive value, and a 69.5% overall accuracy.

By logistic regression analysis of progressive NT-proBNP and BNP quartiles, both tests provided a similar gradient of risk for the diagnosis of decompensated HF in the setting of impaired renal function. This risk was independent of clinical risk factors and renal function (Table 2). Results were not qualitatively different after exclusion of those individuals (n = 20) on maintenance dialysis (data not shown). The association of both NT-proBNP and BNP with decompensated HF did not differ significantly among those with and without impaired renal function (tests for interaction; P >0.2).

PREDICTING 1-YEAR ALL-CAUSE MORTALITY IN PATIENTS WITH IMPAIRED RENAL FUNCTION

One-year all-cause mortality was 25.9% for the entire cohort. Death was more common in patients with impaired renal function (36.3%) vs those with mildly impaired to normal renal function (19.0%; P <0.001). Values of NT-proBNP and BNP were significantly higher in those who died compared with those who survived (Fig. 2). For patients with impaired renal function median NT-proBNP concentrations were 4.3 times as high among those who died as compared with those who survived (P <0.001). In contrast, the difference in BNP concentrations was more muted; median values for those who died were 2.0 times as high as values for those who survived (P <0.001). ROC analysis demonstrated that NT-proBNP concentration was a more accurate predictor of all-cause mortality in those with impaired renal function compared with BNP [AUC for NT-proBNP = 0.69 (95% CI 0.64–0.75) vs AUC for BNP = 0.65 (95% CI 0.60–0.71); P =

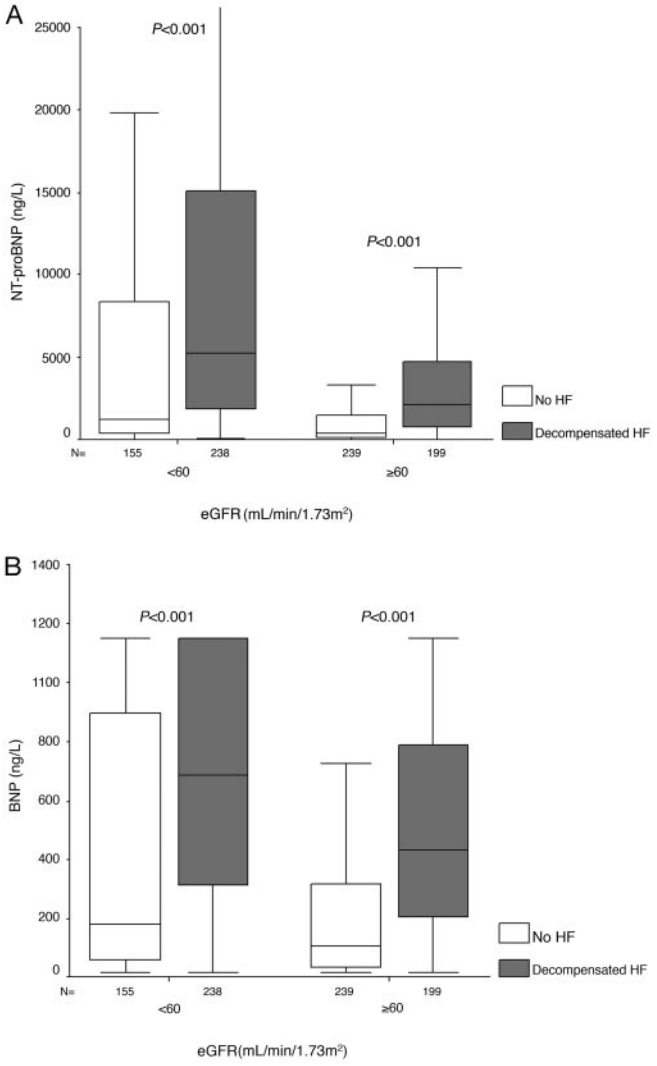

Fig. 1. Natriuretic peptide concentrations, by eGFR and diagnosis of decompensated HF for NT-proBNP (*A*) and BNP (*B*).

To facilitate visual comparison between those with and without acute decompensated HF, the *y-axis scale* is truncated at 25 000 ng/L and outliers are not included in the *plots*.

0.02]. The difference between the natriuretic peptides to predict mortality in those with moderately to severely impaired renal function is reflected over time by a greater difference in Kaplan–Meier cumulative mortality between the highest and lowest quartiles of NT-proBNP vs BNP (Fig. 3). Estimated 12-month survival for patients with NT-proBNP values in quartile 1 (4–472 ng/L) is 87.5% (95% CI 76–94%) vs 48.1% (95% CI 40.1–56.7%) for patients with values in quartile 4 (>6000 ng/L; $P < 0.001$). Estimated survival for patients with BNP values in quartile 1 (19–88 ng/L) is 78.8% (95% CI 66.7–86.7%) vs 50.4% (95% CI 41.2–58.3%) for patients with values in quartile 4 (>800 ng/L; $P < 0.001$).

By Cox regression analysis, progressive quartiles of both NT-proBNP [$\chi^2(3) = 21.4$; $P < 0.01$] and BNP [$\chi^2(3) = 13.5$; $P < 0.01$] significantly predicted all-cause mortality

Table 2. Association of natriuretic peptides with decompensated HF, among individuals with moderate–severe renal impairment (n = 389).[a]

	Adjusted[b] odds ratio (95% CI)	Test of significance of biomarker[c]
BNP		
Q1 (<88 ng/L)	Referent	$\chi^2(3) = 39.2$; $P < 0.001$
Q2 (83–333 ng/L)	2.11 (1.0, 4.6)	
Q3 (334–800 ng/L)	8.0 (3.5, 18.2)	
Q4 (≥800 ng/L)	7.0 (3.2, 15.1)	
NT-proBNP		
Q1 (<472 ng/L)	Referent	$\chi^2(3) = 34.1$; $P < 0.001$
Q2 (472–1728 ng/L)	1.1 (0.5, 2.4)	
Q3 (1729–6000 ng/L)	4.6 (2.0, 10.5)	
Q4 (>6000 ng/L)	5.2 (2.3, 11.6)	

[a] Complete covariate information was unavailable on 4 participants. Q, Quartile.

[b] Adjusted for age, sex, race/ethnicity, eGFR, dialysis treatment, hypertension, diabetes, atrial fibrillation, prior HF, and patient disposition.

[c] Likelihood-ratio test comparing a model with adjustment covariates only to models with adjustment covariates and quartiles of NT-proBNP or BNP.

in patients with impaired renal function after adjustment for other risk factors and diagnosis of decompensated HF (Table 3). The association of NT-proBNP or BNP and mortality did not differ significantly between those with eGFR ≥ 60 mL · min^{-1} · (1.73 m^2)$^{-1}$ and those with eGFR < 60 mL · min^{-1} · (1.73 m^2)$^{-1}$ ($P > 0.3$ for tests of interaction). To determine whether one of the natriuretic peptide tests was a superior predictor for mortality after accounting for potential confounders a multivariate-adjusted model containing both NT-proBNP and BNP as predictor variables was created. Only NT-proBNP remained a significant independent predictor ($P = 0.006$) of death (Table 3). Results were not qualitatively different after exclusion of those individuals (n = 20) on maintenance dialysis. To further examine whether the strength of NT-proBNP compared with BNP as a predictor of mortality was dependent on renal function, we repeated the Cox regression analysis including both biomarkers as primary predictor variables as shown in Table 3 for the 461 patients with follow-up and an eGFR >60 mL · min^{-1} · (1.73 m^2)$^{-1}$. NT-proBNP concentration remained a predictor of mortality in this population, ($\chi^2 = 8.0$; $P < 0.05$), whereas BNP was not significant ($\chi^2 = 1.1$; $P = 0.8$).

Discussion

In this prospective study of an observational cohort of patients with a high prevalence of renal impairment undergoing evaluation for decompensated HF, we demonstrated 3 main findings. First, the accuracies of NT-proBNP and BNP concentrations are similar for diagnosing decompensated HF across a spectrum of renal function, albeit at a lower accuracy for both tests than previously reported from studies of "all-comers" ED patients with dyspnea *(1–4)*. Second, we confirm in a

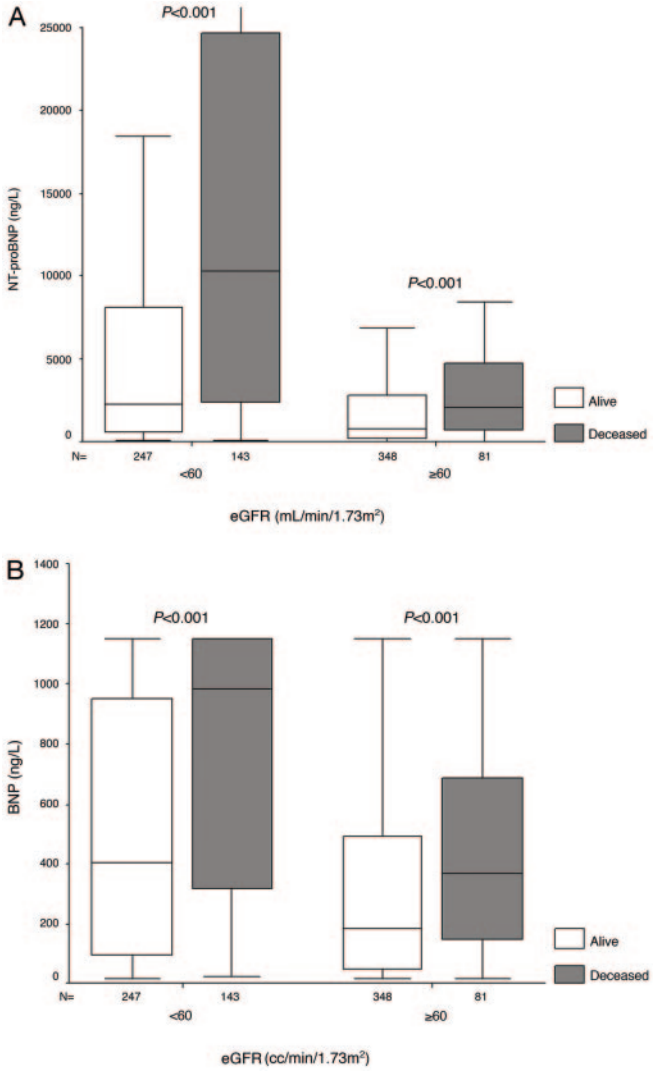

Fig. 2. Natriuretic peptide concentrations as measured on presentation to the emergency department, by level of renal function and vital status at 1 year for NT-proBNP (*A*) and BNP (*B*).

To facilitate visual comparison between those with and without decompensated HF, the *y-axis scale* is truncated at 25 000 ng/L and outliers are not included in the *plots*.

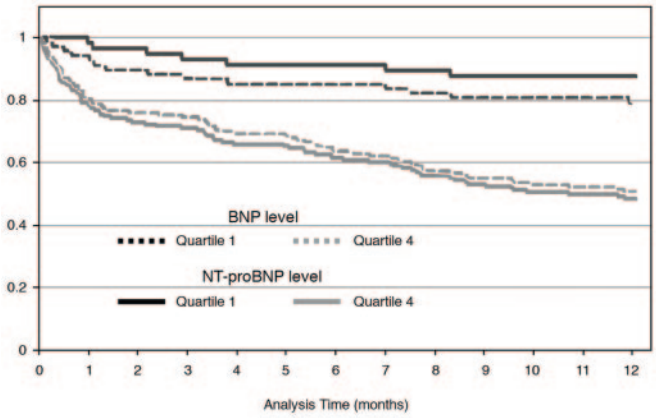

Fig. 3. Kaplan–Meier estimates of cumulative survival are shown for quartiles 1 and 4 of BNP and NT-proBNP in patients with an eGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$.

P values are <0.001 between quartiles 1 and 4 for both NT-proBNP and BNP.

clinician-selected patient population similar optimal cutoff values for both BNP and NT-proBNP to diagnose decompensated HF in patients with an eGFR <60 mL · min^{-1} · (1.73 m^2)$^{-1}$ *(7, 8)*. Third, we identify that both tests can predict all-cause 1-year mortality. However, NT-proBNP better differentiates this risk in patients with impaired renal function than BNP.

In patients with dyspnea, BNP and NT-proBNP concentrations have a high diagnostic accuracy for decompensated HF with ROC-determined AUC >0.88 *(1–6)*. Our results confirm that both tests perform comparably for diagnosing decompensated HF and extend this finding across a broad range of patients with impaired renal function. However, the accuracy of both tests was more limited when applied to our large, heterogeneous, clinician-selected cohort. The phenomenon of spectrum bias may explain the diminished diagnostic accuracy observed when a test is applied from a population in which most individuals have a very high or low probability of the disease (an all-comers dyspnea cohort) to a cohort of patients with clinician-determined indications for testing, in which more patients will have an intermediate probability of disease *(12, 13)*. Insight into this phenomenon is apparent from a substudy analysis of the Breathing Not Properly study in which ED physicians ranked the probability of a decompensated HF diagnosis for enrolled patients *(14)*. In that study 46.9% of enrollees were rated as having ≤20% probability of HF and another 25.4% were rated as having a ≥80% probability of HF, leaving a little more than 1 in 4 enrollees with an intermediate pretest probability of decompensated HF. This relatively dichotomized population may accentuate the accuracy of the test *(12, 13)*.

Differentiating our cohort of patients was a higher prevalence of diabetes, known coronary artery disease, and atrial fibrillation compared with enrollees in the Breathing Not Properly trial *(1)*. All known factors that influence natriuretic peptide concentrations in the absence of HF *(15–17)*. Furthermore, the 1-year mortality in our cohort of 28.0% was substantially higher than the 15.1% mortality reported from the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, again suggesting that the population reported in this study was overall more "ill" than those of previously published studies *(18)*. Severity of illness cannot be accounted for simply by a greater prevalence of decompensated HF, because the prevalence was similar to other studies *(1, 4)*. In patients with multiple comorbidities, particularly impaired renal function, BNP and NT-proBNP concentrations correlate poorly with left ventricular filling pressures and other indices of left ventricular function, potentially decreasing the diagnostic accuracy of the test for HF *(19)*.

Table 3. Association between natriuretic peptides and 1-year all-cause mortality (n = 383).[a]

	Adjusted[b] hazard ratio (95% CI)	Test of significance of biomarker[c]
BNP		
Q1 (<88 ng/L)	Referent	$\chi^2(3) = 13.5$; $P = 0.004$
Q2 (83–333 ng/L)	1.3 (0.7, 2.7)	
Q3 (334–800 ng/L)	1.5 (0.7, 2.9)	
Q4 (≥≥800 ng/L)	2.6 (1.4, 4.8)	
NT-proBNP		
Q1 (<472 ng/L)	Referent	$\chi^2(3) = 21.4$; $P < 0.001$
Q2 (472–1728 ng/L)	2.0 (0.8, 4.9)	
Q3 (1729–6000 ng/L)	2.9 (1.0, 6.7)	
Q4 (>6000 ng/L)	4.5 (2.0, 10.2)	
Additional adjustment with both natriuretic peptides simultaneously		
BNP		
Q1 (<88 ng/L)	Referent	$\chi^2(3) = 4.7$; $P = 0.3$
Q2 (83–333 ng/L)	0.6 (0.2, 1.4)	
Q3 (334–800 ng/L)	0.4 (0.1, 1.1)	
Q4 (≥≥800 ng/L)	0.6 (0.2, 1.6)	
NT-proBNP		
Q1 (<472 ng/L)	Referent	$\chi^2(3) = 12.4$; $P = 0.006$
Q2 (472–1728 ng/L)	3.0 (1.1, 8.5)	
Q3 (1729–6000 ng/L)	5.5 (1.8, 17.6)	
Q4 (>6000 ng/L)	7.9 (2.3, 26.5)	

[a] Complete covariate information was unavailable on 4 participants. Q, Quartile.

[b] Adjusted for age, sex, race/ethnicity, eGFR, dialysis treatment, hypertension, diabetes, atrial fibrillation, coronary disease, prior HF, patient disposition, and diagnosis of acute decompensated HF.

[c] Likelihood-ratio test comparing a model with adjustment covariates only to models with adjustment covariates and quartiles of NT-proBNP or BNP.

The optimal cut-points determined for NT-proBNP and BNP for patients with impaired renal function in our patient cohort were similar to those from the PRIDE and Breathing Not Properly studies, respectively, albeit at a lower overall accuracy *(7, 8)*. Prior concerns have been raised that NT-proBNP is more dependent on renal function than BNP *(20)*. However, recent data have shown that the renal extraction of NT-proBNP and BNP is comparable across a broad range of renal function *(21, 22)*. Increased NT-proBNP concentrations are also highly predictive of mortality in patients with decompensated HF and impaired renal function *(23)*. Potentially, NT-proBNP, with a longer in vivo half-life than BNP, becomes more amplified by a variety of cardiac pathologies that can impact mortality than BNP. This observation is consistent with results from the free-living Olmsted County cohort in which NT-proBNP, compared with BNP, was a superior predictor of mortality in ambulatory individuals from the general population *(24)*. Comparisons between the 2 tests for predicting outcomes have also been done in a large stable HF population and in a smaller ED dyspnea population *(25, 26)*. In the stable HF population NT-proBNP was a superior predictor of hospitalization compared with BNP, but not for all-cause mortality *(25)*. In the smaller dyspnea population, no difference was seen between the 2 markers *(26)*. Based on the population studied, either the 2 tests are equivalent predictors of mortality, or NT-proBNP can show prognostic superiority.

Several limitations are addressed. First, our cohort likely represents a different population than all-comers dyspnea patients evaluated in prior studies *(1–8)*. By relying on clinician selection our study population appears to reflect the exclusion of patients with low probability decompensated HF, and a greater prevalence of comorbidities that could increase natriuretic peptide concentrations in the absence of decompensated HF. Second, adjudication of decompensated HF is in part subjective, and could be further limited by reliance on clinician diagnosis and chart review. However, the accuracy of a treating clinician's initial impression of decompensated HF in this setting can be high (AUC = 0.90), even without the benefit of access to subsequent hospital course and diagnostic tests *(2)*. With access to this additional information, the accuracy of the adjudicated HF diagnosis in our study should be high. Importantly, the prevalence of either LVEF ≥50% or the absence of a prior diagnosis of HF was common in this study and consistent with other adjudicated decompensated HF populations, suggesting that decompensated HF diagnosis was more based on a constellation of symptoms, findings, and response to treatment than categorization based on historical variables or LVEF. Third, similar to the PRIDE and other single-center studies we used a single cardiologist to adjudicate the cases *(2, 4, 6)*. However, in an analysis of 50 randomly selected cases, our agreement between 2 reviewers of 84% was comparable to the BNP study result of 89.3% *(7)*. Fourth, natriuretic peptides, to our knowledge,

were measured in the ED and were the first concentrations measured. However, it is possible that treatment was initiated in some patients before NT-proBNP/BNP measurement that could have resulted in reducing the diagnostic accuracy of both tests. Fifth, the use of a quartiles analysis avoided problems with outcomes analysis using continuous measures of natriuretic peptides in a setting in which 18.3% of patients had BNP concentrations greater than the upper range of the assay. However, we were unable to assess the significance of a change in NT-proBNP:BNP ratio, a measure that may also be of prognostic significance. Sixth, and lastly, the assessment of death relied upon review of the Social Security Death Index, an acceptable method for determining death status *(27)*. However, the cause of death remains unknown and cannot be accurately assessed in the absence of prospectively collected and adjudicated end-points.

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