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Renal Function, Congestive Heart Failure, and Amino-Terminal Pro-Brain Natriuretic Peptide Measurement

Results From the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study

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OBJECTIVES We sought to examine the interaction between renal function and amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

BACKGROUND The effects of renal insufficiency on NT-proBNP among patients with and without acute congestive heart failure (CHF) are controversial. We examined the effects of kidney disease on NT-proBNP–based CHF diagnosis and prognosis.

METHODS A total of 599 dyspneic patients with glomerular filtration rates (GFRs) as low as 14.8 ml/min were analyzed. We used multivariate logistic regression to examine covariates associated with NT-proBNP results and linear regression analysis to analyze associations between NT-proBNP and GFR. Receiver-operating characteristic analysis determined the sensitivity and specificity of NT-proBNP for CHF diagnosis. We also assessed 60-day mortality rates as a function of NT-proBNP concentration.

RESULTS Glomerular filtration rates ranged from 15 ml/min/1.73 m^2 to 252 ml/min/1.73m^2. Renal insufficiency was associated with risk factors for CHF, and patients with renal insufficiency were more likely to have CHF (all $p < 0.003$). Worse renal function was accompanied by cardiac structural and functional abnormalities on echocardiography. We found that NT-proBNP and GFR were inversely and independently related ($p < 0.001$) and that NT-proBNP values of > 450 pg/ml for patients ages <50 years and >900 pg/ml for patients ≥50 years had a sensitivity of 85% and a specificity of 88% for diagnosing acute CHF among subjects with GFR ≥60 ml/min/1.73 m^2. Using a cut point of 1,200 pg/ml for subjects with GFR <60 ml/min/1.73 m^2, we found sensitivity and specificity to be 89% and 72%, respectively. We found that NT-proBNP was the strongest overall independent risk factor for 60-day mortality (hazard ratio 1.57; 95% confidence interval 1.2 to 2.0; $p = 0.0004$) and remained so even in those with GFR <60 ml/min/1.73 m^2 (hazard ratio 1.61; 95% confidence interval 1.14 to 2.26; $p = 0.006$).

CONCLUSIONS The use of NT-proBNP testing is valuable for the evaluation of the dyspneic patient with suspected CHF, irrespective of renal function. (J Am Coll Cardiol 2006;47:91–7) © 2006 by the American College of Cardiology Foundation

Testing for amino-terminal pro-brain natriuretic peptide (NT-proBNP) is valuable for the assessment of dyspneic patients presenting to the emergency department (ED) with suspected acute congestive heart failure (CHF) (1–3). When testing a dyspneic patient with NT-proBNP or the related B-type natriuretic peptide (BNP), important considerations are necessary, including knowledge of the patient's renal function. Chronic kidney disease (CKD) is highly prevalent among patients with CHF; conversely, many of the same factors that place an individual at risk for CHF can have similarly detrimental effects on renal function. This intersection between cardiac and renal insufficiencies—the so-called "cardio-renal" interaction (4–8)—is associated with increased rates of morbidity and mortality in patients so afflicted (5,6,8–15). It is not surprising therefore, that CKD affects the concentrations of both NT-proBNP and BNP; however, it is not yet clear whether this effect reflects the increased release of the markers due to the presence of cardiac disease in patients with CKD or due to reductions in their clearance, as both markers may have a degree of dependence on renal function for their removal from circulation (16–20).

Although the effect of declining renal function on BNP has been examined previously (17,18), less is understood regarding the effects of renal function on NT-proBNP levels in patients both with and without CHF, and it has been suggested the accuracy of NT-proBNP may be more vulnerable than BNP to abnormalities in renal function (21). Accordingly, we undertook the present analysis of partici-

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Abbreviations and Acronyms

BNP	= B-type natriuretic peptide
CHF	= congestive heart failure
CKD	= chronic kidney disease
ED	= emergency department
GFR	= glomerular filtration rate
IQR	= interquartile range
NT-proBNP	= amino-terminal pro-brain natriuretic peptide
PRIDE	= ProBNP Investigation of Dyspnea in the Emergency Department study
ROC	= receiver-operating characteristic

pants from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study (1) to better understand the relationship between renal function, NT-proBNP levels, and CHF.

METHODS

Study sample. The institutional review board approved all investigational procedures involved in this study. The PRIDE study was a prospective study of NT-proBNP testing of 599 dyspneic patients presenting to the ED. The details of the PRIDE study have recently been described (1). In brief, dyspneic patients in an urban ED with suspected CHF were evaluated for inclusion, including blinded assessment of NT-proBNP, drawn at the time of inclusion. Among the exclusion criteria for the PRIDE study was a serum creatinine >2.5 mg/dl.

Using all information pertaining to the presentation, including ED records, hospital records (if applicable), results of diagnostic imaging and laboratory testing (save NT-proBNP values), primary care office notes, and the results of the 60-day follow-up phone call, a cardiologist determined the cause for each patient's presentation. Of the subjects enrolled, 209 (35%) subjects were judged to have acute CHF. In the initial PRIDE study report (1), it was determined that an NT-proBNP level >450 pg/ml for patients <50 years of age and >900 pg/ml for those ≥50 years of age was the most highly sensitive and specific for the diagnosis of acute CHF in the entire cohort. The manufacturer's recommended cut points for excluding CHF (125 pg/ml for patients <75 years and 450 pg/ml for patients ≥75 years) were useful with 99% negative predictive value; however, we found that a single, age-independent threshold of 300 pg/ml was similarly useful for excluding the CHF, with a negative predictive value of 99%.

Plasma natriuretic peptide measurements. At the time of patient enrollment, blood was collected into ethylene diamine tetraacetic acid-containing tubes. After collection, the samples were processed and frozen at −80°C for analysis after the PRIDE study was completed. We measured NT-proBNP using an automated, commercially available immunoassay (Elecsys ProBNP, Roche Diagnostics, Indianapolis, Indiana) using established methodology. The assay for NT-proBNP has <0.001% cross-reactivity with bioactive BNP and an interassay coefficient of variation (CV) of 0.9% for the analyses in the PRIDE study. In addition, BNP also was measured (ADVIA Centaur BNP, Bayer Diagnostics, Tarrytown, New York) on the 209 patients with acute CHF using established methodology. This assay had a CV of 2.6% in the PRIDE study.

Assessment of renal function in the PRIDE study. For the purposes of the present study, subjects in the PRIDE study were grouped by their renal function. Using the Modified Diet in Renal Disease equation (22), we estimated glomerular filtration rate (GFR).

Statistical analyses. Although the GFR distribution was broken into categories for display purposes, all analyses were based on the original continuous distributions. Echocardiography results are presented for those with available data, including those without acute CHF. Associations between baseline GFR and dichotomous patient characteristics (including available echocardiography data) were assessed using a logistic regression model, whereas continuous variables were assessed using the Kruskal-Wallis test.

Values for NT-proBNP and BNP (the latter only from those patients with acute CHF) were log-transformed to achieve normality, and correlations between natriuretic peptide levels and renal function were performed using Pearson's correlation coefficient. In addition, multivariate linear regression analysis analyzed the association between renal function and log-transformed NT-proBNP levels.

To evaluate the effects of renal function on NT-proBNP levels in the presence and absence of CHF, as well as the prognostic impact of NT-proBNP with respect to renal function, univariable and multivariable logistic and linear regression analyses were performed. For the evaluation of the effects of renal function on NT-proBNP, log-transformed NT-proBNP was used as the dependent variable. In the mortality analysis, 60-day vital status was the dependent variable. Covariates that were strongly associated with the dependent variable in univariate analysis ($p < 0.10$) were included in the multivariate analysis. All models were fitted, found to be appropriate, and tested for first-order interactions.

Statistical analyses were performed with the use of either SPSS (SPSS Inc., Chicago, Illinois) or STATA software version 8SE (STATA Corp., College Station, Texas). A two-sided p value of <0.05 was considered significant.

Receiver-operating characteristic analyses. Receiver-operating characteristic (ROC) analyses were performed across the ranges of GFR in the PRIDE study to assess optimal NT-proBNP cut points at different levels of renal function. For the purposes of ROC analyses, allowing for optimal power, we examined patients as a function of normal to mild (i.e., GFR ≥ 60 ml/min/1.73 m^2) and moderate-to-severe CKD (i.e., GFR < 60 ml/min/1.73 m^2). Receiver-operating characteristic analyses were performed with Analyse-it software (Analyse-it Software, Ltd., Leeds, United Kingdom).

Table 1. Clinical Characteristics of All Study Patients, Stratified by Renal Function

	Glomerular Filtration Rate (ml/min/1.73 m^2)				
	<30 (n = 19)	30–59 (n = 188)	60–89 (n = 226)	≥90 (n = 166)	p Value
Age, yrs (mean ± SD)	78.0 ± 7.6	73.1 ± 12.4	60.7 ± 15.7	51.3 ± 15.7	<0.001
Male gender	89%	52%	47%	45%	0.002
Previous CHF	89%	44%	18%	6%	<0.001
Previous atrial fibrillation	16%	20%	10%	7%	0.001
Previous myocardial infarction	16%	24%	10%	5%	<0.001
Diabetes mellitus	26%	9%	5%	2%	<0.001
Systemic hypertension	63%	62%	50%	31%	<0.001
Loop diuretic therapy	74%	49%	23%	12%	<0.001
cTnT, ng/ml (mean ± SD)	0.20 ± 0.36	0.15 ± .55	0.21 ± .48	0.37 ± .80	0.31
Creatinine, mg/dl (mean ± SD)	2.21 ± .31	1.47 ± .33	0.97 ± .16	0.75 ± .14	<0.001
Acute CHF	74%	61%	25%	15%	<0.001
NYHA functional class (CHF patients only)					<0.001
II (n = 29)	5%	15%	16%	8%	
III (n = 73)	19%	33%	40%	36%	
IV (n = 107)	76%	52%	44%	56%	

CHF = congestive heart failure; cTnT = troponin T; NYHA = New York Heart Association.

RESULTS

Renal function and baseline clinical characteristics. Patients with a serum creatinine of 1.5 to 2.5 mg/dl accounted for 14.7% (n = 73) of the total study sample of 599 subjects; however, the estimated GFR varied widely, from 14.8 ml/min/1.72 m^2 to 252 ml/min/1.72 m^2, and 206 patients (34%) had moderate-to-severe renal insufficiency (defined as a GFR < 60 ml/min/1.73 m^2). Across the range of renal function in the PRIDE study, several important associations with clinical factors were noted (Table 1). With decreasing renal function, patients were more likely to be men ($p = 0.002$); to have more prevalent risk factors for CHF, including advancing age ($p < 0.001$); and to have histories of atrial fibrillation, myocardial infarction, or hypertension (all $p < 0.002$). In addition, patients with CKD were more likely to have CHF either in the past and/or at the index presentation, and more likely to use diuretics (all $p < 0.001$). Among patients with acute CHF, worse renal function also was associated with more severe CHF symptoms ($p < 0.001$).

Because 140 of the study subjects underwent echocardiography as standard of care after their enrollment into the PRIDE study, we had an opportunity to perform an analysis of the relationship between changes in renal function and the prevalence of significant structural heart disease. Relative to the group as a whole, more patients with acute CHF underwent echocardiography, particularly in the range of mild renal insufficiency. As demonstrated in Table 2, a strong graded relationship between abnormalities in renal function and the presence of several cardiac structural and functional abnormalities was found; stratifying subjects as a function of GFR > or <60 ml/min/1.73m^2 and diagnosis or absence of CHF illustrates the effects of renal function on the prevalence of structural heart disease in those with and without acute CHF.

Renal function and median NT-proBNP levels. In the 390 subjects without acute CHF in the PRIDE study, median values of NT-proBNP were significantly greater in those with worse renal function ($p < 0.001$) (Fig. 1); however, the values often were well below the cut points for acute CHF; as an example, among those subjects without CHF, with GFR <60 ml/min/1.73 m^2 (n = 78), 64% had NT-proBNP concentrations below the defined cut points for ruling in CHF from the PRIDE study (1). In addition, those with acute CHF and worse renal function also demonstrated significantly higher concentrations of NT-proBNP compared with those with acute CHF and better renal function ($p < 0.001$) (Fig. 1).

Lastly, a similar inverse relationship was noted between GFR and median BNP levels in those with acute CHF with median BNP values observed in these CHF subjects of 175, 280, 412, and 524 pg/ml in categories of ≥90, 60 to 90, 30 to 59, and <30 ml/min/1.73 m^2 ($p = 0.01$) (Fig. 1).

Assessment of NT-proBNP, BNP, and renal function. With lower GFR, log-transformed NT-proBNP levels increased among all patients in the study ($r = -0.55$, $p < 0.001$) (Fig. 2) and in those without acute CHF ($r = -0.41$; $p < 0.001$). In patients with acute CHF, this inverse relationship between NT-proBNP levels and renal function was still significant, although somewhat less robust ($r = -0.33$; $p < 0.001$), suggesting a potentially lesser impact of renal function on NT-proBNP levels in the setting of acute CHF. Among the 209 patients with acute CHF, log-transformed BNP levels were inversely correlated with GFR and increased significantly with decreasing renal function, although to a slightly lesser degree than NT-proBNP ($r = -0.18$; $p = 0.02$).

Factors influencing NT-proBNP values. In multivariable linear regression analysis, after adjusting for relevant covariates, the independent predictors of log-transformed NT-proBNP values included age (categorized by decade; $p <$

Table 2. Results of Two-Dimensional Echocardiography, Categorized With Respect to Renal Function, GFR (Dichotomized With GFR Cut Point of 60 ml/min/1.73 m^2), and the Presence or Absence of CHF

	GFR (ml/min/1.73 m^2)			
	<60 CHF (n = 49)	<60 Not CHF (n = 12)	≥60 CHF (n = 43)	≥60 Not CHF (n = 35)
Apical four-chamber view				
Left ventricular end-diastolic volume (ml)	101.7 ± 42.3	91.1 ± 42.0	111.6 ± 43.8	79.0 ± 23.6
Left ventricular end-systolic volume (ml)	56.8 ± 32.8	44.8 ± 32.6	69.8 ± 41.0	33.8 ± 14.1
Apical two-chamber view				
Left ventricular end-diastolic volume (ml)	102.1 ± 41.5	86.7 ± 45.0	114.9 ± 51.5	73.7 ± 26.2
Left ventricular end-systolic volume (ml)	55.9 ± 31.9	41.7 ± 34.3	70.2 ± 43.2	30.7 ± 15.0
Left atrial volume index	38.3 ± 15.4	25.1 ± 7.6	43.1 ± 27.6	25.0 ± 9.4
Ejection fraction	48.1 ± 15.1	57.0 ± 13.3	42.7 ± 27.6	65.1 ± 22.0
Ejection fraction <50%	49.0%	25.0%	55.8%	5.7%
Left ventricular mass index	106.7 ± 37.1	80.7 ± 20.1	101.3 ± 27.9	89.9 ± 25.2
Left ventricular hypertrophy	20.4%	18.2%	11.6%	12.0%
RV hypokinesis	16.3%	18.2%	31.7%	12.0%
Valvular heart disease				
Tricuspid regurgitation severity ≥ moderate	47.0%	27.3%	30.0%	11.4%
Mitral regurgitation severity ≥ moderate	51.0%	25.0%	31.8%	11.4%
Diastolic function				
Normal	69.4%	66.7%	73.7%	72.8%
Impaired relaxation	6.1%	16.7%	2.3%	2.9%
Pseudonormalized	8.2%	8.3%	4.7%	5.7%
Restrictive	16.3%	8.3%	9.3%	8.6%
RV systolic pressure (mm Hg)	50.4 ± 11.9	41.1 ± 14.2	46.1 ± 13.5	35.6 ± 12.2

The number of subjects with available data in each category is indicated.
CHF = congestive heart failure; GFR = glomerular filtration rate; RV = right ventricular.

0.001), previous CHF ($p = 0.02$), previous cardiomyopathy ($p < 0.001$), New York Heart Association heart failure functional classification ($p = 0.008$), atrial fibrillation at presentation ($p = 0.02$), and GFR ($p < 0.001$). In the presence of all of the independent predictors identified, GFR remained significantly inversely associated with plasma natriuretic peptide levels, both in subjects with and those without acute CHF. The adjusted beta coefficients from multivariable linear regression results examining the change in log-transformed NT-proBNP levels associated with an increase of 1 ml/min/1.73 m^2 in the GFR were significant in the group as a whole (adjusted β coefficient = −0.01; $p < 0.001$), those without acute CHF (adjusted β coefficient = −0.006; $p = 0.01$), and those with acute CHF (adjusted β coefficient = −0.015; $p < 0.001$).

Assessment of NT-proBNP, renal function, and ROC analysis. Among those with a GFR ≥60 ml/min/1.73 m^2 ($n = 393$), the area under the ROC curve (Fig. 3) was 0.95 ($p < 0.001$), indicating extremely high sensitivity and specificity of the assay for the detection of acute CHF. Among patients with a GFR of <60 ml/min/1.73 m^2 ($n = 206$), the assay for NT-proBNP remained sensitive and specific, as indicated by the area under the ROC curve of 0.88 ($p < 0.001$). The difference between the area under the ROC curves of patients with GFR ≥ and <60 ml/min/1.73 m^2 was not statistically significant ($p = 0.36$).

In an effort to better understand the diagnostic performance of NT-proBNP in those with moderate versus severe renal insufficiency (GFR <60 ml/min/1.73 m^2), we divided those patients with respect to the median GFR in this category (44 ml/min/1.73 m^2) and ROC analyses were performed in each group. In those subjects with GFR greater than the median, the area under the ROC curve was 0.89 ($p < 0.0001$), whereas in those below the GFR median in those subjects with moderate or more renal insufficiency, the area under the ROC curve was 0.86 ($p < 0.0001$); the difference between the two ROC curves was not significant ($p = 0.88$).

At the optimal cut point for excluding acute CHF from the PRIDE study (300 pg/ml), NT-proBNP demonstrated negative predictive values of 94% and 100% for patients with GFR <60 ml/min/1.73 m^2 and ≥60 ml/min/1.73 m^2, respectively. At the optimal cut points for identifying CHF from the PRIDE study (of <450 pg/ml for subjects <50 years of age and ≥900 pg/ml for subjects ≥50 years of age), NT-proBNP exhibited a sensitivity of 85% and specificity of 88% for those subjects with a GFR ≥60 ml/min/1.73 m^2. Using similar cut points for patients with GFR <60 ml/min/1.73 m^2, the sensitivity was 97% and specificity was 68%. In an effort to identify a diagnostic cut point that improved on specificity in patients with moderate-to-severe renal impairment, ROC analyses suggested that the use of a single cut point of 1,200 pg/ml for patients with GFR <60 ml/min/1.73 m^2 was optimal, with sensitivity of 89% and specificity to 72%; in those with most severe renal insufficiency in the PRIDE study (those below GFR of 44 ml/min/1.73 m^2), this cut point of 1,200 pg/ml had 92% sensitivity and 70% specificity.

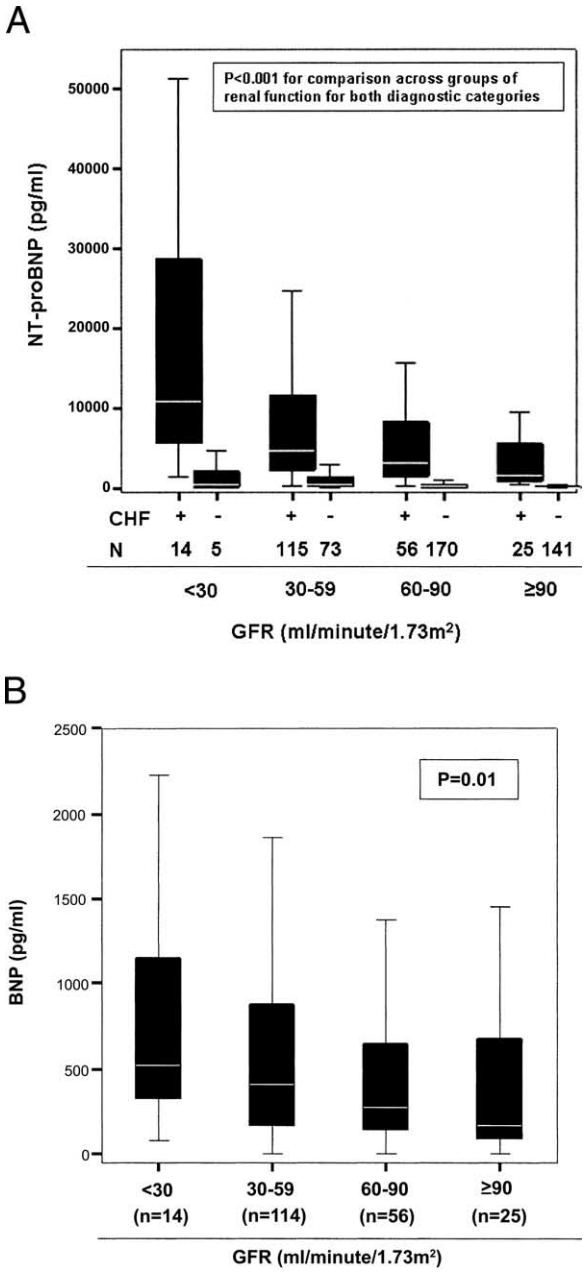

Figure 1. (A) Median amino-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations across categories of renal function for subjects with and without acute congestive heart failure (CHF) in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. In addition, **(B)**, the relationship between B-type natriuretic peptide (BNP) concentrations and renal function in the 209 subjects with acute CHF is demonstrated. **Boxes** denote interquartile ranges, whereas **whiskers** indicate 5th and 95th percentiles. GFR = glomerular filtration rate.

Assessment of NT-proBNP, renal function, and mortality. By 60 days after presentation, 30 subjects (5%) had died. The association between categories of renal function, NT-proBNP, and 60-day mortality is detailed in Figure 4. Median NT-proBNP levels were highest in the subjects with a GFR <60 ml/min/1.73 m^2 who died by 60 days (n = 17; 5,565 pg/ml, interquartile range [IQR] = 1,682 to 13,012); compared with these subjects, NT-proBNP levels

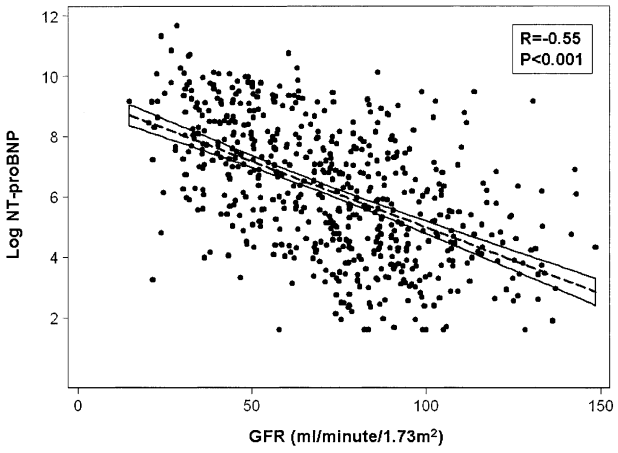

Figure 2. Relationship between renal function, expressed as glomerular filtration rate (GFR), and amino-terminal pro-brain natriuretic peptide (NT-proBNP) results in the entire ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study cohort of 599 subjects.

were lower in survivors with GFR <60 ml/min/1.73^2 (2,528 pg/ml, IQR = 551 to 8,937, p for difference = 0.001). Among those with GFR ≥60 ml/min/1.73 m^2, similar patterns of NT-proBNP values were noted, with the 13 subjects dead at 60 days demonstrating significantly higher NT-proBNP concentrations (1,423 pg/ml [IQR = 491 to 7,572] than 163 pg/ml [IQR = 47 to 869] in survivors, p for difference < 0.001).

In a multivariate analysis examining risk factors for mortality by 60 days, log-transformed NT-proBNP concentrations were the strongest predictor of short-term death and remained so even with the inclusion of GFR into the model (hazard ratio 1.57; 95% confidence interval 1.2 to 2.0; p = 0.0004). Importantly, among those with a GFR <60 ml/min/1.73 m^2, the prognostic ramifications of NT-

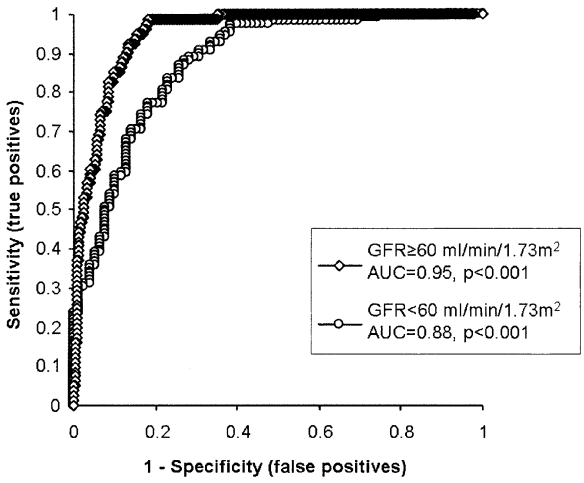

Figure 3. Receiver-operating characteristic curves comparing the performance of amino-terminal pro-brain natriuretic peptide for the diagnosis of acute congestive heart failure in breathless subjects with normal-to-mild renal insufficiency (glomerular filtration rate [GFR] ≥60 ml/min/1.73 m^2, n = 393) versus moderate-to-severely impaired renal function (GFR <60 ml/min/1.73 m^2, n = 206). The difference between the two curves was not statistically significant (p = 0.34). AUC = area under the curve.

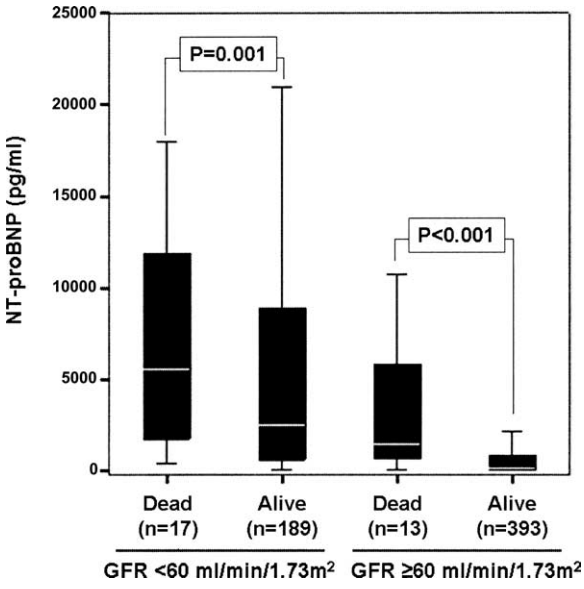

Figure 4. The relationship between median amino-terminal pro-brain natriuretic peptide (NT-proBNP levels), glomerular filtration rate (GFR), and 60-day mortality. **Boxes** denote interquartile ranges, whereas **whiskers** indicate 5th and 95th percentiles.

proBNP concentrations remained significant (hazard ratio 1.61; 95% confidence interval 1.14 to 2.26; p = 0.006).

DISCUSSION

Among our patients in the PRIDE study, a high coincidence of cardiac and renal insufficiencies (in the form of CHF and CKD, respectively) was present. This intersection between cardiac and renal disease has been referred to as the "cardio-renal" interaction (4–8) and has significant implications for the use of natriuretic peptide assays for the evaluation of patients with CKD because these sensitive markers are affected both by structural heart disease—prevalent in patients with CKD in the absence of symptomatic CHF (23)—as well as possibly because of their reduced clearance in the setting of renal dysfunction.

The difference between the effects of CKD on NT-proBNP and BNP levels is controversial. McCullough et al. (17) previously reported an analysis from the Breathing Not Properly Multinational Study, in which BNP levels were found to be related to renal function in patients both with and without acute CHF. In our study, NT-proBNP concentrations appeared to be more affected than BNP by renal function; however, the relationship between NT-proBNP levels and renal function was much more modest than had been previously suggested (18,21); as well, the performance of NT-proBNP was comparable with that reported for BNP: in ROC analyses, we demonstrated an area under the ROC curve for NT-proBNP of 0.88 in analyses among patients with moderate or worse renal insufficiency, and in those with the most severe renal insufficiency in the PRIDE study, the area under the ROC curve remained 0.86. Among patients with similar renal function in the Breathing Not Properly Study (17), ROC analyses for BNP demonstrated an area under the curve range of 0.81 to 0.86, depending on severity of renal function impairment. Importantly, at an optimal cut point (of 1,200 pg/ml) for those with moderate-to-severe renal insufficiency, NT-proBNP had a specificity that compared favorably with results for BNP (24). Thus, despite previous suggestions (18,21), at optimal cut points, it is inaccurate to state that decreasing specificity for acute CHF due to worsening renal insufficiency is an issue unique to NT-proBNP; irrespective of renal function, our data strongly support the value of NT-proBNP testing for dyspneic patients for diagnosis and prognosis.

The current challenge is to ascertain the mechanism of relationship between NT-proBNP levels and renal function. The clearance of NT-proBNP in human subjects is not well understood, but small amounts of intact NT-proBNP may be recovered in urine (25), suggesting a degree of renal dependence on clearance. Among patients requiring hemodialysis, NT-proBNP levels are markedly elevated (7,20,26–29). Thus, renal clearance is likely one mode of removal of NT-proBNP from the circulation, and the more elevated levels of NT-proBNP that were detected in our patients with CKD may simply reflect decreased clearance. However, the wide variety of NT-proBNP levels among patients with CKD in the PRIDE study suggests that reduced clearance is only one mechanism of the elevation in NT-proBNP levels in such patients.

The concurrence of common risk factors for CHF, the high degree of prevalent or incident CHF in those with CKD, expanded plasma volumes in those with CKD, and the high prevalence of structural and functional cardiac abnormalities among those with renal insufficiency in ours and other studies (26,27,29) suggest that the elevated NT-proBNP levels noted among our subjects with poorer renal function likely reflect incident and prevalent structural heart disease. Lending further support to this concept, we demonstrated NT-proBNP as the strongest risk factor for death within 60 days of presentation, maintaining its prognostic value regardless of renal function.

Study limitations. That subjects with serum creatinine >2.5 mg/dl were excluded from the PRIDE study is a limitation of our study because the exclusion of those with severe renal failure might limit the application of our results to the everyday population of patients with dyspnea in the ED. This is unlikely, however, as it has been reported that the majority of patients in the ED with CHF have a GFR between 30 and 90 ml/min/1.73 m^2 (30), as in our study. Further, despite the creatinine exclusion criterion, 38% of subjects in the PRIDE study had a GFR <60 ml/min/1.73 m^2, a comparable distribution of subjects with moderate-to-severe renal insufficiency as in the Breathing Not Properly Multinational study of BNP (19). Finally, among 6,598 subjects presenting with acute CHF in the EuroHeart failure survey (which did not have a creatinine exclusion), more than 90% had a serum creatinine <2.5 mg/dl (31).

Thus, we feel our data are applicable to the real-world population presenting to the ED.

Conclusions. In summary, we found a significant inverse relationship between renal function and NT-proBNP values in dyspneic patients with and without acute CHF. We suggest this inverse relationship between NT-proBNP and GFR is not explainable solely on the basis of reduced clearance and more likely reflects the presence of underlying structural heart disease and increased plasma volume in patients with CKD. Although the perception is that the performance of NT-proBNP as a diagnostic marker is more adversely affected by renal function than BNP (18,21), we found that NT-proBNP was useful for both diagnosing or excluding acute CHF across a wide spectrum of renal function (with results comparable with those reported for BNP) and that regardless of renal function maintained its value for prognostication of short-term mortality in CHF. We therefore conclude that at optimal cut points, even in the presence of impaired renal function, NT-proBNP measurement is a valuable tool for the diagnostic and prognostic evaluation of dyspneic patients.

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