Journal of the American College of Cardiology Vol. 48, No. 8, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.06.056

Amino-Terminal Pro-Brain Natriuretic Peptide, Renal Function, and Outcomes in Acute Heart Failure

Redefining the Cardiorenal Interaction?

Roland R. J. van Kimmenade, MD, PHD,* James L. Januzzi, JR, MD,† Aaron L. Baggish, MD,† John G. Lainchbury, MD,‡ Antoni Bayes-Genis, MD, PHD,§ A. Mark Richards, MD, PHD,‡ Yigal M. Pinto, MD, PHD*

Maastricht, the Netherlands; Boston, Massachusetts; Christchurch, New Zealand; and Barcelona, Spain

OBJECTIVES We sought to study the individual and integrative role of amino-terminal pro-brain natriuretic peptide (NT-proBNP) and parameters of renal function for prognosis in heart failure.

BACKGROUND Amino-terminal pro-BNP and renal impairment both predict death in patients with heart failure. Worsening of renal function in heart failure even defines the "cardiorenal syndrome."

METHODS Seven hundred twenty subjects presenting with acute heart failure from 4 university-affiliated medical centers were dichotomized according to NT-proBNP concentration and baseline glomerular filtration rate. In addition, patients were divided according to changes in renal function. The primary end point was 60-day mortality.

RESULTS The combination of a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 with an NT-proBNP >4,647 pg/ml was the best predictor of 60-day mortality (odds ratio 3.46; 95% confidence interval 2.13 to 5.63). Among subjects with an NT-proBNP above the median, those with a GFR <60 ml/min/1.73 m^2 or a creatinine rise ≥0.3 mg/dl had the worst prognosis, whereas in subjects with a NT-proBNP below the median, prognosis was not influenced by either impaired renal function at presentation or the development of renal impairment during admission.

CONCLUSIONS The combination of NT-proBNP with measures of renal function better predicts short-term outcome in acute heart failure than either parameter alone. Among heart failure patients, the objective parameter of NT-proBNP seems more useful to delineate the "cardiorenal syndrome" than the previous criteria of a clinical diagnosis of heart failure. (J Am Coll Cardiol 2006;48:1621–7) © 2006 by the American College of Cardiology Foundation

In the setting of heart failure (HF), impaired renal function is common and strongly predicts adverse outcomes (1–3). This intersection of cardiac and renal insufficiency has been referred to as the "cardiorenal syndrome," particularly when acute HF is paralleled by a drop in renal function (4,5). The relationship between cardiac and renal insufficiency may reflect common risk factors for both morbidities (such as diabetes, hypertension, and atherosclerosis) or impaired renal blood flow related to HF with resultant progressive deterioration of renal function. Whatever the mechanism, renal insufficiency in a patient with HF is an established marker of risk, which to date has been considered independent of other risk factors in HF, such as advanced age or left ventricular function.

Both B-type, or brain, natriuretic peptide (BNP) and its cleavage equivalent, amino-terminal pro-BNP (NT-proBNP) are rapidly released from cardiomyocytes after stretch (6) and are established diagnostic and prognostic markers in chronic as well as acute HF (7–9). Notably, a significant inverse relationship exists between renal function and these cardiac peptides, with higher levels of both BNP and NT-proBNP observed in patients with impairment in renal function, either with or without clinical HF (10–12). Despite earlier suggestions that such elevations in BNP and NT-proBNP were merely reflective of passive accumulation due to reduced clearance in the setting of renal insufficiency and thus impairing their use in HF patients with renal impairment (13), more recent data suggest that concentrations of natriuretic peptides in patients with renal insufficiency may parallel the presence and severity of cardiac abnormalities in such patients and may offer powerful prognostic information as well (12,14). Thus, the relationship between NT-proBNP, structural heart disease, and renal function remains incompletely understood. Accordingly, in an effort to better understand the interplay between measures of cardiac and renal insufficiencies, we analyzed the relationship between NT-proBNP concentrations, renal function, and outcomes in subjects with acute HF.

METHODS

Patients. The ICON (International Collaborative on NT-proBNP) study has been previously published (15). Briefly, the study population consists of patients from 3 previously reported prospective clinical studies of natriuretic peptide

From the *Department of Cardiology, University Hospital Maastricht, Maastricht, the Netherlands; †Department of Cardiology, Massachusetts General Hospital, Boston, Massachusetts; ‡Christchurch Cardioendocrine Research Group, Christchurch School of Medicine and Health Science, Christchurch, New Zealand; and the §Department of Cardiology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. Supported by grants from Roche Diagnostics and the Ed and Maureen Lewi Fund for Cardiovascular Research. Drs. van Kimmenade and Jannuzzi contributed equally to this work.

Manuscript received January 10, 2006; revised manuscript received May 3, 2006, accepted June 5, 2006.

JACC Vol. 48, No. 8, 2006
October 17, 2006:1621–7

Abbreviations and Acronyms

BNP = brain natriuretic peptide
GFR = glomerular filtration rate
HF = heart failure
ICON = International Collaborative on NT-proBNP
MDRD = Modified Diet in Renal Disease
NT-proBNP = amino-terminal pro-brain natriuretic peptide

testing for the evaluation of dyspneic subjects, from Christchurch, New Zealand (16), Barcelona, Spain (17), and Boston, Massachusetts (8), combined with a registry of consecutively admitted HF patients at the University Hospital of Maastricht, the Netherlands. Of the total of 1,256 subjects, 720 subjects had acute HF and the remainder had dyspnea without acute HF. In the Maastricht, Boston, and Barcelona studies, the final diagnosis for each patient was assigned by a panel of experienced clincial physicians using all available clinical data from presentation to 76-day follow-up (8,15,17). In the Christchurch study, the criteria from the European Society of Cardiology were used to diagnosis or exclude HF (16,18). However, all data sources had compatible inclusion/exclusion criteria and obtained similar clinical information, including standard demographics, medical history, drug therapy, presenting symptoms and signs, physical examination, results of laboratory testing, chest X-ray information, and electrocardiography results.

Laboratory results. In all patients, blood samples were drawn at the moment of presentation, before any therapy was given. From this baseline creatinine, dynamic changes in creatinine concentration were evaluated.

Amino-terminal pro-BNP levels were determined by an immunoelectrochemiluminisence method (Elecsys; Roche Diagnostics, Basel, Switzerland) and expressed in pg/ml.

For conversion, 1.0 pg/ml equals 1.0 ng/l. Creatinine levels were determined by standard laboratory testing at each individual hospital. Glomerular filtration rate (GFR) was calculated based on the creatinine levels on admission using the simplified Modified Diet in Renal Disease (MDRD) formula (19). In an effort to examine the influence of dynamic changes in serum creatinine in the setting of HF, each subject's record was reviewed for serial serum creatinine levels following presentation. An increase or decrease in creatinine was defined by any increase or decrease ≥0.3 mg/dl during admission.

Statistical analyses. Data are presented as median values with intraquartile range (IQR) for non-normally distributed variables and mean ± standard deviation (SD) for all other continuous variables. For NT-proBNP analyses, HF patients were dichotomized to above/below median NT-proBNP levels. For analyses of renal function, patients were dichotomized to GFR above or below 60 ml/min/1.73 m^2, both the mean value for the population as well as reflecting a cut-off value based on the standards of the National Kidney Foundation (2,4,20). To investigate dynamic aspects in renal function, we also divided our population according to previously published criteria for the cardiorenal syndrome (21), namely, an increase in creatinine level during hospital admission ≥0.3 mg/dl. We also identified subjects with a decrease in creatinine level ≥0.3 mg/dl and those with a stable creatinine level.

Differences in baseline variables between survivors and nonsurvivors were analyzed using the Wilcoxon rank sum test for continuous variables and Pearson chi-square testing for categoric variables. Survival curves were computed with the Kaplan-Meier curves, and differences between the curves were evaluated with the log-rank statistic.

Univariate screening of baseline variables was used to identify candidate independent predictors of 60-day mortality. Multivariable analysis with forward stepwise logistic regression, including all candidate variables with p values ≤0.10 or of predetermined clinical interest, was performed to identify independent predictors of 60-day mortality. Goodness of fit was evaluated with the Hosmer-Lemeshow test. Other than an interaction between NT-proBNP > median value and GFR <60 ml/min/1.73 m^2 ($p < 0.001$), all other independent variables were evaluated in pairs for first-order interactions, and none were found. Results are presented as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Of the 1,256 overall patients included in the ICON study, 720 (57%) were diagnosed with acute HF at presentation. Among these 720 subjects with acute HF, the median NT-proBNP concentration was 4,647 pg/ml. The mean serum creatinine was 1.3 ± 0.68 mg/dl, with a corresponding mean GFR of 60.5 ± 26.0 ml/min/1.73 m^2; accordingly, 373 subjects (51.8%) had a GFR below 60 ml/min/1.73 m^2. Comparisons of various characteristics germane to the present analysis, as a function of study site, are demonstrated in Table 1.

Amino-terminal pro-BNP was negatively related to GFR ($r = -0.34$; $p < 0.001$). Subjects with a GFR <60 ml/min/1.73 m^2 ($n = 373$) had higher median NT-proBNP concentrations than those ($n = 347$) with GFR ≥60 ml/min/1.73 m^2 (7,214 pg/ml [IQR = 2,757 to 16,160] vs. 3,054 pg/ml [IQR = 1,345 to 7,620 pg/ml]; $p < 0.001$ for difference).

Mortality analysis. Eighty-nine patients (12.4%) with acute HF died within 60 days. Patient characteristics as a function of survival are shown in Table 2. Subjects dying within 60 days were more likely to be older, to have a history of coronary artery disease and left bundle branch block on electrocardiogram, and to present with fever or the absence of paroxysmal nocturnal dyspnea than survivors. In addition, decedents were also more likely to have worse renal function, to be anemic, to have higher cardiac troponin T

Table 1. Comparisons of Various Characteristics as a Function of the Study Site

Characteristic	Maastricht (n = 365)	Boston (n = 209)	Barcelona (n = 80)	Christchurch (n = 66)
NT-proBNP, pg/ml (median, interquartile range)	6,842 (2,888–12,626)	4,054 (1,674–10,027)	3,538 (2,115–10,017)	854 (441–1,951)
Serum creatinine, mg/dl (mean ± SD)	1.4 ± 0.8	1.3 ± 0.5	1.1 ± 0.7	1.0 ± 0.2
Glomerular filtration rate (mg/min/1.73m^2), mean ± SD	55 ± 24	58 ± 25	77 ± 31	78 ± 22
Serum creatinine patterns following admission				
Rise ≥0.3 mg/dl	45%	37%	N/A	21%
Fall ≥0.3 mg/dl	7.1%	4.8%	N/A	18.2%
60-day mortality	15.6%	8.1%	6.3%	15.2%

N/A = not available; NT-proBNP = amino-terminal pro-brain natriuretic peptide.

(cTnT) concentrations, and to have more elevated NT-proBNP concentrations.

In multivariate analyses that included age, prior HF, prior myocardial infarction, severity of dyspnea (New York Heart Association functional classification), hemoglobin levels, cTnT results, GFR <60 ml/min/1.73 m^2, and NT-proBNP level above the median value, both GFR <60 ml/min/1.73 m^2 (OR 2.03; 95% CI 1.18 to 3.49) and NT-proBNP

Table 2. Comparisons of Patients With Acute Heart Failure Based on the 60-Day Survival

Characteristic	Alive at Day 60 (n = 606)	Deceased by Day 60 (n = 84)	p Value
Age, yrs (mean ± SD)	74.4 ± 11.7	78.5 ± 10.6	0.002
Male gender	51.2%	52.4%	0.833
Black race	2.5%	0%	0.237
Medical history			
Hypertension	62.0%	51.2%	0.056
Coronary artery disease	50.7%	65.5%	0.011
Prior acute myocardial infarction	33.3%	42.2%	0.112
Prior heart failure	51.7%	54.8%	0.593
Prior obstructive airways disease	29.3%	26.2%	0.561
Smoking (past or present)	51.9%	52.4%	0.985
Symptoms/signs			
Paroxysmal nocturnal dyspnea	33.2%	19.0%	0.009
Orthopnea	51.6%	48.4%	0.635
Lower extremity edema	46.5%	45.2%	0.823
Chest pain	33.5%	32.5%	0.861
Cough	32.8%	27.4%	0.361
Fever	4.1%	10.7%	0.009
Increased sputum	18.3%	16.7%	0.713
NYHA functional class 4	44.2%	50.0%	0.319
Physical examination			
Pulse rate (mean ± SD)	92.8 ± 25.8	95.5 ± 26.0	0.381
Jugular venous distension	48.8%	56.0%	0.222
S_3 gallop	6.9%	8.3%	0.639
Lower extremity edema	56.3%	52.4%	0.501
Rales	68.7%	67.9%	0.882
Wheezing	16.9%	10.7%	0.151
Electrocardiographic findings			
Sinus rhythm	59.6%	64.3%	0.408
Atrial fib/flutter	34.5%	32.1%	0.671
Left ventricular hypertrophy	10.7%	8.3%	0.499
Left bundle branch block	15.0%	25.0%	0.02
Chest X-ray findings			
Interstitial edema	37.6%	29.8%	0.161
Infiltrate	11.7%	16.7%	0.196
Pleural effusion	26.6%	22.6%	0.440
Cephalization of vessels	29.4%	35.7%	0.235
Cardiomegaly	37.0%	39.3%	0.680
Laboratory findings			
Creatinine, mg/dl (median, interquartile range)	1.12 (0.87–1.50)	1.41 (1.02–2.10)	<0.001
GFR, ml/min/1.73m^2 (median, interquartile range)	60.7 (42.90–79.22)	43.9 (30.92–64.03)	<0.001
Troponin T ≥0.01 ng/ml	47.5%	77.3%	<0.001
Hemoglobin, g/dl (mean ± SD)	12.7 ± 2.06	12.0 ± 1.97	0.003
NT-proBNP, pg/ml (median, interquartile range)	4,077 (1,740–9,989)	9,448 (3,805–22,179)	<0.001

GFR = glomerular filtration rate; NT-proBNP = amino-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

Table 3. Multivariate Analysis Using Individual and Combined Measures of Cardiac and Renal Insufficiency for the Prediction of Death by 60 Days Following Presentation With Acute Heart Failure (HF)

Predictor	Odds Ratio	95% CI	p Value
Individual Measures			
Age	1.02	0.99–1.05	0.08
Prior HF	0.78	0.48–1.27	0.31
Prior myocardial infarction	1.36	0.84–2.22	0.22
NYHA functional class	1.26	0.86–1.86	0.24
Hemoglobin	0.94	0.88–1.01	0.07
Troponin T ≥0.01 ng/ml	1.52	0.89–2.01	0.08
GFR <60 ml/min/1.73 m^2	2.03	1.18–3.49	<0.001
NT-proBNP >4,647 pg/ml	2.67	1.58–4.51	<0.001
Combined Measures			
Age	1.02	0.99–1.05	0.06
Prior HF	0.78	0.48–1.27	0.31
Prior myocardial infarction	1.37	0.84–2.24	0.20
NYHA functional class	1.24	0.84–1.83	0.28
Hemoglobin	0.94	0.88–1.01	0.07
Troponin T ≥0.01 ng/ml	1.32	0.83–2.05	0.10
GFR <60 ml/min/1.73 m^2 and NT-proBNP >4,647 pg/ml	3.46	2.13–5.63	<0.001

CI = confidence interval; other abbreviations as in Table 2.

concentrations above the median (OR 2.67; 95% CI 1.58 to 4.51) strongly predicted 60-day mortality in an independent fashion (Table 3). Notably, in a secondary analysis, the combination of both GFR <60 ml/min/1.73 m^2 and NT-proBNP level above the median was an even stronger predictor of mortality than either measure alone (OR 3.46; 95% CI 2.13 to 5.63) (Table 3).

Kaplan-Meier survival curves depicting mortality rates as a function of NT-proBNP concentration and GFR (Fig. 1) demonstrate that the majority of fatal events in the first 60 days from presentation occurred in subjects with an NT-proBNP level above the median plus a GFR <60 ml/min/1.73 m^2, with low rates of mortality (and no statistical difference) in the other categories, including HF with a GFR <60 ml/min/1.73^2 but with an NT-proBNP below the median.

Renal function, NT-proBNP, and 60-day survival. In an effort to better understand the relationship between renal function and HF outcomes, we examined the relationship between dynamic changes in serum creatinine in the setting of acute HF, and outcomes (5). This group of subjects (n = 627) with available data was similar to the group as a whole in terms of baseline demographics, including a similar NT-proBNP median of 4,694 pg/ml, and was dichotomized with respect to NT-proBNP concentrations above or below the median and analyzed as a function of serum creatinine changes. In recognition of previous definitions of cardiorenal syndrome (4,5,21), the outcomes of those subjects with an in-hospital rise of serum creatinine ≥0.3 mg/dl were compared with those without a rise in creatinine. In addition, we examined the outcomes of subjects whose creatinine fell by ≥0.3 mg/dl during their hospitalization. This left 3 diagnostic categories within NT-proBNP

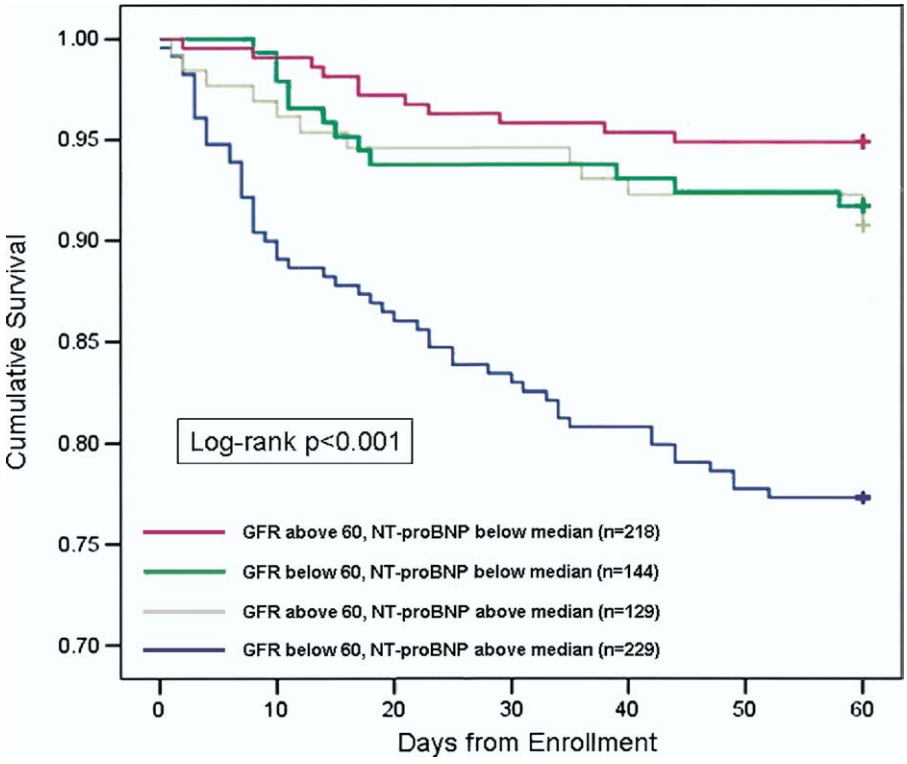

Figure 1. Survival curves of heart failure subjects in ICON (International Collaborative on NT-proBNP) as a function of glomerular filtration rate (GFR) and amino-terminal pro-brain natruiuretic peptide (NT-proBNP) concentration on admission (log-rank $p < 0.001$).

groups, those with: 1) an increase in serum creatinine ≥0.3 mg/dl; 2) those with change in serum creatinine <0.3 mg/dl during hospitalization; and 3) those with a decrease in serum creatinine ≥0.3 mg/dl following presentation.

The outcomes of subjects as a function of NT-proBNP concentration and dynamic changes in serum creatinine are shown in Figure 2. Among the HF patients with an NT-proBNP level above the median, those with a rise in serum creatinine (n = 173) had the worst overall 60-day prognosis, those subjects with high NT-proBNP but with no change in creatinine (n = 110) had intermediate outcomes, and those with a fall in serum creatinine ≥0.3 mg/dl (n = 28) had the most benign outcomes (but which were nonetheless worse than those with an NT-proBNP below the median). In each case, all 3 groups had significantly worse outcomes ($p < 0.001$) than those with NT-proBNP concentrations below the median.

To get a better understanding of the relationship between GFR and dynamic changes in renal function, we examined the relationship between presenting GFR and the prevalence of subsequent dynamic changes in renal function. We found that among those patients with a rise in serum creatinine ≥0.3 mg/dl during treatment for acute HF, more had a presenting GFR <60 ml/min/1.73 m^2 (44.8% vs. 32.9%; $p = 0.01$), and were more likely to have the adverse combination of a low GFR together with an elevated NT-proBNP compared with those with a GFR ≥60 ml/min/1.73 m^2 (29.1% vs. 13.0%; $p < 0.001$).

Notably, in those patients with NT-proBNP levels below the median value of 4,694 pg/ml, we found no graded relationship between dynamic changes in creatinine and rates of mortality.

DISCUSSION

The complex interaction between heart and kidneys remains a poorly understood area and one of great focus in modern medicine. Using data from the ICON study, we demonstrated the dynamic interaction between HF, renal function, and outcomes, emphasizing the value of the addition of an objective measure of HF severity (NT-proBNP) to an objective measurement of renal function (GFR or serum creatinine) to better stratify risk in acute HF.

Besides sharing strong commonality with respect to risk factors for their development, cardiac and renal impairment are strongly connected on a neurohormonal basis via the renin-angiotensin-aldosterone system and its antagonists (BNP and nitric oxide), the sympathetic nervous system, as well as inflammatory pathways (22). Furthermore, in the setting of acute HF, the dynamic relationship between the heart and kidneys may be accentuated: cardiac output is reduced, which may be counteracted by systemic and other responses such as a decrease in renal blood flow to retain circulating fluid and restore cardiac output (5,23). In addition, the uremic milieu itself may further affect cardiac contractility, with promotion of myocyte fibrosis and death (24,25). It is thus not at all surprising that measures of

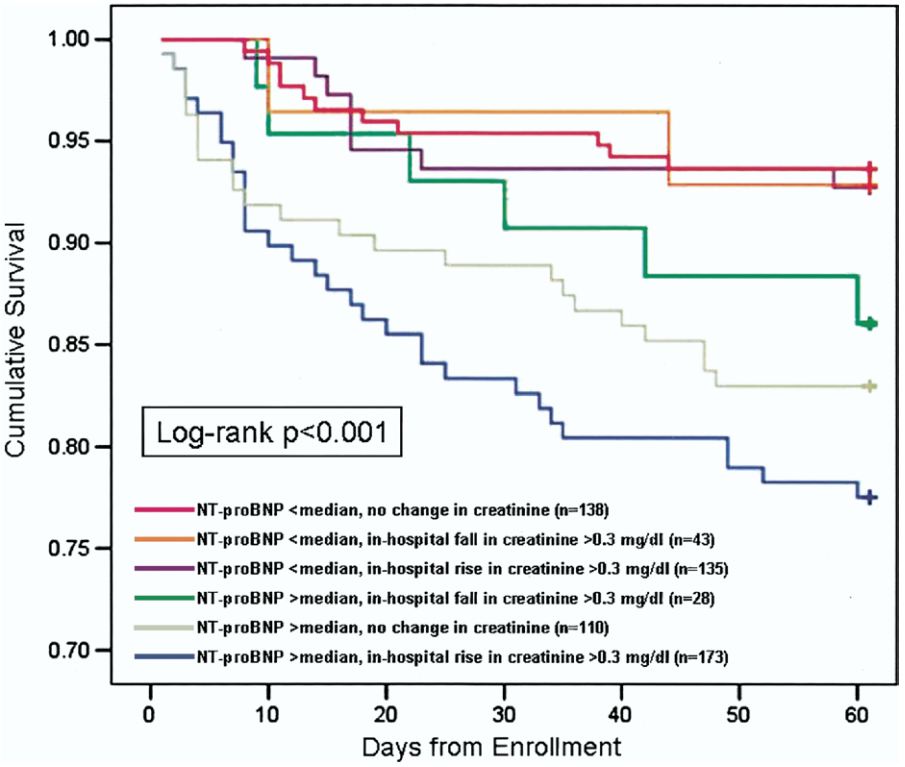

Figure 2. Survival curves of heart failure subjects in ICON as a function of NT-proBNP concentration on admission and dynamic changes in renal function following presentation (log-rank $p < 0.001$). Abbreviations as in Figure 1.

cardiac insufficiency, such as natriuretic peptides, are strongly influenced by the presence and severity of renal insufficiency.

This combination of acute cardiac and renal insufficiency—often termed "cardiorenal syndrome" (4,5)—is a marker of particularly high risk for adverse outcome in the setting of acute HF (26).

In this analysis of NT-proBNP and renal function in subjects with acute HF, we report several important findings with potentially useful clinical implications. Consistent with all other studies (9,27–31), we show NT-proBNP as a powerful predictor of mortality in acute HF, remaining so in the presence of normal or impaired renal function. However, in none of the previously published studies (9,27–31) was GFR taken into account in the multivariate analyses. Notably, although NT-proBNP and GFR were each significantly related to mortality, the novel approach of combining the 2 measures led to our finding that the combination was a superior tool for identifying patients with HF at highest risk for short-term death, while also demonstrating that, in our study, many HF subjects with moderate or worse renal insufficiency but lower NT-proBNP concentrations had 60-day outcomes comparable to those without significant renal insufficiency. Interestingly, as depicted in Figure 1, patients with an elevated NT-proBNP in the absence of renal impairment had a prognosis comparable with patients with renal impairment. In addition, while analyzing the concept of dynamic changes in "cardiorenal" insufficiency, we demonstrated the utility of NT-proBNP to stratify the subjects to a wide range of risks within various categories of renal function. Importantly, though a rise in creatinine indeed identified subjects at higher risk for mortality following presentation (the classic definition of the cardiorenal syndrome), this risk was only present in those with elevated NT-proBNP concentrations. Those subjects with creatinine rise during admission but without a markedly elevated NT-proBNP level demonstrated a relatively low 60-day mortality rate similar to subjects with a low NT-proBNP level, regardless of their evolution in creatinine. Our data suggest that defining the cardiorenal syndrome simply as the development of worsened renal function in a patient with HF may require reconsideration. Indeed, the heterogeneity of cardiorenal insufficiency was recently emphasized by Forman et al. (32), who demonstrated that HF patients with deterioration in renal function are not simply those with the poorest ventricular function, but included patients with preserved systolic function, fewer complaints of low output (such as fatigue), as well as high blood pressure.

Although most prior analyses of cardiorenal interaction have focused on those subjects with HF and a rise in serum creatinine, the outcomes of those subjects with an improvement in renal function (accounting for more than 11% of the present study population) consequent to treatment for HF remains less well described. We also described the group of patients with elevated NT-proBNP in whom serum creatinine fell following presentation. In the subjects with markedly elevated NT-proBNP, a falling creatinine was associated with a statistically significantly lower risk of death compared with those with an elevated NT-proBNP and either a rise or no change in renal measurements. Notably, however, the outcomes of subjects in ICON with a high NT-proBNP and improvement in serum creatinine were still worse than those with low NT-proBNP.

Although it is generally accepted that renal impairment correlates with poor outcome in patients with HF (1–3), there is still some debate whether a rise in serum creatinine is the best expression of renal impairment in HF, or if relative increase in serum creatinine or a high serum creatinine on admission (32–34) better reflect "cardiorenal" risk. Although our data suggest that both GFR or dynamic changes in renal function offer relatively comparable prognostic data, in the setting of a high presenting NT-proBNP, a GFR <60 ml/min/1.73 m^2 on admission provides these prognostic data right at presentation, rather than requiring serial measurements of creatinine.

Study limitations. Limitations of our study include, first, the fact that GFR estimation was performed using the MDRD equation rather than directly measuring renal function. The MDRD equation is accepted to be a generally accurate measure of renal function and in the present study provided robust results regarding prognosis. Second, only a small number of African Americans were included in this trial, and our findings should therefore carefully be extrapolated to this population. Third, as in all studies discussing the cardiorenal syndrome, the measurement of serum creatinine for assessment of dynamic changes in renal function was performed at variable time intervals in our study. Fourth, because the number of creatinine observations would typically be expected to be greater in sicker patients, the risk for confounding/bias is increased owing to the potential for issues pertaining to ascertainment of these sicker patients. Nonetheless, our results are quite consistent with those previously described and make intuitive sense as well. Last, it is important to realize that our study was an observational study and not an interventional study, and although all patients were treated according to guidelines known at that time point it may be that our results would be slightly different if the results from later trials (e.g., the CARE-HF [Cardiac Resynchronization Heart Failure] [35]) would be taken into account.

Conclusions. The combined use of objective parameters of cardiac (NT-proBNP) and renal (GFR) function allowed identification of those HF patients at highest risk for short-term death and argues that elevations of NT-proBNP in the setting of renal insufficiency are not, in fact, spurious. Moreover, analyses of the rates of mortality based on dynamic changes in renal function suggest a graded risk for death among those with highest concentrations of NT-proBNP. This latter finding lends support to the consideration that therapies aimed specifically at the cardiorenal syndrome (36), may improve survival in these patients (5).

Finally, our data may support a reconsideration of the definition of cardiorenal syndrome to include a natriuretic peptide standard rather than the clinical diagnosis of HF to describe the cardiovascular element to this complex syndrome of combined cardiac and renal insufficiencies.

Reprint requests and correspondence: Dr. James L. Januzzi, Jr., Massachusetts General Hospital, Yawkey 5800, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: jjanuzzi@partners.org.

REFERENCES

1. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation 2004;109:1004–9.
2. Mahon NG, Blackstone EH, Francis GS, Starling RC 3rd, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol 2002;40:1106–13.
3. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002;13:1928–36.
4. Shlipak MG, Massie BM. The clinical challenge of cardiorenal syndrome. Circulation 2004;110:1514–1517.
5. Stevenson LW, Nohria A, Mielniczuk L. Torrent or torment from the tubules? Challenge of the cardiorenal connections. J Am Coll Cardiol 2005;45:2004–2007.
6. Bruneau BG, Piazza LA, de Bold AJ. BNP gene expression is specifically modulated by stretch and ET-1 in a new model of isolated rat atria. Am J Physiol 1997;273:H2678–86.
7. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161–7.
8. Januzzi JL Jr., Camargo CA, Anwaruddin S, et al. The N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. Am J Cardiol 2005;95:948–54.
9. Hartmann F, Packer M, Coats AJS, et al. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. Circulation 2004;110: 1780–6.
10. Luchner A, Hengstenberg C, Lowel H, et al. N-terminal pro-brain natriuretic peptide after myocardial infarction: a marker of cardio-renal function. Hypertension 2002;39:99–104.
11. McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly multinational study. Am J Kidney Dis 2003;41:571–9.
12. Anwaruddin S, Lloyd-Jones DM, Baggish AL, et al. Renal function, congestive heart failure and NT-proBNP measurement: results from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. J Am Coll Cardiol 2006;47:91–7.
13. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. Rev Cardiovasc Med 2003;4 Suppl 4:S13–9.
14. DeFilippi CR, Fink JC, Nass CM, Chen H, Christenson R. N-terminal pro-B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. Am J Kidney Dis 2005;46:35–44.
15. Januzzi JL Jr., van Kimmenade RRJ, Lainchbury JG, Bayes-Genis A, Pinto YM, Richards AM. NT-proBNP testing for diagnosis and short-term prognosis in acute congestive heart failure: an international pooled analysis of 1256 patients. The International Collaborative of NT-proBNP (ICON) study. Eur Heart J 2006;27:330–337.
16. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 2003;42:728–35.
17. Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, et al. N-Terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail 2004;6:301–8.
18. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
19. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–70.
20. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–9.
21. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349:747–52.
22. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: "Guyton revisited." Eur Heart J 2005;26: 11–7.
23. Braunwald E. The Denolin lecture. Congestive heart failure: a half century perspective. Eur Heart J 2001;22:825–36.
24. Mall G, Huther W, Schneider J, Lundin P, Ritz E. Diffuse intermyocardiocytic fibrosis in uraemic patients. Nephrol Dial Transplant 1990;5:39–44.
25. Amann K, Breitbach M, Ritz E, Mall G. Myocyte/capillary mismatch in the heart of uremic patients. J Am Soc Nephrol 1998;9:1018–22.
26. Smith GL, Vaccarino V, Kosiborod M, et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Card Fail 2003;9:13–25.
27. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-Terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004; 110:2168–74.
28. Gustafsson F, Steensgaard-Hansen F, Badskjaer J, Poulsen AH, Corell P, Hildebrandt P. Diagnostic and prognostic performance of N-terminal ProBNP in primary care patients with suspected heart failure. J Card Fail 2005;11:15–20.
29. Taniguchi R, Sato Y, Yamada T, et al. Combined measurements of cardiac troponin T and N-terminal pro-brain natriuretic peptide in patients with heart failure. Circ J 2004;68:1160–4.
30. Rothenburger M, Wichter T, Schmid C, et al. Aminoterminal pro type B natriuretic peptide as a predictive and prognostic marker in patients with chronic heart failure. J Heart Lung Transplant 2004;23: 1189–97.
31. Richards AM, Doughty R, Nicholls MG, et al.; Australia-New Zealand Heart Failure Group. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: prognostic utility and prediction of benefit from carvedilol in chronic ischemic left ventricular dysfunction. J Am Coll Cardiol 2001;37:1781–7.
32. Forman DE, Butler J, Wang Y, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol 2004;43:61–7.
33. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. Am Heart J 1999;138:285–90.
34. Leithe ME, Margorien RD, Hermiller JB, Unverferth DV, Leier CV. Relationship between central hemodynamics and regional blood flow in normal subjects and in patients with congestive heart failure. Circulation 1984;69:57–64.
35. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
36. Paterna S, Di Pasquale P, Parrinello G, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. J Am Coll Cardiol 2005;45: 1997–2003.