Relation of Blood Urea Nitrogen to Long-Term Mortality in Patients With Heart Failure

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Patients with chronic kidney disease and heart failure (HF) have been shown to be at higher risk for major adverse cardiovascular events and death. Recent studies have demonstrated that blood urea nitrogen (BUN) might serve as a powerful predictor of mortality in acutely decompensated HF. The goal of this study was to determine the impact of BUN on long-term mortality in patients with stage B and C HF. Our retrospective analysis included patients undergoing percutaneous intervention with a calculated left ventricular ejection fraction ≤50%. Patients on dialysis or with technically inadequate left ventriculograms were excluded. Chart review was performed and mortality data were obtained. Our population included 444 patients with a mean ejection fraction of 38 ± 10%, mean age of 59 ± 11 years, median BUN of 14 mg/dl, and median glomerular filtration rate (GFR) of 81 ml/min/1.73 m^2; 31% had stage C HF, and 33% died during follow-up. Patients with increased BUN (≥17 mg/dl) and decreased GFR (≤69 ml/min/1.73 m^2) had significantly increased long-term mortality on Kaplan-Meier analysis (8-year mortalities of 57% and 55%, respectively). In patients with stage C HF, mortalities at 8 years were 69% and 73% with abnormal BUN and GFR, respectively. Proportional hazard regression analysis demonstrated that BUN and stage C HF were independently associated with increased mortality, whereas GFR was not. In conclusion, we demonstrated that BUN is strongly associated with mortality in patients with stage B and C HF and may serve as a better biomarker than GFR for prognostication. **(Am J Cardiol 2008;101:1643–1647)**

Patients with heart failure (HF) are typically older, have a higher prevalence of chronic kidney disease, and are prone to acute changes in glomerular filtration rate (GFR) during episodes of decompensation. As a result, creatinine-based estimates may not be the optimal method of assessing renal function in patients with HF. Several well-conducted studies have demonstrated that increases in blood urea nitrogen (BUN) are associated with increased in-hospital, short- and intermediate-term mortality.[1–7] Comparative studies of renal indexes have suggested that BUN may be a stronger predictor of cardiovascular outcomes and all-cause mortality.[8–10] We used the HF classification[11] system that delineates patients at risk for HF with left ventricular (LV) systolic dysfunction (stage B) and who have or previously have been diagnosed HF (stage C) to help determine the impact of BUN and GFR on short- and long-term mortalities in patients with HF.

Methods

Patients who underwent percutaneous coronary intervention at a single university from May 1996 to December 2005 were eligible for inclusion in this retrospective observational analysis. Our institutional review board (no. 2670) approved this study design. Patients were eligible for inclusion if they had a digitally calculated LV ejection fraction (EF) ≤50% determined from the preprocedural contrast left ventriculogram. Patients were excluded if they were on dialysis, did not have laboratory values at the time of procedure, or had significant valvular disease, previous valve surgery, or a technically inadequate left ventriculogram. After the initial screening of inclusion and exclusion criteria, 444 patients were selected. Assuming a 10% 3-year mortality in patients with low BUN concentration and an absolute 10% higher risk for patients with high BUN, our sample had a statistical power of 85% (alpha = 0.05).

Demographic data, medical history, angiographic data, blood count, and chemistry values at the time of the procedure and medications at discharge were recorded from patient records. All-cause mortality data were retrieved from the U.S. Social Security Death Index. Because many patients were followed outside the index institution, we lacked the statistical power to adequately access other cardiac end points.

Coronary artery disease was considered to be significant if luminal diameter narrowing was ≥70% in the left anterior descending artery or major branches, the left circumflex artery or its major branches, the right coronary artery or its

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major branches, or the ramus intermedius. Disease of the left main artery was considered significant if luminal diameter narrowing was ≥50%. Stage C HF was defined as use of HF therapy or a diagnosis of HF.[11] We estimated GFR for each patient by using the simplified Modification of Diet in Renal Disease equation (GFR = 186 × [serum creatinine]$^{-1.154}$ × age$^{-0.203}$ × [0.742 if a woman] × [1.212 if African-American]), which has been developed and validated as an accurate estimate of GFR.[12,13]

Student's *t* test or analysis of variance was performed to compare continuous variables between populations (presented as mean ± SD). Kolmogorov-Smirnov z test was performed to validate analysis of variance for nonparametric factors. Two-tailed Fisher's exact test or chi-square tests were used to compare categorical variables. Stepwise multivariable regression analysis was performed to determine which independent variables were significantly associated with the dependent variable of interest. Unadjusted and adjusted odds ratios were calculated using the Mantel-Haenszel test. How well BUN concentrations separated patients with from those without a given outcome (death) was assessed by means of the area under a receiver operating characteristic curve, which was 0 to 1, with 0.5 corresponding to no discrimination (i.e., random performance) and 1.0 to perfect discrimination. Stepwise proportional hazard regression analysis was performed to determine which variables were significantly associated with mortality. Univariate analysis was initially performed to evaluate the association between independent variables and the dependent or outcome variable. Variables selected with univariate analysis were incorporated into multivariable analysis. Multivariable equations were fitted by a forward stepwise selection procedure. Multicollinearity was appraised by means of correlation coefficient matrix. If possible, continuous variables were employed unless otherwise specified, such as anemia or BUN increments, to prevent loss of information during regression analysis.[14] With regard to overfitting, adequate outcome events occurred during follow-up to enable proper analysis.[15] Proportional hazards assumptions for the model were confirmed. A p value <0.05 was considered statistically significant. All statistical analyses were performed using NCSS 2001 (Number Crunching Statistical Software, Kaysville, Utah).

Results

This study included 444 patients with an average age of 59 ± 11 years and average LVEF of 38 ± 10%. Median BUN was 14 mg/dl (interquartile range 6 to 22), GFR was 81 ml/min/1.73 m^2 (interquartile range 35 to 117), 69% had class B HF, 31% had class C HF, and 33% died during follow-up. Average follow-up was 7.5 years (range 4.4 to 10.7). The cause of HF in this cohort was ischemic heart disease. Patients with BUN concentrations in the highest tertile had an increase of baseline co-morbidity and greater cardiovascular disease burden (Table 1).

Stepwise multivariable regression analysis was performed to determine which variables were significantly associated with stage C HF. Increasing concentrations of BUN were found to be significantly associated with stage C HF (regression coefficient 0.009 ± 0.004, p = 0.04) along with previously established variables. Additionally, stepwise multivariable regression analysis was performed to determine which variables were predictive with increasing BUN concentrations and showed that age, GFR, and diabetes were significantly associated with increased BUN.

Increase in BUN was associated with an incremental decrease in long-term survival (Figure 1). Decreases in GFR were also associated with a decrease in long-term survival. Survival analysis by tertiles of GFR demonstrated a significantly lower survival for patients only in the lowest tertile (GFR '71). Analysis at 3 years (94% vs 91% vs 72%, respectively, among tertiles) and at 8 years (73% vs 74% vs 45%, respectively, among tertiles) demonstrated a significant and dramatic increase in mortality. Receiver operating characteristic curve analysis demonstrated that 17 mg/dl and 69 ml/min/1.73 m^2 appeared to be optimal cutpoints to create dichotomous variables for BUN (Figure 2) and GFR, respectively. Selection of a cutpoint was challenging due to the large decreases in specificity as sensitivity increases. BUN ≥17 mg/dl had a significantly decreased survival regardless of whether patients had stage B or stage C HF (Figure 3). Similarly, decreased GFR (GFR ≤69) had a significantly decreased survival regardless of whether patients had stage B or C HF (stage B HF at 3 and 8 years, 90% and 63% survival, respectively; stage C HF at 3 and 8 years, 58% and 27% survival, respectively). Increased BUN and decreased GFR appeared to have the greatest impact on survival in patients with stage C HF.

Stepwise proportional hazard regression analysis demonstrated that BUN, age, chronic obstructive pulmonary disease, statin therapy, coronary disease burden, calculated EF, and stage C HF were significant independent predictors of mortality (Table 2). When incorporating BUN as a continuous variable, we found BUN to be the strongest predictor of mortality with a 4% increase in risk for every 1-mg/dl increase in BUN. Secondary analysis demonstrated that for every 10 mg/dl above a normal cutoff (BUN ≥17 mg/dl) risk of death increased by 21%. Surprisingly, GFR was not found to be an independent predictor of mortality in our patient population. Odds ratios (ORs) were calculated for patients with a BUN ≥17 mg/dl demonstrating a significant increase in mortality (unadjusted OR 2.76, 95% confidence interval [CI] 1.80 to 4.26) and remained significant (adjusted OR 1.64, 95% CI 1.02 to 2.64, p = 0.04) after adjusting for stage C HF, age, chronic obstructive pulmonary disease, number of diseased vessels, statin therapy, hemoglobin, previous coronary artery bypass grafting, diabetes, β-blocker therapy, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy. Similarly, stage C HF demonstrated a significant increase in mortality (unadjusted OR 3.80, 95% CI 2.51 to 5.74) and remained significant (adjusted OR 2.59, 95% CI 1.62 to 4.16) after adjusting for BUN, age, chronic obstructive pulmonary disease, number of diseased vessels, statin therapy, hemoglobin, previous coronary artery bypass grafting, diabetes, β-blocker therapy, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy.

Discussion

In this study, we demonstrated that BUN provides prognostic information on the risk of mortality in a heterogenous

Table 1
Baseline patient characteristics of the study cohort divided by blood urea nitrogen concentration tertiles

Variables	BUN (mg/dl)			p Value
	<12 (n = 128)	12–17 (n = 173)	>17 (n = 142)	
Age (yrs)	57 ± 11	58 ± 12	64 ± 11	<0.0001
Men (%)	65%	70%	69%	0.62
Caucasian (%)	54%	60%	65%	0.47
African-American (%)	43%	38%	32%	0.47
Body mass index (kg/m^2)	28.5 ± 6.2	29.2 ± 6.9	28.7 ± 6.7	0.62
Calculated LVEF (%)	40.8 ± 7.8	37.3 ± 9.9	35.3 ± 10.0	0.008
Medical history				
Stage C HF	25%	39%	60%	<0.0001
Atrial fibrillation	2%	4%	10%	0.02
Diabetes	30%	35%	45%	0.03
Chronic obstructive pulmonary disease	17%	36%	23%	0.008
Hypertension	74%	87%	82%	0.02
Hypercholesterolemia	80%	71%	62%	0.007
Coronary artery bypass graft	12%	19%	29%	0.004
Percutaneous intervention	24%	40%	41%	0.12
Stroke	10%	8%	16%	0.07
Angiographic data				
1-vessel disease	38%	35%	33%	0.75
2-vessel disease	44%	35%	30%	0.05
≥3-vessel disease	19%	30%	37%	0.003
Balloon angioplasty	19%	22%	26%	0.36
Bare metal stent	55%	51%	46%	0.34
Drug-eluting stent	26%	27%	27%	0.95
Intra-aortic balloon pump	2%	9%	7%	0.08
Glycoprotein IIb/IIIa inhibitor	43%	34%	35%	0.24
Medications at discharge				
Diuretics	20%	33%	55%	<0.0001
Digoxin	10%	15%	25%	0.007
β blockers	82%	72%	67%	0.03
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	63%	75%	71%	0.08
Calcium channel blocker	15%	30%	33%	0.002
Statin	77%	72%	67%	0.17
Aspirin	94%	98%	96%	0.35
Adenosine diphosphate inhibitor	88%	79%	77%	0.06
Nitrates	75%	81%	84%	0.26
Laboratory values				
Hemoglobin (g/dl)	13.3 ± 1.8	13.4 ± 1.9	12.7 ± 2.1	0.01
White blood cell count (per mm^3)	9.0 ± 3.1	9.0 ± 3.0	9.6 ± 6.8	0.61
Platelets (per mm^3)	225 ± 71	230 ± 63	222 ± 73	0.62
BUN (mg/dl)	9.1 ± 1.8	14.3 ± 1.7	25.4 ± 10.7	<0.0001
Creatinine (mg/dl)	0.9 ± 0.2	1.0 ± 0.2	1.4 ± 0.5	<0.0001
GFR (ml/min/1.73 m^2)	100.8 ± 23.7	85.0 ± 22.6	61.5 ± 21.9	<0.0001

population of patients with LV systolic dysfunction. Our data confirmed that stepwise increase of BUN and decrease of GFR portend worse short- and long-term mortalities. Interestingly, we found that only mild increases of BUN may affect long-term mortality in patients with HF. Patients with stage B HF and increased BUN concentrations had an 8-year mortality similar to that of patients with stage C HF with lower BUN concentrations. However, mortality in stage C HF was greatly increased at 1 year and 8 years with an increased BUN (16% and 69%, respectively) or decreased GFR (20% and 73%, respectively). Surprisingly, BUN, and not GFR, was significantly associated with increased risk of mortality in our multivariate analysis. These data taken together suggest that worse renal indexes portend worse outcomes regardless of stage of HF, increased BUN and decreased GFR have greater impact on mortality in patients with stage C HF, and that BUN may provide better prognostic information than creatinine-based measurements in patients with HF.

BUN concentration represents the balance between urea production and renal excretion. Because increases in BUN are seen with increased production (steroids, high-protein diet, gastrointestinal bleeding, etc.), it is primarily attributed to decreased excretion due to a decreased GFR. As seen in HF, low cardiac output leads to renal vasoconstriction, thus decreasing GFR, increasing urea reabsorption, and ultimately increasing BUN. Low cardiac output also results in decreased sodium and water excretion by alterations in

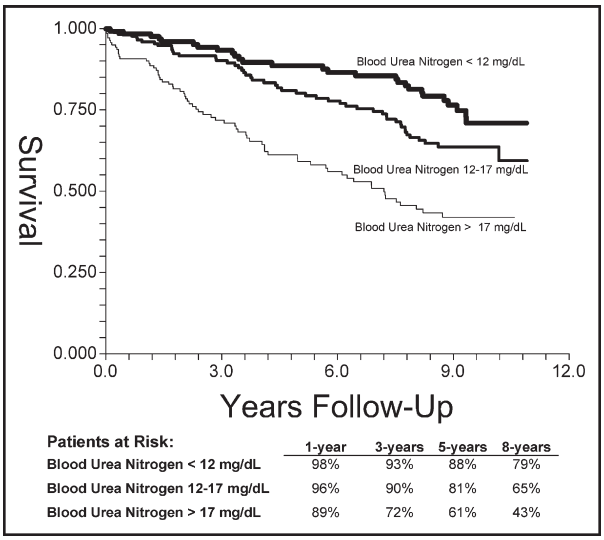

Figure 1. Kaplan-Meier survival curves of BUN concentration divided by tertiles.

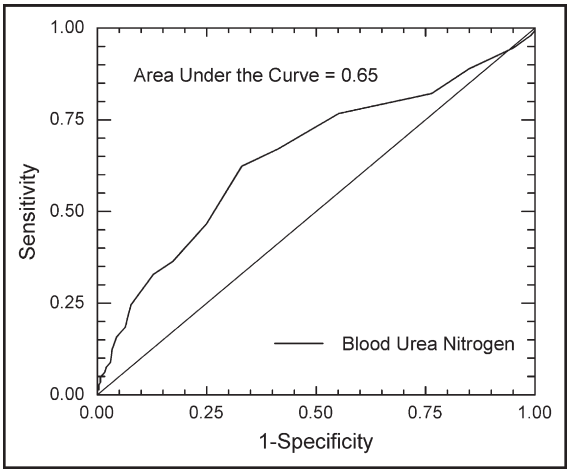

Figure 2. Receiver operating characteristic curve analysis of increasing BUN concentrations determining mortality on follow-up. Area under the curve was 0.65 and BUN cutpoint was 17 mg/dl. Receiver operating characteristic curve analysis of decreasing GFR demonstrated an area under the curve of 0.66 and a cutpoint of 69 ml/min/1.73 m^2 (data not shown).

sympathetic tone, renin-angiotensin activity, and renal perfusion pressures.[16] When sodium and water excretions decrease, urea reabsorption increases and BUN concentration increases. In patients with HF, increases in BUN may reflect not only decreased GFR but also aberrations in fluid volume balance, neurohormonal activities, and hemodynamics. In advanced HF, the more frequent use of high-dose diuretics and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy may potentially contribute to increases in BUN. Muscle wasting and cachexia in patients with advanced HF may also increase BUN. Thus, BUN may serve as a more encompassing biomarker by reflecting the interplay between cardiovascular and renal dysfunctions, serving as a potential surrogate for the increasing use of drugs that affect renal function, and for systemic wasting as a result of advancing HF. Therefore, it is not that surprising

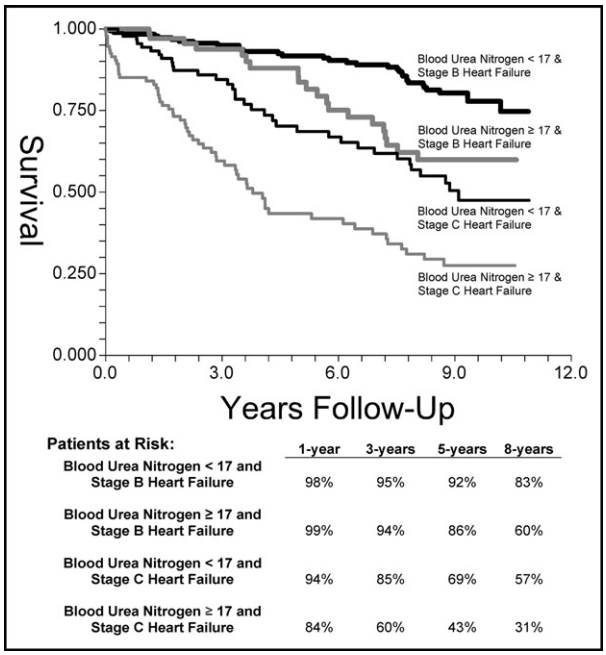

Figure 3. Kaplan-Meier survival curves of BUN ≥17 mg/dl with/without stage C HF.

that we found BUN, not GFR, as the stronger marker of mortality in patients with HF.

Our data further support previous survival analysis comparing BUN, creatinine, and creatinine-based estimates in patients with HF[9,10] that demonstrated that BUN is a stronger predictor of mortality, especially in patients presenting with acute decompensated HF.[2,8,17] The Acutely Decompensated Heart Failure National Registry (ADHERE) database has demonstrated that markedly increased BUN (≥43 mg/dl) concentrations in patients with acutely decompensated HF is the strongest predictor of mortality among the 39 tested variables.[3,7] We found similar results, but differ in that only mild increases in BUN (≥17 mg/dl) appeared to be associated with increased risk mortality in stage B and C HF. It should be noted that the discriminatory power of the BUN cutpoint (BUN ≥17 mg/dl) is of limited clinical value due to the low sensitivity and specificity. Nevertheless, we believe that the lower BUN cutpoint not only reflects an important difference of study populations, where our patients were not admitted primarily for acute decompensation, but most importantly highlights the negative impact of minor increases in BUN for prognostication.

The main limitation of this study is that the patient population is from a nonrandomized, retrospective cohort and the data are observational. As is the case with all retrospective analyses, it is possible that unrecognized and recognized confounders may artificially influence our data despite adjusting for these factors during analysis. Additional factors that influence BUN concentration, such as contrast-induced nephropathy and medication dosage, were not assessed. With respect to contrast-induced nephropathy, most laboratory values were obtained before contrast ventriculography. As a result of our data collection method, a spatial selection bias does exist. This study assessed only all-cause mortality and we therefore lacked data on other

Table 2
Stepwise proportional hazard regression analysis of variables significantly associated with all-cause mortality

Variables	Univariate Model		Multivariate Model		
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	z Value	p Value
BUN (per 1 mg/dl)	1.369 (1.268–1.469)	<0.0001	1.041 (1.025–1.058)	4.822	<0.0001
Stage C HF	2.293 (1.951–2.634)	<0.0001	1.882 (1.510–2.254)	4.64	<0.0001
Age (per yr)	1.051 (1.035–1.066)	<0.0001	1.034 (1.017–1.051)	3.99	0.0001
Chronic obstructive pulmonary disease	2.030 (1.659–2.401)	<0.0001	1.692 (1.301–2.082)	3.47	0.0005
No. of diseased vessels	1.398 (1.240–1.555)	<0.0001	1.265 (1.103–1.426)	3.21	0.001
Statin	0.3651 (0.031–0.699)	0.0002	0.388 (0.050–0.727)	−3.47	0.0004
Calculated LVEF (per percent)	0.958 (0.943–0.974)	<0.0001	0.978 (0.961–0.995)	−2.50	0.01
GFR	0.978 (0.970–0.985)	<0.0001			NS
Previous coronary artery bypass graft	1.798 (1.456–2.140)	<0.0001			NS
Hemoglobin	0.830 (0.742–0.918)	0.0002			NS
β blocker	0.405 (0.065–0.745)	0.0006			NS
Diabetes	1.518 (1.189–1.847)	0.002			NS
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	1.504 (1.125–1.885)	0.009			NS
Hypertension	1.570 (1.050–1.090)	0.03			NS

outcomes such as rehospitalization, cardiovascular morbidity, and mortality.

1. Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF Jr, Gheorghiade M, O'Connor CM. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004;10:460–466.
2. Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, O'Connor C, Adams KF, Orlandi C, Gheorghiade M. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *J Card Fail* 2007;13:360–364.
3. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA* 2005; 293:572–580.
4. Hartz AJ, Kuhn EM, Kayser KL, Johnson WD. BUN as a risk factor for mortality after coronary artery bypass grafting. *Ann Thorac Surg* 1995;60:398–404.
5. Iglesias J, Hom D, Antoniotti M, Ayoub S, Levine JS. Predictors of worsening renal function in adult patients with congestive heart failure receiving recombinant human B-type brain natriuretic peptide (nesiritide). *Nephrol Dial Transplant* 2006;21:3458–3465.
6. Shenkman HJ, Zareba W, Bisognano JD. Comparison of prognostic significance of amino-terminal pro–brain natriuretic Peptide versus blood urea nitrogen for predicting events in patients hospitalized for heart failure. *Am J Cardiol* 2007;99:1143–1145.
7. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol* 2006; 47:76–84.
8. Aronson D, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004;116:466–473.
9. Kirtane AJ, Leder DM, Waikar SS, Chertow GM, Ray KK, Pinto DS, Karmpaliotis D, Burger AJ, Murphy SA, Cannon CP, Braunwald E, Gibson CM. Serum blood urea nitrogen as an independent marker of subsequent mortality among patients with acute coronary syndromes and normal to mildly reduced glomerular filtration rates. *J Am Coll Cardiol* 2005;45:1781–1786.
10. Smith GL, Shlipak MG, Havranek EP, Foody JM, Masoudi FA, Rathore SS, Krumholz HM. Serum urea nitrogen, creatinine, and estimators of renal function: mortality in older patients with cardiovascular disease. *Arch Intern Med* 2006;166:1134–1142.
11. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46(suppl):e1–e82.
12. Levey A, Greene T, Kusek J, Beck G. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). *J Am Soc Nephrol* 2000;11:A0828.
13. 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. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470.
14. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, Habbema JD. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making* 2001;21:45–56.
15. Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. *Ann Intern Med* 1993;118:201–210.
16. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999;341:577–585.
17. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail* 2007;13:422–430.