Heart Failure and Biomarkers

β-Trace Protein and Cystatin C as Predictors of Long-Term Outcomes in Patients With Acute Heart Failure

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Objectives
The purpose of this study was to evaluate the prognostic importance of novel markers of renal dysfunction among patients with acutely destabilized heart failure (ADHF).

Background
β-trace protein (BTP) and cystatin C are newer biomarkers for renal dysfunction; the prognostic importance of these tests, particularly BTP, relative to standard measures of renal function remains unclear.

Methods
A total of 220 consecutive hospitalized patients with ADHF were prospectively studied. Blood samples were collected on presentation. In-hospital worsening renal function, as well as mortality and/or heart failure (HF) hospitalization, over a median follow-up period of 500 days was examined as a function of BTP or cystatin C concentrations; results were compared with creatinine, estimated glomerular filtration rate, and blood urea nitrogen.

Results
Neither BTP nor cystatin C was associated with worsening renal function during the index hospitalization. A total of 116 patients (53%) either died or were hospitalized for HF during follow-up. Those with adverse outcomes had higher BTP (1.04 mg/l [range 0.80 to 1.49 mg/l] vs. 0.88 mg/l [range 0.68 to 1.17 mg/l], p = 0.003) and cystatin C (1.29 mg/l [range 1.00 to 1.71 mg/l] vs. 1.03 mg/l [range 0.86 to 1.43 mg/l], p = 0.001). After multivariable adjustment, both BTP (hazard ratio: 1.41, 95% confidence interval: 1.06 to 1.88; p = 0.018) and cystatin C (hazard ratio: 1.50, 95% confidence interval: 1.13 to 2.01; p = 0.006) were significant predictors of death/HF hospitalization, whereas serum creatinine, estimated glomerular filtration rate, and blood urea nitrogen were no longer significant. In patients with an estimated glomerular filtration rate > 60 ml/min/1.73 m², elevated concentrations of BTP and cystatin C were still associated with significantly higher risk of adverse clinical events (p < 0.05). Net reclassification index analysis suggested cystatin C and BTP deliver comparable information regarding prognosis.

Conclusions
Among patients hospitalized with ADHF, BTP and cystatin C predict risk of death and/or HF hospitalization and are superior to standard measures of renal function for this indication. (J Am Coll Cardiol 2011;57:849–58) © 2011 by the American College of Cardiology Foundation

Kidney dysfunction is an exceptionally important adverse prognostic factor in patients with acutely destabilized heart failure (ADHF) (1). Accordingly, the identification of laboratory parameters capable of more accurately assessing renal function than conventional measures of renal function (e.g., creatinine, estimated glomerular filtration rate [eGFR] or blood urea nitrogen [BUN]) may be particularly relevant for this population. Although prognostically meaningful, conventional measures of renal function have limitations: creatinine and BUN levels are affected by several nonrenal factors including age, body weight, nutritional status, and sex; in addition, creatinine, eGFR, and BUN are generally insensitive for detecting mild chronic kidney disease (2–4).

Cystatin C, a 13-kDa cysteine protease inhibitor, has recently emerged as a novel marker of renal function with a

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high prognostic value in cardiovascular disease, including ADHF (5–13). β-trace protein (BTP) is a low molecular mass protein belonging to the lipocalin protein family that has been established as an accurate marker of cerebrospinal fluid leakage (14). Furthermore, it has also been recently described as a more sensitive marker than serum creatinine in detecting impaired renal function, with performance comparable to that of cystatin C (15–17). The prognostic role of plasma BTP in hospitalized patients with ADHF has not been previously studied, and its comparative value to cystatin C or conventional measures of renal function in these patients is not known. Therefore, in this prospective study of hospitalized patients with ADHF, we aimed to assess the prognostic value of BTP and cystatin C relative to more conventional measures of renal function.

Methods

Study population and design. From September 2006 to March 2009, we prospectively enrolled 220 consecutive patients admitted with an established final diagnosis of ADHF (diagnosed clinically using current guidelines [1]) to the Department of Cardiology at Virgen de la Arrixaca University Hospital (Murcia, Spain). Blood samples were collected for all patients on arrival at the emergency department. Baseline clinical characteristics and hospital events were prospectively recorded. Echocardiography was also performed on all patients before hospital discharge. Left ventricular ejection fraction was measured using Simpson’s biplane method. All patients received standard heart failure (HF) management, as recommended by contemporary guidelines (1). During the entire hospitalization period, clinical management decisions about each patient were made by the cardiologist responsible, who was unaware of the patient’s BTP and cystatin C concentrations.

Determination of both BTP and cystatin C levels was performed using a BN ProSpec analyzer (Dade Behring GmbH, Liederbach, Germany). The intra-assay and interassay coefficients of variation for BTP were 2.5% and 2.0%, respectively. The intra-assay and interassay coefficients of variation for cystatin C were 2.5% and 2.0%, respectively. Conventional measures of renal function included serum creatinine, eGFR (calculated using the simplified Modification of Diet in Renal Disease equation: 186.3 × plasma creatinine − 1.154 × age − 0.203; the correction factor for women was 0.742) (18), and BUN.

Follow-up and clinical end point. We examined worsening renal function (defined as a maximum increase in serum creatinine during hospitalization of ≥0.3 mg/dl [19]) as a function of BTP or cystatin C concentrations; results were compared with creatinine, eGFR, and BUN. For the primary outcome measure as the combination of mortality and/or HF hospitalization, all patients were clinically followed during a median of 500 days (interquartile range 231 to 796). Death was ascertained from available medical records and death certificates. If hospital records were ambiguous or unavailable, National Death Records were consulted. In patients requiring hospitalization, medical records were carefully reviewed to further characterize the cause of hospitalization. The study was approved by the local ethics committee, and informed consent was obtained from each patient at inclusion.

Statistical analysis. Continuous variables were tested for a normal distribution by the Kolmogorov-Smirnov test. Normally distributed data are presented as the mean ± SD and non-normally distributed data as the median (interquartile range, interquartile data). Categorical variables are expressed as percentages. Categorized analyses were performed according to the presence of adverse clinical events during the follow-up. Differences in baseline characteristics were performed using the Student t test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Relationships between BTP, cystatin C, and other clinical and analytical parameters were assessed by Spearman rank correlation. Univariable and multivariable logistic regression analyses were used to examine associations between variables and worsening renal function. To contrast prognostic accuracy, statistical comparison of receiver–operating characteristic curves was performed. To compare different predictive values, we constructed areas under the receiver–operating characteristic curve for sensitivity, specificity, positive predictive value and negative predictive value. The best prognostic cutoff for survival status was defined as the highest product of sensitivity and specificity. Net reclassification improvement and integrated discrimination improvement were performed with biomarkers kept as dichotomous variables, as described by Pencina et al. (20), where the categories of probability for events are defined based on prognostication scheme of the Heart Failure Survival Score (21). We calculated hazard ratios (HRs) derived from the Cox regression analysis to identify predictors of mortality and/or HF hospitalization during follow-up. The independent effect of variables on prognosis was calculated using a Cox multivariable regression analysis, incorporating covariates with p values <0.10 in the univariable analysis. To avoid colinearity effects, due to their extremely high correlation (r = 0.80), serum creatinine and eGFR, as well as BTP and cystatin C, were not entered together in multivariate models. The cumulative incidence of all-cause death or HF hospitalization was estimated according to the Kaplan-Meier method, and the log-rank statistic was used for comparisons. All p values <0.05 were accepted as statistically significant. Statistical analysis was performed using SPSS version 15.0 (SPSS,
Results

Among the 220 subjects with ADHF, the median plasma BTP concentration was 0.97 mg/l (range 0.74 to 1.37 mg/l), the median plasma cystatin C concentration was 1.15 mg/l (range 0.90 to 1.59 mg/l), the median serum creatinine was 1.14 mg/dl (range 0.84 to 1.45 mg/dl), the median eGFR (range 0.90 to 1.59 mg/l), the median serum creatinine was 1.15 mg/l (range 0.85 to 1.49 mg/l), and the median BUN was 24 mg/dl (range 18 to 34 mg/dl).

Plasma BTP concentration was positively correlated with cystatin C concentration (r = 0.86; p < 0.001). Both plasma BTP and cystatin C concentrations were positively correlated with serum creatinine, BUN, age, New York Heart Association functional class, N-terminal pro–B-type natriuretic peptide (NT-proBNP), uric acid, troponin T, and C-reactive protein, whereas both were negatively correlated with eGFR, serum albumin, and hemoglobin. BTP and cystatin C concentrations were not correlated with body mass index or left ventricular ejection fraction (Table 1).

Worsening renal function during hospital admission occurred in 66 patients (30%). Patients with worsening renal function and those without worsening renal function presented similar plasma BTP (1.03 mg/l [range 0.75 to 1.44 mg/l] vs. 0.96 mg/l [range 0.71 to 1.35 mg/l]; p = 0.35), cystatin C (1.12 mg/l [range 0.87 to 1.71 mg/l] vs. 1.19 mg/l [range 0.90 to 1.54 mg/l]; p = 0.73), creatinine (1.11 mg/l [range 0.84 to 1.49 mg/l] vs. 1.15 mg/l [range 0.85 to 1.44 mg/l]; p = 0.83), eGFR (64 ml/min/1.73 m² [range 44 to 77 ml/min/1.73 m²] vs. 64 ml/min/1.73 m² [range 45 to 79 ml/min/1.73 m²]; p = 0.77), and BUN (24 mg/l [range 21 to 34 mg/l] vs. 24 mg/l [range 17 to 34 mg/l]; p = 0.32).

Table 1 Correlations Between β-Trace Protein, Cystatin C, and Clinical Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>β-Trace Protein</th>
<th>Cystatin C</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>p Value</td>
<td>R</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>−0.13</td>
<td>0.05</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>−0.06</td>
<td>0.42</td>
</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>0.16</td>
<td>0.026</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cystatin C, mg/l</td>
<td>0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>−0.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>−0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.07</td>
<td>0.28</td>
</tr>
<tr>
<td>NYHA functional class (I–IV)</td>
<td>0.22</td>
<td>0.001</td>
</tr>
<tr>
<td>Plasma NT-proBNP, pg/ml</td>
<td>0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Troponin T, ng/dl</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>0.40</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

As detailed in Table 4, BTP and cystatin C had comparable...
areas under the curve, with overall performance characteristics that appeared similar, if not slightly superior, to the more conventional measures of renal function. The net reclassification improvement with the addition of cystatin C to eGFR was 0.28 (95% CI: 0.13 to 0.43, \( p = 0.002 \)), whereas the integrated discrimination improvement was 0.05 (95% CI: 0.02 to 0.08, \( p = 0.001 \)). The probability of correctly predicting death and/or HF readmission...
when cystatin C was added to eGFR was particularly reflected in the percentage of nonevents correctly reclassified (44%), whereas the percentage of events reclassified was 16%. Compared with cystatin C, BTP had a net reclassification improvement of 0, with an integrated discrimination improvement of 0.00008; compared with cystatin C, BTP had a 0% reclassification of either events or nonevents, indicating that BTP offered information comparable to that of cystatin C.

In univariable Cox regression analysis, all measures of kidney function were associated with a higher risk of adverse clinical events (Table 5). However, after adjusting for confounding factors in the multivariable Cox regression models, only BTP and cystatin C concentrations remained as significant predictors of adverse events, whereas creatinine, eGFR, and BUN were no longer significant (Table 5). This remained the case when measurements of renal function were evaluated as dichotomous variables in multivariate Cox regression models: BTP and cystatin C were significant predictors of mortality and/or HF readmission (HR: 1.54, 95% CI: 1.10 to 2.38; p = 0.02 for BTP >0.96 mg/l and HR: 1.73, 95% CI: 1.15 to 2.62; p = 0.009 for cystatin C >1.05 mg/l), but creatinine, eGFR, and BUN were not (p > 0.2). Furthermore, when BTP and cystatin C were adjusted for other conventional measures of kidney function, both remained associated with a higher risk of adverse events (log₁₀ BTP, HR: 3.01, 95% CI: 1.08 to 7.87, p = 0.033 and log₁₀ cystatin C, HR: 3.56, 95% CI: 1.22 to 9.35, p = 0.018).

As shown in the Kaplan-Meier survival analyses, increased BTP concentration (>0.96 mg/l) and elevated cystatin C concentration (>1.05 mg/l) were associated with an increased risk of adverse clinical events (Fig. 3) (log-rank test, p < 0.05). In stratified analyses of patients with an eGFR >60 ml/min/1.73 m² (n = 146), increased BTP and cystatin C concentrations were also found to be associated with a higher mortality and/or HF hospitalization risk (Fig. 4) (log-rank test, p < 0.05).

**Discussion**

The importance of parameters of renal function in ADHF is considerable. Indeed, kidney dysfunction represents one of the most dominant variables for predicting adverse outcome in patients with ADHF (22,23). Although powerfully predictive of adverse outcome, conventional tests for...
kidney dysfunction such as creatinine, eGFR, and BUN all have potential limitations (2–4); thus, characterization of newer markers of renal dysfunction for application in patients with ADHF is of considerable significance.

In this study, we examined novel markers of renal dysfunction, BTP, and cystatin C and compared them with conventional measures of renal function for their ability to predict adverse outcome. Neither BTP nor cystatin C at presentation (or other measures of renal function) predicted the onset of renal dysfunction after presentation with ADHF. This suggests that baseline renal function may be less important for predicting subsequent worsening in glomerular filtration rate (GFR) than are the various clinical and therapeutic insults that occur in patients with ADHF that may lead to such a decline. On the other hand, consistent with previous reports (5–13), we found cystatin C to independently predict death/HF hospitalization with greater accuracy than creatinine, eGFR, or BUN; moreover, BTP performed comparably to cystatin C for this indication. Of special note, among patients with an eGFR >60 ml/min (an area of weakness for serum creatinine and eGFR), we found that increased concentrations of both BTP and cystatin C were still associated with significantly higher risk of adverse clinical events. To the best of our knowledge, this is the first study to describe the prognostic usefulness of BTP in ADHF.

Over the past years, kidney dysfunction, including mild and moderate chronic kidney disease, has become increasingly recognized as an independent risk factor for morbidity and mortality in patients with HF (22–28). A recent meta-analysis (29) showed that the majority of patients with HF had some degree of renal impairment, and these patients represent a high-risk group with an approximately 50% increased relative mortality risk compared with patients with normal kidney function. Because serum creatinine, eGFR equations, and BUN are insensitive to mild decrements in renal function (2–4), the detection of mild kidney dysfunction in routine clinical practice remains challenging. It has been suggested that BTP and cystatin C concentrations are more sensitive for the detection of mild decrements

### Table 4
Performance of Measures of Renal Function and NT-proBNP for Prediction of 1-Year Mortality and/or HF Hospitalization in Patients With ADHF

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC</th>
<th>95% CI</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-trace protein, mg/dl</td>
<td>0.62</td>
<td>0.55–0.68</td>
<td>0.96</td>
<td>0.61</td>
<td>0.60</td>
<td>0.66</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Cystatin C, mg/dl</td>
<td>0.63</td>
<td>0.56–0.69</td>
<td>1.05</td>
<td>0.72</td>
<td>0.55</td>
<td>0.64</td>
<td>0.63</td>
<td>0.73</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.58</td>
<td>0.52–0.65</td>
<td>1.07</td>
<td>0.64</td>
<td>0.54</td>
<td>0.61</td>
<td>0.57</td>
<td>0.34</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m²</td>
<td>0.57</td>
<td>0.50–0.64</td>
<td>72</td>
<td>0.65</td>
<td>0.44</td>
<td>0.57</td>
<td>0.53</td>
<td>0.26</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl</td>
<td>0.60</td>
<td>0.53–0.66</td>
<td>25</td>
<td>0.53</td>
<td>0.65</td>
<td>0.63</td>
<td>0.55</td>
<td>0.71</td>
</tr>
<tr>
<td>Plasma NT-proBNP, pg/ml</td>
<td>0.60</td>
<td>0.53–0.67</td>
<td>3.041</td>
<td>0.62</td>
<td>0.57</td>
<td>0.62</td>
<td>0.57</td>
<td>0.70</td>
</tr>
</tbody>
</table>

The p values shown are for comparison among β-trace protein and other variables.

ADHF = acutely destabilized heart failure; AUC = area under the curve; CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 1 and 2.

### Table 5
Cox Regression Risk Analysis for Prediction of Mortality and/or HF Hospitalization

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>p Value</td>
</tr>
<tr>
<td>Age, yr</td>
<td>1.03 (1.01–1.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.99 (0.98–1.01)</td>
<td>0.06</td>
</tr>
<tr>
<td>NYHA functional class III-IV</td>
<td>2.91 (2.01–4.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.39 (0.96–2.00)</td>
<td>0.08</td>
</tr>
<tr>
<td>Previous HF</td>
<td>1.94 (1.29–2.91)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous ST-segment elevation myocardial infarction</td>
<td>1.56 (1.05–2.32)</td>
<td>0.03</td>
</tr>
<tr>
<td>In-hospital inotropic use</td>
<td>2.43 (1.50–4.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log₁₀ glucose</td>
<td>2.71 (1.05–7.02)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sodium, × mEq/l</td>
<td>0.96 (0.93–1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td>Log₁₀ leukocytes</td>
<td>5.26 (1.40–19.8)</td>
<td>0.014</td>
</tr>
<tr>
<td>Log₁₀ plasma NT-proBNP</td>
<td>1.75 (1.18–2.59)</td>
<td>0.006</td>
</tr>
<tr>
<td>Log₁₀ troponin T</td>
<td>1.51 (1.09–2.11)</td>
<td>0.014</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>1.52 (1.04–2.21)</td>
<td>0.031</td>
</tr>
<tr>
<td>Log₁₀ β-trace protein</td>
<td>3.30 (1.39–7.84)</td>
<td>0.007</td>
</tr>
<tr>
<td>Log₁₀ cystatin C</td>
<td>4.57 (1.66–12.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Log₁₀ creatinine</td>
<td>4.21 (1.34–11.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Log₁₀ eGFR</td>
<td>0.47 (0.34–0.85)</td>
<td>0.007</td>
</tr>
<tr>
<td>Log₁₀ blood urea nitrogen</td>
<td>2.58 (1.05–8.8)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Log₁₀ β-trace protein, log₁₀ cystatin C, log₁₀ creatinine, and log₁₀ eGFR were all tested separately and multivariable hazard ratios and p values for other variables shown from the β-trace protein model.

Abbreviations as in Tables 1 and 2.
of GFR (15–17,30,31). Consistent with this suggestion, we found both BTP and cystatin C to be independently superior to standard measures of renal function for predicting death and/or HF hospitalization. Given the reported value of conventional measures of renal function for prognostication in patients with ADHF (22,23), our findings are of significance.

BTP is a low-molecular weight glycoprotein, belonging to the lipocalin protein family, with a molecular weight of 22 to 29 kDa depending on the degree of glycosylation (32,33). BTP is synthesized in the central nervous system, male genital organs, and heart and is secreted into the cerebrospinal fluid, seminal plasma, and plasma, respectively (34–36). Hoffmann et al. (33) showed that “brain type” BTP is absent in serum and urine (because it is cleared by the liver via specific hepatic glycoprotein receptors), whereas sialyzed glycoforms are protected against hepatic metabolism and are eliminated via glomerular filtration, allowing for sensitive estimation of renal function.

As mentioned previously, plasma BTP concentration appears superior to standard means of renal function estimation for the detection of mild decrements of GFR. Thus, our results might indicate that the risk of adverse events attributable to kidney disease is not completely captured by estimates of kidney function routinely used in clinical practice. On the other hand, BTP has also been implicated in numerous other physiologic and pathologic processes including inflammatory responses (37), endo-

![Figure 3](image-url)
theil cell function (38), atherogenesis (36,39), insulin sensitivity (40), and systemic arterial hypertension (41). We therefore cannot exclude the possibility that circulating BTP concentrations reflect (directly or indirectly) pathophysiologic processes pivotal to HF progression.

Cystatin C is a low-molecular weight protein (13 kDa) that is released at a constant rate and expressed in all nucleated cells (42). It has multiple biological functions, including controlling extracellular proteolysis via inhibition of cysteine peptidases (especially cathepsins B, H, L, and S) (43), modulation of the immune system (44), exertion of antibacterial and antiviral activities, and modification of the body’s response to brain injury. Cystatin C is freely filtrated in the glomerulus and subsequently absorbed in the renal tubules where it is fully degraded locally, without re-entering the bloodstream. No active tubular secretion or significant extrarenal elimination occurs (45,46). Therefore, plasma cystatin C concentration is mainly dependent on the GFR. Although several previous studies have shown that plasma cystatin C concentration predicts adverse clinical outcomes across a wide spectrum of patients including those with HF (5–13), it also remains unclear, however, whether the association with adverse outcomes is due to cystatin C being a more precise measure of kidney function or whether
cystatin C is a reflection of other pathologic processes independent of the GFR. Importantly, cystatin C has not been previously compared with BTP as a prognostic risk factor, so the present study adds to the existing literature by demonstrating that BTP is at least comparable to cystatin C for predicting adverse clinical events in hospitalized patients with ADHF.

**Study limitations.** The limitations of our study are similar to those of any single-center prospective, observational study. The small sample size and relatively small number of patients included in each group also make it difficult to draw firm conclusions. In this study, we included unselected hospitalized patients with ADHF due to both systolic and diastolic mechanisms, so the validity of our findings in selected HF populations remains to be established. In addition, the presence of unmeasured variables such as activity of coronary ischemia, diastolic abnormalities, and severity of valvular heart disease were not factored into our multivariable Cox regression analyses for prediction of poor outcomes. For the prediction of outcomes, the number of covariates included in multivariable models was >1 for each 10 events. Therefore, it remains possible that the models were overadjusted, and consequently our results could fail to be replicated in future samples. In our study cohort, we found that increased plasma NT-proBNP concentration did not predict adverse clinical events beyond cystatin C and BTP. However, because several previous studies have demonstrated that NT-proBNP and cystatin C concentrations offered complementary prognostic value in this clinical setting (5,11,12), we cannot exclude that our results may represent a false-negative (type II) error due to overadjustment of covariates in the context of a relatively small number of subjects with ADHF. Furthermore, we also found that worsening of renal function was not associated with adverse clinical events after adjustment for baseline clinical and biochemical risk factors. This likely reflects the dominance of baseline novel renal function parameters over a worsening of renal function definition based on an absolute increase in serum creatinine during hospitalization. Last, we do not have follow-up (post-treatment) values for measures of renal function; such follow-up values would be expected to provide further prognostic information about our patients.

**Conclusions**

In patients with ADHF, BTP and cystatin C appear to add comparable and significant prognostic value and were superior to creatinine, eGFR, and BUN, each a well-established prognostic variable in this context.

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Key Words: acute heart failure † beta-trace protein † cystatin C † prognosis.