Prognostic Value of Biomarkers in Heart Failure
Application of Novel Methods in the Community

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Background—Mortality among patients with heart failure is high. Though individual biomarkers have been investigated to determine their value in mortality risk prediction, the role of a multimarker strategy requires further evaluation.

Methods and Results—Olmsted County residents presenting with heart failure from July 2004 to September 2007 were recruited to undergo biomarker measurement. We investigated whether addition of C-reactive protein, B-type natriuretic peptide, and troponin T to a model including established risk indicators improved 1-year mortality risk prediction using the c statistic, integrated discrimination improvement, and net reclassification improvement. Among 593 participants, the mean age was 76.4 years, and 48% were men. After 1 year of follow-up, 122 (20.6%) participants had died. Patients with C-reactive protein (<11.8 mg/L), B-type natriuretic peptide (<350 pg/mL), and troponin T (≤0.01 ng/mL) less than the median had low 1-year mortality (3.3%), whereas those with 2 or 3 biomarkers greater than the median had markedly increased mortality (30.8% and 35.5%, respectively). The addition of 2 or more biomarkers to the model offered greater improvement in 1-year mortality risk prediction than use of a single biomarker. The combination of C-reactive protein and B-type natriuretic peptide resulted in an increase in the c statistic from 0.757 to 0.810 (P<0.001), an integrated discrimination improvement gain of 7.1% (P<0.001), and a net reclassification improvement of 22.1% (P<0.001). Use of all 3 biomarkers offered no incremental gain (integrated discrimination improvement gain 0.7% versus C-reactive protein+B-type natriuretic peptide, P=0.065).

Conclusions—Biomarkers improved 1-year mortality risk prediction beyond established indicators. The use of a 2-biomarker combination was superior to a single biomarker in risk prediction, though addition of a third biomarker conferred no added benefit. (Circ Heart Fail. 2009;2:393-400.)

Key Words: epidemiology □ heart failure □ prognosis □ inflammation □ community

According to the American College of Cardiology/American Heart Association 2008 update, an estimated 5.3 million Americans are currently living with heart failure (HF).1 Despite advances in HF treatment, mortality remains high, with estimated 5-year mortality rates of nearly 50% in the community.2,3 This persistently high mortality underscores the importance of risk stratification in HF. Although clinical characteristics have historically been investigated to predict mortality risk in HF,4 they fail to fully estimate an individual’s prognosis. Recently, elevated biomarker levels, including C-reactive protein (CRP), B-type natriuretic peptide (BNP), and troponins, have been reported individually to be associated with an increased risk of death in patients with HF.5-15 Indeed, CRP, BNP, and troponins, which reflect distinct pathophysiological mechanisms (ie, inflammation, cardiac stress, and myocyte injury), may improve mortality prediction in HF beyond traditional risk indicators. Incorporation of a multimarker strategy to aid in risk prediction in HF may enhance the ability to accurately identify patients at high-mortality risk, information which could be of critical use in clinical decision-making for both patients and providers.

The methodological requirements for cardiovascular risk prediction using biomarkers have undergone several new developments, as outlined in the recent American Heart Association Scientific Statement.16 It is now recognized that reporting a statistically significant association of a new biomarker with an outcome is not enough to demonstrate its
value in risk prediction. In addition, it has been recently suggested that the $c$ statistic, determined from receiver-operating characteristic (ROC) analyses, "may not be optimal in assessing models that predict future risk," and should not be the sole determinant of clinical utility. Novel measures of predictive ability, including use of reclassification tables and the integrated discrimination improvement (IDI), have been proposed to evaluate biomarker utility in risk prediction. Although individual biomarkers should be assessed using these novel methods, use of a multimarker strategy would likely result in greater improvement in risk prediction.

The critical importance of the evaluation of a set of markers in a prospective cohort of patients with HF to determine their role in risk prediction has been recently underscored. This study aims to address these important gaps in knowledge by examining the distribution of CRP, BNP, and troponin T (TnT), their association with 1-year mortality, and the incremental and complementary benefits in 1-year mortality risk prediction conferred by a multimarker approach. To optimize the applicability of our results, we will do so in a community cohort using novel statistical methods.

Methods

Study Design

This is a population-based study conducted in Olmsted County in southeastern Minnesota (2006 US Census population 137,521, 90% white, 50% female). This type of research is possible in Olmsted County as all providers, including Mayo Clinic, have maintained extensively indexed medical records. Through the Rochester Epidemiology Project, a centralized record linkage system, all medical records are retrievable such that medical information on events is complete and easily searchable for persons living in the county.

Patient Population

To identify potential HF cases, natural language processing of the electronic medical record text is used. After a clinical visit, documentation is transcribed and appears in the record within 24 hours, making prompt ascertainment of newly diagnosed HF cases possible. Records of potential cases are reviewed by trained abstractors to collect data and verify HF cases using Framingham criteria. Patients are contacted to obtain consent for study participation, which involves Doppler echocardiography and obtaining venous blood samples. Hospitalized patients are contacted in the hospital, and patients recruited from a clinical setting are contacted at their next clinic visit for consent, enrollment and data collection. All patients provided written authorization to participate in the study, which was approved by the Mayo Clinic Institutional Review Board.

Data Collection

Echocardiography

All echocardiograms were obtained and analyzed at Mayo Clinic Echocardiography laboratory according to the American Society of Echocardiography guidelines. Left ventricular ejection fraction (EF) was measured using M-mode, quantitative, and semiquantitative methods as previously described and validated with excellent correlation between methods. Though EF was dichotomized (reduced <50%, preserved ≥50%) for descriptive purposes, it was examined as a continuous variable in all analyses. Diastolic function was assessed by an approach that integrates Doppler measurements of the mitral inflow and Doppler tissue imaging of the mitral annulus using the medial annulus velocity, a method similar to that used in the Olmsted County general population. In the study, diastolic function was dichotomized as grade 3 or 4 (moderate or severe diastolic dysfunction) versus normal/mild diastolic dysfunction/indeterminate.

Biomarker Measurements

Serum samples obtained from patients at the time of HF diagnosis were stored at −70°C until laboratory testing was performed. Patients enrolled in the inpatient setting had biomarkers collected as soon as possible after admission. CRP was measured using a latex-enhanced immunoturbidimetric assay on a Hitachi 912 automated analyzer (Hitachi Ltd, Fukushima, Japan) and Diasorin reagents (Stillwater, Minn). BNP was measured by a 2-site immunoenzymatic sandwich assay on the Dxi 800 automated immunoassay system (Beckman Instruments, Chaska, Minn). TnT was measured using a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostic Corp, Indianapolis, Ind). Tests were performed by blinded laboratory personnel in the Immunochemical Core Laboratory of Mayo Clinic.

Additional Patient Data

Baseline patient characteristics were obtained by nurse abstractors from the medical record. Prior myocardial infarction was defined by standardized criteria, which have been previously described and validated. Physician’s diagnosis was used to document history of coronary artery disease (CAD), malignancy, hyperlipidemia, diabetes, and atrial fibrillation/flutter. Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or use of antihypertensive medications. Smoking status was classified as “ever” or “never.” Patient’s height and weight at HF diagnosis were used to calculate body mass index. Creatinine at HF diagnosis was collected and creatinine clearance was calculated using the Cockcroft-Gault equation. New York Heart Association functional class was assessed using standard definitions. Medication use was defined according to physician documentation.

Mortality Follow-Up

Follow-up took place through passive surveillance of the medical records. The ascertainment of death included death certificates filed in Olmsted County, obituary notices and electronic files of death certificates obtained from the State of Minnesota Department of Vital and Health Statistics, and use of the National Death Index.

Statistical Analysis

Subjects were divided by median CRP (<11.8 mg/L, ≥11.8 mg/L), BNP (<350 pg/mL, ≥350 pg/mL), and TnT (<0.01 ng/mL, ≥0.01 ng/mL). Baseline characteristics are reported as frequency or mean with standard deviation. Associations between baseline characteristics and biomarkers (dichotomized at the median) were analyzed using $t$ tests for continuous variables and $\chi^2$ tests for categorical variables. All biomarkers followed a skewed distribution and were log transformed when used as continuous variables. Data were >95% complete for all variables.

The incremental and complementary value of CRP, BNP, and TnT in predicting 1-year mortality was assessed by multiple methods. First, a 1-year mortality risk prediction model incorporating established risk factors was determined using logistic regression analysis. Potential predictors were chosen based on previous literature. Variables were included in the final base model if they were significant univariate predictors of 1-year mortality in this study and included age, body mass index, creatinine clearance, New York Heart Association functional class, serum sodium <135 mmol/L, and systolic blood pressure. As we were limited by our sample size and 1-year mortality rate as to the number of predictors that could be included, sensitivity analyses including additional baseline variables did not improve the predictive ability of the base model (change in c statistic <0.005 for each variable). The resultant 1-year mortality risk prediction model served as the base model for further analyses. Next, we plotted ROC curves using models before and after the addition of biomarkers. The $c$ statistic, a measure of area under the ROC curve, was calculated before and after the addition of biomarkers and...
Results

Patient Population
Five hundred ninety eight patients with HF were enrolled from July 2004 to September 2007, reflecting a 71% consent rate. Follow-up was complete through March 2009. Five patients were excluded as all biomarkers could not be measured, resulting in 593 participants included in analysis. The mean age of participants was 76 years, 284 (47.9%) were men and 302 (53.5%) had preserved EF. Four hundred seventeen (70.3%) patients were enrolled as inpatients, with the remainder enrolled in the outpatient setting. Those who consented to the study were slightly younger than nonparticipants (mean, 76 versus 80 years, P<0.001). No differences in sex or the proportion enrolled as inpatients were observed among participants versus nonparticipants.

Biomarker Levels
CRP ranged from 0.28 to 459 mg/L with a median value of 11.8 mg/L (25th to 75th percentile, 3.7 to 50.6 mg/L). BNP ranged from 5.5 to 6434.0 pg/mL with a median value of 350.0 pg/mL (25th to 75th percentile, 174.0 to 647.0 pg/mL). TNF ranged from <0.01 to 8.6 ng/mL with a median value of 0.01 ng/mL (25th to 75th percentile, 0.01 to 0.05 ng/mL). Persons with higher CRP, BNP, and TnT were more likely to have certain baseline characteristics, as shown in Table 1. Participants enrolled in the inpatient setting had higher biomarker levels than those enrolled as outpatients.

Biomarkers and Mortality
After 1 year, 122 (20.6%) patients had died. A graded increase in 1-year mortality was observed according to the number of biomarkers greater than the median overall, among those with preserved and reduced EF, and among those enrolled as inpatients and outpatients (Figure). Overall, patients with either 2 or 3 biomarkers greater than the median experienced a marked increase in mortality (30.8% and 35.5%, respectively) compared with patients with all biomarkers below the median (3.3%, P<0.001 for both comparisons). When one biomarker was above the median patients had intermediate 1-year mortality (13.6%). Factors related to 1-year mortality in this study were included in a model with established risk factors (base model, Table 2). Higher CRP, BNP, and TnT were independently associated with an increased risk of death when added to the base model. Sensitivity analyses conducted among those enrolled as inpatients yielded similar results.

Evaluation of the Impact of Biomarkers on Risk Prediction Using Novel Methods
The value of each biomarker alone and in combination for risk prediction was assessed using several complementary methods. The c statistics for CRP, BNP, and TnT individually were 0.636, 0.698, and 0.652, respectively (P<0.001 for each). BNP had the highest c statistic of any single predictor evaluated, including age. The c statistic for the base model was 0.757.

Incremental Prognostic Value of a Single Biomarker
Addition of each biomarker individually to the base model resulted in a significant increase in the c statistic, IDI and net reclassification improvement (Table 3), indicating that each biomarker offered value in predicting 1-year mortality beyond traditional prognostic factors.

Incremental Prognostic Value of 2 or More Biomarkers
There was complementary prognostic value gained by adding combinations of biomarkers to the model. The best 2-biomarker combination was CRP+BNP, which increased the c statistic from 0.757 to 0.810, increased the IDI by 7.1%, and improved risk classification for 22.1% of individuals (Tables 3 and 4). This offered a significant improvement over any of the single-biomarker models (IDI gain, 2.8%, P<0.001, compared with base model+BNP). These data suggest that use of 2 biomarkers offers an increase in prognostic value over use of a single biomarker in 1-year mortality risk prediction, and the combination of CRP and BNP offered the greatest increase in risk discrimination.

The addition of a third biomarker to the model resulted in nonsignificant gains in risk discrimination and reclassification, including an increase in the c statistic to 0.815 (versus 0.809 for CRP+BNP), an improvement in risk classification for an additional 4.8% of individuals, and an additional 0.7% gain in the IDI (IDI, 7.8% for all 3 biomarkers versus 7.1% for CRP+BNP, P=0.065).

Discussion
In this community cohort of patients with HF with a wide range of EF and HF severity, higher levels of CRP, BNP, and TnT were associated with a large increase in mortality. Although each biomarker provided individual incremental benefit in mortality risk prediction, combining biomarkers offered the greatest improvement in risk prediction above established risk factors. These findings provide novel data in support of the robust benefit of a multimarker strategy applied to community patients with HF to predict death.

There is a strong rationale for risk prediction in HF. HF is a disease with an overall poor prognosis, with an observed 1-year mortality of 21% in this study and an estimated 5-year mortality near 50% in previous community studies.2-3 How-
ever, an individual’s mortality risk may vary substantially from average values, and use of prognostic variables to more accurately assess risk has been of recent interest. By more accurately identifying individuals at highest mortality risk, clinicians may be more effective at counseling patients, enabling them to make better informed decisions regarding use of medications and invasive procedures. In addition, closer monitoring of hospitalized patients and frequent outpatient follow-up may be possible. Risk assessment in a community population offers clear advantages over trial populations, as clinical trial participants are frequently younger with fewer comorbidities, and thus observed mortality may differ markedly from the general HF population. This underscores the importance of relying on community cohorts, such as the one reported on herein, to assess the ability of potential prognostic factors to enhance mortality risk prediction.

With the development of novel biomarkers, there has been interest in their use for risk prediction. Although an individual biomarker may aid in determining risk, use of a multimarker strategy is likely to provide greater benefit. For example, a recent investigation aimed at predicting death among elderly patients free of cardiovascular disease found that no individual biomarker increased the adjusted c statistic when added separately to a model, but the combination of all biomarkers markedly increased the c statistic.

## Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 593)</th>
<th>CRP &lt;11.8 mg/L (n = 296)</th>
<th>CRP ≥11.8 mg/L (n = 297)</th>
<th>BNP &lt;350 pg/mL (n = 299)</th>
<th>BNP ≥350 pg/mL (n = 294)</th>
<th>TnT ≤0.01 ng/mL (n = 319)</th>
<th>TnT &gt;0.01 ng/mL (n = 274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.4 (12.8)</td>
<td>75.8 (13.3)</td>
<td>77.0 (12.2)</td>
<td>74.6 (13.1)</td>
<td>78.2 (12.3)*</td>
<td>75.7 (13.1)</td>
<td>77.1 (12.4)</td>
</tr>
<tr>
<td>Male</td>
<td>284 (47.9)</td>
<td>141 (47.6)</td>
<td>143 (48.1)</td>
<td>140 (46.8)</td>
<td>144 (49.0)</td>
<td>134 (42.0)</td>
<td>150 (54.7)*</td>
</tr>
<tr>
<td>Inpatient at enrollment</td>
<td>417 (70.3)</td>
<td>158 (53.4)</td>
<td>259 (87.2)*</td>
<td>197 (65.9)</td>
<td>220 (74.8)‡</td>
<td>198 (62.1)</td>
<td>219 (79.9)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>470 (79.3)</td>
<td>231 (78.0)</td>
<td>239 (80.5)</td>
<td>235 (78.6)</td>
<td>235 (79.9)</td>
<td>249 (78.1)</td>
<td>221 (80.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>403 (68.0)</td>
<td>203 (68.6)</td>
<td>200 (67.3)</td>
<td>207 (69.2)</td>
<td>196 (66.7)</td>
<td>212 (66.5)</td>
<td>191 (69.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>54 (9.1)</td>
<td>27 (9.2)</td>
<td>27 (9.1)</td>
<td>28 (9.4)</td>
<td>26 (8.9)</td>
<td>28 (8.8)</td>
<td>26 (9.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>186 (31.4)</td>
<td>99 (33.4)</td>
<td>87 (29.3)</td>
<td>104 (34.8)</td>
<td>82 (27.9)</td>
<td>89 (27.9)</td>
<td>97 (35.4)‡</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>324 (54.6)</td>
<td>166 (58.6)</td>
<td>156 (52.5)</td>
<td>162 (54.2)</td>
<td>162 (55.1)</td>
<td>171 (53.6)</td>
<td>153 (55.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>148 (25.9)</td>
<td>73 (25.6)</td>
<td>75 (26.2)</td>
<td>66 (22.8)</td>
<td>82 (29.2)</td>
<td>73 (23.2)</td>
<td>75 (29.3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>181 (30.5)</td>
<td>90 (30.4)</td>
<td>91 (30.6)</td>
<td>93 (31.1)</td>
<td>88 (29.9)</td>
<td>107 (33.5)</td>
<td>74 (27.0)</td>
</tr>
<tr>
<td>History of Malignancy</td>
<td>191 (32.3)</td>
<td>80 (27.1)</td>
<td>111 (37.4)†</td>
<td>101 (33.8)</td>
<td>90 (30.7)</td>
<td>92 (28.8)</td>
<td>99 (36.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.2 (7.7)</td>
<td>30.2 (8.0)</td>
<td>30.3 (7.3)</td>
<td>32.5 (8.3)</td>
<td>27.9 (6.2)*</td>
<td>30.2 (7.5)</td>
<td>30.3 (7.9)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>59.7 (33.9)</td>
<td>60.9 (32.1)</td>
<td>58.6 (35.6)</td>
<td>69.5 (37.1)</td>
<td>49.8 (27.0)*</td>
<td>64.3 (32.0)</td>
<td>54.5 (35.3)*</td>
</tr>
<tr>
<td>Sodium &lt;135 mmol/L</td>
<td>76 (12.8)</td>
<td>23 (7.8)</td>
<td>53 (17.8)†</td>
<td>29 (9.7)</td>
<td>47 (16.0)‡</td>
<td>37 (11.6)</td>
<td>39 (14.2)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>140.0 (31.8)</td>
<td>138.8 (30.2)</td>
<td>141.2 (33.3)</td>
<td>142.0 (31.7)</td>
<td>137.9 (31.8)</td>
<td>141.1 (32.1)</td>
<td>138.7 (31.4)</td>
</tr>
<tr>
<td>NYHA functional class III or IV</td>
<td>421 (71.0)</td>
<td>198 (66.9)</td>
<td>223 (75.1)‡</td>
<td>196 (65.6)</td>
<td>225 (76.5)†</td>
<td>219 (68.7)</td>
<td>202 (73.7)</td>
</tr>
<tr>
<td>Echocardiographic</td>
<td>48.7 (16.4)</td>
<td>46.3 (16.4)</td>
<td>51.1 (16.2)*</td>
<td>53.7 (14.1)</td>
<td>43.5 (17.1)*</td>
<td>50.3 (16.0)</td>
<td>46.8 (16.8)†</td>
</tr>
<tr>
<td>characteristics</td>
<td>428 (75.8)</td>
<td>213 (75.5)</td>
<td>215 (76.0)</td>
<td>216 (75.0)</td>
<td>212 (76.5)</td>
<td>227 (74.9)</td>
<td>201 (76.7)</td>
</tr>
<tr>
<td>β-blocker</td>
<td>386 (65.1)</td>
<td>194 (65.5)</td>
<td>192 (64.6)</td>
<td>197 (65.9)</td>
<td>189 (64.3)</td>
<td>221 (69.3)</td>
<td>165 (60.2)†</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>347 (58.5)</td>
<td>181 (61.5)</td>
<td>165 (55.6)</td>
<td>175 (58.5)</td>
<td>172 (58.5)</td>
<td>195 (61.1)</td>
<td>152 (55.5)</td>
</tr>
<tr>
<td>Statin</td>
<td>302 (50.9)</td>
<td>168 (56.8)</td>
<td>134 (45.1)†</td>
<td>152 (50.8)</td>
<td>150 (51.0)</td>
<td>163 (51.1)</td>
<td>139 (50.7)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or n (%). ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NYHA, New York Heart Association; SBP, systolic blood pressure.

*P<0.001 compared with patients with biomarker below the median.
†P<0.01 compared with patients with biomarker below the median.
‡P<0.05 compared with patients with biomarker below the median.
prediction analyses.\textsuperscript{16–19,32} It is now recognized that reporting a statistically significant association of a new biomarker with the outcome is not enough to demonstrate its value in risk prediction.\textsuperscript{17} Although studies often report on the \textit{c} statistic derived from ROC analyses, contemporary reports have highlighted the need for methods to establish utility in risk prediction that extend beyond the ROC curve.\textsuperscript{18,19,32} The \textit{c} statistic is less sensitive than other global measures of model fit and does not capture an individual’s predicted risk, which is ultimately important in determining clinical utility.\textsuperscript{18} Newer methods, including use of reclassification tables, and further methods of discrimination have been proposed,\textsuperscript{17} and offer useful information regarding a biomarkers’ utility in risk prediction. These novel methods were evaluated in this study.

CRP, BNP, and TnT have been reported to be associated with increased mortality in HF\textsuperscript{5,7–13} and are of interest in mortality risk prediction. CRP, a marker of inflammation, is produced in the liver in response to an inflammatory stimulus.\textsuperscript{33} Inflammation clearly plays a key role in the pathogenesis of HF.\textsuperscript{34} CRP has been demonstrated to be elevated in a large portion of patients with HF compared with controls\textsuperscript{35} and in patients with both preserved and reduced EF\textsuperscript{7,35} BNP, one of 3 major natriuretic peptides, is released from the heart in response to pressure and volume overload, and acts to promote vasodilatation, natriuresis, and diuresis.\textsuperscript{36,37} Elevated BNP levels have been used to diagnose HF\textsuperscript{38,39} and as a guide to therapy in patients with established HF.\textsuperscript{40} Finally, TnT, a marker of cardiomyocyte injury, has been reported to be detectable in a large portion of patients with HF,\textsuperscript{14} and elevations have been associated with an increased risk of death in both ambulatory\textsuperscript{15} and hospitalized patients with HF.\textsuperscript{13} Based on these data, we hypothesized that use of a
Factors that have added prognostic value above established risk indicators. Furthermore, the combined use of 2 or more biomarkers offers greater incremental value in risk prediction. The 2-marker strategies including CRP and BNP performed slightly better than the other 2-marker combinations by all methods evaluated. Use of the 3-biomarker combination of CRP, BNP, and TnT did not offer significant incremental value in 1-year mortality risk prediction compared with the 2-biomarker combination of CRP and BNP.

**Limitations, Strengths, and Clinical Implications**

Potential limitations should be acknowledged to aid in data interpretation. This study had a relatively small number of deaths, limiting the number of predictors that could be included in the base model. However, the assessment of multiple biomarkers simultaneously in a large cohort of patients is a strength, because it has been lacking from previous reports. Both inpatients and outpatients with HF were enrolled in our study to represent the comprehensive experience of a community by including the entire spectrum of HF as it presented in a geographically defined population. Although sample size issues precluded stratified analyses among outpatients alone, a stepwise increase in mortality according to the number of biomarkers elevated was observed in both inpatients and outpatients. It will be of interest to validate our findings in another cohort, particularly as our study population was primarily white.

This study includes the application of rigorous methodology consistent with American Heart Association recommendations to determine the incremental prognostic value of CRP, BNP, and TnT in HF. The convergence of the results obtained by each risk prediction method assessed provides robust documentation of the incremental value of the multimarker strategy evaluated. As this cohort includes community patients with HF with both preserved and reduced EF, and a wide range of HF severity, these results have, by design, a broad applicability and underscore the potential value of multiple biomarkers simultaneously in a large cohort of patients with HF. Although each biomarker provides incremental prognostic value above established risk factors, the combined use of 2 or more biomarkers confers substantial improvement in the

### Table 3. Incremental Prognostic Value of Biomarkers: Summary of Findings

<table>
<thead>
<tr>
<th>Marker Strategy</th>
<th>ROC Curve Analysis</th>
<th>Integrated Discrimination Improvement</th>
<th>Event-Specific Reclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model + Marker</td>
<td>$c$ statistic</td>
<td>$P$</td>
<td>IDI, %</td>
</tr>
<tr>
<td>CRP</td>
<td>0.782</td>
<td>0.012</td>
<td>2.8</td>
</tr>
<tr>
<td>BNP</td>
<td>0.789</td>
<td>0.005</td>
<td>4.3</td>
</tr>
<tr>
<td>TnT</td>
<td>0.780</td>
<td>0.023</td>
<td>3.2</td>
</tr>
<tr>
<td>CRP + BNP</td>
<td>0.810</td>
<td>$&lt;0.001$</td>
<td>7.1</td>
</tr>
<tr>
<td>CRP + TnT</td>
<td>0.797</td>
<td>0.001</td>
<td>4.7</td>
</tr>
<tr>
<td>BNP + TnT</td>
<td>0.799</td>
<td>0.002</td>
<td>6.0</td>
</tr>
<tr>
<td>CRP + BNP + TnT</td>
<td>0.815</td>
<td>$&lt;0.001$</td>
<td>7.8</td>
</tr>
</tbody>
</table>

NRI indicates net reclassification improvement.

* $P$ value compared with the model including established risk factors (age, body mass index, creatinine clearance, New York Heart Association functional class, serum sodium $<135$ mmol/L, and systolic blood pressure) that has a $c$ statistic of 0.757.

### Table 4. Reclassification of Participants by 1-Year Mortality Status Using Model With CRP and BNP

<table>
<thead>
<tr>
<th>Model With Established Risk Factors</th>
<th>Model With Established Risk Factors, CRP and BNP*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants dead at 1 year (n=122)</strong></td>
<td></td>
</tr>
<tr>
<td>$&lt;10%$ risk</td>
<td>7</td>
</tr>
<tr>
<td>$10%$ to $30%$ risk</td>
<td>3</td>
</tr>
<tr>
<td>$\geq30%$ risk</td>
<td>0</td>
</tr>
<tr>
<td><strong>Participants alive at 1 year (n=471)</strong></td>
<td></td>
</tr>
<tr>
<td>$&lt;10%$ risk</td>
<td>151</td>
</tr>
<tr>
<td>$10%$ to $30%$ risk</td>
<td>19</td>
</tr>
<tr>
<td>$\geq30%$ risk</td>
<td>0</td>
</tr>
<tr>
<td>$10%$ to $30%$ risk</td>
<td>67</td>
</tr>
<tr>
<td>$\geq30%$ risk</td>
<td>35</td>
</tr>
<tr>
<td>$10%$ to $30%$ risk</td>
<td>5</td>
</tr>
<tr>
<td>$\geq30%$ risk</td>
<td>36</td>
</tr>
</tbody>
</table>

* Established risk factors include age, body mass index, creatinine clearance, New York Heart Association functional class, serum sodium $<135$ mmol/L, and systolic blood pressure.

**Conclusions**

Higher levels of CRP, BNP, and TnT are strong, independent predictors of mortality in community patients with HF. Although each biomarker provides incremental prognostic value above established risk factors, the combined use of 2 or more biomarkers confers substantial improvement in the
ability to predict death as assessed by several complementary risk prediction approaches. In particular, the 2-biomarker combination of CRP and BNP was associated with the greatest increase in mortality risk prediction, and further inclusion of a third biomarker, TnT, did not confer significant incremental prognostic value. These results provide a strong rationale for the implementation of such a multimarker strategy in HF.

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Disclosures
None.

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Heart failure (HF) portends a high mortality. The ability to accurately risk stratify patients with HF is important to aggressively treat patients at highest risk and improve their outcomes. Elevated biomarker levels have been associated with increased mortality in HF and have been of particular interest for risk prediction. We investigated whether a multimarker strategy incorporating C-reactive protein, B-type natriuretic peptide, and troponin T would improve mortality risk prediction beyond traditional risk indicators in a large community cohort of patients with HF. As the number of elevated biomarkers per patient increased, so did the observed 1-year mortality rate. The use of a 2-biomarker combination to aid in mortality risk prediction was better than a single biomarker, but the use of a third biomarker conferred no additional benefit. The combination of C-reactive protein and B-type natriuretic peptide was associated with the greatest improvement in risk prediction of the 2-biomarker combinations. Measurement of selected biomarkers in patients with HF improved the ability to risk stratify these patients, and effective strategies are needed to improve outcomes among patients with HF at highest risk of death.

**CLINICAL PERSPECTIVE**

Heart failure (HF) portends a high mortality. The ability to accurately risk stratify patients with HF is important to aggressively treat patients at highest risk and improve their outcomes. Elevated biomarker levels have been associated with increased mortality in HF and have been of particular interest for risk prediction. We investigated whether a multimarker strategy incorporating C-reactive protein, B-type natriuretic peptide, and troponin T would improve mortality risk prediction beyond traditional risk indicators in a large community cohort of patients with HF. As the number of elevated biomarkers per patient increased, so did the observed 1-year mortality rate. The use of a 2-biomarker combination to aid in mortality risk prediction was better than a single biomarker, but the use of a third biomarker conferred no additional benefit. The combination of C-reactive protein and B-type natriuretic peptide was associated with the greatest improvement in risk prediction of the 2-biomarker combinations. Measurement of selected biomarkers in patients with HF improved the ability to risk stratify these patients, and effective strategies are needed to improve outcomes among patients with HF at highest risk of death.
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_Circ Heart Fail_. 2009;2:393-400; originally published online July 29, 2009;
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