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

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### Abstract

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

**Conclusions**—Biomarkers improved 1-year mortality risk prediction beyond established indicators. The use of a two-biomarker combination was superior to a single biomarker in risk prediction, though addition of a third biomarker conferred no added benefit.

### Keywords

epidemiology; heart failure; prognosis; inflammation; community

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### Clinical Significance

Heart failure (HF) portends a high mortality. The ability to accurately risk stratify HF patients 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 (CRP), B-type natriuretic peptide (BNP), and troponin T (TnT) would improve mortality risk prediction beyond traditional risk indicators in a large community cohort of HF patients. As the number of elevated biomarkers per patient increased, so did the observed 1-year mortality rate. The use of a two-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 CRP and BNP was associated with the greatest improvement in risk prediction of the two-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 HF patients at highest risk of death.

### Introduction

According to the ACC/AHA 2008 update, an estimated 5.3 million Americans are currently living with heart failure (HF)<sup>1</sup>. Despite advances in HF treatment, mortality remains high, with estimated 5-year mortality rates of nearly 50% in the community<sup>2,3</sup>. This persistently high mortality underscores the importance of risk stratification in HF. While clinical characteristics have historically been investigated to predict mortality risk in HF<sup>4</sup>, 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 HF patients<sup>5-15</sup>. Indeed CRP, BNP, and troponins, which reflect distinct patho-physiological mechanisms, i.e. 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 (AHA) Scientific Statement<sup>16</sup>. 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<sup>16,17</sup>. 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"<sup>18</sup>, and should not be the sole determinant of clinical utility<sup>19</sup>. 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<sup>17</sup>. While 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 HF patients to determine their role in risk prediction has been recently underscored<sup>20</sup>. The present 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 multi-marker 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 U.S. Census population 137521, 90% Caucasian, 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<sup>21</sup>.

### Patient Population

To identify potential HF cases, natural language processing of the electronic medical record text is utilized. 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<sup>22</sup>. 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<sup>23</sup>. Left ventricular ejection fraction (EF) was measured using M-mode, quantitative, and semi-quantitative methods as previously described and validated<sup>24</sup> with excellent correlation between methods. Though EF was dichotomized (reduced <50%, preserved  $\geq$ 50%<sup>25</sup>) for descriptive purposes, it was examined as a continuous variable in all analyses. Diastolic function was assessed by an approach which 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<sup>26</sup>. In the study, diastolic function was dichotomized as grade 3 or 4 (moderate or severe diastolic dysfunction) vs. normal/mild diastolic dysfunction/indeterminate.

**Biomarker Measurements**—Serum samples obtained from patients at the time of HF diagnosis were stored at -70C 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, Minnesota). BNP was measured by a 2-site immunoenzymatic sandwich assay on the DxI 800 automated immunoassay system (Beckman Instruments, Chaska, MN). TnT was measured using a sandwich electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostic Corp, Indianapolis, IN). 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<sup>27</sup>. 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 >140mmHg, diastolic blood pressure >90mmHg, or use of anti-hypertensive medications<sup>28</sup>. Smoking status

was classified as 'ever' or 'never'. Patient height and weight at HF diagnosis were used to calculate body mass index (BMI). Creatinine at HF diagnosis was collected and creatinine clearance was calculated using the Cockcroft-Gault equation<sup>29</sup>. New York Heart Association (NYHA) 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<sup>21</sup>.

## Statistical Analysis

Subjects were divided by median CRP (<11.8mg/L, ≥11.8mg/L), BNP (<350pg/mL, ≥350pg/mL), and TnT (≤0.01ng/mL, >0.01ng/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 prior literature. Variables were included in the final base model if they were significant univariate predictors of 1-year mortality in the present study and included age, BMI, creatinine clearance, NYHA functional class, serum sodium <135mmol/L, and SBP. As we were limited by our sample size and one-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 significance determined by methods previously described<sup>30</sup>. Then, the IDI, a novel method for evaluating improvement in risk discrimination (a measure of how well a model separates those dead at 1 year from those alive) proposed by Pencina et al<sup>17</sup>, was assessed. The IDI measures the change in the difference in the mean predicted probabilities of death between those dead and alive at 1 year after inclusion of biomarkers in the model (a greater difference reflects a better model). Finally, the improvement in risk classification was assessed using event-specific reclassification tables<sup>17</sup>. Predicted probabilities for 1-year mortality for each patient were determined using the base model. Patients were reclassified according to the 1-year predicted probabilities of death (<10%, 10 to <30%, ≥30%) after addition of biomarkers to the model. The net reclassification improvement (NRI) was determined by assessing net improvement in risk classification (higher predicted risk in subjects dead at 1 year, lower predicted risk in subjects alive at 1 year). A *p* value <0.05 was used as the level of significance. Analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

## Results

### Patient Population

598 patients with HF were enrolled from July 2004 through 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 male, and 302 (53.5%) had preserved EF. 417 (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 non-participants (mean 76 vs. 80 years,  $p < 0.001$ ). No differences in sex or the proportion enrolled as inpatients were observed among participants vs. non-participants.

### Biomarker Levels

CRP ranged from 0.28 to 459mg/L with a median value of 11.8 mg/L (25<sup>th</sup>-75<sup>th</sup> percentile 3.7-50.6mg/L). BNP ranged from 5.5 to 6434.0pg/mL with a median value of 350.0pg/mL (25<sup>th</sup>-75<sup>th</sup> percentile 174.0-647.0pg/mL). TnT ranged from <0.01 to 8.6ng/mL with a median value of 0.01ng/mL (25<sup>th</sup>-75<sup>th</sup> percentile 0.01-0.05ng/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 above the median overall, among those with preserved and reduced EF, and among those enrolled as inpatients and outpatients (Figure 1). Overall, patients with either two or three biomarkers above 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 the present 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.

### Evaluating 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 NRI (Table 3), indicating that each biomarker offered value in predicting 1-year mortality beyond traditional prognostic factors.

**Incremental Prognostic Value of Two or More Biomarkers**—There was complementary prognostic value gained by adding combinations of biomarkers to the model. The best two-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 two biomarkers offer 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 non-significant 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 HF patients with a wide range of EF and HF severity, higher levels of CRP, BNP, and TnT were associated with a large increase in mortality. While 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 HF patients 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 the present study and an estimated 5-year mortality near 50% in prior community studies<sup>2,3</sup>. However, 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<sup>4,20</sup>. While an individual biomarker may aid in determining risk, use of a multimarker strategy is likely to provide greater benefit<sup>4</sup>. For example, a recent investigation aimed at predicting death among elderly patients free of cardiovascular disease found that no individual biomarker increased the *c* statistic when added separately to a model, but the combination of all biomarkers markedly increased the *c* statistic<sup>31</sup>. Though studies have reported on the prognostic value of individual biomarkers in HF, they often failed to report on their incremental value above established risk indicators, thereby obscuring their true prognostic significance. In addition, multimarker strategies in HF risk prediction are currently lacking.

Recently, substantial attention has been focused on the importance of following rigorous methodological steps in risk prediction analyses<sup>16-19,32</sup>. 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<sup>17</sup>. While studies often report on the *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<sup>18,19,32</sup>. The *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<sup>18</sup>. Newer methods, including use of reclassification tables and further methods of discrimination have been proposed<sup>17</sup>, and offer useful information regarding a biomarkers' utility in risk prediction. These novel methods were evaluated in the present study.

CRP, BNP, and TnT have been reported to be associated with increased mortality in HF<sup>5,7-13</sup> and are of interest in mortality risk prediction. CRP, a marker of inflammation, is produced in the liver in response to an inflammatory stimulus<sup>33</sup>. Inflammation clearly plays a key role in the pathogenesis of HF<sup>34</sup>. CRP has been demonstrated to be elevated in a large portion of

HF patients compared with controls<sup>35</sup> and in patients with both preserved and reduced EF<sup>7, 35</sup>. BNP, one of three major natriuretic peptides, is released from the heart in response to pressure and volume overload, and acts to promote vasodilatation, natriuresis, and diuresis<sup>36, 37</sup>. Elevated BNP levels have been used to diagnose HF<sup>38,39</sup> and as a guide to therapy in established HF patients<sup>40</sup>. Finally, TnT, a marker of cardiomyocyte injury, has been reported to be detectable in a large portion of HF patients<sup>14</sup>, and elevations have been associated with an increased risk of death in both ambulatory<sup>15</sup> and hospitalized HF patients<sup>13</sup>. Based on these data, we hypothesized that use of a multimarker strategy incorporating CRP, BNP, and TnT, biomarkers reflecting inflammation, cardiac stress, and myocyte injury in HF, may provide complementary benefit in risk prediction.

Herein, higher levels of CRP, BNP, and TnT are associated with a large increase in 1-year mortality in community HF patients. Patients with two or three biomarkers above the median value had markedly high 1-year mortality of 30.8% and 35.5%, respectively. In addition, CRP, BNP, and TnT were strong predictors of 1-year mortality. BNP had the highest *c* statistic (0.698) of any single predictor evaluated in the study, including age and NYHA functional class. The present findings also extend previous reports<sup>5-13</sup> by underscoring that these biomarkers have added prognostic value above established risk indicators. Furthermore, the combined use of two or more biomarkers offers greater incremental value in risk prediction. The two-marker strategies including CRP and BNP performed slightly better than the other two-marker combinations by all methods evaluated. Use of the three-biomarker combination of CRP, BNP, and TnT did not offer significant incremental value in 1-year mortality risk prediction compared with the two-biomarker combination of CRP and BNP.

### Limitations, Strengths, and Clinical Implications

Potential limitations should be acknowledged to aid in data interpretation. The present 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 as it has been lacking from prior 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. While 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 Caucasian.

The present study includes the application of rigorous methodology consistent with AHA recommendations<sup>16</sup> 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, the present results have, by design, a broad applicability and underscore the potential value of CRP, BNP and TnT to predict death in a wide variety of HF patients.

### Conclusions

Higher levels of CRP, BNP, and TnT are strong, independent predictors of mortality in community HF patients. While each biomarker provides incremental prognostic value above established risk factors, the combined use of two or more biomarkers confers substantial improvement in the ability to predict death as assessed by several complementary risk prediction approaches. In particular, the two-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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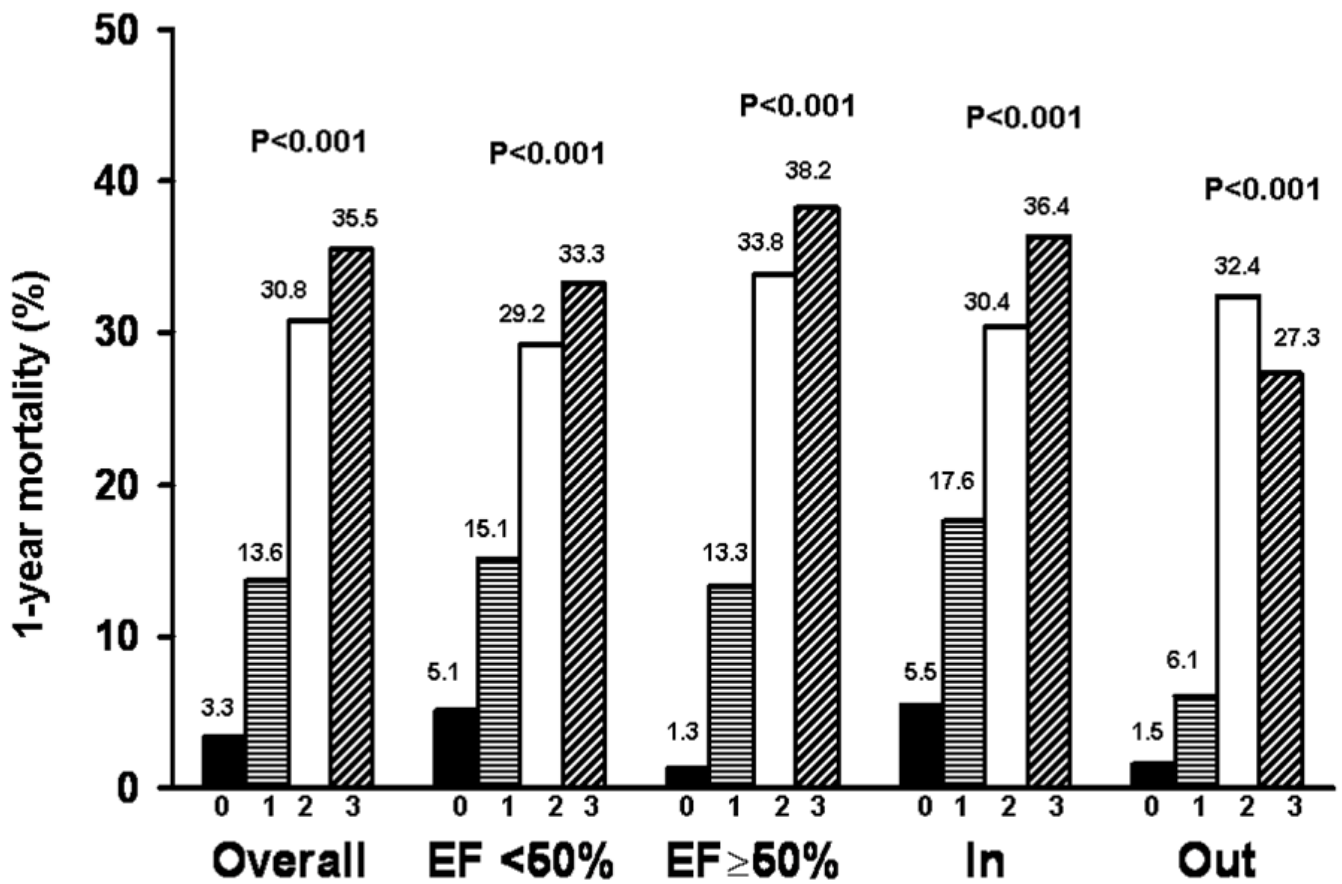
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**Figure 1. Observed 1-year Mortality by Median Biomarker Level**  
 1-year mortality rates according to the number of biomarkers above the median level (0, 1, 2, 3) are shown overall, by ejection fraction, and by inpatient (In)/ outpatient (Out) status at enrollment.

Table 1

Baseline Characteristics

	Overall (n=593)	CRP <11.8mg/L (n=296)	CRP ≥11.8mg/L (n=297)	BNP <350 pg/mL (n=299)	BNP ≥350 pg/mL (n=294)	TnT ≤0.01ng/mL (n=319)	TnT >0.01ng/mL (n=274)
Age (years)	76.4 (12.8)	75.8 (13.3)	77.0 (12.2)	74.6 (13.1)	<b>78.2 (12.3)<sup>‡</sup></b>	75.7 (13.1)	77.1 (12.4)
Male	284 (47.9)	141 (47.6)	143 (48.1)	140 (46.8)	144 (49.0)	134 (42.0)	<b>150 (54.7)<sup>‡</sup></b>
Inpatient at Enrollment	417 (70.3)	158 (53.4)	<b>259 (87.2)<sup>‡</sup></b>	197 (65.9)	<b>220 (74.8)<sup>*</sup></b>	198 (62.1)	<b>219 (79.9)<sup>‡</sup></b>
Hypertension	470 (79.3)	231 (78.0)	239 (80.5)	235 (78.6)	235 (79.9)	249 (78.1)	221 (80.7)
Hyperlipidemia	403 (68.0)	203 (68.6)	200 (67.3)	207 (69.2)	196 (66.7)	212 (66.5)	191 (69.7)
Current smoker	54 (9.1)	27 (9.2)	27 (9.1)	28 (9.4)	26 (8.9)	28 (8.8)	26 (9.5)
Diabetes	186 (31.4)	99 (33.4)	87 (29.3)	104 (34.8)	82 (27.9)	89 (27.9)	<b>97 (35.4)<sup>*</sup></b>
Coronary disease	324 (54.6)	168 (56.8)	156 (52.5)	162 (54.2)	162 (55.1)	171 (53.6)	153 (55.8)
Myocardial infarction	148 (25.9)	73 (25.6)	75 (26.2)	66 (22.8)	82 (29.2)	73 (23.2)	75 (29.3)
Atrial fibrillation	181 (30.5)	90 (30.4)	91 (30.6)	93 (31.1)	88 (29.9)	107 (33.5)	74 (27.0)
History of Malignancy	191 (32.3)	80 (27.1)	<b>111 (37.4)<sup>‡</sup></b>	101 (33.8)	90 (30.7)	92 (28.8)	99 (36.3)
Body mass index (kg/m <sup>2</sup> )	30.2 (7.7)	30.2 (8.0)	30.3 (7.3)	32.5 (8.3)	<b>27.9 (6.2)<sup>‡</sup></b>	30.2 (7.5)	30.3 (7.9)
Creatinine clearance (ml/min)	59.7 (33.9)	60.9 (32.1)	58.6 (35.6)	69.5 (37.1)	<b>49.8 (27.0)<sup>‡</sup></b>	64.3 (32.0)	<b>54.5 (35.3)<sup>‡</sup></b>
Sodium <135 mmol/L	76 (12.8)	23 (7.8)	<b>53 (17.8)<sup>‡</sup></b>	29 (9.7)	<b>47 (16.0)<sup>‡</sup></b>	37 (11.6)	39 (14.2)
SBP (mm Hg)	140.0 (31.8)	138.8 (30.2)	141.2 (33.3)	142.0 (31.7)	137.9 (31.8)	141.1 (32.1)	138.7 (31.4)
NYHA Functional Class III or IV	421 (71.0)	198 (66.9)	<b>223 (75.1)<sup>‡</sup></b>	196 (65.6)	<b>225 (76.5)<sup>‡</sup></b>	219 (68.7)	202 (73.7)
Echocardiographic Characteristics							
Ejection fraction (%)	48.7 (16.4)	46.3 (16.4)	<b>51.1 (16.2)<sup>‡</sup></b>	53.7 (14.1)	<b>43.5 (17.1)<sup>‡</sup></b>	50.3 (16.0)	<b>46.8 (16.8)<sup>*</sup></b>
Diastolic dysfunction Class 3/4	428 (75.8)	213 (75.5)	215 (76.0)	216 (75.0)	212 (76.5)	227 (74.9)	201 (76.7)
Medications Prior to Heart Failure Diagnosis							
Beta blocker	386 (65.1)	194 (65.5)	192 (64.6)	197 (65.9)	189 (64.3)	221 (69.3)	<b>165 (60.2)<sup>*</sup></b>
ACE/ARB	347 (58.5)	181 (61.5)	165 (55.6)	175 (58.5)	172 (58.5)	195 (61.1)	152 (55.5)
Statin	302 (50.9)	168 (56.8)	<b>134 (45.1)<sup>‡</sup></b>	152 (50.8)	150 (51.0)	163 (51.1)	139 (50.7)

Age, body mass index, hemoglobin, creatinine clearance, systolic blood pressure, and ejection fraction are given as mean (standard deviation).

All other values are given as frequency (%).

ACE= Angiotensin converting enzyme inhibitor; ARB= angiotensin II receptor blocker; BNP= B-type natriuretic peptide; CRP= C-reactive protein; NYHA= New York Heart Association; SBP= systolic blood pressure; TnT= troponin T

\* p<0.05 compared with patients with biomarker below the median

<sup>‡</sup> p<0.01 compared with patients with biomarker below the median

<sup>‡</sup> p<0.001 compared with patients with biomarker below the median

Table 2

Predictors of Mortality

Variable	Univariate			Multivariate		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
* Age (yrs)	1.07	1.05-1.10	<0.001	1.06	1.03-1.09	<0.001
* Body mass index (kg/m <sup>2</sup> )	0.95	0.92-0.98	<0.001	1.00	0.96-1.04	0.883
* Creatinine clearance(ml/min)	0.98	0.97-0.98	<0.001	0.99	0.98-1.00	0.073
NYHA Class 3	2.40	1.46-3.40	<0.001	2.86	1.57-5.38	<0.001
NYHA Class 4	3.28	1.97-5.98		4.02	2.21-7.59	
Serum sodium <135 mmol/L	2.12	1.24-3.57	0.007	1.77	0.98-3.15	0.058
* SBP (mm Hg)	0.99	0.99-1.00	0.033	0.99	0.98-1.00	0.010
† Biomarkers entered as continuous predictors into model including established risk factors						
CRP (mg/L)	1.61	1.31-2.00	<0.001	1.54	1.21-1.97	<0.001
BNP (pg/mL)	2.26	1.77-2.93	<0.001	1.92	1.42-2.63	<0.001
TnT (ng/mL)	1.49	1.25-1.79	<0.001	1.29	1.03-1.62	0.029

\* Odds ratios for continuous variables are given per 1-unit increase for age, body mass index, creatinine clearance, and SBP.

† Biomarkers added to the base model (age, body mass index, creatinine clearance, New York Heart Association functional class, serum sodium <135, SBP) as continuous predictors (log transformed). Odds ratios and confidence intervals are expressed per standard deviation increase.

NYHA= New York Heart Association; CRP= C-reactive protein; BNP= B-type natriuretic peptide; SBP= systolic blood pressure; TnT= troponin T

Table 3

Incremental Prognostic Value of Biomarkers: Summary of Findings

	Receiver Operating Characteristic Curve Analysis		Integrated Discrimination Improvement		Event-Specific Reclassification	
	Model + Marker c statistic	* P value	IDI (%)	P value	NRI (%)	P value
CRP	0.782	0.012	2.8%	<0.001	10.7%	0.030
BNP	0.789	0.005	4.3%	<0.001	16.2%	0.003
TnT	0.780	0.023	3.2%	<0.001	11.5%	0.006
CRP + BNP	0.810	<0.001	7.1%	<0.001	22.1%	<0.001
CRP+TnT	0.797	0.001	4.7%	<0.001	16.5%	<0.001
BNP+TnT	0.799	0.002	6.0%	<0.001	18.4%	0.001
CRP+BNP+TnT	0.815	<0.001	7.8%	<0.001	26.9%	<0.001

\* 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, and SBP) that has a c statistic of 0.757

IDI= integrated discrimination improvement;NRI= Net Reclassification Improvement; CRP= C-reactive protein; BNP= B-type natriuretic peptide; TnT= troponin T

**Table 4**

Reclassification of Participants by 1-Year Mortality Status Using Model with CRP and BNP

Frequency	<sup>a</sup> Model with Established Risk Factors, CRP and BNP		
	<10% Risk	10-30% Risk	≥30% Risk
<sup>a</sup> Model with Established Risk Factors			
Participants dead at 1 year (n=122)			
<10% Risk	7	3	0
10-30% Risk	4	25	22
≥30% Risk	0	8	53
Participants alive at 1 year (n=471)			
<10% Risk	151	19	0
10-30% Risk	67	109	35
≥30% Risk	5	36	49

<sup>a</sup> Established risk factors include age, body mass index, creatinine clearance, New York Heart Association functional class, serum sodium <135, and SBP

CRP= C-reactive protein; BNP= B-type natriuretic peptide