Factors Associated With Outcome in Heart Failure With Preserved Ejection Fraction

Findings From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE)

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Background—The determinants of prognosis in patients with heart failure and preserved ejection fraction (HF-PEF) are poorly documented.

Methods and Results—We evaluated data from 4128 patients in the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study). Multivariable Cox regression models were developed using 58 baseline demographic, clinical, and biological variables to model the primary outcome of all-cause mortality or cardiovascular hospitalization (1505 events), all-cause mortality (881 events), and HF death or hospitalization (716 events). Log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, and previous hospitalization for HF were the most powerful factors associated with the primary outcome and with the HF composite. For all-cause mortality, log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, and left ventricular EF were the strongest independent factors. Other independent factors associated with poor outcome included quality of life, a history of chronic obstructive lung disease, log neutrophil count, heart rate, and estimated glomerular filtration rate. The models accurately stratified the actual 3-year rate of outcomes from 8.1% to 59.9% (primary outcome) 2.7% to 36.5% (all-cause mortality), and 2.1% to 38.9% (HF composite) for the lowest to highest septiles of predicted risks.

Conclusions—In a large sample of elderly patients with HF and preserved EF enrolled in I-Preserve, simple clinical, demographic, and biological variables were associated with outcome and identified subgroups at very high and very low risk of events.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00095238. (Circ Heart Fail. 2011;4:27-35.)

Key Words: heart failure ■ preserved ejection fraction ■ outcome ■ prognosis evaluation

Recent surveys suggest that up to half of the patients with heart failure have a preserved left ventricular ejection fraction (HF-PEF).1–3 Patients with HF-PEF are more commonly older women and a greater proportion have hypertensive etiology.4–8 Although some reports suggested that mortality in patients with HF-PEF was similar to that observed in HF with low EF, most studies show that survival is better in HF-PEF suggesting that a continuum of risk exists.1,5 This condition is also associated with a high rate of rehospitalization. In HF-PEF, identification of factors predicting mortality or morbidity in HF-PEF remains largely unexplored, in contrast to patients with HF and low EF. I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fration Study) enrolled 4128 patients with HF-PEF. We used this large database to assess the factors associated with outcome in this condition and to quantify their individual power by the development of prognostic models.

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Methods

The I-PRESERVE design and results have been described and reported previously.9,10 In brief, patients enrolled in the trial were at least 60 years of age and had HF symptoms and a left ventricular EF of at least 45%. In addition, we required patients who had been...
hospitized for HF during the previous 6 months to have current New York Heart Association class II, III, or IV symptoms with corroborative evidence. If they had not been hospitalized, they were required to have ongoing class III or IV symptoms with corroborative evidence. Exclusion criteria have been detailed previously. Patients were enrolled after informed consent was given at 293 sites in 25 countries. End points used for the current analysis were (1) the primary composite end point of the trial: all-cause mortality and protocol-specified cardiovascular hospitalizations (HF, myocardial infarction, stroke, and ventricular or atrial arrhythmias); (2) all-cause mortality; and (3) the composite of HF death or hospitalization. The Minnesota Living with Heart Failure score at baseline was used to assess quality of life (QOL). The plasma level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured at random assignment and analyzed in a central laboratory (Esoterix, Belgium). Values (expressed in pg/mL) were log-transformed.

**Statistical Methods** To develop the final predictive models, we started from the entire list of variables collected at the baseline visit in I-PRESERVE and a variable for irbesartan versus placebo, excluding nonrandomized medical therapy. With the remaining list of 58 variables, univariate Cox proportional hazards models were fit individually for each of the 3 outcomes mentioned above. Association of each variable to the outcomes was determined by comparing with an intercept only base model. Any variable that had a \( \chi^2 \) probability value <0.01 in any of the models was considered as a candidate variable for the final models.

The database for analysis included patients with all 58 variables, which narrowed the study cohort from 4128 to 2563 patients. The baseline characteristics of the subjects with full data and subjects with missing data were examined for significant differences (Table 1). Based on Bonferroni-adjusted probability values, significant differences were noted. Further, examination of the outcomes between the 2 cohorts by log-rank tests showed that those that had missing data had a greater occurrence of primary events and all-cause mortality. Because there were significant differences between those with full data and those with missing data and the number of subjects with missing data was large, we examined multiple methods of imputation and model building. The methods included (1) building and fitting the model based on the full data cohort, (2) building the model based on the full data cohort and fitting the model after imputation with mean or median was used to fill in the missing data, (3) same as 2 but with a regression based imputation after building the model, and (4) building and fitting the model after a regression based imputation for the missing data. The major difference in method 4 compared with methods 1 to 3 was to impute first and then build the model based on all 4128 subjects. There were some differences in model variables between method 4 and methods 1 to 3. All variables in methods 1 to 3 entered into the model while variables were left out of analysis. The effect of missing data on the model was assessed using a forward-only stepwise process with an intercept only base model and then fitting the model to the full cohort of patients. The differences in estimates for each model were marginal, and therefore we decided to include all events. We validated and presented the final models as based on the full cohort with imputed data.

Risk scores were determined for each patient from the final models and split into quintiles of risk. A risk score is the linear combination of the values for each risk factor and their corresponding coefficients. The model for quintiles was used to examine the model calibration by predicted versus observed quintiles of risk within 3 years by risk score quintiles. Kaplan–Meier curves of the quintile groups were used to show the ability to correctly separate populations of patients at risk. The models’ discrimination abilities were assessed by Harrell C-statistic for models with censored data, and internal validity was examined by average C-statistic from 200 Efron bootstrap resamples.

**Results** Table 1 compares the baseline characteristics of the total cohort, the model-building full data cohort, and the missing data cohort. Based on Bonferroni-adjusted (32 tests) probability values, statistically and clinically significant differences between the full data cohort and missing data cohort were seen for left ventricular hypertrophy, hypertension etiology, and anemia and history of hypertension, angina, percutaneous coronary intervention or coronary artery bypass grafting, and diabetes. Also, log-rank tests between the groups showed significantly higher occurrence of the primary outcome and all-cause mortality in those that needed imputed data. During follow-up of the total cohort, 1505 primary end points
Table 1. Clinical, Demographic, and Biological Baseline Characteristics and Rate of Events of the Overall I-PRESERVE Population, of the Cohort of Patients With Full Data, and of the Cohort of Patients With Missing Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Cohort (n=4128)</th>
<th>Full Data Cohort (n=2563)</th>
<th>Missing Data Cohort (n=1656)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>72±7</td>
<td>71±7</td>
<td>72±7</td>
<td>0.2412</td>
</tr>
<tr>
<td>≥75 y, n (%)</td>
<td>1413 (34)</td>
<td>844 (33)</td>
<td>569 (36)</td>
<td>0.8496</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>2491 (60)</td>
<td>1562 (61)</td>
<td>929 (59)</td>
<td>1</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.2782</td>
</tr>
<tr>
<td>White</td>
<td>3859 (93)</td>
<td>2421 (94)</td>
<td>1438 (92)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>82 (2)</td>
<td>45 (2)</td>
<td>37 (2)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>34 (1)</td>
<td>15 (1)</td>
<td>19 (1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>152 (4)</td>
<td>81 (3)</td>
<td>71 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New York Heart Association class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>870 (21)</td>
<td>552 (22)</td>
<td>318 (20)</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>3144 (76)</td>
<td>1944 (76)</td>
<td>1200 (77)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>112 (3)</td>
<td>67 (3)</td>
<td>45 (3)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71±10</td>
<td>71±10</td>
<td>72±11</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>136±15</td>
<td>136±15</td>
<td>136±15</td>
<td>1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79±9</td>
<td>79±9</td>
<td>78±9</td>
<td>0.0181</td>
</tr>
<tr>
<td>Body mass index</td>
<td>30±5</td>
<td>30±5</td>
<td>30±5</td>
<td>1</td>
</tr>
<tr>
<td>ECG findings, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1260 (31)</td>
<td>840 (33)</td>
<td>420 (27)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Left bundle-branch block</td>
<td>336 (8)</td>
<td>210 (8)</td>
<td>126 (8)</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>697 (17)</td>
<td>425 (17)</td>
<td>272 (17)</td>
<td>1</td>
</tr>
<tr>
<td>EF</td>
<td>0.59±0.09</td>
<td>0.59±0.09</td>
<td>0.59±0.09</td>
<td>1</td>
</tr>
<tr>
<td>Cause of HF, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>1036 (25)</td>
<td>618 (24)</td>
<td>418 (27)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2622 (64)</td>
<td>1698 (66)</td>
<td>924 (59)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospitalization for HF within previous 6 mo, n (%)</td>
<td>1816 (44)</td>
<td>1139 (44)</td>
<td>677 (43)</td>
<td>1</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3650 (88)</td>
<td>2303 (90)</td>
<td>1347 (86)</td>
<td>0.0089</td>
</tr>
<tr>
<td>Angina symptoms</td>
<td>1652 (40)</td>
<td>1116 (44)</td>
<td>536 (34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>315 (8)</td>
<td>174 (7)</td>
<td>141 (9)</td>
<td>0.3478</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>969 (23)</td>
<td>626 (24)</td>
<td>343 (22)</td>
<td>1</td>
</tr>
<tr>
<td>PCI or CABG</td>
<td>548 (13)</td>
<td>286 (11)</td>
<td>262 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1209 (29)</td>
<td>717 (28)</td>
<td>492 (31)</td>
<td>0.6228</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1134 (27)</td>
<td>653 (25)</td>
<td>481 (31)</td>
<td>0.0089</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>399 (10)</td>
<td>233 (9)</td>
<td>166 (11)</td>
<td>1</td>
</tr>
<tr>
<td><strong>QOL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score on the Minnesota Living with HF Scale</td>
<td>42</td>
<td>43</td>
<td>40</td>
<td>0.4121</td>
</tr>
<tr>
<td>Median</td>
<td>28–58</td>
<td>28–58</td>
<td>25–56</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, g/dL</td>
<td>13.9±1.9</td>
<td>13.9±1.9</td>
<td>13.7±1.9</td>
<td>0.0262</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>514 (13)</td>
<td>293 (11)</td>
<td>221 (16)</td>
<td>0.0087</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1±0.33</td>
<td>0.99±0.3</td>
<td>1.02±0.37</td>
<td>0.0887</td>
</tr>
</tbody>
</table>

(Continued)
occurred, including 447 all-cause deaths and 1058 prespecified cardiovascular hospitalizations. Overall, there were 881 all-cause deaths and 716 HF events, including 125 fatal HF events.

Table 2 shows the 10 strongest variables from univariate analysis for the 3 outcomes. For each of the 3 outcomes, the strongest associated factors were log plasma level of NT-proBNP, age, renal function assessed either by blood urea nitrogen or by estimated GFR and a history of a HF hospitalization within 6 months before entry.

The rate of event increased progressively with increasing age and log NT-proBNP. In contrast, a different pattern was observed for EF and estimated GFR: For the former, the rate of event increased for EF values below 60% and was constant above 60% for all 3 outcomes, whereas for the latter, the rate increased below 90 mL/min/1.73 m² and was constant above 90 for all 3 outcomes (supplemental material: Figure A, B, C, and D).

Table 3 shows the final models in descending order of variable strength for each of the 3 modeled outcomes. Log NT-proBNP was the strongest independent factor associated with primary outcome and all-cause mortality and the second strongest for HF composite. Previous HF hospitalization was the strongest factor correlated with the HF composite. Age, diabetes mellitus, heart rate, poor QOL, comorbidities such as chronic obstructive pulmonary disease or impaired renal function, EF, and previous myocardial infarction or ischemic etiology were also identified as associated with poor outcome. Overall, there was consistency across the 3 models as to the most important factors associated with outcome.

Figure 1 illustrates the correlative power of the final models: Kaplan–Meier curves for each outcome by septile of the risk scores from the Cox models are shown. For each outcome, patients in the 2 septiles with the higher risk score had a particularly poor outcome.

Figure 2 shows model calibrations of the observed and expected 3-year rates of primary outcome, all-cause mortality, and HF composite by septiles of risk. Predicted and observed scores were well in line with only minor deviations from equality in each outcome.

For the 3 outcomes, there was at least a 7-fold increase in event rate for the highest septile of the risk score compared with the lowest septile. The actual 3-year event rate in the highest septile was 59.9% for the primary outcome, 36.5% for all-cause mortality, and 38.9% for the HF composite. By contrast, it was only 8.2%, 2.7%, and 2.1%, respectively, in the lowest septile. The upper cutoffs of the septiles of risk score are shown in Table 4.

The discrimination ability of the models was robust, with Harrell C-statistics of 0.711 (primary outcome), 0.736 (all-cause mortality), and 0.765 (HF composite), respectively. Results from internal validation resampling showed no overfitting of the models’ discrimination ability, with averaged C-indices of 0.711, 0.735, and 0.765, respectively.

Discussion

This study identified a set of clinical, demographic, and biological variables that were strongly associated with cardiovascular morbidity, all-cause death, and HF events in a large sample of older patients with HF-PEF enrolled in I-PRESERVE. Although NT-proBNP was moderately increased in the overall population, a finding in line with other observations,16–19 baseline NT-proBNP was the most powerful independent factor for the primary event and all-cause mortality models. This observation has important clinical implications for the identification of high-risk patients with this condition and strongly supports using natriuretic peptides as an inclusion criterion in future studies involving HF-PEF patients.

Age was another powerful factor associated with outcome in our study. Older age has also been reported as a strong prognostic factor in HF patients with low EF20–23 and in a clinical trial spanning the full range of left ventricular dysfunction.24 Because patients enrolled in I-PRESERVE were, by protocol, 60 years of age or older, we were unable to verify if there was a threshold value below which age had little impact, as described in the CHARM program.24

The presence of diabetes mellitus was also associated with a poor outcome. Although diabetes mellitus has been associated with poor outcome in patients with HF with low EF,24–26 a population in which ischemic cardiomyopathy predominates, our finding underlines the importance of this comor-

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Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full Cohort (n=4128)</th>
<th>Full Data Cohort (n=2563)</th>
<th>Missing Data Cohort (n=1656)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, mL/min/1.73 m² body surface area</td>
<td>73±22</td>
<td>73±22</td>
<td>72±23</td>
<td>1</td>
</tr>
<tr>
<td>&lt;60 mL/min/1.73 m², n (%)</td>
<td>1245 (31)</td>
<td>763 (30)</td>
<td>482 (33)</td>
<td>1</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.4±0.47</td>
<td>4.4±0.46</td>
<td>4.4±0.5</td>
<td>1</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>Median</td>
<td>339</td>
<td>320</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>134–963.5</td>
<td>126–928</td>
<td></td>
</tr>
<tr>
<td>Outcome, n (%)</td>
<td>Primary outcome</td>
<td>1505 (36)</td>
<td>904 (35)</td>
<td>601 (38)</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>881 (21)</td>
<td>517 (20)</td>
<td>364 (23)</td>
</tr>
<tr>
<td></td>
<td>Composite HF outcome</td>
<td>716 (17)</td>
<td>445 (17)</td>
<td>271 (17)</td>
</tr>
</tbody>
</table>

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft.
bidity in a population consisting exclusively of HF-PEF with lower overt ischemic heart disease.

The presence of a previous hospitalization for HF was associated with a 2-fold increase in the rate of subsequent HF events as it is in patients with HF with low EF.24 Our observation confirms that patients with a recent admission for HF, regardless of their EF, are a high-risk group for readmission and a population that should be targeted in designing future trials on HF-PEF.

EF is a known predictor of outcome in HF with low EF.21,24 We found that EF was also associated with the primary outcome and all-cause mortality in the I-PRESERVE population, although the relationship was observed only when EF was <60%. A weaker association was seen for the HF outcome. Our results are similar to those of the CHARM program, although their results found increased morbidity and mortality risk for subjects with an EF <45%.24 Heart rate was identified as a factor associated with all-cause mortality and with HF events. The relationship of heart rate to morbidity and mortality has been reported previously27–31 in coronary artery disease and in HF with low EF. It has been postulated that increased heart rate is associated with increased oxygen consumption and reduced myocardial oxygen supply resulting in myocardial energy imbalance. Our study suggests that the relationship between heart rate and poor outcome is also present in patients with HF-PEF.

Table 2. Strongest Univariate Association of Candidate Variables With Each Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>χ² Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ten strongest variables from univariate analysis for primary composite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP: log, pg/mL</td>
<td>1.592 (1.525, 1.661)</td>
<td>458.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age per 1-y increase</td>
<td>1.055 (1.048, 1.063)</td>
<td>209.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BUN: log &gt;3.1</td>
<td>4.281 (3.535, 5.183)</td>
<td>172.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR &lt;90 by 1-unit decrease</td>
<td>1.019 (1.016, 1.022)</td>
<td>159.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hosp for HF last 5 mo: Yes vs no</td>
<td>1.915 (1.729, 2.120)</td>
<td>157.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation: Yes vs no</td>
<td>1.926 (1.737, 2.136)</td>
<td>146.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>1.926 (1.771, 2.095)</td>
<td>135.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophil count: log</td>
<td>2.268 (1.945, 2.644)</td>
<td>110.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin: log</td>
<td>2.261 (1.936, 2.639)</td>
<td>107</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF &lt;60% by 1%</td>
<td>1.048 (1.038, 1.058)</td>
<td>83.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ten strongest variables from univariate analysis for all-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP: log, pg/mL</td>
<td>1.715 (1.621, 1.813)</td>
<td>363.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age per 1-y increase</td>
<td>1.071 (1.061, 1.081)</td>
<td>197.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BUN: log &gt;3.1</td>
<td>4.774 (3.792, 6.010)</td>
<td>134.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR &lt;90 by 1-unit decrease</td>
<td>1.021 (1.017, 1.025)</td>
<td>118.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>2.080 (1.876, 2.305)</td>
<td>107</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF &lt;60% by 1%</td>
<td>1.059 (1.046, 1.073)</td>
<td>76.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulmonary congestion: Yes vs no</td>
<td>1.795 (1.569, 2.053)</td>
<td>72.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation Yes vs no</td>
<td>1.792 (1.567, 2.050)</td>
<td>68.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophil count: log</td>
<td>2.316 (1.898, 2.825)</td>
<td>68.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin: log</td>
<td>2.292 (1.874, 2.803)</td>
<td>66.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ten strongest variables from univariate analysis for HF composite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP: log, pg/mL</td>
<td>1.735 (1.631, 1.846)</td>
<td>307.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hosp for last 6 mo: Yes vs no</td>
<td>2.924 (2.502, 3.417)</td>
<td>196.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR &lt;90 by 1-unit decrease</td>
<td>1.026 (1.022, 1.030)</td>
<td>145.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation: Yes vs no</td>
<td>2.517 (2.173, 2.915)</td>
<td>144.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BUN: log &gt;3.1</td>
<td>5.847 (4.543, 7.525)</td>
<td>139.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age per 1-y increase</td>
<td>1.065 (1.054, 1.076)</td>
<td>136.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter: Yes vs no</td>
<td>2.364 (2.013, 2.778)</td>
<td>95.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>2.053 (1.841, 2.289)</td>
<td>89.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophil count: log</td>
<td>2.508 (2.008, 3.131)</td>
<td>66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin: log</td>
<td>2.517 (2.012, 3.149)</td>
<td>65.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BUN indicates blood urea nitrogen; eGFR, estimated GFR (mL/min/m²); and Hosp, hospitalization. Neutrophil count is measured as 1000 cells/μL and albumin as g/dL.
The presence of lung disease was associated with a marked increase in rate of event in the 3 models and particularly in the rate of HF events. This is consistent with previous reports and reflects the complexity of elderly patients with HF-PEF, who often have multiple comorbidities and of their management.32–34 Because by study design, severe pulmonary disease was excluded, the impact of this comorbidity on outcome could be even greater in an unselected population of HF-PEF.

Some factors such as renal function and prior myocardial infarction were not as prominent as in other populations.

Table 3. Final Model Summaries

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>$\chi^2$ Value</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final model for primary composite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, log, pg/mL</td>
<td>1.251 (1.201, 1.304)</td>
<td>0.224</td>
<td>0.021</td>
<td>114.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age per 5-y increase</td>
<td>1.198 (1.151, 1.246)</td>
<td>0.180</td>
<td>0.020</td>
<td>79.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hosp for HF last 6 mo</td>
<td>1.541 (1.386, 1.714)</td>
<td>0.433</td>
<td>0.054</td>
<td>64.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.433 (1.285, 1.597)</td>
<td>0.359</td>
<td>0.056</td>
<td>40.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neutrophils, log, pg/mL</td>
<td>1.458 (1.261, 1.686)</td>
<td>0.377</td>
<td>0.074</td>
<td>26.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF per 5% decrease &lt;60</td>
<td>1.135 (1.078, 1.195)</td>
<td>-0.127</td>
<td>0.026</td>
<td>22.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>1.413 (1.215, 1.643)</td>
<td>0.356</td>
<td>0.077</td>
<td>18.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GFR per 5-unit decrease &lt;90</td>
<td>1.031 (1.015, 1.047)</td>
<td>-0.031</td>
<td>0.008</td>
<td>15.2</td>
<td>0.001</td>
</tr>
<tr>
<td>QOL per 5-unit increase &gt;50</td>
<td>1.044 (1.021, 1.068)</td>
<td>0.043</td>
<td>0.012</td>
<td>13.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.199 (1.052, 1.367)</td>
<td>0.182</td>
<td>0.067</td>
<td>7.3</td>
<td>0.0066</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.177 (0.849, 1.029)</td>
<td>0.163</td>
<td>0.069</td>
<td>5.6</td>
<td>0.0176</td>
</tr>
<tr>
<td>Heart rate per 5-bpm increase</td>
<td>1.021 (0.997, 1.045)</td>
<td>0.021</td>
<td>0.012</td>
<td>2.9</td>
<td>0.0869</td>
</tr>
<tr>
<td>Final model for all-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, log, pg/mL</td>
<td>1.341 (1.271, 1.415)</td>
<td>0.293</td>
<td>0.027</td>
<td>115.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age per 5-y increase</td>
<td>1.277 (1.211, 1.345)</td>
<td>0.244</td>
<td>0.027</td>
<td>83.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.482 (1.287, 1.706)</td>
<td>0.393</td>
<td>0.072</td>
<td>28.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF per 5% decrease &lt;60</td>
<td>1.174 (1.099, 1.253)</td>
<td>-0.160</td>
<td>0.034</td>
<td>22.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate per 5-bpm increase</td>
<td>1.058 (1.027, 1.090)</td>
<td>0.056</td>
<td>0.015</td>
<td>13.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Neutrophils, log, pg/mL</td>
<td>1.387 (1.153, 1.668)</td>
<td>0.327</td>
<td>0.094</td>
<td>12.2</td>
<td>0.0005</td>
</tr>
<tr>
<td>Hosp for HF last 6 mo</td>
<td>1.225 (1.065, 1.410)</td>
<td>0.203</td>
<td>0.071</td>
<td>8.1</td>
<td>0.0043</td>
</tr>
<tr>
<td>QOL per 5-unit increase &gt;50</td>
<td>1.045 (1.014, 1.076)</td>
<td>0.044</td>
<td>0.015</td>
<td>8</td>
<td>0.0047</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>1.320 (1.086, 1.604)</td>
<td>0.277</td>
<td>0.099</td>
<td>7.3</td>
<td>0.0068</td>
</tr>
<tr>
<td>GFR per 5-unit decrease &lt;90</td>
<td>1.027 (1.007, 1.047)</td>
<td>-0.026</td>
<td>0.010</td>
<td>6.8</td>
<td>0.0092</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.192 (1.006, 1.413)</td>
<td>0.176</td>
<td>0.087</td>
<td>4</td>
<td>0.0442</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.194 (1.003, 1.421)</td>
<td>0.178</td>
<td>0.089</td>
<td>3.9</td>
<td>0.0472</td>
</tr>
<tr>
<td>Final model for HF composite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hosp for HF last 6 mo</td>
<td>2.235 (1.901, 2.627)</td>
<td>0.8</td>
<td>0.083</td>
<td>100.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NT-proBNP, log, pg/mL</td>
<td>1.274 (1.201, 1.352)</td>
<td>0.24</td>
<td>0.030</td>
<td>64.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age per 5-y increase</td>
<td>1.216 (1.148, 1.288)</td>
<td>0.2</td>
<td>0.029</td>
<td>44.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.688 (1.447, 1.969)</td>
<td>0.52</td>
<td>0.079</td>
<td>42.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GFR per 5-unit decrease &lt;90</td>
<td>1.056 (1.033, 1.079)</td>
<td>-0.05</td>
<td>0.011</td>
<td>32.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD or asthma</td>
<td>1.528 (1.244, 1.878)</td>
<td>0.42</td>
<td>0.105</td>
<td>14.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Neutrophils, log, pg/mL</td>
<td>1.381 (1.123, 1.698)</td>
<td>0.32</td>
<td>0.105</td>
<td>9.5</td>
<td>0.0020</td>
</tr>
<tr>
<td>Heart rate per 5-bpm increase</td>
<td>1.045 (1.014, 1.083)</td>
<td>0.05</td>
<td>0.017</td>
<td>7.6</td>
<td>0.0059</td>
</tr>
<tr>
<td>EF per 5% decrease &lt;60</td>
<td>1.110 (1.030, 1.196)</td>
<td>-0.1</td>
<td>0.038</td>
<td>7.3</td>
<td>0.0068</td>
</tr>
<tr>
<td>QOL per 5-unit increase &gt;50</td>
<td>1.045 (1.012, 1.079)</td>
<td>0.04</td>
<td>0.016</td>
<td>6.9</td>
<td>0.0087</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.128 (0.931, 1.366)</td>
<td>0.12</td>
<td>0.098</td>
<td>1.5</td>
<td>0.2207</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.085 (0.890, 1.323)</td>
<td>0.08</td>
<td>0.101</td>
<td>0.6</td>
<td>0.4229</td>
</tr>
</tbody>
</table>

Hosp indicates hospitalization; COPD, chronic obstructive pulmonary disease.

The presence of lung disease was associated with a marked increase in rate of event in the 3 models and particularly in the rate of HF events. This is consistent with previous reports and reflects the complexity of elderly patients with HF-PEF, who often have multiple comorbidities and of their management.32–34 Because by study design, severe pulmonary disease was excluded, the impact of this comorbidity on outcome could be even greater in an unselected population of HF-PEF.

Some factors such as renal function and prior myocardial infarction were not as prominent as in other populations. Renal function assessed by estimated GFR, univariately, was strongly associated with poor outcome, but the $\chi^2$ value suggests that renal impairment only had a moderate impact multivariately when the other variables were included. The importance of renal dysfunction as a powerful marker of poor outcome has been recognized in several studies or surveys of patients with low EF as well as in HF-PEF patients.21,22,35–36 The lack of a stronger correlative value observed in the present study may, in part, reflect the exclusion of patients with severe renal impairment or anemia in I-PRESERVE.
Also, none of the previous analyses have included NT-pro-BNP, which may have altered the strength of renal function as associated with outcome.

Log neutrophil count was also correlated to outcome in our 3 models. The association of neutrophil count and outcome has been reported previously in HF with low EF and after myocardial infarction, and increased neutrophil lifespan has been described in this condition. This marker might reflect the deleterious role of chronic inflammation in HF with associated prothrombotic and proatherogenic effects.

Previous models have provided useful prognostic information in HF. Although some of our independent factors are similar to those identified in the CHARM overall population, the CHARM trial included HF patients spanning the full range of EF values, and the prognostic analysis did not include laboratory parameters. The lack of laboratory values is also true for the SEATTLE model, which was constructed in low-EF HF only.

Overall, the 3 models developed in the present study show that a limited set of simple clinical, demographic, and biological variables provides important information for the association with all-cause mortality, cardiovascular morbidity, or HF events. These models are based on a large sample of patients with HF-PEF enrolled in I-PRESERVE with documented inclusion criteria and on a long follow-up period. They have been developed out of a large number of events adjudicated by an end point committee based on predefined criteria. Moreover, the consistency of the variables associated with the 3 different outcomes suggests that these models are robust.

The goodness of fit of our models to predict any individual’s risk of each outcome was also confirmed by the consistency between predicted and observed rates of events and its internal validity verified by C-statistic values. Simple demographic, clinical, and biological data allow to group patients in very low or very high risk groups. In particular, NT-proBNP, age, previous HF hospitalization, and diabetes mellitus are strongly correlated with outcome and should be carefully taken into consideration when assessing risk in HF-PEF. These factors could also enrich populations to be studied in future trials with HF-PEF.

Limitations
The I-PRESERVE population was studied in the context of a clinical trial with exclusion criteria. This population is therefore selective compared with patients with HF-PEF in clinical practice. In particular, patients with moderate or severe renal dysfunction were excluded from the trial. Also diabetes mellitus was reported by investigators but no specific criterion was used for the diagnosis of this important factor. The study cohort was nearly exclusively White and therefore may not be generalizable to other ethnicities.

Further, our model was built based on a subset of the total population albeit a moderate but nonetheless substantial and similar subgroup of 2563 patients for which the full set of baseline variables was available. Moreover, after checking the effect of the missing data by imputation and refitting the models, the effect on the model estimates between the 2 cohorts were marginal and we therefore proceeded to use the entire cohort with imputed data to report our final models.
Finally, the prognostic power of our models was not validated in an independent cohort, though it is supported by statistical techniques such as bootstrapping. Further validation should be performed in other populations.

Conclusion
We report models of associations for 3 important prespecified outcomes in elderly patients with HF-PEF included in the I-PRESERVE trial. We have identified a limited set of demographic, clinical, and biological variables that provide important and independent prognostic information and are consistent across the 3 models developed. These models allow the identification of a subgroup of patients at very high risk of events and should be validated in existing data bases and in future trials on HF-PEF.

Sources of Funding
The I-PRESERVE trial was supported by Bristol-Myers-Squibb and Sanofi Aventis.

Disclosures
Dr Komajda, Carson, McKelvie, Zile, and Massie received consulting fees from Bristol-Myers-Squibb as Executive Committee Members of the I-PRESERVE trial. Dr McMurray received support from Bristol-Myers-Squibb to Glasgow University. Scott Hetzel and Dr DeMets are employed by the Statistical Data Analysis Center at the University of Wisconsin-Madison, which conducted statistical analysis for the study supported by Bristol-Myers-Squibb and Sanofi-Aventis. Dr Ptaszynska is an employee of and has an equity interest in Bristol-Myers-Squibb.

References


**CLINICAL PERSPECTIVE**

Recent surveys suggest that up to half of patients with heart failure have a preserved ejection fraction. In this condition, which is associated with poor outcome and in particular a high rate of rehospitalization, identification of factors predicting mortality or morbidity remains largely unexplored, in contrast to patients with heart failure and low ejection fraction. We evaluated data from 4128 patients in the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study). We report an analysis identifying clinical, demographic, and biological factors associated with the primary end point outcome (all-cause mortality or cardiovascular hospitalization), all-cause mortality, and heart failure death or hospitalization. We found that log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, previous hospitalization for heart failure, ejection fraction, and other simple clinical or biological variables were associated with a more unfavorable outcome. The models were able to identify subgroups of patients at very high and very low risk. Our analysis provides new tools for the prognostic evaluation of heart failure with preserved ejection fraction and the factors that should be taken into consideration when assessing the prognosis of patients with heart failure and preserved ejection fraction.
Factors Associated With Outcome in Heart Failure With Preserved Ejection Fraction: Findings From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE)

Michel Komajda, Peter E. Carson, Scott Hetzel, Robert McKelvie, John McMurray, Agata Ptaszynska, Michael R. Zile, David DeMets and Barry M. Massie

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Supplemental Material

**Figure. A:** Hazard ratios by 5% groups of ejection fraction for each of the three outcomes. **B:** Hazard ratios by septiles of log NT-proBNP plasma level for each of the three outcomes. **C:** Hazard ratios by groups of 10 units of estimated glomerular filtration rate (GFR) for the three outcomes. **D:** Hazard ratios by septiles of age for the three outcomes.