The Seattle Heart Failure Model: Prediction of Survival in Heart Failure

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The Seattle Heart Failure Model
Prediction of Survival in Heart Failure

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Background—Heart failure has an annual mortality rate ranging from 5% to 75%. The purpose of the study was to develop and validate a multivariate risk model to predict 1-, 2-, and 3-year survival in heart failure patients with the use of easily obtainable characteristics relating to clinical status, therapy (pharmacological as well as devices), and laboratory parameters.

Methods and Results—The Seattle Heart Failure Model was derived in a cohort of 1125 heart failure patients with the use of a multivariate Cox model. For medications and devices not available in the derivation database, hazard ratios were estimated from published literature. The model was prospectively validated in 5 additional cohorts totaling 9942 heart failure patients and 17 307 person-years of follow-up. The accuracy of the model was excellent, with predicted versus actual 1-year survival rates of 73.4% versus 74.3% in the derivation cohort and 90.5% versus 88.5%, 86.5% versus 86.5%, 90.9% versus 91.0%, and 89.6% versus 86.7% in the 5 validation cohorts. For the lowest score, the 2-year survival was 92.8% compared with 88.7%, 77.8%, 58.1%, 29.5%, and 10.8% for scores of 0, 1, 2, 3, and 4, respectively. The overall receiver operating characteristic area under the curve was 0.729 (95% CI, 0.714 to 0.744). The model also allowed estimation of the benefit of adding medications or devices to an individual patient’s therapeutic regimen.

Conclusions—The Seattle Heart Failure Model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacological, device, and laboratory characteristics.

Keywords: diuretics ■ heart failure ■ hemoglobin ■ lymphocytes ■ prognosis

In the United States, >5 million individuals have heart failure. Each year, 550 000 new cases are diagnosed, and there are ≈1 million hospitalizations. The direct and indirect costs of heart failure are estimated at $29 billion per year.1 Although heart failure presents enormous healthcare burdens, outcomes in heart failure are highly variable, with annual mortality varying from 5%2 to 75%.3 Physicians need to counsel patients about prognosis to enable informed decisions about medications, devices, transplantation, and end-of-life care.

Clinical Perspective p 1433

Existing models to predict the risk of death/urgent transplantation in heart failure all have features that may limit their applicability. These models relied on either peak oxygen consumption or invasive measures of cardiac performance,2 which were validated during a hospitalization for heart failure,4,5 have not been validated in another database,6 or may be inaccurate with β-blockers.7,8 The predictive accuracy of one such model, the Heart Failure Survival Score (HFSS), has been suboptimal in some validation data sets (Figure 1).

The purpose of this study was to develop and validate a multivariate risk model to estimate survival of heart failure patients that incorporates easily obtainable clinical and laboratory variables, heart failure medications, and devices.

Methods

Participants

The present study used data previously collected in 6 cohorts of patients with predominantly left ventricular systolic heart failure. One cohort was used to develop the model (the Prospective Randomized Amlodipine Survival Evaluation [PRAISE1]; n=1125), and

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5 other cohorts (n=9942) were used to prospectively validate the model. PRAISE1 was a randomized trial of amiodipine versus placebo among 1153 patients in the United States and Canada with ejection fraction (EF) <30% and New York Heart Association (NYHA) functional class IIIB to IV heart failure.9 We excluded 32 patients with incomplete baseline data. Evaluation of Losartan in the Elderly (ELITE2) was a randomized trial of captopril versus losartan among 3152 patients in 46 countries with EF <40%, age ≥60 years, and NYHA class II to IV heart failure.10 We excluded 165 patients with incomplete baseline data. Valsartan Heart Failure Trial (Val-HeFT) was a randomized trial of valsartan versus placebo in 5010 patients in 16 countries with EF ≤40 and NYHA class II to IV heart failure. Allopurinol use and implantable cardioverter/defibrillator (ICD) use were not available. We excluded 1 patient with probable data entry error for bumetidine.11 University of Washington (UW) was a prospective cohort study of 148 consecutive outpatients at a tertiary US heart failure clinic.12,13 Randomized Embrel North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) was a randomized trial of etanercept (Embrel, Amgen, Thousand Oaks, Calif) in 925 patients with NYHA class II to IV heart failure and EF ≤30 in the United States and Canada.14 Italian Heart Failure Registry (IN-CHF) is a database of consecutive heart failure patients seen by local participating cardiologists in Italy and entered into a national database. There were no exclusion criteria for entry in the registry, and patients with any heart failure etiology, age, EF, or comorbidities could be enrolled.15 For the IN-CHF, percent lymphocytes were imputed with the use of white blood cell count and other variables. Potassium-sparing diuretic use was not available. In UW, RENAISSANCE, and Val-HeFT, any patients with missing data were assigned the median value for the covariate in that data set, except for missing drug or device variables, in which case they were assigned no drug/device. The studies were approved by the institutional review boards of each participating institution, and all participants gave informed written consent. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

**Ascertainment of Events**

In PRAISE1, ELITE2, Val-HeFT, RENAISSANCE, and In-CHF, events were classified by a centralized adjudication committee.9–11,14,15 In the UW cohort, events were classified by one of the study cardiologists (W.C.L.) using review of medical records. For this analysis, the primary outcome was survival free of left ventricular assist device (LVAD) implantation or cardiac transplantation. Death, rather than LVAD implantation or transplantation, represented the majority of events (98%) in these data sets.

**Statistical Analysis**

A participant level database from PRAISE1 was used for derivation of the prediction model. All databases were deidentified. Clinical variables previously reported to be associated with mortality were evaluated with the use of the Cox proportional hazards model. In addition, diuretic type and dose were evaluated as predictors. Statistically significant univariate variables were visually inspected for linearity with the use of a plot of the variable by deciles versus the natural log of the hazard ratio. If the response appeared nonlinear, simple transformations or cut points were used. For each covariate, categorical variables and both the continuous and transformed univariate variables were allowed to enter in a stepwise forward multivariate Cox model with the use of a probability value of ≤0.05 for inclusion or deletion. The hazard ratio for certain heart failure medications and devices could not be effectively estimated in the PRAISE1 because of either widespread or rare use, including angiotensin-converting enzyme (ACE) inhibitors, β-blockers, angiotensin receptor blockers, aldosterone blockers, ICDs, biventricular pacing and LVADs. For these medications and devices, benefits were estimated from large published randomized trials or meta-analyses to determine the β-coefficients (natural log of the hazard ratio) for adding the medication/device to a patient’s regimen.3,10,15–29 For patients already on the medication/device, the impact of medication or device use on systolic blood pressure (SBP), NYHA class, and EF were incorporated into the estimate of the hazard ratio with the use of effects seen in large published trials. Thus, these hazard ratios were estimated from published results of clinical trials and not from the validation data sets.

To calculate the Seattle Heart Failure Model (SHFM) Score, each variable in the multivariate model was multiplied by its β-coefficient (natural log of the hazard ratio), and the products were summed.2,6 Baseline survival (survival for score=0) was estimated by Survival=t−e−λ·SHFM Score, where t=time and λ=the slope/year were derived from the PRAISE1 data (see Results; λ=0.0405). Survival at time t (between 0 and 5 years) for any score is estimated by the following equation:

\[
\text{Survival}(t) = e^{-e^{-0.0405 \cdot \text{SHFM Score}}
\]

The SHFM Score derived in PRAISE1 was then prospectively applied to each patient in ELITE2, UW, Val-HeFT, RENAIS-

SANCE, and IN-CHF to provide individual estimates of survival at 1, 2, 3, and 5 years. For each study, the predicted survival by deciles (quantiles for smaller studies) was plotted against the actual (Kaplan-Meier) survival, and at correlation coefficient and standard error of the estimate (SEE) was calculated. Accuracy of the model across data sets was determined by comparing the mean 1-, 2-, and 3-year predicted versus actual survival. Model discriminant ability was determined by the 1-year receiver operating characteristic (ROC) area under the curve for each data set and for all data sets combined. Mean survivals were estimated by integrating the area under the survival curve for an annual mortality ≥30%. Because the former method will overestimate years of life remaining for lower-risk patients, mean survival in these patients (annual mortality <30%) was estimated by using the predicted 5-year mortality from the model and then by deriving total years of life remaining by the mortality life table method,30 combining the most recent mortality tables available for the United States, England and Wales, West Germany, and France.31 The discriminative ability of the Seattle Heart Failure Model was compared with the Toronto4 and Acute Decompensated Heart Failure National Registry (ADHERE) heart failure models.5 For calculation of the Toronto model, comorbidities of cancer, stroke, dementia, cirrhosis, and chronic obstructive pulmonary disease were assumed to be absent, and the resting respiratory rate was ≤20. Statistics were analyzed with the use of Statview 5 (SAS Institute, Cary, NC), with ROC determined with the use of SPSS 11 (SPSS Inc, Chicago, Ill). Statistical significance was defined as P≤0.05 (2 tailed).
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PRAISE1</th>
<th>ELITE2</th>
<th>UW12</th>
<th>RENAISSANCE14</th>
<th>Val-HeFT11</th>
<th>IN-CHF15</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1125</td>
<td>2987</td>
<td>148</td>
<td>925</td>
<td>5010</td>
<td>872</td>
</tr>
<tr>
<td>Age, y</td>
<td>65±11</td>
<td>71±7</td>
<td>53±10</td>
<td>62±12</td>
<td>63±11</td>
<td>64±12</td>
</tr>
<tr>
<td>Range</td>
<td>23–95</td>
<td>52–100</td>
<td>19–74</td>
<td>N/A</td>
<td>18–96</td>
<td>14–93</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>76%</td>
<td>69%</td>
<td>78%</td>
<td>78%</td>
<td>80%</td>
<td>76%</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.6</td>
<td>2.5</td>
<td>2.7</td>
<td>2.9</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Range</td>
<td>38–4</td>
<td>2–4</td>
<td>1–4</td>
<td>2–4</td>
<td>2–4</td>
<td>1–4</td>
</tr>
<tr>
<td>EF</td>
<td>21±6</td>
<td>31±7</td>
<td>27±9</td>
<td>22±6</td>
<td>27±7</td>
<td>35±11</td>
</tr>
<tr>
<td>Range</td>
<td>1–32</td>
<td>4–40</td>
<td>3–53</td>
<td>N/A</td>
<td>4–40</td>
<td>10–75</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>64%</td>
<td>74%</td>
<td>34%</td>
<td>62%</td>
<td>58%</td>
<td>47%</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>118±18</td>
<td>134±19</td>
<td>105±15</td>
<td>109±17</td>
<td>123±18</td>
<td>129±22</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic dose, mg/kg</td>
<td>1.45±1.33</td>
<td>0.41±0.63</td>
<td>1.67±2.05</td>
<td>1.30±1.43</td>
<td>0.82±1.10</td>
<td>0.73±0.94</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>99%</td>
<td>50%</td>
<td>80%</td>
<td>79%</td>
<td>93%</td>
<td>84%</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0%</td>
<td>24%</td>
<td>72%</td>
<td>61%</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>0%</td>
<td>50%</td>
<td>26%</td>
<td>19%</td>
<td>50%</td>
<td>7%</td>
</tr>
<tr>
<td>K-sparing diuretic use</td>
<td>3%</td>
<td>22%</td>
<td>28%</td>
<td>35%</td>
<td>5%</td>
<td>N/A</td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>10%</td>
<td>4%</td>
<td>8%</td>
<td>12%</td>
<td>N/A</td>
<td>18%</td>
</tr>
<tr>
<td>Statin use</td>
<td>8%</td>
<td>13%</td>
<td>36%</td>
<td>52%</td>
<td>32%</td>
<td>16%</td>
</tr>
<tr>
<td>ICD</td>
<td>0%</td>
<td>0%</td>
<td>22%</td>
<td>18%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>139±4</td>
<td>141±4</td>
<td>137±3</td>
<td>139±3</td>
<td>139±3</td>
<td>140±4</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.37±0.48</td>
<td>1.17±0.33</td>
<td>1.25±0.39</td>
<td>1.26±0.43</td>
<td>1.29±0.31</td>
<td>1.27±0.69</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>202±50</td>
<td>207±46</td>
<td>186±55</td>
<td>182±44</td>
<td>205±71</td>
<td>193±46</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>8.9±2.6</td>
<td>6.3±2.0</td>
<td>7.9±2.8</td>
<td>8.4±2.5</td>
<td>7.5±2.1</td>
<td>6.9±2.2</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.9±1.7</td>
<td>14.0±1.6</td>
<td>13.1±1.8</td>
<td>13.8±1.6</td>
<td>13.7±1.4</td>
<td>13.6±1.8</td>
</tr>
<tr>
<td>White blood cells</td>
<td>7.7±2.3</td>
<td>7.2±2.1</td>
<td>7.4±2.3</td>
<td>7.7±2.1</td>
<td>6.9±2.0</td>
<td>7.5±2.2</td>
</tr>
<tr>
<td>Percent lymphocytes</td>
<td>26±9</td>
<td>25±12</td>
<td>22±9</td>
<td>24±8</td>
<td>25±9</td>
<td>25±4 (estimated)</td>
</tr>
</tbody>
</table>

N/A indicates data not available.

Results

Patient Characteristics and Events

The patients in PRAISE1 were younger than those in ELITE2 but had more severe heart failure by most clinical measures, including NYHA class, EF, SBP, and diuretic dose (Table 1). The patients in UW were younger but had lower SBP, hemoglobin, and percent lymphocytes; higher diuretic dose; and greater β-blocker, statin, and ICD use. The patients in RENAISSANCE had lower SBP and cholesterol and the highest use of potassium-sparing diuretics and statins. The patients in IN-CHF had the lowest NYHA class and highest EF, with one third having an EF ≥40%. The Val-HeFT patients were the largest group and were reflective of the broad range of systolic heart failure.

Derivation of the Model

The univariate and multivariate predictors of survival in PRAISE1 are shown in Table 2. In univariate analyses, older age, male gender, ischemic etiology, and lower body mass index, EF, blood pressure, serum sodium, cholesterol, hemoglobin, and percent lymphocytes were associated with increased mortality. Higher NYHA class, white blood cell count, creatinine, uric acid, and allopurinol use were also associated with increased mortality in univariate analysis. Conversion of the various weight-adjusted diuretic regimens into a uniform daily furosemide equivalent dose was performed by comparing the hazard ratio for the individual diuretics in the multivariate model on the basis of the PRAISE1 data. Thiazide diuretics only added risk in the model when added to a loop diuretic. The conversion used was furosemide 80 mg = torsemide 40 mg = bumetidine 3 mg = metolazone 2 mg = hydrochlorothiazide 25 mg. The furosemide equivalent doses of other thiazide and loop diuretics used in ELITE2 and IN-CHF were estimated with the use of Micromedex (Thomson Micromedex, Greenwood, Colo). The resulting calculated daily diuretic dose per kilogram of body weight was the most powerful univariate predictor of mortality (χ² = 77), with a 30% increase in risk of death for each 1 mg/kg per day. Statin use was associated with lower mortality, consistent with prior analyses.24 The 1/x transformations of EF and cholesterol had similar or greater χ² values in comparison to the continuous variables. For serum sodium, the increased risk was associated with values <138 mEq/L, whereas values ≥138 did not alter risk. Hemoglobin had a U-shaped relationship with mortality in univariate analysis (P = 0.001 for the hemoglobin² term) but...
was best fit with the use of a simple linear model >16 and <16 g/dL. Lymphocytes (>47%), uric acid (<3.4 mg/dL), and SBP (>160 mm Hg) were truncated for values outside the database and/or normal range (ie, SBP of 180 mm Hg was assigned a value of 160).

Age and gender were forced into the model as important demographic variables. Potassium-sparing diuretics were forced into the derivation model as a planned addition to the model based on external data. In the multivariate stepwise regression (Table 2, Figure 2), body mass index, blood urea

### TABLE 2. Univariate and Multivariate Predictors of Survival in PRAISE1 Derivation Cohort

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Wald $\chi^2$</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>Wald $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (decade)*</td>
<td>1.134 (1.034–1.245)</td>
<td>7.1</td>
<td>1.090 (0.985–1.205)</td>
<td>2.8</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.256 (0.986–1.599)</td>
<td>3.4</td>
<td>1.089 (0.839–1.414)</td>
<td>0.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.960 (0.943–0.979)</td>
<td>17.9</td>
<td>1.089 (0.839–1.414)</td>
<td>0.4</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.402 (1.546–3.734)</td>
<td>15.2</td>
<td>1.600 (1.019–2.511)</td>
<td>4.2</td>
</tr>
<tr>
<td>Ejection fraction (0–30)</td>
<td>0.971 (0.955–0.987)</td>
<td>12.0</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.483 (1.194–1.841)</td>
<td>12.7</td>
<td>1.354 (1.074–1.707)</td>
<td>6.6</td>
</tr>
<tr>
<td>SBP, 10 mm Hg* (for SBP &lt;160 mm Hg)</td>
<td>0.803 (0.755–0.855)</td>
<td>47.9</td>
<td>0.877 (0.823–0.935)</td>
<td>16.0</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic dose, mg/kg per day</td>
<td>1.305 (1.229–1.386)</td>
<td>77.0</td>
<td>1.178 (1.097–1.266)</td>
<td>20.0</td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>1.520 (1.144–2.021)</td>
<td>8.3</td>
<td>1.571 (1.170–2.109)</td>
<td>9.0</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.600 (0.390–0.922)</td>
<td>5.4</td>
<td>0.63 (0.410–0.978)</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>0.940 (0.916–0.965)</td>
<td>21.6</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.117 (1.074–1.162)</td>
<td>30.2</td>
<td>1.050 (1.005–1.097)</td>
<td>4.8</td>
</tr>
<tr>
<td>Cholesterol,* each 40 mg/dL</td>
<td>0.814 (0.744–0.890)</td>
<td>20.3</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>100/Cholesterol,*mg/dL</td>
<td>8.401 (4.16–16.968)</td>
<td>35.2</td>
<td>2.206 (1.045–4.656)</td>
<td>4.3</td>
</tr>
<tr>
<td>White blood cell</td>
<td>1.079 (1.036–1.123)</td>
<td>13.5</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>0.884 (0.833–0.937)</td>
<td>16.9</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>% Lymphocytes,* each 5% (for lymphocytes &gt;47%)*</td>
<td>0.823 (0.777–0.871)</td>
<td>44.9</td>
<td>0.897 (0.846–0.951)</td>
<td>13.2</td>
</tr>
<tr>
<td>Uric acid, mg/dL (for uric acid &gt;3.4)*</td>
<td>0.112 (1.008–1.16)</td>
<td>36.9</td>
<td>1.064 (1.022–1.108)</td>
<td>9.1</td>
</tr>
</tbody>
</table>

**Medications**

- ACE inhibitor 0.77$^{16}$ 0.77$^{15,17}$
- β-Blocker 0.66$^{19}$ 0.66$^{15,17}$
- Angiotensin receptor blocker 0.87$^{10,20,21}$ 0.85
- K-sparing diuretic 0.70$^{22}$ 0.74$^{23}$
- Statin 0.78$^{18}$ 0.63$^{24}$

**Devices**

- Biventricular pacemaker 0.74$^{25,26,28}$ 1.00
- Implantable cardioverter-defibrillator 0.74$^{27}$ 0.73$^{29}$
- Biventricular implantable cardioverter-defibrillator 0.64$^{25}$ 0.79
- Left ventricular assist device 0.52$^{25}$ N/A

Unadjusted and adjusted hazard ratios with 95% CIs are shown. A $\chi^2$ of $<4$ corresponds to a $P$ value $>0.05$. N/A indicates data not available.

*These characteristics were evaluated as continuous variables in the model. The Seattle Heart Failure Score is calculated with the use of the natural log of the multivariate hazard ratios that are in italic typeface as described in the online-only Data Supplement Appendix. The $\chi^2$ value is shown for adding each of the other variables individually to the Seattle Heart Failure Score. The hazard ratios for adding a medication or device or for a patient who is already on a medication or device were estimated from large randomized trials or meta-analyses (see Methods for details).
The overall model was highly significant, with Wald $\chi^2 = 208$. The baseline survival function was $e^{-0.0405 \times 1} (r=0.999)$. The predicted 1- and 2-year survival rates for the entire cohort were 73.4% and 56.7% versus actual survival of 74.3% and 56.0% (Table 3). The correlation between predicted and actual survival by deciles was 0.97, SEE = ±5% (Figure 3A).

### Validation of the Model

The Seattle Heart Failure Model was applied prospectively to ELITE2, Val-HeFT, UW, RENAISSANCE, and IN-CHF (Table 3). In ELITE2, the Wald $\chi^2$ of the score was 205. The predicted 1- and 2-year survivals for the entire cohort were 90.5% and 82.4% versus actual survival of 88.5% and 80.0%. The correlation between predicted and actual survival by deciles was 0.98, SEE = ±3% (Figure 3B). In Val-HeFT, the Wald $\chi^2$ of the score was 461. The predicted 1-, 2-, and 3-year survivals for the entire cohort were 90.9%, 83.3%, and 76.8% versus actual survival of 91.0%, 81.6%, and 71.7%. The correlation between predicted and actual survival by deciles was 0.98, SEE = ±3% (Figure 3C), although the model overestimated 3-year survival by ≈5%. In the UW study, the Wald $\chi^2$ was 30. The predicted 1-, 2-, and 3-year survivals for the entire cohort were 86.5%, 76.5%, and 68.6% versus actual survival of 86.5%, 79.7%, and 71.8%. The correlation between predicted and actual survival by quintiles was 0.99, SEE = ±2% (Figure 3D). In RENAISSANCE, the Wald $\chi^2$ was 78. The predicted 1- and 2-year survivals for the entire cohort were 83.8% and 72.3% versus actual survival of 83.3% and 65.4%. The correlation between predicted and actual survival by quintiles was 0.97, SEE = ±4% (Figure 3E). In IN-CHF, the Wald $\chi^2$ was 99. The predicted versus actual 1-year survivals for the entire cohort was 89.6% versus 86.7%. The correlation between predicted and actual survival by quintiles was 0.99, SEE = ±1% (Figure 3F).

### Performance of the Model in PRAISE1

The overall model was highly significant, with Wald $\chi^2 = 208$. The baseline survival function was $e^{-0.0405 \times 1} (r=0.999)$. The predicted 1- and 2-year survival rates for the entire cohort were 73.4% and 56.7% versus actual survival of 74.3% and 56.0% (Table 3). The correlation between predicted and actual survival by deciles was 0.97, SEE = ±5% (Figure 3A).
Figure 3. Predicted vs actual survival by deciles of survival in PRAISE1 (the derivation cohort) (A) and validation cohorts ELITE2 (B), Val-HeFT (C), UW (D), RENAISSANCE (E), and IN-CHF (F). G, Predicted vs actual 1-, 2-, and 3-year survival by deciles of survival in all 6 data sets combined. The diagonal line is the line of identity in all 7 graphs.
The Seattle Heart Failure Model (SHFM) is a tool that allows for the computation of estimated survival by hand, making it impractical for clinical use. A Web-based calculator was developed, which allows for a convenient interactive calculation of estimated survival, with the SHFM website (http://www.SeattleHeartFailureModel.org) providing access to this tool. The calculation of estimated survival included 14 continuous variables and 10 categorical values, making it impractical for clinical use.

The 6 data sets were combined into 1 data set. The predicted 1-, 2-, and 3-year survivals were 88.2%, 79.2%, and 71.8% versus actual survival of 87.8%, 77.6%, and 68.0% (Figure 3G). The overall fit by deciles was very good ($r=0.98$, $SEE=±3$) but with a slight underestimation of mortality, most evident at 2 and 3 years for lower-risk patients. The model overestimated survival by $≈2\%$ in the ELITE2 data set, as reflected by the mean 1-year survival. In Val-HeFT, the largest data set, the model correctly predicted 1-year survival and 2-year survival.

When we rounded each individual’s score to the nearest integer between $−1$ and $4$ (a natural log increase in risk $\approx2.7$-fold), the discriminatory power for overall mortality was excellent (Figure 4).

The 1-year ROC for PRAISE1, the derivation cohort, was 0.725 (95% CI, 0.69 to 0.76). In the validation cohorts, the 1-year ROC was 0.682 (95% CI, 0.65 to 0.73) for ELITE2, 0.810 (95% CI, 0.72 to 0.90) for UW, 0.682 (95% CI, 0.63 to 0.73) for RENAISSANCE, 0.694 (95% CI, 0.68 to 0.72) for Val-HeFT, and 0.749 (95% CI, 0.70 to 0.80) for IN-CHF. If outcomes in UW were restricted to death/LVAD/United Network for Organ Sharing (UNOS) 1 transplantations, with censoring alive for UNOS 2 transplantations, the 1-year ROC was 0.88 (95% CI, 0.80 to 0.96). The combined data set of all 6 trials had a 1-year ROC of 0.729 (95% CI, 0.714 to 0.744).

Four data sets (PRAISE1, Val-HeFT, IN-CHF, and UW) had data available to allow comparison of the Seattle Heart Failure Model with the ADHERE and the Toronto heart failure models. In these combined data sets, the 1-year ROC was 0.75 (95% CI, 0.73 to 0.77) for the Seattle Heart Failure Model, 0.59 (95% CI, 0.57 to 0.61) for the ADHERE model, and 0.68 (95% CI, 0.66 to 0.70) for the Toronto model.

**Practical Calculation of the Estimated Survival**

The calculation of estimated survival included 14 continuous variables and 10 categorical values, making it impractical for computer computation by hand (an example is provided in the online Data Supplement). A Web-based calculator (http://www.SeattleHeartFailureModel.org) allows for a convenient interactive calculation of estimated survival and also of the predicted effects on survival of adding (or subtracting) medications or devices to a patient’s regimen (Figures 5 and 6).

**Discussion**

The Seattle Heart Failure Score was derived in the PRAISE1 database and validated prospectively in 5 additional databases: ELITE2, Val-HeFT, UW, RENAISSANCE, and IN-CHF. It accurately predicts survival of heart failure patients with the use of commonly obtained clinical characteristics. Importantly, the validation cohorts included patients with a wide range of countries or origins (46), ages (14 to 100 years), EFs (1% to 75%), and heart failure symptoms (NYHA class I to IV), including patients at intermediate and higher risk in whom prediction of risk can be most problematic. Additionally, 2 of the validation cohorts consisted of patients from a more general population, followed either in a US heart failure clinic (UW) or Italian general cardiology clinics (IN-CHF), representing the populations in whom validation results may be most widely applicable. The model performed extremely well in these groups, among whom the ROC for predicting 1-year survival was highest (0.75 to 0.81).

The score indicated that NYHA class, ischemic etiology, diuretic dose, EF, SBP, sodium, hemoglobin, percent lymphocytes, uric acid, and cholesterol each had independent predictive power. Renal function was not an independent predictor, consistent with the HFSS but inconsistent with other models. In post hoc analyses, adding creatinine had little effect on the ROC (+0.001). Most previous heart failure risk models have not included medications and also required either invasive hemodynamic measurements or peak $V\dot{O}_2$. For example, peak $V\dot{O}_2$ was available in $<1\%$ of the patients in these 6 data sets (95 of 148 from UW) and did not add to the score in this small subset ($P=0.09$). In addition, the Seattle Heart Failure Model incorporates the most current data on medications and devices available in clinical practice.

The Seattle Heart Failure Model also had a higher ROC than the ADHERE or Toronto models applied to the same data sets. ADHERE and Toronto models were derived in hospitalized patients and have not been previously validated among nonhospitilized patients. The accuracy of the previously developed HFSS model has been suboptimal in valida-
tion data sets (Figure 1) and may be particularly problematic for patients on β-blockers.7,8

Neurohormones,33 cytokines,34 and peak \( V\dot{O}_2 \)2 are prognostically important in multivariate models, although recent studies have suggested that peak \( V\dot{O}_2 \) may have limited utility in patients on β-blockers.7,8 The HFSS, which includes peak \( V\dot{O}_2 \), had a 1-year ROC for death/LVAD/UNOS 1 transplantation of 0.69 to 0.762,8 versus 0.88 for the Seattle Heart Failure Model in a similar population (UW). Several variables in the Seattle Heart Failure Model may in part incorporate some of the prognostic power of neurohormones and cytokines, including SBP and sodium (associated with noradrenaline and renin35), diuretic dose (associated with renin35), and cholesterol, uric acid, percent lymphocytes, and hemoglobin (associated with tumor necrosis factor).13,34 In a previous publication from Val-HeFT, B-type natriuretic peptide (BNP) \( (P<0.0001) \) was added to a multivariate model, whereas renin \( (P=0.01) \) and norepinephrine \( (P=0.02) \) had modest effects.33 The addition of BNP in Val-HeFT to the Seattle Heart Failure Model increased the ROC by \( \approx 0.03 \).

The addition of peak \( V\dot{O}_2 \), BNP, and other inflammatory variables may add to the prognostic power of the score, and further investigation is warranted.

The Seattle Heart Failure Model also incorporates the use of medications and devices and predicts the associated change in survival. The inclusion of medications and devices in a prognostic heart failure model is critical because medications and devices are altered by healthcare providers to improve survival in their patients. Furthermore, such a model may facilitate translation of clinical trial results into clinical practice. Additional potential uses include educating patients about the preventive value of medications, listing patients for cardiac transplantation, comparing heart failure severity between various facilities, counseling patients about end-of-life issues, and selecting patients for device use or entry into clinical trials. The Seattle Heart Failure Model can also be updated as new heart failure medications or devices are available in the future.

Although the hazard ratios for individual components of the score may vary in specific databases, the ability of the overall score to predict survival was high in all 5 validation cohorts with minimal systematic bias. Similar results have been shown with the Framingham Coronary Heart Disease Score, in which the hazard ratios for individual components of the score varied between cohorts, but the overall Framingham Coronary Heart Disease Score performed well.36 However, the Framingham score required recalibration for ethnic populations with a markedly lower coronary heart disease risk.36 Whether the Seattle Heart Failure Model will need recalibration in different ethnic populations is unknown, but the model has been validated in data sets with patients from 46 countries.

**Limitations**

The hazard ratios for a subset of medications and devices were estimated from prior published literature, and results from prior clinical trials may not be generalizable to a wider population of heart failure patients. However, large observational databases of nonclinical trial heart failure patients have shown similar hazard ratios for ACE inhibitors, β-blockers, aldosterone blockers, and ICDs as seen in randomized clinical trials.3,10,15–29 Additionally, the model performed extremely well in all 5 validation cohorts, including studies of both heart failure clinic and community-based patients. The model does not provide an estimate of whether a heart failure medication/device can be safely added, which is a clinical judgment, but rather predicts benefit if it were added. The estimated benefit for medications was based on the doses used by patients in clinical trials, and effects may be different if higher or lower doses are used. The Seattle Heart Failure Model was developed and validated among outpatients participating in clinical trials, observational studies, or clinical registries, and the model may not be generalizable to hospitalized patients or

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**Figure 6.** The Seattle Heart Failure Model has been implemented as an interactive program that employs the Seattle Heart Failure Score to estimate mean, 1-, 2-, and 5-year survival and the benefit of adding medications and/or devices for an individual patient. This model is available at www.SeattleHeartFailureModel.org. ACE-I indicates ACE inhibitor; ARB, angiotensin receptor blocker; HCTZ, hydrochlorothiazide; Hgb, hemoglobin; and BiV, biventricular.
those with major life-altering comorbidities such as cirrhosis, renal failure, dementia, or cancer; inclusion of such comorbidities may add prognostic power to the Seattle Heart Failure Model. The potential benefit of statin therapy was based on the benefit on cardiac mortality in a meta-analysis.18 Two large clinical trials of statins in heart failure (Controlled Rosuvastatin Multinational Trial in Heart Failure [CORONA] and Gruppo Italiano per lo Studio della Sopravvenienza Nell’Infarto Miocardioco-Heart Failure [GISSI-HF]) are ongoing. The estimate of mean life-years is provided to illustrate the potential change in long-term mortality with the addition of medications/devices; however, the potential error for such long-term estimates may be large for very-low-risk patients. For the most accurate survival estimate, the score should be recalculated after changes in clinical status or medications/device. The benefit of heart failure medications/devices in diastolic heart failure is less certain because the score was derived and validated mainly in patients with systolic heart failure. However, the accuracy of the model was similar in the IN-CHF population, in whom one third of patients had an EF ≥40%.

In conclusion, the Seattle Heart Failure Model allows prediction of survival of heart failure patients with the use of easily obtained clinical characteristics. The model provides an accurate estimate of mean, 1-, 2-, and 3-year survival and allows estimation of effects of adding medications or devices to a patient’s regimen. Use of this model by both healthcare providers and their patients may facilitate estimation of prognosis, enhance compliance, and increase the use of life-saving medications and devices; further investigation of such potential benefits is needed.

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References


**CLINICAL PERSPECTIVE**

The number of individuals living with heart failure is steadily increasing. A well-validated method has not been available for healthcare providers to estimate the survival of a patient with heart failure. The Seattle Heart Failure Model, derived and validated in >11,000 patients, makes use of commonly assessed clinical variables such as age, gender, weight, systolic blood pressure, New York Heart Association functional class, ejection fraction, basic laboratory values, and heart failure medications and devices (eg, defibrillators and biventricular pacemakers) to provide an estimate of survival in patients with heart failure. The effect on survival of adding medications and devices to the patient’s regimen can be estimated, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, β-blockers, statins, aldosterone blockers, biventricular pacemakers, defibrillators, and left ventricular assist devices. For example, a heart failure patient with an estimated 20% annual mortality would have an average survival of ~4 years without treatment. The addition of an ACE inhibitor, β-blocker, and aldosterone blocker would reduce the predicted annual mortality from 20% to 8%, adding ~4 additional years of life. The authors anticipate that the model could be commonly used in clinical practice to estimate the survival of heart failure patients and illustrate the estimated benefit of adding medications/devices to a given patient’s regimen.