What Influences Survival in Heart Failure?

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San Francisco General Hospital

Speaker Disclosures: None
What Influences Survival in Heart Failure?

2007 Scientific Sessions of the American Heart Association (Orlando)

Abstract 1701: Soluble Receptor for Advanced Glycation End Products (RAGE) Is a Prognostic Factor for Heart Failure

Abstract 1713: Does Body Composition Impact Survival In Patients with Advanced Heart Failure

Abstract 1945: Levels of Circulating Progenitor Cells in Patients with Chronic Heart Failure Predict Outcomes

Abstract 2190: Anemia and Survival in Chronic Heart Failure: Meta-Analysis

Abstract 2502: Renal Dysfunction Is Associated with Increased Risk of Fatal and Non-Fatal Cardiovascular Events in Patients with Heart Failure And Preserved Ejection Fraction - Findings from the Irbesartan in Heart Failure With Preserved Systolic Function Trial (I-PRESERVE)
What Influences Survival in Heart Failure?

Influence of Obstructive Sleep Apnea on Mortality in Heart Failure Patients


Figure 2: Multivariable Cox Proportional Hazards Survival Plots for Patients With M-NSA Versus Untreated OSA
What Influences Survival in Heart Failure?

Limitations of Ejection Fraction for Prediction of Sudden Death Risk in Patients with Coronary Artery Disease: Lessons from the MUSTT Study

Buxton AE et al., J. Am. Coll. Cardiol. 2007;50:1150-1157

Example A
A 60-year-old patient with prior CABG, NSVT only documented within 10 days after CABG, EF 25%, narrow QRS complex, no inducible sustained VT, no current or past heart failure.

Parameter | Arrhythmic Death Score | Total Mortality Score
---|---|---
Age > 60 years | 15 | 5
EF < 25% | 15
Total score | 15 | 20

Figure 3 Example of a Low-Risk Patient With EF <30%

Example C.
A 80-year-old person has never undergone CABG, EF 30%, history of heart failure, currently NYHA class 2, with inducible VT, narrow QRS complex, documented NSVT.

Parameter | Arrhythmic Death Score | Total Mortality Score
---|---|---
Age > 65 years | 8 | 7
No prior CABG | 19 | 13
EF > 30% | 5 | 5
History of heart failure | 17 | 17
NYHA Class 2 | 5
Inducible VT | 17
NSVT not within 10 d of CABG | 17
Total score | 58 | 48

Figure 5 Example of a High-Risk Patient With EF >30%
The Seattle Heart Failure Model

TABLE 1. Potential Benefits of Using Prognostic Models for Heart Failure

<table>
<thead>
<tr>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allows patients and families to have a realistic expectation of the prognosis</td>
</tr>
<tr>
<td>Allows appropriate allocation of resources, including transplantation, mechanical circulatory assist devices, and implantable defibrillators</td>
</tr>
<tr>
<td>Allows selection of therapies most likely to positively affect the quality and quantity of life</td>
</tr>
<tr>
<td>Promotes open, honest communication between clinicians, patients, and their families to define the goals of therapy</td>
</tr>
</tbody>
</table>

Goldberg LR and Jessup M, Circulation 2006;116:360-362
The Seattle Heart Failure Model

Derivation of Prediction Model

Participant level database from PRAISE1 was used for derivation.

Clinical variables previously reported to be associated with mortality were evaluated with the use of the Cox proportional hazards model.

Some hazard ratios could not be effectively estimated in the PRAISE1 because of widespread or rare use, including ACE inhibitors, β-blockers, angiotensin receptor blockers, aldosterone blockers, aldosterone blockers defibrillators, biventricular pacemakers, and left ventricular assist devices.

For these medications and devices, benefits were estimated from large published randomized trials or meta-analyses to determine β-coefficients (natural log of the hazard ratio) for adding interventions to patient regimen.

Levy WC et al. Circulation 2006;113:1424-1433
PRAISE: Prospective Randomized Amlodipine Survival Evaluation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>Ischemic Stratum</th>
<th>Nonischemic Stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Amlodipine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.7±0.5</td>
<td>64.7±0.5</td>
<td>67.3±0.5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>453/129</td>
<td>422/149</td>
<td>304/66</td>
</tr>
<tr>
<td>NYHA class (no. of patients)</td>
<td>471</td>
<td>460</td>
<td>295</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>111</td>
<td>75</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>117.3±0.7</td>
<td>117.8±0.8</td>
<td>116.6±0.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.0±0.5</td>
<td>72.5±0.4</td>
<td>70.9±0.6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>82.9±0.7</td>
<td>83.2±0.7</td>
<td>80.8±0.7</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.57±0.01</td>
<td>0.56±0.01</td>
<td>0.56±0.01</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td><strong>0.21±0.01</strong></td>
<td><strong>0.21±0.01</strong></td>
<td><strong>0.21±0.01</strong></td>
</tr>
<tr>
<td>Other medications (% of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Diuretics</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Dose of digoxin (mg/day)</td>
<td>0.20±0.01</td>
<td>0.20±0.01</td>
<td>0.19±0.01</td>
</tr>
<tr>
<td>Dose of captopril (mg/day)</td>
<td>81</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>Dose of enalapril (mg/day)</td>
<td>14</td>
<td>15</td>
<td>13</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SE. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

Exclusion Criteria

Uncorrected primary valve disease
Active myocarditis
Constrictive pericarditis
History of cardiac arrest
Ventricular fibrillation or ventricular tachycardia during previous year
Unstable angina or acute myocardial infarction during previous month
Cardiac revascularization or stroke during previous 3 months
Severe pulmonary, renal, or hepatic disease
Systolic blood pressure lower than 85 mmHg or higher than 159 mmHg
Diastolic blood pressure higher than 89 mmHg
Serum creatinine concentration higher than 3.0 mg/dL
Serum K⁺ concentration higher lower than 3.5 or higher than 5.5 mmol/L
Beta-blockers, calcium-channel blockers, or class 1C antiarrhythmics
Intravenous diuretic or vasodilator within past 24 hours
Intravenous positive inotropic agents within past 72 hours
Time to First Primary Event (Death or Cardiovascular Morbidity) among 571 Patients with Heart Failure Receiving Amlodipine and 582 Receiving Placebo

Kaplan-Meier Plots of Cumulative Survival in Amlodipine and Placebo Groups

Kaplan-Meier Plots of **Cumulative Survival**
in Amlodipine and Placebo Groups

Ischemic Cardiomyopathy

Kaplan-Meier Plots of **Cumulative Survival** in Amlodipine and Placebo Groups

Nonischemic Cardiomyopathy

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Wald $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (decade)*</td>
<td>1.134 (1.034–1.245)</td>
<td>7.1</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.256 (0.986–1.599)</td>
<td>3.4</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>0.960 (0.943–0.979)</td>
<td>17.9</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.402 (1.546–3.734)</td>
<td>15.2</td>
</tr>
<tr>
<td>Ejection fraction (0–30)</td>
<td>0.971 (0.955–0.987)</td>
<td>12.0</td>
</tr>
<tr>
<td>100/Ejection fraction</td>
<td>1.023 (1.009–1.038)</td>
<td>10.2</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.483 (1.194–1.841)</td>
<td>12.7</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>
</tr>
</tbody>
</table>

### Medications

<table>
<thead>
<tr>
<th>Medications</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Wald $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic dose, mg/kg per day</td>
<td>1.305 (1.229–1.386)</td>
<td>77.0</td>
</tr>
<tr>
<td>Allopurinol use</td>
<td>1.520 (1.144–2.021)</td>
<td>8.3</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.600 (0.390–0.922)</td>
<td>5.4</td>
</tr>
</tbody>
</table>

### Laboratory

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Wald $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L</td>
<td>0.940 (0.916–0.965)</td>
<td>21.6</td>
</tr>
<tr>
<td>If sodium &lt;138, 138–sodium</td>
<td>1.117 (1.074–1.162)</td>
<td>30.2</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.554 (1.319–1.831)</td>
<td>27.9</td>
</tr>
<tr>
<td>Cholesterol,* each 40 mg/dL</td>
<td>0.814 (0.744–0.890)</td>
<td>20.3</td>
</tr>
<tr>
<td>100/Cholesterol,*mg/dl</td>
<td>8.401 (4.16–16.968)</td>
<td>35.2</td>
</tr>
<tr>
<td>White blood cell</td>
<td>1.079 (1.036–1.123)</td>
<td>13.5</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>0.884 (0.833–0.937)</td>
<td>16.9</td>
</tr>
<tr>
<td>If hemoglobin &lt;16, 16–hemoglobin</td>
<td>1.186 (1.110–1.266)</td>
<td>25.9</td>
</tr>
<tr>
<td>If hemoglobin &gt;16, hemoglobin&lt;16</td>
<td>1.363 (1.038–1.79)</td>
<td>5.0</td>
</tr>
<tr>
<td>% Lymphocytes,* each 5% (for lymphocytes &lt;47%)*</td>
<td>0.823 (0.777–0.871)</td>
<td>44.9</td>
</tr>
<tr>
<td>Uric acid, mg/dL (for uric acid &gt;3.4)*</td>
<td>1.12 (1.008–1.16)</td>
<td>36.9</td>
</tr>
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<td>Demographic</td>
<td>Univariate Hazard Ratio (95% CI)</td>
<td>Multivariate Hazard Ratio (95% CI)</td>
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</table>

* Denotes significant predictors.
# The Seattle Heart Failure Model

## Derivation of Prediction Model

<table>
<thead>
<tr>
<th>Medications</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>0.77&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0.66&lt;sup&gt;19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>0.87&lt;sup&gt;10,20,21&lt;/sup&gt;</td>
</tr>
<tr>
<td>K-sparing diuretic</td>
<td>0.70&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Statin</td>
<td>0.78&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Devices</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biventricular pacemaker</td>
<td>0.74&lt;sup&gt;25,26,28&lt;/sup&gt;</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>0.74&lt;sup&gt;27&lt;/sup&gt;</td>
</tr>
<tr>
<td>Biventricular implantable cardioverter-defibrillator</td>
<td>0.64&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Left ventricular assist device</td>
<td>0.52&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Levy WC et al. Circulation 2006;113:1424-1433
The Seattle Heart Failure Model

Validation of Prediction Model

Levy WC et al. Circulation 2006;113:1424-1433
The Seattle Heart Failure Model

Practical Calculation of the Estimated Survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>Baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>2 Year</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>5 Year</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>2 Year</td>
<td>39%</td>
<td>39%</td>
</tr>
<tr>
<td>5 Year</td>
<td>71%</td>
<td>71%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean life expectancy</th>
<th>Baseline</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.8 years</td>
<td>3.8 years</td>
</tr>
</tbody>
</table>

![Image of calculations and data input fields]

Clinical
- Age: 60
- Gender: Male
- NYHA Class: 3B
- Weight (kg): 80
- EF: 20
- Syst BP: 120
- ischemic

Medications
- ACE-I
- Beta-blocker
- ARB
- Statin
- Aldosterone blocker

Diuretics
- Furosemide: 40
- Bumetanide: 0
- Torsemide: 0
- Metolazone: 0
- HCTZ: 0

Lab Data
- Hgb (g/dL): 13.6
- Lymphocyte %: 24
- Uric Acid (mg/dL): 6.5
- Total Chol (mg/dL): 206
- Sodium: 137
- QRS > 120 msec

Devices
- None
- BiV Pacer
- ICD
- BiV ICD

Interventions
- ACE-I
- ARB
- Beta-blocker
- Statin
- Aldosterone blocker

Note: Some devices may be disabled if CMS clinical criteria are not met.

http://www.SeattleHeartFailureModel.org
The Seattle Heart Failure Model

Practical Calculation of the Estimated Survival

http://www.SeattleHeartFailureModel.org
The Seattle Heart Failure Model

Practical Calculation of the Estimated Survival
The Seattle Heart Failure Model

Discussion Points

The Seattle Heart Failure Model accurately predicts the survival of heart failure patients with the use of commonly obtained clinical characteristics.

The validation cohorts included patients with a wide range of countries or origins, ages, ejection fractions, and heart failure symptoms (NYHA I to IV).

Renal function was not an independent predictor of survival in heart failure patients, consistent with the HFSS, but not consistent with different models.

The Seattle Heart Failure Model showed a higher ROC than either ADHERE or Toronto models with each applied prospectively to the identical data sets.

Levy WC et al. Circulation 2006;113:1424-1433
The Seattle Heart Failure Model

Limitations of Model

Hazard ratios for a subset of medications and devices were estimated from prior published literature and may not be generalizable to wider populations.

The model does not generate an estimate of whether a therapy can be added safely, a clinical judgment, but rather predicts the survival effect were it added.

The estimate of mean life-years is provided to illustrate potential changes in long-term survival with therapeutic interventions but is highly subject to error.

Benefits of heart failure medications or devices in diastolic heart failure are less certain because the score was validated in systolic heart failure patients.

Levy WC et al. Circulation 2006;113:1424-1433
The Seattle Heart Failure Model

TABLE 2. Hazards of Using Prognostic Models for Heart Failure

<table>
<thead>
<tr>
<th>Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>The model was derived from a different population of patients</td>
</tr>
<tr>
<td>Patient compliance, preferences, or attitudes are not incorporated</td>
</tr>
<tr>
<td>New therapies become available, making the models obsolete</td>
</tr>
<tr>
<td>The patient is not compensated or on evidence-based therapies</td>
</tr>
<tr>
<td>Scores from the models will replace informed, compassionate, clinician–patient conversations</td>
</tr>
</tbody>
</table>

Goldberg LR and Jessup M, Circulation 2006;116:360-362
The Seattle Heart Failure Model

Prediction of Mode of Death in Heart Failure

Prospectively collected information from ambulatory heart failure patients with predominantly systolic dysfunction enrolled in 6 randomized trials or registries: PRAISE, ELITE2, Val-HeFT, RENAISSANCE, UW, & IN-CHF.

Exclusions: 110 subjects with NYHA class I heart failure

196 subjects with implantable cardioverter-defibrillators

222 subjects with missing risk factor data

203 subjects with missing data on mode of death

Mode of death was classified as sudden death, pump failure, or other death.

The Seattle Heart Failure Model

Prediction of Mode of Death in Heart Failure

| TABLE 2. Relative Risk of Sudden Death and Pump Failure Death According to the SHFM Score Among 10,538 Patients With Heart Failure |
|---|---|---|---|---|---|---|
| | SHFM Score |
| | 0 (n=4043) | 1 (n=4356) | 2 (n=1729) | 3 (n=361) | 4 (n=49) | P for Trend |
| Sudden death |
| No. of events | 265 | 407 | 242 | 90 | 10 | ... |
| Incidence rate, per 100 person-years | 3.8 | 5.8 | 10.3 | 25.1 | 24.9 | ... |
| Relative risk (95% CI) | 1.0 (reference) | 1.5 (1.3–1.8) | 2.7 (2.3–3.2) | 6.5 (5.1–8.3) | 6.5 (3.5–12.2) | <0.001 |
| Pump failure death |
| No. of events | 56 | 227 | 273 | 102 | 26 | ... |
| Incidence rate, per 100 person-years | 0.8 | 3.2 | 11.7 | 28.4 | 64.7 | ... |
| Relative risk (95% CI) | 1.0 (reference) | 4.1 (3.1–5.5) | 15.0 (11.2–20.0) | 48.4 (27.6–53.2) | 87.6 (54.9–139.9) | <0.001 |

The Seattle Heart Failure Model

Prediction of Mode of Death in Heart Failure

**TABLE 2. Relative Risk of Sudden Death and Pump Failure Death According to the SHFM Score Among 10,538 Patients With Heart Failure**

<table>
<thead>
<tr>
<th></th>
<th>SHFM Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n=4043)</td>
</tr>
<tr>
<td>Sudden death</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>265</td>
</tr>
<tr>
<td>Incidence rate, per 100 person-years</td>
<td>3.8</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Pump failure death</td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>56</td>
</tr>
<tr>
<td>Incidence rate, per 100 person-years</td>
<td>0.8</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

Prediction of Mode of Death in Heart Failure

Graph 1: Proportion of Total One Year Mortality (%)
- Other Death
- Sudden Death
- Pump Failure Death

Graph 2: Absolute Risk of One Year Mortality (%)

Seattle Heart Failure Model Score
Prediction of Mode of Death in Heart Failure

Seattle Heart Failure Model Score

Rate of Sudden Death (No. per 100 person-yrs)

NYHA Class 2 (n=3,560) NYHA Class 3 (n=2,093) NYHA Class 4 (n=1,259)

Rate of Pump Failure Death (No. per 100 person-yrs)

NYHA Class 2 (n=3,560) NYHA Class 3 (n=2,093) NYHA Class 4 (n=1,259)
The Seattle Heart Failure Model

Prediction of Mode of Death in Heart Failure

Modes of death may have been misclassified, with potential resulting bias.

The addition of other laboratory measures, such as brain natriuretic peptide or inflammatory marker levels, might increase SHFM discriminatory power.

The participants were all ambulatory, and findings may not be generalizable to hospitalized heart failure patients or those with life-threatening co-morbidities.

Most patients had systolic heart failure, and validation of these observations in populations with predominantly diastolic heart failure will be necessary.

The great majority of participants (99%) were followed for less than 3 years.

The Seattle Heart Failure Model

Prediction of Mode of Death in Heart Failure

The absolute rates of sudden death and pump-failure death were similar among younger versus older patients, ischemic versus non-ischemic heart failure patients, patients with lower versus higher left ventricular ejection fraction, and patients who took K+-sparing diuretics versus patients who did not receive K+-sparing diuretics.

Evaluation of >2000 deaths among >10,000 patients provides power.

Investigation of the utility of the SHFM for prediction of clinical responses to heart failure therapies should be explored in future research, particularly in randomized trials (completed or planned) of specific drugs or devices.

Advances in Heart Disease