Application of the Seattle Heart Failure Model in Ambulatory Patients Presented to an Advanced Heart Failure Therapeutics Committee

Eiran Z. Gorodeski, MD, MPH; Eric C. Chu, MD; Chen H. Chow, MD; Wayne C. Levy, MD; Eileen Hsich, MD; Randall C. Starling, MD, MPH

Background—We sought to assess the predictive value of the Seattle Heart Failure Model (SHFM) when applied to ambulatory patients with advanced heart failure (HF) presented to an advanced HF therapeutics committee at a tertiary care US institution.

Methods and Results—We evaluated model discrimination and calibration in 215 consecutive ambulatory patients who were presented to the Cleveland Clinic advanced HF therapeutics committee between 2004 to 2007 for evaluation for advanced options including transplantation and ventricular assist device (VAD). Analyses were stratified by committee decision (not listed versus listed United Network of Organ Sharing [UNOS] Status 2). Eighty-five percent had 1 or no missing SHFM variables. The primary outcome was a composite of all-cause mortality, VAD, or urgent (UNOS Status 1) transplantation. During a median follow-up of 24 months, 68 died, 18 received VAD support, and 81 underwent heart transplantation. Discrimination was modest both for those not listed (c-index, 0.683 at 1 year and 0.648 at 2 years), and for those listed UNOS status 2 (c-index, 0.629 at 1 year and 0.628 at 2 years). Calibration was acceptable among those patients not listed for heart transplantation but with substantial underestimation of risk (ie, overestimation of survival free of VAD or urgent transplantation) among UNOS status 2 patients.

Conclusions—In ambulatory patients presented to an advanced HF therapeutics committee for evaluation for heart transplantation, the SHFM offers modest discrimination of risk for the primary composite outcome of mortality, VAD, or urgent transplantation, with underestimation of risk in those patients listed for nonurgent transplantation. Interpretation of risk prediction by the SHFM in this patient population must be done with caution. (Circ Heart Fail. 2010;3:706-714.)

Key Words: heart failure ■ risk prediction

Identification of individuals with advanced heart failure (HF) who are at high risk for poor outcomes is important for assessment of urgency and candidacy for heart transplantation and mechanical circulatory support.1 Heart transplant committees often struggle with candidacy decisions because assessment of prognosis is difficult.2 Current American College of Cardiology Foundation/American Heart Association and International Society for Heart and Lung Transplantation (ISHLT) HF guidelines reaffirm the importance of identifying high-risk individuals,3,4 but provide no standardized approach for the use of risk assessment tools. At our institution we use clinical assessment; laboratory values (brain natriuretic peptide, renal function, etc); peak Vo2; and the opinions and experience of an advanced heart failure therapeutics committee to risk-stratify ambulatory patients and make decisions regarding timing and suitability for advanced therapies.

Clinical Perspective on p 714

In an attempt to better predict an individual patient’s event-free survival, Levy et al5 developed the Seattle Heart Failure Model (SHFM), a multivariable risk model that predicts the 1-, 2-, and 3-year event-free survival of HF patients with the use of characteristics relating to clinical status, therapy, and laboratory findings (www.SeattleHeartFailureModel.org). Although this model was found to predict outcome adequately in various heart failure populations,6–10 it has not been externally validated in patients being presented to a heart transplant committee—a circumstance in which a valid risk-assessment tool may play a critical role in guiding decision-making.

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The online-only Data Supplement is available at http://circheartfailure.ahajournals.org/cgi/content/full/CIRCHEARTFAILURE.110.944280/DC1. © 2010 American Heart Association, Inc.

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The purpose of this study was to assess the predictive accuracy of the SHFM when applied to ambulatory patients with refractory HF presented to an advanced HF therapeutics committee at a high-volume US institution offering all modalities of treatment.

Methods
We included all consecutive patients presented to the Cleveland Clinic advanced HF therapeutics committee for the first time between January 2004 and December 2007. These patients were generally functionally impaired but ambulatory. The purpose of this multidisciplinary committee is to consider all options including medical, surgical, and device therapy as well as mechanical ventricular assist devices and heart transplantation. We excluded patients who were listed for urgent cardiac transplantation (United Network of Organ Sharing (UNOS) status because risk stratification for this critically ill cohort is less relevant. We further excluded those with any prior organ transplant, those with preexisting ventricular assist devices (VAD), and those considered for multigraft transplantation.

Variables required for validation of SHFM were age, sex, New York Heart Association (NYHA) class, weight, ejection fraction, systolic blood pressure, etiology of cardiomyopathy, medication use (ACE inhibitors, β-blockers, angiotensin II receptor blocker, statins, allopurinol, and aldosterone blockers), diuretic dose (furosemide, bumetanide, torsemide, metolazone, and hydrochlorothiazide), laboratory values (hemoglobin, lymphocyte percent, uric acid, total cholesterol, and sodium), and implanted device status.

The primary outcome, similar to the outcome used in the original SHFM publication, was the first occurrence of all-cause mortality, VAD, or urgent cardiac transplantation (defined as UNOS status 1 at transplantation) as assessed by hospital records and the Social Security Death Index. The secondary outcome was all-cause mortality, whereby patients who received a VAD or urgent cardiac transplantation were censored as alive. For both the primary composite outcome and secondary mortality outcome, patients who went on to receive UNOS status 2 transplantation were censored as alive at time of transplantation. These outcomes were identical to those used by Kalogeropoulos et al. We recognize that local factors, including organ allocation, VAD implant criteria, and physician preferences probably influenced the event rate.

A Seattle Heart Failure Score (SHFS) was calculated for each individual patient and then converted to 1- and 2-year event-free survival probabilities as detailed in the original SHFM publication. Eighty-five percent of patients had 1 or no missing SHFM variables. The highest burden of missing was uric acid (64%), total cholesterol (11%), and percent lymphocytes (10%). Other variables had <2% missing. Because of concern that SHFM variables would have been collected in greater proportion after the date of publication of the original SHFM manuscript, we examined the distribution of missingness in these variables over time and found that they were missing at random. This was done by plotting kernel density estimation for each variable stratified by calendar year and stratified at the date of publication of the original SHFM manuscript. Imputation for missing covariates was performed in R, using the aregImpute multiple imputation function from Harrell’s Hmisc package. For purposes of comparison, we also calculated the Heart Failure Survival Score (HFSS) for each individual patient by use of the following variables: etiology of cardiomyopathy, serum sodium concentration, resting heart rate, mean arterial pressure, presence of interventricular conduction delay, ejection fraction, and peak oxygen consumption (peak V02). Of these, peak V02 had 35.8% missing data, which was imputed as described above. HFSS was then constructed by summing the products of these variables by their previously published coefficients.

Three additional predictors of risk were collected, including brain natriuretic peptide (BNP), blood urea nitrogen (BUN), and serum creatinine. All had <5% missing data, which were imputed as described above.

Statistical Analysis
We validated SHFM and HFSS models by assessing discrimination and calibration. To assess discrimination, we used Harrell’s concordance index (c-index), which is the ROC equivalent for right-censored data. Conservative estimates of c-index values were produced using out-of-bag estimation. In this approach, 1000 bootstrap samples of the data were derived and each sample was then split into test (“in-bag”) and training (“out-of-bag”) subsets. The test subset was used to construct a prediction model, which was then used to produce a c-index value in the training subset. Finally, the means and 95% confidence intervals of all 1000 c-index values were calculated. C-index values were calculated at 1 and 2 years.

To compare SHFM predicted probabilities with actual outcomes (ie, calibration), we grouped patients into quintiles according to

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
<th>Not Listed (n=110)</th>
<th>UNOS Status 2 (n=105)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>55 (46, 64)</td>
<td>54 (49, 63)</td>
<td>0.74</td>
</tr>
<tr>
<td>Male, %</td>
<td>82 (75)</td>
<td>83 (79)</td>
<td>0.44</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.20 (0.14, 0.25)</td>
<td>0.20 (0.15, 0.20)</td>
<td>0.87</td>
</tr>
<tr>
<td>Ischemic etiology, %</td>
<td>61 (55)</td>
<td>58 (55)</td>
<td>0.98</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>85 (71, 97)</td>
<td>83 (73, 95)</td>
<td>0.77</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>100 (90, 110)</td>
<td>101 (92, 109)</td>
<td>0.27</td>
</tr>
<tr>
<td>NYHA functional class ≥3</td>
<td>104 (95)</td>
<td>94 (90)</td>
<td>0.17</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>92 (84)</td>
<td>93 (89)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>14 (13)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Device, %</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>None</td>
<td>31 (28)</td>
<td>11 (10)</td>
<td></td>
</tr>
<tr>
<td>Defibrillator</td>
<td>47 (43)</td>
<td>49 (47)</td>
<td></td>
</tr>
<tr>
<td>Biventricular pacemaker/defibrillator</td>
<td>1 (4)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Medications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>62 (56)</td>
<td>71 (68)</td>
<td>0.09</td>
</tr>
<tr>
<td>β-blocker</td>
<td>79 (72)</td>
<td>88 (84)</td>
<td>0.04</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker</td>
<td>13 (12)</td>
<td>16 (15)</td>
<td>0.46</td>
</tr>
<tr>
<td>Statin</td>
<td>59 (54)</td>
<td>60 (57)</td>
<td>0.61</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>13 (12)</td>
<td>14 (13)</td>
<td>0.74</td>
</tr>
<tr>
<td>Aldosterone blocker</td>
<td>56 (51)</td>
<td>54 (51)</td>
<td>0.94</td>
</tr>
<tr>
<td>Furosomide equivalent, mg/kg</td>
<td>1.8 (0.5, 2.3)</td>
<td>1.2 (0.6, 1.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Inotrope infusion</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>12 (10, 13)</td>
<td>13 (12, 14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>18 (9, 23)</td>
<td>20 (13, 26)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>136 (132, 138)</td>
<td>136 (134, 139)</td>
<td>0.02</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>9 (7, 11)</td>
<td>9 (8, 10)</td>
<td>0.78</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>133 (103, 146)</td>
<td>150 (116, 173)</td>
<td>0.002</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.6 (1, 1.7)</td>
<td>1.3 (1, 1.4)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Continuous variables are presented as means (25th to 75th percentiles).
SHFM predicted probabilities and then compared the mean of the group with the actual observed Kaplan-Meier end point estimates at 1 and 2 years. HFSS calibration was based on 3 strata of risk defined in the original HFSS publication. We assessed whether known predictors of cardiovascular risk, including peak VO₂, BNP, BUN, and serum creatinine, added incremental value to SHFM by addressing changes in discrimination and reclassification of risk. The steps taken to do this are described in the Appendix.

Analyses were performed using R version 2.10.1 (www.r-project.org). We used Harrell’s Design and Hmisc libraries for modeling and graphics, as well as a macro written by Ishwaran for the out-of-bag estimation.

**Results**

**Patient Characteristics**

We identified 215 consecutive ambulatory patients who were presented to the Cleveland Clinic advanced HF therapeutics committee between January 2004 and December 2007 (Table 1). Of these, 105 were listed as UNOS status 2 and 110 were not considered transplant candidates at the time of the initial review. Reasons patients were declined from being listed included considered too well (12%), comorbid conditions (48%), psychosocial issues (21%), obesity (8%), high PRA titers (6%), advanced age (4%), and patient declined (1%). Although many patients had multiple contraindications for transplantation, these percentages reflect the primary reasons that patients were declined listing.

**Outcomes**

During a median follow-up of 24 months (range for survivors, 0.5 to 60 months), 68 patients died (32%), 18 received VAD support (8%), and 81 underwent heart transplantation (38%). Figure 1 details the outcomes stratified by listing status. Kaplan-Meier curves for the primary and secondary outcomes (Figure 2) were stratified by SHFS tertiles (Figure 3). The SHFM-estimated 1-year mortality was 33% (standard deviation ±28%) for those patients not listed and 16% (standard deviation ±14%) for those listed UNOS status 2.

**SHFM Performance**

Assessment of SHFM discrimination is presented in Table 2. In those patients deemed not be transplant candidates, model accuracy was modest both for the combined end point of death, urgent heart transplantation, or left VAD implantation (c-index, 0.683 at 1 year and 0.648 at 2 years) and the end point of death (c-index, 0.709 at 1 year and 0.666 at 2 years). In those patients listed as UNOS Status 2 for heart transplantation, model accuracy was modest (c-index, 0.629 at 1 year and 0.628 at 2 years) for the combined end point. Discrimination could not be ascertained for the outcome of death because there were only 2 deaths in this group (Figure 1A).

Assessments of how prediction compared with actual outcomes (calibration) at 1 and 2 years are presented in

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**Figure 1. CONSORT diagram.**
Figure 4. For the combined outcome, calibration was adequate for those patients deferred from listing, with systematic underestimation of risk (ie, overestimation of survival) for those listed UNOS Status 2 (Figure 4A and 4B). For the outcome of death, calibration was adequate for those patients deferred from listing. Calibration was not assessed for the outcome of death in those listed for transplantation because of the limited numbers of end points in this group.

We attained similar c-index values (0.614 and 0.647) when using the date of publication of the SHFM report arguing against a change in pattern of care delivery based on results of the SHFM.

Incremental Prognostic Value
We assessed whether BNP, serum creatinine, BUN, or peak VO₂ added incremental value to SHFS. Variables contributing to discriminative prediction are shown in Figure 5A and 5B. In addition to SHFS, BNP, and peak VO₂ contributed to discriminative prediction for combined outcome, whereas BNP and BUN did the same for mortality outcome.

We further assessed whether variables identified above had an impact on reclassification of risk at 1 year, beyond a model with SHFS alone. For composite outcome, neither BNP (net reclassification index [NRI], 0.05 \( P=0.7 \)); integrated discrimination improvement [IDI], 0.007 \( P=0.4 \)) nor peak VO₂ (NRI, 0.1 \( P=0.4 \); IDI, 0.002 \( P=0.7 \)) were found to significantly improve measures of reclassification. Similarly, BNP (NRI, 0.2 \( P=0.2 \); IDI, 0.01 \( P=0.3 \)) and BUN (NRI, 0.3 \( P=0.2 \), IDI 0.02 \( P=0.2 \)) did not significantly improve reclassification for mortality outcome.

HFSS Performance
Assessment of HFSS discrimination is presented in the Appendix Table. In those patients deemed not to be transplant candidates, model accuracy was modest both for combined end point (c-index, 0.616 at 1 year and 0.614 at 2 years) and death (c-index, 0.598 at 1 year and 0.606 at 2 years). In those patients listed as UNOS Status 2 for heart transplantation, model accuracy was very modest (c-index, 0.532 at 1 year and 0.522 at 2 years) for the combined end point.

Assessment of HFSS calibration at 1 year is presented in the Appendix (Figure). For both outcomes, there was underestimation of risk (ie, overestimation of survival) both for those deferred from transplantation and for those listed UNOS Status 2. This was more pronounced in the later group.
Discussion

We performed an external validation of the SHFM in consecutive ambulatory patients with systolic HF presented to a multidisciplinary advanced HF therapeutic committee for consideration of heart transplantation and/or mechanical circulatory support at a high-volume US institution. Overall, we found that the SHFM yielded only modest predictive accuracy (c-index range between 0.63 and 0.68) for the primary combined outcome, or the outcome of death alone. Correlation between predicted and observed risks (ie, calibration) was acceptable among those patients deferred from transplantation but with substantial underestimation of risk (ie, overestimation of survival) among those listed as UNOS status 2 for transplantation. Our findings further suggest that the SHFM really estimates mortality and that a combined end point of death, VAD, or urgent transplantation will have a substantially higher risk, depending on the proportion of patients who receive these treatments.

In additional analyses, we also found that 3 established cardiovascular risk factors (BNP, peak VO\textsubscript{2}, and BUN) improved discrimination beyond SHFS alone but did not appear to significantly improve reclassification of risk beyond a model with SHFS.

Last, we compared SHFM with the HFSS, another established risk model for patients with HF. In applying HFSS to our cohort, we found that it performed similarly or less well compared with SHFM.

The SHFM was derived from the PRAISE I database, which consisted of 1125 patients with left ventricular ejection fraction <30% and NYHA class IIIB-IV HF symptoms and validated in 5 other cohorts: ELITE2, Val-HeFT, RENAISSANCE, In-CHF, and the University of Washington outpatient HF clinic. Although the model was created to predict death, left VAD, or heart transplantation, the majority of events in all these cohorts was death (98%). Since the original publication, the SHFM has been validated in more than 3 other HF centers and found to be predictive of survival,

<table>
<thead>
<tr>
<th>Table 2. Predictive Accuracy of the Seattle Heart Failure Model in Ambulatory Patients Presented to an Advanced Heart Failure Therapeutics Committee</th>
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</thead>
<tbody>
<tr>
<td>Concordance Index†</td>
</tr>
<tr>
<td>Not listed</td>
</tr>
<tr>
<td>Combined end point*</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Listed, UNOS status 2</td>
</tr>
<tr>
<td>Combined end point*</td>
</tr>
</tbody>
</table>

*All-cause mortality, VAD implantation, or urgent cardiac transplantation (UNOS 1 at transplantation).†Out-of-bag estimates.
but these studies had few patients (<5%) who required urgent heart transplantation or mechanical circulatory support.6,10,18

Our study is consistent with previous work demonstrating underestimation of risk by the SHFM10 but is the first to assess the utility of the model to predict the combined end point of death, urgent heart transplantation, or VAD in a contemporary cohort of advanced ambulatory systolic HF patients with more than 40% requiring heart transplantation or VAD implantation. We limited our cohort to those who did not initially require urgent listing for heart transplantation (ie, UNOS status 1) because of the controversy regarding listing patients as UNOS status 219 and the challenge for transplant centers to predict survival in ambulatory patients who are referred for advance HF therapy. Although implantation of a VAD may be elective, the majority of the VADs implanted at the Cleveland Clinic were urgent (ie, equivalent to INTERMACS levels 1 and 2), and we only included heart transplantation as an end point if the patient deteriorated and became UNOS status 1.

Should the SHFM play a role in estimation of risk for patients being considered for advanced HF treatments including transplantation? Based on our findings, we believe that it can be used with caution. Among our UNOS status 2 patients, the concordance index was 0.63. This implies that for 2 randomly selected patients, if the patient with the shorter follow-up dies or has urgent transplantation or VAD implantation, then the SHFM had a 63% chance of predicting a longer end-point–free survival for the other patient. This represents a modest level of predictive accuracy, as the c-index ranges from 0.5 (chance) to 1.0 (perfect discrimination). As a comparison, the Framingham score had a discriminatory accuracy of approximately 0.75,20 whereas the TIMI risk score had a discriminatory accuracy of 0.65.21 Further, tests of calibration demonstrated underestimation of risk by the SHFM, most pronounced in the UNOS Status 2 patients. This may lead to more conservative decision-making by clinicians and advanced therapeutics committees. Outcomes with newer VADs have improved, and less-ill patients appear to have better outcomes; hence, a prediction model that underestimates risk could result in delayed referral of appropriate patients for this therapy.22,23

Figure 4. Calibration plots at 1 and 2 years for (A) composite outcome and (B) all-cause mortality.
An emerging role for the SHFM may be to determine the appropriateness of various therapeutic interventions. For example, the model was recently applied to determine potential benefit of implantable cardioverter-defibrillator therapy. It has also been suggested that SHFM can be used to identify patients who would benefit from VAD therapy. There has been recent interest in conducting a clinical trial of VAD therapy in less-ill patients, such as those NYHA class III or IV advanced HF patients who have not yet developed serious consequences from their disease and are not receiving inotropes. Our findings suggest that use of SHFM to assess inclusion into such a trial could potentially lead to enrollment of a higher-risk cohort (overestimation of event-free survival) than sought. We encourage investigators involved in contemporary clinical trials and registries to prospectively collect SHFM variables to allow future validation and model improvement efforts.

We believe that novel risk-prediction models specifically tailored for patients with advanced HF being considered for advanced therapeutic options are needed. Investigators constructing these should consider using cohorts enriched with patients who underwent VAD therapy and/or transplantation. They should use mortality as the primary end point, with VAD/transplant as competing risks, and consider a variety of recently identified predictors of cardiovascular risk possibly including laboratory values (markers of renal function, inflammatory and molecular markers, and hematologic markers), pathophysiological findings, exercise testing findings, and imaging findings.

Limitations of this study include a single-center experience, retrospective analysis of data, imputation of missing values, and a relatively small cohort. Most other studies validating the SHFM have been retrospective and consequently had missing data—most prominently, uric acid. This laboratory value was not routinely collected in our center between 2004 and 2007, and, consequently, we too had a large amount of missingness for uric acid (64% in our cohort). However, we had few other missing data with 85% of patients with either all data or only missing one variable (10% missing lymphocyte percent, 9% missing total cholesterol), unlike the REMATCH study that imputed 100% for 4 variables (furosemide dosing, lymphocyte percent, uric acid, and total cholesterol) and the largest published cohort assessing the SHFM in a community-based HF population, which had 72% patients missing NYHA, 35% missing lymphocyte percent, 66% missing uric acid, 25% missing LVEF, and 20% missing total cholesterol. Our cohort was relatively small, but, given the large number of events, it appears adequate as a single center study. We excluded patients who were listed for urgent transplantation (UNOS status 1) from the analyses but did not exclude the 2 inotrope-dependent patients in the deferred group who may have otherwise qualified for UNOS status 1. As such, model calibration for this subset may be slightly overestimated.

Figure 5. Change in prediction error in training (“out-of-bag”) data for (A) composite outcome and (B) all-cause mortality. Results based on 1000 bootstrapped samples.
In conclusion, in ambulatory patients with severe HF being presented to an advanced HF therapeutics committee, we found that the SHFM performed modestly in predicting outcomes, with underestimation of risk (ie, overestimation of survival free of VAD or urgent transplantation) in those patients deemed to be transplant candidates. Regardless, it outperformed a second well-established HF risk model, the HFSS. Interpretation of risk prediction by the SHFM in the setting of an advanced therapeutics committee evaluating ambulatory NYHA class III and IV patients must be done with caution.

Disclosures
Dr Levy received research support from HeartWare >$10,000; UW Tech Transfer holds the licensing rights to the Seattle Heart Failure Model; licensing fees from Epocrates were >$10,000; he serves on the steering committee for ASCEND-HF; Scios J&J <$10,000; RED-HF, Scios J&J <$10,000; Amgen, End Point Committee: CHAMPION–CardioMEMS >$10,000; he is on the speakers bureau for GSK >$10,000. Dr Starling received research support from Thoratec; he is a Medtronic advisory board member; consultant <$10,000 per year; he received research support from HeartWare and Syncardia; he serves on the UNOS Board of Directors, an unpaid position.

References


**CLINICAL PERSPECTIVE**

Identification of individuals with advanced heart failure who are at high risk for poor outcomes is important for assessment of urgency and candidacy for heart transplantation and mechanical circulatory support. The Seattle Heart Failure Model (SHFM) is a multivariable risk model that predicts event-free survival of patients with heart failure. We applied the SHFM to ambulatory patients with advanced heart failure who were presented to the advanced heart failure therapeutics committee at our institution. We found that SHFM offered modest discrimination of risk for the primary composite outcome of mortality, ventricular assist device, or urgent transplantation, with underestimation of risk in those patients listed for nonurgent transplantation. Clinicians can use the SHFM for patients being evaluated for advanced therapies but should interpret risk prediction with caution.
Application of the Seattle Heart Failure Model in Ambulatory Patients Presented to an Advanced Heart Failure Therapeutics Committee

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Appendix Figure. Calibration plots at 1-year for (A) composite outcome and (B) all-cause mortality. Low (43%, HFSS score ≤ 7.19), intermediate (72%, HFSS score 7.20-8.09), and high (93%, HFSS score ≥ 8.10) predicted risk cut points as published in original HFSS manuscript.
Methods appendix

Statistical approach used to assess incremental benefit of peak VO2, BNP, and BUN

We assessed whether known predictors of cardiovascular risk including, peak VO2, BNP, BUN, and serum creatinine, added incremental value to SHFM in a two step approach addressing changes in discrimination and reclassification of risk. First, we created Cox models containing these variables and calculated their out-of-bag c-index. We determined change in prediction error attributable to each variable by recalculating prediction error after random permutation of that variable in the training (“out-of-bag”) data. A variable with a high degree of importance would be expected to yield a greater change in the c-index.1 This process was repeated 1000 times for each variable. Second, variables identified by above procedure were assessed for their ability to reclassify risk beyond SHFM by use of net reclassification index (NRI), and integrated discrimination improvement (IDI).2 Because there are no established categories of risk for composite outcome or mortality in patients with advanced heart failure, NRI was calculated without cutoffs3 using Harrell’s improveProb function.4

References

**Appendix Table.** Side by side comparison of predictive accuracy of the Seattle Heart Failure Model (SHFM) and Heart Failure Survival Score (HFSS) in ambulatory patients presented to an advanced heart failure therapeutics committee.

<table>
<thead>
<tr>
<th></th>
<th>Seattle Heart Failure Model</th>
<th>Heart Failure Survival Score</th>
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</thead>
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<tr>
<td></td>
<td>Concordance Index⁺</td>
<td>Concordance Index⁺</td>
</tr>
<tr>
<td></td>
<td>At 1-year</td>
<td>At 2-years</td>
</tr>
<tr>
<td><strong>Not listed</strong></td>
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</tr>
<tr>
<td>Combined end point</td>
<td>0.683 (0.630-0.736)</td>
<td>0.648 (0.596-0.700)</td>
</tr>
<tr>
<td>Death</td>
<td>0.709 (0.650-0.768)</td>
<td>0.666 (0.604-0.728)</td>
</tr>
<tr>
<td><strong>Listed, UNOS status 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined end point</td>
<td>0.629 (0.566-0.692)</td>
<td>0.628 (0.569-0.687)</td>
</tr>
</tbody>
</table>

* All-cause mortality, VAD implantation, or urgent cardiac transplantation (UNOS 1 at transplantation).

* Out-of-bag estimates
Appendix Figure. HFSS Calibration plots.

At 1-Year

Observed survival free of VAD or urgent transplantation vs Predicted survival free of VAD or urgent transplantation.

- Not listed
- Listed, UNOS status 2