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

Running Title: Gorodeski et al: SHFM validation

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Abstract

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 Cleveland Clinic advanced HF therapeutics committee between 2004-2007 for evaluation for advanced options including transplantation and ventricular assist device (VAD). Analyses were stratified by committee decision (not listed vs. listed UNOS Status 2). Eighty five percent had one 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 amongst those patients not listed for heart transplantation, but with substantial underestimation of risk (i.e., overestimation of survival free of VAD or urgent transplantation) amongst 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 non-urgent transplantation. Interpretation of risk prediction by the SHFM in this patient population must be done with caution.

Key Words: heart failure, risk prediction
Introduction

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 as assessment of prognosis is difficult.² Current ACCF/AHA and ISHLT HF guidelines reaffirm the importance of identifying high-risk individuals³,⁴, 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.

In an attempt to better predict an individual patient’s event-free survival, Levy and colleagues⁵ 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). While this model was found to predict outcome adequately in various heart failure populations⁶-¹⁰, 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.

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 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 multi-disciplinary 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 1) since risk stratification for this critically ill cohort is less relevant. We further excluded those with any prior organ transplant, those with pre-existing ventricular assist devices (VAD), and those considered for multi-organ 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, beta-blockers, angiotensin II receptor blocker, statin, allopurinol, aldosterone blocker), diuretic dose (furosemide, bumetanide, torsemide, metolazone, hydrocholothiazide), laboratory values (hemoglobin, lymphocyte percent, uric acid, total cholesterol, 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 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 and colleagues.\textsuperscript{10} We recognize that local factors, including organ allocation, VAD implant criteria, and physician preferences likely 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.\textsuperscript{5}

Eighty five percent of patients had one or no missing SHFM variables. The highest burden of missing was uric acid (64%), total cholesterol (11%), and percent lymphocytes (10%). Other variables had \leq 2\% missing. Because of concern that SHFM variables would have been collected in greater proportion after date of publication of 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 date of publication of original SHFM manuscript. Imputation for missing covariates was performed in R, using the aregImpute multiple imputation function from Harrell’s Hmisc package.\textsuperscript{11, 12}

For purposes of comparison we also calculated the Heart Failure Survival Score (HFSS)\textsuperscript{13} 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 (IVCD), ejection fraction, and peak oxygen consumption (peak VO2). Of
these, peak VO2 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.13

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.11 Conservative estimates of c-index values were produced using out-of-bag estimation.14 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 mean and 95% confidence interval of all 1000 c-index values was calculated.15,16 C-index values were calculated at 1- and 2-years.

To compare SHFM predicted probabilities with actual outcomes (i.e., calibration) we grouped patients into quintiles according to SHFM predicted probabilities and then compared the mean of the group with the actual observed Kaplan-Meier endpoint estimates at 1- and 2-years. HFSS calibration was based on three strata of risk defined in the original HFSS publication.13
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\(^\text{11}\), as well as a macro written by Ishwaran\(^\text{15-17}\) for the out-of-bag estimation.

Results

Patient characteristics

We identified 215 consecutive ambulatory patients who were presented to 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 time of 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%). While 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 to be transplant candidates model accuracy was modest both for the combined endpoint of death, urgent heart transplantation, or LVAD implantation (c-index 0.683 at 1-year, and 0.648 at 2-years), and the endpoint 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 endpoint. Discrimination could not be ascertained for the outcome of death as 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 Figure 4. For the combined outcome, calibration was adequate for those patients deferred from listing, with systematic underestimation of risk (i.e., 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 due to 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 paper 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, while 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 (NRI 0.05 [P-value=0.7], IDI 0.007 [P-value=0.4]) nor peak VO2 (NRI 0.1 [P-value=0.4], IDI 0.002 [P-value 0.7]) were found to significantly improve measures of reclassification. Similarly, BNP (NRI 0.2 [P-value=0.2], IDI 0.01 [P-value=0.3]) and BUN (NRI 0.3 [P-value=0.2], IDI 0.02 [P-value=0.2]) did not significantly improve reclassification for mortality outcome.

HFSS performance

Assessment of HFSS discrimination is presented in Appendix Table. In those patients deemed not be transplant candidates model accuracy was modest both for combined endpoint (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 combined endpoint.

Assessment of HFSS calibration at 1-year is presented in Appendix Figure. For both outcomes there was underestimation of risk (i.e., 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 multi-disciplinary 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 (i.e., calibration) was acceptable amongst those patients deferred from transplantation, but with substantial underestimation of risk (i.e., overestimation of survival) amongst those listed as UNOS status 2 for transplantation. Our findings further suggest that the SHFM really estimates mortality and that a combined endpoint 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 three established cardiovascular risk factors (BNP, peak VO2, and BUN) improved discrimination beyond SHFS alone, but did not seem to significantly improve reclassification of risk beyond a model with SHFS.

Lastly, we compared SHFM to the Heart Failure Survival Score (HFSS), another established risk model for patients with heart failure. In applying HFSS to our cohort we found that it performed similarly or less well as compared to SHFM.
The SHFM was derived from the PRAISE I database which consisted of 1125 patients with LVEF <30% and NYHA class IIIB-IV HF symptoms and validated in five other cohorts: ELITE2, Val-HeFT, RENAISSANCE, In-CHF, and 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, but these studies had few patients (less than 5%) who required urgent heart transplantation or mechanical circulatory support.

Our study is consistent with previous work demonstrating underestimation of risk by the SHFM, but is the first to assess the utility of the model to predict the combined endpoint of death, urgent heart transplantation or VAD in a contemporary cohort of advanced ambulatory systolic HF patients with over 40% requiring heart transplantation or VAD implantation. We limited our cohort to those who did not initially require urgent listing for heart transplantation (i.e., UNOS status 1) due to the controversy regarding listing patients as UNOS status 2 and the challenge for transplant centers to predict survival in ambulatory patients who are referred for advance HF therapy. Although implantation of VAD may be elective, the majority of the VADs implanted at Cleveland Clinic were urgent (i.e., equivalent to INTERMACS level 1 and 2) and we only included heart transplantation as an endpoint 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. Amongst our UNOS status 2 patients the concordance index was 0.63. This implies that for two randomly selected patients, if the patient with the shorter follow-up suffers death, 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\textsuperscript{20}, while the TIMI risk score had a discriminatory accuracy of 0.65\textsuperscript{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.\textsuperscript{22, 23}

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 ICD therapy.\textsuperscript{24} It has also been suggested that SHFM can be used to identify patients who would benefit from VAD therapy.\textsuperscript{25, 26} 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 on 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 heart failure 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, 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 Seattle Heart Failure Model have been retrospective and consequently had missing data, most prominently uric acid. This lab value was not routinely collected in our center between 2004-2007, 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 four variables (furosemide dosing, lymphocyte percent, uric acid, and total cholesterol) and the largest published cohort assessing the Seattle Heart Failure Model in a community based heart failure population which had 72% patients missing NYHA, 35% missing lymphocyte percent, 66% missing uric acid, 25% missing
LVEF, and 20% missing total cholesterol⁶. 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 over-estimated.

In conclusion, in ambulatory patients with severe heart failure being presented to an advanced heart failure therapeutics committee, we found the SHFM performed modestly in predicting outcomes, with underestimation of risk (i.e., overestimation of survival free of VAD or urgent transplantation) in those patients deemed to be transplant candidates. Regardless, it out-performed a second well established heart failure 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

Eiran Z. Gorodeski  None
Eric C. Chu  None
Chen H. Chow  None

Wayne C. Levy
Research Support:  HeartWare>$10,000
UW Tech Transfer holds the licensing rights to the Seattle Heart Failure Model:
Licensing fees from Epocrates >$10,000
Steering Committee:  ASCEND-HF, Scios J&J <$10,000
RED-HF, Scios J&J <$10,000 Amgen
End Point Committee: CHAMPION - CardioMems >$10,000
Speakers Bureau:  GSK>$10,000

Eileen Hsich  None

Randall C. Starling
Thoratec:  Sponsored research
Medtronic:  Advisory board member, consultant: modest <$10,000 per year
HeartWare:  Sponsored research
Syncardia:  Sponsored research
UNOS:  Board of directors; unpaid position
References


6. May HT, Horne BD, Levy WC, Kfoury AG, Rasmusson KD, Linker DT, Mozaffarian D, Anderson JL, Renlund DG. Validation of the seattle heart failure model in a community-


Table 1. Baseline characteristics

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<th>Not listed (n=110)</th>
<th>Listed, UNOS status 2 (n=105)</th>
<th>P-Value</th>
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<td>Age, yrs</td>
<td>55 (46, 64)</td>
<td>54 (49, 63)</td>
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<td>Male, %</td>
<td>82 (75)</td>
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<td>Ejection fraction</td>
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<td>58 (55)</td>
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<td>Weight, kg</td>
<td>85 (71, 97)</td>
<td>83 (73, 95)</td>
<td>0.77</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>101 (92, 109)</td>
<td>0.27</td>
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<td>94 (90)</td>
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<td>Device, %</td>
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<td>Beta-blocker</td>
<td>79 (72)</td>
<td>88 (84)</td>
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<td>Treatment</td>
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<td>Study 2</td>
<td>p-value</td>
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<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
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<tr>
<td>Angiotensin II receptor blocker</td>
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<td>Aldosterone blocker</td>
<td>56 (51)</td>
<td>54 (51)</td>
<td>0.94</td>
</tr>
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<td>Furosemide equivalent, mg/kg</td>
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<tr>
<td>Inotrope infusion</td>
<td>2 (2)</td>
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Laboratory values

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<th>Study 2</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12 (10, 13)</td>
<td>13 (12, 14)</td>
<td>&lt;0.001</td>
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<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>
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<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-75th percentile)
Table 2. Predictive accuracy of the Seattle Heart Failure Model in ambulatory patients presented to an advanced heart failure therapeutics committee.

<table>
<thead>
<tr>
<th></th>
<th>Concordance Index+</th>
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<tr>
<td></td>
<td>At 1-year</td>
</tr>
<tr>
<td><strong>Not listed</strong></td>
<td></td>
</tr>
<tr>
<td>Combined end point*</td>
<td>0.683 (0.630-0.736)</td>
</tr>
<tr>
<td>Death</td>
<td>0.709 (0.650-0.768)</td>
</tr>
<tr>
<td><strong>Listed, UNOS status 2</strong></td>
<td></td>
</tr>
<tr>
<td>Combined end point*</td>
<td>0.629 (0.566-0.692)</td>
</tr>
</tbody>
</table>

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

+ Out-of-bag estimates
Figure Legends

**Figure 1.** CONSORT diagram.

**Figure 2.** Kaplan-meier plots for (A) composite outcome and (B) all-cause mortality.

**Figure 3.** Kaplan-meier plots stratified by SHFS tertiles for (A) composite outcome and (B) all-cause mortality.

**Figure 4.** Calibration plots at 1- and 2-years for (A) composite outcome and (B) all-cause mortality.

**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.
Figure 1. CONSORT diagrams

A.

- **Alive without VAD or Transplant** 
  - n=21
  - Transplanted UNOS 1 
    - n=8
    - Died Post-Tx 
      - n=3
  - Transplanted UNOS 2 
    - n=1
    - Died Post-Tx 
      - n=1
  - Listed UNOS 2 
    - n=105
    - VAD 
      - n=32
      - Died 
        - n=2
    - Transplanted UNOS 1 
      - n=40
      - Died 
        - n=5
  - Died on waiting list 
    - n=2

B.

- **Alive without VAD or Transplant** 
  - n=56
  - Transplanted UNOS 1 
    - n=2
    - Died Post-Tx 
      - n=1
  - Not listed 
    - n=110
    - VAD 
      - n=8
      - Died 
        - n=3
    - Died 
      - n=46
Figure 3.

A. Survival free of VAD or urgent transplantation, with survival rates shown for different groups. The p-value is less than 0.001.

B. Survival rates showing similar trends with survival rates at different time points.
Figure 4. Calibration plots.
Figure 5. Change in prediction error.
Application of the Seattle Heart Failure Model in Ambulatory Patients Presented to an Advanced Heart Failure Therapeutics Committee


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http://circheartfailure.ahajournals.org/content/early/2010/08/26/CIRCHEARTFAILURE.110.944280

Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2010/08/26/CIRCHEARTFAILURE.110.944280.DC1

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Supplemental Material

Legend

Appendix Figure. Calibration plots at 1-year for (A) composite outcome and (B) all-cause mortality. Low (43%, HFSS score \( \leq 7.19 \)), intermediate (72%, HFSS score 7.20-8.09), and high (93%, HFSS score \( \geq 8.10 \)) 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>
</tr>
</thead>
<tbody>
<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>Not listed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined end point</td>
<td>0.683 (0.630-0.736)</td>
<td>0.648 (0.596-0.700)</td>
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<tr>
<td>Death</td>
<td>0.709 (0.650-0.768)</td>
<td>0.666 (0.604-0.728)</td>
</tr>
<tr>
<td>Listed, UNOS status 2</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.

- Black line: Not listed
- Red line: Listed, UNOS status 2

At 1-Year

Observed survival vs. Predicted survival.