Prediction of Mode of Death in Heart Failure

The Seattle Heart Failure Model

Dariush Mozaffarian, MD, DrPH; Stefan D. Anker, MD; Inder Anand, MD; David T. Linker, MD; Mark D. Sullivan, MD, PhD; John G.F. Cleland, MD; Peter E. Carson, MD; Aldo P. Maggioni, MD; Douglas L. Mann, MD; Bertram Pitt, MD; Philip A. Poole-Wilson, MD; Wayne C. Levy, MD

Background—Prognosis and mode of death in heart failure patients are highly variable in that some patients die suddenly (often from ventricular arrhythmia) and others die of progressive failure of cardiac function (pump failure). Prediction of mode of death may facilitate decisions about specific medications or devices.

Methods and Results—We used the Seattle Heart Failure Model (SHFM), a validated prediction model for total mortality in heart failure, to assess the mode of death in 10 538 ambulatory patients with New York Heart Association class II to IV heart failure and predominantly systolic dysfunction enrolled in 6 randomized trials or registries. During 16 735 person-years of follow-up, 2014 deaths occurred, which included 1014 sudden deaths and 684 pump-failure deaths. Compared with a SHFM score of 0, patients with a score of 1 had a 50% higher risk of sudden death, patients with a score of 2 had a nearly 3-fold higher risk, and patients with a score of 3 or 4 had a nearly 7-fold higher risk (P<0.001 for all comparisons; 1-year area under the receiver operating curve, 0.68). Stratification of risk of pump-failure death was even more pronounced, with a 4-fold higher risk with a score of 1, a 15-fold higher risk with a score of 2, a 38-fold higher risk with a score of 3, and an 88-fold higher risk with a score of 4 (P<0.001 for all comparisons; 1-year area under the receiver operating curve, 0.85). The proportion of deaths caused by sudden death versus pump-failure death decreased from a ratio of 7:1 with a SHFM score of 0 to a ratio of 1:2 with a SHFM score of 4 (P trend <0.001).

Conclusions—The SHFM score provides information about the likely mode of death among ambulatory heart failure patients. Investigation is warranted to determine whether such information might predict responses to or cost-effectiveness of specific medications or devices in heart failure patients.

Key Words: arrhythmia ■ death, sudden ■ heart failure ■ mortality ■ prognosis

In the United States and Europe, ≈15 million individuals have heart failure,1,2 with direct and indirect costs of $30 000 000 000 per year in the United States alone.1 With increasing incidence and prevalence, the number of heart failure deaths continues to rise.1 However, mortality rates among groups of heart failure patients are highly variable and range from 5% to 75% per year.3,4 Furthermore, the mode of death is also divergent, in that some patients die suddenly (many of ventricular arrhythmia) and others die of progressive failure of cardiac function (pump failure). Prediction of the likely mode of death in an individual heart failure patient, and of the relative and absolute risks of the different modes of death among different heart failure patients, might allow more rational or cost-effective use of specific heart failure medications or devices. Prior reports have investigated the relationship of single risk factors with mode of death in heart failure,5,6 but prediction models that combine the information from multiple risk factors may more optimally capture overall risk. The Seattle Heart Failure Model (SHFM)1 is a validated prediction model that estimates total mortality in patients with heart failure by using commonly obtained clinical, laboratory, medication, and device variables.7 We evaluated the extent to which the SHFM predicts the mode of death in heart failure using prospectively collected information among 10 844 patients enrolled in 6 studies.

Editorial p 360
Clinical Perspective p 398

Methods

Participants

We used prospectively collected information from ambulatory heart failure patients with predominantly systolic dysfunction enrolled in 6 randomized trials or heart failure registries: the Prospective Random-
TABLE 1. Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th>Demographics</th>
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<tr>
<td>No.</td>
<td>10,538</td>
</tr>
<tr>
<td>Age, y</td>
<td>65 (18–96)</td>
</tr>
<tr>
<td>Percent male</td>
<td>76</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>25</td>
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<table>
<thead>
<tr>
<th>Heart failure characteristics</th>
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<tbody>
<tr>
<td>NYHA class II, %</td>
<td>49</td>
</tr>
<tr>
<td>NYHA class III, %</td>
<td>37</td>
</tr>
<tr>
<td>NYHA class IV, %</td>
<td>14</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>28 (1–75)</td>
</tr>
<tr>
<td>Ischemic, %</td>
<td>62</td>
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<td>SBP (mm Hg)</td>
<td>125 (70–210)</td>
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<table>
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<th>Medications</th>
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<tr>
<td>ACE inhibitor, %</td>
<td>80</td>
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<tr>
<td>Angiotensin receptor blocker, %</td>
<td>39</td>
</tr>
<tr>
<td>β Blocker, %</td>
<td>31</td>
</tr>
<tr>
<td>K-Sparing diuretic, %</td>
<td>13</td>
</tr>
<tr>
<td>Allopurinol, %</td>
<td>8</td>
</tr>
<tr>
<td>Statin, %</td>
<td>25</td>
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</table>

<table>
<thead>
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<th>Laboratory</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sodium, mEq/L</td>
<td>140 (120–175)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3 (0.1–8.2)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>201 (33–600)</td>
</tr>
<tr>
<td>Uric acid, g/dL</td>
<td>7.3 (0.1–20)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.8 (5.0–21.1)</td>
</tr>
<tr>
<td>Percent lymphocytes</td>
<td>25 (1–91)</td>
</tr>
</tbody>
</table>

Values are mean (range) or proportion.
*Not assessed in 1 study (n missing = 763).
†Not assessed in 1 study (n missing = 4921).

The development of the SHFM has been previously described.7 The evaluation of Losartan in the Elderly Trial (ELITE2),9 the Valsartan Heart Failure Trial (Val-HeFT),10 the Randomized Enbrel North American Stratification Study (RENAISSANCE),11 the University of Washington prospective cohort of heart failure patients (UW),12 and the Italian Heart Failure Registry (IN-CHF).13 We included 110 subjects with New York Heart Association (NYHA) class I heart failure, 196 patients with implantable cardioverter-defibrillators (ICDs) (which would alter the mode of death), 222 subjects with missing risk factor data², and 203 subjects with missing data on mode of death; a total of 10,538 heart failure patients were included in the present analysis. Each of the studies was approved by the institutional review boards of the participating institutions, and all participants gave informed written consent. The study-specific patient characteristics have been previously described; the characteristics of the overall population are presented in Table 1.

Determination of the SHFM Score

The development of the SHFM has been previously described.7 Briefly, the model was derived in 1 population and validated in 5 additional populations of heart failure patients. Commonly obtained clinical variables (eg, age, gender, NYHA class, medications, and laboratory values such as sodium, hemoglobin, and cholesterol) were evaluated as predictors of mortality, transformed as appropriate for nonlinear relationships, and selected for final inclusion by stepwise forward selection in multivariable Cox proportional hazards analysis. The hazard ratios for heart failure medications and devices were estimated, when such data were available, from randomized clinical trials or meta-analyses. To calculate the SHFM score for each patient, each variable in the model was multiplied by its β coefficient and the products were summed. In the 5 validation cohorts, the 1-year receiver operating characteristic area under the curve (ROC AUC) for total mortality predicted by the SHFM varied from 0.68 to 0.81; the 1-year ROC AUC for total mortality for all patients combined was 0.73 (95% confidence interval [CI], 0.71 to 0.74).²

Ascertainment of Mortality

Mortality and mode of death were adjudicated in each study by means of a review of medical records by the study investigators or centralized adjudication committees.²-¹³ Mode of death was classified as sudden death (unexpected death in a clinically stable patient, typically within 1 hour of symptom onset, from documented or presumed cardiac arrhythmia and without a clear noncardiovascular cause), pump failure (progressively reduced cardiac output and failure of organ perfusion), or other death. All events were prospectively ascertained and classified by physicians unaware of the patients’ SHFM scores. For the present analysis, the primary outcomes were sudden death and pump-failure death. Left ventricular assist device implantations or cardiac transplantations (n=80; <4% of events) were defined as pump-failure deaths at the time of surgery.

Statistical Analysis

Cause-specific mortality determined by the SHFM score was evaluated with survival-time methods. For each mode of death (sudden death or pump failure), patients who died of other causes were censored (as non-events) at the time of death. For categorical analyses, the score for each patient was rounded to the nearest integer between 0 and 4 (patients with scores >4 were considered to have a score of 4). Kaplan-Meier methods were used to evaluate survival according to the SHFM, with significance of differences evaluated with the log rank test. Cox proportional hazards analyses were used to estimate relative risk (hazard ratios) according to the SHFM. Differences in 1-year mortality were evaluated with logistic regression. Tests for trend were calculated by evaluation of the SHFM score as an ordinal variable. The ROC AUC was calculated with Stata 8.2 (College Station, Tex.). All probability values were two-tailed (P<0.05).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Participants were followed for a mean±SD of 1.6±0.7 years. During 16,735 person-years of follow-up, 2014 deaths occurred, an incidence rate of 12.0 deaths per 100 patients per year. Of these, 1014 were sudden deaths (6.1 deaths per 100 patients per year), 684 were pump-failure deaths (4.1 deaths per 100 patients per year), and 316 were the result of other causes. The SHFM strongly predicted total mortality: compared with patients with a score of 0 (in whom the annual mortality rate was 5.4 per 100 patients per year), the relative risk of death was 2.1 (95% CI, 1.8 to 2.3) for a score of 1, 4.8 (95% CI, 4.2 to 5.5) for a score of 2, 11.7 (95% CI, 9.9 to 13.8) for a score of 3, and 19.1 (95% CI, 13.8 to 26.5) for a score of 4 (P trend <0.001).
Cause-specific mortality according to the SHFM is shown in Figure 1. The SHFM predicted survival free of sudden death ($P < 0.0001$) and survival free of pump-failure death ($P < 0.0001$). Relative risks of sudden death and pump-failure death according to the SHFM are presented in Table 2. Compared with patients with a score of 0, patients with a score of 1 had a 50% higher risk of sudden death, patients with a score of 2 had a nearly 3-fold higher risk of sudden death, and patients with a score of 3 or 4 had a nearly 7-fold higher risk of sudden death ($P < 0.0001$ for all comparisons). The ROC AUC for 1-year mortality from sudden death was 0.68 (95% CI, 0.65 to 0.70). Stratification of risk of pump-failure death was even more pronounced, with a 4-fold higher risk with a score of 1, a 15-fold higher risk with a score of 2, a 38-fold higher risk with a score of 3, and an 88-fold higher risk with a score of 4 ($P < 0.0001$ for all comparisons). The ROC AUC for 1-year mortality from pump failure was 0.85 (95% CI, 0.83 to 0.87).

The SHFM was highly predictive of the proportion of total mortality that resulted from sudden death versus pump-failure death (Figure 2). At lower scores (0 or 1), most deaths resulted from sudden death. At mid-range to high scores (2 or 3), sudden death and pump failure contributed relatively equally to mortality. Among patients with the highest scores (4), the majority of deaths were the result of pump failure. As a proportion of total deaths, the contribution from sudden deaths progressively decreased with higher scores ($P$ trend $< 0.0001$), whereas the contribution from pump failure progressively increased with higher scores ($P$ trend $< 0.0001$). The proportion of deaths that resulted from other causes was relatively low and consistent across different SHFM scores ($P$ trend, 0.31). The absolute risks of cause-specific mortality according to the SHFM are also shown in Figure 2. Mortality from both sudden death and pump failure increased with higher scores ($P$ trend $< 0.0001$ for each), whereas mortality from other causes was relatively low across all SHFM scores.

The absolute rates and relative risks of sudden death according to the SHFM were similar among younger versus older patients, men versus women, ischemic versus nonischemic heart failure patients, patients with lower versus higher left ventricular ejection fraction, and patients who took K-sparing diuretics versus patients who did not take K-sparing diuretics (Table 3). The absolute rates and relative risks of pump-failure death according to the SHFM were also generally similar across these subgroups. Among patients who took β-blockers, the magnitudes of the differences in relative risk of sudden death and pump-failure death according to the SHFM were slightly less than among patients who did not take β-blockers, but the score was still discriminatory among both subgroups (Table 3).

![Figure 1. Survival free of sudden death (top) and pump-failure death (bottom) according to the SHFM score. *Log rank test for equality of survivor functions.](image-url)

**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>SHFM Score</th>
<th>0 (n=4043)</th>
<th>1 (n=4356)</th>
<th>2 (n=1729)</th>
<th>3 (n=361)</th>
<th>4 (n=49)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sudden death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>265</td>
<td>407</td>
<td>242</td>
<td>90</td>
<td>10</td>
<td>...</td>
</tr>
<tr>
<td>Incidence rate, per 100 person-years</td>
<td>3.8</td>
<td>5.8</td>
<td>10.3</td>
<td>25.1</td>
<td>24.9</td>
<td>...</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0 (reference)</td>
<td>1.5 (1.3–1.8)</td>
<td>2.7 (2.3–3.2)</td>
<td>6.5 (5.1–8.3)</td>
<td>6.5 (3.5–12.2)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td><strong>Pump failure death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events</td>
<td>56</td>
<td>227</td>
<td>273</td>
<td>102</td>
<td>26</td>
<td>...</td>
</tr>
<tr>
<td>Incidence rate, per 100 person-years</td>
<td>0.8</td>
<td>3.2</td>
<td>11.7</td>
<td>28.4</td>
<td>64.7</td>
<td>...</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>1.0 (reference)</td>
<td>4.1 (3.1–5.5)</td>
<td>15.0 (11.2–20.0)</td>
<td>38.4 (27.6–53.2)</td>
<td>87.6 (54.9–139.9)</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>
Sudden Death
Pump Failure Death
both relative risk differences (50% to a 7-fold higher risk of
sudden death and pump-failure death. The SHFM predicted
to IV heart failure, the SHFM strongly predicted risk of
In the present analysis of 10,538 patients with NYHA class II
/11021
for trend
0.001 across higher
/9252
Randomised Intervention Trial in Congestive Heart
Failure (MERIT-HF), the proportion of deaths that resulted
from sudden death in NYHA class II, III, and IV patients was
64%, 57%, and 33%, respectively, whereas 1-year absolute
risk (cumulative incidence) of sudden death was 4%, 6%, and
6% (only 145 patients were NYHA class IV).14 In the present
study, the proportion of deaths that resulted from sudden
death in NYHA class II, III, and IV patients was 65%, 51%,
and 45%, respectively, whereas 1-year absolute risk was 4%,
7%, and 13%. In comparison, across increasing SHFM scores
(0 to 4), the proportion of deaths that resulted from sudden
death was 79%, 57%, 43%, 40%, and 28%, whereas the
absolute risk at 1-year was 4%, 6%, 10%, 23%, and 25%,
respectively (Figure 2). These findings suggest that the
SHFM more finely discriminates between heart failure severity
and related risk than does NYHA class.

Optimal heart failure therapy as tolerated is appropriate
across the whole spectrum of the SHFM Score. However,
several treatment decisions must be made, such as optimal
doses of angiotensin-converting enzyme inhibitors and
β-blockers, use of additional medications (eg, spironolac-
tone), appropriateness of device therapy (eg, resynchroniza-
tion devices or ICDs), and referral for evaluation for left
ventricular assist device implantation or cardiac transplant.
Furthermore, some of these medications or devices may be
more appropriate or more cost-effective in different patients.
It is possible that the SHFM could provide, in the context of
a patient’s overall clinical picture, important prognostic
information about predicted mode of death that could facil-
itate discussions and decision-making with regard to optimal
use of various medications or devices.

The SHFM has been shown to predict all-cause mortality.7
Although the prediction of sudden death and pump-failure
death might simply mirror this global risk, the relative
proportions of deaths that resulted from sudden death versus
pump failure were very different among patients with differ-
ent SHFM scores. The efficacy and cost-effectiveness of
different medications or devices depend on several factors:
the absolute risk of death, the proportion of deaths that result
from sudden death versus pump failure, and the extent to
which the medication or device affects these causes of death
differently. The information provided by the SHFM will

**Discussion**

In the present analysis of 10,538 patients with NYHA class II
to IV heart failure, the SHFM strongly predicted risk of
sudden death and pump-failure death. The SHFM predicted
both relative risk differences (50% to a 7-fold higher risk of

![Figure 2. Proportions of deaths at 1 year (top) and absolute risk
of 1-year mortality (bottom panel) from sudden death, pump fail-
ure, or other causes according to the SHFM score.](image)
allow specific hypotheses to be tested on the basis of expected effects of medication or devices, and the SHFM-predicted absolute and relative rates of death from sudden death, pump failure, and other competing causes.

Clinically defined modes of death (such as sudden death or pump failure) that might help characterize appropriate treatments may be inappropriately classified as a result of overlapping pathophysiologies or bias related to a patient’s underlying heart failure severity. For example, a patient with severe heart failure who dies may be more likely to have the cause of death classified as pump failure rather than sudden death. Thus, although modes of death were classified without knowledge of patients’ SHFM scores, the differing proportions of modes of death (as seen in Figure 2) may at least in part reflect classification bias. Even if modes of death were appropriately classified and predicted by the SHFM with reasonable accuracy, this might not translate into prediction of the response to treatment. The definition of a “better” response may also vary depending on whether efficacy was defined in absolute terms, in relative terms, or by cost-effectiveness. Investigation of the utility of the SHFM for the prediction of clinical responses to particular therapies should be explored in future research, particularly in randomized trials (completed or planned) of specific medications or devices. Future research could also examine the prediction of sudden death versus pump-failure death among patients who would or would not meet guidelines for some treatments, such as prophylactic ICD placement, to determine how the SHFM might interact with treatment guidelines.

In the present data set, only 197 patients (1.8%) had an ICD. In these patients, the SHFM strongly predicted both total mortality (P trend <0.001) and pump failure mortality (P trend <0.001). Only 1 sudden death occurred among these patients (because ICDs prevent sudden death; classification bias may also contribute), which precludes analysis of this mode of death. Some preliminary evidence suggests that ICD placement in some patients may prevent sudden death but be associated with some patients may prevent sudden death but be associated with higher risk of pump failure or other cardiac death15–17; future research in ICD trial databases may elucidate whether the SHFM can predict these responses to ICD placement.

The present analysis had several strengths. Data on risk factors and events were collected prospectively to minimize mortality (P trend <0.001) and pump failure mortality (P trend <0.001). Only 1 sudden death occurred among these patients (because ICDs prevent sudden death; classification bias may also contribute), which precludes analysis of this mode of death. Some preliminary evidence suggests that ICD placement in some patients may prevent sudden death but be associated with higher risk of pump failure or other cardiac death15–17; future research in ICD trial databases may elucidate whether the SHFM can predict these responses to ICD placement.

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Figure 3. Rates of sudden death (top) and pump-failure death (bottom) according to both SHFM score and NYHA class. Findings are shown for the 6912 heart failure patients in whom participant-level data were available. *In some strata (eg, class II + score 4), numbers of patients or events were too small to estimate risk.

Figure 4. Proportions of different modes of death according to both SHFM score and NYHA class. Findings are shown for the 6912 heart failure patients in whom participant-level data were available. *In some strata, (eg, class II + score 4), numbers of patients were too small to estimate risk.

In conclusion, the SHFM predicts relative risks and proportions of sudden death and pump-failure death among ambulatory heart failure patients. The magnitudes of relative risk differences were particularly large for pump-failure death. Further investigation is warranted to determine whether this prognostic information may facilitate decision-making with regard to optimal use of specific medications or devices in heart failure patients.

Acknowledgments
We extend our gratitude to the patients and investigators who participated in the heart failure trials and registries included in the present report. We especially thank the investigators and event adjudication committees for their work to classify the modes of death. The SHFM is available to healthcare providers free of charge as an online interactive Java application at www.seattleheartfailuremodel.org. The SHFM can be used to estimate mean, 1-year, 2-year, and 5-year survival and to estimate the benefit of the addition of medications and/or devices, for an individual heart failure patient.

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The University of Washington Depression Study was funded by the American Heart Association (Dallas, Tex) and the Dana Foundation (New York, NY). Data on mortality and risk factors for calculation of the SHFM score were provided by Pfizer Laboratories for PRAISE1, by Novartis for Val-HeFT, and by the Italian Heart Failure Registry for IN-CHF; data on mortality and the SHFM score were provided by Merck Research Laboratories for ELITE2 and by Amgen, Inc, for RENAISSANCE. The funding sources and companies who provided data access had no role in study conception, conduct, or design; performance or interpretation of data analysis; interpretation of results; or manuscript preparation or approval.

Disclosures
Dr Anand has received grant support and speaker’s honoraria from Novartis and has served as consultant to Amgen and Guidant. Dr Linker has an ownership interest and licensing income as copyright holder of the specific programming implementations of the SHFM and institutional copyright (through the University of Washington, Seattle) of the Web-based and Palm version implementations of the SHFM. Dr Cleland has received grant support and speaker’s honoraria from Roche, AstraZeneca, Medtronic, and GlaxoSmithKline. Dr Carson has received speaker’s honoraria from Novartis. Dr Mann has served as consultant to Acorn Cardiovascular. Dr Pitt has served as consultant to Pfizer, Novartis, Alector, AstraZeneca, and Takeda. Dr Levy has received grant support from GlaxoSmithKline, Thoratec, Amgen, Vasogen, and Medtronic, and speaker’s honoraria from GlaxoSmithKline, Pfizer, Medtronic, and Scios. Dr Levy also has an ownership interest in Cardiac Dimensions and has served as consultant and on the advisory board for GlaxoSmithKline, Pfizer, Cardiac Dimensions,
Medscape, General Electric, Scios, and the National Anemia Action Council; he also has an ownership interest and licensing income as copyright holder of the specific programming implementations of the SHFM and institutional copyright (through the University of Washington, Seattle) of the Web-based and Palm version implementations of the SHFM. The remaining authors report no conflicts.

References

CLINICAL PERSPECTIVE
Rates of death in heart failure patients are extremely variable, with annual mortalities that range from 5% to 75%. Two major modes of death occur. Some patients die suddenly (“sudden death”), typically from causes related to acute ventricular arrhythmia. Other patients die of progressive failure of cardiac function (“pump failure”), which ultimately causes pulmonary, renal, or multisystem failure. For individual patients with heart failure, an understanding of their absolute and relative risks of sudden death and pump-failure death might allow more rational or cost-effective use of specific heart failure medications or devices. For example, patients at risk of sudden death might benefit from an implantable cardioverter defibrillator, particularly if the related risk of pump-failure death (which would not be ameliorated by an implantable cardioverter defibrillator) is relatively low. Conversely, the absolute risk of pump failure might guide decisions with regard to resynchronization therapy, assist device implantation, or listing for transplantation. In the present analysis of 10,538 ambulatory patients with predominantly systolic heart failure (New York Heart Association class II to IV), we found that the Seattle Heart Failure Model, a previously validated model to predict total mortality in heart failure, provided information about the likely mode of death. For example, compared with patients with a SHFM score of 0, the risk of sudden death progressively increased with higher scores, up to a 7-fold higher risk with a score of 4. Conversely, the proportion of deaths caused by sudden death versus pump failure decreased from a ratio of 7:1 with a SHFM score of 0 to a ratio of 1:2 with a SHFM score of 4. These findings should not by themselves modify clinical practice. However, these results indicate a need to evaluate in future studies the utility of the SHFM for the prediction of responses to specific heart failure treatments.

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