Predictors of Sudden Cardiac Death: A Competing Risk Approach in the Hemodialysis Study

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Summary

Background and objectives There are few data on risk factors for sudden cardiac death (SCD) in patients undergoing hemodialysis (HD). The study objective was to identify predictors associated with various causes of death in the Hemodialysis (HEMO) Study and to develop a prediction model for SCD using a competing risk approach.

Design, setting, participants, & measurements In this analysis of 1745 HEMO participants, all-cause mortality was classified as SCD, non-SCD, and noncardiac death. Predictors for each cause of death were evaluated using cause-specific Cox proportional hazards models, and a competing risk approach was used to calculate absolute risk predictions for SCD.

Results During a median follow-up of 2.5 years, 808 patients died. Rates of SCD, non-SCD, and noncardiac death were 22%, 17%, and 61%, respectively. Predictors of various causes of death differ somewhat in HD patients. Age, diabetes, peripheral vascular disease, ischemic heart disease, serum creatinine, and alkaline phosphatase were independent predictors of SCD. The 3-year C-statistic for SCD was 0.75 (95% confidence interval, 0.70–0.79), and calibration was good ($\chi^2=1.1; P=0.89$). At years 3 and 5 of follow-up, the standard Cox model overestimated the risk for SCD as compared with the competing risk approach on the relative scale by 25% and 46%, respectively, and on the absolute scale by 2% and 6%, respectively.

Conclusions Predictors of various causes of death differ in HD patients. The proposed prediction model for SCD accounts for competing causes of death. External validation of this model is required.

Introduction

Cardiovascular disease is a major cause of morbidity and mortality in hemodialysis (HD) patients, accounting for more than 40% of deaths (1). The US Renal Data System (USRDS) report attributes the single largest specific cause of death from cardiovascular disease to arrhythmias or cardiac arrest (1). Although certain risk factors associated with sudden cardiac death (SCD) in HD patients are similar to those in the general population, factors unique to kidney failure and the HD procedure play a prominent role but remain poorly understood (2–7).

Several studies have identified risk factors for SCD in HD patients, but few have compared predictors for SCD with other causes of death (2–8). The latter is important given that treatment recommendations may vary depending on the risk factor profile of the patient. For example, an individual at high risk for SCD may benefit from a defibrillator or $\beta$-blockers, whereas an individual with an indwelling catheter who is at high risk for noncardiac death may benefit from an antibiotic lock.

There are also limited data on prediction equations for SCD in HD patients, and previous studies have not incorporated competing risk into these equations (9). In the presence of high competing risks as seen in HD populations, competing events may preclude the event of interest and thus the benefit of an intervention. In addition, without incorporation of competing risk, the probability of SCD is overestimated and incorrect conclusions can be drawn. In this study, we evaluated the predictors of SCD, non-SCD, and noncardiac deaths in the Hemodialysis (HEMO) Study using cause-specific Cox proportional hazards models, and a competing risk approach was used to derive absolute risk predictions for SCD.

Materials and Methods

Study Population

The design and methods of the HEMO Study have been described in detail elsewhere (10,11). In brief, the HEMO Study enrolled 1846 patients undergoing long-term HD from 15 clinical centers comprising 72 dialysis units. Exclusion criteria included, but were not limited to, unstable angina, serum albumin level less than 2.6 g/dl, current hospitalization, New York Heart Association class IV congestive heart failure, and active systemic infection. Eligible participants...
were randomly assigned between May 1995 and February 2001 in a 2×2 factorial design to a standard or a high
dalysis dose and to a low-flux or a high-flux dialyzer. Part-
icipants were followed until death, kidney transplantation,
or the end of the study period in December 2001, which-
ever came first. The Tufts Medical Center Institutional Re-
view Board approved these retrospective analyses.

Covariates
Baseline demographic data were collected through self-
reported questionnaires. Clinical and laboratory data were
obtained using standardized protocols (11). Serum creat-
nine, calcium, and phosphorous levels were obtained from
local laboratory measurements, whereas predialysis serum
albumin and urea were determined monthly at the HEMO
central laboratory. Comorbid conditions were assessed us-
ing the Index of Coexisting Disease (ICED) and were as-
certained from review of medical records (12). ICED is a
standardized method of assessing comorbidity that has
been shown to be a valid predictor of mortality (13). ICED
aggregated the presence and severity of 19 medical con-
ditions, including peripheral vascular disease, cerebrovas-
cular disease, diabetes, and hypertension. To capture the
evidence and additional details of existing or history of
cardiac disease, the category for cardiovascular disease
was expanded to four categories: ischemic heart disease
(IHD), heart failure (HF), arrhythmias, and other heart dis-
eases. Each category of cardiac disease was scored from
0 to 3; 0 indicated no disease in that category, and 3 in-
dicated the presence of moderate or severe manifestations
of the disease regardless of treatment. For purposes of this
analysis, scores of 1, 2, or 3 were used to denote the pres-
ence of baseline disease.

The list of candidate predictors considered for the pre-
diction model included the following: (1) demographic
factors (age, sex, race); (2) cardiovascular risk factors (his-
tory of diabetes, smoking, systolic and diastolic BP, body
mass index); (3) cardiovascular disease (including IHD,
HF, arrhythmias, other heart disease, peripheral vascular
disease, and cerebrovascular disease); (4) HD-related fac-
tors (dialysis vintage, randomly assigned flux and dose
groups); and (5) laboratory data (including hematocrit
and serum levels of creatinine, potassium, albumin, cal-
cium, phosphorus, and alkaline phosphatase).

Outcome
The primary outcome of the HEMO Study was all-cause
mortality. For each death, the principal investigator of each
clinical center completed a form that included the cause of
death according to the HEMO Study classification and a
brief narrative summary describing the events leading to
death (14). All death classifications required independent
audits by two members of the Outcome Review Committee.
SCD was a secondary outcome of interest in the HEMO
Study.

Sudden death in the HEMO Study was defined as a
witnessed or unwitnessed unexpected death, with pre-
ceding duration of symptoms less than 24 hours for
witnessed deaths and less than the interval since the last
dialysis session for unwitnessed deaths. Sudden death was
attributed to IHD if the patient had a history of this
condition, to arrhythmias if the patient had a history of
arrhythmias in the absence of IHD, and to other heart
diseases if the patient had a history of other causes of heart
disease in the absence of IHD or arrhythmias. Sudden
death due to IHD, arrhythmias, or other heart disease met
criteria for SCD. Deaths were subsequently classified into
three mutually exclusive groups: SCD, non-SCD, and
noncardiac death.

Statistical Analyses
Descriptive analyses were used to summarize baseline
characteristics of the study participants according to their
final event status (i.e., alive, SCD death, non-SCD death,
and noncardiac death). Continuous variables are presented
as mean ± SD or median (interquartile range) as appropri-
ate, and categorical variables are given as proportions.
Continuous variables were compared using ANOVA or a
Kruskal-Wallis test as appropriate, and categorical vari-
bles were compared using a χ² test.

Cause-Specific Cox Hazard Model. The associations
between baseline covariates and various causes of death
were assessed using cause-specific Cox proportional haz-
ards models that censored for the respective competing
events. Covariates were selected for the analyses according
to their biologically plausible potential to act as confound-
ers. Using forward-selection process, we developed mul-
tivariable models in which all covariates with a P value of
0.1 or less in univariate analysis for any cause of death
were entered in the model selection process. The func-
tional form of continuous predictors and their association
with each outcome was explored using restricted cubic
splines. To assess the association of predictors on each
cause of death and to examine whether these associations
differed among the causes of death, we fitted a stratified
Cox model by including any covariate that remained sig-
nificant after the forward-selection process for each cause
of death. We tested for differences between the cause-
specific hazards ratios for each covariate by including an
interaction term between the covariate and the cause of
death in a stratified Cox model.

Absolute Risk Prediction Using a Competing Risk
Approach. A competing risk approach was used to calcu-
late absolute risk predictions for SCD (15). Because we
were interested in developing a model for SCD, only co-
variates with a P value of 0.1 or less in the univariate
analysis for SCD were included in the model selection pro-
cess. The standard Cox model and the competing risk
approach differ in the way absolute risk predictions are
calculated. Whereas predictions from the standard Cox
model depend only on the cause-specific hazard of the
event of interest and thus overestimate absolute risk in the
presence of competing events, the competing risk approach
consists of developing a cause-specific hazards models for
both the event of interest and the competing event sepa-
ately, and then combining them according to the cumula-
tive incidence function (16). The competing risk approach
calculates the cumulative incidence of SCD as follows:

\[ I_{SCD} = \sum L_{iscd}(t_i) S(t_{i-1}). \]

The quantities under the summation denote the instan-
taneous hazard of SCD at event time \( t_i \) and survival rate
from any cause of death past event time \( t_{i-1} \).
Model Performance and Internal Validation. Model performance was assessed at 3 years of follow-up for discrimination using the Harrell global C-statistic and for calibration using the modified Hosmer-Lemeshow statistic for survival analysis. The Efron bootstrap resampling technique was used to estimate the optimism in the discrimination statistic and calibration. To account for final model uncertainty, the internal validation technique consisted of repeating the full model-building process described above in 300 bootstrap resamples of equal sample size as our original sample (17). The expected optimism was calculated as the average difference between the performance of models developed in each bootstrap sample when applied to the bootstrap sample and the performance of the same models when applied to the original sample.

An Excel worksheet (Microsoft Corp., Redmond, WA) was created to calculate absolute risk prediction for SCD using the competing risk approach to facilitate application by clinicians.

Analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). Cumulative incidence probabilities were calculated using an SAS macro (18). We considered two-tailed P<0.05 to indicate statistically significant differences.

Results
Characteristics of Study Participants

Of the 1846 HEMO participants, 101 (5.5%) were excluded because they lacked complete data on all the predictors. Thus, the sample available for analysis consisted of 1745 participants. Participants excluded for missing data at baseline were younger and more likely to be of nonblack ethnicity. The prevalence of cardiovascular and cerebrovascular disease did not differ between the included and excluded participants. The participants included in these analyses had a mean age of 58 years, and 44% were male. Sixty-three percent of the participants were African American, and 44% had a history of diabetes. The prevalence rates of IHD, HF, arrhythmias, and other heart diseases were 39%, 40%, 31%, and 63%, respectively.

The median duration of follow-up was 2.5 years. A total of 808 patients died. Among these, 319 (39%) and 489 (61%) deaths were attributed to cardiac and noncardiac causes, respectively. One hundred eighty-two (57%) of the cardiac deaths were due to SCD. Participants who died of SCD were more likely to be older, to be male, and to have a higher burden of comorbid conditions (including cardiovascular disease, diabetes, and peripheral vascular disease) compared with those who survived (Table 1).

Predictors for Each Cause of Death

Older age was independently associated with each cause-specific death (Table 2). Diabetes was a significant predictor of SCD but not other deaths. IHD was a predictor of both SCD and non-SCD but not noncardiac deaths, and was significantly different when compared between cardiac and noncardiac deaths. Heart failure was a predictor of non-SCD and noncardiac deaths but not SCD. Lower serum creatinine was independently associated with SCD and noncardiac deaths. White race and lower systolic BP were significant predictors of non-SCD.

Multivariable Model for SCD

For the purpose of easy clinical applicability, a parsimonious model for SCD using the competing risk approach was developed by including only predictors that were found to be significant for SCD (Table 3). Serum phosphorus and body mass index were not statistically significant in univariate analysis (P>0.16 for both) and therefore were not entered into this forward-selection process. Heart failure was also not significant in a model that included IHD (Table 3); however, if IHD was excluded from the model, HF became significant (hazard ratio, 1.53 (95% confidence interval [CI], 1.13–2.06)).

Model Performance

The 3-year C-statistic for the SCD model using the competing risk approach was 0.75 (95% CI, 0.70–0.79). Model fit was good for comparing observed cumulative incidence with predicted cumulative incidence across quintiles of risk (χ²=1.1; P=0.89; Figure 1). As the follow-up time increased, the standard Cox model increasingly overestimated the risk for SCD compared with the competing risk model (Figure 2). The standard Cox model overestimated the probability of SCD by 25% and 46% on the relative scale and 2% and 6% on the absolute scale at 3 and 5 years of follow-up, respectively.

All the continuous variables evaluated were noted to have a linear association with SCD except for systolic BP, which had a U-shaped association. Inclusion of a quadratic term for systolic BP was found to be a significant predictor of SCD in the univariate analysis; however, it was not significant after multivariable analysis in the forward or stepwise model. In a backward-selection model, systolic BP and its quadratic term were significant predictors of SCD despite multivariate adjustment. In this backward-selection model, the hazard ratio estimates for other variables were very similar to those in our initial model, and the 3-year C-statistic (0.75 [95% CI, 0.70–0.80]) and model calibration (χ²=0.83; P=0.93) were essentially unchanged. We therefore retained our initial model.

Bootstrap Performance of C-Statistic and Calibration

With use of 300 bootstrap resamples, the average 3-year C-statistics of the models developed on the bootstrap samples and when applied to our original sample were 0.77 and 0.75, respectively. Thus, we expect the 3-year predictive discrimination of our model to drop to 0.73 when applied to an external validation dataset. Figure 3 shows that the bias-corrected estimate of the calibration curve at 3-year is good. The apparent predictive accuracy and the bootstrap-corrected estimates are close except for the highest-risk quintile, in which the observed risk is slightly lower than predicted risk.

Discussion

In this study, we identify predictors for SCD and show that predictors of various causes of death varied among HD patients. We also demonstrate that if competing risk is not taken into account, the probability of SCD will be overestimated by approximately 25%–50%. Finally, we present a prediction model for SCD that incorporates
Table 1. Baseline characteristics by different causes of death

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sudden Cardiac Death</th>
<th>Nonsudden Cardiac Death</th>
<th>Noncardiac Deaths</th>
<th>Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (%)</td>
<td>182 (10)</td>
<td>137 (8)</td>
<td>489 (28)</td>
<td>937 (54)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62±11</td>
<td>64±11</td>
<td>63±12</td>
<td>53±14</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>86 (47)</td>
<td>63 (46)</td>
<td>212 (43)</td>
<td>401 (43)</td>
</tr>
<tr>
<td>Black patients, n (%)</td>
<td>105 (58)</td>
<td>72 (53)</td>
<td>312 (64)</td>
<td>611 (65)</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td>never</td>
<td>82 (45)</td>
<td>63 (46)</td>
<td>223 (46)</td>
</tr>
<tr>
<td></td>
<td>past</td>
<td>71 (39)</td>
<td>54 (39)</td>
<td>179 (37)</td>
</tr>
<tr>
<td></td>
<td>current</td>
<td>29 (16)</td>
<td>20 (15)</td>
<td>87 (18)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.0±4.6</td>
<td>25.7±5.5</td>
<td>24.9±5.5</td>
<td>25.8±5.2</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>115 (63)</td>
<td>72 (53)</td>
<td>236 (48)</td>
<td>347 (37)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>117 (64)</td>
<td>85 (62)</td>
<td>215 (44)</td>
<td>266 (28)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>98 (54)</td>
<td>78 (57)</td>
<td>238 (49)</td>
<td>278 (30)</td>
</tr>
<tr>
<td>Arrhythmia, n (%)</td>
<td>78 (43)</td>
<td>64 (47)</td>
<td>207 (42)</td>
<td>195 (21)</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>55 (30)</td>
<td>36 (26)</td>
<td>109 (22)</td>
<td>134 (14)</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>52 (29)</td>
<td>31 (23)</td>
<td>96 (20)</td>
<td>101 (11)</td>
</tr>
<tr>
<td>Other heart disease, n (%)</td>
<td>132 (73)</td>
<td>102 (74)</td>
<td>352 (72)</td>
<td>513 (55)</td>
</tr>
<tr>
<td>Dialysis vintage (yr)</td>
<td>1.9 (0.9–5)</td>
<td>2.4 (1.2–4.7)</td>
<td>2.5 (1.0–5.1)</td>
<td>2.0 (0.9–4.2)</td>
</tr>
<tr>
<td>Predialysis systolic BP (mmHg)</td>
<td>153±25</td>
<td>148±21</td>
<td>153±23</td>
<td>152±21</td>
</tr>
<tr>
<td>Predialysis diastolic BP (mmHg)</td>
<td>80±13</td>
<td>73±18</td>
<td>80±13</td>
<td>83±13</td>
</tr>
<tr>
<td>High-flux hemodialysis group, n (%)</td>
<td>89 (49)</td>
<td>57 (42)</td>
<td>250 (51)</td>
<td>473 (50)</td>
</tr>
<tr>
<td>High-Kt/V group, n (%)</td>
<td>99 (54)</td>
<td>64 (47)</td>
<td>237 (48)</td>
<td>469 (50)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>33.7±4.6</td>
<td>33.1±4.3</td>
<td>32.8±4.5</td>
<td>34.0±4.5</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>9.0±2.8</td>
<td>9.8±2.6</td>
<td>9.5±2.4</td>
<td>11.0±3</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>4.8±0.8</td>
<td>4.9±0.8</td>
<td>4.8±0.8</td>
<td>4.9±0.8</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>3.5±0.4</td>
<td>3.6±0.3</td>
<td>3.5±0.4</td>
<td>3.7±0.4</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.2±0.9</td>
<td>9.4±1.1</td>
<td>9.3±1.0</td>
<td>9.3±1.0</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>5.8±1.8</td>
<td>5.9±1.7</td>
<td>5.6±1.9</td>
<td>5.8±1.9</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (IU/L)</td>
<td>101 (72–145)</td>
<td>91 (67–132)</td>
<td>105 (78–149)</td>
<td>93 (71–131)</td>
</tr>
<tr>
<td>Follow-up time (mo)</td>
<td>25±18</td>
<td>24±18</td>
<td>29±19</td>
<td>40±23</td>
</tr>
</tbody>
</table>

Data expressed with a plus/minus sign are the mean ± SD. Data for dialysis vintage and serum alkaline phosphatase are the median (25th–75th percentiles).
we acknowledge the potential for misclassification, as non-SCD therefore have similar predictors, and the standard Cox model, which ignores other competing risks for deaths, overestimated the risk for SCD by 25% and 46% on the relative scale at 3 and 5 years, respectively.

These results have several potential implications. First, identifying predictors of various causes of death may help improve understanding of the pathophysiology of the disease. Second, knowledge of predictors or prediction equations for SCD and other outcomes may lead to different interventions in a particular patient. Third, appreciation of the risk factor profile in a particular patient may lead to identification of patients most suitable for a clinical trial targeting a specific intervention.

To our knowledge, this is the first study to compare predictors of different causes of death in HD patients. Another strength of the study is that we have developed a prediction model for SCD that takes into account competing causes of death. Finally, the HEMO Study was a randomized clinical trial targeting a specific intervention.

Table 2. Multivariable-adjusted cause-specific hazard ratios

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sudden Cardiac Death</th>
<th>Nonsudden Cardiac Death</th>
<th>Noncardiac Death</th>
<th>P Value^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.35 (1.11–1.65)</td>
<td>1.77 (1.39–2.25)</td>
<td>1.51 (1.34–1.70)</td>
<td>0.24</td>
</tr>
<tr>
<td>Black patients</td>
<td>0.77 (0.56–1.06)</td>
<td>0.56 (0.39–0.81)</td>
<td>0.89 (0.73–1.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.76 (1.25–2.48)</td>
<td>1.37 (0.94–2.00)</td>
<td>1.06 (0.87–1.30)</td>
<td>0.04^b</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1.99 (1.43–2.78)</td>
<td>1.63 (1.11–2.39)</td>
<td>0.89 (0.73–1.08)</td>
<td>&lt;0.001^b,c</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.21 (0.88–1.65)</td>
<td>1.50 (1.04–2.17)</td>
<td>0.25 (1.03–1.51)</td>
<td>0.63</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1.07 (0.77–1.48)</td>
<td>1.14 (0.79–1.65)</td>
<td>1.30 (1.07–1.58)</td>
<td>0.55</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.57 (1.12–2.20)</td>
<td>1.26 (0.83–1.92)</td>
<td>1.25 (0.99–1.58)</td>
<td>0.54</td>
</tr>
<tr>
<td>Other heart disease</td>
<td>1.25 (0.88–1.77)</td>
<td>1.35 (0.89–2.04)</td>
<td>1.28 (1.03–1.58)</td>
<td>0.96</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.78 (0.66–0.92)</td>
<td>0.93 (0.77–1.12)</td>
<td>0.80 (0.72–0.88)</td>
<td>0.31</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.96 (0.83–1.12)</td>
<td>0.76 (0.64–0.91)</td>
<td>0.99 (0.90–1.09)</td>
<td>0.03^c,d</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.71 (0.58–0.86)</td>
<td>1.07 (0.86–1.33)</td>
<td>0.78 (0.69–0.88)</td>
<td>0.02^c,d</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td>1.18 (1.05–1.32)</td>
<td>1.18 (1.02–1.37)</td>
<td>1.08 (0.99–1.17)</td>
<td>0.37</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.87 (0.73–1.03)</td>
<td>0.80 (0.66–0.99)</td>
<td>0.76 (0.69–0.84)</td>
<td>0.44</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>1.22 (1.05–1.42)</td>
<td>1.22 (1.02–1.47)</td>
<td>1.12 (1.01–1.23)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Hazard ratios for continuous predictors are given per 1 SD increase. The likelihood ratio test statistic for any differences in the hazards ratios between any two causes of death for any variable in the above model was highly significant ($\chi^2=73.4$; degrees of freedom = 28; $P<0.001$). CI, confidence interval.

^aP values for testing equality of hazard ratios between the three causes of death in the multivariable cause-specific hazards model. For those statistically different, the differences were compared across each group.

^bSudden cardiac death versus noncardiac death ($P<0.05$).

^cNoncardiac death versus nonsudden cardiac death ($P<0.05$).

Table 3. Multivariable model for sudden cardiac death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.31 (1.08–1.59)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.52 (1.11–2.09)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.27 (1.65–3.13)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.62 (1.17–2.26)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.66 (0.55–0.79)</td>
</tr>
<tr>
<td>Serum alkaline phosphatase</td>
<td>1.19 (1.06–1.34)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

^aHazard ratios for continuous predictors are given per 1 SD increase.
or natriuretic peptides, and markers of inflammation, such as IL-6, were not collected (26,39,40). High-sensitivity C-reactive protein was available in only a subset of participants and was therefore not included. However, it is important to note that these variables are also not routinely obtained in clinical practice for inclusion in a prediction equation. We used only baseline variables to determine the association with SCD and did not include changes in clinical measures over time. Thus, we were unable to adjust for dialysis-related factors (i.e., dialysate potassium concentration) more proximate to the time of death (41). We acknowledge that because HD patients are a “captive audience” who are seen three times a week, classification of SCD may differ from definitions in the general population. Furthermore, the definition may lead to an HD patient who does not have known heart disease being classified as having SCD and to an HD patient with cardiovascular disease who had an unwitnessed death due to cerebrovascular accident being classified as having SCD. Despite these limitations, the HEMO Study is one of the few studies that a priori defined SCD as an outcome of interest; the incidence of SCD in our study is in accordance with findings from the USRDS. Finally, although we internally validated the model using bootstrapping techniques and accounted for over-optimism, external validation was not performed.
In conclusion, to provide appropriate intervention, select patients for future trials, and evaluate new treatments for SCD, it is important to identify HD patients at high risk for SCD. We have shown that predictors of various causes of death differ to some extent in HD patients. We have also developed a predictive model for SCD using a competing risk approach. This model requires external validation.

Acknowledgments
The participation by patients and the staff in the HEMO Study is greatly appreciated. We thank the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center for helping us host the Web-based calculator.

The study was funded by National Institutes of Health Grants T32 DK07777 and K24 DK078204.

An abstract representing this work was published at the American Society of Nephrology Annual Meeting in Denver, Colorado, in 2010.

Disclosures
C.H. served as a consultant for Amgen, Abbott, Affymax, and Fibrogen; has an equity interest in Cambridge Heart and Boston Scientific; and has received research support from Johnson & Johnson and the National Institutes of Diabetes and Digestive and Kidney Diseases/National Institutes of Health.


References


33. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW: Body mass index and mortality in ‘healthier’ as compared with ‘sicker’ haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 16: 2386–2394, 2001


Received: June 27, 2011 Accepted: October 9, 2011

Published online ahead of print. Publication date available at www.jasn.org.

See related editorial, “Expect the Unexpected: Sudden Cardiac Death in Dialysis Patients,” on pages 8–11.