Risk Factor and Prediction Modeling for Sudden Cardiac Death in Women With Coronary Artery Disease

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**Background:** To our knowledge, the risk of sudden cardiac death (SCD) and the assessment of risk factors in prediction models have not been evaluated in women with coronary artery disease (CAD). We sought to evaluate the incidence of SCD as well as its risk factors and their predictive accuracy among a population of women with CAD.

**Methods:** The Heart and Estrogen/progestin Replacement Study evaluated the effects of hormone replacement therapy on cardiovascular events among 2763 postmenopausal women with CAD. Sudden cardiac death was defined as death resulting from a cardiac origin that occurred within 1 hour of symptom onset. The associations between candidate predictor variables and SCD were evaluated in a Cox proportional hazards model. The C-index was used to compare the predictive value of the clinical risk factors with left ventricular ejection fraction (LVEF) alone and in combination. The net reclassification improvement was also computed.

**Results:** Over a mean follow-up of 6.8 years, SCD comprised 136 of the 254 cardiac deaths. The annual SCD event rate was 0.79% (95% confidence interval, 0.67-0.94). The following variables were independently associated with SCD in the multivariate model: myocardial infarction, heart failure, an estimated glomerular filtration rate of less than 40 mL/min/1.73 m², atrial fibrillation, physical inactivity, and diabetes. The incidences of SCD among women with 0 (n=683), 1 (n=1224), 2 (n=610), and 3 plus (n=246) risk factors at baseline were 0.3%, 0.5%, 1.2%, and 2.9% per year, respectively. The combination of clinical risk factors and LVEF (C-index, 0.681) were better predictors of SCD than LVEF alone (C-index, 0.600) and resulted in a net reclassification improvement of 0.20 (P<.001).

**Conclusions:** Sudden cardiac death comprised the majority of cardiac deaths among postmenopausal women with CAD. Independent predictors of SCD, including myocardial infarction, congestive heart failure, an estimated glomerular filtration rate of less than 40 mL/min/1.73 m², atrial fibrillation, physical inactivity, and diabetes, improved SCD prediction when they were considered in addition to LVEF.

See Invited Commentary at end of article

Sudden cardiac death (SCD) is an important clinical and public health problem, causing approximately 250,000 to 300,000 deaths each year in the United States. Several population-based studies have suggested that women who experience SCD are less likely to have a history of clinical cardiovascular disease, evidence of structural heart disease, or left ventricular (LV) dysfunction than men with SCD. In the Nurses’ Health Study, more than two-thirds of women with SCD events had no reported history of cardiac disease. Women with CAD are also reported to have a lower risk of ventricular arrhythmias and SCD events than men. These studies have also identified SCD risk factors that include both traditional ones associated with CAD and nontraditional measures such as depression and dietary factors. Although these studies provide important insights into SCD among women across the general population, very little data exist on the risk factors and predictors of SCD in women with CAD.

See also page 1712

In clinical practice, the only established predictor for SCD is severely decreased LV systolic function. Recent studies, however, suggest that ejection fraction alone is unlikely to be sufficient for effective SCD risk prediction, because it lacks
both sensitivity and specificity. Fewer than one-third of all SCD cases have severely decreased LV ejection fraction (LVEF) that would have qualified them as candidates for an implantable cardioverter defibrillator. As a result of these studies, recent reports from the National Heart, Lung, and Blood Institute and the Heart Rhythm Society emphasize the need to identify risk factors early in the course of the SCD pathway before LV dysfunction develops and to assess their utility in prediction algorithms.

We evaluated these research questions in a study of postmenopausal women with established CAD. Our first goal was to quantify SCD risk in this population and to compare it with risks for mortality from other cardiac and noncardiac conditions. The second goal was to identify the most relevant risk factors for SCD among a large number of candidate variables using both traditional longitudinal methods and competing risk models. Finally, we determined the extent to which the identified risk factors could predict SCD risk and compared their incremental predictive value with prediction based on LVEF alone.

**METHODS**

**DESIGN**

The trial design, methods, baseline findings, and main outcomes of the Heart and Estrogen/progestin Replacement Study (HERS) have been published previously. All participants provided written informed consent before study entry. The trial was randomized, double-blinded, placebo-controlled trial of the effect of treatment with 0.25 mg of conjugated estrogens plus 2.50 mg of medroxyprogesterone acetate daily vs placebo on the CAD event rate among 2763 postmenopausal women with documented CAD. The participants were postmenopausal women younger than 80 years with no previous hysterectomy and a history of at least 1 of the following: myocardial infarction (MI), coronary artery bypass graft surgery, percutaneous coronary angioplasty, or prior congestive heart failure.19 All other deaths were categorized as noncardiac causes, and death due to coronary revascularization or congestive heart failure required the participant to have been observed alive within the previous hour and did not include fatal events that occurred during sleep. A central committee adjudicated all of the events. Data from all deaths, hospitalizations, and other suspected outcome events were reviewed and classified according to pre-specified criteria by an independent morbidity and mortality subcommittee blinded to treatment assignment. Family members reported suspected outcome events within 24 hours to the HERS Coordinating Center, which had the primary responsibility for the outcome database. Clinics then obtained and sent specified documentation to the coordinating center that included hospital discharge summaries, electrocardiograms, cardiac enzyme levels, and other test results.

**BASELINE CHARACTERISTICS**

In this analysis, a series of baseline characteristics were evaluated as potential risk factors for SCD, non-SCD, death from other causes, and survivors. Sociodemographic factors included age, race, and education. Lifestyle factors included physical activity, cigarette smoking within 1 year of enrollment, regular alcohol use, and body mass index. Physical activity was defined by participation in a regular exercise program, such as cardiac rehabilitation, aerobics, or vigorous walking for at least 10 minutes per session, at least 3 times per week. Additional candidate risk factors from baseline included diabetes, systolic blood pressure, high-density lipoprotein, low-density lipoprotein, triglycerides, and estimated glomerular filtration rate (eGFR) from creatinine (categorized as >60, 40-60, and <40 mL/min/1.73 m²). The eGFR was evaluated with the use of the 4-variable simplified Modification of Diet in Renal Disease equation.21 Heart disease severity was evaluated by the presence of LV hypertrophy on the 12-lead electrocardiogram, previous MI, history of percutaneous coronary angioplasty, and prior congestive heart failure. Electrocardiographic abnormalities that were evaluated included left bundle branch block, corrected QT interval, and atrial fibrillation. The presence of atrial fibrillation was assessed by standard 12-lead electrocardiograms obtained at study enrollment and at yearly follow-up visits. Finally, we retrospectively reviewed 1773 of the 2763 participants’ medical records (66% of the HERS cohort) to obtain echocardiographic data on the LVEF. The LVEF was modeled as normal (>50%), mildly decreased (40%-50%), moderately decreased (35%-39%), and severely decreased (<35%). We divided the LVEF into multiple categories to optimize its ability to predict SCD. The LVEF was not modeled as a linear variable because its association with SCD risk was found to be nonlinear.

**OUTCOME VARIABLES**

Sudden cardiac death was defined as death that occurred within 1 hour of the onset of symptoms. This definition, which matches the one proposed by the National Heart, Lung, and Blood Institute and the Heart Rhythm Society working group on SCD, required the participant to have been observed alive within the previous hour and did not include fatal events that occurred during sleep. A central committee adjudicated all of the events. Data from all deaths, hospitalizations, and other suspected outcome events were reviewed and classified according to pre-specified criteria by an independent morbidity and mortality subcommittee blinded to treatment assignment. Family members reported suspected outcome events within 24 hours to the HERS Coordinating Center, which had the primary responsibility for the outcome database. Clinics then obtained and sent specified documentation to the coordinating center that included hospital discharge summaries, electrocardiograms, cardiac enzyme levels, and other test results.

**STATISTICAL ANALYSIS**

We estimated annual SCD, non-SCD, and noncardiac death rates with 95% confidence intervals (CIs). We then compared these 3 groups with survivors using the χ² test for categorical variables and 1-way analysis of variance for continuous variables. Time-dependent risk factors for SCD were screened using unadjusted Cox models, in which other causes of death, unavailability for follow-up, and the end of the study were treated as censoring. Variables associated with SCD at P < 0.1 were considered for inclusion in a multivariate analysis. Backward deletion with a retention criterion of P < .20 was then used to select the final multivariate model. Also, we repeated this analysis using the Fine-Gray model, in which non-SCD and noncardiac death were treated as competing risks. In contrast to the Cox model, the Fine-Gray model is sensitive to indirect adverse or protective effects.
in particular, a factor strongly associated with the competing risks could appear protective against SCD essentially by reducing the time at risk. We also repeated the assessment of risk factors for SCD in the subcohort with echocardiograms.

Our next series of methods evaluated baseline clinical characteristics as well as LVEF for SCD risk prediction. We first compared SCD event rates by the number of risk factors as a rough clinical guideline. Then, focusing on the subset of women with echocardiograms, we used the C-index, a measure of discrimination, to evaluate risk prediction models using LVEF only, selected clinical characteristics (MI, heart failure, low eGFR, atrial fibrillation, physical inactivity, diabetes, and alcohol use), and both. C-indexes were estimated using 20 repetitions of 10-fold cross-validation. We assessed net reclassification improvement to determine how well the addition of clinical characteristics to an LVEF-only prediction model reclassifies SCD cases into higher risk strata and other women into lower categories. Finally, we calculated the C-index for non-SCD and noncardiac death using the model with LVEF and clinical characteristics. To evaluate whether the risk model differentially predicted these end points, we used bootstrap resampling to estimate bias-corrected 95% CIs for the pairwise difference between the C-indexes for SCD, non-SCD, and noncardiac death.

RESULTS

Among the 2763 women enrolled in HERS, there were 254 cardiac deaths and 246 noncardiac deaths during the 6.8-year follow-up period. Sudden cardiac death made up 54% (136 events) of the cardiac-related deaths and 27% of all deaths, with an annual event rate of 0.79% per year (95% CI, 0.67-0.94) (Figure 1). Also, there were 118 non-SCDs (0.69% per year; 95% CI, 0.57-0.82) and 246 noncardiac deaths (1.43% per year; 95% CI, 1.27-1.63). The baseline clinical characteristics and laboratory values of the study participants stratified by SCD, non-SCD, other causes of death, and survivors are presented in Table 1. There were no differences in most of the baseline characteristics across the different groups. In particular, electrocardiographic parameters, including the corrected QT interval, history of left bundle branch block, and LV hypertrophy, did not differ significantly across the categories. The participants who died of cardiac causes (either sudden or nonsudden) had a higher prevalence of congestive heart failure and diabetes, a higher body mass index, and a lower low-density lipoprotein level than those who died of noncardiac causes. In comparison between participants who had subsequent SCD (n=136) and non-SCD events (n=118), all characteristics were nonsignificant at P=0.05 (Table 1).

CLINICAL VARIABLES ASSOCIATED WITH SCD

In unadjusted models, MI, heart failure, an eGFR of less than 40 mL/min/1.73 m², atrial fibrillation, physical inactivity, diabetes, alcohol use, percutaneous coronary angioplasty, left bundle branch block, and LV hypertrophy were associated with SCD at P<0.1. Of these variables, MI, heart failure, a low eGFR, atrial fibrillation, physical inactivity, diabetes, and alcohol use were retained in the final multivariate model (Table 2). Myocardial infarction, heart failure, and a low eGFR were associated with an approximate 2-fold or higher risk for SCD after adjustment. Results using the competing risks analysis were essentially the same.

The LVEF assessments were based on clinical echocardiograms that were obtained before randomization (median, 32 months; interquartile range, 17-56 months). The LVEF was normal in 1226 participants (69%), mildly decreased in 318 participants (18%), moderately decreased in 137 participants (8%), and severely decreased in 92 participants (5%). In the echocardiogram subcohort, 319 deaths occurred during follow-up: 90 SCD events (0.81% per year; 95% CI, 0.66-1.00), 78 non-SCD events (0.71% per year; 95% CI, 0.57-0.88), and 151 noncardiac deaths (1.37% per year; 95% CI, 1.16-1.60). Women with echocardiograms accounted for 90 of the 136 SCD cases (66%). Myocardial infarction, heart failure, a low eGFR, atrial fibrillation, diabetes, left bundle branch block, and LVEF were retained in the final multivariate model selected using data for this subcohort (Table 2).

PREDICTION OF SCD USING NUMBERS OF CLINICAL RISK CHARACTERISTICS

Of the 2763 women in the HERS cohort, 25% had none of the 7 risk factors identified in the full cohort, 44% had 1 risk factor, 22% had 2 risk factors, and 9% had 3 or more risk factors at baseline. The SCD risk increased almost 10-fold across the 4 groups (Figure 2). The participants with no risk factors had an annualized SCD risk of 0.34% compared with 2.90% for those with at least 3 risk factors.

PREDICTION OF SCD USING LVEF AND CLINICAL RISK CHARACTERISTICS

C-indexes for the models with LVEF alone, clinical characteristics alone, and both were 0.600, 0.666, and 0.681, respectively. The net reclassification for the addition of clinical characteristics to the LVEF-only model was 20% (P<0.001) (Table 3), mostly owing to the reclassification of 24% of the women who died of SCD into a higher-risk category.

PREDICTION OF NON-SCD AND NONCARDIAC DEATH

The C-index for predicting non-SCD in the model with both LVEF and clinical characteristics was 0.702, whereas
Table 2. Risk Factors for Sudden Cardiac Death Among Women With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Complete HERS Cohort (n=2763)</th>
<th>LVEF Subcohort (n=1773)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cox Model</td>
<td>Fine-Gray Model</td>
</tr>
<tr>
<td></td>
<td>HR (95% Confidence Interval)</td>
<td>P Value</td>
</tr>
<tr>
<td>Nonuse of alcohol</td>
<td>1.42 (0.94-2.15)</td>
<td>.09</td>
</tr>
<tr>
<td>Prior MIs</td>
<td>1.13 (0.77-1.65)</td>
<td>.54</td>
</tr>
<tr>
<td>&gt;1</td>
<td>2.13 (1.32-3.44)</td>
<td>.002</td>
</tr>
<tr>
<td>CHF</td>
<td>2.15 (1.49-3.11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>1.96 (1.18-3.23)</td>
<td>.009</td>
</tr>
<tr>
<td>&lt;40</td>
<td>0.92 (0.59-1.45)</td>
<td>.72</td>
</tr>
<tr>
<td>40-60</td>
<td>1.92 (1.02-3.61)</td>
<td>.04</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>1.61 (1.04-2.50)</td>
<td>.04</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.52 (1.06-2.17)</td>
<td>.02</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>40-50</td>
<td>1.22 (0.68-2.19)</td>
<td>.50</td>
</tr>
<tr>
<td>35-39</td>
<td>1.54 (0.96-2.47)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; HERS, Heart and Estrogen/progestin Replacement Study; HR, hazard ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MIs, myocardial infarctions; NA, not applicable (this variable was nonsignificant in the backward selection model and was not evaluated further as a risk factor); NE, not evaluated among entire cohort.
the C-index for predicting noncardiac death was substantially lower, at 0.404. We found no significant difference in the model’s ability to discriminate risk for SCD and non-SCD (C-index pairwise difference, −0.021; 95% CI, −0.405 to 0.100). The model predicted SCD significantly better than noncardiac death (C-index pairwise difference, 0.277; 95% CI, 0.116-0.413).

In this cohort study of postmenopausal women with CAD, SCD made up most of the cardiac-related deaths during the 6.8-year follow-up period. We found that heart failure, reduced kidney function, atrial fibrillation, and diabetes were independent risk factors for SCD in both the overall analysis and the echocardiogram subgroup. Myocardial infarction and physical inactivity were additional risk factors for SCD in the original analysis; however, these variables were not independent markers of risk when LVEF was added to the model. In a competing risks analysis, we confirmed that MI, heart failure, reduced kidney function, and diabetes were associated with SCD in the overall cohort. In developing a risk-stratification approach, we delineated nearly a 10-fold gradient in SCD risk by using the number of risk factors present at baseline. Clinical characteristics were better predictors of SCD risk than LVEF alone, and the combination did better still.

Our study quantifies the risk of SCD events in an ambulatory cohort of women with CAD. During the 6.8-year follow-up period, 136 of the 254 cardiovascular deaths were adjudicated as sudden, making SCD the leading cause of cardiovascular-related mortality among this group. Prior population-based studies have found approximately a 10-fold lower risk of SCD in women.2 Furthermore, the annual rate of SCD among women in HERS is lower than SCD rates observed in populations with an established cardiomyopathy (eg, participants in the implantable cardioverter defibrillator trials). In this context, we have identified a group of well-functioning women at intermediate risk of SCD.

**COMMENT**

Most SCD cases occur in the general population or among individuals without advanced cardiovascular disease.1,16.26 With the exception of LVEF, other risk stratification variables are not used routinely in clinical practice. Our findings show that a simple assessment of clinical risk factors has a better predictive value for SCD than LVEF alone. These findings complement those of prior studies in higher-risk populations that suggest that there is an improvement in SCD risk prediction when clinical risk factors are combined with ejection fraction.27,28 Our final model, which consisted of both LVEF and clinical risk factors, also differentiated between SCD and noncardiac deaths; however, it did not discriminate between sudden and nonsudden cardiac events. This latter finding remains an area of important investigation and will require the evaluation of unique risk factors associated with cardiac arrhythmias. From the standpoint of clinical relevance, our model improves SCD prediction compared with LVEF alone, which may affect the care of women with CAD, given that SCD made up most of the cardiac-related deaths.

Among the identified risk factors, the strength of atrial fibrillation as an independent predictor of SCD was surprising. This finding suggests that a history of atrial arrhythmias increases the risk of ventricular tachyarrhythmias, which are the presumed cause of most SCD events, especially in patients with structural heart disease. Electrical remodeling processes in the atria, characterized by shorter action potential duration and refractoriness, un-
derlie the mechanisms that are implicated in atrial fibrillation. Similar changes may also occur in ventricular myocytes and subsequently increase the risk of ventricular tachycardia or ventricular fibrillation in susceptible patients. Also, the short-long-short sequences of ventricular conduction in atrial fibrillation may trigger ventricular arrhythmias. Alternatively, atrial fibrillation may be an additional marker of underlying structural heart disease. Regardless of the mechanism, our study indicates a need to evaluate atrial fibrillation further in another risk-based or predictive model for SCD events. This approach may require combining several cohorts of women with CAD.

Exercise and regular physical activity in women have been strongly associated with improved cardiovascular outcomes and lower all-cause mortality. Our findings suggest a strong association between regular exercise consisting of at least 3 sessions per week and a lower risk of SCD events. Given that very few noninvasive therapies protect against SCD, it is important to evaluate whether regular exercise reduces the incidence of SCD.

Diabetes and impaired glucose tolerance are other well-established risk factors for SCD in both men and women. Population-based studies, including the Paris Prospective Study and the Honolulu Heart Program, each of which enrolled approximately 8000 men, have demonstrated independent associations of diabetes and impaired glucose tolerance with SCD risk. Similarly, the Nurses’ Health Study also identified diabetes as one of the strongest clinical risk factors for SCD in women.

The echocardiogram subgroup analysis confirmed that many of the risk factors identified in the original analysis remained independent predictors of SCD risk after including LVEF. An LVEF lower than 35% is currently considered the most clinically relevant risk factor for SCD risk stratification and identifies patients who may benefit from an implantable cardioverter defibrillator. Although we did not have measures of LVEF in the entire cohort, our subgroup analysis demonstrated that heart failure, reduced kidney function, atrial fibrillation, and diabetes remained independent risk factors for SCD after adjustment for LVEF. Prior MI and physical inactivity likely cosegregate with LV function, as the inclusion of LVEF in the subgroup analysis precluded their addition to the model. Finally, although LVEF measures were not standardized in a core imaging laboratory, their assessment via chart review mimics echocardiographic-based methods of risk stratification in clinical practice. Furthermore, echocardiograms were not obtained at the outset of the study unlike other predictors of SCD in our study; however, the application of a LVEF measure from earlier time points also represents clinical practice.

Several limitations of our study should be considered. First, the limited number of SCD events may have resulted in a relatively small number of potential risk factors. Also, we did not validate our prediction model in other cohorts. Future studies will require collaborations across multiple cohorts to refine further SCD risk discrimination and to provide a means for both replication and cross-validation. Most women in this analysis were white; therefore, further assessment is required in postmenopausal women of other ethnicities. Left ventricular ejection fraction, a powerful predictor of risk for SCD, was not measured in all the participants of this study. Although we included a separate subgroup analysis, our findings may be limited given the lower number of SCD events. Finally, the variables identified in our analysis also appeared to be associated with non-SCD. This current limitation in risk prediction will require future studies to identify unique predictors of SCD.

In conclusion, SCD comprised the majority of cardiac-related deaths among postmenopausal women with CAD. We found that, in addition to LVEF, MI, heart failure, an eGFR lower than 40 mL/min/1.73 m², atrial fibrillation, physical inactivity, and diabetes were independently associated with SCD in this large, multicenter sample of women with CAD. The risk factors served as better predictors of SCD than LVEF alone and enhanced risk discrimination when both were combined. A simple risk stratification based on the number of risk factors predicted a 10-fold gradient in the incidence of SCD. Future projects should focus on combining studies to allow more robust estimates for established risk factors and to identify additional markers that augment the predictive ability of an SCD risk model.

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