Kidney Dysfunction and Sudden Cardiac Death Among Women With Coronary Heart Disease

Rajat Deo, Feng Lin, Eric Vittinghoff, Zian H. Tseng, Stephen B. Hulley, Michael G. Shlipak

Abstract—We evaluated the association between kidney dysfunction and sudden cardiac death risk among ambulatory women with coronary heart disease. The Heart and Estrogen Replacement Study evaluated the effects of hormone treatment on cardiovascular events among 2763 postmenopausal women with coronary heart disease. Kidney dysfunction was categorized by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation. Multivariate proportional hazards models were used to adjust for cardiovascular risk factors, congestive heart failure, and myocardial infarction. At baseline, 37% (n=1027) had an eGFR of >60 mL/min, 54% (n=1503) had an eGFR of 40 to 60 mL/min, and 8% (n=230) had an eGFR of <40 mL/min. During the 6.8-year follow-up period, there were 136 adjudicated sudden cardiac deaths. The rate of sudden cardiac death was higher in those with lower kidney function (0.5% per year among those with an eGFR >60; 0.6% per year with an eGFR between 40 and 60; and 1.7% per year with an eGFR <40 mL/min; P for trend <0.001). After multivariate analysis with baseline risk factors, eGFR at 40 to 60 mL/min was not a significant predictor, but eGFR at <40 mL/min remained strongly associated with sudden cardiac death (hazard ratio: 3.2; 95% CI: 1.9 to 5.3); adjustment for incident congestive heart failure and myocardial infarction during follow-up diminished this association (hazard ratio: 2.3; 95% CI: 1.3 to 3.9), suggesting that congestive heart failure and myocardial infarction mediated only part of the association between kidney dysfunction and sudden cardiac death. Advanced kidney dysfunction is an independent predictor of sudden cardiac death among women with coronary heart disease. (Hypertension. 2008;51:1-5.)

Key Words: kidney dysfunction ■ women ■ sudden cardiac death

Sudden cardiac death (SCD) is an important clinical and public health problem: >450,000 Americans died in 1998 from SCD, defined as a sudden pulseless death attributed to cardiovascular disease occurring outside of the hospital.1 The proportion of cardiovascular deaths caused by SCD has increased over time, as have absolute rates of SCD among women aged 35 to 44 years.2 The presence and severity of underlying heart disease, including coronary heart disease, chronic heart failure, and depressed left ventricular ejection fraction, are the most predictive risk factors for the future occurrence of SCD.3–6 In addition, 1 population-based study among women has demonstrated an association between traditional coronary heart disease risk factors and SCD.2 Another population at high risk for SCD are persons with end-stage renal disease.7 According to the US Renal Data System, ~22% of all deaths are caused by SCD, and the incidence increases with age: 2% per year for ages 20 to 44 years, 3.7% per year for ages 45 to 64 years, and 7% per year for ages 65 years and older.7,8

Despite the high risk for SCD in patients with end-stage renal disease, few studies have evaluated the association between less severe reductions in kidney function and SCD incidence. Two recent studies found that chronic kidney disease was associated with increased SCD risk among subjects with advanced heart failure who were enrolled in clinical trials involving implantable cardioverter-defibrillators.9,10 In this setting, however, it is difficult to discern whether chronic kidney disease was merely a marker of heart failure severity or an independent predictor of SCD risk. Moreover, further evaluation is required to determine whether the results from these studies are applicable to women who are significantly less likely than men to receive implantable cardioverter-defibrillator therapy for the primary or secondary prevention of SCD.11

We hypothesized that chronic kidney disease would have an independent association with SCD incidence. We investigated this hypothesis among postmenopausal women with coronary heart disease who participated in the Heart and Estrogen/Progestin Replacement Study (HERS).

Methods

The trial design, methods, baseline findings, and main outcomes of the HERS have been published previously.12,13 The trial was a...
randomized, double-blinded, placebo-controlled trial of the effect of 0.625 mg of conjugated estrogens plus 2.500 mg of medroxyprogesterone acetate daily versus placebo on coronary heart disease (CHD) event risk among 2763 postmenopausal women with documented CHD.13 Participants were postmenopausal women 80 years of age with no previous hysterectomy and a history of ≥1 of the following: myocardial infarction (MI), coronary artery bypass graft surgery, percutaneous angioplasty, or >50% angiographic narrowing of a coronary artery. Among the reasons for exclusion were heart failure of New York Heart Association class III or IV.12,13

A total of 2763 postmenopausal women with CHD and an average age of 67 years were enrolled in HERS for a mean follow-up of 4.1 years; 2321 women (93% of those surviving) consented to follow-up in HERS II for a median additional follow-up of 2.7 years. There was no significant decrease in the rates of primary CHD events or secondary cardiovascular events among women assigned to the hormone group compared with the placebo group in HERS, HERS II, or overall.

### Kidney Function

Of the 2763 women enrolled in HERS, creatinine was measured at baseline in 2760 women. Estimated glomerular filtration rate (eGFR) was evaluated with the use of the 4-variable simplified Modification of Diet in Renal Disease equation.14

### Secondary Predictors

Other characteristics were used in this analysis as adjustment variables in multivariate models. These included sociodemographic factors (age and race), lifestyle factors (baseline exercise status), cardiovascular risk factors (current smoking, alcohol use, body mass index, diabetes, fasting blood glucose, systolic blood pressure [per 10 mm Hg], high-density lipoprotein, and triglycerides), heart disease severity (heart rate, atrial fibrillation, left bundle branch block on ECG, baseline heart failure, previous MI, and history of percutaneous angioplasty), and medication use (aspirin or β-blocker use).

Baseline heart failure was documented during the initial history and physical examination at the time of enrollment. Participants were noted to have a history of heart failure if they had dyspnea either at rest or with exertion and evidence of increased intravascular volume on physical examination.15 Signs for volume overload included jugular venous distention, rales on auscultation, and lower extremity edema. Incident heart failure was defined as hospitalizations to treat either increased intravascular volume or low cardiac output that was because of cardiac disease.16 We classified the severity of incident heart failure as requiring either 1 hospitalization during the follow-up period or ≥2 hospitalizations. Finally, incident MI was also included as an adjustment variable.
Kidney Dysfunction and Sudden Death in Women

Deo et al

Outcome

The primary outcome of HERS was nonfatal MI and CHD death. SCD was included in the primary CHD outcome but was adjudicated as a distinct clinical end point. SCD was defined as death that occurred within 1 hour of the onset of symptoms. This definition required the participant to have been observed alive within the previous hour and did not include fatal events that occurred during sleep. All of the events were adjudicated by a central committee. Data from all of the death and suspected primary outcome events were reviewed and classified according to prespecified criteria by an independent morbidity and mortality subcommittee blinded to treatment assignment. Suspected outcome events were reported by family members within 24 hours to the HERS Coordinating Center, which had 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 compared the distribution of participant characteristics across estimated glomerular filtration rate categories using the χ² test for categorical variables and ANOVA for continuous variables. Cox proportional hazards models were used to estimate the association between kidney function and incident SCD. We entered all of the variables into a backward stepwise elimination model. Variables associated with SCD at P<0.1 were retained in the final model. We tested for interactions of CrCl with baseline or incident heart failure on SCD risk using interaction product terms. Finally, we adjusted for heart failure and MI as time-dependent covariates.

Results

This analysis included 2760 participants: 1027 with eGFR at >60 mL/min, 1503 with eGFR at 40 to 60 mL/min, and 230 with eGFR at <40 mL/min. The mean eGFR and serum creatinine concentrations for participants in HERS were 58±14 mL/min and 1.1±0.3 mg/dL, respectively. The baseline clinical characteristics and laboratory values of the study participants stratified by eGFR are listed in Table 1. Participants with impaired kidney function were more likely older, African American, nonsmokers, and nonusers of alcohol. Women with kidney dysfunction were also more likely to have hypertension, diabetes, previous coronary artery bypass graft surgery, and heart failure. They also had higher fasting glucose levels. In addition, participants with impaired kidney function were less likely to be on aspirin and were more likely to be on a diuretic, angiotensin-converting enzyme inhibitor, and statin (Table 1).

Among the 2760 women originally enrolled in HERS, there were 136 adjudicated SCD events (4.9%) during the 6.8-year follow-up period. The rate of SCD was higher in those with lower kidney function: 0.5% per year among those with an eGFR at >60 mL/min, 0.6% per year with an eGFR at 40 to 60 mL/min, and 1.7% per year with an eGFR at <40 mL/min (Figure). The overall association of kidney function categories with SCD incidence remained significant after adjustment for baseline, potential confounding variables including sociodemographic and lifestyle factors, cardiovascular risk factors, and a history of heart failure (Table 2). However, the differences in incidence between women with CrCl at 40 to 60 and >60 were not statistically significant in unadjusted or adjusted analyses. When eGFR was evaluated as a continuous variable, it remained associated with SCD risk (hazard ratio [HR]: 0.62; 95% CI: 0.51 to 0.74 in unadjusted analysis; HR: 0.79; 95% CI: 0.66 to 0.96 after multivariate adjustment for baseline variables and incident congestive heart failure [CHF]). Finally, after adjustment for eGFR as a time-varying covariate, the risk for SCD is similar to the values in our original analysis after multivariate adjustment (HR: 1.02, 95% CI: 0.67 to 1.55 for eGFR 40 to 60 mL/min; HR: 2.27, 95% CI: 1.35 to 3.82 for eGFR <40 mL/min).

At the time of enrollment, 345 participants had a history of CHF. During the follow-up period, 197 participants required

Table 2. Association of Impaired Kidney Function With SCD

<table>
<thead>
<tr>
<th>Measure and Outcome</th>
<th>eGFR &gt;60</th>
<th>eGFR 40 to 60</th>
<th>eGFR &lt;40</th>
<th>P (Trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at baseline</td>
<td>1027</td>
<td>1503</td>
<td>230</td>
<td></td>
</tr>
<tr>
<td>No. of SCD events (%)</td>
<td>36 (3.5)</td>
<td>69 (4.6)</td>
<td>30 (13)</td>
<td></td>
</tr>
<tr>
<td>HR for SCD (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.36 (0.91 to 2.04)</td>
<td>4.65 (2.86 to 7.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for baseline variables*</td>
<td>1.00</td>
<td>1.14 (0.75 to 1.74)</td>
<td>3.16 (1.88 to 5.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for baseline variables plus incident CHF and MI</td>
<td>1.00</td>
<td>1.08 (0.70 to 1.65)</td>
<td>2.27 (1.33 to 3.88)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*All of the variables from Table 1 were entered into a backwards–elimination model. Those variables that were associated with SCD (at P<0.10) and included in the multivariate analysis were history of heart failure, age, current smoking, heart rate, and high-density lipoprotein.
1 hospitalization for CHF, and 150 required ≥2 hospitalizations for CHF exacerbations. We observed no evidence for effect modification by the presence or absence of CHF on the association between eGFR and incident SCD (P for interaction = 0.69). However, CHF was a strong predictor of sudden death: in full multivariate analysis, ≥2 CHF hospitalizations during follow-up had an HR at 8.15 (95% CI: 5.02 to 13.56); 1 CHF hospitalization had an HR at 3.2 (95% CI: 1.9 to 5.7); and history of CHF at baseline had HR at 1.9 (95% CI: 1.3 to 2.8). Incident MI was also a predictor of SCD events. Adjustment for both incident heart failure and MI as time-dependent covariates moderately attenuated the association of kidney function categories with SCD risk (Table 2).

**Discussion**

In summary, our analysis found that moderate-to-advanced kidney dysfunction (CrCl <40) was associated with significant elevations in SCD risk over 6.8 years of follow-up among women with CHD. The category of most impaired kidney function remained independently associated with SCD risk after adjustment for intervening cardiovascular events. Finally, our study demonstrates that CHF and incident MI, in addition to renal dysfunction, are strongly associated with SCD in women with CHD.

Our results extend the observation that impaired kidney function predicts SCD risk to a much healthier cohort than in previous studies conducted within implantable cardioverter-defibrillator trials. In these trials, only 15% to 30% of the participants were women, and the mean left ventricular ejection fraction was 20% to 25%. In addition, 30% of the participants in Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and all of the persons in Comparison Of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) had New York Heart Association III or IV CHF. The rate of all-cause mortality in MADIT II was ~17% per year. These baseline characteristics and outcomes differ markedly from our study, in which heart failure with New York Heart Association III or IV at baseline was an exclusion criterion, and the rate of all-cause mortality was 3% per year. Thus, kidney dysfunction was less likely to be a proxy for heart failure severity; although some residual confounding at moderate levels of heart failure is possible. Our findings suggest that impaired kidney function is independently associated with SCD among women with CHD.

The increased risk of SCD for women with kidney disease observed in this study may have been attributable to higher rates of malignant ventricular arrhythmias. Kidney dysfunction may cause structural changes of the heart, including left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction, and cardiac fibrosis, all of which may contribute to the increased arrhythmic risk. In addition, autonomic dysfunction, myocyte dysfunction, and altered electrolyte metabolism may contribute to arrhythmic risk in patients with kidney dysfunction.

This study has several strengths. HERS is a unique study with well-characterized women with CHD and rigorous follow-up and adjudication procedures. SCD was a specific end point of HERS, which differs from many epidemiological studies. Our analysis included an adequate number of SCD events for multivariate analysis, which allowed us to evaluate the association between kidney function and SCD in an ambulatory cohort with moderate risk.

The limitations of our study should also be considered. Residual confounding cannot be excluded; eg, left ventricular ejection fraction, a powerful predictor of risk for SCD, was not measured in all of the participants in our study. We relied on the clinically available test of kidney function, the serum creatinine. A stronger or more linear association may have been detectable had we used a direct measure of glomerular filtration rate (iothalamate clearance) or cystatin C, an alternate indirect measure of kidney function. Finally, our study did not measure the severity of CHD, which could affect the association between kidney dysfunction and SCD risk.

**Perspectives**

In conclusion, advanced kidney dysfunction is an independent risk factor for SCD among women with CHD, an association that appears to be mediated in part by the development of CHF and incident MI. Future studies in populations or cohorts without cardiovascular disease are necessary to evaluate whether kidney dysfunction is independent of prevalent cardiovascular disease as a predictor of SCD risk. Studies should carefully evaluate the onset of kidney dysfunction and heart failure and the timing of their associations with SCD risk. Finally, prospective studies are required to evaluate whether kidney dysfunction is useful for SCD risk stratification among persons at moderate risk for cardiovascular complications.

**Source of Funding**

Funding for this work was provided by the American Heart Association Established Investigator Award, awarded to M.G.S.

**Disclosures**

None.

**References**


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Hypertension, published online April 7, 2008;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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