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Renal Insufficiency and Cardiovascular Events in Postmenopausal Women With Coronary Heart Disease

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OBJECTIVES This study sought to determine the independent association of renal insufficiency with cardiovascular risk among women with known coronary heart disease (CHD).

BACKGROUND Although patients with end-stage renal disease and proteinuria are at high risk for cardiovascular events, little is known about the cardiovascular risk associated with moderate renal insufficiency.

METHODS The Heart and Estrogen/progestin Replacement Study (HERS) was a clinical trial among 2,763 women with coronary disease who were randomized to conjugated estrogen plus progestins or identical placebo and followed for a mean of 4.1 years. Women were categorized as having normal renal function (creatinine < 1.2 mg/dl; n = 2,012), mild renal insufficiency (1.2 mg/dl to 1.4 mg/dl; n = 567) and moderate renal insufficiency (>1.4 mg/dl; n = 182). We examined the independent association of renal function with incident cardiovascular events including CHD death, nonfatal myocardial infarction, hospitalization for unstable angina, stroke and transient ischemic attacks.

RESULTS Compared with women with normal renal function, those with mild and moderate renal insufficiency were older, more likely to be black, have a history of hypertension and diabetes and have higher serum levels of triglycerides and lipoprotein(a). After multivariate adjustment, both mild (relative hazards [RH] = 1.24; 95% confidence interval [CI]: 1.0 to 1.5) and moderate renal insufficiency (RH = 1.57; 95% CI: 1.2 to 2.1) were independently associated with increased risk for cardiovascular events compared with women with normal renal function.

CONCLUSIONS Renal insufficiency is an independent risk factor for cardiovascular events in postmenopausal women with known coronary artery disease. Renal function may add helpful information to CHD risk stratification. (J Am Coll Cardiol 2001;38:705–11) © 2001 by the American College of Cardiology

Patients with end-stage renal disease have a markedly elevated risk of coronary heart disease (CHD) and other vascular disease events (1,2), perhaps as a result of lipoprotein abnormalities, elevated serum homocysteine levels and an increased risk of thrombosis (3–5). Several of these abnormalities, such as elevated lipoprotein(a) and homocysteine, are also present in patients with moderate renal insufficiency. The most common causes of renal insufficiency, hypertension and diabetes mellitus are also independent risk factors for CHD events. Although there is considerable evidence that end-stage renal disease independently increases the risk of CHD, less is known about the relation between mild-to-moderate renal insufficiency and CHD (6).

Studies in subjects without CHD have found that renal insufficiency is associated with all-cause mortality, and some studies have found an independent association of renal insufficiency with cardiovascular events (7–11). One study found renal insufficiency to increase the risk of CHD events in a sample that included persons with and without prevalent vascular disease (12). To test the hypothesis that mild-to-moderate renal insufficiency increases the risk for CHD events, we analyzed data collected in the Heart and Estrogen/progestin Replacement Study (HERS), a clinical trial of the effect of hormone therapy among 2,763 postmenopausal women.

METHODS

Subjects. The design, methods and primary results of HERS have been published (13,14). Briefly, HERS participants were postmenopausal women aged <80 years with established CHD who had not had a hysterectomy. Inclusion criteria were prior myocardial infarction (MI), coronary artery bypass graft surgery (CABG), percutaneous coronary revascularization (PTCA) or angiographic evidence of a 50% occlusion of one or more major coronary arteries. Exclusion criteria were a recent CHD event, New York

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CABG = coronary artery bypass graft surgery
CHD = coronary heart disease
CI = confidence interval
ECG = electrocardiogram
HERS = Heart and Estrogen/progestin Replacement Study
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
RH = relative hazards
TIA = transient ischemic attack

Heart Association class IV or severe class III congestive heart failure, serum triglyceride level >300 mg/dl, recent use of any hormone therapy, uncontrolled hypertension or diabetes, a disease (other than CHD) judged likely to be fatal within four years or intolerance to hormone replacement therapy. Participants were randomly assigned to receive a single identical tablet containing either conjugated equine estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg or placebo.

Measurements. Demographic characteristics, health history, CHD risk factors, medication use, educational level and quality of life were assessed at baseline. Baseline levels of fasting total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and lipoprotein(a) were determined by the Lipoprotein Analytical Laboratory at Johns Hopkins Hospital. Serum creatinine levels were measured at the initial examination visit in all but one participant. We excluded one additional participant with an initial serum creatinine level of 9.3 mg/dl. The serum creatinine level was measured on unfrozen serum at SmithKline Beecham Clinical Labs. In addition, we estimated the creatinine clearance for each participant using the Cockcroft-Gault equation [(140 − age) · body mass/72 · creatinine] · 0.85 (in women) (15).

Follow-up and outcome assessment. Follow-up visits to the clinical centers occurred every four months over a mean of 4.1 years. All suspected outcome events were classified independently by two physician reviewers unaware of treatment assignment, and discordant classifications were resolved in discussions between the reviewers.

The primary outcome of this study was a composite cardiovascular disease outcome that included CHD death, nonfatal MI, unstable angina and cerebrovascular disease events. Coronary heart disease death was defined as fatal MI, sudden death within 1 h of symptoms, unobserved death that occurred out of the hospital in the absence of other known causes or death due to a coronary revascularization procedure or congestive heart failure. Diagnosis of MI was based on an algorithm that incorporated clinical symptoms, electrocardiogram (ECG) abnormalities and cardiac enzyme levels (13). The diagnosis of unstable angina required a hospital admission for suspected coronary ischemia and the presence of ST-segment or T-wave changes on the ECG. Cerebrovascular disease included both stroke and transient ischemic attacks (TIA). We did not include PTCA and CABG as outcomes in these analyses because of concern that participants with elevated serum creatinine levels might be less likely to be referred for these procedures. We also analyzed the data using a composite cardiovascular outcome that included revascularization events, and the results were virtually identical.

Statistical analysis. To evaluate the association of baseline serum creatinine levels and incident cardiovascular events, we began by calculating unadjusted cardiovascular event rates for each 0.1 mg/dl and 0.5 mg/dl increment in serum creatinine. We then used multivariate proportional hazards models, including all the variables listed in Table 1, to determine the independent association of serum creatinine and cardiovascular events. Using stepwise regression procedures, we retained in the model only those variables that were associated with the outcome at a significance level of $p < 0.2$. We tested the assumption of log-linearity of serum creatinine level with cardiovascular events by including linear and quadratic terms for serum creatinine and found that the association was unchanged.

The serum creatinine level was also analyzed as an ordinal categorical variable. We defined moderate renal insufficiency as a serum creatinine level >1.4 mg/dl, the 95th percentile among women in the Framingham Heart study (16). Based on the National Kidney Foundation definition of normal creatinine levels in women (1.2 mg/dl), we divided the remaining participants into two groups: mild renal insufficiency (1.2 to 1.4 mg/dl) and normal renal function (<1.2 mg/dl) (17). The time to first new cardiovascular event was initially compared among the three groups using Kaplan-Meier survival curves, and the log-rank test was used to test for differences in the survival curves. We then evaluated the multivariate-adjusted relative hazards (RH) associated with mild and moderate renal insufficiency compared with women with normal renal function using the methods described above. For comparison, we contrasted the risk of cardiovascular events associated with diabetes mellitus with the risk associated with moderate renal insufficiency.

In addition, we determined the association of estimated creatinine clearance (categorized as >60 ml/min, 40 to 60 ml/min and <40 ml/min) with cardiovascular events. Using proportional hazards models, we determined the risk of cardiovascular disease events for women in each category of reduced creatinine clearance.

We hypothesized that four variables might interact with renal function in predicting CHD events: prior history of diabetes or hypertension, use of angiotensin-converting enzyme (ACE) inhibitors and hormone therapy. We tested for interactions with these variables and calculated adjusted RH for patients with moderate renal insufficiency after stratifying for these characteristics.

Table 1. Characteristics of Participants by Creatinine Level at Baseline

Characteristics	<1.2 mg/dl (n = 2,012)	1.2–1.4 mg/dl (n = 567)	>1.4 mg/dl (n = 182)	p Value*
	Mean ± SD or Percent			
Age (yrs)	66 ± 7	68 ± 6	68 ± 7	<0.001
Race (%)				
White	91	87	76	<0.001
Black	6	11	21	
Other	4	2	3	
Diabetes (%)	20	26	44	<0.001
Hypertension (%)	55	66	77	<0.001
Prior myocardial infarction (%)	51	53	59	0.14
Prior PTCA (%)	45	43	38	0.22
Prior CABG (%)	40	42	51	0.01
Current tobacco use (%)	14	12	12	0.46
LDL-cholesterol (mg/dl)	145 ± 38	145 ± 36	147 ± 43	0.72
HDL-cholesterol (mg/dl)	51 ± 13	49 ± 13	49 ± 14	0.12
Triglyceride level (mg/dl)	160 ± 61	168 ± 64	182 ± 67	0.002
Lipoprotein(a) (mg/dl)	33 ± 32	35 ± 33	38 ± 36	0.05
Body mass index (kg/m^2)	28 ± 6	29 ± 6	29 ± 5	0.01
Education (yrs)	13 ± 3	13 ± 3	12 ± 3	0.02
Alcohol consumption (%)				
None	58	68	72	<0.001
<5 drinks/week	19	15	14	
≥5 drinks/week	23	17	14	
Activity less than peers (%)	23	28	47	<0.001
Aspirin use (%)	80	76	72	0.004
Lipid-lowering agent use (%)	36	37	42	0.17
Beta-blocker use (%)	32	34	32	0.70
ACE inhibitor use (%)	15	24	30	<0.001
Calcium channel blockers (%)	54	56	60	0.27
Randomization to postmenopausal hormone therapy (%)	50	50	54	0.55

*p values based on chi-square tests for proportions and analysis of variance for continuous values.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass grafting; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTCA = percutaneous transluminal coronary angioplasty.

All analyses were conducted using SAS 6.12 software. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics. Among the 2,761 participants included in this analysis, 2,012 (73%) had normal renal function (creatinine level < 1.2 mg/dl); 567 (21%) had mild renal insufficiency (creatinine level 1.2 mg/dl to 1.4 mg/dl), and 182 (7%) had moderate renal insufficiency (creatinine level > 1.4 mg/dl) at baseline (Fig. 1).

Compared with women with normal renal function, women with mild and moderate renal insufficiency were older and more often black and had a higher prevalence of hypertension, diabetes mellitus and prior CABG (Table 1). Participants with renal insufficiency were also less likely to use alcohol and were more likely to rate their activity level as "less active than peers" than women with normal renal function. Baseline serum triglyceride and lipoprotein(a) levels were highest among women with moderate renal insufficiency. Among the three groups of women, aspirin use was lowest in women with renal insufficiency and use of ACE inhibitors was highest.

Association between serum creatinine level and cardiovascular events. In unadjusted analysis, cardiovascular event rates increased with increasing creatinine levels ($p < 0.001$) (Fig. 2). After multivariate adjustment, each 0.5 mg/dl increase in serum creatinine was independently associated with 23% increased risk (95% confidence interval [CI]: 10 to 38%) for all cardiovascular events, a 36% increased risk (95% CI: 11 to 65%) for CHD death and an 18% increased risk (95% CI: 8 to 30%) for stroke and TIA. Higher serum creatinine levels were marginally associated with increased risk for nonfatal MI (20%; 95% CI: −1 to 46%) and unstable angina (15%; 95% CI: −7 to 42%).

Association of mild and moderate renal insufficiency with cardiovascular events. Mild (1.2 to 1.4 mg/dl) and moderate (>1.4 mg/dl) renal insufficiency were associated with increased risk for cardiovascular events (Fig. 3). After multivariate adjustment, mild and moderate renal insufficiency remained independent predictors of cardiovascular events (Table 2). The independent association of moderate

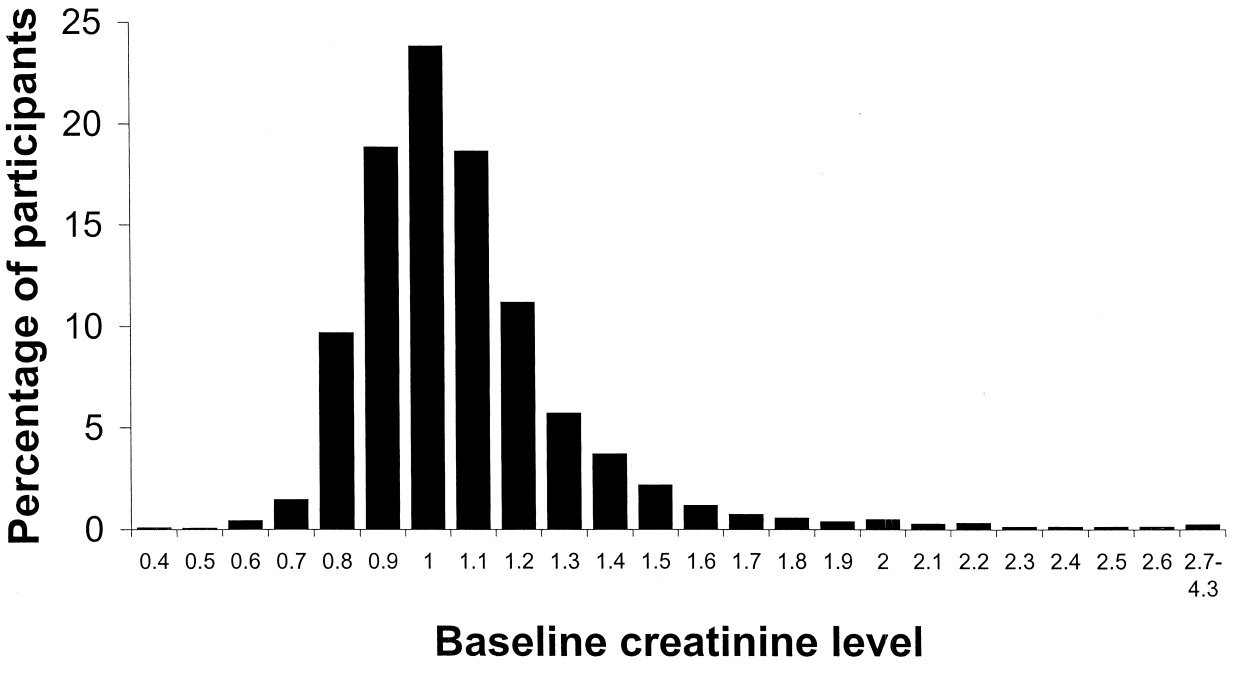

Figure 1. Distribution of serum creatinine levels (mg/dl) among 2,761 Heart and Estrogen/progestin Replacement study participants.

renal insufficiency with CHD death and stroke/TIA reached statistical significance, but the association with nonfatal MI or unstable angina did not. For comparison, diabetes was associated with a 47% increased risk (95% CI: 20 to 80%) for cardiovascular events, whereas moderate renal insufficiency was associated with a 57% (95% CI: 20 to 110%) increased risk.

Estimated creatinine clearance and cardiovascular events. A total of 322 (12%) women had an estimated creatinine clearance of <40 ml/min, and 1,135 (41%)

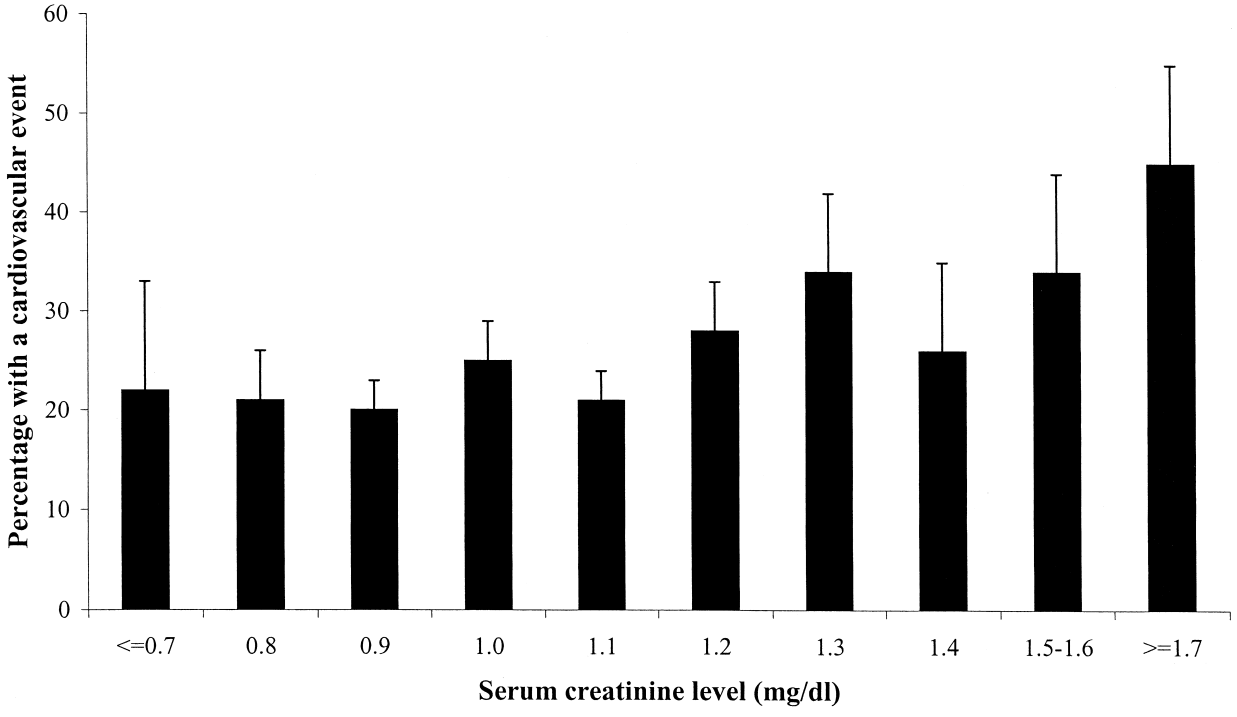

Figure 2. Cardiovascular event rates by serum creatinine level at entry into the Heart and Estrogen/progestin Replacement study. The percentage of women experiencing an event is displayed with 95% confidence intervals. Cardiovascular events include coronary heart disease death, nonfatal myocardial infarction, hospitalization for unstable angina, stroke and transient ischemic attacks.

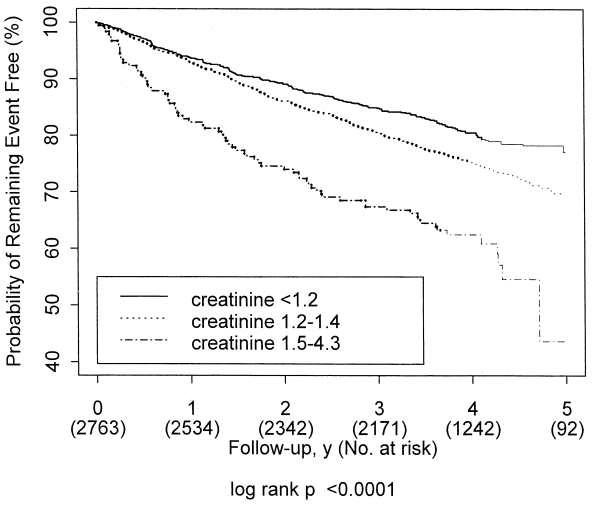

Figure 3. Kaplan-Meier curve demonstrating cardiovascular event-free survival among women in the Heart and Estrogen/progestin Replacement study based on the presence of renal insufficiency. Increasing levels of renal insufficiency were associated with greater cardiovascular event rates.

participants had an estimated creatinine clearance between 40 to 60 ml/min. Creatinine clearance <40 ml/min was associated with increased risks for all cardiovascular events, nonfatal MI, CHD death and stroke and TIA that were similar in magnitude to the risks associated with a serum creatinine level >1.4 mg/dl (Table 3). Creatinine clearance of 40 to 60 ml/min was associated with a modest elevation in risk for all cardiovascular events compared with women who had a creatinine clearance >60 ml/min.

Potential interactions. The increased risk for cardiovascular events associated with moderate renal insufficiency (serum creatinine level >1.4 mg/dl) was similar among women with hypertension (RH = 1.57; 95% CI: 1.2 to 2.1) and without hypertension (1.63; 95% CI: 0.9 to 3.0), with diabetes (RH = 1.74; 95% CI: 1.1 to 2.7) and without diabetes (RH = 1.48; 1.0 to 2.1), women using ACE inhibitors (RH = 1.46; 0.9 to 2.5) and women not using ACE inhibitors (RH = 1.62; 1.2 to 2.2) and among women randomly assigned to hormone therapy (RH = 1.47; 1.0 to 2.2) and those assigned to placebo (RH = 1.73; 1.2 to 2.5).

DISCUSSION

New findings. The prevalence of chronic renal insufficiency, defined as a serum creatinine level >1.4 mg/dl, was estimated to be 10.9 million persons in the U.S. in the Third National Health and Nutrition Examination Survey (NHANES III) (18). Despite the high prevalence, chronic renal insufficiency has not been well characterized (6). We found that mild and moderate renal insufficiency were independent predictors of cardiovascular events in postmenopausal women with CHD.

Characterized either as a serum creatinine level >1.4 mg/dl or an estimated creatinine clearance of <40 ml/min, moderate renal insufficiency was associated with 60% to 80% increased risk of cardiovascular events. For comparison, diabetes was associated with a 50% increased risk for cardiovascular events among HERS participants. The association of renal insufficiency with cardiovascular outcomes persisted among subgroups with and without hypertension and diabetes and treatment with ACE inhibitors or hormone therapy. Even mild renal insufficiency, defined by

Table 2. Association of Serum Creatinine Level With Cardiovascular Events

	<1.2 mg/dl (n = 2,012)	1.2–1.4 mg/dl (n = 567)	>1.4 mg/dl (n = 182)
All cardiovascular events			
Number	442	168	72
Incidence (per 1,000 person-years)	60	88	131
Multivariate-adjusted RH (95% CI)	1.0	1.24 (1.0–1.5)	1.57 (1.2–2.1)
Nonfatal myocardial infarction			
Number	169	62	25
Incidence (per 1,000 person-years)	21	29	40
Multivariate-adjusted RH (95% CI)	1.0	1.24 (0.9–1.7)	1.46 (0.9–2.3)
CHD death			
Number	69	37	22
Incidence (per 1,000 person-years)	8	17	33
Multivariate-adjusted RH (95% CI)	1.0	1.43 (0.9–2.2)	1.99 (1.2–3.4)
Unstable angina			
Number	153	57	19
Incidence (per 1,000 person-years)	19	28	30
Multivariate-adjusted RH (95% CI)	1.0	1.23 (0.9–1.7)	1.21 (0.7–2.0)
Stroke and TIA			
Number	126	57	31
Incidence (per 1,000 person-years)	16	27	51
Multivariate-adjusted RH (95% CI)	1.0	1.29 (0.9–1.7)	2.06 (1.4–3.1)

Variables retained in the multivariate models include age, race, hypertension, diabetes, tobacco use, prior coronary artery bypass surgery, body mass index, waist-to-hip ratio, high-density lipoprotein level, triglyceride level, lipoprotein(a) level, alcohol use, physical activity, education level, aspirin use, angiotensin-converting enzyme inhibitor use and diuretic use. The stroke/TIA model is also adjusted for the presence of baseline atrial fibrillation.

CHD = coronary heart disease; CI = confidence interval; RH = relative hazards; TIA = transient ischemic attack.

Table 3. Association of Estimated Creatinine Clearance With Cardiovascular Events

	>60 ml/min (n = 1,306)	40–60 ml/min (n = 1,135)	<40 ml/min (n = 322)
All cardiovascular events			
Number	275	287	119
Incidence (per 1,000 person-years)	56	72	118
Multivariate-adjusted RH (95% CI)	1.0	1.28 (1.0–1.6)	1.76 (1.3–2.3)
Myocardial infarction			
Number	112	105	39
Incidence (per 1,000 person-years)	22	24	35
Multivariate-adjusted RH (95% CI)	1.0	1.24 (0.9–1.6)	1.65 (1.1–2.4)
CHD death			
Number	49	48	30
Incidence (per 1,000 person-years)	9	10	25
Multivariate-adjusted RH (95% CI)	1.0	1.33 (0.9–2.1)	2.56 (1.5–4.3)
Unstable angina			
Number	89	109	31
Incidence (per 1,000 person-years)	17	25	28
Multivariate-adjusted RH (95% CI)	1.0	1.40 (1.0–1.9)	1.37 (0.9–2.2)
Stroke and TIA			
Number	70	93	51
Incidence (per 1,000 person-years)	13	21	46
Multivariate-adjusted RH (95% CI)	1.0	1.31 (0.9–1.9)	2.03 (1.3–3.3)

Variables retained in the multivariate models include age, race, hypertension, diabetes, tobacco use, prior coronary artery bypass surgery, body mass index, waist-to-hip ratio, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, lipoprotein(a) level, physical activity, lipid lowering medication use and diuretic use. The stroke/TIA model is also adjusted for the presence of baseline atrial fibrillation.

CHD = coronary heart disease; CI = confidence interval; RH = relative hazards; TIA = transient ischemic attack.

serum creatinine 1.2 to 1.4 mg/dl or an estimated creatinine clearance of 40 to 60 ml/min, was associated with a 20% to 30% increased risk for cardiovascular events.

Our study provides evidence that the cardiovascular risk associated with decrements in renal function may increase steadily from near-normal renal function to end-stage renal disease. Prior studies have demonstrated that end-stage renal disease is associated with a substantial increase in the risk for cardiovascular events (19,20). Microalbuminuria, a marker for early renal damage, is also associated with increased cardiovascular risk (21,22). Our findings lend support to the hypothesis that the increased cardiovascular risk associated with renal disease increases on a continuum from preclinical renal injury to end-stage renal disease, as suggested by the National Kidney Foundation Task Force on cardiovascular disease (6,17,23).

Potential mechanisms. The mechanism by which renal insufficiency might increase the risk for cardiovascular events is not clear. Renal insufficiency is associated with a greater prevalence of cardiovascular risk factors, such as diabetes, hypertension and lipid abnormalities, but we adjusted for these in our multivariate analyses. We were unable to adjust for other potential risk factors associated with renal dysfunction, such as higher homocysteine levels and increased systemic inflammation (24–28). Direct effects of renal disease that could lead to greater cardiovascular disease risk also include extracellular volume overload, electrolyte imbalances, anemia, thrombogenic factors, oxidative stress and uremic toxins (6). These mechanisms may be intermediaries on a causal pathway leading from renal dysfunction to cardiovascular events. Alternatively, chronic renal insufficiency could merely be a marker for target organ damage that parallels the progression of vascular disease.

Prior studies. Several prior studies have demonstrated an association between renal insufficiency and all-cause mortality and stroke (7–9,29–31). The Framingham Heart study, however, did not find chronic renal insufficiency to be an independent predictor of cardiovascular risk (9). Although renal insufficiency was associated with cardiovascular events in unadjusted analyses, the association was markedly attenuated after multivariate adjustment. The major difference between HERS and the Framingham study was the composition of the population. The Framingham cohort included a minority of subjects with known cardiovascular disease (<20%), whereas HERS included only postmenopausal women with CHD. In the Heart Outcomes Prevention Evaluation (HOPE) study, which was comprised of persons both with and without prevalent cardiovascular disease, renal insufficiency was a strong predictor of both MI and cardiovascular death (12).

Study limitations. One limitation of this study is the reliance on the serum creatinine level and estimated creatinine clearance, which are less precise measures of renal function than creatinine clearance measured with 24-h urine collection. Furthermore, we relied on a single measurement of serum creatinine, which may be less reliable than the mean of a series of measurements. This potential misclassification, however, would tend to weaken the association between renal function and cardiovascular events. In addition, our participants were postmenopausal women with documented coronary artery disease; our findings may not be generalizable to men or to those without CHD.

Conclusions. In conclusion, renal insufficiency was a strong and independent predictor of cardiovascular events in postmenopausal women with known coronary artery disease. This study supports the hypothesis that declining renal function, from mild reductions to end-stage renal disease, may steadily increase the risk for cardiovascular events. Future investigations should evaluate the mechanisms for this association and devise strategies to improve prevention in these patients at increased cardiovascular risk.

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