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# Renal Insufficiency as a Predictor of Cardiovascular Outcomes and Mortality in Elderly Individuals

Linda F. Fried, MD, MPH,\*† Michael G. Shlipak, MD, MPH,‡§ Casey Crump, MD, PhD,|| Anthony J. Bleyer, MD,¶ John S. Gottdiener, MD, FACC,# Richard A. Kronmal, PhD,|| Lewis H. Kuller, MD, DRPH, FACC,\*\* Anne B. Newman, MD, MPH\*\*\*††

*Pittsburgh, Pennsylvania; San Francisco, California; Seattle, Washington; Winston-Salem, North Carolina; and Roslyn, New York*

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<b>OBJECTIVES</b>	This study was designed to evaluate the relationship between elevated creatinine levels and cardiovascular events.
<b>BACKGROUND</b>	End-stage renal disease is associated with high cardiovascular morbidity and mortality. The association of mild to moderate renal insufficiency with cardiovascular outcomes remains unclear.
<b>METHODS</b>	We analyzed data from the Cardiovascular Health Study, a prospective population-based study of subjects, aged >65 years, who had a serum creatinine measured at baseline (n = 5,808) and were followed for a median of 7.3 years. Proportional hazards models were used to examine the association of creatinine to all-cause mortality and incident cardiovascular mortality and morbidity. Renal insufficiency was defined as a creatinine level $\geq 1.5$ mg/dl in men or $\geq 1.3$ mg/dl in women.
<b>RESULTS</b>	An elevated creatinine level was present in 648 (11.2%) participants. Subjects with elevated creatinine had higher overall (76.7 vs. 29.5/1,000 years, $p < 0.001$ ) and cardiovascular (35.8 vs. 13.0/1,000 years, $p < 0.001$ ) mortality than those with normal creatinine levels. They were more likely to develop cardiovascular disease (54.0 vs. 31.8/1,000 years, $p < 0.001$ ), stroke (21.1 vs. 11.9/1,000 years, $p < 0.001$ ), congestive heart failure (38.7 vs. 17/1,000 years, $p < 0.001$ ), and symptomatic peripheral vascular disease (10.6 vs. 3.5/1,000 years, $p < 0.001$ ). After adjusting for cardiovascular risk factors and subclinical disease measures, elevated creatinine remained a significant predictor of all-cause and cardiovascular mortality, total cardiovascular disease (CVD), claudication, and congestive heart failure (CHF). A linear increase in risk was observed with increasing creatinine.
<b>CONCLUSIONS</b>	Elevated creatinine levels are common in older adults and are associated with increased risk of mortality, CVD, and CHF. The increased risk is apparent early in renal disease. (J Am Coll Cardiol 2003;41:1364-72) © 2003 by the American College of Cardiology Foundation

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Individuals with end-stage renal disease have a cardiovascular mortality rate that is 10 to 20 times greater than that in the general population (1). However, whether milder degrees of renal insufficiency are an independent predictor of cardiovascular outcomes is unclear. In several prospective studies, renal insufficiency, as documented by elevated creatinine levels, has been associated with an increased risk of cardiovascular events and mortality (2-5). In other studies, however, elevated creatinine was no longer an

independent predictor after adjustment for other risk factors (6). Renal insufficiency is associated with a high prevalence of traditional cardiovascular risk factors, which may explain the association with cardiovascular events. Renal insufficiency may also amplify the severity of these risk factors, thus promoting cardiovascular risk (7). In addition, renal insufficiency is associated with higher levels of novel risk factors, such as C-reactive protein (CRP), homocysteine, asymmetric dimethylarginine, and fibrinogen (8-10).

The prevalence of renal dysfunction rises with age, particularly after age 70 (11). The elderly also have the highest incidence of cardiac events (12) and thus would experience the greatest burden from both cardiovascular disease (CVD) and renal disease. The Cardiovascular Health Study (CHS) is a population-based, longitudinal study of CVD and stroke in men and women aged >65 years. Previous analyses of CHS have found elevated creatinine levels to be among the predictors of total mortality (13) and congestive heart failure (CHF) (14). This report investigates in depth the association of elevated creatinine with cardiovascular events and mortality.

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From the \*Renal Section, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania; †Renal-Electrolyte Division, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; ‡Medicine Service, Veterans Affairs Medical Center, San Francisco, California; §Departments of Medicine, Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California; ||Department of Biostatistics, University of Washington, Seattle, Washington; ¶Section of Nephrology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; #Division of Cardiology, St. Francis Hospital, Roslyn, New York; \*\*Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania; and the ††Division of Geriatric Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. The researchers received funding from the National Heart, Lung, and Blood Institute, contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129 and N01-HC-15103.

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#### Abbreviations and Acronyms

AAI	=	ankle-arm index
CHF	=	congestive heart failure
CHS	=	Cardiovascular Health Study
CI	=	confidence interval
CRP	=	C-reactive protein
CVD	=	cardiovascular disease
HDL	=	high-density lipoprotein
HR	=	hazards ratio
IMT	=	intima-media thickness
LDL	=	low-density lipoprotein
MI	=	myocardial infarction

## METHODS

**Subjects.** The CHS participants were recruited from Medicare eligibility lists at four locations: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania (15). They were invited to participate if they were community dwelling adults over the age of 65, were expected to remain in the area for the next three years, and were able to give informed consent without a proxy. There was not an upper limit of creatinine that defined ineligibility for CHS. The initial cohort was recruited from 1989 to 1990, and a second cohort of 687 African Americans was recruited from 1992 to 1993, resulting in a total of 5,888 participants. Baseline serum creatinine measurements were missing for 80 participants (1.4%), so the final sample for this report is 5,808.

The details of the initial exam have been described elsewhere (15). The baseline examination included interviews and questionnaires regarding medical history, medication use, physical activity, and functional status. Laboratory tests were performed after an 8- to 12-h fast. Baseline cardiovascular status was determined by a review of old records and by electrocardiogram, echocardiography, carotid artery ultrasound, and ankle-arm index (15-17).

We defined an elevated creatinine level using a gender-defined cutoff ( $\geq 1.3$  mg/dl for women and  $\geq 1.5$  mg/dl for men), based on prior studies (4,6). We also categorized serum creatinine levels as  $<1.10$ , 1.10 to 1.29, 1.30 to 1.49, 1.50 to 1.69, and  $\geq 1.70$  mg/dl to evaluate the presence of a trend with renal dysfunction and cardiovascular risk.

**Variables.** Detailed methods for blood drawing, quality assurance, and assay performances have been described previously (17). Serum chemistries, including creatinine, were performed on the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, New York); The Olympus Demand System (Olympus, Lake Success, New York) was used for total and high-density lipoprotein (HDL) cholesterol and triglycerides; low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula (18). Fibrinogen was measured in a BBL fibrometer (Becton Dickinson, Cockeysville, Maryland); factor VII was performed using Coag-A-Mate (Organon Teknika, Durham,

North Carolina). C-reactive protein was measured using an enzyme-linked immunosorbent assay (19).

Diabetes was defined as the use of insulin or oral hypoglycemic agents, a fasting glucose level  $\geq 140$  mg/dl, or a 2-h glucose level after a 75-g glucose challenge of  $>200$  mg/dl. Impaired glucose tolerance was defined as a fasting glucose level  $<140$  mg/dl but 2-h glucose level between 140 and 199 mg/dl. Prevalent coronary heart disease was defined as the history of any of the following: reported or silent MI or angina, previous coronary bypass surgery or angioplasty, or use of nitrates. Subclinical CVD was defined for subjects without prevalent CVD at baseline as: ankle-arm index (AAI)  $\leq 0.9$ , common carotid intima-media thickness (IMT) in upper quintile ( $>1.20$  mm), maximum carotid stenosis  $\geq 50\%$ , major ECG abnormality (ventricular conduction defect, major Q-wave abnormalities, left ventricular hypertrophy, isolated ST-T wave abnormalities, atrial fibrillation, first degree AV block, or left ventricular ejection fraction borderline or abnormal (20).

Clinical outcomes were ascertained every six months. The primary endpoints collected were all-cause mortality, cardiovascular mortality and morbidity (myocardial infarction [MI], angina, CHF, peripheral vascular disease, stroke, and transient ischemic attack). Event ascertainment followed a defined protocol, and events were adjudicated by committee (21). Cardiovascular disease was defined as any of the following: reported or silent MI, reported angina, coronary artery bypass surgery or angioplasty, use of nitrates, stroke, or transient ischemic attack. The current report examines events through June 30, 1997. The median follow-up was 7.3 years (mean 6.5, range 0.0 to 8.1).

**Statistical analysis.** Demographic characteristics, cardiovascular risk factors, and subclinical CVD prevalence at baseline were compared using *t* test, Kruskal Wallis test, or chi-square test where appropriate. Event rates were compared with Poisson. For nonfatal events, only time to the first event was included in the calculation of rates. For the survival curves, we fitted a Cox proportional hazards model and plotted predicted survival at the average predictor, adjusting for age within the model. Cox proportional hazards models were used to examine the relationship of creatinine with total mortality and each of the cardiovascular outcomes. The main focus was on incident CVD events. Therefore, for these analyses, those with a prior history of the event were excluded. In order to examine subjects with prevalent disease at baseline, we examined the first recurrent MI or cerebrovascular accident event in subjects who had prior MI or cerebrovascular accident. The whole CHS sample was used to evaluate mortality outcomes. Multivariate analysis was conducted to determine the independent association of creatinine categories with each outcome. A backwards stepwise model was used (subject to  $p < 0.2$ ). The relationship of creatinine with outcomes was nonlinear. Creatinine was categorized and forced into the model.

As renal impairment and CVD rise with age, the initial model was age-adjusted. The second model adjusted for age

**Table 1.** Baseline Characteristics of Cardiovascular Health Study Participants With and Without Gender-Specific Creatinine Elevation\*

Variable	Creatinine Normal (n = 6160)		Creatinine Elevated (n = 648)		p Value
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Age (yrs)		72.5 ± 5.4		75.7 ± 6.5	< 0.001
Race					0.06
White	4,358 (84.5)		537 (82.9)		
Black	769 (14.9)		107 (16.5)		
Other	33 (0.6)		4 (0.6)		
Gender					< 0.001
Male	2,077 (40.3)		394 (60.8)		
Female	3,083 (59.7)		254 (39.2)		
Diabetes status					0.007
Normal	3,660 (70.9)		425 (65.6)		
Impaired fasting glucose	696 (13.5)		90 (13.9)		
Diabetes	804 (15.6)		133 (20.5)		
Systolic BP (supine, mm Hg)		139.4 ± 20.3		144.0 ± 22.2	< 0.001
Diastolic BP (supine, mm Hg)		70.8 ± 11.9		71.8 ± 12.2	0.05
LDL (adjusted, mg/dl)		127.8 ± 35.4		126.8 ± 38.9	0.52
HDL (mg/dl)		54.9 ± 15.7		48.6 ± 14.7	< 0.001‡
Triglycerides (mg/dl)		137.9 ± 76.3		153.7 ± 80.8	< 0.001‡
Lipoprotein(a)† (mg/dl)		53.3 ± 56.3		58.2 ± 51.2	< 0.001‡
C-reactive protein (μg/dl)		3.5 ± 6.0		5.1 ± 8.2	< 0.001‡
Albumin (g/dl)		4.0 ± 0.3		4.0 ± 0.3	0.22
Fibrinogen (mg/dl)		321.3 ± 66.2		344.5 ± 71.8	< 0.001
Factor VII (mg/dl)		122.6 ± 28.8		130.3 ± 34.1	< 0.001
Factor VIII† (mg/dl)		120.4 ± 36.3		138.1 ± 42.2	< 0.001
Smoking status					0.14
Never	2,409 (46.7)		282 (43.5)		
Former	2,136 (41.4)		285 (44.0)		
Current	609 (11.8)		81 (12.5)		
Smoking pack-years		17.4 ± 26.4		22.4 ± 30.6	0.001
Physical activity (kcal)		1,774 ± 2,062		1274 ± 1723	< 0.001‡
Aspirin	178 (3.5)		40 (6.2)		< 0.001

\*≥ 1.5 mg/dl for men or ≥1.3 mg/dl for women; †not available for African-American cohort; ‡analyzed with Kruskal-Wallis test.  
BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

and subclinical cardiovascular variables (AAI, common carotid IMT, maximum carotid stenosis, major electrocardiographic abnormalities [yes/no], and left ventricular ejection fraction) to determine the extent to which prevalent vascular disease confounded the association of creatinine levels with CVD. Ankle-arm index and common carotid IMT were entered as continuous variables. Maximum carotid stenosis was classified as none, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, and 100%. Left ventricular ejection fraction was classified as normal, borderline, or abnormal.

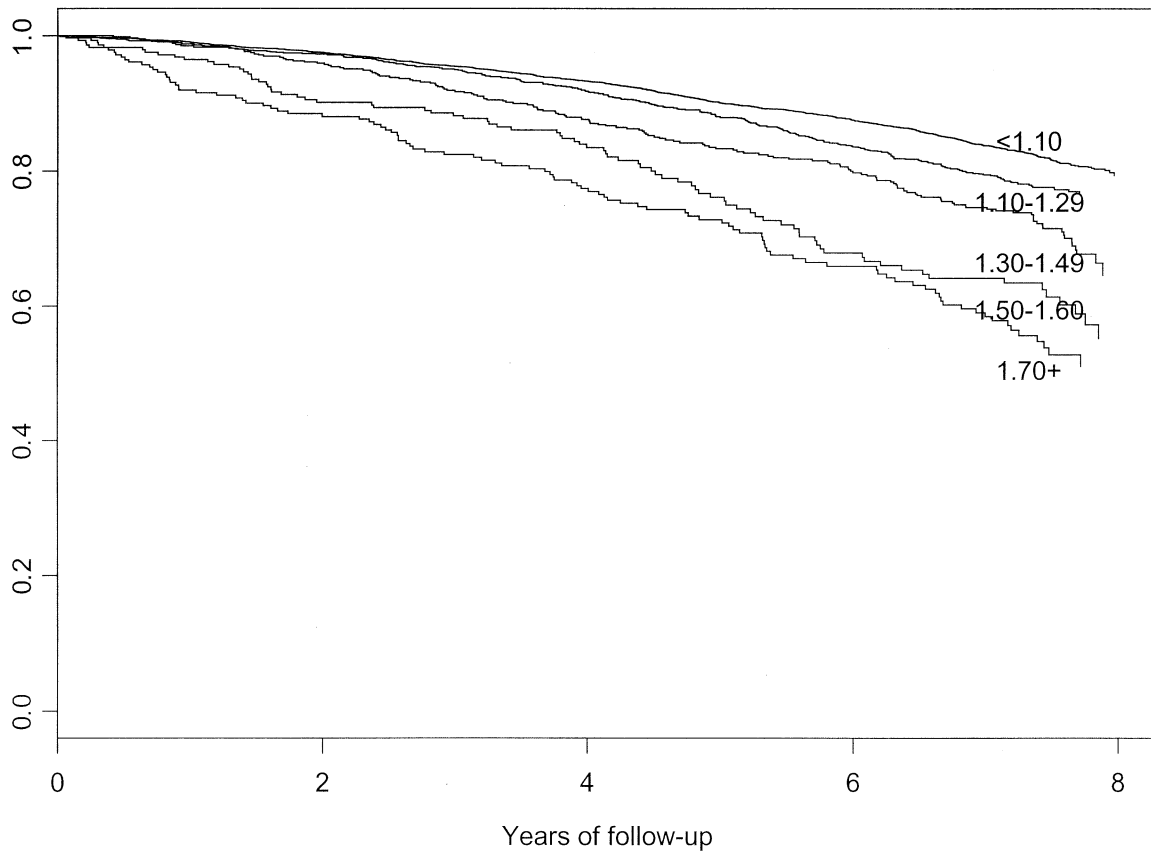
The third model included age, gender, race, physical activity, LDL cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, diabetes, smoking status, fibrinogen, factor VII, aspirin use, and CRP. Lipid values, systolic and diastolic blood pressure, fibrinogen, factor VII, and CRP values were entered as continuous variables. The fourth model adjusted for all the above demographic, comorbidity, biochemical, and vascular disease measures. Interactions of creatinine with gender, diabetes, and race were examined.

STATA Statistical Software, Release 7.0 (Stata Corporation, Inc., College Station, Texas) was used for the

analyses. A p value <0.05 was considered statistically significant. Confidence intervals (CI) are expressed as 95% CI.

## RESULTS

The number of participants in CHS who had elevated creatinine was 648 (11.2%) at baseline, as defined by a serum creatinine ≥1.3 mg/dl for women and ≥1.5 mg/dl for men. The mean serum creatinine was 1.2 ± 0.4 mg/dl (range 0.6 to 10.0) in men and 0.9 ± 0.3 mg/dl (range 0.4 to 7.3) in women. The characteristics of those with and without an elevated creatinine are summarized in Table 1. Those with an elevated creatinine were older, more likely to smoke, and had higher levels of inflammatory and prothrombotic markers. Low-density lipoprotein cholesterol levels in both groups were similar, but participants with elevated creatinine had higher triglycerides and lower HDL levels. Those with elevated creatinine had a higher prevalence at baseline of clinical and subclinical CVD; 278 (42.9%) of people with an elevated creatinine had prevalent disease at baseline compared with 1,200 (23.2%) of people without (p < 0.0001). The prevalence of subclinical disease was 446 (68.8%) among



**Figure 1.** Age-adjusted survival of subjects in Cardiovascular Health Study (CHS), by serum creatinine (mg/dl).

individuals with elevated creatinine levels versus 2,260 (43.8%) of those without elevated creatinine ( $p < 0.001$ ).

Subjects with elevated creatinine had higher all-cause (76.7 vs. 29.5/1,000 years,  $p < 0.001$ ) and cardiovascular (35.8 vs. 13.0/1,000 years,  $p < 0.001$ ) mortality and were more likely to develop incident CVD (54.0 vs. 31.8/1,000 years,  $p < 0.001$ ), MI (18.4 vs. 11.6/1,000 years,  $p < 0.001$ ), stroke (21.1 vs. 11.9/1,000 years,  $p < 0.001$ ), angina (31.5 vs. 20.1/1,000 years,  $p < 0.001$ ), CHF (38.7 vs. 17.0/1,000 years,  $p < 0.001$ ), or claudication (10.6 vs. 3.5/1,000 years,  $p < 0.001$ ). Figure 1 shows the age-adjusted survival curve for all-cause mortality by creatinine

level. The rates of events by level of creatinine are shown in Table 2.

The risk of mortality, CVD, and CHF increased steadily with increased creatinine levels (Table 3). Adjustment for cardiovascular risk factors and subclinical vascular disease decreased the relative risks somewhat. However, creatinine levels remained significantly associated with all-cause mortality, cardiovascular mortality, noncardiovascular mortality, CVD, and CHF. Table 4 shows the detailed results of the final model for cardiovascular mortality. Elevated creatinine was associated with a similar risk of death as other cardiovascular risk factors, such as smoking and diabetes. We

**Table 2.** Incidence of Selected Outcomes in Cardiovascular Health Study Participants by Creatinine Level

Outcome	Creatinine Levels (mg/dl)				
	<1.10 Rate/1,000 yrs	1.10-1.29 Rate/1,000 yrs	1.30-1.49 Rate/1,000 yrs	1.50-1.69 Rate/1,000 yrs	≥1.70 Rate/1,000 yrs
All-cause mortality	26.2	38.4	55.6	85.3	121.6
CVD death	11.3	17.6	28.6	34.5	57.2
Non-CVD death	14.9	20.7	27.1	50.8	64.4
CHD, stroke, or TIA	29.6	38.2	50.9	62.2	73.3
Congestive heart failure	15.4	21.7	29.2	43.7	59.0
Myocardial infarction	10.3	14.6	20.2	19.4	24.4
Angina	17.9	26.4	31.5	35.3	40.1
Claudication	3.0	4.4	9.8	10.7	14.7
Stroke	10.9	15.2	15.8	26.0	33.1
TIA	2.7	5.3	5.5	3.2	11.4

CHD = coronary heart disease; CVD = cardiovascular disease; TIA = transient ischemic attack.

**Table 3.** Hazard Ratios and 95% CIs for Association Between Baseline Serum Creatinine and Incident Cardiovascular Outcomes

Model	Serum Creatinine, mg/dl				
	<1.10 (n = 3,980)	1.10-1.29 (n = 1,040) HR (95% CI)	1.30-1.49 (n = 438) HR (95% CI)	1.50-1.69 (n = 180) HR (95% CI)	≥1.70 (n = 170) HR (95% CI)
All-cause mortality					
Age-adjusted model	1.00	1.26 (1.09-1.46)	1.75 (1.47-2.10)	2.54 (2.02-3.20)	3.24 (2.62-4.02)
Subclinical variables and age	1.00	1.12 (0.97-1.30)	1.50 (1.25-1.80)	1.83 (1.43-2.33)	2.16 (1.73-2.71)
Traditional risk factors	1.00	1.07 (0.91-1.26)	1.40 (1.15-1.71)	1.71 (1.33-2.21)	2.25 (1.76-2.87)
All above variables	1.00	0.98 (0.83-1.16)	1.27 (1.04-1.56)	1.42 (1.09-1.85)	1.71 (1.33-2.20)
CVD death					
Age-adjusted model	1.00	1.36 (1.10-1.69)	2.13 (1.65-2.74)	2.45 (1.71-3.50)	3.67 (2.69-5.02)
Subclinical variables and age	1.00	1.10 (0.88-1.38)	1.62 (1.25-2.10)	1.45 (0.99-2.12)	1.90 (1.36-2.65)
Traditional risk factors	1.00	1.13 (0.89-1.44)	1.63 (1.23-2.16)	1.52 (1.03-2.26)	2.44 (1.72-3.47)
All above variables	1.00	0.99 (0.77-1.27)	1.40 (1.05-1.86)	1.16 (0.78-1.74)	1.63 (1.13-2.33)
Non-CVD death					
Age-adjusted model	1.00	1.18 (0.97-1.43)	1.48 (1.15-1.90)	2.60 (1.93-3.51)	2.93 (2.19-3.92)
Subclinical variables and age	1.00	1.12 (0.92-1.37)	1.40 (1.08-1.81)	2.18 (1.59-2.98)	2.39 (1.76-3.26)
Traditional risk factors	1.00	1.00 (0.81-1.25)	1.19 (0.90-1.57)	1.83 (1.31-2.54)	1.98 (1.42-2.76)
All above variables	1.00	0.97 (0.78-1.22)	1.15 (0.87-1.53)	1.66 (1.18-2.34)	1.74 (1.23-2.46)
CVD					
Age-adjusted model	1.00	1.32 (1.19-1.45)	1.72 (1.51-1.95)	2.13 (1.77-2.56)	2.80 (2.34-3.36)
Subclinical variables and age	1.00	1.15 (1.03-1.29)	1.44 (1.25-1.66)	1.83 (1.47-2.26)	1.76 (1.43-2.16)
Traditional risk factors	1.00	1.13 (1.01-1.26)	1.28 (1.11-1.48)	1.48 (1.21-1.81)	2.03 (1.66-2.49)
All above variables	1.00	1.03 (0.91-1.16)	1.19 (1.02-1.39)	1.44 (1.14-1.82)	1.54 (1.23-1.94)
Congestive heart failure					
Age-adjusted model	1.00	1.26 (1.04-1.53)	1.62 (1.26-2.08)	2.47 (1.77-3.44)	3.04 (2.21-4.19)
Subclinical variables and age	1.00	1.15 (0.94-1.40)	1.37 (1.06-1.76)	1.80 (1.26-2.56)	2.12 (1.51-2.98)
Traditional risk factors	1.00	1.17 (0.94-1.46)	1.37 (1.04-1.81)	1.82 (1.27-2.60)	2.40 (1.68-3.43)
All above variables	1.00	1.13 (0.91-1.41)	1.27 (0.96-1.68)	1.48 (1.01-2.15)	1.92 (1.32-2.80)

Variables were selected using backward stepwise procedure with  $p \geq 0.2$  as criterion for exclusion. Subclinical and age model was adjusted for age, ankle-arm index, common carotid intima-media thickness, maximum carotid stenosis (none, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, 100%), major electrocardiographic abnormalities (yes, no), and left ventricular ejection fraction (normal, borderline, abnormal). Traditional risk factor model was adjusted for the following baseline variables: age, gender, race, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, diabetes, smoking status, fibrinogen, factor VII, C-reactive protein, hemoglobin, and aspirin use.

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.

**Table 4.** Characteristics Associated With Cardiovascular Mortality in Elderly Participants of the Cardiovascular Health Study

Variable*	HR	95% CI	p Value
Age	1.07	1.06-1.09	< 0.001
Ankle-arm index	0.28	0.17-0.44	< 0.001
Common carotid intima-medial thickness	2.01	1.38-2.95	< 0.001
Maximum carotid stenosis	1.22	1.09-1.37	< 0.001
Major electrocardiogram abnormalities	1.84	1.50-2.26	< 0.001
Left ventricular ejection fraction	1.68	1.45-1.94	< 0.001
Gender (men)	1.19	0.93-1.52	0.172
Diabetes	1.47	1.31-1.65	< 0.001
Smoking	1.18	1.02-1.38	0.030
Diastolic blood pressure (1 mm Hg)	1.01	1.00-1.02	0.063
Fibrinogen (1 mg/dl)	1.002	1.000-1.003	0.033
Creatinine (mg/dl)			0.001
<1.1	1.0 (reference)		
1.1-1.29	0.99	0.77-1.27	
1.3-1.49	1.40	1.05-1.86	
1.5-1.69	1.16	0.78-1.74	
≥1.7 mg/dl	1.63	1.13-2.33	

\*Variables were selected using backward stepwise procedure with  $p \geq 0.2$  as criterion for exclusion. Variables were creatinine, age, ankle-arm index, common carotid intima-media thickness, maximum carotid stenosis (none, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, 100%), major electrocardiographic abnormalities (yes, no), left ventricular ejection fraction (normal, borderline, abnormal), gender, race, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, diabetes, smoking status, fibrinogen, factor VII, C-reactive protein, hemoglobin, and aspirin use.

CI = confidence interval; HR = hazard ratio.

performed a subgroup analysis in individuals with and without significant subclinical disease. There was a linear relationship of elevated creatinine levels with CVD mortality in those with subclinical disease. In those without significant subclinical disease (n = 3,122), the only significant risk factors were age, diabetes, and a creatinine level  $\geq 1.7$  mg/dl.

We found no evidence for a center effect, nor did we observe any significant gender, race, or diabetes interactions with creatinine levels. However, in the unadjusted models for all-cause mortality, cardiovascular mortality, and CHF, the risk began at a lower serum creatinine level for women compared with men (Table 5). With adjustment, the risks were similar for men and women. We evaluated the association of creatinine levels with the incidence of each cardiovascular outcome, using the dichotomized gender-based cutoff to define elevated creatinine. An elevated creatinine level was associated with each individual outcome in the univariate analysis. However, after multivariate analysis, we no longer found significant associations with MI (hazard ratio [HR] 1.00, 95% CI 0.74, 1.36), angina (HR 1.12, 95% CI 0.87, 1.43), stroke (HR 1.22, 95% CI 0.93, 1.61) and transient ischemic attack (HR 1.39, 95% CI 0.84, 2.29). Elevated creatinine remained a significant predictor for the development of claudication (HR 1.61, 95% CI 1.05, 2.49), but we found a significant gender interaction. After multivariate adjustment, the HR for men was 1.38 (0.78, 2.43) and for women was 2.29 (1.11, 4.73).

There were 159 recurrent MIs and 141 recurrent strokes. Patients with elevated creatinine were more likely to have recurrent events. After adjustment for risk factors and subclinical disease, there was no longer a significant relationship with recurrent MI, but we still observed a linear trend of increasing risk for recurrent stroke with increasing creatinine (Table 6).

## DISCUSSION

We found that elderly individuals with mildly elevated serum creatinine levels had a greater incidence of cardiovascular events and mortality compared with other elderly individuals with normal creatinine levels. The value of elevated creatinine levels in predicting the development of CHF, CVD morbidity and mortality, and all-cause mortality remained after adjustment for many cardiovascular risk factors and subclinical disease measures. That the increased risk of death began at low creatinine levels in our study is noteworthy, as the values are near or below the normal value for many laboratories. Many physicians and patients may not, therefore, recognize the increased risk associated with mildly elevated creatinine.

Hemmelgram et al. (22) found that elevated creatinine predicted poor long-term survival in patients undergoing coronary angiography. Mildly to moderately elevated creatinine levels are a risk factor for adverse outcomes after cardiac and noncardiac surgery (23,24). However, these

**Table 5.** Hazard Ratios and 95% CIs for Association Between Serum Creatinine and Incident Cardiovascular Outcomes, Stratified by Gender

Outcome	Men (n = 2,471, Relative to a Creatinine of <1.10)				Women (n = 3,337, Relative to a Creatinine of <1.10)			
	1.10-1.29 (n = 755)	1.30-1.49 (n = 355)	1.50-1.69 (n = 145)	$\geq 1.70$ (n = 129)	1.10-1.29 (n = 285)	1.30-1.49 (n = 83)	1.50-1.69 (n = 35)	$\geq 1.70$ (n = 41)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
<b>Unadjusted</b>								
All-cause mortality	1.07 (0.89-1.29)	1.48 (1.19-1.83)	2.40 (1.84-3.12)	3.35 (2.60-4.32)	1.48 (1.13-1.95)	2.66 (1.82-3.90)	3.46 (2.03-5.89)	5.87 (3.89-8.86)
CVD death	1.12 (0.85-1.47)	1.63 (1.20-2.23)	2.07 (1.36-3.14)	3.36 (2.30-4.90)	1.55 (1.03-2.34)	3.83 (2.33-6.30)	4.09 (1.92-8.70)	7.52 (4.29-13.2)
Non-CVD death	1.03 (0.81-1.33)	1.36 (1.01-1.83)	2.67 (1.90-3.75)	3.35 (2.38-4.71)	1.43 (1.00-2.06)	1.81 (0.99-3.31)	3.00 (1.41-6.35)	4.67 (2.55-8.54)
CVD	1.10 (0.97-1.25)	1.42 (1.21-1.65)	1.89 (1.53-2.34)	2.52 (2.04-3.12)	1.41 (1.18-1.68)	2.24 (1.69-2.97)	2.40 (1.58-3.67)	4.29 (3.02-6.10)
Congestive heart failure	1.02 (0.75-1.39)	1.36 (1.06-1.75)	2.21 (1.38-3.53)	2.93 (2.09-4.12)	1.56 (1.03-2.37)	1.79 (1.18-2.69)	1.94 (0.48-7.82)	4.87 (2.94-8.08)
<b>Adjusted model</b>								
All-cause mortality	0.96 (0.79-1.18)	1.20 (0.95-1.51)	1.40 (1.04-1.88)	1.61 (1.20-2.14)	1.02 (0.75-1.40)	1.56 (1.01-2.40)	1.41 (0.76-2.62)	2.20 (1.29-3.76)
CVD death	0.96 (0.72-1.29)	1.29 (0.93-1.79)	1.09 (0.69-1.73)	1.48 (0.97-2.27)	0.97 (0.59-1.60)	1.95 (1.10-3.43)	1.41 (0.55-3.58)	2.53 (1.24-5.16)
Non-CVD death	0.96 (0.73-1.26)	1.16 (0.84-1.61)	1.75 (1.19-2.59)	1.75 (1.18-2.59)	1.03 (0.68-1.54)	1.33 (0.52-2.02)	1.29 (0.56-2.97)	1.56 (0.67-3.62)
CVD	1.01 (0.87-1.17)	1.18 (0.99-1.41)	1.49 (1.15-1.92)	1.50 (1.16-1.94)	1.01 (0.80-1.27)	1.38 (0.96-1.97)	1.09 (0.61-1.94)	1.56 (0.96-2.50)
Congestive heart failure	1.09 (0.83-1.44)	1.30 (0.94-1.79)	1.66 (1.07-2.55)	2.08 (1.35-3.22)	1.33 (0.92-1.94)	1.17 (0.63-2.17)	1.28 (0.58-2.79)	1.81 (0.83-3.91)

\*Adjusted for the following variables using backward stepwise regression, subject to  $p < 0.2$ : age, gender, race, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, diabetes, smoking status, fibrinogen, factor VII, C-reactive protein, hemoglobin, aspirin use, ankle-arm index, common carotid intima-media thickness, maximum carotid stenosis (none, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, 100%), major electrocardiographic abnormalities (yes, no), and left ventricular ejection fraction (normal, borderline, abnormal).  
 CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio.

**Table 6.** Hazard Ratios and 95% CIs for Association Between Baseline Serum Creatinine and First Recurrent MI and Cerebrovascular Accidents

Model	Serum Creatinine, mg/dl				
	<1.10 (n = 3,980)	1.10–1.29 (n = 1,040) HR (95% CI)	1.30–1.49 (n = 438) HR (95% CI)	1.50–1.69 (n = 180) HR (95% CI)	≥1.70 (n = 170) HR (95% CI)
<b>Recurrent MI</b>					
Age-adjusted model	1.00	1.97 (1.34–2.90)	2.85 (1.78–4.56)	2.36 (1.09–5.15)	5.52 (3.02–10.08)
Traditional risk factors*	1.00	1.58 (1.02–2.43)	1.74 (1.03–2.93)	1.37 (0.61–3.08)	2.97 (1.51–5.86)
Traditional risk factors and subclinical disease*	1.00	1.27 (0.80–2.03)	1.54 (0.89–2.64)	1.31 (0.58–2.98)	1.56 (0.73–3.36)
<b>Recurrent stroke</b>					
Age-adjusted model	1.00	1.29 (0.82–2.03)	2.26 (1.34–3.80)	3.37 (1.73–6.56)	5.73 (3.17–10.34)
Traditional risk factors	1.00	1.10 (0.66–1.83)	1.60 (0.89–2.89)	2.01 (0.96–4.21)	3.53 (1.81–6.88)
Traditional risk factors and subclinical disease	1.00	0.85 (0.47–1.53)	1.32 (0.69–2.51)	1.56 (0.67–3.60)	2.22 (1.03–4.82)

\*Variables were selected using backward stepwise procedure with  $p \geq 0.2$  as criterion for exclusion. Traditional risk factor model was adjusted for the following baseline variables: age, gender, race, physical activity, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, diabetes, smoking status, fibrinogen, factor VII, C-reactive protein, hemoglobin, and aspirin use. Traditional risk factors and subclinical disease was adjusted for the traditional risk factors plus ankle-arm index, common carotid intima-media thickness, maximum carotid stenosis (none, 1% to 24%, 25% to 49%, 50% to 74%, 75% to 99%, 100%), major electrocardiographic abnormalities (yes, no), and left ventricular ejection fraction (normal, borderline, abnormal).

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

findings may not be generalizable to other populations. In the Framingham study, Culleton et al. (6) found that all-cause mortality was higher than in men with normal creatinine levels. In contrast to our study, however, they did not find that it was a risk factor in women, once they adjusted for age and cardiac risk factors. A recent analysis of the NHANES 2 follow-up data found that those with renal insufficiency had a higher total and cardiovascular mortality rate, after controlling for traditional risk factors (3). They did not have data on nonfatal events or on subclinical disease measurements.

The reasons mild elevation of creatinine is associated with adverse outcomes are not clear. Some risk factors, such as an elevated calcium-phosphorus product, which could promote vascular calcification, do not appear to increase until the glomerular filtration rate is  $<30$  ml/min (25). A possible explanation is that persons with renal insufficiency have greater atherosclerosis burden. However, despite adjustment for several measures of subclinical atherosclerosis, a greater cardiovascular risk remained associated with elevated creatinine levels. Though elevated creatinine was a predictor of CVD as a combined outcome, for many of the individual cardiovascular outcomes, it was no longer an independent predictor after adjustment for other risk factors. It could be that elevated creatinine is a marker of the presence of multiple metabolic abnormalities and that the unexplained risk associated with an elevated creatinine level is due to other factors that were not measured. In particular, we do not have data on proteinuria. In the HOPE trial (2), microalbuminuria was a significant risk factor for CVD events, which was independent of an elevated creatinine level or history of diabetes.

Many of the features associated with renal insufficiency are similar to those described in the metabolic syndrome: hypertension, high triglyceride levels, and low HDL cholesterol. This syndrome has also been associated with increased cardiovascular risk (26). Like the metabolic syndrome (27,28), elevated creatinine levels have been associ-

ated with small dense LDL and hyperfibrinogenemia (29,30). Elevated creatinine levels may not be merely a marker of atherosclerosis and increased prevalence of risk factors. Renal disease could also worsen the severity of risk factors, such as hypertension and hyperlipidemia (7). If this hypothesis is true, risk factors would be mediators of the increased risk and could explain why elevated creatinine was no longer a predictor for MI or stroke after adjustment. We do not have longitudinal data on the change in risk factors with the change in creatinine to test this hypothesis.

The kidney is the site of metabolism of many molecules. Chronic renal insufficiency is associated with higher levels of inflammatory markers and homocysteine (10,31–33), which have been associated with cardiovascular events (34–36). Cytokines have been implicated in the pathogenesis of heart failure (37,38). This may be one explanation for why elevated creatinine was a predictor of CHF in our study. Anemia is a common feature of renal disease, as the kidney is the site of erythropoietin synthesis. Levin et al. (39) found that a decline in hemoglobin and an increase in systolic blood pressure predicted an increase in left ventricular mass index in persons with chronic kidney disease, which may be a precursor to the development of heart failure. In our study, we controlled for CRP, systolic blood pressure, and hemoglobin. Elevated creatinine remained an independent predictor of CHF after controlling for these factors.

**Study limitations.** Muscle mass tends to decline with age. Therefore, a creatinine level of 1.5 mg/dl in a 75-year-old does not represent the same degree of renal impairment as it does in a 55-year-old (40). A limitation of our study is the lack of more precise measurements of renal function. More precise methods, such as iothalamate clearances, are difficult and expensive to do in large epidemiologic studies, and 24-h creatinine clearances are unreliable (41). The Modification of Diet in Renal Disease formulas, which have been advocated as a more accurate measure of renal function, have not been validated in the elderly (42). Serum creatinine has the advantage of being widely available and a common

part of routine chemistry panels. It would, therefore, be relatively easy to use as a screening test for identifying patients at increased risk.

**Conclusions.** More than 10% of our cohort had elevated serum creatinine levels, defined as  $\geq 1.5$  mg/dl in men or  $\geq 1.3$  mg/dl in women. As there is an increased risk of CVD in individuals with an elevated creatinine, this implies that an elevated creatinine, defined this way, may have a substantial attributable risk for CVD and mortality in the elderly population. As the population ages, the prevalence of renal insufficiency and CVD may also grow. That elevated creatinine is associated with a high prevalence of cardiac risk factors suggests that attention to risk factor reduction may impact the high risk of CVD. A recent Canadian study suggests that cardiac risk factors are inadequately addressed in patients with renal insufficiency (43). In that study, 35% of those with renal insufficiency and established CVD had a blood pressure  $>140/90$  mm Hg; 45% were receiving aspirin, 50% were receiving beta-blockers and only 50% of those with hyperlipidemia were on statins. There is a lack of research on prevention of CVD in individuals with renal insufficiency. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III recommended that diabetes be considered a coronary heart disease equivalent (44). In a similar fashion, the National Kidney Foundation Task Force on Cardiovascular Disease recommended that patients with chronic kidney disease be considered in the highest risk group for cardiovascular events (45). Although this recommendation was not adopted by NCEP, our study supports this recommendation.

In summary, our study found that mildly elevated creatinine levels are predictive of cardiovascular morbidity and mortality. Elevated creatinine was associated with a high prevalence of cardiac risk factors. Further studies aimed at risk reduction of traditional and novel risk factors in those with renal insufficiency are needed in order to have an impact in this high-risk population.

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**Reprint requests and correspondence:** Dr. Linda F. Fried, VA Pittsburgh Healthcare System, 111F-U, University Drive C, Pittsburgh, Pennsylvania 15240. E-mail: lff9+@pitt.edu.

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**Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals**

Linda F. Fried, Michael G. Shlipak, Casey Crump, Anthony J. Bleyer, John S. Gottdiener, Richard A. Kronmal, Lewis H. Kuller, and Anne B. Newman

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