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Cystatin C and the Risk of Death and Cardiovascular Events among Elderly Persons

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ABSTRACT

BACKGROUND

Cystatin C is a serum measure of renal function that appears to be independent of age, sex, and lean muscle mass. We compared creatinine and cystatin C levels as predictors of mortality from cardiovascular causes and from all causes in the Cardiovascular Health Study, a cohort study of elderly persons living in the community.

METHODS

Creatinine and cystatin C were measured in serum samples collected from 4637 participants at the study visit in 1992 or 1993; follow-up continued until June 30, 2001. For each measure, the study population was divided into quintiles, with the fifth quintile subdivided into thirds (designated 5a, 5b, and 5c).

RESULTS

Higher cystatin C levels were directly associated, in a dose-response manner, with a higher risk of death from all causes. As compared with the first quintile, the hazard ratios (and 95 percent confidence intervals) for death were as follows: second quintile, 1.08 (0.86 to 1.35); third quintile, 1.23 (1.00 to 1.53); fourth quintile, 1.34 (1.09 to 1.66); quintile 5a, 1.77 (1.34 to 2.26); 5b, 2.18 (1.72 to 2.78); and 5c, 2.58 (2.03 to 3.27). In contrast, the association of creatinine categories with mortality from all causes appeared to be J-shaped. As compared with the two lowest quintiles combined (cystatin C level, ≤ 0.99 mg per liter), the highest quintile of cystatin C (≥ 1.29 mg per liter) was associated with a significantly elevated risk of death from cardiovascular causes (hazard ratio, 2.27 [1.73 to 2.97]), myocardial infarction (hazard ratio, 1.48 [1.08 to 2.02]), and stroke (hazard ratio, 1.47 [1.09 to 1.96]) after multivariate adjustment. The fifth quintile of creatinine, as compared with the first quintile, was not independently associated with any of these three outcomes.

CONCLUSIONS

Cystatin C, a serum measure of renal function, is a stronger predictor of the risk of death and cardiovascular events in elderly persons than is creatinine.

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THE PRESENCE OF RENAL DYSFUNCTION in elderly persons has been associated with an increased risk of death among healthy persons in outpatient care^{1,2} and among those with several clinical factors, including heart failure,³ acute hospitalization,⁴ inpatient surgery,^{5,6} and acute myocardial infarction.^{7,8} However, the primary clinical tool for measuring renal function, the serum creatinine level, is insensitive for the detection of moderate reductions in renal function and is affected by factors unrelated to renal function, such as age, sex, race, and lean muscle mass. Creatinine-based equations to estimate the glomerular filtration rate (GFR) have been derived to compensate for these nonrenal influences on the relationship between creatinine and GFR, but their precision when applied to elderly patients is unclear.⁹⁻¹¹

Cystatin C is a cysteine protease inhibitor produced by nearly all human cells and excreted into the bloodstream. At a molecular weight of 13 kD, the protein is freely filtered by the renal glomerulus and then metabolized by the proximal tubule.^{12,13} Given its reported superiority over creatinine as a proxy for GFR, we hypothesized that cystatin C would be a stronger and more linear predictor of the risk of illness and death among elderly persons than either the serum creatinine level or the estimated GFR.¹⁴ To that end, we compared the associations of cystatin C, creatinine, and the estimated GFR with the risk of cardiovascular events and death in a population-based cohort study of elderly adults.

METHODS

STUDY DESIGN

The Cardiovascular Health Study (CHS) is a community-based, longitudinal study of adults who were 65 years of age or older at the study's inception. Its main purpose is to evaluate risk factors for the development and progression of cardiovascular disease in elderly persons.¹⁵ The study recruited participants from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and the city of Pittsburgh. To be eligible, persons had to be at least 65 years of age, not institutionalized (i.e., living in the community), expected to remain in the current community for three years or longer, and not under active treatment for cancer, and be able to provide written informed consent without the

need for a proxy respondent. The initial 5201 participants were enrolled from January 1989 to June 1990; an additional 687 black participants (with race self-reported) were recruited and enrolled by June 1993. The study design, quality-control procedures, laboratory methods, and procedures for blood-pressure measurement have been published previously.^{15,16}

This analysis includes all 4637 participants who attended the annual study visit in 1992 or 1993 and for whom serum was available for measurement of creatinine and cystatin C. Creatinine measurements were performed in proximity to the 1992-1993 visit, whereas cystatin C was measured in 2003 using frozen serum. Follow-up for events continued until June 30, 2001 (median follow-up, 7.4 years; maximum, 8.1).

RENAL-FUNCTION ASSAYS

All assays were performed in serum specimens that had been obtained from participants after a fast and were stored at -70°C . Cystatin C was measured by means of a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).¹⁷ Among 61 healthy persons with three cystatin C measurements during a six-month period, the intraindividual coefficient of variation was 7.7 percent, reflecting the long-term stability of the cystatin C level. The range of detection of the assay is 0.195 to 7.330 mg per liter, with the reference range for young, healthy persons reported as 0.53 to 0.95 mg per liter. The assay remained stable, with no change in the values measured, over five cycles of freezing and thawing.

Serum creatinine was measured by a colorimetric method (Ektachem 700, Eastman Kodak). The mean coefficient of variation for monthly controls was 1.94 percent (range, 1.16 to 3.90). We estimated the GFR with the use of the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation.^{9,18}

MULTIVARIATE ADJUSTMENT

Information on characteristics that might confound the association of renal function with the risk of cardiovascular events and death was obtained from the records of the 1992-1993 visit. These included the demographic factors age, sex, and race (self-reported); the cardiovascular risk factors body-mass index (BMI, the weight in kilograms divided by the square of the height in meters),

smoking status (current smoker vs. former smoker or never smoked), presence or absence of diabetes (defined by a history of diabetes, use of a hypoglycemic agent or insulin, or a fasting glucose level of 126 mg per deciliter [6.99 mmol per liter] or higher), presence or absence of hypertension (defined by an average systolic blood pressure, measured with the participant seated, of 140/90 mm Hg or higher or a history of treated hypertension), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels, and left ventricular hypertrophy as detected on electrocardiography; the inflammatory factors C-reactive protein level, fibrinogen level, leukocyte count, and albumin level; the hemoglobin level; the presence or absence of clinical disease (a history of myocardial infarction, heart failure, stroke, chronic obstructive pulmonary disease, or cancer); and self-reported health status (fair or poor vs. good, very good, or excellent).

OUTCOMES

Follow-up visits were conducted by telephone every six months and in person annually. All events were adjudicated by a CHS outcome-assessment committee. Participants with a history of myocardial infarction or stroke were excluded from the analyses of the incidence of events. Myocardial infarction was ascertained from hospital records and was indicated by a clinical history of cardiac symptoms, elevated cardiac enzyme levels, and serial electrocardiographic changes.¹⁹ Cases of possible stroke were adjudicated by a committee of neurologists, neuroradiologists, and internists on the basis of interviews with patients, medical records, and brain imaging studies.²⁰ Deaths were identified by a review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care–utilization database for hospitalizations and from household contacts; 100 percent complete follow-up for ascertainment of mortality status was achieved. Death from cardiovascular causes was defined as death caused by coronary heart disease, heart failure, peripheral vascular disease, or cerebrovascular disease.²¹

STATISTICAL ANALYSIS

To evaluate the association of each renal measurement with the outcomes, we initially created quintiles of the study population according to cystatin C and creatinine levels and estimated GFR. Because creatinine levels differ substantially between men

and women, we used sex-specific quintiles for creatinine so as to equalize the distribution of men and women.¹ A previous study from the CHS found substantial increases in the risk of death only for persons with creatinine levels greater than 1.5 mg per deciliter (133 μ mol per liter) — which corresponds to the highest 6 percent of the cohort¹; therefore, we subdivided the fifth quintile of each measure into thirds. These subdivisions of the fifth quintile for each measurement were designated 5a (the lowest third), 5b (the middle third), and 5c (the highest third). For cystatin C and creatinine, the fifth quintile was made up of the participants with the highest values. For estimated GFR, because lower values are associated with worse renal function, the fifth quintile comprised the participants with the lowest values.

We began our analysis by examining the distribution of the adjustment variables, listed above, according to the quintile of cystatin C. The annual risk for each outcome was determined for each of the seven levels of the measures of renal function. To evaluate the joint effects of cystatin C and creatinine on mortality, we also cross-tabulated quintiles of both measures and determined the annual risk within each of the 25 resulting categories.

We used Cox proportional-hazards models to evaluate the association of each measure of renal function, categorized in the seven subgroups, with each outcome. Covariates were identified with use of a model that included cystatin C as a continuous predictor of each outcome; each candidate variable was entered separately, and variables that changed the parameter estimate (beta coefficient) of cystatin C by 5 percent or more were retained in the final model. For each outcome, the same covariates were entered into the models for the categories of cystatin C, creatinine, and estimated GFR. For the outcome of death, we determined the population attributable risk for cystatin C and compared it with those for the other significant predictors in the final model. Predictors that were on a continuous scale were dichotomized by using the fifth quintile as a cutoff point. S-Plus software (version 6.1, Insightful) and SPSS statistical software (version 12.0.0) were used for the analyses.

This study was designed by Drs. Shlipak, Katz, Fried, Siscovick, and Stehman-Breen. Drs. Shlipak, Katz, and Siscovick vouch for the data and the analysis. The manuscript was written solely by the listed authors. The CHS was approved by the institutional review boards of the University of Washington

and the affiliated clinical centers; these analyses were approved by the Committee on Human Research of the University of California, San Francisco. All participants gave written informed consent for enrollment and follow-up in CHS and for the future use of biologic specimens.

RESULTS

CHARACTERISTICS ASSOCIATED WITH CYSTATIN C
Participants with the highest cystatin C levels were older and more likely to be male, but less likely to

be black, than participants with lower cystatin C levels (Table 1). Nearly all of the coexisting conditions we assessed were more prevalent among those with elevated levels of cystatin C, who also had a greater waist-to-hip ratio, higher leukocyte count, and higher C-reactive protein levels and lower levels of HDL cholesterol and hemoglobin (Table 1). In contrast, the prevalence of current smoking did not vary significantly among the quintiles of cystatin C; in addition, among current smokers the mean number of cigarettes smoked per day was similar among the cystatin C quintiles, ranging from 12 to 15 (*P* for trend=0.09).

Table 1. Baseline Characteristics of Elderly Participants in the Cardiovascular Health Study, According to Quintiles of Cystatin C.*

Characteristic	Quintile 1 (≤0.89 mg per liter)	Quintile 2 (0.90–0.99 mg per liter)	Quintile 3 (1.00–1.10 mg per liter)	Quintile 4 (1.11–1.28 mg per liter)	Quintile 5 (≥1.29 mg per liter)	P Value for Linear Trend
No. of participants	942	892	943	947	913	
Age — yr	73±4	74±4	74±5	76±5	78±6	<0.001
Male sex — no. (%)	282 (30)	334 (37)	411 (44)	451 (48)	455 (50)	<0.001
Black race — no. (%)	276 (29)	174 (20)	129 (14)	116 (12)	107 (12)	<0.001
Hypertension — no. (%)	505 (54)	477 (53)	498 (53)	557 (59)	596 (65)	<0.001
Diabetes — no. (%)	162 (17)	113 (13)	119 (13)	147 (16)	175 (19)	0.08
Current smoker — no. (%)	78 (8)	92 (10)	83 (9)	101 (11)	96 (11)	0.12
Weight — kg	70±14	72±14	73±14	75±16	74±15	<0.001
Waist-to-hip ratio	0.93±0.08	0.94±0.08	0.95±0.07	0.96±0.07	0.96±0.07	<0.001
HDL cholesterol — mg/dl	59±15	55±15	54±13	50±13	48±13	<0.001
LDL cholesterol — mg/dl	128±33	128±32	127±33	128±35	125±35	0.07
Albumin — mg/dl	4.0±0.3	3.9±0.3	3.9±0.3	3.9±0.2	3.9±0.3	<0.001
Leukocyte count — per mm ³	5900±1700	6200±1600	6200±1800	6500±1900	7200±6200	<0.001
Hemoglobin — mg/dl	13.7±1.5	13.7±1.3	13.9±1.3	13.8±1.4	13.3±1.5	<0.001
C-reactive protein — log	0.8±1.1	0.9±1.1	0.9±1.1	1.1±1.1	1.4±1.2	<0.001
Fibrinogen — mg/dl	318±64	320±63	324±63	335±68	353±80	<0.001
Self-reported health fair or poor — no. (%)	171 (18)	159 (18)	163 (17)	198 (21)	275 (30)	<0.001
Left ventricular hypertrophy — no. (%)	41 (4)	32 (4)	40 (4)	53 (6)	70 (8)	<0.001
History of MI — no. (%)	59 (6)	63 (7)	77 (8)	105 (11)	164 (18)	<0.001
History of stroke or TIA — no. (%)	32 (3)	28 (3)	39 (4)	43 (5)	107 (12)	<0.001
History of CHF — no. (%)	23 (2)	33 (4)	26 (3)	58 (6)	127 (14)	<0.001
History of cancer — no. (%)	116 (12)	106 (12)	111 (12)	140 (15)	155 (17)	<0.001
COPD at baseline visit — no. (%)	113 (12)	128 (14)	106 (11)	109 (12)	106 (12)	0.32
Estimated GFR — ml/min/1.73 m ²	88±18	79±14	72±12	66±12	52±14	<0.001
Creatinine — mg/dl	0.81±0.16	0.90±0.17	0.97±0.17	1.06±0.20	1.38±0.69	<0.001
Cystatin C — mg/liter	0.81±0.07	0.95±0.03	1.05±0.03	1.18±0.05	1.61±0.48	<0.001

* Plus-minus values are means ±SD. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, MI myocardial infarction, TIA transient ischemic attack, CHF congestive heart failure, COPD chronic obstructive pulmonary disease, and GFR glomerular filtration rate. To convert values for HDL and LDL cholesterol to millimoles per liter, multiply by 0.0259; to convert values for fibrinogen to micromoles per liter, multiply by 0.0294; to convert values for creatinine to micromoles per liter, multiply by 88.4. C-reactive protein was measured in milligrams per liter.

CORRELATION AMONG MEASURES OF RENAL FUNCTION

Overall, the cystatin C level had a strong, direct correlation with the creatinine level ($r=0.79$, $P<0.001$) and an inverse correlation with the estimated GFR ($r=-0.63$, $P<0.001$). However, correlations stratified according to the quintile of creatinine were somewhat weak, except in the fifth quintile (correlation coefficients: first quintile, 0.18; second quintile, 0.23; third quintile, 0.29; fourth quintile, 0.23; and fifth quintile, 0.80 [$P<0.001$ for all quintiles]). Correlations of estimated GFR values and cystatin C levels also varied markedly, with stratification according to the quintile of estimated GFR (first through fifth quintiles, -0.31 [$P<0.001$], -0.09 [$P=0.006$], -0.06 [$P=0.08$], -0.13 [$P<0.001$], and -0.75 [$P<0.001$]).

RISK OF DEATH FROM ALL CAUSES

The incidence of death from all causes was determined for each of the seven categories of cystatin C, creatinine, and estimated GFR, revealing substantive differences (Fig. 1). The cystatin C categories were nearly linearly associated with the risk of death. In contrast, creatinine and estimated GFR appeared to have J-shaped associations with the risk of death. We found no interactions of cystatin C levels with age, sex, race, or BMI; in contrast, creatinine levels had significant interactions with each of these covariates ($P<0.001$).

To explore the joint effects of cystatin C and creatinine in predicting mortality, we determined the incidence of death within each of the 25 subgroups defined by quintiles of cystatin C and creatinine (Fig. 2). Within each quintile of creatinine, increasing levels of cystatin C were associated with increased mortality.

After multivariate analysis, the first and second quintiles of cystatin C had a similar mortality rate, the third and fourth quintiles were associated with significantly, albeit moderately, increased risk, and all three subgroups of the fifth quintile were associated with roughly a doubling of mortality (Table 2). Among the predictors of mortality that were retained in the final model, the highest quintile of cystatin C was associated with the greatest population attributable risk (12.7 percent), followed by fair or poor self-reported health status (10.6 percent) and the presence of diabetes (7.4 percent).

For creatinine, the J-shaped association with mortality persisted in the multivariate analyses, and only the highest creatinine subgroup (5c, account-

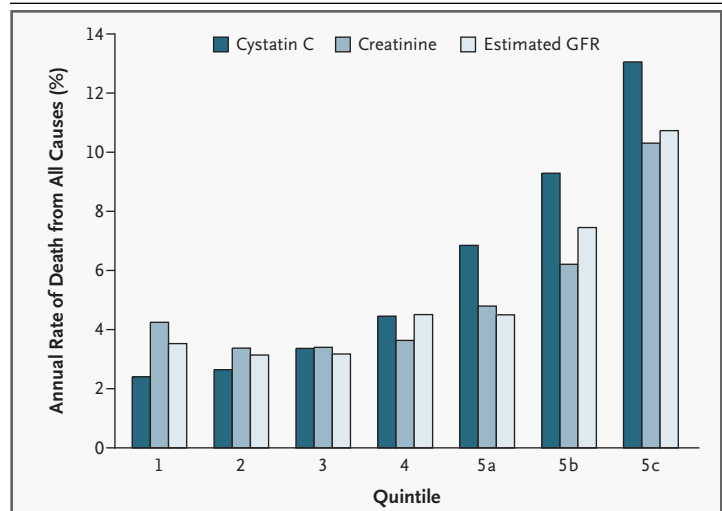


Figure 1. Mortality from All Causes According to Quintile of Measures of Renal Function.

For cystatin C, creatinine, and estimated glomerular filtration rate (GFR), the fifth quintile was subdivided into three roughly equal groups, labeled 5a, 5b, and 5c.

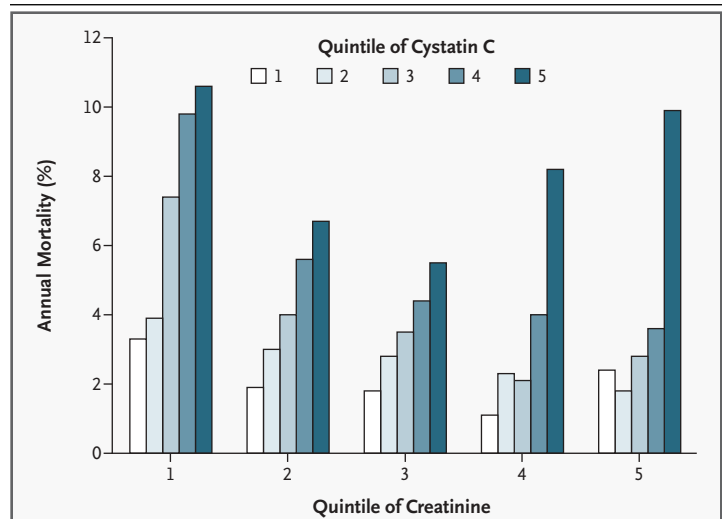


Figure 2. Mortality from All Causes According to Quintile of Both Cystatin C and Creatinine.

Participants in the Cardiovascular Health Study were divided into 25 subgroups defined according to quintiles of both creatinine and cystatin C. Within each quintile of creatinine, higher quintiles of cystatin C appeared to be associated with increased mortality. Conversely, within each quintile of cystatin C, the lowest creatinine quintile appeared to have the greatest risk of death.

ing for 7 percent of the cohort) had a significantly increased risk of death as compared with the risk in the lowest quintile. Only the two subgroups with

Table 2. Risk of Adverse Outcomes According to Measures of Renal Function among Elderly Participants in the Cardiovascular Health Study.*

Measure and Outcome	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5a	Quintile 5b	Quintile 5c
Cystatin C							
Range of values — mg/liter	≤0.89	0.90–0.99	1.00–1.10	1.11–1.28	1.29–1.39	1.40–1.59	≥1.60
Death from all causes							
No. at risk	942	892	943	947	308	302	303
No. of deaths	158	164	219	279	131	161	204
Hazard ratio (95% CI)							
Unadjusted	1.00	1.19 (0.95–1.49)	1.50 (1.21–1.86)	1.94 (1.58–2.38)	3.10 (2.44–3.95)	4.18 (3.32–5.26)	6.18 (4.97–7.70)
Adjusted†	1.00	1.08 (0.86–1.35)	1.23 (1.00–1.53)	1.34 (1.09–1.66)	1.77 (1.34–2.26)	2.18 (1.72–2.78)	2.58 (2.03–3.27)
Death from cardiovascular causes							
No. at risk	942	892	943	947	308	302	303
No. of deaths	45	58	99	122	56	68	82
Hazard ratio (95% CI)							
Unadjusted	1.00	1.47 (0.98–2.20)	2.37 (1.63–3.43)	3.01 (2.10–4.31)	4.70 (3.12–7.07)	6.25 (4.21–9.28)	8.23 (5.59–12.12)
Adjusted‡	1.00	1.33 (0.88–2.00)	1.93 (1.33–2.80)	1.99 (1.38–2.87)	2.48 (1.63–3.77)	2.73 (1.81–4.13)	2.83 (1.85–4.31)
Myocardial infarction§							
No. at risk	882	828	862	841	256	250	242
No. of events	59	57	82	82	32	26	32
Hazard ratio (95% CI)							
Unadjusted	1.00	1.03 (0.71–1.48)	1.45 (1.04–2.02)	1.54 (1.10–2.16)	2.08 (1.35–3.20)	1.94 (1.22–3.07)	2.69 (1.75–4.14)
Adjusted¶	1.00	0.97 (0.67–1.41)	1.26 (0.89–1.78)	1.14 (0.80–1.63)	1.44 (0.91–2.28)	1.30 (0.80–2.11)	1.65 (1.03–2.64)
Stroke							
No. at risk	910	864	901	903	280	268	258
No. of strokes	63	73	76	81	33	42	37
Hazard ratio (95% CI)							
Unadjusted	1.00	1.25 (0.89–1.75)	1.22 (0.87–1.71)	1.37 (0.98–1.91)	1.97 (1.29–3.00)	2.82 (1.90–4.19)	2.89 (1.92–4.35)
Adjusted**	1.00	1.22 (0.87–1.72)	1.17 (0.83–1.65)	1.15 (0.82–1.62)	1.43 (0.92–2.21)	1.97 (1.31–2.98)	1.80 (1.16–2.79)

Creatinine									
Range of values in men — mg/dl	≤0.85	0.86–1.05	1.06–1.15	1.16–1.25	1.26–1.35	1.36–1.55	≥1.56		
Range of values in women — mg/dl	≤0.65	0.66–0.75	0.76–0.85	0.86–0.95	0.96–1.05	1.06–1.15	≥1.16		
Death from all causes									
No. at risk	571	1287	966	716	433	321	343		
No. of deaths	159	298	225	175	135	125	199		
Hazard ratio (95% CI)									
Unadjusted	1.00	0.78 (0.64–0.96)	0.83 (0.67–1.02)	0.88 (0.70–1.10)	1.18 (0.93–1.50)	1.51 (1.19–1.93)	2.56 (2.06–3.19)		
Adjusted†	1.00	0.70 (0.57–0.85)	0.84 (0.68–1.04)	0.83 (0.66–1.03)	1.00 (0.79–1.27)	0.95 (0.74–1.22)	1.48 (1.18–1.85)		
Death from cardiovascular causes									
No. at risk	571	1287	966	716	433	321	343		
No. of deaths	54	124	94	72	55	53	78		
Hazard ratio (95% CI)									
Unadjusted	1.00	0.96 (0.69–1.34)	1.04 (0.73–1.47)	1.06 (0.73–1.53)	1.46 (0.99–2.14)	1.89 (1.28–2.81)	2.75 (1.91–3.98)		
Adjusted‡	1.00	0.84 (0.60–1.18)	1.07 (0.75–1.51)	0.98 (0.68–1.42)	1.18 (0.80–1.74)	1.04 (0.70–1.55)	1.38 (0.94–2.03)		
Myocardial infarction§									
No. at risk	526	1154	885	659	389	268	280		
No. of events	48	97	67	70	32	28	28		
Hazard ratio (95% CI)									
Unadjusted	1.00	0.86 (0.61–1.22)	0.78 (0.54–1.13)	1.13 (0.78–1.63)	0.89 (0.57–1.38)	1.20 (0.75–1.91)	1.25 (0.78–1.99)		
Adjusted¶	1.00	0.76 (0.53–1.09)	0.82 (0.56–1.20)	1.08 (0.74–1.59)	0.84 (0.53–1.33)	0.99 (0.61–1.59)	0.93 (0.57–1.52)		
Stroke									
No. at risk	551	1225	924	686	405	293	300		
No. of strokes	45	103	78	59	44	38	38		
Hazard ratio (95% CI)									
Unadjusted	1.00	0.95 (0.67–1.35)	0.95 (0.65–1.37)	1.01 (0.68–1.48)	1.29 (0.85–1.97)	1.65 (1.07–2.54)	1.71 (1.11–2.64)		
Adjusted**	1.00	0.98 (0.69–1.39)	1.00 (0.69–1.45)	1.02 (0.69–1.50)	1.17 (0.77–1.79)	1.34 (0.86–2.07)	1.18 (0.76–1.85)		

Estimated GFR		≥82.84	73.87–82.83	66.63–73.86	55.70–66.62	53.46–55.69	45.65–53.45	≤45.64
Range of values — ml/min/1.73 m ²								
Death from all causes								
No. at risk		921	927	935	930	301	315	308
No. of deaths		217	200	206	277	89	143	184
Hazard ratio (95% CI)								
Unadjusted		1.00	0.90 (0.73–1.09)	0.91 (0.75–1.11)	1.32 (1.10–1.58)	1.34 (1.04–1.72)	2.23 (1.79–2.77)	3.23 (2.63–3.96)
Adjusted†		1.00	0.91 (0.74–1.11)	0.85 (0.70–1.04)	1.06 (0.88–1.28)	1.21 (0.94–1.56)	1.30 (1.03–1.62)	1.78 (1.44–2.21)
Death from cardiovascular causes								
No. at risk		921	927	935	930	301	315	308
No. of deaths		80	86	81	117	36	59	71
Hazard ratio (95% CI)								
Unadjusted		1.00	1.09 (0.80–1.50)	0.96 (0.70–1.33)	1.54 (1.15–2.07)	1.49 (0.99–2.23)	2.47 (1.74–3.51)	3.18 (2.26–4.47)
Adjusted‡		1.00	1.15 (0.84–1.58)	0.92 (0.66–1.27)	1.26 (0.93–1.70)	1.32 (0.88–1.98)	1.28 (0.89–1.84)	1.55 (1.08–2.22)
Myocardial infarction§								
No. at risk		843	847	857	838	267	262	247
No. of events		74	64	65	92	18	29	28
Hazard ratio (95% CI)								
Unadjusted		1.00	0.82 (0.58–1.14)	0.82 (0.59–1.15)	1.26 (0.93–1.71)	0.76 (0.46–1.28)	1.37 (0.90–2.11)	1.52 (0.99–2.35)
Adjusted¶		1.00	0.91 (0.64–1.30)	0.88 (0.62–1.24)	1.14 (0.82–1.58)	0.85 (0.50–1.44)	1.14 (0.72–1.79)	1.22 (0.77–1.94)
Stroke								
No. at risk		884	896	888	875	284	288	269
No. of strokes		73	73	74	82	29	38	36
Hazard ratio (95% CI)								
Unadjusted		1.00	0.94 (0.68–1.31)	0.95 (0.69–1.32)	1.15 (0.84–1.58)	1.18 (0.76–1.84)	1.76 (1.19–2.61)	1.92 (1.29–2.86)
Adjusted**		1.00	0.94 (0.68–1.31)	0.96 (0.69–1.34)	1.07 (0.77–1.48)	1.16 (0.75–1.81)	1.23 (0.82–1.85)	1.27 (0.84–1.91)

* For cystatin C, creatinine, and the estimated glomerular filtration rate (GFR), the fifth quintile was subdivided into three roughly equal groups, labeled 5a, 5b, and 5c. For estimated GFR, the fifth quintile comprised the participants with the lowest values. To convert values for creatinine to micromoles per liter, multiply by 88.4. CI denotes confidence interval.

† The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

‡ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, hemoglobin level, high-density lipoprotein cholesterol level, and presence or absence of a history of stroke or transient ischemic attack.

§ A total of 476 participants who had myocardial infarction before the 1992–1993 visit were excluded from the analyses of newly diagnosed myocardial infarction (remaining sample size, 4161).

¶ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, presence or absence of hypertension, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, hemoglobin level, high-density lipoprotein cholesterol level, and presence or absence of a history of stroke or transient ischemic attack.

|| A total of 254 participants who had stroke before the 1992–1993 visit were excluded from the analyses of newly diagnosed stroke (remaining sample size, 4383).

** The hazard ratios have been adjusted for age, weight, presence or absence of diabetes, presence or absence of hypertension, self-reported health status, fibrinogen levels, and presence or absence of a history of myocardial infarction.

the lowest estimated GFR levels (5b and 5c) had a significantly increased risk of death in adjusted analyses.

RISK OF CARDIOVASCULAR EVENTS

The association of cystatin C with mortality from cardiovascular causes was even stronger than its association with mortality from all causes (Table 2). As compared with the first quintile in the adjusted analysis, the second quintile had a similar risk, quintiles 3 and 4 had approximately a doubled risk, and the subgroups of the fifth quintile had nearly a tripled risk. None of the creatinine subgroups were at significantly increased risk in the adjusted analysis, and only the subgroup with the lowest estimated GFR values was at increased risk.

The associations of cystatin C with newly diagnosed myocardial infarction and stroke were less strong than was the case for the mortality outcomes. In unadjusted analysis, a significant increase in the risk of myocardial infarction was observed for all subgroups of cystatin C above the second quintile. However, in adjusted analysis, only the subgroup with the highest values (5c) was at significantly increased risk for myocardial infarction. Creatinine and estimated GFR subgroups had no significant association with myocardial infarction in either unadjusted or adjusted analyses. In an unadjusted analysis of newly diagnosed stroke, the fifth cystatin C quintile had twice the risk of the lowest quintile. After multivariate adjustment, the highest two subgroups of the fifth quintile remained at significantly increased risk. In unadjusted analysis, the one or two subgroups of creatinine and estimated GFR that indicated the worst renal function were associated with the risk of stroke; however, no significant associations remained after multivariate adjustment.

LOW, INTERMEDIATE, AND HIGH CYSTATIN C LEVELS

On the basis of the findings presented in Table 2, we combined subgroups into categories designated low-risk (quintiles 1 and 2), intermediate-risk (quintiles 3 and 4), and high-risk (quintile 5), corresponding to cystatin C levels of less than 1.00 mg per liter, 1.00 to 1.28 mg per liter, and 1.29 mg per liter or more (Table 3). The intermediate-risk group had an annual risk of death of 3.9 percent, which was similar to the average risk of 4.3 percent for the entire cohort. As compared with the low-risk group, the intermediate-risk group had a moderately elevated risk of death from all causes and death

from cardiovascular causes; the high-risk group had a substantially greater risk of both outcomes than did either the intermediate-risk or the low-risk group (Table 3). For newly diagnosed myocardial infarction and stroke, being in the intermediate-risk group was not independently associated with greater risk. The high-risk group had a doubling of the risk of myocardial infarction and stroke in the unadjusted analysis and an increase in risk of roughly 50 percent for each outcome after multivariate adjustment.

DISCUSSION

In this study, we found cystatin C to be a strong and independent predictor of overall mortality and mortality from cardiovascular causes in a population-based cohort of ambulatory elderly persons. Using cutoff points at the 40th and 80th percentiles of cystatin C, we defined groups at low, intermediate, and high risk with respect to death from all causes and from cardiovascular causes (cystatin C levels: <1.00, 1.00 to 1.28, and \geq 1.29 mg per liter, respectively). High cystatin C levels were also independently associated with the risk for newly diagnosed myocardial infarction and stroke. In contrast, only the participants in the highest 7 percent of the cohort with respect to creatinine levels had a significantly increased risk of death from all causes in the adjusted analysis, and we found no independent association of this creatinine category with the risk of death from cardiovascular causes, myocardial infarction, or stroke. The estimated GFR value, derived with use of the MDRD equation, was only a slightly better predictor of mortality than was the creatinine level. Thus, the cystatin C level appears to provide a stronger estimate of the risk of cardiovascular events and death among elderly persons than either the creatinine level or the estimated GFR.

In part, these results are consistent with previous studies demonstrating that renal dysfunction predicts adverse cardiovascular outcomes and death in a variety of clinical settings. However, the insensitivity of creatinine levels and estimated GFR values for detecting renal dysfunction has limited their value as prognostic factors. We previously reported that elevated creatinine levels had a linear association with the rates of cardiovascular events and with mortality.²² In fact, this linear increase in risk was observed only among participants with creatinine levels of 1.3 mg per deciliter (115 μ mol per liter) or more — the upper 14 percent of the cohort.

Table 3. Risk of Death and Cardiovascular Events According to Cystatin C Risk Categories among Elderly Participants in the Cardiovascular Health Study.*

Variable	Cystatin C Category		
	Low Risk	Intermediate Risk	High Risk
Range of cystatin C values (mg/liter)	<0.99	1.00–1.28	>1.29
No. of participants	1834	1890	913
Death from all causes			
No. of events	322	498	496
Annual incidence (%)	2.5	3.9	9.5
Hazard ratio (95% CI)			
Unadjusted	1.00	1.57 (1.36–1.82)	3.98 (3.44–4.60)
Adjusted†	1.00	1.23 (1.07–1.43)	2.05 (1.74–2.40)
Death from cardiovascular causes			
No. of events	103	221	206
Annual incidence (%)	0.8	1.7	4.0
Hazard ratio (95% CI)			
Unadjusted	1.00	2.18 (1.71–2.78)	5.07 (3.97–6.49)
Adjusted‡	1.00	1.67 (1.31–2.14)	2.27 (1.73–2.97)
Myocardial infarction			
No. of events	116	164	90
Annual incidence (%)	1.0	1.5	2.2
Hazard ratio (95% CI)			
Unadjusted	1.00	1.49 (1.17–1.90)	2.29 (1.73–3.03)
Adjusted§	1.00	1.22 (0.95–1.57)	1.48 (1.08–2.02)
Stroke			
No. of events	136	157	112
Annual incidence (%)	1.1	1.3	2.5
Hazard ratio (95% CI)			
Unadjusted	1.00	1.18 (0.93–1.49)	2.13 (1.64–2.77)
Adjusted¶	1.00	1.06 (0.83–1.35)	1.47 (1.09–1.96)

* CI denotes confidence interval.

† The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

‡ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, hemoglobin level, presence or absence of a history of myocardial infarction, presence or absence of a history of stroke or transient ischemic attack, and presence or absence of heart failure.

§ The hazard ratios have been adjusted for age, sex, presence or absence of diabetes, presence or absence of hypertension, self-reported health status, presence or absence of left ventricular hypertrophy, fibrinogen level, log C-reactive protein level, hemoglobin level, high-density lipoprotein cholesterol level, and presence or absence of a history of stroke or transient ischemic attack.

¶ The hazard ratios have been adjusted for age, weight, presence or absence of diabetes, presence or absence of hypertension, self-reported health status, fibrinogen level, and presence or absence of a history of myocardial infarction.

Not only did cystatin C levels define a subgroup (the top 20 percent) of elderly persons in the CHS cohort who had a substantially elevated risk of death, but they also defined a large subgroup (the lowest 40 percent) at below-average risk of death. This observation is intriguing and provocative, since earlier studies in which creatinine or estimated GFR was used had found only a high-risk group associated with high creatinine levels or low estimated GFR values; renal function had appeared to affect the

risk of death only when it dropped below a certain threshold, such as a GFR of 60 ml per minute per 1.73 m² of body-surface area.¹⁻³ The linear association of cystatin C with the risk of death among participants with predominantly “normal” renal function may indicate that differences in renal function well within the normal range have clinical significance. Future research should evaluate distinctions between persons with low, intermediate, and high cystatin C levels to evaluate other potential consequences of declining renal function. In addition, though we observed no interactions with race or sex in our study, this absence of association should be confirmed in other cohorts, since our study may have had inadequate statistical power to detect such interactions.

An additional task for future studies will be to determine whether cystatin C could have value in clinical medicine as an improved measure of renal function in elderly patients. Our findings indicate that cystatin C is a better marker of the risk of death than creatinine or the estimated GFR. However, to establish that cystatin C has clinical value, studies would have to demonstrate that knowledge of cystatin C levels could improve clinical decision making — as in the evaluation of the risk–benefit trade-offs in prescribing medication, administration of intravenous contrast material, or surgical procedures — over that based on creatinine levels. Although its clinical role has not yet been delineated, measurement of cystatin C is approved by the Food and Drug Administration as a diagnostic test for kidney dysfunction.

Cystatin C may have important limitations as a marker of kidney function in certain disease states. In particular, cystatin C levels appear to be elevated in patients with hypothyroidism and depressed in those with hyperthyroidism²³⁻²⁵; yet the effect of thyroid function on cystatin C levels could reflect actual changes in GFR, which appears to vary directly with basal metabolic rate.²⁶ Knight and colleagues from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study reported that the association of cystatin C with kidney function was influenced by multiple factors; however, their findings may have been biased by their use of creatinine clearance as the gold standard for kidney function, so it is unclear whether these influences are independent of kidney function.²⁷ In contrast to the findings from PREVEND, we found no significant

association between cystatin C levels and the prevalence of current smoking or the number of cigarettes smoked per day. Future research should clarify the effects of tobacco use and clinical disease status on the capacity of cystatin C levels to predict the GFR.

Our study does have certain limitations. Most important, we cannot be certain whether the strong association of cystatin C with the outcomes we studied is due solely to its correlation with kidney function. Cystatin C may have unforeseen toxic effects that also contribute to the strength of its association with mortality and cardiovascular risk. We also cannot exclude the possibility of confounding due to potential associations of cystatin C with diseases that are independent of its correlation with kidney function. Since the adjusted hazard ratios are substantially different from the unadjusted estimates, we may have overlooked additional, residual confounding. In addition, CHS enrolled only elderly persons, so we do not know whether cystatin C would be a stronger predictor of mortality than creatinine for younger persons, in whom lean muscle makes up a greater proportion of body mass. We also did not calibrate serum creatinine to the methods of the Cleveland Clinic for estimating GFR, as has been recommended.²⁸ However, since we grouped participants according to quintiles of creatinine and estimated GFR, any arithmetic conversion of the creatinine levels would have no impact on our findings, because their distribution would be unchanged.

In summary, we found that cystatin C, an alternative measure of kidney function, was a stronger predictor of the risk of cardiovascular events and death than either creatinine or the estimated GFR. If this result is confirmed in other studies, cystatin C could be a useful prognostic tool in the evaluation of elderly patients.

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A full list of participating CHS investigators and institutions can be found at <http://www.chs-nhlbi.org>.

REFERENCES

1. Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA* 1998;279:585-92.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
3. Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy, and heart failure outcomes: evidence from the Digoxin Intervention Group Trial. *J Am Soc Nephrol* 2004;15:2195-203.
4. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA* 2001;285:2987-94.
5. Browner WS, Li J, Mangano DT. In-hospital and long-term mortality in male veterans following noncardiac surgery. *JAMA* 1992;268:228-32.
6. Chertow GM, Lazarus JM, Christiansen CL, et al. Preoperative renal risk stratification. *Circulation* 1997;95:878-84.
7. Anavekar NS, McMurray JJV, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351:1285-95.
8. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 2002;137:555-62.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;130:461-70.
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
11. Garg AX, Papaioannou A, Ferko N, Campbell G, Clarke JA, Ray JG. Estimating the prevalence of renal insufficiency in seniors requiring long-term care. *Kidney Int* 2004;65:649-53.
12. Coll E, Botev A, Alvarez L, et al. Serum cystatin C as a new marker for noninvasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis* 2000;36:29-34.
13. Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis* 2001;37:79-83.
14. Herget-Rosenthal S, Trabold S, Pietruck F, Holtmann M, Philipp T, Kribben A. Cystatin C: efficacy as screening test for reduced glomerular filtration rate. *Am J Nephrol* 2000;20:97-102.
15. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263-76.
16. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem* 1995;41:264-70.
17. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest* 1999;59:1-8.
18. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* 2000;11:Suppl:155A. abstract.
19. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol* 1995;5:278-85.
20. Price TR, Psaty B, O'Leary D, Burke G, Gardin J. Assessment of cerebrovascular disease in the Cardiovascular Health Study. *Ann Epidemiol* 1993;3:504-7.
21. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. *Ann Epidemiol* 1995;5:270-7.
22. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 2003;41:1364-72.
23. Fricker M, Wiesli P, Brandle M, Schwegler B, Schmid C. Impact of thyroid dysfunction on serum cystatin C. *Kidney Int* 2003;63:1944-7.
24. Jayagopal V, Keevil BG, Atkin SL, Jennings PE, Kilpatrick ES. Paradoxical changes in cystatin C and serum creatinine in patients with hypo- and hyperthyroidism. *Clin Chem* 2003;49:680-1.
25. Wiesli P, Schwegler B, Spinass GA, Schmid C. Serum cystatin C is sensitive to small changes in thyroid function. *Clin Chim Acta* 2003;338:87-90.
26. Singer MA. Of mice and men and elephants: metabolic rate sets glomerular filtration rate. *Am J Kidney Dis* 2001;37:164-78.
27. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 2004;65:1416-21.
28. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002;39:920-9.

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