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Cystatin C as a Risk Factor for Outcomes in Chronic Kidney Disease

Vandana Menon, MD, PhD; Michael G. Shlipak, MD, MPH; Xuelei Wang, MS; Josef Coresh, MD, PhD; Tom Greene, PhD; Lesley Stevens, MD, MS; John W. Kusek, PhD; Gerald J. Beck, PhD; Allan J. Collins, MD; Andrew S. Levey, MD; and Mark J. Sarnak, MD, MS

Background: No study has compared cystatin C level, serum creatinine concentration, and estimated glomerular filtration rate (GFR) as risk factors for outcomes in chronic kidney disease (CKD), and none has compared measured GFR with CKD in any population.

Objective: To compare cystatin C level with serum creatinine concentration and iothalamate GFR as risk factors for death and kidney failure.

Design: Observational study using serum cystatin C assayed from baseline samples of the Modification of Diet in Renal Disease Study (1989–1993).

Setting: 15 clinical centers in the United States that participated in the Modification of Diet in Renal Disease Study.

Participants: 825 trial participants with stage 3 or 4 nondiabetic CKD who had measurements of serum cystatin C.

Measurements: All-cause mortality, cardiovascular (CVD) mortality, and kidney failure until December 2000.

Results: Mean cystatin C level, creatinine concentration, and GFR were 2.2 mg/L (SD, 0.7), 212.16 μmol/L (SD, 88.4) (2.4 mg/dL [SD, 1.0]), and 33 mL/min per 1.73 m^2 (SD, 12), respectively. Median follow-up was 10 years. Twenty-five percent of patients (n = 203) died of any cause, 15% (n = 123) died of CVD, and 66% (n = 548) reached kidney failure. In multivariate-adjusted models, 1-SD decreases in 1/creatinine, GFR, and 1/cystatin C were associated with increased risks for all-cause mortality of 1.27 (95% CI, 1.06 to 1.49), 1.27 (CI, 1.08 to 1.49), and 1.41 (CI, 1.18 to 1.67), respectively. For CVD mortality, the increased risks were 1.32 (CI, 1.05 to 1.64), 1.28 (CI, 1.04 to 1.59), and 1.64 (CI, 1.28 to 2.08), respectively. For kidney failure, the increased risks were 2.81 (CI, 2.48 to 3.18), 2.41 (CI, 2.15 to 2.70), and 2.36 (CI, 2.10 to 2.66), respectively.

Limitation: The Modification of Diet in Renal Disease Study cohort may not be representative of all patients with nondiabetic CKD because participants were more likely to reach kidney failure than death in follow-up.

Conclusion: The association of cystatin C level with all-cause and CVD mortality was as strong as or perhaps stronger than that of iothalamate GFR with these outcomes in stage 3 or 4 CKD.

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For author affiliations, see end of text.

Mild to moderate reductions in kidney function are associated with a marked increase in the risk for cardiovascular disease (CVD) (1–4). Assessing the degree of kidney function is now recognized as an important component of risk stratification for CVD morbidity and mortality. Cystatin C is a novel measure of kidney function (5, 6) that seems to be less sensitive than creatinine to factors other than glomerular filtration rate (GFR), particularly muscle mass (7). Thus, the serum cystatin C level may be a better marker of kidney function than the serum creatinine concentration, especially in elderly persons and in the setting of mild kidney dysfunction (8, 9). Cystatin C is easily measured in serum, making it a practical alternative to measured GFR, which is too cumbersome for clinical practice.

Studies in elderly persons suggest that the cystatin C level has a stronger association with CVD events than do creatinine concentration and GFR estimated from serum creatinine (10–12). No study has compared cystatin C and serum creatinine as risk factors for outcomes in persons with established chronic kidney disease (CKD). Furthermore, no study has compared outcomes on the basis of cystatin C level versus measured GFR, the gold standard for measurement of kidney function. We examined the associations of cystatin C level, creatinine concentration, and measured GFR with all-cause and CVD mortality and kidney failure in patients with CKD stages 3 to 4.

METHODS

Study Sample

The Modification of Diet in Renal Disease (MDRD) Study, conducted from 1989 to 1993, was a randomized, controlled trial of the effect of dietary protein restriction and blood pressure control on the progression of kidney disease (13). In brief, 840 patients with predominantly nondiabetic kidney disease and reduced GFR were included in the MDRD Study. Key inclusion criteria were age 18 to 70 years and a serum creatinine concentration of 106.08 to 618.81 μmol/L (1.2 to 7.0 mg/dL) in women and 123.76 to 618.81 μmol/L (1.4 to 7.0 mg/dL) in men. Glomerular filtration rate was measured at screening and again after a 3-month baseline period, during which patients were instructed about the study procedures, dietary protein intake, and control of blood pressure. We use the

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Appendix Table
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Audio summary

Context

Does cystatin C, glomerular filtration rate (GFR), or creatinine better predict mortality?

Contribution

This study examined long-term outcomes of 825 adults with nondiabetic chronic kidney disease who had participated in 2 trials of protein restriction in the early 1990s. Higher cystatin C and creatinine levels and lower GFR at baseline were all associated with an increased risk for kidney failure and for all-cause and cardiovascular mortality. Associations between cystatin C and cardiovascular mortality seemed slightly stronger than those between GFR or creatinine and cardiovascular mortality.

Implication

Cystatin C levels seem to be at least as strongly associated with mortality as either GFR or creatinine concentration in adults with nondiabetic chronic kidney disease.

—The Editors

term *screening GFR* to refer to the first baseline GFR for screening and the term *3-month baseline GFR* to refer to the GFR measured at the end of the 3-month baseline period. The range of screening GFR (10 to 65 mL/min per 1.73 m^2) was less restrictive than the range for 3-month baseline GFR (13 to 55 mL/min per 1.73 m^2). Patients were eligible for study A if their 3-month baseline GFR was 25 to 55 mL/min per 1.73 m^2 and for study B if it was 13 to 24 mL/min per 1.73 m^2. Patients in studies A and B were combined for the current analyses. Because the measured GFR ranged from 13 to 55 mL/min per 1.73 m^2, with 6% of the cohort having a GFR less than 15 mL/min per 1.73 m^2, the study sample consists predominantly of patients with stage 3 or 4 CKD, as defined by the National Kidney Foundation Kidney Disease Outcomes and Quality Initiative (14).

Baseline Measurement of Kidney Function

Glomerular filtration rate was measured by using iothalamate clearance (15). After subcutaneous injection of ^{125}I-iothalamate, investigators collected 4 consecutive urine and 5 serum samples after an equilibration period of 1 hour. Measurements of serum and urine radioactivity were performed at the central MDRD Study laboratory. Glomerular filtration rate was calculated as the time-weighted averages of urine excretion rates and the serum concentration of the marker over the collection periods and was adjusted for body surface area. Estimated GFR was calculated from baseline serum creatinine concentration by using the 4-variable MDRD Study equation: $186.3 \times (\text{serum creatinine concentration}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$ (if black) $\times$ 0.742 (if female) (16). Serum creatinine was measured at baseline at the Cleveland Clinic Foundation, Cleveland, Ohio, by using the kinetic alkaline picrate assay on a Beckman Astra CX3 (Beckman, Fullerton, California). Cystatin C was measured in frozen samples collected at baseline from 825 participants of the MDRD Study. Samples were assayed for cystatin C by using a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring, Deerfield, Illinois). Measurement of a quality control specimen was included in each analytic run. Calculation of the SD and the coefficient of variation demonstrated an interrun precision for the assay of 5.6% (mean cystatin C level, 1.62 mg/L [SD, 0.09]; $n = 14$).

Outcomes

We assessed 4 outcomes: all-cause mortality, CVD mortality, kidney failure (the need for renal replacement therapy with dialysis or transplantation), and a composite outcome of kidney failure and all-cause mortality. We ascertained survival status and cause of death from the National Death Index and ascribed deaths to CVD if the primary cause of death was International Classification of Diseases, Ninth Revision, codes 390 to 459 or if kidney disease was listed as the primary cause of death and CVD was the secondary cause. We defined survival time as the time from randomization to death or end of follow-up (31 December 2000). We obtained kidney failure outcomes from the U.S. Renal Data System. The institutional review boards of The Cleveland Clinic, Cleveland, Ohio, and Tufts–New England Medical Center, Boston, Massachusetts, approved the data collection procedures.

Statistical Analysis

We compared baseline characteristics of the study sample across quartiles of serum cystatin C values and calculated *P* values for linear trend. We also compared baseline characteristics across quartiles of estimated GFR (**Appendix Table**, available at www.annals.org). Because serum cystatin C and creatinine vary as the inverse of GFR, we used the inverse of serum cystatin C (1/cystatin C) and creatinine (1/creatinine) to facilitate direct comparison with GFR. Pearson correlations were used to examine univariate associations among the 3 measures of kidney function. We calculated incidence rates for all-cause mortality, CVD mortality, and kidney failure by quartiles of each baseline measure of kidney function: 1/creatinine, GFR, estimated GFR, and 1/cystatin C.

We compared the association of the baseline measures of kidney function with outcomes by using unadjusted and adjusted Cox proportional hazards models. Covariates specified a priori in the adjusted models were age, race, sex, smoking, history of diabetes and CVD, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, and log-transformed proteinuria. Models for kidney failure and the composite outcome were adjusted for cause of kidney disease in addition to the previously listed covariates. The models for the mortality outcomes included patients with kidney failure and were censored only at death or the end of follow-up. The models for kidney failure and the composite outcome were censored at kidney failure, death, or the end of follow-up.

We repeated the adjusted Cox models for each of the 4 outcomes after additional adjustment for log-transformed C-reactive protein (CRP) level. We entered the measures of kidney function as continuous variables (1/creatinine, GFR, and 1/cystatin) and calculated the hazard ratios and 95% CIs per 1-SD change in each measure to allow a standardized comparison across measures with the same scale. We tested for nonlinearity by examining the functional form of the relationship of all-cause mortality risk and CVD mortality risk versus each marker of kidney function as a continuous variable while controlling for the covariates by fitting a cubic smoothing spline. We tested proportional hazards assumptions by using log(−log) survival plots and plots of Schoenfeld residuals versus survival time. We used S-Plus, version 6.2 (Insightful Corp., Seattle, Washington), and SPSS, version 14.0 (SPSS, Chicago, Illinois), to perform the statistical analyses.

Additional Analyses

We repeated the adjusted Cox models for each outcome by using 2 additional measures of kidney function. First, we used estimated GFR because measuring GFR is impractical in clinical practice and research settings and, hence, GFR estimated from the serum creatinine concentration is often used as a surrogate measure. Second, to reduce variability in GFR measurements, we used the average of 2 baseline iothalamate GFR measurements performed 3 months apart.

Sensitivity Analyses

Transformation of cystatin C and serum creatinine values may make the expressions of their effects relative to SDs less comparable than if no transformation had been performed. To address this issue, we repeated the unadjusted Cox models with hazard ratios comparing the 80th to the 20th percentile of decreasing kidney function.

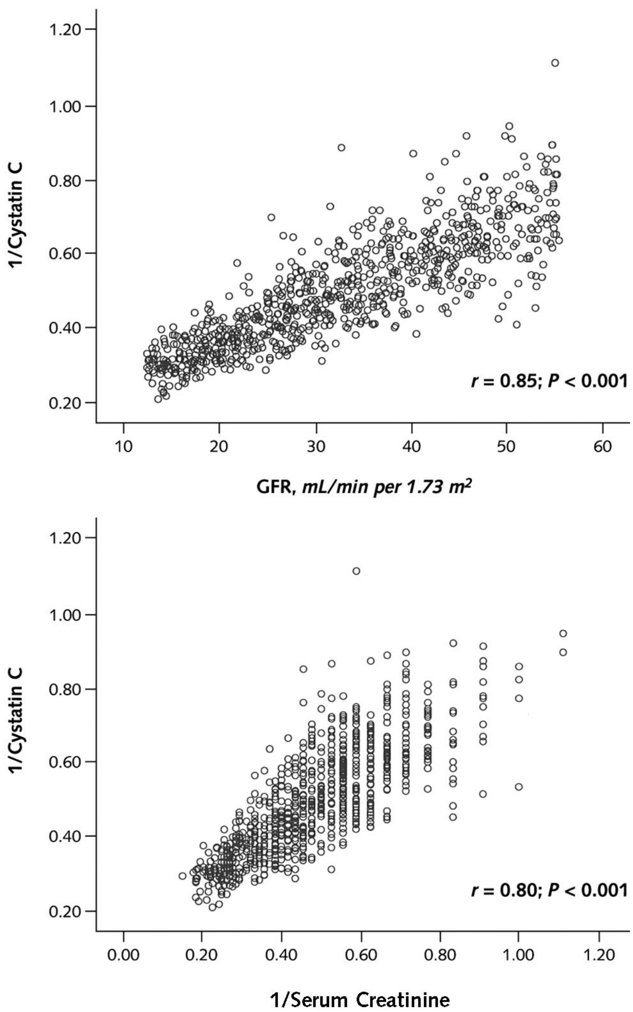
Because entry criteria into the MDRD Study were based on GFR values, the range of GFR, but not of cystatin C or creatinine, is artificially restricted by study design. To address this limitation, we performed 2 sets of sensitivity analyses. First, because study entry was based on the 3-month baseline GFR, we repeated analyses by using screening GFR, which was less restrictive than the 3-month baseline GFR. Second, we examined the effects of all 3 indices (1/cystatin C, 1/creatinine, and iothalamate GFR) after excluding the top and bottom quintiles for each marker. That is, we restricted the cohort to quintiles 2 to 4 on the basis of cystatin C values and repeated our analyses for each measure (1/cystatin, 1/creatinine, and GFR). We

Table 1. **Baseline Characteristics, by Quartiles of Cystatin C***

Characteristic	Quartile 1 (*n* = 208)	Quartile 2 (*n* = 204)	Quartile 3 (*n* = 208)	Quartile 4 (*n* = 205)	*P* Value†
Mean cystatin C level (SD), *mg/L*	1.45 (0.15)	1.87 (0.12)	2.37 (0.17)	3.17 (0.39)	–
Mean age (SD), *y*	52 (11)	52 (12)	52 (13)	51 (13)	0.3
Male, %	44	40	42	32	0.05
White, %	84	84	86	86	0.48
Current smoker, %	7	9	11	12	0.05
Diabetes, %	3	6	7	4	0.71
History of cardiovascular disease, %	11	12	14	16	0.08
Mean BMI (SD), *kg/m²*	27.4 (4.3)	27.8 (4.5)	27.1 (4.5)	26.2 (4.2)	0.002
Mean HDL cholesterol level (SD)					<0.001
mmol/L	1.10 (0.35)	1.04 (0.37)	1.03 (0.37)	0.95 (0.36)	
mg/dL	42.5 (13.6)	40.4 (14.4)	39.9 (14.2)	36.6 (14.0)	
Mean LDL cholesterol level (SD)					0.17
mmol/L	3.85 (0.32)	3.88 (1.12)	3.84 (1.10)	3.71 (0.97)	
mg/dL	148.7 (12.3)	149.8 (43.1)	148.4 (42.4)	143.2 (37.5)	
Mean systolic blood pressure (SD), *mm Hg*	128.6 (16.4)	132.5 (18.5)	132.7 (17.8)	133.9 (17.4)	0.003
Median CRP level (IQR‡), *mg/L*	2.1 (4.1)	3.0 (5.4)	2.5 (6.1)	2.1 (4.4)	0.13
Mean albumin level (SD), *g/L*	4.0 (0.34)	4.0 (0.33)	4.0 (0.37)	4.0 (0.35)	0.20
Median proteinuria (IQR‡), *g/d*	0.10 (0.52)	0.17 (1.20)	0.52 (1.63)	0.77 (2.12)	<0.001
Mean GFR (SD), *mL/min per 1.73 m²*	45.7 (6.9)	37.2 (7.4)	28.1 (7.1)	18.9 (4.5)	<0.001
Mean creatinine concentration (SD)					<0.001
μmol/L	141.44 (26.52)	167.96 (35.36)	221.00 (53.04)	309.41 (79.56)	
mg/dL	1.6 (0.3)	1.9 (0.4)	2.5 (0.6)	3.5 (0.9)	
Cause of kidney disease, %					0.32
Polycystic kidney disease	23	28	23	22	
Glomerular diseases	28	31	30	38	
Other	49	41	47	40	

* Quartile 1, 0.9–1.66 mg/L; quartile 2, 1.67–2.08 mg/L; quartile 3, 2.09–2.68 mg/L; quartile 4, 2.69–4.82 mg/L. BMI = body mass index; CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.
† *P* value for trend.
‡ The IQR presented is the difference between the 25th and 75th percentiles.

Figure. **Correlations between 1/cystatin C and measured glomerular filtration rate (*GFR*) (*top*) and 1/serum creatinine (*bottom*).**



repeated these analyses, restricting the cohort to quintiles 2 to 4 on the basis of creatinine values and GFR.

Role of the Funding Source

The study was funded through grants and contracts from the National Institute of Diabetes and Digestive and Kidney Diseases. The funding source had no role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication. Drs. Sarnak, Menon, and Greene and Ms. Wang had full access to the data.

RESULTS

Baseline Characteristics

The study cohort had a mean age of 52 years (SD, 13). The sample was predominantly white (85%), 61% were male, 5% had a history of diabetes, and 10% were current smokers. Mean cystatin C level, creatinine concentration, and GFR were 2.2 mg/L (SD, 0.7), 212.16 μmol/L (SD, 88.4) (2.4 mg/dL [SD, 1.0]), and 33 mL/min per 1.73 m^2 (SD, 12), respectively. At baseline, 1% and 8% of the cohort were receiving steroids and thyroid-related medications, respectively.

Higher levels of cystatin C were associated with lower body mass index and high-density lipoprotein cholesterol levels and higher systolic blood pressure and proteinuria (**Table 1**). Prevalence of diabetes and CVD, mean CRP level, or cause of CKD did not differ among the quartiles. A strong direct association of GFR with 1/cystatin C (r = 0.85; $P < 0.001$) and 1/creatinine (r = 0.80; $P < 0.001$) was evident (**Figure**).

Kidney Function and All-Cause Mortality

Median follow-up for survival analyses was 10 years (range, 3 to 140 months). Of the participants, 203 (25%) died of any cause. Unadjusted all-cause mortality rates were calculated by quartiles of each measure of kidney function (**Table 2**). Quartiles of 1/cystatin C and GFR, but not of 1/creatinine or estimated GFR, had a graded relationship with the all-cause mortality rate.

In the unadjusted Cox models with each measure of kidney function as a continuous variable, a 1-SD decrease in 1/creatinine, GFR, and 1/cystatin C was associated with a 15%, 28%, and 45% increase, respectively, in the risk for all-cause mortality ($P < 0.001$) (**Table 3**). Adjustment for previously described covariates did not appreciably alter the magnitude of these associations.

In nonparametric regression analyses, the log-adjusted risk ratio for all-cause mortality had a linear relationship with 1/creatinine (P = 0.019, for linear effect), GFR (P = 0.004, for linear effect), and 1/cystatin C ($P < 0.001$, for linear effect).

Kidney Function and CVD Mortality

One hundred twenty-three (15%) participants died of CVD during follow-up. We found a graded relationship of 1/cystatin C and GFR, but not 1/creatinine or estimated GFR, with CVD mortality (**Table 2**). In unadjusted Cox models with each measure of kidney function as a continuous variable, a 1-SD decrease in 1/creatinine, GFR, and 1/cystatin C was associated with a 15%, 28%, and 59% increase, respectively, in the risk for CVD mortality ($P <$ 0.001) (**Table 3**). Covariate adjustment did not attenuate these associations. In nonparametric regression analyses, the log-adjusted risk ratio for CVD mortality had a linear relationship with 1/creatinine (P = 0.028, for linear effect), GFR (P = 0.016, for linear effect), and 1/cystatin ($P < 0.001$, for linear effect).

Kidney Function and Kidney Failure and the Composite Outcome

Five hundred forty-eight participants (66%) reached kidney failure and 614 (74%) reached the composite outcome during a median follow-up of approximately 6 years. We found a similar graded inverse relationship between all

4 measures of kidney function and kidney failure (**Table 2**). In adjusted Cox models, a 1-SD decrease in each measure of kidney function was associated with risk for kidney failure and the composite outcome greater than 2-fold (**Table 3**).

Additional Analyses

We repeated the adjusted Cox models (model 2 in **Table 3**) by using estimated GFR. The mean estimated GFR was 33 mL/min per 1.73 m^2 (SD, 12). A 1-SD decrease in estimated GFR was associated with an increased risk for all-cause mortality (hazard ratio, 1.23 [CI, 1.05 to 1.45]), CVD mortality (hazard ratio, 1.28 [CI, 1.04 to 1.56]), kidney failure (hazard ratio, 2.60 [CI, 2.30 to 2.92]), and the composite outcome (hazard ratio, 2.35 [CI, 2.11 to 2.62]).

We also repeated the adjusted Cox models by using the mean of 2 baseline iothalamate GFR measurements (average GFR). The mean of the average GFR was 33 mL/min per 1.73 m^2 (SD, 12). A 1-SD decrease in mean GFR was associated with an increased risk for all-cause mortality (hazard ratio, 1.27 [CI, 1.08 to 1.49]), CVD mortality (hazard ratio, 1.30 [CI, 1.06 to 1.61]), kidney failure (hazard ratio, 2.34 [CI, 2.10 to 2.63]), and the composite outcome (hazard ratio, 2.15 [CI, 1.94 to 2.39]). The results were similar to those obtained by using a single GFR measure.

Sensitivity Analyses

The association of cystatin C with all-cause and CVD mortality remained stronger than that of GFR in unadjusted Cox models, with hazard ratios comparing the 80th to the 20th percentiles for each index of kidney function. A change from the 80th to the 20th percentile in 1/creatinine was associated with hazard ratios of 1.28 (CI, 1.00 to 1.65) for all-cause mortality, 1.28 (CI, 0.92 to 1.77) for CVD mortality, and 5.88 (CI, 4.81 to 7.19) for kidney failure. The same change in GFR was associated with hazard ratios of 1.68 (CI, 1.26 to 2.24), 1.68 (CI, 1.16 to 2.43), and 5.92 (CI, 4.78 to 7.30), respectively. For 1/cystatin, the hazard ratios were 1.98 (CI, 1.51 to 2.62) for all-cause mortality, 2.31 (CI, 1.60 to 3.32) for CVD mortality, and 4.74 (CI, 3.92 to 5.75) for kidney failure.

We performed additional analyses to examine whether the truncation of GFR biased the results. The hazard ratios for all-cause mortality (1.26 [CI, 1.10 to 1.46]) and CVD mortality (1.29 [CI, 1.07 to 1.56]) did not change appreciably when the 3-month baseline GFR was substituted with the screening GFR. Results also suggested that higher hazard ratios for all-cause and CVD mortality would have been detected for cystatin C compared with creatinine or GFR even if we had selected the patients on the basis of cystatin C or creatinine entry criteria rather than GFR (data not shown).

DISCUSSION

In the MDRD Study cohort of patients with stage 3 or 4 CKD, cystatin C level and the gold standard of measured GFR were strongly correlated. The association of cystatin C with all-cause and CVD mortality was as strong as and perhaps stronger than the relationship of iothalamate GFR, serum creatinine concentration, and estimated GFR with these outcomes.

Chronic kidney disease is now recognized as a risk factor for CVD, and several studies have shown an independent and graded relationship between the degree of kidney dysfunction and risk for CVD (1, 2, 17–20). Data from the general population suggest that cystatin C level has a stronger association with CVD outcomes than does

Table 2. **Event Rates, by Quartiles of Markers of Kidney Function***

Variable	Event Rate per 100 Person-Years (Patients with Events), *n (n)*			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
All-cause mortality				
1/creatinine	2.74 (55)	2.56 (45)	3.12 (64)	1.93 (39)
Estimated GFR†	2.91 (56)	2.91 (57)	2.95 (57)	1.63 (33)
Measured GFR	3.36 (64)	2.90 (56)	2.52 (50)	1.63 (33)
1/cystatin C	3.72 (70)	2.80 (55)	2.58 (50)	1.36 (28)
CVD mortality				
1/creatinine	1.69 (34)	1.31 (23)	2.05 (42)	1.17 (24)
Estimated GFR†	1.87 (36)	1.58 (31)	1.81 (35)	1.04 (21)
Measured GFR	1.99 (38)	1.60 (31)	1.77 (35)	0.94 (19)
1/cystatin C	2.23 (42)	1.78 (35)	1.60 (31)	0.73 (15)
Kidney failure				
1/creatinine	28.42 (201)	13.32 (145)	8.10 (127)	4.21 (75)
Estimated GFR†	28.63 (193)	13.06 (161)	7.89 (117)	4.38 (77)
Measured GFR	26.35 (191)	13.21 (156)	8.09 (122)	4.55 (79)
1/cystatin C	23.82 (185)	14.70 (167)	7.99 (116)	4.49 (80)

* Quartiles 1 to 4 refer to the first to fourth quartiles of 1/creatinine, estimated GFR, measured GFR, and 1/cystatin C. CVD = cardiovascular disease; GFR = glomerular filtration rate.
† Estimated by using the Modification of Diet in Renal Disease Study (16) equation.

Table 3. **Association between Markers of Kidney Function and Adverse Outcomes***

Outcome	Hazard Ratio (95% CI)†		
	1/Creatinine	GFR‡	1/Cystatin C
All-cause mortality			
Unadjusted	1.15 (1.00–1.32)	1.28 (1.12–1.49)	1.45 (1.25–1.69)
Adjusted§			
Model 1	1.22 (1.04–1.44)	1.26 (1.08–1.48)	1.39 (1.17–1.65)
Model 2	1.27 (1.06–1.49)	1.27 (1.08–1.49)	1.41 (1.18–1.67)
CVD mortality			
Unadjusted	1.15 (0.95–1.37)	1.28 (1.08–1.54)	1.59 (1.28–1.92)
Adjusted§			
Model 1	1.24 (1.00–1.53)	1.27 (1.04–1.56)	1.60 (1.27–2.01)
Model 2	1.32 (1.05–1.64)	1.28 (1.04–1.59)	1.64 (1.28–2.08)
Kidney failure			
Unadjusted	2.68 (2.40–2.99)	2.39 (2.16–2.65)	2.36 (2.12–2.62)
Adjusted§			
Model 1	2.82 (2.49–3.20)	2.43 (2.17–2.73)	2.35 (2.10–2.65)
Model 2	2.81 (2.48–3.19)	2.41 (2.15–2.70)	2.36 (2.10–2.66)
Composite			
Unadjusted	2.43 (2.19–2.69)	2.23 (2.02–2.45)	2.21 (2.01–2.44)
Adjusted§			
Model 1	2.53 (2.27–2.85)	2.23 (2.01–2.48)	2.18 (1.96–2.43)
Model 2	2.50 (2.27–2.86)	2.22 (2.00–2.44)	2.17 (1.96–2.44)

* CVD = cardiovascular disease; GFR = glomerular filtration rate.
† Per 1-SD decrease.
‡ Measured by using iothalamate clearance.
§ Model 1 is adjusted for age, sex, race, smoking, history of diabetes and CVD, body mass index, systolic blood pressure, low-density lipoprotein cholesterol level, high-density lipoprotein cholesterol level, log-transformed proteinuria, and cause of kidney disease for the kidney failure and composite outcomes. Model 2 is adjusted for all covariates in model 1 plus log-transformed C-reactive protein level.

creatinine concentration or estimated GFR, especially in elderly persons (10–12, 21, 22). The cystatin C level also had a stronger risk relationship with mortality than did creatinine concentration and creatinine clearance, as estimated by using the Cockcroft–Gault equation, in patients with non–ST-segment elevation acute coronary syndrome (23) and a stronger risk relationship with recurrent CVD events in patients with established ischemic heart disease (24). In the Cardiovascular Health Study cohort of community-dwelling elderly patients (12), higher cystatin C levels were associated with increased risk for mortality and CVD outcomes. In contrast, the study showed a J-shaped relationship of creatinine concentration with mortality and no independent relationship with CVD outcomes. Lowest estimated GFR levels, computed by using the 4-variable MDRD Study equation (16), were associated with increased risk for death but were not associated with CVD outcomes in multivariable models. In the Cardiovascular Health Study cohort, cystatin C level was predictive of incident peripheral arterial disease (25). In contrast, a nested case–control study in apparently healthy men found no association between elevated cystatin C levels and peripheral arterial disease (26). The cystatin C level was also associated with a higher risk for mortality than was serum creatinine concentration in the Healthy Aging and Body Composition Study cohort of black and white ambulatory elderly persons (11).

These data suggest that cystatin C either is a better index of kidney function in elderly persons and therefore is a better predictor of outcomes than creatinine, or it reflects other pathologic processes that are independent of kidney function. The MDRD Study cohort allowed us to investigate this issue further through direct comparison of cystatin C values and kidney function measured as iothalamate GFR as predictors of outcomes in patients with established CKD. Our results show that cystatin C seems to have as good as or perhaps a stronger risk relationship with all-cause and CVD mortality than does either serum creatinine concentration or measured or estimated GFR. We acknowledge, however, that this data set was used to develop the MDRD Study equation. Because the hazard ratios from the Cox models had relatively wide and overlapping CIs, the results suggest, but do not prove, that cystatin C is associated with a higher risk for mortality than are other indices of kidney function.

Creatinine concentration, a commonly used index of kidney function, is affected by factors other than GFR, such as age, sex, muscle mass, diet, and physical activity, and therefore is insensitive to mild reductions in GFR (27, 28). Data from several studies, but not all (29–31), suggest that cystatin C more closely approximates GFR (32, 33), is more sensitive to changes in GFR, and is less subject to extrarenal factors than creatinine concentration (7, 8, 34–38). These data led to the hypothesis that cystatin C may be a better marker of kidney function in elderly persons and in persons with mild reductions in kidney function.

If cystatin C is in fact a stronger risk factor among patients with advanced CKD, 2 reasons may explain this finding. Cystatin C may be a better measure of kidney function than is actual GFR because of considerable variability in iothalamate clearance due to short-term changes in true GFR and to measurement error (39). As reported elsewhere, the median intratest variability for iothalamate GFR was 9.4% in the MDRD Study and the intertest coefficient of variation for 2 measurements of GFR performed 3 months apart was 6.3% (15). The reported intratest coefficient of variation for the cystatin C assay ranged from 2.1% to 4.8%, and reported intertest coefficients of variation for the cystatin C assay were 2.3% to 3.1% (10) and 3.8% (23). Thus, cystatin C may be measured more precisely than GFR (40). On the other hand, the average of 2 measured GFRs provided risk estimates similar to models that used 1 measure of GFR. This suggests that the strength of the relationship between measured GFR and outcomes was not weakened by the imprecision of GFR measurements, although bias (measurement error) cannot be excluded.

An alternate explanation is that cystatin C provides prognostic information beyond its role as an index of kidney function and is a better overall measure of the spectrum of pathophysiologic abnormalities that accompany kidney disease. This hypothesis is supported by several facts: the differential association of cystatin C level with all-cause mortality and mortality due to CVD, the similar magnitude of associations of serum creatinine concentration and GFR with mortality, and the similar relationship of all 3 measures of kidney function with kidney failure. The slightly higher hazard ratio for serum creatinine for kidney failure may be attributed to the fact that decisions of when to initiate kidney replacement therapy were based on the serum creatinine concentration because neither iothalamate GFR nor cystatin C values were available to clinicians.

Mechanisms for a greater association of cystatin C with mortality than kidney failure could include direct toxicity or a reflection of some other deleterious process that may parallel reductions in kidney function. One such example is inflammation. Some studies have found a relationship between cystatin C and markers of inflammation, specifically CRP (30, 41), although CRP and cystatin C had no association in our current study. In a nested case–control analysis of the Prospective Epidemiology Study of Myocardial Infarction, which followed almost 10 000 men without heart disease at baseline for 5 years, the association between cystatin C and CVD outcomes was abolished by the addition of CRP to the model (42). However, in our study cohort, similar to several other studies (11, 12), the association between cystatin C and outcomes was independent of CRP. Of note, cystatin C level and GFR had a close correlation, suggesting that any direct mechanism would be relatively minor compared with its reflection of underlying kidney function.

Our study has limitations. The generalizability is limited because the MDRD Study cohort consists of nondiabetic, predominantly white patients, with few elderly patients and a low burden of CVD, who are more likely to reach kidney failure than death in follow-up. In addition, because entry criteria for the MDRD Study were based on GFR values, the study design includes an artificial restriction of GFR range, but not cystatin C or creatinine values. We may have underestimated the magnitude of the association between GFR and outcomes owing to the bias introduced by the truncation of the distribution of GFR. However, sensitivity analyses to address this issue did not suggest that our results were dominated by this bias. In addition, the MDRD Study cohort represents a 4-fold variation in GFR. Therefore, we believe that the GFR range is large enough, despite the truncation, to examine the associations studied. We could not assess nonfatal CVD events, which may have different associations with cystatin C than mortality end points. We also lack follow-up measurements of cystatin C. Although our analyses establish an association between cystatin C and outcomes, they do not provide information on the clinical predictive utility of this marker (43). Finally, the hazard ratios from the Cox models had relatively wide and overlapping CIs; therefore, although these results suggest that cystatin C had a stronger association, they are not definitive. The advantages of our study include a cohort of patients with measured GFR, a wide range of cystatin C levels, and many outcomes during follow-up.

In summary, the association of cystatin C seems to be as strong as and perhaps stronger than the association of measured GFR with all-cause and CVD mortality in patients with advanced CKD. Studies are needed to examine whether measurement of this novel marker can be used in risk stratification of these vulnerable patients.

From Tufts-New England Medical Center, Boston, Massachusetts; Veterans Affairs Medical Center, San Francisco, California; The Cleveland Clinic Foundation, Cleveland, Ohio; Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; University of Utah, Salt Lake City, Utah; National Institutes of Health, Bethesda, Maryland; and Hennepin County Medical Center, Minneapolis, Minnesota.

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Requests for Single Reprints: Mark J. Sarnak, MD, MS, Division of Nephrology, Tufts-New England Medical Center, 750 Washington Street, #391, Boston, MA 02111; e-mail, msarnak@tufts-nemc.org.

Current author addresses and author contributions are available at www.annals.org.

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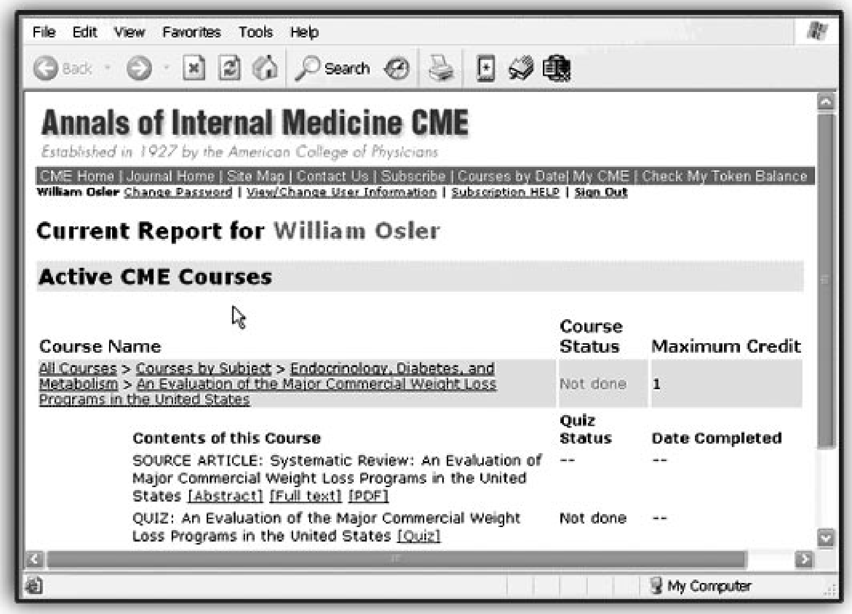

Current Author Addresses: Drs. Menon, Stevens, Levey, and Sarnak: Division of Nephrology, Tufts-New England Medical Center, 750 Washington Street, #391, Boston, MA 02111.
Dr. Shlipak: General Internal Medicine Section, Veterans Affairs Medical Center (111A1), 4150 Clement Street, San Francisco, CA 94121.
Ms. Wang and Dr. Beck: Department of Quantitative Health Sciences, The Cleveland Clinic Foundation, Desk Wb-4, 9500 Euclid Avenue, Cleveland, OH 44195.
Dr. Coresh: Epidemiology, Biostatistics and Medicine, The Johns Hopkins University, 2024 East Monument Street, Suite 2-600, Baltimore, MD 21287.
Dr. Greene: Division of Clinical Epidemiology, 30 North 1900 East, Room AC221, Salt Lake City, UT 84132.
Dr. Kusek: Clinical Trials, Division of Kidney, Urologic, and Hematologic Diseases, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Building 45, Room 6AS-13J, 45 Center Drive, Bethesda, MD 20892-6600.
Dr. Collins: Hennepin Faculty Associates, 914 South 8th Street, Suite S206, Minneapolis, MN 55404.

Author Contributions: Conception and design: V. Menon, M.G. Shlipak, A.J. Collins, M.J. Sarnak.
Analysis and interpretation of the data: V. Menon, M.G. Shlipak, X. Wang, T. Greene, L. Stevens, J.W. Kusek, G.J. Beck, A.S. Levey, M.J. Sarnak.
Drafting of the article: V. Menon, A.J. Collins, A.S. Levey, M.J. Sarnak.
Critical revision of the article for important intellectual content: V. Menon, M.G. Shlipak, J. Coresh, T. Greene, L. Stevens, J.W. Kusek, G.J. Beck, A.S. Levey, M.J. Sarnak.
Final approval of the article: V. Menon, M.G. Shlipak, J. Coresh, T. Greene, L. Stevens, J.W. Kusek, G.J. Beck, A.J. Collins, A.S. Levey, M.J. Sarnak.
Statistical expertise: X. Wang, J. Coresh, T. Greene, G.J. Beck.
Obtaining of funding: J. Coresh, J.W. Kusek, G.J. Beck, M.J. Sarnak.
Administrative, technical, or logistic support: X. Wang, J.W. Kusek.
Collection and assembly of data: G.J. Beck, M.J. Sarnak.

Appendix Table. **Baseline Characteristics, by Quartile of Estimated Glomerular Filtration Rate***

Characteristic	Quartile 1 (*n* = 206)	Quartile 2 (*n* = 207)	Quartile 3 (*n* = 206)	Quartile 4 (*n* = 206)	*P* Value
Mean estimated GFR (SD), *mL/min per 1.73 m²*	17.4 (3.1)	27.6 (2.6)	36.4 (3.0)	49.1 (5.8)	–
Mean age (SD), *y*	50.1 (12.8)	51.6 (13.0)	52.5 (11.6)	52.5 (12.0)	0.16
Male, %	59	59	59	66	0.40
White, %	83	89	84	85	0.35
Current smoker, %	9	12	8	10	0.67
Diabetes, %	4	6	3	7	0.31
History of cardiovascular disease, %	12	14	16	11	0.48
Mean BMI (SD), *kg/m²*	25.8 (4.1)	26.9 (4.7)	28.1 (4.5)	27.6 (4.1)	<0.001
Mean HDL cholesterol level (SD)					0.74
mmol/L	1.02 (0.40)	1.04 (0.35)	1.05 (0.39)	1.02 (0.33)	
mg/dL	39.2 (15.4)	40.3 (13.4)	40.5 (15.1)	39.4 (12.6)	
Mean LDL cholesterol level (SD)					0.70
mmol/L	3.76 (1.02)	3.79 (1.09)	3.87 (1.04)	3.86 (1.15)	
mg/dL	145.3 (39.3)	146.5 (41.9)	149.4 (40.2)	149.0 (44.3)	
Mean systolic blood pressure (SD), *mm Hg*	133.2 (17.3)	131.7 (18.1)	131.81 (16.2)	130.9 (18.7)	0.63
Median CRP level (IQR†), *mg/L*	3.9 (5.7)	5.3 (8.0)	5.4 (6.1)	4.3 (4.6)	0.05
Median proteinuria (IQR†), *g/d*	1.4 (1.7)	1.3 (1.7)	0.8 (1.4)	0.9 (1.7)	<0.001
Mean GFR (SD), *mL/min per 1.73 m²*	18.5 (4.2)	28.0 (5.8)	36.8 (6.9)	46.8 (6.1)	<0.001
Mean creatinine concentration (SD)					<0.001
μmol/L	324.09 (61.88)	212.16 (35.36)	167.96 (26.52)	132.60 (26.52)	
mg/dL	3.7 (0.7)	2.4 (0.4)	1.9 (0.3)	1.5 (0.3)	
Cause of kidney disease, %					0.09
Polycystic kidney disease	29	23	24	20	
Glomerular diseases	34	31	26	36	
Other	37	46	50	44	

* Quartile 1, 9.4–22.6 mL/min per 1.73 m²; quartile 2, 22.7–31.8 mL/min per 1.73 m²; quartile 3, 31.8–41.8 mL/min per 1.73 m²; quartile 4, 41.9–69.5 mL/min per 1.73 m². BMI = body mass index; CRP = C-reactive protein; GFR = glomerular filtration rate; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.
† The IQR presented is the difference between the 25th and 75th percentiles.