Rapid Decline of Kidney Function Increases Cardiovascular Risk in the Elderly

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ABSTRACT

Chronic kidney disease (CKD), defined at a specific time point, is an important risk factor for cardiovascular disease. Whether the rate of kidney function decline contributes additional cardiovascular risk is unknown. In the Cardiovascular Health Study, we compared the associations of changes in kidney function during the first 7 yr with the incidence of heart failure (HF), myocardial infarction (MI), stroke, and peripheral arterial disease (PAD) during the subsequent 8 yr. We defined a rapid decline in cystatin C–based estimated GFR as >3 ml/min per 1.73 m^2/yr, on the basis of determination at baseline, year 3, and year 7. Among eligible participants, 1083 (24%) had rapid kidney decline. The incidence of each type of cardiovascular event was significantly higher among patients with rapid decline (all $P < 0.001$). After multivariate adjustment for demographics, cardiovascular disease risk factors, and baseline kidney function, rapid kidney function decline was significantly associated with HF (adjusted hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.13 to 1.53), MI (HR 1.48; 95% CI 1.21 to 1.83), and PAD (HR 1.67; 95% CI 1.02 to 2.75) but not with stroke (HR 1.19; 95% CI 0.97 to 1.45). The association of rapid decline with each outcome did not differ by the presence or absence of CKD. In conclusion, declining kidney function associates with higher risk for HF, MI, and PAD among patients with or without CKD.

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Chronic kidney disease (CKD) is an important risk factor for the development of heart failure (HF), myocardial infarction (MI), stroke, and peripheral arterial disease (PAD).[1–5] The use of cystatin C in older adults has extended these associations across a broader range of kidney function than could be appreciated with creatinine-based estimated GFR (eGFR). Nonetheless, the mechanisms underlying the association between CKD and cardiovascular risk remain incompletely determined. Current understanding of kidney–cardiovascular disease (CVD) relationships is limited by the measurement of kidney function on a single occasion. This approach fails to discriminate people with declining kidney function from those with diminished but stable kidney function. An association between dynamic changes in kidney function with cardiovascular events independent of both other cardiovascular risk factors and the current level of kidney function would add risk information and strengthen the argument that reduced kidney function has a causal role in CVD.

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In the Cardiovascular Health Study (CHS), a community-based cohort of ambulatory elderly individuals, kidney function was measured at the baseline visit and at years 3 and 7 of follow-up. In a recent article, we evaluated the associations of changes in kidney function using each measure with subsequent mortality risk.[6] Using either cystatin C ($eGFR_{cys}$) or creatinine ($eGFR_{creat}$), annual eGFR declines of >3 ml/min per 1.73 m^2 were independently associated with elevated all-cause and cardiovascular mortality risk; however, no association was observed for milder changes in kidney function.

In this study from CHS, we evaluated the associations of rapid decline in kidney function with the incidence of specific cardiovascular end points: HF, MI, stroke, and PAD. We hypothesized that rapid kidney function decline would have independent associations with higher incidence of each outcome but with the strongest association with HF on the basis of our previous studies using baseline kidney function.[7–9]

RESULTS

Characteristics of Study Population

Among 5888 participants with baseline levels of kidney function, 4380 had repeated measurements of both creatinine and cystatin C. Of the remaining 1508, 204 died before the second measurement of kidney function; the remainder either lacked adequate blood samples or did not present for follow-up clinic visits (Supplemental Table 1). Overall, among the 4378 participants, 1083 (25%) had rapid decline (Table 1) in kidney function on the basis of $eGFR_{cys}$. Patients with rapid decline were slightly older at baseline and more likely to be black. Risk factors more common in patients with rapid decline included diabetes and hypertension but not smoking or lipoprotein levels. Those with rapid decline had somewhat higher baseline $eGFR_{cys}$ and $eGFR_{creat}$ but substantially lower follow-up measures of $eGFR_{cys}$ and $eGFR_{creat}$.

We initially evaluated the association of quintiles of kidney function decline by $eGFR_{cys}$ with each CVD outcome. For the outcomes of HF, MI, and stroke, we observed little difference across the lower four quintiles in either demographic adjusted or fully adjusted analyses, and each hazard ratio (HR) was approximately 1.0 for quintiles 2 through 4. In contrast, for PAD events, intermediate risk was observed for quintiles 2 and 3 and much higher risk for quintiles 4 and 5. Compared with the lowest quintile of decline, the highest quintile was associated with adjusted HRs of 1.33 (95% confidence interval [CI] 1.08 to 1.65) for HF, 1.35 (95% CI 1.01 to 1.81) for MI, 1.16 (95% CI 0.87 to 1.55) for stroke, and 2.93 (95% CI 1.21 to 7.09) for PAD. All results were similar using quintiles of rapid decline by $eGFR_{creat}$ except for PAD events; none of the quintiles of change in $eGFR_{creat}$ was significantly associated with PAD.

We next dichotomized change in kidney function at >3 ml/min per 1.73 m^2 and found the incidences of HF, MI, stroke, and PAD events to be significantly higher among participants with previous rapid kidney function decline (Table 2). After adjustment for demographic characteristics, rapid decline remained associated with a higher risk for each CVD event (Table 2); however, after further adjustment for CVD risk factors, rapid decliners had an approximately 30% higher risk for HF, 40% higher risk for MI, and 60% higher risk for

Table 1. Characteristics at baseline of participants with and without subsequent rapid decline in kidney function based on cystatin C

Characteristic	(−) Rapid Decline by $eGFR_{cys}$ (n = 3295)	(+) Rapid Decline by $eGFR_{cys}$ (n = 1083)	P
Age at baseline (yr; mean ± SD)	72 ± 5	73 ± 5	<0.001
Age at final cystatin C measurement (yr; mean ± SD)	78 ± 5	78 ± 5	0.69
Female gender (n [%])	1965 (60)	644 (60)	0.92
Black race (n [%])	398 (12)	186 (17)	<0.001
Body mass index (kg/m^2; mean ± SD)	27 ± 5	27 ± 5	0.84
Tobacco use, current or former (n [%])	1746 (53)	591 (55)	0.36
Diabetes (n [%])	412 (13)	204 (19)	<0.001
Hypertension (n [%])	1330 (40)	517 (48)	<0.001
SBP (mmHg; mean ± SD)	134 ± 20	141 ± 22	<0.001
DBP (mmHg; mean ± SD)	71 ± 11	72 ± 11	0.01
LDL cholesterol (mg/dl; mean ± SD)	130 ± 35	130 ± 36	0.66
HDL cholesterol (mg/dl; mean ± SD)	54 ± 16	55 ± 16	0.13
Triglycerides (mg/dl; median [interquartile range])	122 (92, 166)	118 (90, 163)	0.96
C-reactive protein (mg/L; median [interquartile range])	2.41 (1.23, 4.27)	2.32 (1.18, 4.46)	0.12
Self-reported health fair/poor (n [%])	562 (18)	232 (24)	<0.001
Baseline $eGFR_{cys}$ (ml/min per 1.73 m^2; mean ± SD)	77 ± 18	85 ± 21	<0.001
Final measure of $eGFR_{cys}$ (ml/min per 1.73 m^2; mean ± SD)	72 ± 18	61 ± 19	<0.001
Baseline $eGFR_{creat}$ (ml/min per 1.73 m^2; mean ± SD)	79 ± 22	82 ± 24	<0.001
Final measure of $eGFR_{creat}$ (ml/min per 1.73 m^2; mean ± SD)	81 ± 22	70 ± 24	<0.001

DBP, diastolic BP; SBP, systolic BP.

Table 2. Association of rapid kidney function decline with CVD events in the elderly

Parameter	No Rapid Decline	Rapid Decline
HF		
rates (events/1000 patient-years)	30	42
demographic adjusted HR	1.00 (reference)	1.40 (1.20 to 1.65)
multivariate adjusted HR	1.00 (reference)	1.24 (1.05 to 1.46)
MI		
rates (events/1000 patient-years)	16	24
demographic adjusted HR	1.00 (reference)	1.53 (1.24 to 1.88)
multivariate adjusted HR	1.00 (reference)	1.42 (1.14 to 1.76)
Stroke		
rates (events/1000 patient-years)	17	22
demographic adjusted HR	1.00 (reference)	1.29 (1.05 to 1.57)
multivariate adjusted HR	1.00 (reference)	1.11 (0.89 to 1.37)
PAD		
rates (events/1000 patient-years)	3	5
demographic adjusted HR	1.00 (reference)	1.86 (1.12 to 3.08)
multivariate adjusted HR	1.00 (reference)	1.67 (1.02 to 2.75)

Data are presented as HR (95% CI).
Demographic adjustment: Adjusted for age, gender, race, and average kidney function. Multivariate adjustment depends on outcomes: HF = SBP, DBP, hypertension medications, and diabetes; MI = SBP, DBP, hypertension medications, HDL, and diabetes; stroke = SBP, DBP hypertension medications, self-reported health, and diabetes; PAD = SBP, DBP, hypertension medications, diabetes, HDL, fibrinogen, and self-reported health.

PAD, although the PAD finding did not reach statistical significance. In models using $eGFR_{creat}$, rapid kidney decline was significantly associated with only incident HF; HRs were 1.45 (95% CI 1.22 to 1.74) for HF, 1.22 (95% CI 0.94 to 1.58) for MI, 1.21 (95% CI 0.95 to 1.53) for stroke, and 1.36 (95% CI 0.76 to 2.46) for PAD.

We next categorized participants by their CKD status at the final kidney measurement and by whether they had previous rapid kidney function decline (Table 3). Overall, participants who had either CKD or rapid decline had higher event rates compared with participants with neither. In multivariate analysis, no interactions were observed between CKD and rapid decline for any of the four outcomes; however, for HF, rapid decline seemed associated with increased risk only among participants with CKD. In contrast, for MI and PAD, rapidly declining kidney function was independently associated with higher risk even among participants without CKD.

DISCUSSION

In this study, we evaluated the independent associations of longitudinal declines in kidney function with four CVD end points. Independent of demographic characteristics and CVD risk factors and of baseline kidney function, rapid declines in kidney function (>3 ml/min per 1.73 m^2/yr) detected by $eGFR_{cys}$ were associated with higher risk for HF, MI, and PAD events but not stroke. Analyses using creatinine found rapid decline to be associated only with risk for HF. To our knowledge, this is the first study to determine the association between longitudinal changes in cystatin C and risk for CVD events. If confirmed in future studies, then the findings suggest

Table 3. Joint associations of rapid kidney function decline and CKD status with cardiovascular events in the elderly

Parameter	Rapid Decline				Interaction *P*
	No CKD		CKD		
	No	Yes	No	Yes	
HF					
rates (events/1000 patient-years)	25	28	52	69	
adjusted HR	1.00 (reference)	1.01 (0.80 to 1.27)	1.58 (1.32 to 1.90)	1.96 (1.57 to 2.44)	0.82
MI					
rates (events/1000 patient-years)	14	19	21	33	
adjusted HR	1.00 (reference)	1.31 (0.99 to 1.75)	1.24 (0.95 to 1.62)	1.74 (1.28 to 2.37)	0.35
Stroke					
rates (events/1000 patient-years)	15	19	24	26	
adjusted HR	1.00 (reference)	1.18 (0.90 to 1.55)	1.32 (1.03 to 1.69)	1.20 (0.87 to 1.64)	0.60
PAD					
rates (events/1000 patient-years)	2.8	4.3	4.3	5.7	
adjusted HR	1.00 (reference)	1.87 (1.00 to 3.50)	1.46 (0.76 to 2.78)	1.81 (0.88 to 3.72)	0.68

Multivariate adjustment: HF = adjusted for age, gender, race, SBP, DBP, and hypertension medications, and diabetes; MI = adjusted for age, gender, race, SBP, DBP, hypertension medications, HDL, and diabetes; stroke = adjusted for age, gender, race, SBP, DBP, hypertension medications, self-reported health, and diabetes; PAD = adjusted for age, gender, race, SBP, DBP, hypertension medications, diabetes, HDL, fibrinogen, and self-reported health.

that both the current level of kidney function and the trajectory are important for assessing cardiovascular risk.

The primary importance of this article is that it provides additional evidence regarding the likelihood that reduced kidney filtration has a causal association with CVD. Although the presence of CKD is generally considered to be a risk factor for CVD, proving a causal association is challenging.[10] The finding that dynamic changes in kidney function are independently associated with CVD risk adds to the likelihood that reduced kidney function is causally related to CVD onset and progression. Potential pathways that could mediate this association include the kidney's effects on BP regulation, sodium handling, retention of toxic solutes, and disrupted mineral metabolism. Regardless of the underlying mechanisms, our findings raise the hypothesis that interventions that slow the decline of kidney function could have salient effects on CVD risk even in patients without overt CKD.

From the clinical perspective, our findings in Table 3 suggest that a provider would gain insight into a patient's cardiovascular risk by considering not only the current kidney function but also the recent trajectory. Although this would be obvious for estimating the risk for progression to kidney failure, to our knowledge, it has never been demonstrated for CVD risk. Because the risk for rapid decline was apparent before the onset of CKD, these results suggest that interventions to stabilize kidney function in the normal range could have substantial health benefits. The association of rapid kidney decline with CVD events was stronger using cystatin C than creatinine as the indicator of kidney function decline. Our previous studies found that cystatin C identified a larger proportion of participants as having rapid decline than did creatinine but that rapid decline by either measure was strongly associated with mortality risk. It is not clear why creatinine changes are more prognostic for mortality than CVD, but we believe cystatin C likely offers a more accurate reflection of longitudinal kidney function.

The primary limitation of this study is that we still cannot determine definitively whether the associations of changes in kidney function are causally related to the incidence of CVD. Although we adjusted for confounding factors, it is possible that another process caused both the declines in kidney function and the increase in CVD events in parallel. An additional limitation is that we used indirect measurements of kidney function that were measured at most three times during 7 yr of follow-up, and we did not have baseline measurements of albuminuria. The infrequency of kidney function measurement allowed many participants to be censored before their repeat measurements. Because these excluded participants had worse kidney function at baseline than included participants, our results may not necessarily generalize to patients with advanced kidney disease; however, we believe that rapid kidney decline would be at least as deleterious in patients with low eGFR, who have less physiologic reserve.

Previously observed evaluations of the association of kidney disease with CVD have overlooked the dynamic aspects of kidney function, which may play an integral role in CVD risk. Using longitudinal measurements of cystatin C, we found rapid declines in kidney function to be independently associated with higher risk for HF, MI, and PAD, even in patients without CKD. If replicated in future studies, then these findings suggest that interventions to stabilize kidney function over time could have the additional benefits of decreasing CVD risk. Future studies should consider not only static measures of kidney function but also ongoing changes in function to appreciate fully the cardiovascular consequences of kidney disease.

CONCISE METHODS

Study Design

The objective of this longitudinal study was to evaluate the association of changes in kidney function during the first 7 yr of CHS follow-up with incident cardiovascular events that occurred after the final measurement of kidney function. The timeline of this study is illustrated in Figure 1. For each of the four cardiovascular outcomes, participants were excluded if they had experienced that outcome at any time before their final measurement of kidney function.

The CHS is a longitudinal study of community-dwelling older adults designed to evaluate risk factors for CVD. The design of this study has been described previously.[11] In brief, participants ≥65 yr of age were recruited from Medicare eligibility lists in four US communities (Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh). An initial 5201 participants were recruited between 1989 and 1990. Blood samples were drawn from these individuals in 1989 to 1990 (baseline), 1992 to 1993 (year 3), and 1996 to 1997 (year 7). 687 black participants were added to the study in 1992 to 1993; these individuals had blood samples drawn in 1992 to 1993 (year 3) and 1996 to 1997 (year 7). In total, 4380 of the 5888 participants in CHS had at least two blood samples from these visits available for measurement of cystatin C and thus met criteria for potential inclusion in analysis of cardiovascular outcomes.

Measurements of Kidney Function

The primary measure of kidney function for analysis was cystatin C. Frozen sera stored at −70°C from the visits at baseline, year 3, and year 7 were available for measurement of cystatin C. Cystatin C was measured using a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Siemens) with a nephelometer (BNII; Siemens). Previous work showed this assay to be stable through several freeze–thaw cycles.[12] For cystatin C, intra-assay coefficients of variation (CVs) range from 2.0 to 2.8% and interassay CVs range from 2.3 to 3.1%. The 1992 to 1993 blood samples for cystatin C were assayed first, in 2003. Subsequently, the 1989 to 1990 and 1996 to 1997 levels were assayed in 2006.

As a confirmatory measure, kidney function was also analyzed using creatinine. Creatinine was measured immediately after each group of samples were drawn, using a colorimetric method (Ektachem 700; Eastman Kodak). The mean CV for monthly controls was 1.94 (range 1.16 to 3.60%).

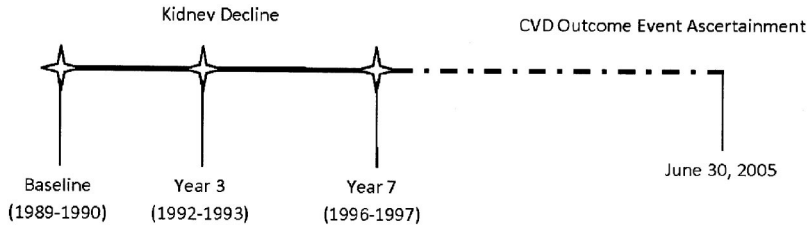

Figure 1. Time course of this study.

Predictor Variables: Change in eGFR Using Cystatin C and Creatinine

For measurement of ($eGFR_{cys}$), we used the CKD epidemiology equation, which was derived from a pooling of cohorts that used iothalamate clearance as the criterion standard ($eGFR_{cys} = 76.7 * cysC^{-1.19}$).[13] This cystatin C equation is based on the largest cohort of individuals from multiple data sources that all used nephelometric methods for cystatin C. We indirectly calibrated the measured serum creatinine in the CHS cohort to the Cleveland Clinic Laboratory using Third National Health and Nutrition Examination Survey (NHANES III) data, as described previously[14,15]

As a secondary measure of kidney function, we estimated GFR using indirectly calibrated serum creatinine ($eGFR_{creat}$), and the four-variable Modification of Diet in Renal Disease (MDRD) equation: $eGFR_{creat} = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212$ (if black) $\times$ 0.742 (if female).[16]

Rates of annual change in eGFR for each marker were calculated using the two or three available measurements. We defined a "rapid decline" in kidney function by an annual loss >3 ml/min per 1.73 m^2.[17] This magnitude of change is three times the expected rate previously described in aging studies, which represents the highest quartile of kidney function loss in CHS.[18] Although we had observed a threshold effect in our previous study,[6] in this study we also evaluated quintiles of eGFR decline to determine whether smaller changes were associated with each CVD end point.

Outcome: Cardiovascular Events

CVD events were ascertained by annual examinations and interim 6-mo telephone interviews through June 30, 2005, with a median follow-up time of 9.9 yr (maximum 11.1 yr). The methods of ascertaining and adjudicating events have been described previously.[19] Briefly, the definitions of each end point are described next.

For the diagnosis of incident HF, a physician's diagnosis was followed by a review of the participant's medical records; the CHS Cardiovascular Events Committee based the diagnosis on physician report, as well as consideration of symptoms, signs, chest x-ray findings, and treatment of HF.[2,19] MI was defined from hospital records by the clinical history of cardiac symptoms, cardiac enzymes, and serial electrocardiogram changes. Stroke cases were adjudicated by a committee of neurologists, neuroradiologists, and internists on the basis of patient interviews, medical records, and brain imaging studies.[20] Incident PAD events were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure codes for lower extremity bypass surgery, major lower extremity amputation, and peripheral angioplasty.

Covariates

We chose a broad range of candidate covariates as potential confounding factors on the basis of their biologic plausibility or on previous studies linking them to CVD. The following covariates were examined: Baseline cystatin C and creatinine; demographic variables (age, gender, and race); cardiovascular risk factors, hypertension defined by history and use of antihypertensive agents, or an average of three BP measurements >140/90 mmHg; diabetes defined by use of insulin or an oral hypoglycemic agent or a fasting blood sugar >126 mg/dl; total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides; and novel cardiovascular risk factors (C-reactive protein, fibrinogen, and hemoglobin). For the multivariate models, BP was included both using a categorical variable and as the systolic and diastolic BP reading.

Statistical Analysis

Rate of change in kidney function using cystatin C was categorized by quintiles and also as a dichotomous variable, with the cut point at 3 ml/min per 1.73 m^2. Unadjusted incidence rates for each cardiovascular outcome were calculated per 1000 person-years by kidney function category. Characteristics of participants were compared with and without rapid decline in kidney function.

Patients were followed from the completion of kidney function measurements until the first cardiovascular outcome of interest or until they were censored because of death, loss to follow-up, or the end of outcome ascertainment for this study in June 2005. Cox proportional hazards models were used to estimate the association of kidney function decline with each cardiovascular outcome. To address the possibility of regression to the mean, we considered several different statistical adjustments for baseline kidney function: Adjustment for baseline kidney function, final kidney function, and average kidney function.[21,22] Our results were robust regardless of the method used. We present results adjusted for the average kidney function over the two or three measured values.

The initial multivariate analysis, model 1, included adjustment for kidney function, age, gender, and race. The final model, model 2, included model 1 covariates and added selected covariates from the candidates listed above in the covariate section. Variables were retained in the final model when their inclusion altered the coefficient for the primary predictor variable (rapid decline in kidney function) by at least 5%. Interactions between baseline and change in kidney function were evaluated for each outcome. Analyses were performed using S-Plus 8.0 (Insightful, Inc., Seattle, WA) and SPSS 15.0.1.1 (SPSS, Inc., Chicago, IL).

We also conducted analyses that categorized participants at their final kidney measurement by the presence or absence of CKD ($eGFR_{cys}$ <60) and by whether they had rapid decline in kidney function. This analysis reflects the clinician's perspective by asking whether a participant's recent trajectory of kidney function decline is a risk factor independent of the current eGFR. Both demographic-adjusted and full multivariate analyses were conducted, and interactions were tested between rapid decline and CKD status.

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DISCLOSURES

None.

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See related editorial, "It's about Time: Extending our Understanding of Cardiovascular Risk from Chronic Kidney Disease," on pages 2486–2487.

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