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Change in Novel Filtration Markers and Risk of ESRD

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Abstract

Background—Chronic kidney disease (CKD) progression is a risk factor for end-stage renal disease (ESRD). A 57% decline in creatinine-based estimated glomerular filtration rate (eGFR_{cr}) is an established surrogate outcome for ESRD in clinical trials, and 30% decrease has recently been proposed as a surrogate endpoint. However, it is unclear if change in novel filtration markers provides additional information for ESRD risk to change in eGFR_{cr}.

Study Design—Cohort study.

Setting & Participants—Atherosclerosis Risk in Communities (ARIC) Study participants from four US communities

Predictors—Percent change in filtration markers (eGFR_{cr}, cystatin C–based eGFR (eGFR_{cys}), the inverse of β_2 -microglobulin concentration [1/B2M]) over a 6-year period.

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Supplementary Material

Table S1: Demographic characteristics and risk factors assessed at baseline, by percent change in eGFR_{cys}.

Table S2: Demographic characteristics and risk factors assessed at baseline, by percent change in 1/B2M.

Table S3: HRs for ESRD, by percent change in filtration markers, adjusted for covariates and first measurement of respective filtration marker.

Table S4: HRs for ESRD, by percent change in filtration markers, adjusted for covariates, first eGFR measurement, and albuminuria.

Table S5: Adjusted HRs for ESRD, by mean percent change in combinations of 2 filtration markers.

Table S6: HRs for kidney failure, by percent change in filtration markers.

Note: The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

Outcome—Incident ESRD.

Measurements—Cox proportional hazards regression with adjustment for demographics, kidney disease risk factors, and first measurement of $eGFR_{cr}$.

Results—During a median follow-up of 13 years, there were 142 incident ESRD cases. In adjusted analysis, declines of >30% in $eGFR_{cr}$, $eGFR_{cys}$, and $1/B2M$ were significantly associated with ESRD compared to stable concentrations of filtration markers (HRs of 19.96 [95% CI, 11.73-33.96], 16.67 [95% CI, 10.27-27.06], and 22.53 [95% CI, 13.20-38.43], respectively). Using the average of declines in the three markers, >30% decline conferred higher ESRD risk than that for $eGFR_{cr}$ alone (HR, 31.97 [95% CI, 19.40-52.70; $p=0.03$] vs. $eGFR_{cr}$).

Limitations—Measurement error could influence estimation of change in filtration markers.

Conclusions—A >30% decline in kidney function assessed using novel filtration markers is strongly associated with ESRD, suggesting the potential utility of measuring change in cystatin C and B2M in settings where improved outcome ascertainment is needed, such as clinical trials.

Keywords

β_2 -microglobulin (B2M); creatinine; cystatin C; filtration marker; chronic kidney disease (CKD); disease progression; end-stage renal disease (ESRD); kidney disease outcome; surrogate endpoint

A doubling of serum creatinine, equivalent to a 57% decline in creatinine-based estimated glomerular filtration rate ($eGFR_{cr}$), is an established surrogate endpoint for end-stage renal disease (ESRD) in clinical trials.^{1,2} However, a decline of this magnitude may take decades to develop.^{3,4} Thus, the US Food and Drug Administration and National Kidney Foundation sponsored a large effort to evaluate the prognostic value of smaller changes in $eGFR_{cr}$. The investigators concluded that a 57% decline was strongly associated with ESRD but rare, whereas a 30% decline in $eGFR_{cr}$ was an order of magnitude more common but perhaps sufficiently robust as a surrogate of future ESRD risk.^{5,6}

$eGFR_{cr}$ is an imperfect measure of kidney function, owing to variability in creatinine due to its non-GFR determinants, such as muscle mass and dietary protein intake.⁷ Novel markers of kidney filtration, individually or combined with serum creatinine, have been shown to improve estimation of directly measured GFR.^{8,9} Two such proteins, cystatin C (13.3 kDa) and β_2 -microglobulin (B2M; 11.8 kDa), are freely filtered by the glomerulus, absorbed, and fully degraded by the proximal tubules.^{10,11} Cystatin C and B2M may be influenced by different non-GFR determinants such as age, sex, race/ethnicity, body mass index, inflammation, smoking, blood pressure, and cholesterol.¹⁰⁻¹⁸ As individual markers, cystatin C-based $eGFR$ ($eGFR_{cys}$) and $1/B2M$ are strongly associated with kidney disease outcomes, similar to or perhaps even more so than $eGFR_{cr}$.^{16,19-22} Furthermore, the use of multiple markers in combination may improve ESRD risk estimation, beyond $eGFR_{cr}$ alone.^{22,23} However, the usefulness of change in these novel kidney filtration markers as surrogates for chronic kidney disease (CKD) progression is not known.

Our objective was to determine whether percent change in novel kidney filtration markers ($eGFR_{cys}$ and $1/B2M$) over a six-year period were independently associated with increased risk of ESRD during 15 years of follow-up within a community-based population.

METHODS

Study Design

The Atherosclerosis Risk in Communities (ARIC) study is a community-based, prospective cohort study of 15,792 healthy, middle-aged, predominantly black and white men and women initially recruited in 1987-1989 from four US communities: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and suburbs of Minneapolis, Minnesota. In the overall ARIC Study population at the time of enrollment, participants were 45-64 years of age, 55.2% were women, and 27.0% were African-American. More details about the ARIC study design are provided elsewhere.²⁴

Study Population

Our study population consisted of ARIC Study participants with measured values for creatinine, cystatin C, and B2M at two time points: ARIC study visits 2 (1990-1992) and 4 (1996-1998). Participants with ESRD at or before visit 4 were excluded from the analysis (n=13). After exclusions, the analytic sample size in the present study was 9,703 (Figure 1). Participants provided written documentation of informed consent at each study visit, and procedures were approved by the institutional review board at each study center.

Data Collection

During each study visit, trained staff administered questionnaires to participants to collect information on demographics (age, race, sex) and kidney disease risk factors (medical history, medication use, cigarette smoking status). Body mass index was calculated as weight (kg)/height (m)² using measurements taken while participants wore light clothing without shoes. Two seated measurements of blood pressure were taken by a certified technician using a random-zero sphygmomanometer after five minutes of rest, and the mean of the measurements was used for analysis. Study participants provided 12-hour fasting blood samples and spot urine samples at both measurement times. Blood samples were centrifuged within 30 minutes of collection at 3,000×g for 10 minutes at 4°C and stored at -70°C for future laboratory analysis. High-density cholesterol was measured enzymatically after precipitation with dextran sulfate-magnesium.²⁵ Total cholesterol was determined automatically after oxidation by cholesterol oxidase and measured colorimetrically.²⁶

Kidney Filtration Markers

Creatinine was measured at study visit 2 in serum specimens and at study visit 4 in plasma specimens according to the original study protocol by the modified kinetic Jaffe method. In 2012-2013, cystatin C was measured using the Gentian immunoassay (Gentian, Moss, Norway) and B2M was measured using Roche β_2 -microglobulin reagent on the Roche Modular P800 Chemistry analyzer in stored serum samples collected at study visit 2. In 2010, cystatin C and B2M were measured using a particle-enhanced immunonephelometric assay with a BNII nephelometer (Siemens Healthcare Diagnostics) using stored plasma samples collected at study visit 4. Creatinine, cystatin C, and B2M values were standardized and calibrated to account for differences in methods across laboratories.²⁷ eGFR_{cr} and eGFR_{cys} were calculated using the 2009 CKD-EPI (CKD Epidemiology Collaboration)

creatinine equation and 2012 CKD-EPI cystatin C equation, respectively.^{8,28} For ease of comparison to GFR estimates, we calculated the inverse of the values for B2M. The primary exposure of interest was percent change in circulating concentrations of filtration markers between the first measurement (study visit 2, 1990-1992) and the last measurement (study visit 4, 1996-1998) as a proportion of the first measurement. The three marker composite was calculated as: (percent change in $eGFR_{cr}$ + percent change in $eGFR_{cys}$ + percent change in $1/B2M$)/3.

Definition of ESRD

Incident ESRD was defined as entry into the US Renal Data System (USRDS) registry between study visit 4 (1996-1998) through the end of follow-up (December 31, 2010). The USRDS registry consists of individuals receiving kidney dialysis or kidney transplant based upon the Centers for Medicare and Medicaid Services Medical Evidence Form-2728 as reported within 45 days of initiation of renal replacement therapy. As a sensitivity analysis, we used an alternative outcome—incident kidney failure—encompassing treated and untreated kidney failure and death due to kidney failure, which has been previously described and validated (C.M.R., manuscript under consideration).

Statistical Analysis

Descriptive statistics (mean $\pm$ standard deviation, median with interquartile range, and proportion) were used to assess baseline participant characteristics, concentrations of and percent change in filtration markers, and ESRD according to categories of percent change in $eGFR_{cr}$, $eGFR_{cys}$, and $1/B2M$ (greater than 30% decline [$< -30\%$]; 10%-30% decline [-30% to -10%]; less than 10% decline to less than 10% increase [$> -10\%$ to $< 10\%$; denoted as -9.9% to 9.9% for convenience], and 10% or greater increase [$\geq 10\%$]). Pearson's correlation was used to assess the relationship between percent change in the filtration markers ($eGFR_{cr}$, $eGFR_{cys}$, $1/B2M$).

To assess the independent effect of percent change in kidney filtration markers on risk of incident ESRD, Cox proportional hazards regression was used with adjustment for demographics (age, sex, race) and kidney disease risk factors (body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes status, total and high-density lipoprotein cholesterol, history of coronary heart disease, and current cigarette smoking status). In separate models, we additionally adjusted for first measurement of $eGFR_{cr}$.

In addition to categories of percent change, percent change in filtration markers was modelled continuously using linear spline terms with one knot at 0%. Hazard ratios (HRs) for ESRD risk were estimated per 30% decline in the filtration marker (i.e. negative percent change). Seemingly unrelated regression was used to test for difference in the coefficient for continuous decline in an individual filtration marker ($eGFR_{cys}$, $1/B2M$) or three marker composite and ESRD risk compared to the coefficient for continuous decline in $eGFR_{cr}$ and ESRD risk.

As a sensitivity analysis, we adjusted for first measurement of the respective filtration marker (i.e. first measurement of $eGFR_{cys}$, first measurement of $1/B2M$) instead of first measurement of $eGFR_{cr}$. For the three marker composite, we adjusted for first measurement

eGFR_{cr}, eGFR_{cys}, and 1/B2M. Albuminuria was not measured at the same time point as the other covariates (study visit 2, 1990-1992). We therefore adjusted for albuminuria at the second time point (study visit 4, 1996-1998) in a sensitivity analysis. In addition to the three-marker composite, other combinations of filtration markers were explored in sensitivity analyses, including the average of percent change in two markers (eGFR_{cr} and eGFR_{cys}; eGFR_{cr} and 1/B2M; eGFR_{cys} and 1/B2M) and a risk score determined by the number of filtration markers that declined greater than 30% (range, 0-3). Competing risk regression was used to account for the competing risk of death.³⁰ Analyses were conducted using Stata version 12 (StataCorp LP, College Station, TX, USA).

RESULTS

Among 9,703 study participants, 142 (1.5%) reached ESRD during a median follow-up of 13.1 years. During the six years between study visits, over half of the study population had “stable” eGFR_{cr} (defined as a change from baseline between -9.9% and +9.9%) and 7% of participants had greater than 30% decline in eGFR_{cr} (Table 1). Compared to participants with stable eGFR_{cr}, those with greater than 30% decline in eGFR_{cr} were more likely to be older, black, and have a higher body mass index. In addition, those with greater than 30% decline in eGFR_{cr} were more likely to have higher systolic blood pressure and to have diabetes, and to be taking anti-hypertensive medication. Median initial eGFR_{cr} values were 95.8, 96.7, 99.0, and 78.6 mL/min/1.73 m² among those with greater than 30% decline, 10%-30% decline, with stable eGFR_{cr}, and 10% or greater increase, respectively (Table 2). Baseline demographic characteristics and risk factors demonstrated similar patterns by categories of percent change in eGFR based on cystatin C (eGFR_{cys}) and 1/B2M (Tables S1 and S2, available as online supplementary material).

Percent change in eGFR_{cr} was moderately, positively correlated with percent change in eGFR_{cys} ($r = 0.35$) and percent change in 1/B2M ($r = 0.36$). Percent change in eGFR_{cys} was strongly, positively correlated with 1/B2M ($r = 0.56$).

Compared to eGFR_{cr}, there were fewer individuals with greater than 30% decline in other filtration markers (eGFR_{cys}, 1/B2M) and the average of change in all three filtration markers (three-marker composite; Table 2). However, the incidence of ESRD in the greater than 30% decline category was similar for eGFR_{cys} and 1/B2M, and higher for the composite of all three markers compared to eGFR_{cr}.

For the individual filtration markers, participants with greater than 30% decline in the filtration marker had 17- to 23-times higher risk of ESRD than those with a stable concentration of the filtration marker (-9.9% to 9.9% change from baseline) after adjustment for demographic characteristics, established risk factors for kidney disease, as well as first measurement of eGFR_{cr} (Table 3). Participants with 10%-30% decline in an individual filtration marker had statistically significant two- to four-times higher risk of ESRD than those with a stable concentration of the filtration marker. Decline in eGFR_{cr} was more strongly associated with risk of ESRD than decline in eGFR_{cys} ($p < 0.001$) and not significantly different than 1/B2M ($p = 0.9$). The association between 10% or greater increase in individual filtration markers and ESRD risk was not statistically significant.

For the three-marker composite, calculated as the mean of change in $eGFR_{cr}$, $eGFR_{cys}$, and $1/B2M$, those with greater than 30% decline had a 32-fold increased risk of ESRD than those with a stable concentration of the mean of three filtration markers after adjusting for covariates and first measurement of $eGFR_{cr}$ (HR, 31.97; 95% CI, 19.40-52.70; Table 3). Estimates of ESRD risk among participants with 10%-30% decline in the three-marker composite were similar in magnitude to estimates for individual filtration markers. Percent change in the three-marker composite was more strongly associated with ESRD risk than $eGFR_{cr}$ decline in models accounting for covariates and first measurement of $eGFR_{cr}$ ($p=0.03$).

Patterns were similar when percent change in filtration markers was modelled continuously (Table 3). Results were not substantially different after adjustment for first measurement of $eGFR_{cr}$ (Table 3) or adjustment for first measurement of the respective filtration marker (Table S3). After adjusting for albuminuria at a different time point, the results were attenuated but similar to the main results (Table S4).

ESRD risk estimates associated with decline in the two-marker combination of $eGFR_{cr}$ and $eGFR_{cys}$ (HR for greater than 30% decline, 20.12; 95% CI, 12.60-32.13) and the two-marker combination $eGFR_{cys}$ and $1/B2M$ (HR for greater than 30% decline, 26.85; 95% CI, 15.67-46.04) were not significantly different than that for decline in $eGFR_{cr}$ (Table S5). Compared to the individual filtration markers, ESRD risk estimates were stronger for decline in the two-marker combination of $eGFR_{cr}$ and $1/B2M$ (HR for greater than 30% decline, 37.82; 95% CI, 22.13-64.61; p for all comparisons to individual filtration markers <0.001).

A risk score determined by the number of filtration markers that declined greater than 30% (range, 0-3) was strongly, monotonically associated with ESRD risk. Compared to having no markers that declined greater than 30%, the risk of ESRD for one, two, and all three markers that declined greater than 30% was 3.67 (95% CI, 2.26-5.96), 12.83 (95% CI, 7.58-21.72), and 36.23 (95% CI, 23.20-56.59), respectively, after adjusting for demographics, kidney disease risk factors, and first measurement of $eGFR_{cr}$.

The estimates of association between percent change in filtration markers and kidney failure were weaker but demonstrated similar patterns as the results for ESRD (Table S6).

Competing risk analyses were conducted to account for the competing risk of death before ESRD, and the results were slightly attenuated but consistent with the main findings.

DISCUSSION

In this community-based population, progression of CKD assessed using greater than 30% percent change in novel filtration markers ($eGFR_{cys}$ and $1/B2M$) over a six-year period was a strong, independent risk factor for ESRD during 15 years of follow-up, similar in magnitude to decline in $eGFR_{cr}$. Compared to $eGFR_{cr}$ decline, risk of ESRD was substantially higher when percent change in $eGFR_{cr}$, $eGFR_{cys}$, and $1/B2M$ were combined together. Substantial (greater than 30%) decline in novel filtration markers may be less common, but appears to be more specific for ESRD than equivalent changes in $eGFR_{cr}$.

To the best of our knowledge, this study is the first to examine change in novel filtration markers as a surrogate for ESRD risk. Two previous studies have investigated the relationship between change in $eGFR_{cr}$ and ESRD.^{31,32} In the Alberta Kidney Disease Network study of 598,397 adults with a median follow-up of 3.5 years, study participants with a “certain drop” in kidney function, defined as 25% or greater decline in $eGFR_{cr}$ over a one-year period, had a 5-fold increased risk of ESRD after adjusting for first measurement of $eGFR_{cr}$, age, sex, diabetes, hypertension, socioeconomic status, kidney function, proteinuria, and history of comorbidities (HR, 5.11; 95% CI, 4.56-5.71).³¹ Participants with an “uncertain drop” in kidney function, corresponding to less than 25% change in $eGFR_{cr}$, had 2.13-fold (95% CI, 1.84-2.47) increased risk of ESRD compared to those with stable kidney function. The Chronic Kidney Disease Prognosis Consortium conducted a large meta-analysis of 1.5 million participants with 12,344 ESRD events during a mean follow-up of 3.1 years within 22 cohorts. In a continuous analysis with 0% change as the reference, 30% decline in $eGFR_{cr}$ was associated with 6.7-fold (95% CI, 3.9-11.5) increased risk of ESRD among those with baseline $eGFR \geq 60$ mL/min/1.73 m² after adjusting for first measurement of $eGFR$ and potential confounders.³²

The ESRD risk estimates associated with change in $eGFR_{cr}$ in the present study were considerably stronger than those previously reported. The use of a higher cut-point for CKD progression (greater than 30% $eGFR_{cr}$ decline in the present study versus 25% or greater $eGFR_{cr}$ decline in the Alberta Kidney Disease Network study) may explain the higher estimates of ESRD risk in the present study. However, the same threshold for CKD progression was used in the Chronic Kidney Disease Prognosis Consortium as in the present study, but ESRD risk estimates in the consortium were also lower than in the present study, and similar in magnitude to the Alberta study. The longer time period between measurements of creatinine (six years in the present study versus one year in the Alberta study and one to three years in the consortium) and longer follow-up time (15 years in the present study versus 3.5 years in the Alberta study and 3.1 years in the consortium) may allow for more reliable estimates of kidney disease progression and ESRD risk. Lastly, the Canadian registry consisted of clinic-based patients with two measurements of serum creatinine in a one-year period, which is a more selective and perhaps a higher risk population than the present community-based study population.

Among those with 10% or greater increase in $eGFR_{cr}$ in the present analysis, the median of the initial $eGFR_{cr}$ measurements was lower than that for other categories of $eGFR_{cr}$ change. Regression towards the mean may explain this increase in the lowest initial $eGFR_{cr}$ measurements towards the average population value at the subsequent measurement.³³ Another possibility is that the rise in $eGFR_{cr}$ may be due to the return of kidney function following an episode of acute kidney injury. However, we expect that the occurrence of acute kidney injury would have minimal influence on this analysis due to the assessment of creatinine at planned study visits in this community-based population, rather than a nephrology clinic-based study. A 10% or greater increase in $eGFR_{cr}$ was not significantly associated with ESRD risk in the present study, which is consistent with results from analyses adjusting for covariates and first measurement of $eGFR_{cr}$ in previous studies.^{31,32}

An important limitation of this study is the potential for selection bias due to non-random loss to follow-up. Defining ESRD case status based on the USRDS registry, instead of a study visit-based definition, reduced the likelihood of this selection bias influencing these results. Participants with missing data for first or last measurement of filtration markers, precluding the calculation of percent change, were excluded from the analysis. Participants with kidney disease may be less likely to attend study visits than healthier participants. As such, exclusion due to missing study visit data may result in an underestimation of the strength of the association between change in filtration markers and risk of ESRD, and reduced the precision of the risk estimate. Another limitation is the lack of baseline measurement of urine albumin-creatinine ratio, which is a strong risk factor for ESRD.³⁴ However, in a sensitivity analysis adjusting for albuminuria at the second time point, the associations between percent change in filtration markers and ESRD risk were attenuated but similar to the overall results. Values of filtration markers may be subject to measurement error due to differences in laboratory methods at the two time points. However, an extensive calibration study among 200 ARIC participants was conducted to quantify and correct for this source of error across all study visits over 25 years of follow-up.²⁷ Random error or bias in the assays, if still present after calibration, would be expected to underestimate the association between change in filtration markers and ESRD risk. Although measured GFR was not available, CKD-EPI eGFR is well-established as an approximation of measured GFR particularly in populations with higher levels of kidney function, such as in the ARIC Study.²⁸ It is possible that some participants were misclassified, (eg, those with lower creatinine generation due to sarcopenia but with actual decline in true GFR). In this scenario, those with declining kidney function would instead be classified as having stable eGFR_{Cr} (the reference group) and this would result in an underestimate of the true risk of ESRD. Our finding of the strong association between multiple markers and ESRD should be replicated in other cohorts, particularly CKD populations and those with higher proportions of moderately and severely increased albuminuria.

Strengths of this study include the use of a large, well-characterized, prospective cohort. Furthermore, long-term follow-up was available for the ascertainment of incident ESRD through linkage with the USRDS registry. In addition, we measured and adjusted for many important kidney disease risk factors, including first measurement of eGFR_{cr} as well as the other filtration markers. The ARIC Study is representative of community-dwelling, middle- and older-aged adults (aged 53-75 years at the beginning of the risk period) with a wide range of kidney function.

In conclusion, CKD progression assessed using mean change in multiple filtration markers is a strong risk factor for ESRD risk, similar to or greater than that for any one filtration marker. Measuring mean change in novel filtration markers (eGFR_{cys} and 1/B2M) in addition to creatinine may provide a stronger surrogate for ESRD than change in eGFR_{cr} alone in epidemiologic research, clinical trials, and clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow Chart of Study Participant Selection

Table 1

Demographic Characteristics and Risk Factors Assessed at Baseline

	Category of Percent Change in eGFR _{cr} Over 6 Years				
	< -30%	-30% to -10%	-9.9% to 9.9%	10%	
No. of participants	657 (6.8%)	3,588 (37.0%)	5,004 (51.6%)	454 (4.7%)	
Age (y)	58.3 ±5.7 ^b	56.8 ±5.7	56.5 ±5.6	56.3 ±5.5	
Female sex	404 (61.5%)	2,004 (55.9%)	2,893 (57.8%)	274 (60.4%)	
Black race	226 (34.4%) ^b	881 (24.6%) ^b	856 (17.1%)	104 (22.9%) ^b	
Body mass index (kg/m ²)	28.9 ±5.7 ^b	27.6 ±5.1	27.8 ±5.3	28.7 ±5.6 ^b	
Systolic blood pressure (mm Hg)	127.9 ±21.8 ^b	120.6 ±18.3 ^b	119.1 ±16.8	120.0 ±17.9	
Anti-hypertensive medication use	303 (46.1 %) ^b	1,103 (30.7%) ^b	1,336 (26.7%)	188 (41.4%) ^b	
Diabetes mellitus	169 (25.8%) ^b	428 (11.9%)	568 (11.4%)	68 (15.0%)	
Total cholesterol (mg/dL)	213.1 ±41.7	207.8 ±37.6	209.0 ±37.5	212.6 ±47.3	
HDL cholesterol (mg/dL)	48.5 ±16.6 ^b	50.2 ±16.6	50.6 ±17.0	48.9 ±15.4	
History of coronary heart disease	69 (10.6%) ^b	212 (6.0%)	249 (5.1%)	27 (6.1%)	
Current smoker	127 (19.4%)	677 (18.9%)	961 (19.2%)	76 (16.7%)	
ACR category ^c					
<30 mg/g	493 (76.1%)	3,285 (92.5%)	4,642 (93.4%)	410 (91.3%)	
30-300 mg/g	94 (14.5%)	219 (6.2%)	285 (5.7%)	30 (6.7%)	
>300 mg/g	61 (9.4%)	49 (1.4%)	41 (0.8%)	9 (2.0%)	

Note: N=9,703. Baseline is study visit 2 (1990-1992). Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation. Conversion factor for cholesterol in mg/dL to mmol/L, ×0.02586.

ACR, albumin-creatinine ratio; eGFR_{cr}, creatinine-based estimated glomerular filtration rate; HDL, high-density lipoprotein;

^b p<0.05 for comparison to reference group (-9.9% to +9.9% change in eGFR_{cr} category)

^c Urine ACR was measured at study visit 4 (1996-1998) only

Table 2

ESRD, Concentrations of Filtration Markers, and Percent Change in Filtration Markers

	Category of Percent Change in Filtration Marker Over 6 Years			
	< -30%	-30% to -10%	-9.9% to 9.9%	10%
eGFR _{cr}				
No. of participants	657 (6.8%)	3,588 (37.0%)	5,004 (51.6%)	454 (4.7%)
Incident ESRD	76 (11.6%) ^a	44 (1.2%) ^a	19 (0.4%)	3 (0.7%)
Incidence rate (95% CI) ^b	10.80 (8.63-13.52) ^a	0.99 (0.74-1.33) ^a	0.31 (0.20-0.48)	0.53 (0.17-1.65)
First value ^c	95.8 (86.5, 104.6) ^a	96.7 (88.4, 106.5) ^a	99.0 (92.6, 105.3)	78.6 (70.4, 83.4) ^a
Last value ^c	60.1 (50.6, 67.0) ^a	78.6 (71.8, 88.7) ^a	94.2 (88.6, 100.3)	91.0 (85.1, 99.1) ^a
Percent change ^c	-35.3 (-42.2, -32.6) ^a	-15.5 (-22.4, -13.8) ^a	-3.1 (-8.5, -1.5)	15.8 (11.7, 23.3) ^a
eGFR _{cys}				
No. of participants	555 (5.7%)	3,562 (36.7%)	4,946 (51.0%)	640 (6.6%)
Incident ESRD	53 (9.6%) ^a	54 (1.5%) ^a	26 (0.5%)	9 (1.4%)
Incidence rate (95% CI) ^b	9.49 (7.25-12.43) ^a	1.23 (0.94-1.60) ^a	0.42 (0.29-0.62)	1.18 (0.61-2.27)
First value ^c	89.5 (75.1, 101.9) ^a	97.5 (85.3, 106.0) ^a	95.5 (80.7, 105.8)	72.5 (63.1, 81.6) ^a
Last value ^c	50.0 (28.6, 63.1) ^a	79.8 (70.7, 88.8) ^a	93.0 (79.3, 101.3)	86.7 (76.0, 95.9) ^a
Percent change ^c	-39.5 (-58.1, -33.3) ^a	-15.7 (-20.4, -12.6) ^a	-3.7 (-6.8, 0.6)	16.1 (12.9, 22.9) ^a
1/B2M				
No. of participants	500 (5.2%)	3,332 (34.3%)	4,878 (50.3%)	993 (10.2%)
Incident ESRD	58 (11.6%) ^a	55 (1.7%) ^a	20 (0.4%)	9 (0.9%)
Incidence rate (95% CI) ^b	11.64 (9.00-15.06) ^a	1.36 (1.04-1.77) ^a	0.33 (0.21-0.51)	0.72 (0.37-1.38)
First value ^c	0.52 (0.44, 0.61) ^a	0.57 (0.50, 0.64) ^a	0.55 (0.49, 0.62)	0.50 (0.43, 0.57) ^a
Last value ^c	0.32 (0.25, 0.39) ^a	0.47 (0.41, 0.53) ^a	0.53 (0.48, 0.61)	0.59 (0.52, 0.67) ^a
Percent change ^c	-36.5 (-44.4, -32.7) ^a	-15.8 (-20.4, -12.6) ^a	-2.3 (-6.2, 2.4)	17.5 (12.9, 24.3) ^a

	Category of Percent Change in Filtration Marker Over 6 Years			
	< -30%	-30% to -10%	-9.9% to 9.9%	10%
3-Marker composite [^]				
No. of participants	347 (3.6%)	3,638 (37.5%)	5,393 (55.6%)	325 (3.4%)
Incident ESRD	60 (17.3%) ^a	51 (1.4%) ^a	25 (0.5%)	6 (1.9%) ^a
Incidence rate (95% CI) ^b	18.95 (14.71-24.40) ^a	1.14 (0.87-1.51) ^a	0.37 (0.25-0.55)	1.53 (0.69-3.40) ^a
Percent change ^c	-36.0 (-43.9, -32.7) ^d	-15.0 (-19.0, -12.3) ^d	-4.1 (-7.1, 0.2)	15.3 (12.1, 21.5) ^d

Note: N=9,703. Unless otherwise indicated, values are given as number (percentage) or median [interquartile range].

B2M, β_2 -Microglobulin; CI, confidence interval; eGFR_{cr}, creatinine-based estimated glomerular filtration rate-creatinine; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; ESRD, end-stage renal disease

^a p<0.05 for comparison to reference group (-9.9% to +9.9% change in eGFR_{cr} category)

^b Incidence rate per 1,000 person-years

^c Median [interquartile range] for first measurement (study visit 2 [1990-1992]), last measurement (study visit 4 [1996-1998]), and percent change [(first measurement - last measurement)/first measurement]

[^] 3-Marker Composite: mean of percent change in eGFR_{cr}, eGFR_{cys}, and 1/B2M

Table 3
Adjusted Hazard Ratios for ESRD by Percent Change in Filtration Markers Over 6 Years

	Categorical Percent Change				Continuous Percent Change	
	< -30%	-30% to -10%	-9.9% to 9.9%	10%	Per -30% ^c	P vs. eGFR _{cr} ^d
Adjusted for covariates ^a						
eGFR _{cr}	21.42 (12.62, 36.36)	2.92 (1.68, 5.07)	1.00 (reference)	1.42 (0.42, 4.83)	11.70 (8.80, 15.58)	--
eGFR _{cys}	16.34 (10.05, 26.56)	2.92 (1.83, 4.68)	1.00 (reference)	1.77 (0.80, 3.93)	4.71 (3.81, 5.83)	<0.001
1/B2M	24.36 (14.30, 41.49)	4.16 (2.46, 7.03)	1.00 (reference)	2.02 (0.91, 4.48)	11.35 (8.63, 14.92)	0.6
3-Marker Composite [^]	32.35 (19.65, 53.25)	3.10 (1.90, 5.05)	1.00 (reference)	3.02 (1.23, 7.42)	15.37 (11.58, 20.39)	0.05
Adjusted for covariates ^a + first eGFR _{cr} value						
eGFR _{cr}	19.96 (11.73, 33.96)	2.61 (1.50, 4.55)	1.00 (reference)	0.59 (0.17, 2.04)	10.77 (8.14, 14.24)	--
eGFR _{cys}	16.67 (10.27, 27.06)	3.00 (1.88, 4.81)	1.00 (reference)	1.31 (0.59, 2.93)	4.82 (3.87, 5.99)	<0.001
1/B2M	22.53 (13.20, 38.43)	4.03 (2.38, 6.81)	1.00 (reference)	1.90 (0.86, 4.20)	10.69 (8.09, 14.11)	0.9
3-Marker Composite [^]	31.97 (19.40, 52.70)	3.16 (1.94, 5.16)	1.00 (reference)	1.77 (0.71, 4.44)	14.76 (11.07, 19.69)	0.03

Note: N=9,703. Values are given as adjusted hazard ratio (95% confidence interval).

B2M, β 2-Microglobulin; Cr eGFR_{cr}, creatinine-based estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; ESRD, end-stage renal disease

^a Adjusted for age, sex, race, body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes status, total cholesterol, high-density lipoprotein cholesterol, history of coronary heart disease, current cigarette smoking status

^c Continuous percent change was modelled using Cox proportional hazard regression with linear spline terms with one knot at 0%. Hazard ratios express ESRD risk per 30% decline in the filtration marker (i.e. negative percent change).

^d P-value corresponds to the test of difference in the coefficient for decline in an individual filtration marker or 3-marker composite and ESRD risk compared to the coefficient for decline in eGFR_{cr} and ESRD risk (reference group indicated by the dash mark) using seemingly unrelated regression. Poisson models were used for the seemingly unrelated regression analysis, using linear spline terms with one knot at 0% to represent continuous decline in filtration markers.

[^] 3- Marker Composite: mean of percent change in eGFR_{cr}, eGFR_{cys}, and 1/B2M