Albuminuria and the risk of incident stroke and stroke types in older adults

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ABSTRACT

Background: The kidney biomarker that best reflects risk of stroke is unknown. We sought to evaluate the association of stroke with 3 kidney biomarkers: albuminuria, cystatin C, and glomerular filtration rate.

Methods: These 3 biomarkers were determined in 3,287 participants without history of stroke from the Cardiovascular Health Study, a longitudinal cohort study of men and women age 65 years and older from 4 US communities. The biomarkers were albuminuria ascertained using urinary albumin-to-creatinine ratio (UACR) from morning spot urine, creatinine-based estimated glomerular filtration rate (eGFR), and cystatin C. Outcomes were incident stroke (any, ischemic, or hemorrhagic) during follow-up between 1996 and 2006.

Results: A total of 390 participants had an incident stroke: 81% ischemic, 12% hemorrhagic, and 7% unclassified. In adjusted Cox regression models, UACR was more strongly related to any stroke, ischemic stroke, and hemorrhagic stroke than eGFR and cystatin C. The hazard ratio (HR) of any stroke comparing the top to bottom quintile of UACR was 2.10 (95% confidence interval [CI] 1.47–3.00), while HR for eGFR was 1.29 (95% CI 0.91–1.84) and for cystatin C was 1.22 (95% CI 0.85–1.74). When considering clinically relevant categories, elevated UACR was associated with increased hazard of any stroke and ischemic stroke regardless of eGFR or cystatin C categories.

Conclusions: UACR was the kidney biomarker most strongly associated with risk of incident stroke. Results in this elderly cohort may not be applicable to younger populations. These findings suggest that measures of glomerular filtration and permeability have differential effects on stroke risk. *Neurology*® 2010;75:1343–1350

GLOSSARY

AF = atrial fibrillation; **CHS** = Cardiovascular Health Study; **CI** = confidence interval; **eGFR** = estimated glomerular filtration rate; **HR** = hazard ratio; **LVH** = left ventricular hypertrophy; **UACR** = urinary albumin-to-creatinine ratio.

The risk of vascular disease, including stroke, is elevated in patients with chronic kidney disease, independent of hypertension, diabetes, or other vascular risk factors.^{1,2} Kidney disease can be quantified either by measures of filtration of substances, such as creatinine or cystatin C, or by measures of glomerular permeability of substances, such as albumin. Creatinine-based estimates of the glomerular filtration rate (eGFR), cystatin C, and albuminuria have all been associated with an increased risk of incident stroke or ischemic stroke, independent of hypertension^{3,4} and diabetes.^{5,6} Information specific to incident hemorrhagic stroke is limited to

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studies of eGFR⁷ and cystatin C.⁸ The Cardiovascular Health Study (CHS) offers an opportunity to study associations between kidney biomarkers and vascular events in a large number of well-characterized elderly people followed longitudinally. Prior studies in CHS have evaluated the association of eGFR and cystatin C with vascular outcomes, including stroke,⁹ and the association of albuminuria with clinical and subclinical vascular disease.¹⁰ Cystatin C was more strongly associated with incident stroke than was eGFR.¹¹ No previous study has compared these 3 kidney biomarkers as risk factors for overall stroke and for specific types of stroke, namely ischemic and hemorrhagic. Such analyses will help clarify the relation between kidney disease and vascular events of the brain, which may suggest new preventive strategies.

METHODS The CHS is a community-based longitudinal study of risk factors for vascular disease in the elderly, previously detailed.¹² Briefly, a random sample of men and women aged 65 and older were recruited from Medicare eligibility files in 4 US communities (Sacramento County, CA; Washington County, MA; Forsyth County, NC; and Pittsburgh, PA). CHS enrolled 5,201 participants in 1989–1990 and an additional 687 African American participants in 1992–1993. Annual clinic visits occurred through 1998–1999 and included medical history interviews, physical examinations, and blood draws. The institutional review board at each site approved the study, and all participants gave written informed consent.

Measures of the 3 kidney biomarkers used in these analyses were made at the 1996–1997 visit, when urine samples were obtained in addition to blood. Other participant characteristics measured at the 1996–1997 visit were used as covariates. If a value was missing, the most recent available value from the previous 4 years was used. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or a physician's diagnosis of hypertension plus the use of antihypertensive medications. Diabetes mellitus was defined by fasting serum glucose of at least 126 mg/dL or the use of insulin or oral hypoglycemic medications.¹³ Atrial fibrillation (AF) and left ventricular hypertrophy (LVH) were identified on the basis of 12-lead resting electrocardiogram.¹⁴ Ultrasonography of the carotid arteries was performed at the 1992–1993 examination. Stenosis of the internal carotid artery lumen of $\geq 75\%$ was defined as peak flow velocity ≥ 2.5 m/s or no flow.¹⁵

Ascertainment of stroke. The CHS Cerebrovascular Adjudication Committee, a physician review panel including neurologists and a neuroradiologist, adjudicated all suspected events according to previously detailed standard criteria.¹⁶ Strokes were identified at semi-annual contacts, still ongoing. Medicare utilization files for hospitalization were searched to ascertain events that may have been missed. Strokes were classified as ischemic or hemorrhagic using all available information from interviews, medical records, and brain imaging studies. Participants with

history of stroke at the 1996–1997 examination—baseline for this analysis—were excluded because we were interested in incident stroke.

Kidney biomarkers. Albuminuria was based on random morning spot urine collection in the fasting state. Urine albumin was measured soon after collection on the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA); serum and urine creatinine, on the Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY). Urinary albumin excretion was estimated as the urinary albumin-to-creatinine ratio (UACR) in mg albumin per g creatinine. This method based on a spot urine yields results comparable to those from a 24-hour urine collection.¹⁷ Cystatin C was measured from frozen sera stored at -70°C with a particle-enhanced immunonephelometric assay using the BN II nephelometer (Dade Behring, Deerfield, IL). Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease Study Group formula, which incorporates age, race, and sex.¹⁸

We evaluated the kidney biomarkers as clinically relevant categories, quintiles, and continuous variables. Based on standard definitions for albuminuria,¹⁹ we categorized UACR as ≤ 30 mg albumin/g creatinine (normal), >30 to ≤ 300 (microalbuminuria), and >300 (macroalbuminuria). Some analyses combined microalbuminuria and macroalbuminuria into a single category due to the low number of participants with macroalbuminuria. Because prior studies suggest that small differences in UACR even below 30 predict vascular risk,^{20,21} we further categorized UACR into quintiles, with cutpoints at 4.7, 7.6, 12.9, and 29.8. We also examined UACR continuously, with results shown per SD of the logarithm-transformed linear term. The 305 participants with urinary albumin concentration below the level of detection (<0.1 mg/dL) were assumed to have normal albumin excretion rates and were classified into the UACR ≤ 30 category, but because a finer level of albuminuria is uncertain, the quintile and continuous analyses exclude these participants. We examined the impact of this exclusion in sensitivity analyses for which an undetectable urinary albumin concentration was set to 0.1 mg/dL.

We treated eGFR ($\text{mL}/\text{min}/1.73\text{ m}^2$) categorically as <60 or ≥ 60 based on standard definitions¹⁹; and by quintiles, with cutpoints at 56.3, 64.7, 74.0, and 85.9. Because eGFR represents a 4-way interaction of age, sex, race, and creatinine, we did not analyze it as a continuous variable. We treated cystatin C (mg/L) categorically as <1 , 1–1.28, and >1.28 using cutpoints previously demonstrated to correlate with risk of vascular events²²; by quintiles,¹¹ with cutpoints at 0.91, 1.01, 1.13, and 1.31; and continuously, by SD of the linear term.

Statistical analysis. Baseline characteristics were compared between participants with and without UACR ≤ 30 . Those with a history of stroke at the 1996–1997 examination were excluded from analysis. Stroke rates during follow-up were estimated by dividing number of strokes by person-time at risk. Follow-up began at the 1996–1997 clinic visit and ended on the date of stroke, death, loss to follow-up, or June 30, 2006, whichever occurred first. Median follow-up was 8.7 years. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of time to incident stroke (any, ischemic, and hemorrhagic) associated with the 3 renal biomarkers in prespecified models of clinically relevant categories, quintiles, or continuous variables. Cox models were adjusted for age, sex, race (African American or not), body mass index (<25 , 25–30, or $\geq 30\text{ kg}/\text{m}^2$), current smoking, hypertension (and in sensitivity analyses systolic and diastolic blood pres-

tures, with or without antihypertensive medication use, controlled vs uncontrolled hypertension, and mean blood pressures from CHS enrollment through baseline for this analysis), diabetes, LVH, and AF. Analyses of stroke of any type and ischemic stroke were also adjusted for $\geq 75\%$ stenosis of the internal carotid artery; this factor was omitted from models of hemorrhagic stroke because no one with stenosis $\geq 75\%$ had an incident hemorrhagic stroke. In another set of models, we adjusted for other kidney biomarkers using quintiles for UACR and the continuous term for cystatin C. We also examined clinically relevant categories of UACR cross-classified with eGFR and cystatin C. To assess effect modification, we examined the significance of interaction terms between UACR and 1) eGFR and 2) cystatin C by using the likelihood ratio test. All statistical tests were 2-sided. Data were analyzed using Stata statistical software (release 10, StataCorp LP; College Station, TX).

RESULTS Of the 5,888 CHS participants, 1,567 had a stroke or died before the time of the 1996–1997 examination and were excluded from analysis.

Table 1 Characteristics at the 1996–1997 Cardiovascular Health Study examination among participants without a history of stroke, by urinary albumin-to-creatinine ratio (UACR) in mg albumin/g creatinine^a

Characteristic	UACR ≤ 30 (n = 2,630)	UACR >30 (n = 575)	p ^b
Age, y	78.2 (4.6)	79.6 (5.5)	<0.001
Male	38	46	<0.001
African American	16	19	0.08
Body mass index, kg/m ²	27.0 (4.7)	26.6 (4.7)	0.09
Current smoker	7	11	0.002
Ever smoker	51	59	<0.001
Hypertension	58	79	<0.001
Systolic blood pressure, mm Hg	135 (19)	147 (24)	<0.001
Diastolic blood pressure, mm Hg	69.5 (10.1)	71.7 (12.5)	<0.001
Diabetes	11	30	<0.001
Atrial fibrillation	3	8	<0.001
Left ventricular hypertrophy	4	12	<0.001
Internal carotid artery stenosis $\geq 75\%$	1.0	2.8	0.001
Kidney function			
UACR (mg albumin/g creatinine), median (interquartile range)	7.6 (4.7–12.9)	77.5 (45.6–186.4)	<0.001
UACR >300 mg/g creatinine	0	15	—
Serum creatinine, mg/dL	0.99 (0.29)	1.23 (0.74)	<0.001
eGFR, mL/min per 1.73 m ²	71 (17)	64 (22)	<0.001
eGFR <60 mL/min per 1.73 m ²	25	39	<0.001
Cystatin C, mg/L	1.10 (0.27)	1.37 (0.65)	<0.001
Cystatin C category			<0.001
≤ 1 mg/L	39	25	
1–1.28 mg/L	43	36	
>1.28 mg/L	18	39	

Abbreviation: eGFR = estimated glomerular filtration rate.

^a Values are mean (SD) or percentage.

^b p Value is based on either t test for continuous variables or χ^2 test for discrete variables.

Of the remaining 4,321 participants: urinary albumin and creatinine were measured on 3,205 (2,900 with urinary albumin above the detectable level), serum creatinine was measured on 3,178, and cystatin C was measured on 3,187; 3,287 participants had at least one of these measurements and were available for analysis; and 3,091 participants had all three measurements and were included in a subset of analyses. Participants who were otherwise eligible for the analysis but did not have kidney function measured tended to be older and were more likely to be female and to have hypertension, diabetes, and LVH than those with non-missing data. Other factors did not differ significantly.

Of the 3,287 included participants, 390 (12%) had an incident stroke before the end of June 2006; of these, 316 (81%) were ischemic, 48 (12%) were hemorrhagic, and 26 (7%) had insufficient data for classification. Only 4 of the participants with hemorrhagic strokes had subarachnoid hemorrhages. The rate of incident stroke of any type was 16.4 per 1,000 person-years (95% CI 14.8–18.1); of incident ischemic stroke 13.3 (95% CI 11.9–14.8); and hemorrhagic stroke 2.0 (95% CI 1.5–2.7).

Participants differed significantly on several baseline characteristics by UACR (table 1). Participants with microalbuminuria or macroalbuminuria (UACR >30 mg albumin/g creatinine) compared with those without albuminuria (≤ 30 mg albumin/g creatinine) were more likely to be older, male, and to have hypertension, diabetes, AF, LVH, severe stenosis of the internal carotid artery, and a history of smoking. The median UACR in the abnormal group was 77 mg albumin/g creatinine and 15% of this group had UACR >300 mg albumin/g creatinine, which defines macroalbuminuria. Participants in the abnormal group were also more likely to have abnormal levels of eGFR and cystatin C.

Whether considered as clinically relevant categories, quintiles, or a continuous variable, UACR was associated with increased risk of incident stroke in models that do not include the other renal markers (table 2). The HR for the top quintile of UACR was 2-fold when compared with the bottom quintile adjusted for stroke risk factors (2.11; 95% CI 1.49–3.00). HRs were not significantly elevated in the other quintiles. Similar patterns were seen for ischemic stroke. For hemorrhagic stroke, the HRs were elevated for clinically relevant categories, but not significantly. The analysis using quintiles suggested that the risk of hemorrhagic stroke may be elevated even among those with UACR ≤ 30 . Because of small number of hemorrhagic strokes, the lower 2 quintiles were combined to form the reference group. Sensitivity analyses were performed including participants

Table 2 Risk of incident stroke by individual measures of kidney function

Kidney function measure ^a and level	Any stroke		Ischemic stroke		Hemorrhagic stroke	
	No. of events	HR (95% CI) ^b	No. of events	HR (95% CI) ^b	No. of events	HR (95% CI) ^b
UACR						
≤30	269	1 (reference)	219	1 (reference)	36	1 (reference)
>30–≤300	90	1.91 (1.48–2.46)	75	1.91 (1.44–2.52)	9	1.76 (0.81–3.79)
>300	16	2.18 (1.29–3.67)	12	1.90 (1.05–3.46)	2	3.02 (0.69–13.3)
Quintile 1	54	1 (reference)	47	1 (reference)	11	1 (reference) ^c
Quintile 2	55	0.99 (0.68–1.44)	45	0.91 (0.61–1.38)		
Quintile 3	58	1.04 (0.72–1.52)	41	0.83 (0.54–1.27)	14	2.81 (1.27–6.24)
Quintile 4	72	1.30 (0.91–1.86)	63	1.26 (0.86–1.86)	6	1.26 (0.46–3.46)
Quintile 5	106	2.11 (1.49–3.00)	87	1.91 (1.31–2.78)	11	2.91 (1.19–7.10)
Per SD of ln (UACR)		1.34 (1.21–1.48)		1.31 (1.17–1.46)		1.59 (1.20–2.10)
eGFR						
≥60	261	1 (reference)	208	1 (reference)	35	1 (reference)
<60	112	1.14 (0.91–1.43)	96	1.21 (0.95–1.55)	10	0.81 (0.39–1.65)
Quintile 5	66	1 (reference)	49	1 (reference)	13	1 (reference)
Quintile 4	76	1.15 (0.82–1.60)	62	1.28 (0.87–1.86)	11	0.72 (0.32–1.62)
Quintile 3	84	1.22 (0.88–1.69)	71	1.41 (0.97–2.05)	6	0.36 (0.13–0.96)
Quintile 2	55	0.73 (0.51–1.06)	44	0.80 (0.53–1.22)	6	0.34 (0.12–0.91)
Quintile 1	92	1.40 (1.00–1.95)	78	1.59 (1.09–2.32)	9	0.63 (0.25–1.56)
Cystatin C						
<1	128	1 (reference)	97	1 (reference)	23	1 (reference)
1–1.28	155	1.02 (0.80–1.30)	130	1.12 (0.85–1.47)	11	0.39 (0.18–0.81)
>1.28	93	1.29 (0.97–1.72)	79	1.43 (1.04–1.96)	12	0.93 (0.43–2.01)
Quintile 1	71	1 (reference)	52	1 (reference)	15	1 (reference)
Quintile 2	70	1.07 (0.77–1.50)	54	1.13 (0.77–1.67)	9	0.61 (0.26–1.41)
Quintile 3	86	1.20 (0.87–1.65)	72	1.36 (0.95–1.96)	7	0.43 (0.17–1.07)
Quintile 4	64	0.99 (0.70–1.41)	56	1.18 (0.80–1.74)	4	0.27 (0.09–0.85)
Quintile 5	85	1.40 (1.00–1.96)	72	1.60 (1.10–2.35)	11	0.85 (0.36–2.00)
Per SD		1.16 (1.06–1.27)		1.11 (0.99–1.24)		1.27 (1.00–1.61)

^a Urinary albumin-to-creatinine ratio (UACR) with quintile cutpoints at 4.7, 7.6, 12.9, and 29.8 and SD of 1.32 in mg albumin/g creatinine; estimated glomerular filtration rate (eGFR) with quintile cutpoints at 56.3, 64.7, 74.0, and 85.9; and cystatin C with quintile cutpoints at 0.91, 1.01, 1.13, and 1.31 and SD of 0.41 mg/L.

^b Hazard ratio (HR) and 95% confidence interval (CI) estimated from Cox regression with adjustment for age (y), sex, race (black/other), body mass index (<25 or 25–30 or ≥30 kg/m²), current smoking, hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, and, for analyses of stroke of any type and ischemic stroke, internal carotid artery stenosis ≥75%.

^c Only 2 participants in the lowest quintile of UACR had an incident hemorrhagic stroke; to avoid unstable estimates, quintiles 1 and 2 were combined into a reference group for this model.

with urinary albumin below the detectable level in the reference group; results did not change substantially. UACR >30 was associated with increased risk of any stroke and ischemic stroke.

Results for eGFR and cystatin C were less remarkable. Overall, the lowest quintile had a 40% higher stroke risk compared with the highest quintile of eGFR, although the HR for eGFR <60 mL/min, compared to ≥60 mL/min, was not significant. Similar patterns were seen for ischemic stroke. Risk of hemorrhagic stroke was not elevated for eGFR <60.

The highest compared to the lowest quintile of cystatin C was also associated with a 40% increased risk of overall stroke and a 60% higher risk of ischemic stroke. Cystatin C >1.28 was associated with increased risk of ischemic but not with any stroke or hemorrhagic stroke, compared to normal (<1 mg/L).

Results were similar when analyses were restricted to participants who had values for all 3 kidney measures, when adjusting for alternative measures of hypertension, and when an estimate of GFR based on cystatin C was used (data not shown).²³

Table 3 Risk of incident stroke by individual measures of kidney function adjusted for other measures of kidney function

Kidney function measure ^a and level	Any stroke, HR (95% CI) ^b	Ischemic stroke, HR (95% CI) ^b	Hemorrhagic stroke, HR (95% CI) ^b
UACR			
≤30	1 (reference)	1 (reference)	1 (reference)
>30 to ≤300	1.92 (1.48–2.49)	1.87 (1.40–2.49)	1.92 (0.88–4.18)
>300	1.94 (1.10–3.43)	1.62 (0.84–3.12)	2.90 (0.60–14.0)
Quintile 1	1 (reference)	1 (reference)	1 (reference) ^c
Quintile 2	0.99 (0.68–1.45)	0.94 (0.62–1.42)	
Quintile 3	1.03 (0.70–1.51)	0.82 (0.53–1.26)	2.97 (1.29–6.83)
Quintile 4	1.30 (0.91–1.88)	1.28 (0.87–1.89)	1.42 (0.51–3.97)
Quintile 5	2.10 (1.47–3.00)	1.86 (1.26–2.75)	3.22 (1.27–8.18)
Per SD of ln (UACR)	1.32 (1.18–1.48)	1.28 (1.13–1.44)	1.61 (1.20–2.16)
eGFR			
≥60	1 (reference)	1 (reference)	1 (reference)
<60	1.12 (0.88–1.42)	1.19 (0.92–1.54)	0.73 (0.33–1.61)
Quintile 5	1 (reference)	1 (reference)	1 (reference)
Quintile 4	1.16 (0.81–1.65)	1.25 (0.84–1.86)	0.71 (0.30–1.68)
Quintile 3	1.14 (0.80–1.63)	1.28 (0.86–1.91)	0.35 (0.12–1.03)
Quintile 2	0.78 (0.53–1.15)	0.81 (0.52–1.25)	0.42 (0.15–1.17)
Quintile 1	1.29 (0.91–1.84)	1.45 (0.97–2.15)	0.54 (0.20–1.45)
Cystatin C			
<1	1 (reference)	1 (reference)	1 (reference)
1–1.28	1.02 (0.79–1.32)	1.09 (0.82–1.45)	0.45 (0.21–0.99)
>1.28	1.19 (0.88–1.61)	1.29 (0.92–1.80)	0.99 (0.44–2.24)
Quintile 1	1 (reference)	1 (reference)	1 (reference)
Quintile 2	1.01 (0.70–1.44)	1.06 (0.70–1.59)	0.56 (0.22–1.43)
Quintile 3	1.18 (0.84–1.65)	1.32 (0.91–1.93)	0.46 (0.17–1.24)
Quintile 4	0.95 (0.65–1.37)	1.06 (0.70–1.60)	0.33 (0.10–1.07)
Quintile 5	1.22 (0.85–1.74)	1.37 (0.92–2.04)	0.81 (0.32–2.05)
Per SD	1.07 (0.96–1.19)	1.05 (0.93–1.19)	1.23 (0.97–1.56)

^a Urinary albumin-to-creatinine ratio (UACR) with quintile cutpoints at 4.7, 7.6, 12.9, and 29.8 and SD of 1.32 in mg albumin/g creatinine; estimated glomerular filtration rate (eGFR) with quintile cutpoints at 56.3, 64.7, 74.0, and 85.9; and cystatin C with quintile cutpoints at 0.91, 1.01, 1.13, and 1.31 and SD of 0.41 mg/L.

^b Hazard ratio (HR) and 95% confidence interval (CI) estimated from Cox regression with adjustment for age (y), sex, race (black/other), body mass index (<25 or 25–30 or ≥30 kg/m²), current smoking, hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, and, for analyses of stroke of any type and ischemic stroke, internal carotid artery stenosis ≥75%. Models of UACR are adjusted for cystatin C. Models of eGFR and cystatin C are adjusted for UACR.

^c Only 2 participants in the lowest quintile of UACR had an incident hemorrhagic stroke; to avoid unstable estimates, quintiles 1 and 2 were combined into a reference group for this model.

After adjusting for cystatin C, the HRs associated with UACR changed only slightly (table 3). For example, the HR for the highest compared to lowest quintile was 2.10 (95% CI 1.47–3.00) for any stroke and 1.86 (1.26–2.75) for ischemic stroke. On the other hand, the associations of eGFR and cystatin C were attenuated and nonsignificant after adjusting for UACR.

A combined model that included quintiles of all 3 kidney measures was compared to models that included the individual kidney measures using likelihood ratio tests. The combined model was significantly better than models of eGFR alone and cystatin C alone, but was not significantly better than a model of UACR alone, supporting the assertion that UACR is the best stroke predictor among the 3 kidney measures.

Significant interactions with age were present in the models of UACR, but not eGFR or cystatin C, such that the HR of any stroke or ischemic stroke was higher in younger than older participants. For any stroke, the adjusted HR for UACR was 2.85 (95% CI 1.74–4.66) among those who were younger than the median age (78 years) and 1.57 (95% CI 0.97–2.56) in those who were older (*p* value for interaction in the quintile model = 0.02). We did not examine interactions for hemorrhagic stroke because of the small number of events. Interactions between individual kidney markers and the other covariates were also assessed, but were not significant.

We next categorized participants by UACR and each measure of kidney filtration (table 4). Compared to those with normal kidney biomarkers, those with UACR >30 had greater risk of any stroke and ischemic stroke whether or not they had normal or abnormal measures of eGFR or cystatin C. Conversely, neither eGFR nor cystatin C levels were associated with stroke risk among participants with UACR ≤30 compared to those with normal values for the markers in the model, with one exception: cystatin C >1.28 mg/L was associated with borderline increased risk of ischemic stroke. In another set of models, UACR >30 compared to ≤30 was associated with increased total and ischemic stroke risk within each category of eGFR or cystatin C (data not shown). Formal tests of interaction between UACR and eGFR or cystatin C were not significant. Small numbers precluded analyses based on hemorrhagic stroke.

DISCUSSION Among community-dwelling older adults free of prior stroke, albuminuria as reflected by UACR was more strongly associated than eGFR and cystatin C with risk of incident stroke of any type and ischemic stroke. An association is also suggested with risk of hemorrhagic stroke, although wide CIs and small event numbers warrant caution interpreting the data. The strong associations for UACR were independent of established stroke risk factors. The pattern of associations for quintiles of UACR seemed to differ for ischemic and hemorrhagic stroke. For ischemic stroke, risk was concentrated in the top

Table 4 Risk of incident stroke by combined measures of kidney function

Kidney function measures ^a and level		Any stroke		Ischemic stroke	
eGFR	UACR	No. of events	HR (95% CI) ^b	No. of events	HR (95% CI) ^b
≥60	≤30	192	1 (reference)	154	1 (reference)
	>30	63	1.86 (1.38–2.52)	50	1.79 (1.28–2.50)
<60	≤30	68	1.04 (0.78–1.37)	60	1.13 (0.83–1.53)
	>30	38	2.27 (1.58–3.27)	32	2.24 (1.50–3.35)
Cystatin C					
<1	≤30	97	1 (reference)	72	1 (reference)
	>30	29	2.11 (1.38–3.23)	24	2.28 (1.42–3.66)
1–1.28	≤30	114	1.05 (0.79–1.38)	96	1.18 (0.86–1.61)
	>30	37	2.01 (1.35–2.99)	31	2.18 (1.41–3.39)
>1.28	≤30	51	1.22 (0.86–1.74)	47	1.50 (1.02–2.20)
	>30	36	2.20 (1.46–3.33)	28	2.21 (1.38–3.52)

^a Urinary albumin-to-creatinine ratio (UACR) in mg albumin/g creatinine; estimated glomerular filtration rate (eGFR) in mL/min per 1.73 m²; and cystatin C in mg/L.

^b Hazard ratio (HR) and 95% confidence interval (CI) estimated from Cox regression with adjustment for age (y), sex, race (black/other), body mass index (<25 or 25–30 or ≥30 kg/m²), current smoking, hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, and, for analyses of stroke of any type and ischemic stroke, internal carotid artery stenosis ≥75%.

quintile. For hemorrhagic stroke, although the number of events was very small, risk was elevated even with smaller elevations in UACR below 30 mg albumin/g creatinine.

Another novel finding of this study was that associations between UACR and incident stroke were independent of biomarkers of renal filtration function creatinine-based eGFR and cystatin C, which have themselves been linked with stroke risk in CHS^{9–11,22} and other studies.^{3–8,24} In this study, the majority of patients with elevated albumin excretion (UACR >30) had cystatin C levels below the level previously demonstrated to confer an excess vascular risk¹¹ and had eGFR ≥60 mL/min per 1.73 m². Further, a greater degree of albuminuria was associated with higher stroke risk among individuals with or without elevated cystatin C levels or low eGFR (table 4). Similar findings were observed in the National Health and Nutrition Examination Survey and other cohorts with regard to cardiovascular mortality and cardiac events.^{25,26} Taken together, these findings support the hypothesis that albuminuria and reduced filtration function are separate pathologic processes, with albuminuria conferring risk of incident stroke independent of filtration function. On the other hand, none of the associations between eGFR or cystatin C and incident stroke were significantly elevated after controlling for albuminuria (table 3).

The appropriateness of specific cutoffs, such as UACR >30, is questionable, and the mechanisms

that relate albuminuria to a higher risk of stroke are not fully elucidated. Others have found that small increments in UACR at levels ≤30 are associated with increased risk of vascular disease,²⁷ as we found—although the possible association with hemorrhagic stroke has not been described previously. Perhaps those elderly participants with more albuminuria had a greater long-term cumulative burden of hypertension, which accounted for their excess stroke risk, especially for hemorrhagic stroke. However, the association with stroke was observed even after adjustment for LVH and for several different formulations of blood pressure, including the average of multiple blood pressures measured annually over 4–7 years. Albuminuria may indicate a generalized systemic vasculopathy,^{25,28} independent of hypertension and diabetes.^{5,20,29} It may reflect physiologic derangements including endothelial dysfunction, microinflammation,³⁰ elevated central aortic pressures, and oxidative stress—factors that may increase the risk of stroke. Our findings for stroke types require confirmation, but tentatively suggest that even low levels of albuminuria may affect the risk of hemorrhagic stroke.

Strengths of this study include the community-based nature of the sample, which provides for greater external validity compared to clinic-based or hospital-based populations. Other strengths include the large sample size, availability of all 3 renal biomarkers, long-term follow-up, expert adjudication of stroke events, and characterization of multiple other vascular risk factors to allow adjustment for important potential confounders.

This study also has limitations. The number of events for hemorrhagic stroke was small, resulting in compromised ability to adjust for covariates and wide CIs and thus demanding caution when interpreting these results. The day-to-day variability of UACR within individuals is high, such that a single sample may not accurately characterize the true level of albumin excretion; however, such imprecision in the measurement would be expected to bias our observed HRs toward the null hypothesis of no association between albuminuria and stroke. The study population consisted of older adults who were not institutionalized at baseline. The results may not be generalizable to younger adults or residents of nursing facilities.

Future studies are needed to replicate these findings. They should not limit themselves to specific cutoffs of UACR and should include stroke types and subtypes. Assuming these findings are confirmed, we need to learn more about how albuminuria could affect risk through hemodynamic and nonhemodynamic effects, seeking novel preventive

strategies. Finally, the relation of albuminuria to covert brain vascular disease defined by MRI, including leukoaraiosis, infarcts, and hemorrhages, should be explored further.³¹⁻³⁴

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Ellen S. O'Meara and Dr. Ronit Katz.

DISCLOSURE

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