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Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: the chronic renal insufficiency cohort (CRIC) study

Danielle K. Sandsmark, MD, PhD[1,*], **Steven R. Messé, MD**[1], **Xiaoming Zhang, MS**[2], **Jason Roy, PhD**[2], **Lisa Nessel, MSS, MLSP**[2], **Lotuce Lee Hamm, MD**[3], **Jiang He, MD, PhD**[4], **Edward J. Horwitz, MD**[5], **Bernard G. Jaar, MD, MPH**[6], **Radhakrishna R. Kallem, MD, MPH**[7], **John W. Kusek, PhD**[8], **Emile R. Mohler III, MD**[9], **Anna Porter, MD**[10], **Stephen L. Seliger, MD, MS**[11], **Stephen M. Sozio, MD, MHS**[12], **Raymond R. Townsend, MD**[7], **Harold I. Feldman, MD, MSCE**[2], **Scott E. Kasner, MD**[1], and **the CRIC Study Investigators**

[1]Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA

[2]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA

[3]Department of Medicine, Tulane University, New Orleans, LA

[4]Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana

[5]Metrohealth, Cleveland, OH

[6]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

[7]Renal, Electrolyte, and Hypertension Division, Hospital of the University of Pennsylvania, Philadelphia, PA

[8]Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD

[9]Section of Vascular Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

[10]Department of Nephrology, University of Illinois, Chicago, IL

[11]Department of Medicine, University of Maryland, Baltimore, MD

[12]Department of Medicine, Johns Hopkins University, Baltimore, MD

Abstract

Background and Purpose—Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular events. However, the impact of CKD on cerebrovascular disease is less well understood. We hypothesized that renal function severity would be predictive of stroke risk, independent of other vascular risk factors.

[*]Address correspondence to: Danielle Sandsmark, M.D., Ph.D., Department of Neurology, University of Pennsylvania Perelman School of Medicine, 3400 Spruce Street, 3W Gates Building, Philadelphia, PA 19104. Phone: (215) 662-6738; Fax: 215-349-5579; danielle.sandsmark@uphs.upenn.edu.

DISCLOSURES

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Methods—The study population included 3939 subjects enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study, a prospective observational cohort. Stroke events were reported by participants and adjudicated by two vascular neurologists. Cox proportional hazard models were used to compare measures of baseline renal function with stroke events. Multivariable analysis was performed to adjust for key covariates.

Results—In 3939 subjects, 143 new stroke events (0.62 events per 100 person-years) occurred over a mean follow-up of 6.4 years. Stroke risk was increased in subjects who had worse baseline measurements of renal function (estimated glomerular filtration rate (eGFR) and total proteinuria or albuminuria). When adjusted for variables known to influence stroke risk, total proteinuria or albuminuria, but not eGFR, were associated with an increased risk of stroke. Treatment with blockers of the renin-angiotensin system did not decrease stroke risk in individuals with albuminuria.

Conclusions—Proteinuria and albuminuria are better predictors of stroke risk in patients with chronic kidney disease than eGFR. The impact of therapies targeting proteinuria/albuminuria in individuals with CKD on stroke prevention warrants further investigation.

Keywords

stroke; kidney disease; albuminuria; risk factor

INTRODUCTION

Chronic kidney disease (CKD), characterized by reduced kidney function or kidney damage for at least 3 months[1] affects more than 11% of adults in the United States.[2] CKD is often associated with other chronic diseases, such as hypertension and diabetes, and is independently associated with an increased risk of cardiovascular events.[3] Furthermore, individuals with CKD have worse functional outcomes and increased mortality following cardiovascular events.[3] Thus, CKD imposes a significant disease burden, both for individuals suffering from the disease and on the healthcare system as a whole.

While the association between CKD and cardiovascular risk has been well established, the impact of CKD on cerebrovascular disease is less well characterized. Certainly, kidney disease and stroke share traditional cardiovascular risk factors, including diabetes, hypertension, obesity, and smoking. The kidney and brain may be uniquely susceptible to vasculature insults given that the two rely on similar microvasculatures that allow for continuous high volume perfusion. Most of the studies which have identified an increased risk of stroke in patients with CKD have been retrospective cohorts data and meta-analyses.[4–7] The few prospective studies of the relationship between CKD and stroke report on either specific underlying causes of CKD, such as diabetes[8], or patients undergoing maintenance hemodialysis.[9,10] The generalizability of these results to the larger population with CKD is uncertain. Individuals who have kidney dysfunction at the time of a stroke event have worse outcomes[11,12], though whether kidney dysfunction was a causative factor in the stroke mechanism is unclear. Together, these data suggest that CKD may have important implications for risk of stroke and sequelae.

The Chronic Renal Insufficiency Cohort (CRIC) study was established in 2001 to prospectively follow patients with CKD from a variety of underlying causes to better understand the relationship between progressive renal disease and cardiovascular disease.[13] We hypothesized that a lower level of kidney function at baseline is associated with an increased risk of stroke, independent of other vascular risk factors. We also hypothesized that use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which decrease urinary albumin excretion[14], would also be associated with a reduced risk of stroke.

METHODS

Study population

The CRIC study is a prospective multicenter observational cohort of adults with moderate to advanced CKD that aims to evaluate risk factors for progression of CKD and cardiovascular disease. The study design and methods have been described in detail previously.[13] The protocol was approved at each center's institutional review board and all patients provided informed consent. Briefly, 7 clinical centers recruited adults aged 21–74 years who had CKD but were not on dialysis using age-based eGFR inclusion criteria. All patients had eGFR≥20 ml/min/1.73m^2 at baseline; older patients were required to have the lowest baseline eGFR to avoid inclusion of subjects with age-related declines in eGFR.[13] Fifty percent of study participants had diabetes. Study recruitment was conducted by the individual clinical centers and recruited an ethnically and racially diverse study population. Subjects were followed prospectively until death or study dropout. Exclusion criteria included a diagnosis of polycystic kidney disease, prior dialysis treatment, prior organ/bone marrow transplant, immunotherapy for renal disease or systemic vasculitis affecting the kidneys in the prior 6 months, chemotherapy/ alkylating agents for systemic cancer (other than non-melanoma skin cancer) within 2 years prior to study enrollment, prior diagnosis of multiple myeloma or renal carcinoma, New York Heart Association class III or IV heart failure at baseline, known diagnosis of cirrhosis or HIV/AIDs, women pregnant or breast-feeding, participants in active interventional clinical trials, or those unable or unwilling to provide informed consent. Proteinuria and albuminuria was quantified by 24-hour urine collection measured at the first study visit. Information on medication use was obtained by self-report at annual clinic visits and semi-annual phone interviews.

Stroke outcomes

Participants or their proxies were contacted every 6 months about possible cardiovascular hospitalizations as well as outpatient cardiovascular tests or interventions. Stroke was defined as a fixed neurologic deficit lasting >24h due to a presumed vascular cause. For all potential stroke events, reported either by the subject or their physicians, the medical records were independently reviewed and adjudicated by two vascular neurologists and classified as definite/probable stroke, or no stroke. Strokes were classified as ischemic or hemorrhagic using all available information from medical records and imaging studies.

Statistical methods

The baseline eGFR measurements, collected within 3 months of study recruitment, of participants who suffered a fatal and non-fatal stroke event during the follow-up period were compared to those who remained stroke free. Cox proportional hazard models were used to calculate hazard ratios and 95% confidence intervals for time to first stroke after study enrollment associated with baseline glomerular filtration rate and other markers of renal function, including 24 hour proteinuria and albuminuria.

Multivariable analysis was performed to adjust for key covariates, defined as those associated with stroke in univariate analysis at a $p<0.05$ level, and *a priori* included age, sex, and race. Each indicator of renal impairment (eGFR, proteinuria, and albuminuria) was first analyzed separately with adjustment for these covariates. Next, eGFR and albuminuria were included simultaneously. Finally, use of ACEIs or ARBs was included in the models as a potential disease-modifying therapy.

All analyses were performed using SAS software. All statistical tests were two-sided and a result was considered significant if $p<0.05$.

RESULTS

Subject characteristics

Baseline characteristics are summarized in Table 1. Among 3939 participants in the present CRIC analysis with a median follow-up of 6.4 years, 143 stroke events were identified in 143 patients (incidence rate: 0.62 per 100 person-years). Of the 143 stroke events, 118 were ischemic strokes while the remaining 25 were intracerebral hemorrhages. Participants who suffered stroke were older, were more likely to be black, and were more likely to have a history of diabetes, prior myocardial infarction or stroke, were active smokers, and used alcohol (Table 1). The systolic blood pressure at the baseline study visit was higher in patients who subsequently had a stroke. The reported use of medications that may modify stroke risk, including aspirin, statin drugs, erythropoietin, or blockers of the renin-angiotensin system were not different between groups (Table 1). During the follow-up period, there were 716 deaths (18.2%) and 205 patients (2.1%) who withdrew consent or were lost to follow-up.

Kidney function and stroke

Baseline kidney function measures included eGFR, total protein excreted in 24 hours and albumin excretion in 24 hours (Table 2). Characteristics of subject groups based on kidney function measurements are included in supplemental tables 1–3.

Mean baseline eGFR measurements were lower in participants who experienced a stroke event as compared to those who did not, while proteinuria/albuminuria was increased in subjects with strokes (Table 2). When subjects were categorized into groups based on baseline eGFR (Table 3), there was a significantly greater risk of stroke in patients in the lowest categories of kidney function ($eGFR<45$ ml/min/1.73m^2) as compared to those with the highest kidney function ($eGFR>60$ ml/min/1.73m^2). In this regard, there was a dose-

response relationship whereby increasing urinary protein or albumin excretion was associated with an increased risk of stroke (Table 3).

After adjustment for age, race, sex, vascular risk factors (including diabetes, systolic blood pressure, hyperlipidemia, smoking and alcohol use) and medications which modify urinary protein excretion (use of ACEI/ARBs) was performed. When these variables were controlled for, eGFR was no longer associated with a risk of stroke events (Table 4). In contrast, proteinuria >0.50 g/day or albuminuria >30 mg/day were associated with a significant increase in stroke risk after accounting for these other stroke risk factors (Table 4; Figure 1A).

Finally, when both eGFR and albuminuria were included simultaneously in the model (Table 5), albuminuria remained significantly associated with stroke risk, as did many known vascular risk factors, including age, black race, diabetes, systolic blood pressure, current smoking, and alcohol use.

Self-reported use of either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) did not modify the risk of stroke in individuals with albuminuria (Figure 1B).

DISCUSSION

The CRIC study cohort provides a unique opportunity to assess the relationship between CKD and stroke risk using a variety of measures of kidney disease severity.

CKD is associated with cardiovascular disease as well as all-cause and cardiovascular-related mortality.[15] In routine clinical practice, the degree of kidney dysfunction is typically determined by measuring serum creatinine and calculating creatinine-based eGFR. However, serum creatinine is influenced by age, sex, and lean muscle mass, confounding the associations between creatinine-based eGFR measurements and outcomes. Proteinuria and albuminuria are alternative and complementary measures of renal function that measure injury to the renal filtration barrier.[16–18] Our study, performed in a large, diverse cohort of patients with CKD of a variety of underlying causes, indicate that small increases in protein and/or albumin excretion are associated with an increased risk of stroke. By contrast, eGFR was not associated with stroke risk after accounting for the most common vascular risk factors. This suggests that eGFR measurements alone are a poor biomarker of cerebrovascular risk in patients with CKD.

Several prior studies found that subjects with a decreased eGFR had an increased risk of stroke when compared to subjects with normal eGFR (>60 ml/min/1.73m^2). Lee et al.[6] performed a meta-analysis that found that decreased eGFR (<60 ml/min/1.73m^2) was associated with an increased risk of stroke. Similarly, Piccini et al.[19] found that eGFR<60 ml/min/1.73m^2 increased the risk of stroke in individuals with atrial fibrillation who were not on anticoagulation therapy. These studies differ from CRIC cohort in that all subjects in the CRIC cohort had existing renal dysfunction at the time of study enrollment as determined by age-based eGFR enrollment criteria[13] (supplemental table 1). In these individuals with known kidney dysfunction, proteinuria and albuminuria are more sensitive

to stroke risk than eGFR measurement alone. In this regard, proteinuria was associated with an increased risk of stroke in patients with atrial fibrillation not treated with anticoagulation even after accounting for a decrease in eGFR.[20]

These data support recent evidence suggesting that albuminuria may be a more sensitive biomarker for incident cardiovascular events in the general population[15,21] and in certain disease states, such as diabetes[22], than other markers of kidney disease such as eGFR. Our study extends this finding to cerebrovascular disease and suggests that albuminuria can be used to predict the risk of stroke in individuals with known CKD. Prior studies have found an association of albuminuria with incident stroke in the general population[23–26], but this is the first study to assess the association of renal biomarkers with stroke risk specifically in individuals with CKD. Our study bolsters these earlier reports in a diverse sample of patients with CKD from a variety of etiologies.

In addition to the conventional vascular risk factors that are common in patients with CKD, there may be pathophysiologic mechanisms unique to CKD that predispose patients to cardiovascular and cerebrovascular events. Reduced kidney function has been associated with inflammation, thromboembolism, endothelial dysfunction, and arterial stiffness/calcification and other factors, all of which may contribute to stroke risk.[27–29] The kidney and brain both have low-resistance microvasculatures exposed to high volume, continuous perfusion. Small vessel cerebrovascular disease in the brain is mediated by endothelial dysfunction, arteriosclerosis, and blood-brain barrier disruption. Similarly, kidney dysfunction is associated with endothelial dysfunction and lipohyalinosis, both features of small vessel disease.[30] In fact, CKD has been associated with subclinical white matter abnormalities, suggesting that the two may share similar pathogenic mechanisms.[31]

Albumin is a large protein that is normally excreted by the kidney at very low levels (<30 mg/day) with 99% of filtered albumin being reabsorbed, such that less than 1% reaches the urine.[32] Albuminuria, therefore, reflects either an increase in the filtered albumin load or a decrease in the tubular reabsorption capacity and, in that way, has been proposed as a marker of glomerular damage.[33] Further studies have suggested that, in addition to reflecting glomerular injury, albumin secretion is also pathogenic, leading to proinflammatory and profibrotic events within the proximal tubule.[34–35] While the mechanisms by which albuminuria is associated with cardiovascular events are not fully understood, it has been postulated that albuminuria may reflect systemic endothelial dysfunction[36–37] that alters inflammatory and thrombotic cascades[38–39] and contributes to atherothrombotic events, including stroke.

Albuminuria has important implications as a biomarker for stroke risk in CKD, as it is a modifiable risk factor. Angiotensin converting enzyme inhibitors and angiotensin receptor blocker agents have been shown to decrease albuminuria in individuals with diabetes and hypertension[40] and decrease cardiovascular events in these patients.[2] Our data suggest that albuminuria severity may be useful to stratify patients with CKD who are at higher risk of suffering a cerebrovascular event and may aid in identifying individuals in whom therapy should be intensified. When we looked specifically at the use of ACEI/ARBs, there was a

suggestion patients with mild albuminuria (30–299 mg/day; Figure 1B) might benefit from ACEI/ARB therapy, though this failed to reach statistical significance.

Limitations of our study include the relatively few strokes observed in the CRIC cohort, precluding examination of differential associations of proteinuria with subtypes of stroke. The incidence of stroke in our population is similar to that reported in other studies of stroke in patients with kidney dysfunction.[23] Medical history and medication use were self-reported by participants. Medication indication, compliance and/or effectiveness were not assessed. In addition, we used medication use data collected at the first study visit; changes in medication use and dose titrations were not included in the analysis. In our study, there were a small number of hemorrhagic strokes (n=25) as compared to ischemic strokes (n=118). In our analysis, we considered all strokes together. The small number of hemorrhagic stroke limited our ability to determine which factors where associated with this specific stroke type. To patients and their providers, identifying risk factors for all potential types of strokes is important and thus we chose to analyze all strokes together. As additional stroke events accrue over time, it may be possible to determine risk factors for ischemic or hemorrhagic stroke separately in patients with kidney dysfunction.

In conclusion, the CRIC cohort study supports the growing body of evidence that proteinuria is a biomarker for cardiovascular risk and extends these findings to include proteinuria and albuminuria as markers of cerebrovascular risk in subjects with CKD. These data suggest that therapies aimed at treating proteinuria/albuminuria may be worthy of further investigation for stroke prevention. In addition, the longitudinal study of the CRIC cohort will allow us to further examine how changes in albuminuria and renal function over the 10 year planned follow-up time influence stroke risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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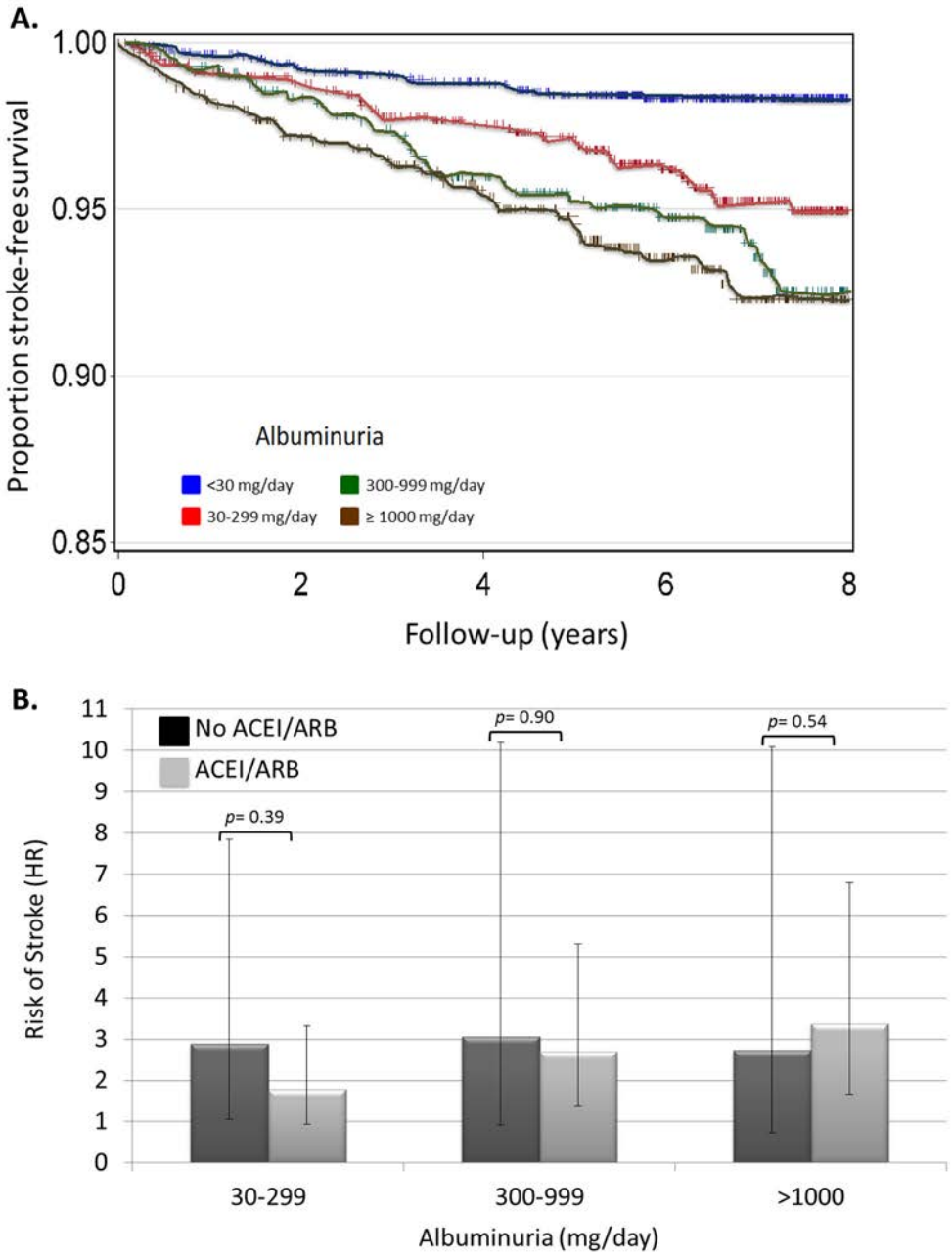

Figure 1.

(A) Kaplan-Meier curves of stroke-free survival according to degree of albuminuria. (B) Risk of stroke in subjects with albuminuria and treatment with inhibitors of the renin-angiotensin system (ACEI/ARB). Error bars indicate 95% confidence intervals.

Table 1

Baseline Patient Characteristics

	Stroke (n=143)	No stroke (n=3796)	*p* value
Age (years)	61 ± 8	58 ± 11	**<0.001**
Race (white)	42 (29%)	1596 (42%)	**<0.001**
Sex (male)	61%	55%	0.14
Systolic blood pressure (mmHg)	138 ± 24	128 ± 22	**<0.001**
Medical history			
Hyperlipidemia	87%	82%	0.09
Diabetes	61%	48%	**0.003**
Cardiac arrhythmia	15%	17%	0.47
Cardiovascular dx*	57%	33%	**<0.001**
Peripheral vascular dx	14%	6%	**<0.001**
Social history			
Current smoker	24%	13%	**<0.001**
Alcohol use	51%	63%	**0.003**
Medication use			
Aspirin	50%	43%	0.09
Statin	59%	55%	0.28
Erythropoiesis-stimulating agents	4%	4%	0.90
ACEI/ARB	76%	69%	0.75

*Cardiovascular disease includes a self-reported history of coronary artery disease, prior myocardial infarction or stroke, or heart failure.

Table 2

Baseline Kidney Function Measures

	Stroke (n=143)				No Stroke (n=3796)			
	Mean (std dev)	**Median**	**Lower quartile**	**Upper quartile**	**Mean (std dev)**	**Median**	**Lower quartile**	**Upper quartile**
eGFR	40.7 (14.0)	40.1	30.6	49.9	45.1 (16.9)	43.2	32.3	55.7
Proteinuria (g/24h)	1.7 (2.5)	0.6	0.1	2.4	1.0 (2.3)	0.2	0.1	0.9
Albuminuria (mg/24h)	1225.9 (2035.5)	347.5	40.2	1314.8	678.4 (1631.8)	60.1	9.7	536.3

*Baseline proteinuria and albuminuria data available for 132 and 133 subjects in stroke group and 3609 and 3626 subjects in the no stroke group respectively.

Table 3

Renal Function and Stroke Risk

	Stroke (n=143)	No stroke (n=3796)	Hazard Ratio (95%CI)	*p* value	Incidence rate (per 1000 person years)
eGFR category (mL/min/1.73m^2)					
>60	13 (9%)	689 (18%)	(Ref)		3.0
45–<60	34 (24%)	1057 (28%)	1.7 (0.91–3.26)	0.09	5.1
30–<45	63 (44%)	1276 (34%)	**2.8 (1.52–5.01)**	**<0.001**	8.2
<30	33 (23%)	774 (20%)	**2.6 (1.37–4.95)**	**0.004**	7.8
Urine protein (g/24h)					
<0.10	27 (21%)	1348 (37%)	(Ref)		3.2
0.10–<0.50	34 (26%)	1060 (29%)	**1.6 (1.00–2.73)**	**0.05**	5.3
0.50–<1.50	28 (21%)	554 (15%)	**2.7 (1.58–4.54)**	**0.0003**	8.6
>1.50	43 (33%)	647 (18%)	**3.5 (2.17–5.69)**	**<0.0001**	11.3
Albuminuria (mg/day)					
<30	24 (18%)	1483 (41%)	(Ref)		2.6
30–299	39 (29%)	977 (27%)	**2.6 (1.54–4.25)**	**0.0003**	6.6
300–999	31 (23%)	547 (15%)	**3.6 (2.14–6.22)**	**<0.0001**	9.5
≥1000	39 (29%)	619 (17%)	**4.2 (2.55–7.05)**	**<0.0001**	11.1

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Table 4

Multivariable Analyses

	Hazard Ratio (95% CI)	*p* value
eGFR (mL/min/1.73m^2)		
45–<60	1.2 (0.65–2.39)	0.50
30–<45	1.7 (0.93–3.21)	0.08
<30	1.6 (0.82–3.07)	0.17
Proteinuria (g/day)		
0.10–<0.50	1.5 (0.90–2.53)	0.12
0.50–<1.50	**2.2 (1.27–3.93)**	**0.005**
≥1.50	**3.1 (1.76–5.37)**	**<0.0001**
Albuminuria (mg/day)		
30–299	**2.2 (1.29–3.66)**	**0.004**
300–999	**3.0 (1.71–5.34)**	**0.0001**
≥1000	**3.6 (2.00–6.38)**	**<0.0001**

* Each indicator of renal dysfunction is adjusted for age, sex, race, systolic blood pressure, history of hyperlipidemia, diabetes, current smoking and/or alcohol use, and ACEI/ARB use in these models, but not for each other.

Table 5

eGFR and albuminuria multivariable analysis

	Hazard Ratio (95% CI)	*p* value
Age	1.0 (1.02–1.06)	**0.0007**
Race: Black	1.5 (0.99–2.28)	0.06
Race: Other	0.9 (0.49–1.66)	0.73
Sex: Male	1.2 (0.84–1.74)	0.32
Diabetes	1.1 (0.74–1.60)	0.67
Systolic BP	1.0 (1.00–1.02)	**0.007**
Hyperlipidemia	1.1 (0.62–1.80)	0.84
Alcohol use	0.7 (0.49–1.01)	**0.05**
Current smoker	2.0 (1.32–3.08)	**0.001**
ACEI/ARB use	1.1 (0.74–1.66)	0.61
eGFR (ml/min/1.73m^2)*		
45–<60	1.3 (0.60–2.74)	0.52
30–<45	1.7 (0.84–3.63)	0.14
<30	1.3 (0.61–2.96)	0.46
Albuminuria (mg/day)**		
30–299	2.1 (1.22–3.51)	**0.007**
300–999	2.8 (1.54–5.00)	**0.0007**
≥ 1000	3.2 (1.76–5.99)	**0.0002**

Variables adjusted for both eGFR and albuminuria

* eGFR adjusted for albuminuria, age, sex, systolic blood pressure, history of hyperlipidemia, diabetes, current smoking and/or alcohol use, and ACEI/ARB use

** Albuminuria adjusted for eGFR, age, sex, systolic blood pressure, history of hyperlipidemia, diabetes, current smoking and/or alcohol use, and ACEI/ARB use