Association of Kidney Disease Measures With Ischemic Versus Hemorrhagic Strokes
Pooled Analyses of 4 Prospective Community-Based Cohorts

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Background and purpose—Although low glomerular filtration rate (GFR) and albuminuria are associated with increased risk of stroke, few studies compared their contribution to risk of ischemic versus hemorrhagic stroke separately. We contrasted the association of these kidney measures with ischemic versus hemorrhagic stroke.

Methods—We pooled individual participant data from 4 community-based cohorts: 3 from the United States and 1 from The Netherlands. GFR was estimated using both creatinine and cystatin C, and albuminuria was quantified by urinary albumin-to-creatinine ratio (ACR). Associations of estimated GFR and ACR were compared for each stroke type (ischemic versus intraparenchymal hemorrhagic) using study-stratified Cox regression.

Results—Among 29595 participants (mean age, 61 [SD 12.5] years; 46% men; 17% black), 1261 developed stroke (12% hemorrhagic) during 280549 person-years. Low estimated GFR was significantly associated with increased risk of ischemic stroke, but not hemorrhagic stroke, whereas high ACR was associated with both stroke types. Adjusted hazard ratios for ischemic and hemorrhagic stroke at estimated GFR of 45 (versus 95) mL/min per 1.73 m^2 were 1.30 (95% confidence interval, 1.01–1.68) and 0.92 (0.47–1.81), respectively. In contrast, the corresponding hazard ratios for ACR of 300 (versus 5) mg/g were 1.62 (1.27–2.07) for ischemic and 2.57 (1.37–4.83) for hemorrhagic stroke, with significantly stronger association with hemorrhagic stroke (P=0.04). For hemorrhagic stroke, the association of elevated ACR was of similar magnitude as that of elevated systolic blood pressure.

Conclusions—Whereas albuminuria showed significant association with both stroke types, the association of decreased estimated GFR was only significant for ischemic stroke. The strong association of albuminuria with both stroke types warrants clinical attention and further investigations. (Stroke. 2014;45:00-00.)

Key Words: cardiovascular ■ epidemiology ■ renal insufficiency, chronic ■ risk factors ■ stroke

Stroke is a leading cause of mortality and morbidity and requires substantial healthcare expenditures.1 Excluding subarachnoid hemorrhages from consideration, strokes are broadly classified as ischemic and intraparenchymal hemorrhagic.1 Whereas the incidence rate of ischemic versus hemorrhagic strokes and their treatment are distinct, some risk factors such as blood pressure have similar effects in both stroke types, whereas others such as cholesterol do not.2

However, head-to-head comparison of the strength of associations between traditional cardiovascular risk factors and ischemic versus hemorrhagic is lacking, perhaps because of the generally low incidence of hemorrhagic stroke in Western populations.

Chronic kidney disease (CKD), defined by reduced kidney function (estimated glomerular filtration rate [eGFR], <60 mL/min per 1.73 m^2), elevated albuminuria (albumin-to-creatinine
Stroke Types
Incident stroke types were divided into ischemic stroke and hemorrhagic stroke and were verified by computed tomography, MRI, or at autopsy (online-only Data Supplement). Participants with hemorrhagic stroke included those with intraparenchymal hemorrhages but excluded those with subarachnoid hemorrhages. Ischemic stroke subtypes were not determined in a similar fashion in all cohorts and thus were not considered in these analyses.

Statistical Analysis
Individual participant data from the 4 cohorts were pooled. Participants were excluded if demographics or measurements of all 3 kidney measures (ie, creatinin, creatinine, and albuminuria) were missing. For all other participants, missing values of the kidney measures and potential confounders were imputed using stochastic multiple imputations using the chained equation method (online-only Data Supplement).20 Except for 12% missing ACR in the CHS study, all other variables had <5% of missing values.

Stratified Cox proportional hazards models, allowing for cohort-specific baseline hazard, were used to estimate hazard ratios (HRs) for stroke types. Fully adjusted models included eGFR, log-ACR, sex, black ethnicity, age (continuous), diabetes mellitus, current smoking, systolic blood pressure (continuous), total cholesterol (continuous), history of cardiovascular disease, BMI (continuous), statins, and antihypertensive drug use. To assess nonlinear associations of eGFR and ACR with risk of stroke types, we modeled eGFR and ACR using restricted cubic splines with knots at 45, 60, 75, 90, and 105 mL/min per 1.73 m² for eGFR and 10, 30, and 300 mg/g (to convert to mg/mmol multiply by 0.113) for ACR. eGFR of 95 mL/min per 1.73 m² and ACR of 5 mg/g were selected as reference points, based on previous literature.31–32 HRs of stroke types for eGFR were estimated at each 1 mL/min per 1.73 m² from 15 to 120 mL/min per 1.73 m². HRs for ACR were estimated at every 8% increase of ACR from 2.5 to 1000 mg/g. Overall P values for eGFR and ACR splines were obtained from the inverse variance average of the 6 spline linear coefficients for eGFR and the 4 linear spline coefficients for log-ACR, respectively.

When assessing differences in the strength of eGFR– and ACR–risk association between ischemic and hemorrhagic stroke, eGFR and log-ACR were modeled linearly. Differences in log-HRs were obtained by subtracting log-HRs for hemorrhagic strokes from the log-HRs for ischemic strokes. SEs for the differences in log-HRs were estimated by 1000 bootstrap of the difference of log-HRs.

We also evaluated the association of combined categories of eGFR and ACR according to the Kidney Disease: Improving Global Outcomes classification36 with both stroke types. Interaction between eGFR and ACR was assessed by likelihood ratio tests between the models with and without product terms of eGFR and ACR in the complete data set. P values for the differences were obtained using a Wald test. Statistical significance was considered as a 2-tailed P < 0.05. All statistical analyses were performed using Stata software version 11.2 (StataCorp LP; College Station, TX) and R software version 2.14.1.

Results
The Table depicts the characteristics of the 4 cohorts. Overall, 29,595 participants (mean age, 61 [SD 12.5] years; 46% men; 17% black) contributed to a total follow-up of 280,549 person-years. During average follow-up of 9.5 years, 1261 strokes occurred, of which 156 (12%) were classified as hemorrhagic. Participants of the Dutch (PREVEND) cohort, almost exclusively whites, were on average younger, less often hypertensive, and diabetic and had lower BMI and higher eGFR compared with the other 3 cohorts. However, the prevalence of current smoking and hyperlipidemia was higher in the PREVEND cohort.
Independent and Combined Associations of the Kidney Measures With Stroke Types

When the kidney measures were modeled continuously with spline terms, low eGFR was significantly associated with increased risk of ischemic stroke but not with hemorrhagic stroke (Figure 1). The association of low eGFR and hemorrhagic stroke started to increase only at eGFR ≤ 45 mL/min per 1.73 m² but did not reach statistical significance even at eGFR of 15 mL/min per 1.73 m². Relative to eGFR of 95 mL/min per 1.73 m², adjusted HRs for ischemic and hemorrhagic stroke at eGFR of 45 mL/min per 1.73 m² were 1.30 (1.01–1.68) and 0.92 (0.47–1.81), respectively. Nonetheless, difference in the association of continuous eGFR with ischemic versus hemorrhagic stroke was not significant (P for difference=0.69).

Similarly, when GFR was estimated with equations using either cystatin C or creatinine as filtration marker, differences in the association of eGFR between stroke types were not significant (Figure I in the online-only Data Supplement). The associations of eGFR remained similar, even when systolic blood pressure and antihypertensive drug use were dropped from the fully adjusted model (Figure II in the online-only Data Supplement).

In contrast, ACR was significantly positively associated with both types of stroke without any threshold effects (Figure 1). The risk gradient was steeper for hemorrhagic stroke than for ischemic stroke. For example, the HRs for ischemic and hemorrhagic stroke at ACR of 300 mg/g compared with ACR of 5 mg/g were 1.62 (1.27–2.07) and 2.57 (1.37–4.83), respectively. The associations of ACR with both stroke types became even stronger when systolic blood pressure and antihypertensive drug use were dropped from the fully adjusted model (Figure II in the online-only Data Supplement). Furthermore, overall linear log-ACR was more strongly associated with hemorrhagic stroke than with ischemic stroke (P for difference=0.04).

When combined categories of eGFR and ACR were assessed, higher risk was generally observed for both ischemic and hemorrhagic stroke than for ischemic stroke. For example, the HRs for ischemic and hemorrhagic stroke at ACR of 5 mg/g compared with ACR of 30 mg/g were 1.62 (1.27–2.07) and 2.57 (1.37–4.83), respectively. The associations of ACR with both stroke types became even stronger when systolic blood pressure and antihypertensive drug use were dropped from the fully adjusted model (Figure II in the online-only Data Supplement). Furthermore, overall linear log-ACR was more strongly associated with hemorrhagic stroke than with ischemic stroke (P for difference=0.04).

When combined categories of eGFR and ACR were assessed, higher risk was generally observed for both ischemic and hemorrhagic stroke than for ischemic stroke. For example, the HRs for ischemic and hemorrhagic stroke at ACR of 5 mg/g compared with ACR of 3 mg/g were 1.62 (1.27–2.07) and 2.57 (1.37–4.83), respectively. The associations of ACR with both stroke types became even stronger when systolic blood pressure and antihypertensive drug use were dropped from the fully adjusted model (Figure II in the online-only Data Supplement). Furthermore, overall linear log-ACR was more strongly associated with hemorrhagic stroke than with ischemic stroke (P for difference=0.04).
there was no significant interaction between continuous eGFR and log-ACR (ischemic stroke: overall P for interaction = 0.66; hemorrhagic stroke: overall P for interaction = 0.50).

**Traditional Cardiovascular Risk Factors Versus Kidney Measures**

Generally, traditional cardiovascular risk factors showed significantly positive associations with ischemic stroke but not necessarily with hemorrhagic stroke (Figure 3A). Male sex, diabetes mellitus, history of cardiovascular disease, BMI, and cholesterol were inversely associated with hemorrhagic stroke, although only cholesterol reached significance (HR of 0.77 per 1-SD increase [95% confidence interval, 0.64–0.92; P = 0.003]). The HR differences between ischemic and hemorrhagic stroke were significant for cholesterol (P = 0.001), sex (P = 0.01), and BMI (P = 0.04).

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**Figure 1.** Adjusted associations of continuous estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) with ischemic and hemorrhagic strokes. **Top,** The association of the cystatin C and creatinine combined equation-based eGFR (eGFRCyCr) with ischemic (A) and hemorrhagic (B) strokes. **Bottom,** The association of ACR with ischemic (C) and hemorrhagic (D) stroke. ● represents the reference points (eGFR = 95 mL/min/1.73 m², ACR = 5 mg/g). Error bars denote 95% confidence intervals of the adjusted hazard ratios (HRs), and black circles denote P < 0.05 compared with the reference. HRs were adjusted for sex, age, black ethnicity, diabetes mellitus, current smoking, systolic blood pressure, total cholesterol, history of cardiovascular disease, body mass index, statins, antihypertensive drug use, and either eGFRCyCr or ACR as appropriate.

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**Figure 2.** Adjusted risk of ischemic (left) and hemorrhagic (right) stroke according to clinical categories of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR). The diamond sizes are proportional to the hazard ratio (HR) estimates with full cells corresponding to the highest HR (ie, HR = 3.2) and empty cells corresponding to HR = 1.0 or no data. HRs were adjusted for sex, age, black ethnicity, diabetes mellitus, current smoking, systolic blood pressure, total cholesterol, history of cardiovascular disease, body mass index, statins, and antihypertensive drug use. The dark-gray diamond color corresponds to P < 0.05. eGFRCyCr indicates cystatin C and creatinine combined equation-based eGFR.
To facilitate comparison between kidney measures and cardiovascular risk factors, kidney measures were modeled per SD difference and as binary variables (eGFR < 60 [versus ≥ 60 mL/min per 1.73 m²], ACR ≥ 30 [versus < 30] mg/g, and their combination [CKD versus non-CKD]; Figure 3B). Among the continuous traditional predictors, age was most strongly associated with both stroke types, followed by systolic blood pressure. Compared with systolic blood pressure, log-ACR was slightly less strongly associated with ischemic stroke (HR per 1-SD increment, 1.30 [95% confidence interval, 1.23–1.38] versus 1.17 [1.11–1.24]) but was more strongly associated with hemorrhagic stroke (1.25 [1.16–1.35] versus 1.39 [1.29–1.50]). HR per 1-SD lower eGFR (1.09 [95% confidence interval, 1.02–1.17] versus 1.39 [1.29–1.50], when both were modeled together along with other confounders. HR per 1-SD lower eGFR (1.09 [95% confidence interval, 1.02–1.17]) was only significant for ischemic stroke in a magnitude similar to total cholesterol (HR per 1-SD decrement, 1.07 [95% confidence interval, 1.01–1.14]). The HR for elevated ACR (ie, ≥30 versus <30 mg/g) was comparable with that for diabetes mellitus and history of cardiovascular disease for ischemic stroke but was higher for hemorrhagic stroke. This association of ACR with stroke types was largely consistent across the cohorts (Figure 3B in the online-only Data Supplement).

**Discussion**

In this pooled analysis of 4 population-based prospective cohorts with 29,595 participants experiencing 1,261 strokes during 280,549 person-years of follow-up, both lower eGFR and higher albuminuria were associated with higher risk of ischemic stroke independently of each other and traditional stroke risk factors. In contrast, only higher albuminuria, but not lower eGFR, was significantly associated with increased risk of hemorrhagic stroke. Of note, at a given level of elevated albuminuria, HRs were significantly greater for hemorrhagic stroke compared with ischemic stroke. The association of albuminuria with increased risk of hemorrhagic stroke was independent of potential confounders, including blood pressure.

Several studies have documented a positive association of albuminuria with ischemic stroke. In a recent meta-analysis of 13 studies, risk of ischemic stroke was 2-fold in subjects with microalbuminuria compared with subjects with normoalbuminuria. In contrast, data on hemorrhagic stroke are limited because only 1 prospective study was identified in the aforementioned systematic review. In that study with a total of 49 hemorrhagic strokes, ascertained from hospital discharge registries of Norfolk (United Kingdom), the association of albuminuria with increased risk of hemorrhagic stroke was independent of potential confounders, including blood pressure.
was modeled continuously, implicating limited power for categorical ACR analysis.

In our pooled analysis, notably the association of albuminuria with hemorrhagic stroke was stronger than with ischemic stroke. This association was independent of blood pressure, and the strength of association was comparable with systolic blood pressure. A plausible explanation for this observation may include a suggestion that albuminuria might be particularly reflecting damage of strain vessels that are abundantly present not only in the kidneys but also in the brain. In fact, an association of albuminuria with increased risk of deep or infratentorial microbleeds, which anatomically correspond with the brain strain vessels, has been reported. It could be argued that blood pressure may be in the causal pathway for the association of kidney measures with stroke, and therefore adjustment for blood pressure may have resulted in conservative estimates. The relative risks of both stroke types for albuminuria became higher when systolic blood pressure and antihypertensive drug use were dropped from the model (Figure II in the online-only Data Supplement).

Regarding the association with stroke, kidney function has been more intensively assessed compared with albuminuria. In a meta-analysis of 21 studies addressing the association of eGFR (based on the Modification of Diet in Renal Disease study or Cockcroft–Gault equations) with stroke, eGFR <60 mL/min per 1.73 m² was associated with a 43% risk increase of overall unspecified stroke compared with the reference eGFR (generally ≥60 or ≥90 mL/min per 1.73 m²). No differences in the strength of associations with ischemic versus hemorrhagic stroke were observed in a subgroup analysis of studies that reported separate estimates for ischemic (6 studies) and hemorrhagic (3 studies) stroke. However, none of these studies conducted head-to-head comparisons of the 2 stroke types, and the pooled estimate for the association of eGFR with hemorrhagic stroke did not reach statistical significance in this meta-analysis. Similarly, our pooled analysis showed no significant difference in the HRs associating eGFR with hemorrhagic versus ischemic stroke, although only the association with ischemic stroke was statistically significant. The lack of a significant association of eGFR with hemorrhagic stroke needs to be interpreted with caution in light of relatively limited statistical power for hemorrhagic stroke.

The association of decreased eGFR with increased stroke risk may be explained by its association with atherosclerosis, atrial fibrillation, and cerebral small-vessel disease. Although we used the best available equation incorporating creatinine and cystatin C for our primary analysis, the association of eGFR with ischemic stroke was weaker for eGFR based on creatinine compared with eGFR based on cystatin C (Figure I in the online-only Data Supplement), suggesting the involvement of non-GFR determinants surrounding creatinine and cystatin C. In fact, stronger relationships to other cardiovascular end points have been previously reported for cystatin C levels compared with creatinine-based eGFR.

Our study extended previous literature in various aspects. First, we used state-of-the-art equations for eGFR, which improves estimation of measured GFR and risk prediction of clinical outcomes. Second, our analysis fully accounted for traditional cardiovascular risk factors and both key kidney measures, whereas only 2 previous studies investigated both kidney measures simultaneously. Third, stroke was verified by an independent committee in 3 of the 4 cohorts. Fourth, we explored the eGFR and albuminuria association with both types of stroke in various categorical and continuous analyses. Fifth, unlike the previous meta-analysis of eGFR and albuminuria associations with stroke, our analyses used the same adjustment variables and the same reference range across the 4 studies.

Several limitations of this study warrant acknowledgment. First, some studies measured albumin in fresh urine samples, whereas other studies used frozen samples, and single centralized laboratory was not used by all studies. Care was taken, however, to use the same definitions for exposure variables. Regardless, any misclassification because of nonstandardization is likely to result in underestimation of the exposure–risk relationship. Second, information was not available on anticoagulant and antplatelet medication use, which may be associated with higher risk of hemorrhagic stroke. However, the association of albuminuria with hemorrhagic stroke was independent of conditions predisposing to the use of these drugs, such as history of cardiovascular disease and diabetes mellitus.

Third, although we adjusted for various cardiovascular risk factors, residual confounding cannot be completely ruled out. Fourth, the comparison of kidney measure versus traditional cardiovascular risk may be hampered by the differences in distributions and prevalence of the risk factors. Despite these limitations, this report is the most comprehensive analysis on the association of kidney disease measures with stroke types.

In conclusion, decreased eGFR showed comparable risk gradients for both stroke types, although statistical significance was only observed for ischemic stroke. In contrast, elevated albuminuria was significantly associated with increased risk of both ischemic and hemorrhagic strokes, with quantitatively stronger relationship with hemorrhagic stroke. Notably, the association of albuminuria with hemorrhagic stroke was independent of and at least as strong as for systolic blood pressure, one of the most potent risk factors for this stroke type, suggesting that kidney damage, systemic vessel strain, or both play an important role in the pathophysiology of hemorrhagic stroke. The strong association of albuminuria with both stroke types warrants clinical attention and further investigations.

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SUPPLEMENTAL MATERIAL

Supplement to: Association of kidney disease measures with ischemic versus hemorrhagic strokes: Pooled analyses of 4 prospective community-based cohorts.
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METHODS

Study characteristics

Details of the study protocols of the four studies included in the current analyses have been published elsewhere.\textsuperscript{1-4} In short, the ARIC study enrolled middle-aged (45-64 years) predominantly whites and blacks from four US communities between 1987 and 1989. Since serum cystatin C and albuminuria were only measured at the fourth visit (1996-1998), the fourth visit was considered baseline in the current analysis. Similarly CHS enrolled white and black participants in late 1980s and early 1990s, but first measured serum cystatin C and albuminuria at visit 9 (1996-1997); hence visit 9 served as the baseline. In contrast, the MESA and PREVEND studies measured cystatin C and albuminuria at their initial visits. The MESA study enrolled individuals of multiple ethnicities (whites, blacks, Hispanics, and Asians) who were 45-84 years of age and free of cardiovascular disease at baseline (2000-2002). The PREVEND study was established to assess the association of CKD with cardiovascular and renal disease in the general Dutch population of 28-76 years of age at baseline (1997-1998).

Kidney disease measures

In all studies cystatin C was measured by particle-enhanced immunonephelometric assay (N Latex Cystatin C) with a nephelometer (BNII) provided by Dade Behring/Siemens. In each cohort, measured cystatin C was calibrated to standardized serum cystatin C. Since the creatinine equation requires serum creatinine standardized to isotope dilution mass spectrometry (IDMS), we utilized a previously established calibration factor, which reduces creatinine levels by 5%.\textsuperscript{5}

Stroke types

Because only incident strokes were considered in these pooled analyses of four cohorts, participants with prevalent stroke at baseline were excluded. Strokes ascertainment methods for the three US cohorts consisted of telephone contacts every half (CHS) or every year (ARIC,
MESA) to identify hospitalizations and obtain medical charts for review by stroke adjudication committees. In addition hospital discharge records were screened for stroke diagnosis and neurologic symptoms suggestive stroke. Stroke adjudication committees existed of trained physicians including radiologists and neurologists. Details on the stroke ascertainment for each study have been described elsewhere. The PREVEND cohort was annually linked to Dutch vital statistics and national Dutch hospital discharge records using International Classification of Diseases coding.

**Statistical analysis**

Participants were excluded if demographics or measurements of all three kidney measures (i.e., cystatin C, creatinine and albuminuria) were missing. For all other participants, missing values of the kidney measures and potential confounders were imputed using stochastic multiple imputations using the chained-equation method. Using this method, a total of 10 datasets with imputed values were created. Gender, race, age, hypertension, diabetes, systolic and diastolic blood pressure, hypercholesterolemia, cholesterol, BMI, antihypertensive drugs and statins use, eGFRs based on creatinine, cystatin C, and both, log ACR, log follow-up time and the two stroke types were included in the multiple imputations.
Supplemental Figure I. Adjusted associations of continuous eGFR with ischemic and hemorrhagic strokes.

Top panels show the association of creatinine-based eGFR with ischemic (A) and hemorrhagic (B) strokes. Bottom panels displays the association of cystatin C-based eGFR with ischemic (C) and hemorrhagic (D) stroke. Diamond represents the reference points (eGFR=95 mL/min/1.73m², ACR=5 mg/g). Error bars denote 95% CIs of the adjusted hazard ratios, and the blue and red circles denote P <0.05 compared to the reference (diamond). Hazard ratios were adjusted for sex, age, black ethnicity, diabetes, current smoking, systolic blood pressure, total cholesterol, history of cardiovascular disease, body mass index, statins, antihypertensive drug use, and ACR.
Supplemental Figure II. Associations of continuous eGFR and ACR with ischemic and hemorrhagic strokes without adjustment for systolic blood pressure and antihypertensive medication use.

Top panels show the association of the creatinine and cystatin C combined equation based eGFR with ischemic (A) and hemorrhagic (B) strokes. Bottom panels display the association of ACR with ischemic (C) and hemorrhagic (D) stroke. Diamonds represent the reference points (eGFR=95 mL/min/1.73m², ACR=5 mg/g). Error bars denote 95% CIs of the adjusted hazard ratios, and the blue and red circles denote P <0.05 compared to the reference. Hazard ratios were adjusted for sex, age, black ethnicity, diabetes, current smoking, total cholesterol, history of cardiovascular disease, body mass index, statins use, and either eGFR_{CyCr} or ACR as appropriate. eGFR_{CyCr} = cystatin C and creatinine combined equation based estimated glomerular filtration rate; ACR= albumin-to-creatinine ratio.
Supplemental Figure III. Study-specific associations of eGFR and albuminuria with ischemic and hemorrhagic strokes.

HRs are for the association of eGFR <60 vs. ≥60 mL/min/1.73m$^2$ (top panel) and ACR ≥30 versus <30 mg/g (bottom panel) with hemorrhagic (red error-bars) or ischemic (blue error-bars) strokes. Hazard ratios are adjusted for sex, age, black ethnicity, diabetes, current smoking, systolic blood pressure, total cholesterol, history of cardiovascular disease, body-mass index, statins, antihypertensive drug use, and either eGFR$_{CyCr}$ or ACR as appropriate. The sizes of the boxes around the hazard ratios estimates are proportional to the inverse of the hazard ratios variances.
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