Impairment in Glomerular Filtration Rate or Glomerular Filtration Barrier and Occurrence of Stroke

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**Background:** Chronic kidney disease (CKD) is associated with substantial burden and is a strong risk factor for cardiovascular disease. However, data on the relationship between CKD and stroke are few and are limited by unreliable or inadequate assessment of renal function.

**Objective:** To properly assess the relationship between renal insufficiency and stroke in stroke survivors in the United States by simultaneously examining the effect of guideline-recommended indices of renal disease that measure glomerular filtration rate (creatinine clearance) and glomerular filtration barrier (proteinuria).

**Design:** Cross sectional.

**Setting:** Nationally representative survey of the United States.

**Subjects:** Participants aged 55 or older who participated in the National Health and Nutrition Examination Survey from 1999 to 2004.

**Main Outcome Measures:** Indices of renal disease that measure glomerular filtration rate (creatinine clearance) and glomerular filtration barrier (microalbuminuria).

**Results:** Of 6382 adults who met inclusion criteria, 5624 (88%) had full and complete data, of which 414 (6%) reported having had a stroke. Stroke survivors were older and more likely to have CKD, diabetes, hypertension, coronary artery disease, elevated blood pressure, increased glycohemoglobin concentration, and lower hematocrit compared with respondents who did not report stroke. Multivariate models showed that microalbuminuria (odds ratio, 1.51; 95% confidence interval, 1.02-2.24), decreased glomerular filtration rate (odds ratio, 1.93; 95% confidence interval, 1.28-2.91), and stage 3 CKD (odds ratio, 2.09; 95% confidence interval, 1.38-3.16) were significantly associated with stroke.

**Conclusion:** Stroke is independently associated with impairment in structure and function of the glomerulus, which supports the need to consider screening patients with stroke for CKD and to simultaneously assess for both indices of renal disease.

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Although the incidence of chronic kidney disease (CKD) is increasing, this disease often is undetected in clinical settings. This is particularly worrisome in the setting of vascular disease because the prevalence of CKD is higher among persons with cardiovascular disease than in the general population and CKD is an independent risk factor for recurrent cardiovascular disease and death. Early identification of undiagnosed CKD could enable initiation of treatment geared toward limiting further renal function deterioration and reducing the risk of adverse vascular sequelae. The American Heart Association recently issued an advisory recommending that all patients with atherosclerotic disease be screened for undiagnosed chronic renal insufficiency and provided guidance about the best validated clinical measures of renal function to use for this purpose.

The association between indices of renal dysfunction and stroke outcomes has not been broadly examined, and the few available data are from studies that either used somewhat unreliable renal function measures or did not account for the impairment of both glomerular filtration rate (GFR) and glomerular filtration barrier. For example, although a link between higher serum creatinine concentration and greater risk of stroke has been suggested, measurements of serum creatinine concentration can be inaccurate, and renal measures that consider age and sex have been deemed by experts to be preferable. Furthermore, most studies that evaluated the effect of renal insufficiency on stroke risk measured either kidney function or structure (ie, estimated GFR) or proteinuria, not both, although only a minority of individuals with proteinuria have a low GFR, and vice versa. A study from Japan assessed the associa-
tion of both GFR and proteinuria with stroke, but the method of estimating renal function used is less informative than the recommended Modification of Diet in Renal Disease formula and the index of proteinuria used macroalbuminuria detected by a semiquantitative dipstick, which can be inaccurate and would not detect individuals with microalbuminuria. The objective of the present study was to properly assess the relationship between renal insufficiency and stroke in stroke survivors in the United States by simultaneously examining the effect of guideline-recommended indices of renal disease that measure GFR (creatinine clearance) and glomerular filtration barrier (microalbuminuria).4

METHODS

SUBJECTS

The Centers for Disease Control and Prevention conducted the National Health and Nutrition Examination Surveys (NHANES) in 1999-2000, 2001-2002, and 2003-2004 to estimate the prevalence of common chronic conditions and associated risk factors in a nationally representative sample of the civilian, noninstitutionalized US population. The surveys included oversampling of individuals with low income, those aged 12 to 19 years or older than 60 years, and African Americans and Mexican Americans.

The present study sample included only subjects aged 55 or older who participated in the NHANES from 1999 to 2004. Because the incidence of stroke begins to double for every decade after age 55 years, this older age cutoff was chosen to include persons more likely to have had a stroke and to reduce the percentage of persons having strokes due to unusual causes, often seen at younger ages. The NHANES detailed interview included demographic, dietary, health-related, and socioeconomic questions. The clinical component consisted of laboratory tests, physiologic measurements, and medical and dental examinations. During the household interview, participants were asked whether a physician had ever told them that they had had a stroke; persons who answered in the affirmative were defined as having the condition. All data were obtained once at the time of the survey.

STATISTICAL ANALYSIS

The NHANES data sets were downloaded from the National Center for Health Statistics website (http://www.cdc.gov/nchs) for the survey years 1999-2000, 2001-2002, and 2003-2004. Clinical, demographic, and biomarker data were analyzed on the basis of previous English-language medical literature reporting major stroke risk factors. The demographic variables analyzed included age, sex, and race/ethnicity. Medical history variables studied included smoking status, hypertension, diabetes mellitus, coronary artery disease, and hypercholesterolemia. Biomarkers evaluated included hematocrit, body mass index, systolic blood pressure, total cholesterol concentration, and glycohemoglobin and homocysteine levels, assessed as continuous and dichotomized (target levels) measures. Glomerular filtration rate was calculated from the plasma creatinine concentration using the recommended adjustment for the survey years 1999-2000 (new value = 0.147 + 1.013 × old value). The Modification of Diet in Renal Disease formula for GFR calculation was taken from the National Kidney Disease Education Program website (available at http://www.nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm) and was GFR (mL/min/1.73 m²) = 186 × (Sₐ`)⁻¹.²¹⁴ × (age)⁻².⁰³⁷ × (0.⁷⁴² if female) × (1.210 if African American) (conventional units). Where Sₐ` indicates serum creatinine level. Several individual values were entered at the website and compared for validation. In addition, the urinary albumin to creatinine ratio was analyzed. “Abnormal GFR” was defined as a value less than 60 mL/min/1.73 m². “Abnormal urine albumin to creatinine ratio” was defined as a value greater than 30 mg per g of creatinine. The association of kidney disease severity with stroke using the National Kidney Foundation guidelines was also assessed, as follows: stage 1, microalbuminuria with a GFR greater than or equal to 90 mL/min/1.73 m²; stage 2, microalbuminuria with a GFR from 60 to 89 mL/min/1.73 m²; stage 3, a GFR from 30 to 59 mL/min/1.73 m² regardless of the presence of microalbuminuria; stage 4, a GFR from 15 to 29 mL/min/1.73 m² regardless of the presence of microalbuminuria; and stage 5, a GFR less than 15 mL/min/1.73 m² regardless of the presence of microalbuminuria. Stages 1 and 2 and stages 4 and 5 were combined for this analysis.

Data analysis was performed using commercially available software (SAS version 9.1; SAS Institute, Inc, Cary, North Carolina). The analysis accounted for weighting, clustering, and stratification according to the NHANES Analytic and Reporting Guidelines. Multivariate logistic regression analysis was used to evaluate vascular risk factors associated with the occurrence of stroke. The primary reported statistics are the estimated odds ratios.

RESULTS

Among 6382 adults aged 55 years or older surveyed from 1999 to 2004 in NHANES, 5624 (88%) responded to the interview question about stroke and had valid laboratory data for creatinine clearance. Of these respondents, 414 (6%; 43% men; and 79% non-Hispanic white) reported occurrence of a stroke. More subjects with a GFR less than 60 mL/min/1.73 m² reported stroke occurrence compared with those with a GFR of 60 mL/min/1.73 m² (12.82% vs 4.72%; P < .001), and stroke occurred more frequently in those with a urinary albumin to creatinine ratio greater than 30 mg per 1 g of creatinine compared with those with levels of 30 mg per 1 g of creatinine or lower (11.39% vs 4.80%; P < .001). Reported stroke seemed to increase with a decreasing level of GFR (P < .001): 3.60% in those with a GFR of 90 mL/min/1.73 m² or greater, 6.38% in those with a GFR of 45 to 89 mL/min/1.73 m², and 15.73% in those with a GFR of 45 mL/min/1.73 m² or less. A breakdown of the study sample by frequency of National Kidney Foundation kidney disease severity stage was as follows: stages 1 and 2, 79.33%; stage 3, 16.04%; and stages 4 and 5, 1.13%.

In general, stroke survivors were older and more likely to have hypertension, diabetes mellitus, elevated blood pressure, coronary artery disease, elevated glycohemoglobin and homocysteine levels and albumin to creatinine ratio, as well as low GFR, hematocrit, and cholesterol concentration, compared with respondents not reporting stroke (Table 1). The multivariate model including both low GFR and microalbuminuria as indices of renal disease showed that older age; low GFR; the presence of hypertension, coronary artery disease, and microalbuminuria; and an elevated systolic blood pressure were all statistically significantly associated with stroke (Table 2). A test of interaction in this multivariate model for GFR times urinary albumin to creatinine ratio was not significant (P = .35). A separate multivariate model using dichotomized measures rather than continuous measures of the 6 biomarker covariates also showed significant associations with stroke: GFR <60 mL/min/
In this nationally representative cohort of the United States, reduced serum creatinine clearance and elevated microalbuminuria level were independently associated with stroke. Unlike most of the previous studies that examined the relationship between CKD and stroke, the present study simultaneously assessed the effect of well-validated clinical measures of both kidney structure and function on the occurrence of stroke in accord with the recommendations of consensus guidelines for detecting CKD in the general population and in patients with or at risk of vascular disease.\(^1\,\,2,\,21,\,22\) The results of the present study strongly reinforce data from the few previous studies that demonstrated an association between various indices of CKD vs stroke risk but further indicate that any screening of CKD in patients who have had a stroke should include assessment of impairment of both glomerular structure and function. 

Previous data have linked a low GFR to increased stroke risk.\(^9\,\,14\) The present study also categorized kidney disease severity according to the National Kidney Foundation guidelines yielded similar associations of stroke with the classic vascular risk factors but also revealed stage 3 kidney disease severity to be independently associated with stroke (Table 3).
severity using National Kidney Foundation staging guidelines and found that stroke was twice as likely to occur in individuals with stage 3 disease severity than in those with stages 1 and 2 disease severity. The relationship between stroke occurrence and stages 4 and 5 disease severity closely approached statistical significance, but it may have been limited by the relatively small sample size. Even fewer studies have examined the relationship between albuminuria and stroke.23-25 Although these studies have tied the presence of albuminuria with stroke risk, many included only patients of a particular sex or racial/ethnic group, and the less accurate method of urine dipstick screening was used to assess proteinuria.21,22 However, the relationship between microalbuminuria and stroke was prospectively studied in a British population that found that microalbuminuria is associated with a 50% increased risk of stroke,25 the same as that found in the present study. A small, prospective, case-control study assessed the association of microalbuminuria with recurrent stroke risk and found that after controlling for major clinical risk factors, microalbuminuria remained an independently significant predictor of future stroke.10

Screening patients with stroke for CKD could be useful for several reasons. Detecting undiagnosed CKD may serve as a prognosticator in further identifying those patients with stroke who are at high risk of recurrent vascular events, thereby alerting clinicians and patients to undertake aggressively optimizing proved vascular risk reduction strategies. Most patients with a GFR of 60 mL/min/1.73 m² tend to die of cardiovascular causes and not progression to end-stage renal disease; thus, averting vascular events in these patients should be a primary goal.20 For example, angiotensin-converting enzyme inhibitors reduce the high rate of cardiovascular events in patients with mild renal insufficiency27 and could be part of a multipronged therapeutic approach. Beyond identifying those unusual individuals with severe CKD who may benefit from dialysis,9 those with mild CKD might benefit from therapies that can limit the progression of renal disease.4 Treatment with statins seems to reduce proteinuria modestly, resulting in a small reduction in the rate of loss of renal function.26 There is also evidence that angiotensin-converting enzyme inhibitors, apart from preventing vascular events, may improve renal outcomes in renal insufficiency, particularly in the presence of proteinuria.28,29 Clinicians caring for patients with stroke may not have to perform calculations each time they see a patient. Many laboratories around the United States routinely report estimated GFR using the Modification of Diet in Renal Disease formula along with serum creatinine concentration to enhance early detection of CKD as recommended by the National Kidney Disease Education Program, National Kidney Foundation, and the American Society of Nephrology.1,21,22

Although both GFR and microalbuminuria were independently associated with stroke in the present study, the association was stronger for GFR. Nevertheless, experts maintain that assessing microalbuminuria along with GFR is important because obtaining urine samples is relatively simple; albuminuria has consistently been shown to be a potent independent marker of vascular risk; sometimes outgrowing the predictive strengths of other classic vascular risk factors; and development of albuminuria often precedes a decrease in GFR.20 Furthermore, albuminuria may be an expression of generalized endothelial dysfunction; several studies have shown a correlation between microalbuminuria and endothelial dysfunction in peripheral blood vessels.26

Multiple explanations have been proposed for the association of CKD with vascular risk.26 Reduction in kidney function is often linked with prevalence of other less classic vascular risk factors such as anemia, oxidative stress, electrolyte imbalances, and hyperhomocysteinemia.26 Reduced kidney function may also reflect both the duration and severity of other cardiovascular conditions such as hypertension or may bolster the adverse effects of anemia, hypertension, and chronic inflammation. Chronic kidney disease is associated with higher levels of uremic toxins that inhibit synthesis of nitric oxide,30 which has effects that include promoting vasodilation and neurotransmission and inhibiting smooth muscle cell proliferation.31

The present study has limitations. First, it was based on a cross-sectional survey, thereby limiting any causal inferences. Second, NHANES did not differentiate stroke subtypes, and inasmuch as only stroke survivors were surveyed, the study sample was probably overenriched with ischemic strokes because of the higher risk of associated mortality with hemorrhagic stroke. Furthermore, the cutoff age of 55 years likely excluded several individuals with rare causes of stroke. However, because ischemic stroke generally accounts for about 85% of overall strokes and most of these strokes occur after age 55 years, the effects of such

### Table 3. Multivariate Logistic Regression Analysis for Variables Associated With Stroke Including NKF Stages of Chronic Renal Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>1.38 (0.10-2.60)</td>
<td>0.07</td>
</tr>
<tr>
<td>75-84</td>
<td>2.22 (1.35-3.65)</td>
<td>0.002</td>
</tr>
<tr>
<td>≥85</td>
<td>1.93 (0.99-3.83)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.02 (0.71-1.45)</td>
<td>0.93</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.46 (0.93-2.30)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.06 (1.52-2.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.18 (1.37-3.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.91 (0.76-1.36)</td>
<td>0.92</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>1.10 (0.78-1.55)</td>
<td>0.59</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.01 (1.00-1.02)</td>
<td>0.003</td>
</tr>
<tr>
<td>BMI</td>
<td>0.10 (0.97-1.03)</td>
<td>0.96</td>
</tr>
<tr>
<td>Total cholesterol concentration, mg/dL</td>
<td>1.00 (1.01-1.00)</td>
<td>0.85</td>
</tr>
<tr>
<td>Glycohemoglobin, %</td>
<td>1.12 (0.99-1.28)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>0.10 (0.74-1.43)</td>
<td>0.86</td>
</tr>
<tr>
<td>Homocysteine, µmol/L</td>
<td>0.10 (0.97-1.02)</td>
<td>0.68</td>
</tr>
<tr>
<td>NKF kidney severity stage</td>
<td></td>
<td></td>
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<tr>
<td>1 and 2</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.09 (1.38-3.16)</td>
<td>0.005</td>
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<tr>
<td>4 and 5</td>
<td>2.33 (1.01-5.46)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CI, confidence interval; GFR, glomerular filtration rate; NKF, National Kidney Foundation; OR, odds ratio.

## SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; hematocrit to proportion of 1.0, multiply by 0.01.
stroke subtype selection biases may not be profound. Third, these data may underestimate the prevalence and strength of the association of CKD in patients with stroke because NHANES surveyed primarily generally healthy individuals. Fourth, NHANES has not validated self-reporting of stroke; however, several studies have shown self-reporting of stroke to have sensitivity of 80% to 95% and a specificity of 96% to 99%.32,33

In conclusion, using the best validated clinical indices of renal disease, the present study shows that chronic renal insufficiency is independently associated with stroke occurrence in older persons in a manner comparable to classic vascular risk factors and that both serum creatinine clearance and microalbuminuria are independently associated with stroke. These results in the context of previous data showing a link between 2 presumably related burdensome diseases should prompt consideration to include CKD screening in the routine assessment of patients with stroke.

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Additional Contributions: Dr Ovbiagele had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES