ORIGINAL RESEARCH

Proteinuria Is an Independent Risk Factor for First Incident Stroke in Adults Under Treatment for Hypertension in China

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***Background*—**Conflicting evidence exists regarding whether reduced estimated glomerular filtration rate (eGFR) and proteinuria are independent risk factors for stroke and its subtypes in hypertensive patients. This study investigated the association of these renal measures with first incident stroke in adults under treatment for hypertension in China.

***Methods and Results*—**The study included 19 599 adults aged 45 to 75 years who participated in the China Stroke Primary Prevention Trial. Baseline eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation. Proteinuria was assessed by qualitative dipstick urinalysis and in a subset by the quantitative albumin–creatinine ratio method. Cox regression analysis was used to examine the effects of eGFR and proteinuria on the risk of first incident stroke. During a median of 4.5 years of follow-up, a total of 585 first strokes (472 ischemic strokes) were identified. Compared to participants without proteinuria, participants with proteinuria (trace or more by dipstick) had a 35% increased risk of first stroke: the adjusted hazard ratio (HR) (95% CI) was 1.35 (1.09–1.66, P=0.005). The results were robust in subgroup analyses. In a subset with data on proteinuria measured by quantitative albumin–creatinine ratio, a similar association was found. In both independent and combined analyses with proteinuria, eGFR was not significantly associated with stroke.

***Conclusions*—**In adults under treatment for hypertension in China, baseline proteinuria measured by dipstick or quantitative albumin–creatinine ratio, but not reduced eGFR, was found to be an independent risk factor for first incident stroke and ischemic stroke. **(*J Am Heart Assoc*. 2015;4:e002639 doi: 10.1161/JAHA.115.002639)**

Key Words: albumin–creatinine ratio • Chinese hypertensive adults • estimated glomerular filtration rate • first incident stroke • proteinuria

In the past decade, growing evidence has suggested an association between low estimated glomerular filtration rate (eGFR) or the presence of protein in the urine (proteinuria or albuminuria) and risk of stroke.[1–5] Data are conflicting regarding whether reduced eGFR and proteinuria can be independent or joint risk factors for stroke and its subtypes in adults under treatment for hypertension.[6–8] The Hypertension Optimal Treatment (HOT) study found that reduced GFR is a risk factor of cardiovascular disease events in treated hypertensive patients.[6] However, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial[7] and the Japanese Trial to Assess

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Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) study[8] both showed that proteinuria but not eGFR at baseline constituted a strong risk factor for stroke or cardiovascular events, and revealed a prognostic value only in patients with a baseline eGFR <60 mL/min per 1.73 m^2. Most previous studies were conducted in Western countries, and none had stroke as the primary outcome. In addition, their generalizability to a Chinese population is uncertain.

Hypertension, chronic kidney disease (CKD), and stroke have become major disease burdens worldwide, and a high prevalence of these chronic diseases has been reported in China in recent years.[9,10] In 2012, a national survey reported that the prevalence of CKD was 10.8% with about 119.5 million adults aged 18 years or older diagnosed with CKD in China.[11] Stroke has been the leading cause of death in China for decades and confers astronomical clinical, public health, and economic burdens.[12] Moreover, high blood pressure affects 270 million Chinese,[13] can be both a cause and a consequence of CKD, and is the major risk factor for cardiovascular disease and stroke.[9] To our knowledge, no studies have investigated the independent and combined effects of eGFR and proteinuria on the risk of stroke in adults under treatment for hypertension using a large prospective cohort in China.

This study aimed to investigate whether baseline eGFR and proteinuria are independent and/or joint risk factors for first incident stroke in adults under treatment for hypertension during a median 4.5-year prospective follow-up in China.

Methods

Study Population and Design

This is an ancillary study of the China Stroke Primary Prevention Trial (CSPPT). The CSPPT study was a randomized, double-blind clinical trial to test the primary hypothesis that therapy with enalapril and folic acid is more effective in reducing first stroke than enalapril alone among Chinese adults with hypertension. Details on the CSPPT study design, inclusion/exclusion criteria, and participant characteristics can be found online (http://clinicaltrials.gov, NCT00794885); the main results were recently published (Huo et al, JAMA, 2015).[14] In brief, a total of 20 702 participants aged 45 to 75 years old who had hypertension, defined as either systolic blood pressure of 140 mm Hg or greater, or diastolic blood pressure of 90 mm Hg or greater, or were using antihypertensive medications, were recruited from 32 communities in the Jiangsu and Anhui provinces of China from May 19, 2008 to August 2009. All participants provided written informed consent prior to data collection. This study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China (FWA assurance number FWA00001263).

Follow-up

Participant follow-up was conducted every 3 months by trained research staff and physicians and occurred until August 24, 2014 (a median of 4.5 years). A total of 67 (0.3%) were lost to follow-up before completion of the study.

For this study, data from 19 599 participants were analyzed (all from the CSPPT) after excluding 1103 subjects with missing serum creatinine and dipstick proteinuria measurements at baseline. There was no significant difference in major baseline characteristics, including sex, age, and eGFR between included and excluded participants.

Measurements and Definitions

Baseline information on lifestyle habits, sociodemographic variables, and medical history was obtained during in-person interviews by trained research staff according to a standard protocol. Smoking and drinking status was determined by self-report (never, former, and current). Anthropometric and blood pressure measurements were taken using standard operating procedures. Fasting serum glucose, fasting lipids, homocysteine, and serum creatinine were measured using automatic clinical analyzers (Beckman Coulter) at the core lab of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. Serum creatinine concentrations were determined by an enzymatic method (sarcosine oxidase–PAP) using a commercial kit, standardized to isotope dilution mass spectrometry, with a coefficient of variation of 1.1%. Serum folate was measured at a commercial laboratory using a chemiluminescent immunoassay (New Industrial).[14] Proteinuria was assessed by qualitative dipstick urinalysis using an automatic urine analyzer (Dirui-H100; Changchun DIRUI Medical Technology Co., Ltd, Jilin, China) and, in a subset of the study population, spot urine samples collected at the baseline clinical examination were analyzed by the quantitative method for calculating the urinary albumin-to-creatinine ratio (ACR). Urinary albumin levels were determined using an automatic protein analyzer (BN II; Dade Behring) and urinary creatinine levels were determined using an automatic biochemical analyzer (Dimension RxL Max; Dade Behring). Baseline eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15] Body mass index was calculated as weight in kilograms divided by height in meters squared. Diabetes mellitus was defined as self-reported physician-diagnosed diabetes or use of hypoglycemic agents or a fasting blood glucose concentration ≥7.0 mmol/L.

End Points

The primary outcome of interest was first incident symptomatic stroke (nonfatal or fatal) occurring between baseline and follow-up (a median of 4.5 years). As detailed in a recent report (Huo, JAMA, 2015, Supplement 1),[14] all stroke cases were adjudicated by experts of the end point adjudication committee using predefined criteria. Incident stroke types were divided into ischemic stroke and hemorrhagic stroke. Participants with hemorrhagic stroke included those with intraparenchymal hemorrhages but excluded those with subarachnoid hemorrhages.

Statistical Analysis

Continuous variables are reported as mean±SD. Prevalences are presented as percentages. We examined the linear trend distributions of the selected risk factors according to the 3 categories of dipstick proteinuria and eGFR. Because urinary ACR had a highly skewed distribution, the values were log-transformed before analysis. Baseline eGFR values were divided into 3 categories: ≥90, 60–89, and <60 mL/min per 1.73 m^2 based on standard definitions, and then were further divided into ≥90 and <90 mL/min per 1.73 m^2. We considered dipstick proteinuria as a categorical variable and hazard ratios (HRs) were calculated for each category: none, trace (±), + or more; we then combined the "trace" and "+ or more" categories for further analysis. In a sensitivity analysis, we considered an alternate definition of proteinuria that was based on urinary ACR and defined as <30 mg albumin/g creatinine (normal to mildly increased), 30 to 300 (moderately increased), and >300 (severely increased).[16] In a seperate analysis, we treated the group with eGFR ≥90 mL/min per 1.73 m^2, proteinuria "none" or ACR <30 mg/g as the referent. In the combined analyses, we defined a composite variable combining the eGFR (≥90, <90 mL/min per 1.73 m^2) and dipstick proteinuria ("none," "trace or more") or ACR (<30, ≥30 mg/g) categories. We treated the group with both eGFR ≥90 mL/min per 1.73 m^2 and dipstick proteinuria "none" or ACR <30 mg/g as the referent.

The relationships between baseline eGFR, proteinuria, and stroke types were assessed using Cox-proportional hazard models. We constructed 2 models: Model 1 was adjusted for age, study center (Jiangsu, Anhui), sex (male or female), and treatment group (enalapril or enalapril and folic acid group); Model 2 was adjusted for the same variables as Model 1 plus the following confounders: smoking and alcohol consumption status (never, former, and current), body mass index, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at baseline, mean SBP and DBP over the treatment period, baseline serum total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, homocysteine, folate, and either eGFR or proteinuria. We also evaluated whether risk of stroke increased with low eGFR estimated by using a modified Modification of Diet in Renal Disease (MDRD) equation for a Chinese population (Chinese equation) and the CKD-EPI 4-level race equation.[17] All P values were 2-tailed. A $P<0.05$ was considered to be statistically significant. All analyses were performed using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc, Boston, MA) and R (http://www.R-project.org).

Results

General Characteristics

Baseline eGFR and dipstick proteinuria levels were available for 19 599 participants. A subset of 3217 (15.8%) participants had an ACR measurement of proteinuria. At baseline, mean age was 60 years (SD 7.5) and 59% were female. Baseline characteristics of participants according to eGFR levels and dipstick proteinuria categories are listed in Table 1. The proportions with an eGFR of ≥90, 60 to 89, and <60 mL/min per 1.73 m^2 were 68%, 30%, and 2%, respectively. The numbers of participants according to the presence of proteinuria were as follows: 16 633 (85%) of participants without detectable proteinuria, 1812 (9%) of participants with proteinuria "trace," and 1154 (6%) with proteinuria "+ or more." Participants in the lower eGFR categories were more likely to be older and former or current smokers and former drinkers. In addition, they were more likely to have higher baseline SBP, homocysteine, and total cholesterol and have lower body mass index and folate levels. The eGFR levels were lower in participants with proteinuria than in nonproteinuric participants. Patients with proteinuria "trace or more" were older and showed higher mean values of SBP and DBP, glucose levels, homocysteine, and folate, as well as had a higher prevalence of diabetes mellitus and were former drinkers, but had lower total cholesterol (Table 1).

Independent and Combined Associations of eGFR and Proteinuria Levels With Incident Stroke

Table 2 shows the number of cases for the incidence of total and ischemic stroke for participants stratified by baseline eGFR and proteinuria categories. There were 585 total strokes during a median follow-up of 4.5 years. Of these, 472 (80.7%) were defined as ischemic, 111 (19.0%) were hemorrhagic, and 2 (0.3%) were undefined. In the unadjusted Cox regression analysis, compared to participants with an eGFR of at least 90 mL/min per 1.73 m^2, there was a significant increased risk of total stroke or ischemic stroke for the participants with

Table 1. Baseline Demographic Characteristics of the Study Population Stratified by eGFR and Dipstick Proteinuria

	Overall	Dipstick Proteinuria			*P* for Trend	eGFR, mL/min per 1.73 m^2			*P* for Trend
		None	Trace	+ or More		≥90	60 to 89	<60	
	n=19 599	n=16 633	n=1812	n=1154		n=13 418	n=5768	n=413	
Age, y	60.0±7.5	59.9±7.5	60.8±7.7	60.9±7.9	<0.001	57.9±6.8	64.4±7.0	65.3±7.2	<0.001
Male, n (%)	8006 (40.8)	6634 (39.9)	854 (47.1)	518 (44.9)	<0.001	5068 (37.8)	2740 (47.5)	198 (47.9)	<0.001
BMI,* kg/m^2	24.9±3.7	25.0±3.7	24.8±3.8	24.4±3.8	<0.001	25.1±3.7	24.6±3.7	24.2±3.6	<0.001
Systolic blood pressure, mm Hg	166.8±20.4	166.5±19.9	167.6±22.9	170.2±23.5	<0.001	166.2±19.8	168.1±21.5	170.9±23.5	<0.001
Diastolic blood pressure, mm Hg	94.1±11.9	93.9±11.7	94.7±12.6	95.6±13.9	<0.001	94.7±11.5	92.7±12.4	93.6±14.2	<0.001
Smoking, n (%)					0.039				<0.001
Never	13 525 (69.0)	11 552 (69.5)	1191 (65.7)	782 (67.9)		9636 (71.8)	3642 (63.2)	247 (59.8)	
Former	1466 (7.5)	1212 (7.3)	158 (8.7)	96 (8.3)		847 (6.3)	565 (9.8)	54 (13.1)	
Current	4603 (23.5)	3866 (23.2)	463 (25.6)	274 (23.8)		2932 (21.9)	1559 (27.0)	112 (27.1)	
Alcohol consumption, n (%)					0.053				0.003
Never	13 533 (69.1)	11 565 (69.5)	1185 (65.4)	783 (68.0)		9446 (70.4)	3805 (66.0)	282 (68.3)	
Former	1377 (7.0)	1131 (6.8)	141 (7.8)	105 (9.1)		824 (6.1)	496 (8.6)	57 (13.8)	
Current	4681 (23.9)	3931 (23.6)	486 (26.8)	264 (22.9)		3142 (23.4)	1465 (25.4)	74 (17.9)	
Diabetes mellitus,† n (%)	2167 (11.1)	1738 (10.4)	251 (13.9)	178 (15.4)	<0.001	1519 (11.3)	552 (9.6)	96 (23.2)	0.037
Laboratory results									
Total cholesterol, mmol/L	5.5±1.2	5.6±1.2	5.4±1.1	5.3±1.2	<0.001	5.5±1.2	5.6±1.2	5.9±2.0	<0.001
HDL cholesterol, mmol/L	1.3±0.4	1.3±0.4	1.3±0.4	1.3±0.4	0.020	1.3±0.4	1.4±0.3	1.3±0.4	<0.001
Homocysteine, μmol/L	14.4±8.3	14.3±8.3	15.4±9.0	15.5±±8.3	<0.001	13.2±7.1	16.7±9.8	22.7±12.9	<0.001
Folate, ng/mL	8.6±3.9	8.4±3.8	9.2±4.5	9.7±4.4	<0.001	8.7±3.9	8.2±3.8	8.0±4.1	<0.001
Fasting glucose, mmol/L	5.8±1.7	5.8±1.6	5.9±2.0	5.9±2.3	<0.001	5.8±1.8	5.7±1.4	6.3±2.5	0.019
eGFR, mL/min per 1.73 m^2	93.5±13.2	94.1±12.3	91.5±15.0	87.4±19.5	<0.001	100.4±6.9	80.7±7.5	48.8±11.2	<0.001
Dipstick proteinuria									<0.001
None	16 633 (84.9)					11 673 (87.0)	4719 (81.8)	241 (58.4)	
Trace	1812 (9.2)					1111 (8.3)	638 (11.1)	63 (15.3)	
+ or more	1154 (5.9)					634 (4.7)	411 (7.1)	109 (26.4)	

Values are presented as mean±SD for continuous variables and n (%) for categorical variables. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

*BMI was calculated as weight in kilograms divided by height in meters squared.

†Diabetes mellitus was defined as self-reported physician diagnosed diabetes or use of hypoglycemic agents or a fasting blood glucose concentration ≥7.0 mmol/L.

an eGFR of 60 to 89 mL/min per 1.73 m^2 (data not shown). However, after adjusting for age, sex, study center, and treatment group, there was no significant association between eGFR and total stroke (HR 1.12; 95% CI 0.93–1.35) or ischemic stroke (HR 1.07; 95% CI 0.87–1.32). Similarly, after multivariate adjustment, no independent associations were observed between eGFR and incident total and ischemic stroke. In unadjusted and adjusted analyses, there were no independent associations between eGFR <60 mL/min per 1.73 m^2 and total and ischemic stroke.

Table 2. Adjusted Hazard Ratios (95% CIs) for Incidence of Total and Ischemic Stroke by Baseline Dipstick Proteinuria and eGFR Categories

		Total Stroke			Ischemic Stroke		
			Hazard Ratio (95% CI)			Hazard Ratio (95% CI)	
	Number at Risk	Events (n/%)	Model 1	Model 2	Events (n/%)	Model 1	Model 2
Dipstick proteinuria category							
None	16 633	459/2.8	1.00	1.00	375/2.3	1.00	1.00
Trace or more	2966	126/4.2	1.77 (1.44, 2.17)	1.35 (1.09, 1.66)	97/3.3	1.78 (1.41, 2.23)	1.35 (1.06, 1.71)
Trace	1812	76/4.2	1.67 (1.31, 2.14)	1.29 (1.01, 1.67)	59/3.3	1.65 (1.25, 2.18)	1.28 (0.97, 1.70)
+ or more	1154	50/4.3	1.96 (1.45, 2.65)	1.45 (1.06, 1.97)	38/3.3	2.02 (1.43, 2.85)	1.47 (1.03, 2.09)
eGFR category, mL/min per 1.73 m^2							
≥90	13 418	354/2.6	1.00	1.00	283/2.1	1.00	1.00
<90	6181	231/3.7	1.12 (0.93, 1.35)	1.03 (0.85, 1.24)	189/3.1	1.07 (0.87, 1.31)	0.98 (0.79, 1.21)
60 to 89	5768	216/3.7	1.12 (0.93, 1.35)	1.05 (0.86, 1.27)	177/3.1	1.07 (0.87, 1.32)	1.01 (0.82, 1.25)
<60	413	15/3.6	1.11 (0.66, 1.87)	0.70 (0.41, 1.21)	12/2.9	1.03 (0.57, 1.84)	0.62 (0.33, 1.14)

Model 1: adjusted for age, sex, study center, and treatment group. Model 2: adjusted for age, sex, study center, treatment group, BMI, smoking and alcohol drinking status, baseline serum total cholesterol, HDL-cholesterol, folate, homocysteine, fasting glucose, systolic and diastolic blood pressure at baseline, mean systolic and diastolic blood pressure over the treatment period, and either baseline eGFR or dipstick proteinuria. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

Similar results were found in the eGFR <90 mL/min per 1.73 m^2 group, compared with the eGFR ≥90 mL/min per 1.73 m^2 group. In the overall population, the association between eGFR <90 mL/min per 1.73 m^2 and total stroke or ischemic stroke was no longer significant after adjustment for age and other confounders.

In contrast, proteinuria was significantly positively associated with stroke. In the multivariable adjustment model, we found a significant increased risk of total stroke (HR 1.29; 95% CI 1.01–1.67) for participants with proteinuria "trace" compared to participants with proteinuria "none." The association between proteinuria "+ or more" and the risk of stroke was stronger; in the multivariable adjustment model, the increased risk of total stroke and ischemic stroke was 1.45 (95% CI 1.06–1.97) and 1.47 (95% CI 1.03–2.09), respectively. The patterns were consistent when dipstick proteinuria "trace or more" was compared with proteinuria "none."

To assess generalizability, a fully adjusted regression model was created for the subgroups of sex, age, diabetes mellitus, baseline blood pressure levels, mean SBP/DBP levels over the treatment period, and treatment group (Figures 1 and 2). The results were similar in the subgroup analyses. The risks of total stroke were higher in the presence of proteinuria, and there were no independent associations between reduced eGFR and incident total stroke in any of the subgroup analyses. However, there were no significant interactions among any of the stratified variables (male versus female, age <65 versus ≥65 years, diabetes mellitus absence versus presence, baseline blood pressure group: grade 1 versus 2 versus 3, follow-up SBP/DBP dichotomized group: higher versus lower, enalapril group versus enalapril and folic acid group) with eGFR or proteinuria for total stroke (*P*-values for interactions were all >0.05).

When combined categories of eGFR (<90, ≥90 mL/min per 1.73 m^2) and proteinuria (none, trace, or more) were analyzed, the risk of total stroke was significantly higher in those participants with proteinuria "trace or more," 1.45-fold higher (95% CI 1.11–1.91) for eGFR ≥90, and 1.30-fold higher (95% CI 0.95–1.77) for eGFR <90 mL/min per 1.73 m^2 compared to those lacking proteinuria who had an eGFR level of ≥90 mL/min per 1.73 m^2 in the fully adjusted model (Table 3).

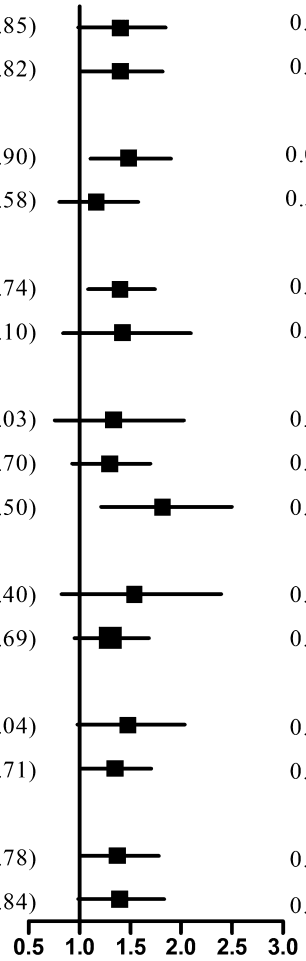
Sensitivity Analyses

The results were essentially unchanged when the analyses were restricted to the subset of 3127 participants with urinary ACR measurements. Compared to the participants with ACR <30 mg/g in the fully adjusted analysis, those with ACR 30 to 300 mg/g had a significantly higher risk of total stroke (HR 1.59; 95% CI 1.05–2.41) and ischemic stroke (HR 1.62; 95% CI 1.02–2.56). Similarly, the risk increased in participants with an ACR >300 mg/g. This positive association between ACR and the total or ischemic stroke outcomes persisted when ACR was analyzed as a continuous variable (Table 4). Results were similar when the analysis combined eGFR (≥90, <90 mL/min per 1.73 m^2) and ACR (<30, ≥30 mg/g) for total stroke (Table 3).

We also estimated the effects of baseline eGFR levels on the risk of stroke using the Chinese equation and the CKD-EPI

Proteinuria and stroke (Trace or more vs None)

Subgroups	None No of events/No of participants	Trace or more No of events/No of participants	HR(95%CI)	*P* Value	*P* for interaction
Gender					0.729
Male	212 (3.2)/6634	61 (4.4)/1372	1.36 (0.99, 1.85)	0.052	
Female	247 (2.5)/9999	65 (4.1)/1594	1.36 (1.02, 1.82)	0.036	
Age,years					0.341
<65	287 (2.4)/12137	78 (4.0)/1964	1.45 (1.11, 1.90)	0.006	
⩾65	172 (3.8)/4496	48 (4.8)/1002	1.12 (0.80, 1.58)	0.502	
Diabetes status					0.524
Absence	377 (2.5)/14895	99 (3.9)/2537	1.37 (1.08, 1.74)	0.009	
Presence	82 (4.7)/1738	27 (6.3)/429	1.33 (0.84, 2.10)	0.222	
Baseline BP group, # mmHg					0.724
Grade 1	91(1.7)/5274	22(2.4)/905	1.23 (0.75, 2.03)	0.407	
Grade 2	244/(2.8)/8613	59(4.1)/1452	1.26 (0.93, 1.70)	0.140	
Grade 3	124(4.5)/2746	45(7.4)/609	1.74 (1.21, 2.50)	0.003	
Follow-up mean SBP, mmHg					0.847
Lower <138.4	122(1.4)/8551	24(1.9)/1244	1.40 (0.82, 2.40)	0.217	
Higher ⩾138.4	337(4.2)/8082	102(5.9)/1721	1.27 (0.95, 1.69)	0.102	
Follow-up mean DBP, mmHg					0.835
Lower <82.7	154(1.8)/8350	41(2.9)/1429	1.42 (0.98, 2.04)	0.062	
Higher ⩾82.7	305(3.7)/8283	85(5.5)/1536	1.32 (1.02, 1.71)	0.034	
Treatment group					0.492
Enalapril	265 (3.2)/8360	65(4.5)/1440	1.34 (1.00, 1.78)	0.048	
Enalapril and folic acid	194 (2.3)/8273	61 (4.0)/1526	1.35 (0.99, 1.84)	0.062	



Adjusted, if not stratified, for age, gender, study center, treatment group, BMI, smoking and alcohol consumption status, baseline serum total cholesterol, HDL-cholesterol, folate, homocysteine, fasting glucose, systolic and diastolic blood pressure at baseline, mean systolic and diastolic blood pressure over the treatment period, and baseline estimated glomerular filtration rate.

Baseline blood pressure group: Grade 1: baseline SBP<160 and DBP<100; Grade 2: baseline SBP 160-179 and/or DBP 100-109; Grade 3: baseline SBP≥ 180 and/or DBP≥ 110mmHg.

Figure 1. Multivariable adjusted HRs for the associations between baseline dipstick proteinuria levels and incident stroke within subgroups. BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HRs, hazard ratios; SBP, systolic blood pressure.

4-level race equation. The results were similar and we did not observe an association between low eGFR and incidence of total and ischemic stroke (Table 5).

Discussion

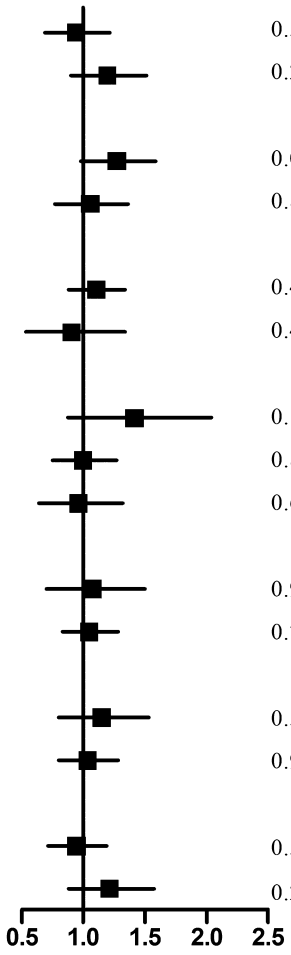
This study found that, in adults under treatment for hypertension in China, baseline proteinuria measured by dipstick or ACR, but not reduced eGFR, was an independent predictor of first incident stroke and ischemic stroke. This association was independent of eGFR and other cardiovascular risk factors.

eGFR and Stroke

Our study showed that eGFR at baseline was not an independent risk factor of the subsequent development of

eGFR and stroke (<90 vs $\geqslant 90$ ml/min/1.73m^2)

Subgroups	⩾90 No of events/No of participants	<90 No of events/No of participants	HR(95%CI)	*P* Value	*P* for interaction
Gender					0.307
Male	159 (3.1)/5068	114 (3.9)/2938	0.91 (0.69, 1.21)	0.528	
Female	195 (2.3)/8350	117 (3.6)/3243	1.17 (0.90, 1.51)	0.248	
Age,years					0.114
<65	268 (2.4)/11158	97 (3.3)/2943	1.25 (0.98, 1.59)	0.068	
⩾65	86 (3.8)/2260	134 (4.1)/3238	1.03 (0.77, 1.36)	0.856	
Diabetes status					0.129
Absence	280 (2.4)/11899	196 (3.5)/5533	1.09 (0.88, 1.34)	0.423	
Presence	74(4.9)/1519	35 (5.4)/648	0.84 (0.53, 1.34)	0.471	
Baseline BP group, # mmHg					0.423
Grade 1	67(1.6)/4289	46(2.4)/1890	1.33 (0.87, 2.04)	0.191	
Grade 2	183(2.6)/6932	120(3.8)/3133	0.97 (0.75, 1.27)	0.830	
Grade 3	104(4.7)/2197	65(5.6)/1158	0.92 (0.64, 1.32)	0.644	
Follow-up mean SBP, mmHg					0.950
Lower <138.4	93(1.3)/6896	53(1.8)/2899	1.02 (0.70, 1.50)	0.908	
Higher ⩾138.4	261(4.0)/6521	178(5.4)/3282	1.03 (0.83, 1.28)	0.794	
Follow-up mean DBP, mmHg					0.576
Lower <82.7	107(1.7)/6263	88(2.5)/3516	1.11 (0.80, 1.53)	0.540	
Higher ⩾82.7	247(3.5)/7154	143(5.4)/2665	1.01 (0.80, 1.28)	0.947	
Treatment group					0.199
Enalapril	208 (3.1)/6741	122 (4.0)/3059	0.92 (0.71, 1.19)	0.541	
Enalapril and folic acid	146 (2.2)6677	109 (3.5)/3122	1.18 (0.88, 1.57)	0.265	



Adjusted, if not stratified, for age, gender, study center, treatment group, BMI, smoking and alcohol consumption status, baseline serum total cholesterol, HDL-cholesterol, folate, homocysteine, fasting glucose, systolic and diastolic blood pressure at baseline, mean systolic and diastolic blood pressure over the treatment period, and baseline dipstick proteinuria.

Baseline blood pressure group: Grade 1: baseline SBP<160 and DBP<100; Grade 2: baseline SBP 160-179 and/or DBP 100-109; Grade 3: baseline SBP≥ 180 and/or DBP≥ 110mmHg.

Figure 2. Multivariable adjusted HRs for the associations between baseline eGFR levels and incident stroke within subgroups. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HRs, hazard ratios; SBP, systolic blood pressure.

first stroke and ischemic stroke. This result was not in agreement with previous reports including those from China, which showed that reduced eGFR and even a mild impairment of renal function (eGFR 60–89 mL/min per 1.73 m^2) was associated with an increased risk of total and ischemic stroke.[18] Recently, a meta-analysis reported by Lee et al indicated that a baseline eGFR <60 mL/min per 1.73 m^2 was independently related to incident stroke.[4] Results from another meta-analysis including 83 studies showed that stroke risk increases linearly and additively with declining GFR and that the threshold is at eGFR 90 mL/min per 1.73 m^2.[2] The mechanism responsible for the association between eGFR and stroke is incompletely understood and is likely multifactorial. Several reasons may explain the conflicting results between our findings and previous observations.

Table 3. Relative Risks and 95% CI of Stroke by Levels of eGFR and Proteinuria Measured by Dipstick or ACR

GFR, mL/min per 1.73 m^2	Dipstick Proteinuria Categories		Urinary ACR (mg/g) Categories	
	None	Trace or More	<30	≥30
≥90				
Number at risk	11 673	1745	1351	930
Events, n/%	284/2.4	70/4.0	29/2.1	40/4.3
Hazard ratio (95% CI)				
Model 1	1.00	1.95 (1.49, 2.55)	1.00	2.02 (1.24, 3.23)
Model 2	1.00	1.45 (1.11, 1.91)	1.00	1.64 (1.00, 2.69)
<90				
Number at risk	4960	1221	497	439
Events, n/%	175/3.5	56/4.6	14/2.8	26/5.9
Hazard ratio (95% CI)				
Model 1	1.14 (0.93, 1.40)	1.76 (1.30, 2.38)	0.95 (0.49, 1.84)	1.99 (1.13, 3.50)
Model 2	1.08 (0.87, 1.33)	1.30 (0.95, 1.77)	0.89 (0.45, 1.76)	1.52 (0.84, 2.73)

Model 1: adjusted for age, sex, study center, and treatment group. Model 2: adjusted for age, sex, study center, treatment group, BMI, smoking and alcohol consumption status, baseline serum total cholesterol, HDL-cholesterol, folate, homocysteine, fasting glucose, systolic and diastolic blood pressure at baseline, and mean systolic and diastolic blood pressure over the treatment period. ACR indicates albumin–creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

First, the inconsistent results may be attributable to differences between the study populations in terms of the severity of renal function impairment. The PREVEND (Prevention of Renal and Vascular Endstage Disease) study found that the renal risk marker albuminuria, but not eGFR, is independently associated with cardiovascular outcome in the general population. The authors pointed out that most of the study participants had normal kidney function.[19] The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study also did not observe an indepentent association between low eGFR and stroke risk and is possibly due to the relatively few stroke events among participants with eGFR <60 mL/min per 1.73 m^2.[20] The CSPPT study was not primarily designed to examine the association between CKD

Table 4. Adjusted Hazard Ratios (95% CIs) for Incidence of Total and Ischemic Stroke by Baseline Urinary ACR Levels

	Urinary Albumin-to-Creatinine Ratio (ACR) (mg/g)			
	<30	30 to 300	>300	Log-ACR (mg/g)
Number at risk	1848	1200	169	3217
Total stroke				
Events, n/%	43/2.3	54/4.5	12/7.1	109/3.4
Hazard ratio (95% CI)				
Model 1	1.00	1.88 (1.26, 2.81)	3.19 (1.68, 6.06)	1.96 (1.43, 2.69)
Model 2	1.00	1.59 (1.05, 2.41)	2.17 (1.09, 4.29)	1.54 (1.09, 2.19)
Ischemic stroke				
Events (n/%)	34/1.8	46/3.8	11/6.5	91/2.8
Hazard ratio (95% CI)				
Model 1	1.00	2.00 (1.28, 3.12)	3.69 (1.87, 7.30)	2.11 (1.50, 2.96)
Model 2	1.00	1.62 (1.02, 2.56)	2.42 (1.17, 4.99)	1.61 (1.10, 2.36)

Model 1: adjusted for age, sex, study center and treatment group. Model 2: adjusted for age, sex, study center, treatment group, BMI, smoking and alcohol consumption status, baseline serum total cholesterol, HDL-cholesterol, estimated glomerular filtration rate, folate, homocysteine, fasting glucose, systolic and diastolic blood pressure at baseline, and mean systolic and diastolic blood pressure over the treatment period. ACR indicates albumin–creatinine ratio; BMI, body mass index; HDL, high-density lipoprotein.

Table 5. Adjusted Hazard Ratios (95% CIs) for Incidence of Total and Ischemic Stroke by Baseline eGFR Categories Estimated Using Different Equations

		Total Stroke			Ischemic Stroke		
			Hazard Ratio (95% CI)			Hazard Ratio (95% CI)	
	Number at Risk	Events (n/%)	Model 1	Model 2	Events (n/%)	Model 1	Model 2
$eGFR_{Chinese\ equation}$ category, mL/min per 1.73 m^2							
≥90	16 019	454/2.8	1.00	1.00	367/2.3	1.00	1.00
<90	3580	131/3.7	1.11 (0.91, 1.35)	0.97 (0.79, 1.20)	105/2.9	1.06 (0.85, 1.33)	0.92 (0.73, 1.16)
60 to 89	3313	119/3.6	1.09 (0.88, 1.34)	0.98 (0.79, 1.21)	95/2.9	1.04 (0.82, 1.30)	0.93 (0.73, 1.18)
<60	267	12/4.5	1.40 (0.79, 2.49)	0.88 (0.49, 1.61)	10/3.7	1.38 (0.74, 2.60)	0.82 (0.42, 1.58)
$eGFR_{CKD\text{-}EPI\ 4\text{-}level\ race}$ category, mL/min per 1.73 m^2							
≥90	15 623	434/2.8	1.00	1.00	349/2.2	1.00	1.00
<90	3976	151/3.8	1.13 (0.93, 1.38)	0.99 (0.81, 1.21)	123/3.1	1.09 (0.88, 1.36)	0.96 (0.77, 1.20)
60 to 89	3670	140/3.8	1.14 (0.93, 1.39)	1.03 (0.84, 1.26)	114/3.1	1.10 (0.88, 1.37)	0.99 (0.79, 1.25)
<60	306	11/3.6	1.09 (0.60, 1.98)	0.67 (0.36, 1.25)	9/2.9	1.04 (0.54, 2.03)	0.61 (0.30, 1.20)

Model 1: adjusted for age, sex, study center, and treatment group. Model 2: adjusted for age, sex, study center, treatment group, BMI, smoking and alcohol consumption status, baseline serum total cholesterol, HDL-cholesterol, folate, homocysteine, fasting glucose, systolic and diastolic blood pressure at baseline, mean systolic and diastolic blood pressure over the treatment period, and baseline dipstick proteinuria. BMI indicates body mass index; $eGFR_{Chinese\ equation}$, glomerular filtration rate estimated using the modified Modification of Diet in Renal Disease (MDRD) equation for Chinese; $eGFR_{CKD\text{-}EPI4\text{-}level\ race}$, glomerular filtration rate estimated using the Chinese Kidney Disease Epidemiology Collaboration 4-level race equation; HDL, high-density lipoprotein.

and incident stroke; the majority of participants in this study had relatively mild reductions in eGFR. Therefore, due to the small number of participants with baseline eGFR <60 mL/min per 1.73 m^2 (n=413) in this study, results should be interpreted with caution. The study might be underpowered to detect the effect of eGFR <60 mL/min per 1.73 m^2 on first stroke.

Another potential reason is that eGFR is a less sensitive measure of renal function. Although eGFR calculated using the CKD-EPI equation is more accurate than the MDRD equation in mild to moderately impaired renal function populations,[15,21] eGFR still may not adequately reflect real GFR.[22] Reduced eGFR is typically not an early sign of renal disease since serum creatinine may be stable during the early stage of CKD due to hyperfiltration or increased tubular secretion.[23] Among the elderly, since there is a known physiological decline in kidney function with age, eGFR alone may not be sufficient to define CKD in the absence of albuminuria.[24] Ohsawa et al found that neither $eGFR_{CKD\text{-}EPI}$ nor $eGFR_{MDRD}$ can predict the risk of stroke in the general population.[25] Aguilar et al compared 3 kidney biomarkers as risk factors for incident stroke in the Cardiovascular Health Study (CHS), and found that albuminuria as reflected by urinary ACR was more strongly associated with risk of incident stroke than eGFR and cystatin C; the adjusted HRs were as follows: for urinary ACR: 2.10 (95% CI 1.47–3.00), and for eGFR and cystatin C 1.29 (95% CI 0.91–1.84) and 1.22 (95% CI 0.85–1.74), respectively, which support the assertion that urinary ACR is the best stroke risk factor among the 3 kidney biomarkers.[26]

The third possibility is that the drug therapy may have influenced the relationship between eGFR levels and risk of stroke in our study. Most participants from the above 2 meta-analyses were not hypertensive and did not accept antihypertension therapy. There were only 2 hypertensive cohorts in the meta-analysis reported by Lee et al. Of the 2 hypertensive cohorts, no association between lower eGFR and stroke was found in the VALUE study, in which the antihypertensive therapy was an angiotensin II antagonist or a third-generation calcium channel blocker. In the HOT study, patients were given antihypertensive therapy with a long-acting calcium antagonist, whereas all participants in the CSPPT were on an angiotensin-converting enzyme inhibitor–based antihypertensive treatment. Differences in population and therapy modalities may contribute to the discrepancy with the recent meta-analysis. Our previously published meta-analysis indicated that homocysteine-lowering therapy with folic acid is effective in preventing cardiovascular disease in patients with kidney disease.[27] Our published report from the CSPPT demonstrated that folic acid supplementation significantly reduces the risk of stroke.[14] The kidney is an important site for the synthesis and metabolism of many amino acids, including homocysteine. In fact, plasma homocysteine is inversely correlated with GFR. Even patients with moderately decreased renal function have elevated plasma homocysteine.[28] It is possible that the antihypertensive and folic acid therapy

affected eGFR, and thus attenuated its effect on stroke. However, the analyses stratified by folic acid treatment groups did not alter our main results.

Proteinuria and Stroke

Most but not all studies have suggested that kidney damage estimated by proteinuria is an independent risk factor for some types of stroke.[5,29] Our results showed that, in the absence of proteinuria, an eGFR <90 mL/min per 1.73 m^2 (but mostly >60) had no relationship with risk of stroke; however, the presence of proteinuria amplified the stroke risk. These findings are similar to previous studies. Recently, reports from the Kailuan study and the Chronic Renal Insufficiency Cohort (CRIC) study both showed that proteinuria but not reduced eGFR increased the risk of stroke in a general and CKD population, respectively.[30,31] The JATOS study demonstrated that baseline reduced eGFR per se (<60 versus ≥60 mL/min per 1.73 m^2) was not significantly associated with cardiovascular events (P=0.1723); however, the presence of proteinuria was significantly correlated with cardiovascular event rates (P=0.0001), an association that was more apparent in patients with an eGFR <60 mL/min per 1.73 m^2 (P<0.0001).[8] A large population-based longitudinal study indicated that the measurement of proteinuria (based on dipstick and ACR testing) is of incremental prognostic benefit at every level of eGFR for major cardiovascular events.[32] These results identify the prognostic value of proteinuria with respect to the incidence of cardiovascular disease including stroke.

The precise pathophysiologic mechanisms that underlie the link between proteinuria and stroke are not known and require further elucidation. As it stands, there are several potential explanations for why the presence of proteinuria may be a risk factor for incident stroke in treated hypertensives. First, individuals with proteinuria tend to have a higher prevalence of traditional risk factors than those without proteinuria. In our study, the participants with proteinuria had a higher prevalence of cardiovascular disease risk factors including older age, higher prevalence of diabetes mellitus, current alcohol intake, increased systolic and diastolic blood pressure, higher fasting blood glucose, and higher homocysteine than participants without proteinuria. Second, it is likely that proteinuria and stroke may be linked by a common pathophysiologic process, such as endothelial dysfunction; chronic, low-grade inflammation; or increased transvascular leakage of macromolecules.[33,34] Third, proteinuria may denote a greater severity of end organ damage.[35]

Our findings support the hypothesis that proteinuria and reduced filtration function may operate through different pathophysiologic mechanisms. Our results suggest that the measurements of urinary protein both with a dipstick (even if it is a trace amount) and using ACR are good biomarkers for stroke events and confer a risk of incident stroke independent of filtration function. The association between dipstick proteinuria and stroke was similar irrespective of age, sex, diabetes, hypertension, or treatment (P-value for interaction all >0.05). The measurement of urinary albumin is costly and requires strict specimen storage and laboratory testing methods, whereas dipstick urinalysis is considerably less expensive, quicker and easier to perform, and thus is more widely used in clinical settings. Sam et al indicated that qualitative testing for proteinuria has a high sensitivity and specificity for diagnosing or ruling out microalbuminuria. They examined 185 urine samples with trace proteinuria using both Chemstrips and sulfosalicylic acid testing and found abnormal albumin excretion in 87% and abnormal total protein excretion in 88% of the trace samples, respectively, which indicated that trace proteinuria usually means microalbuminuria.[36] As such, the clinical significance of trace proteinuria should not be ignored.

Our study had the following limitations. First, we did not use specific factors for evaluating renal function, such as cystatin C. The CKD-EPI equation we used in this study had greater accuracy than the MDRD equation, especially at GFR ≥60 mL/min per 1.73 m^2.[21] This equation was developed, based on creatinine, age, sex, and a 2-level variable for race (black versus white and other). Nevertheless, the applicability of the CKD-EPI equation to estimate glomerular filtration rate in Chinese patients has been validated and the findings indicated that the CKD-EPI 2-level race equation and the Chinese equation performed similarly in the Chinese population, and both performed better than the MDRD study equation and the CKD-EPI 4-level race equation.[17] Moreover, in a sensitivity analysis, using either the Chinese equation or the CKD-EPI 4-level race equation to estimate GFR did not substantially change the results. We only measured 3217 participants using the ACR method; however, we found similar associations for proteinuria measured by dipstick versus ACR. Second, our study population contained a small number of participants with CKD (eGFR <60 mL/min per 1.73 m^2) and incident hemorrhagic stroke, which limited our ability to detect a relationship between baseline eGFR <60 mL/min per 1.73 m^2 and incident stroke and hemorrhagic stroke. An increased number of CKD and hemorrhagic stroke events is needed to detect any association between lower eGFR with stroke and its subtypes. Third, baseline serum creatinine and urinary proteinuria were only measured once. This could bias their estimated effects toward the null value and possibly result in misclassification of the exposure variable so that the true relation between proteinuria, low eGFR, and stroke is probably stronger than our findings indicate.[37] Finally, we acknowledge the possibility of residual confounding by other unmeasured covariates, such as C-reactive protein.The

strengths of this study include its large sample size and 4.5 years of prospective follow-up. In addition, all of the lab samples were measured at a central laboratory.

Conclusions

Our findings suggest that spot urinary protein, collected in the morning and detected by dipstick or ACR, but not reduced eGFR, is a feasible and independent risk factor for first incident stroke in adults under treatment for hypertension in China.

These findings suggest that clinicians and public health practitioners should be aware that, despite treatment for hypertension, the presence of even trace amounts of urinary protein by dipstick or ACR may indicate additionally increased risk of first stroke. It emphasizes the need and possibility for early detection and early stroke prevention.

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