Hypertensive Retinopathy and the Risk of Stroke Among Hypertensive Adults in China

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Purpose. This study aimed to investigate the association between hypertensive retinopathy and the risk of first stroke, examine possible effect modifiers in hypertensive patients, and test the appropriateness of the Keith-Wagener-Barker (KWB) classification for predicting stroke risk.

Methods. In total, 9793 hypertensive participants (3727 males and 6066 females) without stroke history from the China Stroke Primary Prevention Trial were included in this study. The primary outcome was first stroke.

Results. Over a median follow-up of 4.4 years, 592 participants experienced their first stroke (509 ischemic, 77 hemorrhagic, and six unclassifiable strokes). In total, 5590 participants were diagnosed with grade 1 retinopathy (57.08%), 1466 with grade 2 retinopathy (14.97%), 231 with grade 3 retinopathy (2.36%), and three with grade 4 retinopathy (0.03%). Grades 1 and 2 were merged and classified as mild retinopathy, and grades 3 and 4 were merged and classified as severe retinopathy. There was a significant positive association between hypertensive retinopathy and the risk of first stroke and first ischemic stroke, and no effect modifiers were found. The hazard ratios (HRs) for first stroke were as follows: mild versus no retinopathy, 1.26 (95% confidence interval [CI], 1.01–1.58, $P = 0.040$), and severe versus no retinopathy, 2.40 (95% CI, 1.49–3.84, $P < 0.001$). The HRs for ischemic stroke were as follows: severe versus no retinopathy, 2.35 (95% CI, 1.41–3.90, $P = 0.001$), and nonsignificantly increased HRs for mild versus no retinopathy, 1.26 (95% CI, 0.99–1.60, $P = 0.057$).

Conclusions. There was a significant positive association between hypertensive retinopathy and the risk of first stroke in patients with hypertension, indicating that hypertensive retinopathy may be a predictor of the risk of stroke. A simplified two-grade classification system based on the KWB classification is recommended for predicting stroke risk.

Keywords: stroke, hypertension, hypertensive retinopathy, keith-wagener-barker classification, fundus photograph

Stroke is the most common cause of death in China.[1,2] Hypertension is the most significant modifiable risk factor for stroke and a major public health concern.[3,4] Therefore, among hypertensive patients, it is imperative to identify individuals at high risk of stroke. Assessment of the cerebral vasculature is important in determining an individual's risk of stroke.[5,6] However, the techniques for the assessment of the cerebral microvasculature, such as transcranial Doppler ultrasonography, positron emission tomography, functional neuroimaging using magnetic resonance imaging, and

digital subtraction angiography, are highly specialized, expensive, and not suitable for widespread screening of patients.[7] A simpler, more accessible technique is required.

The retinal vasculature is unique in that it can be directly and noninvasively visualized in vivo and displays cumulative changes in microcirculation.[8] The retinal and cerebral microvasculatures share many physiological and morphological properties,[9] and both undergo morphological changes in the context of increasing blood pressure.[10–12] Hypertensive retinopathy has been suggested to be a significant sign of hypertensive target-organ damage.[13,14] A considerable amount of literature has provided convincing evidence supporting the value of hypertensive retinopathy for stroke risk prediction[15,16]; however, most available studies on hypertensive retinopathy and stroke have been conducted in European countries or in the United States, and evidence from Asian populations is scarce. Therefore further replication of these findings in different populations is needed. To our knowledge, few large-sample studies have been conducted in Chinese hypertensive participants. Furthermore, whether this association was modified by traditional risk factors for stroke needs to be verified.

In addition, there is no recognized standardized classification system for hypertensive retinopathy that is able to show good reproducibility and validity in predicting stroke events.[17] The Keith-Wagener-Barker (KWB) classification system is the most classic classification method of hypertensive retinopathy and was first proposed for prognosticating survival, and it is also the foundation of many other classification methods.[18] However, some reviews on hypertensive retinopathy have challenged the usefulness of the KWB classification system.[19,20]

Therefore, the main purpose of our current investigation was to examine whether hypertensive retinopathy is a risk indicator for stroke in a Chinese population with hypertension and to examine any possible effect modifiers in hypertensive patients, such as age, sex, body mass index (BMI, kg/m²), blood pressure, blood glucose, and blood lipids. In addition, we aimed to examine the appropriateness of the KWB classification system in predicting stroke risk.

METHODS

The China Stroke Primary Prevention Trial (CSPPT) is a large, community-based, randomized, multicenter, double-blind, and actively controlled trial designed to evaluate whether a combination therapy of enalapril maleate and folic acid tablets was more effective in preventing stroke in Chinese adults with hypertension than enalapril maleate alone.[21] The CSPPT complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China. Our current study was approved by the Ethics Committee of the First People's Hospital of Lianyungang. The requirement for informed consent was waived because of the retrospective nature of the study and the lack of any participant interaction. The data that support the findings of this study will be available from the corresponding authors upon request after the request is submitted and formally reviewed and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China, and the Ethics Committee of the First People's Hospital of Lianyungang.

Study Participants

All participants in this study were participants in the CSPPT, conducted from May 19, 2008, to August 24, 2013, with 20,702 hypertensive adults in 32 communities in two study centers, Lianyungang in Jiangsu Province and Anqing in Anhui Province of China. Eligible participants were men and women aged 45 to 75 years who had hypertension, defined as seated, resting systolic blood pressure (SBP) of 140 mm Hg or higher, diastolic blood pressure (DBP) of 90 mm Hg or higher at both the screening and recruitment visits or the use of antihypertensive medication. The major exclusion criteria included a history of physician-diagnosed stroke, myocardial infarction, heart failure, coronary revascularization, or congenital heart disease.

As a post-trial follow-up of the CSPPT, our current study was conducted from August 24, 2013, to December 31, 2017, in Lianyungang, Jiangsu Province. Overall, of the 15,486 participants enrolled at Lianyungang Center, 365 were deceased at the start of follow-up, 2476 failed to undergo fundus photograph collection, and 520 had a history of physician-diagnosed stroke at the time of study initiation. In total, 12,645 participants completed the exit site visit and were included and followed up for stroke in the study. All subjects received fundus photographs at the start point (2013). After excluding the subjects without endpoint information (n = 2332, 2320 remained unmatched with the Centers for Disease Control and Prevention data, and 12 had missing stroke outcome data), 9793 hypertensive subjects were included in the final analysis (Fig. 1). There was some missing information from the personal history questionnaire from the subjects enrolled, including data on smoking status for 32 subjects (0.33%) and on alcohol consumption for 440 subjects (4.49%); 12 subjects (0.12%) were missing data on both of them (Table 2).

Classification of Hypertensive Retinopathy

For all subjects, a high-quality, macular-centered fundus photograph was obtained using three nonmydriatic fundus cameras (Kowa Nonmyd 7, Kowa Company, Ltd., Tokyo, Japan; Canon CR-2 AF, Canon Inc., Tokyo, Japan; Topcon TRC-NW8, Topcon Optical Company, Tokyo, Japan) through constricted pupils. Nonmydriatic fundus photographs were taken at the posterior pole and macula center. All photographs were randomly assessed by four experienced, double-blinded ophthalmologists who received detailed training and were tested for consistency before the study as follows. Sixty patients were randomly selected from the whole study population. The four ophthalmologists independently evaluated their fundus photographs, and consistency was assessed. If the consistency value was poor, the training was repeated, controversial photographs were discussed, and the consistency test was repeated with another 60 patients. The consistency test was conducted at least three times until good consistency values (κ, 0.71-0.95) were obtained. Hypertensive retinopathy was classified into grades 1 to 4 according to the KWB classification (Table 1; Fig. 4 for examples).[18] Additionally, we tested the different categories, that is, a grouping of the KWB classification and KWB classification in two categories (grades 1–2 as mild retinopathy and grades 3–4 as severe retinopathy), to compare the hazard ratios (HRs) of strokes in the different categories.
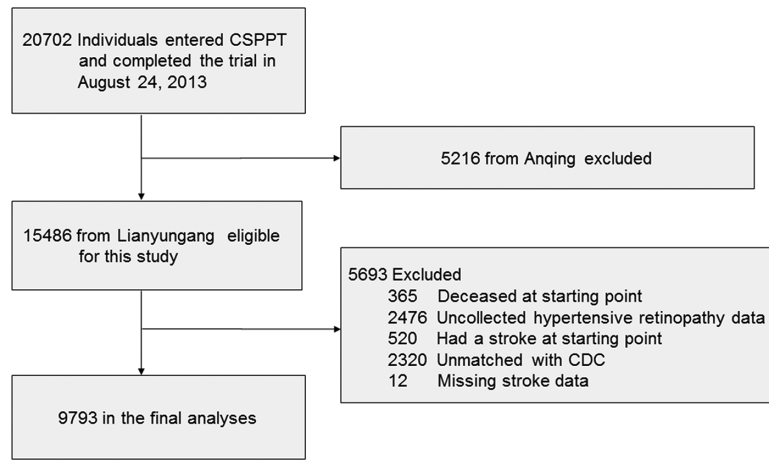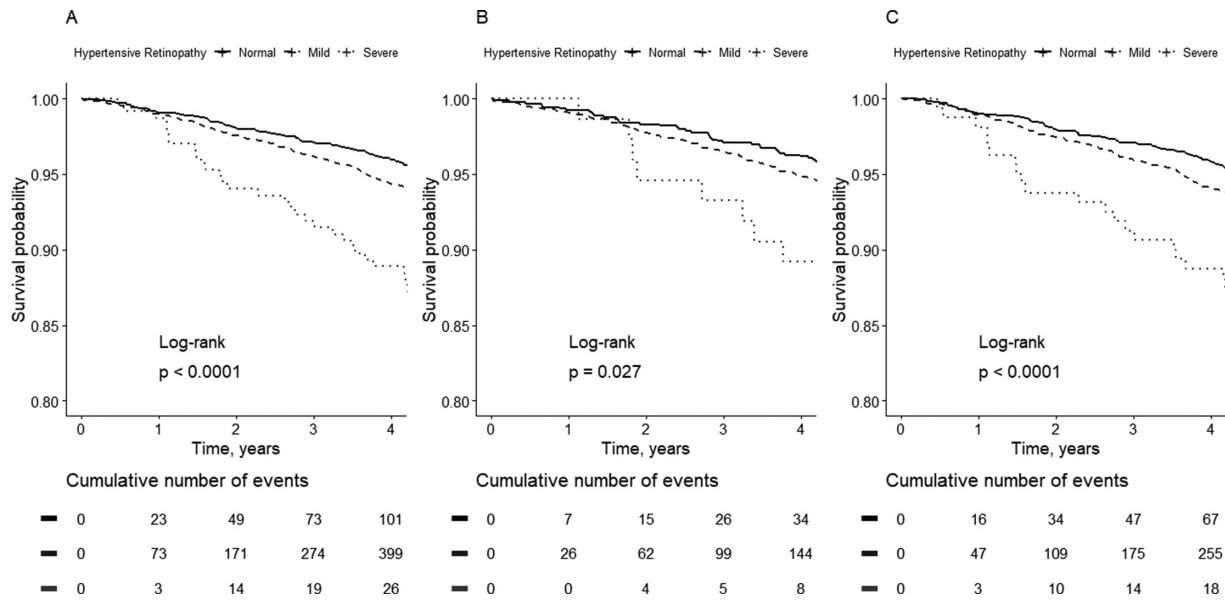
FIGURE 1. Flow chart of participants.

FIGURE 2. Survival curves constructed for incident stroke according to sex and hypertensive retinopathy classification (normal; mild retinopathy = Grade 1–2 according to the Keith-Wagener-Barker classification system; severe retinopathy = Grade 3–4 according to the Keith-Wagener-Barker classification system). (**A**) Total, (**B**) Male, (**C**) Female.

TABLE 1. The Keith-Wagener-Barker Classification System for Hypertensive Retinopathy

Grade	Features
1	Mild or moderate generalized retinal arteriolar narrowing, arteriovenous tortuosity
2	Definite focal narrowing and arteriovenous nipping
3	Signs of grade 2 retinopathy plus retinal hemorrhages, exudates and cotton-wool spots
4	Severe grade 3 retinopathy plus papilledema or retinal edema

Laboratory Assays

Overnight fasting venous blood samples were obtained from each study participant at baseline. Serum creatinine, total homocysteine (tHcy), fasting lipids, and fasting glucose were measured using automatic clinical analyzers (Beckman Coulter, Inc, Southfield, MI, USA) at the core laboratory of the National Clinical Research Center for Kidney Disease, Nanfang Hospital, Guangzhou, China. Serum folate was measured using a chemiluminescent immunoassay (New Industrial, Shenzhen, China). Urine protein was assessed by qualitative dipstick urinalysis using an automatic urine analyzer (Dirui-H100; Dirui Industrial Co., Jilin, China).

TABLE 2. Baseline Characteristics of Participants Stratified by Hypertensive Retinopathy Categories[*]

| | Hypertensive Retinopathy Grading | | | |
| | Normal | Mild Grade 1-2 | Severe Grade 3-4 | |
Characteristics				*P* Value
No.	2503	7056	234	
Male, (%)	886 (35.4)	2767 (39.2)	74 (31.6)	<0.001
Age, y	63.2 ± 7.3	63.3 ± 7.3	63.3 ± 7.2	0.654
BMI, kg/m^2	25.3 ± 3.7	25.6 ± 3.7	25.8 ± 4.3	0.009
SBP, mm Hg	135.0 ± 16.7	136.7 ± 17.5	140.8 ± 19.9	<0.001
DBP, mm Hg	81.8 ± 10.5	83.1 ± 10.9	84.8 ± 12.7	<0.001
Diabetes, no. (%)	467 (19.3)	1381 (20.4)	77 (34.1)	<0.001
Triglycerides, mmol/L	1.8 ± 1.4	1.9 ± 1.5	1.8 ± 1.3	0.040
Total cholesterol, mmol/L	5.4 ± 1.1	5.4 ± 1.1	5.3 ± 1.1	0.123
High-density lipoprotein, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.035
Serum folic acid, ng/mL	17.5 ± 12.4	17.9 ± 14	18.7 ± 15.7	0.207
tHcy, µg/mL	13.3 ± 8.0	13.5 ± 6.8	13.1 ± 5.2	0.443
Fasting glucose, mmol/L	6.3 ± 1.9	6.3 ± 2.1	7.2 ± 3.4	<0.001
Serum creatinine, µmol/L	66.1 ± 22.7	67.6 ± 23.0	72.2 ± 80.2	<0.001
Treatment group, (%)				0.661
Enalapril alone	1265 (50.5)	3552 (50.3)	111 (47.4)	
Enalapril-folic acid	1238 (49.5)	3504 (49.7)	123 (52.6)	
MTHFR C677T polymorphisms, (%)				1.000
CC	588 (23.5%)	1652 (23.4%)	54 (23.1%)	
CT	1245 (49.7%)	3512 (49.8%)	118 (50.4%)	
TT	670 (26.8%)	1892 (26.8%)	62 (26.5%)	
Smoking status, (%)				0.020
Never	1736 (69.6)	4816 (68.5)	184 (78.6)	
Former	246 (9.9)	723 (10.3)	18 (7.7)	
Current	512 (20.5)	1494 (21.2)	32 (13.7)	
Alcohol consumption, (%)				0.008
Never	1790 (74.7)	4788 (71.1)	173 (76.2)	
Former	125 (5.2)	420 (6.2)	14 (6.2)	
Current	481 (20.1)	1522 (22.6)	40 (17.6)	

Mild retinopathy = Grade 1-2 according to the Keith-Wagener-Barker classification system; Severe retinopathy = Grade 3-4 according to the Keith-Wagener-Barker classification system.

[*] For continuous, normally distributed variables, the values are presented as the mean ± SD. The differences between categories of hypertensive retinopathy were compared using ANOVA, signed-rank tests, or χ^2 tests as appropriate. The included population comprised 9793 patients with 440 missing for alcohol consumption, 32 missing for smoking status, and 12 missing for both alcohol consumption and smoking status.

Outcomes

The primary outcome was a first nonfatal or fatal stroke. Secondary outcomes included first ischemic stroke (fatal and nonfatal) and first hemorrhagic stroke (fatal and nonfatal), excluding subarachnoid hemorrhage and silent stroke.

Information concerning the incidence of stroke among all participants was obtained via the Centers for Disease Control and Prevention of Ganyu and Donghai counties and checked against the national health insurance system with electronic linkage to all hospitalizations, and some cases were ascertained through active follow-up by the Centers for Disease Control and Prevention.[22] Diseases were coded according to the International Classification of Diseases, 10th Revision. Secondary outcomes included first ischemic stroke (I63) and first hemorrhagic stroke (I60-I61). The primary outcome (first nonfatal or fatal stroke) included first ischemic stroke, first hemorrhagic stroke, and unknown stroke type (I64).

As described in the government procedures,[23,24] local authorities from medical institutions are required to report all new cases of stroke to the local Centers for Disease Control and Prevention. A report card that includes information on demographics, diagnostic basis and date of stroke must be submitted on the 28th of each month. Quality control, including finding and deleting repeated cases, checking for errors, and determining any missed cases, is conducted by trained officials. Furthermore, the local Centers for Disease Control and Prevention are also responsible for deleting repeated cases and identifying logistical errors and missed cases. In addition, 5% of all uploaded cases were randomly chosen for further confirmation by phone or door-to-door interviews.

Statistical Analysis

Baseline characteristics are presented as the mean ± standard deviation (SD) for continuous variables and as frequency (%) for categorical variables. The differences in population characteristics were compared using ANOVA tests, signed rank tests, or χ^2 tests, as appropriate.

The HRs of the primary and secondary outcomes were estimated by the baseline hypertensive retinopathy severity as graded and rank variables using Cox proportional hazards models without and with adjustment for age and sex

TABLE 3. Hazard Ratios for Stroke According to Severity of Hypertensive Retinopathy

Type of Stroke	Hypertensive Retinopathy Grading	Events/Total (%)	Crude Model		Model I*		Model II†	
			HR (95% CI)	_P_ Value	HR (95% CI)	_P_ Value	HR (95% CI)	_P_ Value
All stroke								
	Normal	119/2503 (4.8)	Ref (1.0)		Ref (1.0)		Ref (1.0)	
	Mild (grade 1-2)	441/7056 (6.2)	1.34 (1.08, 1.64)	0.006	1.34 (1.09, 1.65)	0.006	1.26 (1.01, 1.58)	0.040
	Severe (grade 3-4)	32/234 (13.7)	3.17 (2.09, 4.81)	<0.0001	3.18 (2.09, 4.82)	<0.0001	2.40 (1.49, 3.84)	<0.001
_P_ for trend			0.002		0.002		0.021	
Ischemic stroke								
	Normal	104/2503 (4.2)	Ref (1.0)		Ref (1.0)		Ref (1.0)	
	Mild (grade 1-2)	379/7056 (5.4)	1.30 (1.05, 1.62)	0.017	1.29 (1.04, 1.60)	0.021	1.26 (0.99, 1.60)	0.057
	Severe (grade 3-4)	26/234 (11.1)	2.80 (1.82, 4.30)	<0.001	2.76 (1.80, 4.25)	<0.001	2.35 (1.41, 3.90)	0.001
_P_ for trend			0.007		0.006		0.033	
Hemorrhagic stroke								
	Normal	14/2503 (0.6)	Ref (1.0)		Ref (1.0)		Ref (1.0)	
	Mild (grade 1-2)	57/7056 (0.8)	1.46 (0.81, 2.61)	0.207	1.45 (0.81, 2.60)	0.213	1.23 (0.67, 2.25)	0.505
	Severe(grade 3-4)	6/234 (2.6)	4.79 (1.84, 12.47)	0.001	4.80 (1.84, 12.5)	<0.001	2.51 (0.79, 7.97)	0.118
_P_ for trend			0.139		0.142		0.432	

Mild retinopathy = Grade 1-2 according to the Keith-Wagener-Barker classification system; Severe retinopathy = Grade 3-4 according to the Keith-Wagener-Barker classification system.

* Adjusted for age and sex.

† Adjusted for age, sex, BMI, SBP, DBP, diabetes, triglycerides, total cholesterol, high-density lipoprotein, serum folic acid, total homocysteine, fasting glucose, serum creatinine, treatment group, methylenetetrahydrofolate reductase C677T genotype, and smoking and alcohol consumption status. Model II was run on 9333 patients for 460 patients missing covariates (440 missing for alcohol consumption, 32 missing for smoking status, and 12 missing for both alcohol consumption and smoking status).

(model I) and with adjustment for age, sex, BMI (kg/m²), SBP, DBP, diabetes, total cholesterol, triglycerides, high-density lipoprotein, serum folic acid, tHcy, fasting glucose, serum creatinine, treatment group (enalapril or enalapril-folic acid treatment), methylenetetrahydrofolate reductase (_MTHFR_) C677T (rs1801133) genotypes (CC, CT or TT) (which play a key role in folate metabolism and homocysteine homeostasis), current smoking and alcohol consumption status (model II). In addition, possible modifications of the association between hypertensive retinopathy and primary outcome were also assessed for the following variables: sex, age (<65 vs. ≥65 years), BMI (<24 vs. ≥24 kg/m²), diabetes status (yes or no), SBP (<140.0 vs. ≥140.0 mm Hg), treatment group (enalapril or enalapril-folic acid treatment), _MTHFR_ C677T polymorphism (CC/CT vs. TT), and tHcy (<12 vs. ≥12 µmol/L) (model II). Survival curves were constructed for incident stroke by hypertensive retinopathy classification.

A two-tailed _P_ value < 0.05 was considered statistically significant. All analyses were performed using Empower Stats statistical software (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) and the statistical package R (version 3.4.3, http://www.r-project.org).

RESULTS

Baseline Characteristics of the Participants

As shown in the flow chart (Fig. 1), a total of 9793 subjects with hypertension were included in the present study. The characteristics of all participants by category and grade of hypertensive retinopathy are listed in Table 2 and Supplemental Table S1. The mean age was 63.3 ± 7.3 years; 3727 (38.06%) were males; 7290 (74.4%) patients had hypertensive retinopathy; and the prevalence among males and females was 76.2% and 73.3%, respectively. Grade 4 (n = 3, 0.03%) subjects were combined with grade 3 subjects in the

analysis. Participants with a higher hypertensive retinopathy grading seemed to have higher SBP, DBP, proteinuria, and fasting glucose (Table 2).

Association Between Hypertensive Retinopathy and the Risk of Study Outcomes

Over a median follow-up period of 4.4 years, 592 first-time strokes were identified, of which 509 were ischemic strokes, 77 were hemorrhagic strokes, and six were undetermined strokes. The first stroke occurred in 119 (4.8%), 350 (6.3%), 91 (6.2%) and 32 (13.7%) participants with hypertensive retinopathy grades zero to 3–4, respectively.

Overall, in the multivariate regression models, grade 1 and grade 2 had similar HRs and statistical results (Table S2 in the online-only Data Supplement). Moreover, when retinopathy was assessed as a new combined category (grades 1–2 as mild retinopathy and grades 3–4 as severe retinopathy), a significantly higher risk of first stroke (HR, 1.26 [95% CI, 1.01–1.58], _P_ = 0.040) and a nonsignificantly higher risk of first ischemic stroke (HR, 1.26 [95% CI, 0.99–1.60], _P_ = 0.057) and first hemorrhagic stroke (HR, 1.23 [95% CI, 0.67–2.25], _P_ = 0.505) were found in the participants with mild retinopathy compared with those without retinopathy (Table 3). Survival curves were constructed for incident stroke by hypertensive retinopathy classification (Fig. 2) suggested that there was a significant difference in risk of stroke in the 3 groups, in both men and women, because pairwise Mantel–Cox Log Rank comparisons were all significant (P < 0.05). In addition, there was a significant positive association between severe hypertensive retinopathy and the risk of first stroke (HR: 2.40 [95% CI, 1.49–3.84], _P_ < 0.001) or first ischemic stroke (HR: 2.35 [95% CI, 1.41–3.90], _P_ = 0.001). Overall, the results were similar between the crude models and model 1, and the HRs were decreased (but still highly significant for grades 3–4) after adjustment for numerous potential confounders.
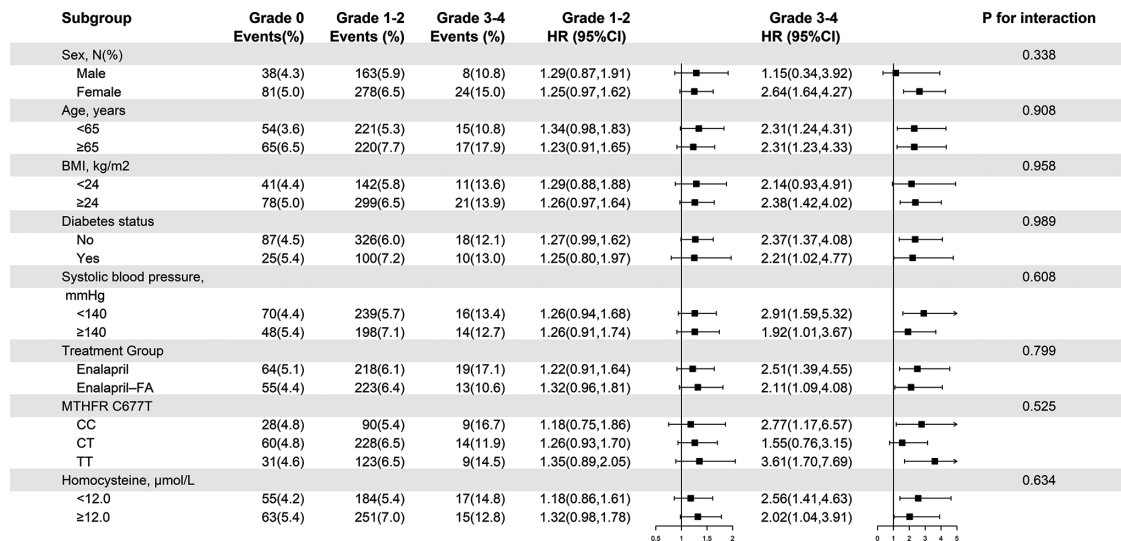
Subgroup	Grade 0 Events(%)	Grade 1-2 Events (%)	Grade 3-4 Events (%)	Grade 1-2 HR (95%CI)	Grade 3-4 HR (95%CI)	P for interaction
Sex, N(%)						0.338
Male	38(4.3)	163(5.9)	8(10.8)	1.29(0.87,1.91)	1.15(0.34,3.92)	
Female	81(5.0)	278(6.5)	24(15.0)	1.25(0.97,1.62)	2.64(1.64,4.27)	
Age, years						0.908
<65	54(3.6)	221(5.3)	15(10.8)	1.34(0.98,1.83)	2.31(1.24,4.31)	
≥65	65(6.5)	220(7.7)	17(17.9)	1.23(0.91,1.65)	2.31(1.23,4.33)	
BMI, kg/m2						0.958
<24	41(4.4)	142(5.8)	11(13.6)	1.29(0.88,1.88)	2.14(0.93,4.91)	
≥24	78(5.0)	299(6.5)	21(13.9)	1.26(0.97,1.64)	2.38(1.42,4.02)	
Diabetes status						0.989
No	87(4.5)	326(6.0)	18(12.1)	1.27(0.99,1.62)	2.37(1.37,4.08)	
Yes	25(5.4)	100(7.2)	10(13.0)	1.25(0.80,1.97)	2.21(1.02,4.77)	
Systolic blood pressure, mmHg						0.608
<140	70(4.4)	239(5.7)	16(13.4)	1.26(0.94,1.68)	2.91(1.59,5.32)	
≥140	48(5.4)	198(7.1)	14(12.7)	1.26(0.91,1.74)	1.92(1.01,3.67)	
Treatment Group						0.799
Enalapril	64(5.1)	218(6.1)	19(17.1)	1.22(0.91,1.64)	2.51(1.39,4.55)	
Enalapril–FA	55(4.4)	223(6.4)	13(10.6)	1.32(0.96,1.81)	2.11(1.09,4.08)	
MTHFR C677T						0.525
CC	28(4.8)	90(5.4)	9(16.7)	1.18(0.75,1.86)	2.77(1.17,6.57)	
CT	60(4.8)	228(6.5)	14(11.9)	1.26(0.93,1.70)	1.55(0.76,3.15)	
TT	31(4.6)	123(6.5)	9(14.5)	1.35(0.89,2.05)	3.61(1.70,7.69)	
Homocysteine, μmol/L						0.634
<12.0	55(4.2)	184(5.4)	17(14.8)	1.18(0.86,1.61)	2.56(1.41,4.63)	
≥12.0	63(5.4)	251(7.0)	15(12.8)	1.32(0.98,1.78)	2.02(1.04,3.91)	

FIGURE 3. Association between hypertensive retinopathy (mild/grade 1-2 and severe/grade 3-4 *vs.* normal) and first stroke in subgroups*. *Adjusted for age, sex, BMI, SBP, DBP, diabetes, triglycerides, total cholesterol, high-density lipoprotein, serum folic acid, tHcy, fasting glucose, serum creatinine, treatment group, methylenetetrahydrofolate reductase C677T genotype, and smoking and alcohol consumption status.

Subgroup Analyses

We further performed stratified analyses and interaction tests to assess the relationship of hypertensive retinopathy with first stroke in various subgroups. None of the variables, including sex (*P*-interaction = 0.338), age (<65 vs. ≥65 years, *P*-interaction = 0.908), BMI (<24 vs. ≥24 kg/m², *P*-interaction = 0.958), diabetes status (no vs. yes, *P*-interaction = 0.989), SBP (<140 vs. ≥140 mmHg, *P*-interaction = 0.608), treatment group (enalapril vs. enalapril-folic acid, *P*-interaction = 0.799), *MTHFR* C677T polymorphism (CC/CT vs. TT, *P*-interaction = 0.525) and tHcy (<12 vs. ≥12 μmol/L, *P*-interaction = 0.634), significantly modified the association between hypertensive retinopathy and first stroke (Fig. 3).

Discussion

This study, which is a post-trial follow-up of the CSPPT, revealed that hypertensive retinopathy was associated with first stroke in Chinese hypertensive patients, and we did not observe significant differences in the subgroup analyses. In addition, a simplified two-grade classification system based on the KWB grading system is recommended for predicting stroke risk.

The association between retinal microvascular anomalies and stroke has been investigated in many previous studies. The Atherosclerosis Risk in Communities study carried out in the United States reported that any retinopathy was associated with incident total stroke (RR, 2.58 [95% CI, 1.59–4.20]) and incident ischemic stroke (RR, 2.60 [95% CI, 1.55–4.34]).[25] The Cardiovascular Health Study revealed that retinopathy was associated with prevalent stroke (OR, 2.0 [95% CI, 1.1–3.6]) in a multiethnic community-based cross-sectional study of white and black individuals.[26] The Blue Mountains Eye Study reported that retinopathy was significantly associated with combined stroke events in Australians without diabetes (RR, 1.7 [95% CI, 1.0–2.8]).[27] In addition, there are some studies on the Asian population. In the Shibata study carried out in Japan, Nakayama et al.[28] found that funduscopic abnormalities (Keith-Wagner II or higher) were associated with stroke in men (RR, 3.42 [95% CI, 1.03–11.31]). Of note, only a few studies have investigated the hypertensive retinopathy-stroke association in hypertensive patients. In a cohort study of hypertensive patients in Korea, the presence of hypertensive retinopathy (using the KWB classification) increased the risk of subclinical stroke (OR, 2.17 [95% CI, 0.95–4.96] for grade 1; OR, 2.98 [95% CI, 1.20–7.42] for grade 2).[29] A previous prospective study that included hypertensives from the Atherosclerosis Risk in Communities study revealed that participants with moderate hypertensive retinopathy had a higher stroke risk (HR, 2.37 [95% CI 1.39–4.02]).[30]

Interestingly, our results showed that the HR in our patients was lower than that in previous Asian studies (Japanese or Korean) and was closer to the results of Western studies. This is probably because all of our participants used antihypertensive agents (enalapril + folate or enalapril alone), and their blood pressure (BP) was better controlled. In the days when BP was not treated, 20% of strokes (or more) were due to hypertensive intracerebral hemorrhage.[31] However, in our primary outcomes, only 13% (77/592) of the strokes were hemorrhagic strokes, which means that BP was well controlled in most of the participants. Most participants had grade 1 hypertension and below, accounting for 85.77% (BP distribution is shown in Supplemental Fig. S1).

However, the discrepancy may also be attributed to different primary outcomes in Japanese or Korean studies (the Japanese primary outcomes included intracerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage and stroke of undetermined type[28]; the Korean study's primary outcome was silent brain infarction).[29] Moreover, our results reveal no interaction with sex; however, an increased stroke risk was observed among men but not among women in Shibata's study.[28] Our study and Shibata's study are both based on a rural Asian population; however, our study only included hypertensive patients, and we had a higher female percentage in our study population (58.3% in Shibata's study
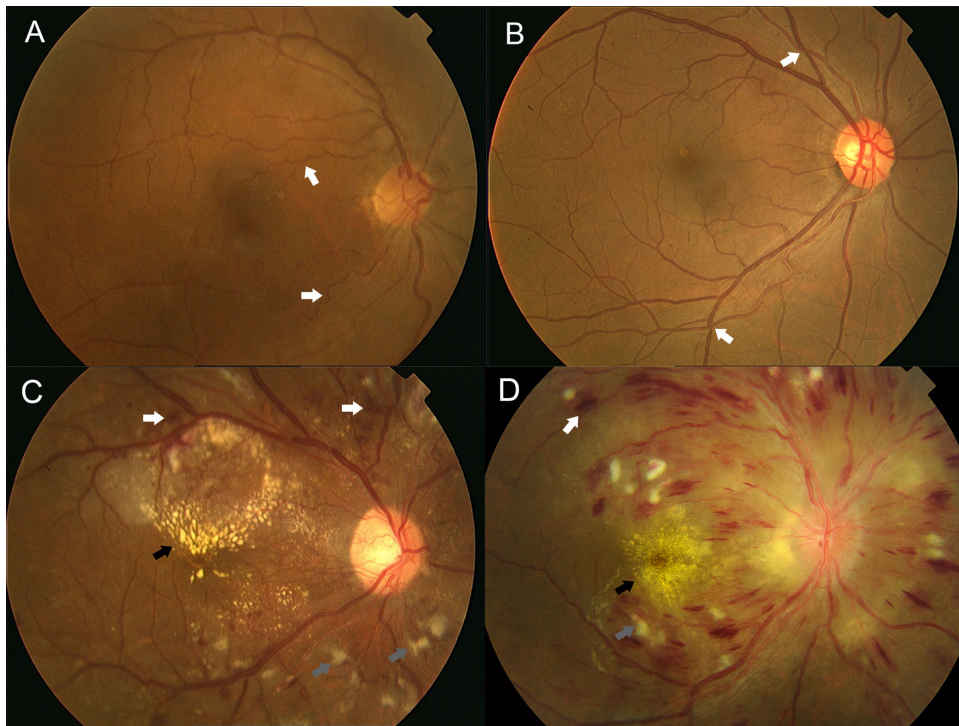
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FIGURE 4. Examples of four grades of hypertensive retinopathy (Keith-Wagener-Barker Classification System). (**A**) Grade 1 hypertensive retinopathy showing mild generalized retinal arteriolar narrowing and arteriovenous tortuosity (*white arrow*). (**B**) Grade 2 hypertensive retinopathy showing focal narrowing and arteriovenous nicking (*white arrow*). (**C**) Grade 3 hypertensive retinopathy showing multiple retinal hemorrhages (*white arrows*), exudates (*black arrow*) and cotton-wool spots (*gray arrow*). (**D**) Grade 4 hypertensive retinopathy showing multiple retinal hemorrhages (*white arrows*), exudates (*black arrow*), cotton-wool spots (*gray arrow*), and swelling of the optic disk.

and 61.9% in our study). The high percentage of females in our cohort may reflect the unique situation of rural areas in China in which most adult men leave town to work while most women stay in their hometown to take care of the family and children, so female residents were easier to include and follow up in our study. Therefore we speculate that our study confirmed the significant relationships between hypertensive retinopathy and both cerebral infarction and intracerebral hemorrhage in women, possibly because of the accumulation of a statistically sufficient number of events. The unique background of the examined population should be considered while interpreting and generalizing these findings.

Our study provides some new insights into this field. First, there was a positive relationship of hypertensive retinopathy with the risk of first ischemic and hemorrhagic stroke. Possible mechanisms for the association between hypertensive retinopathy and the incidence of first stroke include the following: (1) Hypertension causes microvascular damage in both cerebral and retinal circulation.[20] In retinal circulation, the main manifestations in the sclerotic phase are tunica media hyperplasia, hyaline degeneration of the arteriolar wall and vessel attenuation, which may be associated with arteriovenous nicking and arteriolar tortuosity. Continuously high BP may lead to exudative changes and blood-retinal barrier breakdown, with fibrinoid necrosis, luminal narrowing and ischemia.[9] Similar changes also occur in the cerebral microvasculature, including hyaline arteriosclerosis,[32] leading to luminal narrowing, which correlates with systemic BP.[33] Pathologically, the tunica media and internal elastic lamina degenerate and are replaced by fibrous tissue. This leads to increased vessel tortuosity and permeability[34] because of the breakdown of the blood-brain barrier. Goto et al.[35] confirmed this point by finding that stroke patients showed similar histological changes in retinal and cerebral vessels on autopsy. (2) Retinal vessels share embryological, anatomical, physiological, and circulatory routes similar to those of cerebral vessels.[36,37] Embryologically, the retina is an extension of the diencephalon, and both organs share a similar pattern of vascularization during development.[38–41] The retinal and cerebral microcirculations share anatomical and physiological properties because of their similar functions, namely, acting as barrier endothelia.[42–44] The signals of blood-retinal barrier disruption, including retinal hemorrhages, microaneurysms, exudation, and cotton-wool spots, are thought to disrupt the blood-brain barrier[45] and serve as precursors to the development of cerebrovascular disease.[37,46] However, more studies are needed to further examine the underlying mechanisms.

Second, our study confirmed that a simplified two-grade classification system based on the KWB grading system is recommended for predicting stroke risk, and mild retinopathy also has significant predictive value for stroke in hypertensive patients. The current literature has challenged the prognostic significance of early retinopathy grades (grades 1 and 2) because early grades are difficult to assess clinically,[18,47] and the prognostic implications are unclear.[48] The significant angiographic differences in the perifoveal capillary density and capillary blood velocity between mild and severe hypertensive retinopathy correlate with a two-grade

rather than a four-grade classification system.[49] Wong et al.[50] proposed a simple three-grade classification system including mild, moderate, and malignant retinopathy. The theoretical basis of this grading system is that signs of mild hypertensive retinopathy have a weak and less consistent association with systemic vascular diseases, and signs of moderate hypertensive retinopathy have a strong association with subclinical cerebrovascular disease, incident clinical stroke, congestive heart failure, and cardiovascular mortality. Our two-grade classification is similar to the simple three-grade classification proposed by Wong et al.[50] The main differences between our results and Wong et al.'s results are as follows: we found a clinically significant association between mild retinopathy and first stroke and no effect-modifying factors were found (Fig. 3). However, Wong et al.[50] reported weak associations between mild retinopathy and stroke. Our data support the prognostic significance of retinopathy signs and show that patients with mild hypertensive retinopathy signs should also be on alert for first stroke, should more closely monitor their stroke risk, and may benefit from further assessment of their vascular risk. Several experimental studies[51,52] and clinical reports[53–55] conducted regressions of hypertensive retinopathy signs while controlling for blood pressure. With adequate hypertension treatment, the resolution of hypertensive retinopathy signs may occur over a period of 6 months[53] to a year.[55] Thus some hypertensive retinopathy signs are reversible, and follow-up of patients for up to a year after diagnosis may be needed. However, whether the resolution of retinopathy changes will result in a reduced stroke risk is currently unclear.

Hypertensive retinopathy is more useful in stroke risk management than other traditional stroke risk factors (e.g., age, sex, blood pressure, lipid levels, diabetes mellitus, cigarette smoking status and lifestyle factors, such as obesity, poor diet/nutrition, and physical inactivity[56]). Some traditional risk factors, such as cigarette smoking status and lifestyle factors, are difficult to quantify. Additionally, measured blood pressure provides a "snapshot" measurement in time, whereas retinopathy is stable and persistent and reflects a relatively long period of blood pressure. In addition, fundus examinations are simple, noninvasive, effective, and particularly useful in persons who do not have traditional risk factors.

Briefly, our results indicate that retinal vessels in the sclerotic phase (grades 1-2)[9] had significantly different stroke HRs than those in the exudative and blood-retinal barrier breakdown phases (grades 3-4).[8,57] Moreover, whether grade 3 (moderate) and grade 4 (malignant) retinopathy have different HRs for first stroke should be investigated in future studies.

There are several limitations of this study. First, participants were all hypertensive individuals from China; therefore, generalizability to the general population or other ethnic groups should be further verified. Second, the sample size of patients with grade 4 retinopathy was too small to conclude its relationship with stroke risk independently. Third, although many related factors were adjusted in the models, we could not exclude residual confounding effects from unmeasured factors. In our current study, the measurements of hypertensive retinopathy were conducted only at baseline, and more frequent measurements of hypertensive retinopathy would provide more important information. Confirmation of our results in more studies is needed.

CONCLUSIONS

Among adults with hypertension in China without a history of stroke, hypertensive retinopathy is associated with an increased risk of first stroke, and the predictive value of hypertensive retinopathy is independent of traditional risk factors. A simplified two-grade classification system based on the KWB grading system is recommended for predicting stroke risk, and mild retinopathy also has significant predictive value. Retinal examination should be recommended as a part of the routine assessment of stroke risk.

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