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Retinal Microvascular Abnormalities and Risk of Lacunar Stroke: The Atherosclerosis Risk in Communities Study

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Abstract

Background and Purpose—Retinal microvasculature reflects cumulative small vessel damage from hypertension and other vascular processes. No study has prospectively examined retinal findings in relation to incidence of clinical lacunar stroke in comparison with other ischemic stroke subtypes.

Methods—In 10,496 adults initially free of stroke, we related retinal findings imaged during 1993-95 with incidence of hospitalized ischemic strokes through 2005.

Results—During a median of 11.2 years 338 incident ischemic strokes occurred (lacunar: 66, nonlacunar thrombotic: 192, cardioembolic: 80). Generalized arteriolar narrowing as measured by central retinal arteriole equivalent (CRAE) was associated with an increased incidence of lacunar stroke (multivariate-adjusted hazard ratio (HR) per 1-standard deviation (SD) decrement of CRAE: 1.67, 95% confidence interval (CI): 1.23-2.26), but was not associated with other ischemic stroke subtypes. Generalized venular widening as measured by central venule equivalent (CRVE) was also positively associated with only lacunar stroke (multivariate-adjusted HR per 1-SD increment: 1.44, 95% CI: 1.09-1.91). Retinal microvascular abnormalities were positively associated with lacunar stroke incidence (HR for focal arteriolar narrowing: 2.22, 95% CI: 1.11-4.48; for arteriovenous nicking: 2.38, 95% CI: 1.20-4.71), whereas retinopathy signs (microaneurysms, retinal hemorrhages, and others) were positively associated with nonlacunar thrombotic (HR: 2.41, 95% CI: 1.47-3.95) and cardioembolic stroke incidence (HR: 2.25, 95% CI: 1.09-4.65).

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Disclosures
None.

Conclusions—Narrower CRAE, wider CRVE, focal arteriolar narrowing and arteriovenous nicking were predictive of lacunar stroke. Retinal imaging is useful in understanding the pathophysiology and mechanisms of cerebral small vessel disease.

Introduction

Retinal imaging has been increasingly used as a noninvasive tool to directly evaluate subtle abnormalities or damage in the retinal microvasculature such as focal arteriolar narrowing, arteriovenous (AV) nicking, retinopathy and retinal vascular caliber.[1] Because the retinal microvasculature shares embryologic and anatomic characteristics with that of the cerebral circulation,[2] studying the associations of retinal abnormalities may provide clues to understanding the underlying pathophysiology of different cerebrovascular diseases.[3] In the Atherosclerosis Risk in Communities (ARIC) Study, retinal microvascular abnormalities and generalized arteriolar narrowing were associated with an increased incidence of clinical stroke events,[4] and in persons without clinical stroke, with a higher prevalence of MRI-defined subclinical cerebral infarction[5] and white matter lesions.[6] These findings have been confirmed in other populations.[7-9] Furthermore, a clinic-based cross-sectional study among acute stroke patients found an association between retinal microvascular abnormalities and generalized arteriolar narrowing, and the presence of lacunar stroke, suggesting that microvascular disease pathways were more important in lacunar stroke.[10] No previous studies, however, have prospectively examined whether the presence of retinal microvascular abnormalities is associated with an increased incidence of lacunar stroke in comparison with other ischemic stroke subtypes.[11]

We conducted a prospective analysis in the ARIC Study, where the standardized measurements of retinal images were performed for over 10,000 participants and the subsequent occurrence of stroke followed up for more than 10 years. We hypothesized that retinal microvascular abnormalities are associated prospectively with increased incidence of clinical lacunar stroke but not with other subtypes of ischemic stroke.

Methods

Study population

The ARIC Study included a cohort of 15,792 persons between 45 and 64 years of age at recruitment in 1987 through 1989.[12] The present study sample is composed of individuals who participated in the third examination in 1993-95, when retinal photography was first performed. Of the 12,887 who participated in this examination, we excluded 38 whose race was neither black nor white, 245 with no retinal photographs, 1,566 with ungradeable photographs, 20 with retinal vein occlusions and 2 with retinal artery occlusions, and 303 with missing information on any of the covariates. We further excluded 120 with a history of stroke at visit 1, and 56 who developed stroke (43 ischemic and 13 hemorrhagic) between visit 1 and visit 3, leaving 10,496 subjects (1,381 black women, 797 black men, 4,485 white women, and 3,833 white men) free of stroke at visit 3 for the present analysis.

Assessment of retinal vascular caliber

The retinal photography procedure and grading of retinal microvascular signs are described elsewhere.[13] Briefly, a 45-degree retinal photograph of 1 randomly selected eye of each participant was taken at visit 3 following 5 minutes of dark adaptation. This photograph was centered on the region of the optic disc and the macula and was taken using an autofocus camera.

Trained graders masked to participant characteristics used a computer-assisted approach to measure the calibers of all arterioles and venules coursing through a specified area surrounding the optic disc. Individual vessel measurements were combined into summary indices—the central retinal arteriole equivalent (CRAE) and the central retinal venule equivalent (CRVE). These indices represent the estimated central retinal arteriolar and venular caliber of the eye after taking into account the branching patterns. These measurements are reliable, with intragrader and intergrader reliability coefficients of 0.69 and 0.74 for CRAE and 0.89 and 0.77 for CRVE, respectively.[13]

Retinal microvascular abnormalities

Trained graders masked to the clinical status of the participants also assessed for presence of microvascular abnormalities. Definite focal arteriolar narrowing was defined if an arteriole estimated to be 50-μm diameter of greater had a constricted area of 2/3 or less the width of proximal and distal vessel segments. Definite AV nicking was defined if the venous blood column was tapered on both sides of its crossing under the arteriole. Retinopathy signs were evaluated without assumption of cause as described previously, and were considered present if any of the following findings (definite) were noted: retinal hemorrhages, microaneurysms, soft and hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, fibrovascular proliferation, vitreous hemorrhage, disc swelling, and laser photocoagulation scars.[4]

Ascertainment of incident stroke

Hospitalized ischemic strokes that occurred by December 31, 2005 (median follow-up 11.2 years, from visit 3) were included in the present study. Details on quality assurance for ascertainment and classification of stroke are described elsewhere.[14] All definite ischemic strokes were further classified as either lacunar or nonlacunar on the basis of the recorded neuroimaging results. A stroke was classified as “lacunar” when two criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤ 2 cm or unstated size. Definite or probable “cardioembolic” stroke required the same criteria as ischemic infarction, plus either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain or (2) medical record evidence of a possible source of embolus such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure, or intracardiac thrombus. Definite or probable ischemic strokes that were not deemed lacunar or embolic were labeled “nonlacunar.” CT or MRI was available for all the ischemic stroke cases except one case adjudicated as cardioembolic stroke with carotid ultrasound information. Strokes secondary to trauma, neoplasm, hematological abnormality, infection, or vasculitis were excluded.

Statistical analysis

Since no interactions of race or sex with retinal vascular caliber quintiles or retinal microvascular abnormality categories was observed ($P>0.1$, Wald test), analyses were done combining the race- and sex-groups. Age-, sex- and race- adjusted means and proportions among categories of retinal findings were calculated and tested by a general linear model. Since arteriolar and venular calibers are positively correlated, and the width of these calibers are determined not only by pathological processes but normal anatomical variation or measurement error, we simultaneously adjusted for the fellow-vessel caliber as a covariate in the analyses for retinal vascular calibers, as described previously.[15] Cox proportional hazards regression was used to calculate minimally-adjusted (as described above) and multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for subtypes of ischemic stroke incidence in relation to quintiles of the retinal vascular calibers or the presence of microvascular

abnormalities. Multivariate-adjusted models included variables in the minimal model plus educational level (more than high school graduate or not), smoking status (current, past, or never), usual ethanol intake (grams/week), leisure time sport index score (1.0-1.9, 2.0-2.4, 2.5-2.9, 3.0-5.0),[16] systolic blood pressure (SBP), antihypertensive medication use or antiplatelet medication use, prevalent diabetes, waist circumference, and plasma high-density lipoprotein (HDL) cholesterol. All the covariates were assessed at visit 3[5] except for SBP for which we used the average value of visit 1 and visit 3 measurements. A sport score was calculated ranging from 1 (lowest) to 5 (highest). Diabetes was defined a history of, or treatment for, diabetes, a fasting glucose level of 126 mg/dl or greater, or a casual blood glucose level of 200 mg/dl or greater. Aspirin use encompassed use for seven or more days in the previous two weeks of the interview for the prevention of heart attack or stroke. A trend test for the retinal vascular caliber analysis was performed by assigning the median value of each quintile to corresponding individuals and treating it as a continuous variable in the model.

CRAE and CRVE were also examined as continuous variables as divided by one standard deviation (SD) of each variable. For both vessel quintiles and each microvascular abnormality, the hazard proportionality assumption was verified prior to the analyses. We tested whether proportional hazard regression coefficients for each retinal finding variable differed significantly by subtype, that is, between lacunar and nonlacunar and between lacunar and cardioembolic, using competing risks analysis.[17] This was done by computing a test statistic: $(b_1\text{-}b_2)^2/\{[se(b_1)]^2+[se(b_2)]^2\}$ where b_1 is the coefficient for a retinal finding variable for lacunar stroke, and b_2 is the corresponding coefficient for the outcome to be compared, and se (b_1) is the standard error of the variable for lacunar stroke and $se(b_2)$ is the corresponding standard error for the other outcome. The test statistic was compared to a 1-degree of freedom Wald chi-square distribution (two-sided, $\alpha=0.05$). All statistical analyses were performed by SAS.

Results

Mean (SD) CRAE and CRVE were 162.4 (16.7) μm and 193.1 (16.7) μm, respectively. Men had a narrower CRAE than women (160.3 vs. 164.0 μm, $p<0.0001$) and blacks had a narrower CRAE than whites (160.9 vs. 162.7 μm, $p<0.0001$). Men had a wider CRVE than women (195.2 vs. 191.4 μm) and blacks had wider CRVE than whites (198.5 vs. 191.6 μm), both $p<0.0001$. CRAE was inversely associated with age (Table 1). Usual ethanol intake, antihypertensive medication use, SBP, and waist circumference were inversely associated with CRAE. In contrast, the prevalence of current smoking, ethanol intake, antihypertensive medication use, SBP, and diabetes were positively and HDL cholesterol was inversely associated with CRVE.

The prevalence of definite focal arteriolar narrowing, AV nicking, and retinopathy signs were 7.0%, 5.8%, and 3.8%, respectively (Table 2). All the microvascular abnormalities were significantly associated with older age, greater antihypertensive medication use, higher SBP, and greater waist circumference.

During a median of 11.2 years of follow-up (max=12.8 y), there were 338 incident ischemic strokes, 66 of which were lacunar, 192 nonlacunar thrombotic, and 80 cardioembolic. In the Cox regression analyses, CRAE was inversely associated only with lacunar stroke incidence (multivariate-adjusted HR for Q1 vs. Q5: 5.21, 95% CI: 1.92-14.1; HR for 1 SD decrement of CRAE: 1.67, 95% CI: 1.23-2.26, Table 3). A borderline association between CRAE and nonlacunar thrombotic stroke was totally attenuated by adjustment for SBP (66% reduction in the parameter estimate for CRAE after inclusion of SBP in the model). Competing risks analysis confirmed that the HR for 1 SD decrement of CRAE was significantly greater for lacunar stroke than nonlacunar thrombotic (P=0.03) or cardioembolic stroke (P=0.005).

CRVE was positively associated also only with lacunar stroke incidence (multivariate-adjusted trend p=0.032; HR for 1 SD increment of CRVE: 1.44, 95% CI: 1.09-1.91, Table 4). Similarly to the CRAE analyses, SBP alone eliminated the significant associations between CRVE and nonlacunar thrombotic and cardioembolic stroke (25% and 20% reductions in the parameter estimates, respectively, after inclusion of SBP in the model) (data not shown). Despite the apparent stronger association of CRVE with lacunar stroke than other ischemic stroke subtypes, competing risks analysis showed that the HRs for 1 SD increment of CRVE were not significantly different across subtypes.

Focal arteriolar narrowing and AV nicking were significantly and positively associated with lacunar stroke incidence (multivariate-adjusted HR for focal arteriolar narrowing: 2.22, 95% CI: 1.11-4.48, multivariate-adjusted HR for AV nicking: 2.38, 95% CI: 1.20-4.71, Table 5). Although retinopathy signs were significantly associated with lacunar stroke incidence in minimally-adjusted model, multivariate adjustment attenuated the association. This attenuation was explained by the adjustment for prevalent diabetes (43% reduction in the parameter estimate in the Cox model). In contrast, higher incidence of both nonlacunar thrombotic and cardioembolic stroke were significantly associated with retinopathy signs even after multivariate adjustment (HR for nonlacunar thrombotic stroke: 2.41, 95% CI: 1.47-3.95, HR for cardioembolic stroke: 2.25, 95% CI: 1.09-4.65). Despite these apparent differences among subtypes, the HR values were not significantly different. Results from sub-analyses with further adjustment for intima-media thickness were essentially the same.

Although subjects with hypertension and diabetes had about four times higher incidence rates of lacunar stroke than those without (1.2 vs. 0.3 and 1.8 vs. 0.4 per 1,000 person-years, respectively), there was no evidence hypertension or diabetes modified the associations of CRAE, CRVE, or other retinal microvascular abnormalities with stroke subtypes. However, the number of lacunar stroke events was low and power to detect interactions was limited.

Discussion

The main finding of this prospective population-based study is that narrower retinal arteriolar caliber and larger venular caliber, measured quantitatively from photographs, were associated significantly with incident lacunar stroke, independent of confounding variables such as SBP and diabetes. Similarly, focal arteriolar narrowing and AV nicking were also associated with lacunar stroke independent of the confounding variables, including SBP. However, one caveat is that formal statistical testing suggested that the HRs differed significantly between lacunar and other ischemic stroke subtypes only for CRAE. Yet, we consider it important that HRs for retinal findings were statistically significantly greater than 1.0 for lacunar stroke, despite the fewest number of events.

Our prospective population-based study demonstrating an association between retinal microvascular signs and incident lacunar stroke is consistent with a recent clinic-based cross-sectional study that showed acute lacunar stroke cases were more likely to have retinal focal arteriolar narrowing, AV nicking, generalized retinal arteriolar narrowing and generalized venular widening.[10] The current finding further supports our previous analysis in an ARIC sub-sample in which MRI-defined subclinical cerebral infarct was associated positively with AV nicking and focal arteriolar narrowing, independent of blood pressure, diabetes and other factors.[5] Taken in totality, these data provide further evidence that lacunar stroke is associated with retinal microvascular changes possibly reflecting similar pathological processes in the cerebrovasculature.

In contrast to retinal arteriolar narrowing, recent studies suggest that retinal venular widening is a risk marker of stroke, and is associated with measures of atherosclerosis, inflammation and

dyslipidemia.[18, 19] However, retinal venular widening remained independently associated with lacunar stroke incidence. Recently, retinal venular width was related to reduced arterial wall compliance in small arterial beds,[20] which has been suggested to be a marker of endothelial dysfunction. Our finding would reinforce the view of possible involvement of endothelial dysfunction in the pathogenesis of lacunar stroke.[21-23]

In the present analysis, retinopathy signs were not significantly associated with lacunar stroke independent of diabetes status. Since the confidence interval was wide and the number of lacunar stroke cases with retinopathy signs was small (n=9), this finding might have arisen by chance. Further follow-up studies in patients with diabetes are probably needed to examine the significance of retinopathy signs for the prediction of lacunar stroke.

The present study provides further support that retinal imaging may yield significant predictive information for lacunar stroke that could not be obtained by measurements of conventional risk factors. There are several possible explanations for this finding. First, retinal microvascular signs may reflect susceptibility, vulnerability or damage of cerebral small vessels. Although such damage may be attributed to hypertension, retinal findings may be providing more information than just the degree of blood pressure elevation.[24] Such vulnerability may be determined genetically,[25] embryonically,[26] or by other environmental factors;[27] however, whether or not these factors modify the effect of blood pressure on retinal microcirculation has yet to be elucidated. Other confounding or mediating variables exist besides those related to blood pressure, which were not measured, such as markers of inflammation/immunity,[28] autonomic function,[29, 30] endothelial dysfunction,[22] and lifestyle factors including diet.[31]

There are several limitations that warrant discussion. First, there was a certain degree of imprecision in the retinal measurements, which, however, would likely have attenuated the association toward the null. Second, the number of cases for each ischemic stroke subtype was small. To confirm the present findings, a larger study would be needed. A strength of the present study is that we analyzed the association of retinal microvascular variables and ischemic stroke subtypes using prospective population-based data, including both blacks and whites, with a relatively large numbers of events. There are no prior prospective studies that specifically addressed the association between these measures and ischemic stroke subtypes in detail.

In conclusion, retinal vessel calibers and the presence of retinal microvascular abnormalities, measured from photographs, were predictive of lacunar stroke. These data suggest that retinal imaging is useful in understanding the pathophysiology and mechanisms of cerebral small vessel disease.

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Table 1

Age-, sex-, race, and CRVE- or CRAE-adjusted baseline characteristics according to generalized arteriolar width (CRAE quintile) and generalized venular width (CRVE quintile), ARIC, 1993-95

	Generalized arteriolar width (CRAE quintile)*						Generalized venular width (CRVE quintile)†					
	Q1	Q2	Q3	Q4	Q5		Q1	Q2	Q3	Q4	Q5	
Range (Minimum-Maximum, µm)	**81.4 148.6**	**148.7 158.4**	**158.5 166.2**	**166.3 176.0**	**176.1 240.9**	**p‡**	**127.4 179.1**	**179.2 188.6**	**188.7 196.7**	**196.8 206.5**	**206.6 276.0**	**p‡**
Age	60.0	60.0	59.7	59.3	58.9	<.0001	60.2	59.7	59.4	59.3	59.2	<.0001
Men (%)	54.7	47.3	43.9	40.3	34.1	<.0001	32.1	40.7	44.6	48.3	54.9	<.0001
Black (%)	23.2	20.7	22.4	21.2	16.2	<.0001	9.2	15.3	19.8	25.9	33.6	<.0001
More than high school graduate (%)	48.7	50.2	46.7	46.5	45.7	0.042	49.5	51.2	48.3	45.8	42.9	<.0001
Current smoker (%)	17.4	15.1	15.6	16.2	22.5	<.0001	9.2	12.0	15.2	19.4	31.1	<.0001
Usual ethanol intake (g/week)	49.3	44.7	40.7	42.4	31.2	<.0001	33.3	37.0	40.0	45.1	53.3	<.0001
Leisure time sports index (>=3) (%)	30.8	32.8	33.4	36.0	36.5	0.0029	37.6	35.7	33.5	33.0	29.5	<.0001
Antihypertensive medication use (%)	38.2	33.3	28.9	26.7	21.0	<.0001	25.4	28.7	28.9	30.2	35.0	<.0001
Diabetes mellitus (%)	15.0	13.3	14.5	13.8	13.0	0.38	11.8	13.0	12.8	13.1	18.8	<.0001
Aspirin use (%)	10.3	10.9	9.9	10.3	11.0	0.78	11.2	10.7	10.6	9.7	10.2	0.64
Waist circumference (cm)	103.0	101.4	100.3	100.0	97.5	<.0001	98.2	99.1	100.6	101.7	102.6	<.0001
Mean systolic blood pressure (mmHg)	128.9	124.1	121.2	119.3	114.2	<.0001	118.5	120.6	121.4	122.5	124.8	<.0001
High density lipoprotein cholesterol (IU/L)	1.36	1.35	1.35	1.34	1.35	0.71	1.39	1.38	1.35	1.33	1.31	<.0001

CRAE denotes central retinal arteriole equivalent; CRVE, central retinal vein equivalent.

*Age, sex, race, and CRVE (continuous) adjusted.

†Age, sex, race, and CRAE (continuous) adjusted.

‡Adjusted means and proportions and according to quintiles, and p-values for overall difference, were calculated by a general linear model.

Table 2

Age-, sex-, and race-adjusted baseline characteristics according to presence of focal narrowing, arteriovenous nicking and retinop signs, ARIC, 1993-95

	Focal narrowing*			Arteriovenous nicking*			Retinopathy signs*		
	Absent n=9,671	Present n=731	p†	Absent n=9,828	Present n=609	p‡	Absent n=9,597	Present n=375	p‡
Age (y)‡	59.4	61.8	<0.0001	59.5	60.8	<0.0001	59.4	60.3	0.003
Men (%)‡	44.2	42.9	0.5	44.1	44.1	1.0	43.6	50.1	0.01
Black (%)‡	21.2	15.8	<0.001	20.5	26.4	<0.001	19.6	43.3	<0.0001
More than high school graduate (%)	47.8	45.3	0.2	47.9	42.5	0.010	48.1	37.5	<0.0001
Current smoker (%)	17.4	16.1	0.4	17.1	21.7	0.004	17.3	16.5	0.7
Usual ethanol intake (g/week)	41.5	42.6	0.7	41.2	46.0	0.2	41.7	23.0	<0.0001
Leisure time sports index (>=3) (%)	34.1	30.3	0.04	34.0	31.2	0.2	34.2	26.2	0.001
Antihypertensive medication use (%)	29.1	37.3	<0.0001	29.1	38.1	<0.0001	29.0	46.9	<0.0001
Diabetes mellitus (%)	13.9	13.5	0.8	13.8	14.2	0.8	12.1	56.0	<0.0001
Aspirin use (%)	10.6	8.5	0.08	10.3	13.0	0.03	10.3	14.7	0.005
Waist circumference (cm)	100.3	102.5	<0.0001	100.3	103.2	<0.0001	100.3	105.1	<0.0001
Mean systolic blood pressure (mmHg)	120.8	131.1	<0.0001	121.3	125.7	<0.0001	121.3	126.2	<0.0001
High density lipoprotein cholesterol (IU/L)	1.35	1.36	0.8	1.35	1.32	0.05	1.36	1.24	<0.0001

*The numbers of subjects missing information were 94 for focal narrowing, 59 for arteriolar nicking, and 524 for retinopathy signs.

†Age-, sex-, and race-adjusted means and proportions and according to presence of each microvascular abnormality, and p-values were calculated by a general linear model.

‡Sex- and race-adjusted mean age, Age- and race-adjusted proportion of men, and Age- and sex-adjusted proportion of blacks.

Table 3

Generalized arteriolar width (CRAE quintile) and incidence and hazard ratios (95% CIs) of ischemic stroke subtypes, ARIC, 1993-2005

	Generalized arteriolar width (CRAE quintile)						
Ischemic stroke subtype	**Q5**	**Q4**	**Q3**	**Q2**	**Q1**	**trend p**	**HR1**
Lacunar							
Number of cases	7	12	17	10	20		
Person-years	22,598	22,617	22,134	22,107	22,048		
Incidence rate*	0.3	0.5	0.8	0.5	0.9		
Minimally-adjusted†	1 (reference)	2.15 (0.84-5.53)	3.70 (1.49-9.21)	2.68 (0.97-7.40)	7.06 (2.69-18.49)	<0.001	1.85 (1.38-2.48)§
Multivariate-adjusted‡	1 (reference)	1.95 (0.75-5.03)	3.31 (1.32-8.30)	2.19 (0.78-6.12)	5.21 (1.92-14.13)	0.0014	1.67 (1.23-2.26)§
Nonlacunar thrombotic							
Number of cases	37	28	38	46	43		
Person-years	22,598	22,617	22,134	22,107	22,048		
Incidence rate*	1.6	1.2	1.7	2.1	2.0		
Minimally-adjusted†	1 (reference)	0.76 (0.46-1.25)	1.08 (0.67-1.73)	1.35 (0.85-2.15)	1.36 (0.82-2.25)	0.065	1.18 (0.99-1.40)
Multivariate-adjusted‡	1 (reference)	0.73 (0.44-1.19)	1.00 (0.62-1.61)	1.22 (0.76-1.96)	1.05 (0.62-1.77)	0.4	1.07 (0.90-1.28)
Cardioembolic							
Number of cases	18	20	15	12	15		
Person-years	22,598	22,617	22,134	22,107	22,048		
Incidence rate*	0.8	0.9	0.7	0.5	0.7		
Minimally-adjusted†	1 (reference)	1.19 (0.63-2.28)	0.99 (0.49-2.02)	0.87 (0.40-1.89)	1.25 (0.57-2.74)	0.8	1.05 (0.81-1.36)
Multivariate-adjusted‡	1 (reference)	1.06 (0.55-2.03)	0.85 (0.41-1.74)	0.67 (0.31-1.45)	0.78 (0.35-1.76)	0.3	0.89 (0.68-1.17)

HR denotes hazard ratio; CI, confidence interval; CRAE, central retinal artery equivalent.

Trend test was performed by assigning the median value of each quintile to corresponding individuals and treating it as a continuous variable in the model. HR1: HR per 1 standard deviation (16.7 μm) decrement of CRAE.

*Incidence rate is expressed as rate per 1,000 person-years.

†Minimally-adjusted model includes age, sex, race and central retinal vein equivalent (CRVE).

‡Multivariate model includes age, sex, race, CRVE, smoking status, usual alcohol consumption, physical activity, education level, antihypertensive medication, prevalent diabetes, waist circumference, and HDL cholesterol all assessed at visit 3, and mean systolic blood pressure assessed at visit 1 and 3.

[§] HR1 for lacunar stroke significantly stronger than for nonlacunar (p=0.03) or cardioembolic (p=0.005) by competing risks analysis.

Table 4

Generalized venular width (CRVE quintile) and incidence and hazard ratios (95% CIs) of ischemic stroke subtypes, ARIC, 1993-2005

	Generalized venular width (CRVE quintile)						
						trend p	HR1
Ischemic stroke subtype	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**		
Lacunar							
Number of cases	12	6	14	12	22		
Person-years	22,467	22,322	22,469	22,398	21,848		
Incidence rate*	0.5	0.3	0.6	0.5	1.0		
Minimally-adjusted†	1 (reference)	0.61 (0.23-1.66)	1.52 (0.68-3.44)	1.39 (0.58-3.32)	2.93 (1.26-6.84)	0.0028	1.71 (1.29-2.25)§
Multivariate-adjusted‡	1 (reference)	0.54 (0.20-1.47)	1.32 (0.58-3.02)	1.20 (0.50-2.91)	2.03 (0.86-4.83)	0.032	1.44 (1.09-1.91)§
Nonlacunar thrombotic							
Number of cases	32	43	36	29	52		
Person-years	22,467	22,322	22,469	22,398	21,848		
Incidence rate*	1.4	1.9	1.6	1.3	2.4		
Minimally-adjusted†	1 (reference)	1.48 (0.93-2.37)	1.30 (0.79-2.15)	1.09 (0.64-1.87)	2.15 (1.28-3.62)	0.019	1.26 (1.06-1.49)
Multivariate-adjusted‡	1 (reference)	1.44 (0.90-2.29)	1.20 (0.73-1.97)	0.95 (0.55-1.64)	1.62 (0.95-2.75)	0.2	1.12 (0.94-1.33)
Cardioembolic							
Number of cases	14	11	13	13	29		
Person-years	22,467	22,322	22,469	22,398	21,848		
Incidence rate*	0.6	0.5	0.6	0.6	1.3		
Minimally-adjusted†	1 (reference)	0.77 (0.35-1.72)	0.89 (0.41-1.96)	0.86 (0.38-1.93)	1.90 (0.89-4.07)	0.045	1.38 (1.06-1.78)
Multivariate-adjusted‡	1 (reference)	0.75 (0.34-1.67)	0.85 (0.39-1.86)	0.77 (0.34-1.74)	1.46 (0.67-3.16)	0.2	1.26 (0.97-1.63)

HR denotes hazard ratio; CI, confidence interval; CRVE, central retinal vein equivalent.

Trend test was performed by assigning the median value of each quintile to corresponding individuals and treating it as a continuous variable in the model. HR1: HR per 1 standard deviation (16.7 μm) increment of CRVE.

*Incidence rate is expressed as rate per 1,000 person-years.

†Minimally-adjusted model includes age, sex, race and central retinal artery equivalent (CRAE).

‡Multivariate model includes age, sex, race, CRAE, smoking status, usual alcohol consumption, physical activity, education level, antihypertensive medication, prevalent diabetes, waist circumference, and HDL cholesterol all assessed at visit 3, and mean systolic blood pressure assessed at visit 1 and 3.

§HR1 for lacunar stroke not significantly different (p>0.05) from nonlacunar and cardioembolic by competing risks analysis.

Table 5

Retinal microvascular abnormalities and incidence and hazard ratios (95% CIs) of ischemic stroke subtypes, ARIC, 1993-2005

	Retinal microvascular abnormalities					
	Focal narrowing		Arteriovenous nicking		Retinopathy signs‡	
Ischemic stroke subtypes	Absent	Present	Absent	Present	Absent	Present
Lacunar						
Number of cases	56	10	56	10	53	9
Person-years	102,972	7,515	104,648	6,211	102,466	3,553
Incidence rate*	0.5	1.3	0.5	1.6	0.5	2.5
Age-, sex-, race-adjusted	1 (reference)	2.69 (1.36-5.32)§	1 (reference)	2.75 (1.40-5.40)§	1 (reference)	3.62 (1.77-7.42)§
Multivariate-adjusted †	1 (reference)	2.22 (1.11-4.48)§	1 (reference)	2.38 (1.20-4.71)§	1 (reference)	1.90 (0.88-4.100§
Nonlacunar thrombotic						
Number of cases	164	25	173	19	159	21
Person-years	102,972	7,515	104,648	6,211	102,466	3,553
Incidence rate*	1.6	3.3	1.7	3.1	1.6	5.9
Age-, sex-, race-adjusted	1 (reference)	1.77 (1.16-2.71)	1 (reference)	1.60 (1.00-2.57)	1 (reference)	3.21 (2.03-5.10)
Multivariate-adjusted †	1 (reference)	1.48 (0.96-2.29)	1 (reference)	1.43 (0.89-2.30)	1 (reference)	2.41 (1.47-3.95)
Cardioembolic						
Number of cases	72	8	75	5	65	10
Person-years	102,972	7,515	104,648	6,211	102,466	3,553
Incidence rate*	0.7	1.1	0.7	0.8	0.6	2.8
Age-, sex-, race-adjusted	1 (reference)	1.46 (0.70-3.05)	1 (reference)	1.02 (0.41-2.53)	1 (reference)	3.67 (1.87-7.22)
Multivariate-adjusted †	1 (reference)	1.05 (0.49-2.22)	1 (reference)	0.85 (0.34-2.12)	1 (reference)	2.25 (1.09-4.65)

*Incidence rate is expressed as rate per 1,000 person-years.

†Multivariate model includes age, sex, race, smoking status, usual alcohol consumption, physical activity, education level, antihypertensive medication, prevalent diabetes, waist circumference, HDL cholesterol all assessed at visit 3, and mean systolic blood pressure assessed at visit 1 and 3.

‡Retinopathy signs are any one of the following abnormalities: hemorrhages, microaneurysms, soft and hard exudates, intraretinal microvascular abnormalities, neovascularization at the disc and elsewhere, vitreous and preretinal hemorrhage, fibrovascular proliferation, macular edema, and laser photocoagulation scar.

§HR for lacunar stroke not significantly different (p>0.05) from nonlacunar and cardioembolic by competing risks analysis.