Quantitative Retinal Venular Caliber and Risk of Cardiovascular Disease in Older Persons

The Cardiovascular Health Study

Tien Yin Wong, MD, PhD; Aruna Kamineni, MPH; Ronald Klein, MD, MPH; A. Richey Sharrett, MD, DrPH; Barbara E. Klein, MD, MPH; David S. Siscovick, MD, MPH; Mary Cushman, MD, MSc; Bruce B. Duncan, MD, PhD

Background: Small vessel disease may contribute to the risk of cardiovascular disease in older persons. We describe the relation of retinal vascular caliber to incident coronary heart disease (CHD) and stroke in elderly persons.

Methods: Prospective population-based cohort study composed of 1992 men and women aged 69 to 97 years living in 4 US communities. Retinal arteriolar and venular calibers were measured from retinal photographs using a computer-assisted method. Incident CHD and stroke events were ascertained using standardized methods.

Results: After 5 years of follow-up, there were 115 incident CHD events and 113 incident stroke events. Participants with larger retinal venular caliber had a higher incidence of CHD (11.7%; 95% confidence interval [CI], 8.7%-15.8%, vs 8.1%; 95% CI, 5.7%-11.6%), comparing largest with smallest venular caliber quartiles, and stroke (8.4%; 95% CI, 6.0-11.7, vs 5.8%; 95% CI, 3.9-8.4). At multivariable analysis, controlling for age, sex, race, arteriolar caliber, systolic and diastolic blood pressure, diabetes, glucose concentration, cigarette smoking, pack-years of smoking, and high-density-lipoprotein and low-density lipoprotein cholesterol levels, larger retinal venular caliber was associated with incident CHD (rate ratio, 3.0; 95% CI, 1.6-5.7, comparing largest with smallest venular caliber quartiles; $P_{trend}=.001$) and incident stroke (rate ratio, 2.2; 95% CI, 1.1-4.3; $P_{trend}=.02$). Additional adjustment for C-reactive protein and common and internal carotid artery intimal-media thickness had minimal effect on these associations. At multivariable analysis, smaller retinal arteriolar caliber was associated with incident CHD (rate ratio, 2.0; 95% CI, 1.1-3.7, comparing largest with smallest arteriolar caliber quartiles; $P=.03$) but not stroke (rate ratio,1.1; 95% CI, 0.5-2.2; $P=.73$).

Conclusion: Larger retinal venular caliber is independently associated with risk of cardiovascular disease in elderly persons.

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CARDIOVASCULAR DISEASE IS a leading cause of death in persons aged 65 years or older in the United States.[1] Traditional risk factors do not have the same predictive value in older persons[2-8] and, thus, identification of new risk factors is important. There is increasing recognition that small vessel disease (microvascular disease) may have a possible pathophysiologic role in the development of both subclinical and clinical cardiovascular disease.[9-11] Microvascular disease affecting cerebral arterioles, for example, is linked to a large proportion of subclinical and lacunar strokes defined at magnetic resonance imaging,[12-14] whereas coronary microvascular dysfunction may explain the occurrence of myocardial ischemia in persons without overt coronary artery occlusion.[15,16] Most studies of microvascular disease have been conducted in small numbers of patients with symptomatic disease in specialized laboratory settings,[10,11] and few have been conducted in older persons.

The retinal microcirculation is accessible to noninvasive visualization, providing a unique opportunity to investigate the relationship between microvascular changes and risk of cardiovascular disease.[17] Changes in retinal arteriolar and venular caliber may represent structural damage or functional alterations.[18] Recent data from the Atherosclerosis Risk in Communities (ARIC) study, a population-based cohort study in middle-aged (51-72 years) persons, showed that a smaller arteriolar-venular caliber ratio (AVR), reflecting narrowed arterioles or enlarged venules, was associated with risk of incident stroke events and coronary heart disease (CHD) events, independent of standard risk factors.[19,20] Whether retinal arteriolar narrowing and venular dilation have similar predictive values in older persons is less clear and has not been consis-

Author Affiliations are listed at the end of this article.

tently demonstrated in 3 cohort studies with older participants (the Beaver Dam Eye Study, the Blue Mountains Eye Study, and the Rotterdam Study).[21-24]

In the Cardiovascular Health Study (CHS), a population-based study of persons 65 years or older, we have previously described cross-sectional associations of narrowed retinal arterioles with higher blood pressure and prevalent cardiovascular disease.[25,26] In the current study, we examine prospectively the association of retinal vascular caliber to incident CHD and stroke.

METHODS

STUDY POPULATION

The CHS is a population-based, longitudinal investigation of CHD and stroke in adults 65 years of age and older.[27] The study design and methods are described in detail elsewhere.[28] In brief, 5201 eligible persons were recruited in 1989 through 1990 in 4 field centers: Allegheny County (Pennsylvania), Forsyth County (North Carolina), Sacramento County (California), and Washington County (Maryland). An additional 687 eligible African Americans aged 65 years or older were recruited from Forsyth County, Sacramento County, and Allegheny County in 1992 through 1993. Differences between those recruited and those not recruited are described elsewhere.[28] At the study clinic, all participants underwent a standardized interview, physical examination including blood pressure and anthropometric measurements, carotid ultrasonography, and phlebotomy for blood chemistry studies.[29-32]

Photographic examination of the retina was first offered to participants during the 1997-1998 clinic visit.[25,26] Of the 4249 participants (95.5% of the survivors) who were contacted for this examination, 2824 (66.5%) underwent retinal photography, which was performed at the clinic. Of these, 832 (29.5%) had photographs that were ungradeable for retinal vascular caliber, leaving 1992 persons for this study. Comparisons of persons with and without gradable photographs have been previously reported.[26] Persons who did not undergo retinal photography or who had ungradeable photographs were older and more likely to be men and to be African Americans; were more likely to have hypertension and diabetes, higher systolic and diastolic blood pressure, and higher fasting glucose and total cholesterol levels; and were more likely to be current cigarette smokers.

MEASUREMENT OF RETINAL VASCULAR CALIBER

Retinal photography procedures in the CHS have been reported in detail.[25,26] In brief, after 5 minutes of dark adaptation, a 45° retinal photograph centered between the optic disc and the macula was obtained of 1 randomly selected eye. Photographs were evaluated at the Fundus Photograph Reading Center in Madison, Wis, by 2 trained and certified graders who were blinded to subject characteristics, according to a standardized protocol.

For the evaluation of retinal vascular caliber, photographs were digitized with a high-resolution scanner, and the diameters of all arterioles and venules coursing through an area ½ to 1 disc diameter from the optic disc margin were measured on a computer monitor.[25,26] The results from this image analysis were summarized as central arteriolar and venular equivalents, using formulas by Hubbard et al,[33] representing the average central arteriolar and venular caliber in that eye, respectively. These measurements were also expressed as an AVR, which represents the relative caliber of arterioles to venules and introduces some adjustment for variable magnification owing to differences in refractive errors. In addition to retinal vascular caliber, the presence of focal retinal microvascular signs (retinopathy, focal arteriolar narrowing, and arteriovenous nicking) was graded from photographs using a standardized light box protocol.[25,26]

Quality control procedures were implemented throughout the grading process.[26] In the CHS, there were 71 intragrader and 69 intergrader rereadings. The intragrader and intergrader intraclass correlation coefficients for retinal vascular caliber equivalents ranged from 0.67 to 0.91.

INCIDENT CARDIOVASCULAR DISEASE

Prebaseline and incident cardiovascular diseases were ascertained in the CHS using a detailed standardized protocol.[34,35] Participants, family members, or other previously identified informants reported new cardiovascular events during semiannual contacts by telephone or at a clinic visit. Medical records were obtained to confirm the diagnosis, and events were adjudicated by a committee.[34,35] The 2 cardiovascular outcomes of interest in this study were incident CHD, including fatal and nonfatal myocardial infarction, fatal CHD, and other CHD-attributed deaths (eg, sudden cardiac death),[34] and incident stroke, including fatal and nonfatal stroke.[35] Adjudicated events occurring through June 30, 2002, were available for analysis, providing a maximum of 5 years of follow-up for the present study.

For the analysis of incident CHD, we excluded 477 subjects with prevalent CHD (fatal and nonfatal myocardial infarction, fatal CHD, other CHD-attributable deaths, angina pectoris, coronary bypass surgery, and coronary angioplasty), leaving 1515 subjects for analysis. For incident stroke, we excluded 104 subjects with prevalent stroke, leaving 1888 subjects for analysis.

DEFINITIONS OF OTHER RISK FACTORS

Participants underwent an assessment of cardiovascular risk factors during the course of the study.[29-32] Blood pressure was measured according to a standardized protocol,[29] and the means of the first and second readings were computed for the systolic and diastolic values. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or the combination of self-reported hypertension and use of antihypertensive medications. Diabetes was defined as fasting glucose concentration of 126 mg/dL (7.0 mmol/L) or greater or self-reported use of insulin or oral hypoglycemic agents. Medical history, medication use, cigarette smoking, and alcohol consumption were ascertained from questionnaires. Technicians assessed weight and standing height. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood sample collection, and processing and laboratory methods for fasting glucose concentration; total, low-density-lipoprotein, and high-density-lipoprotein cholesterol levels; and C-reactive protein (CRP) levels are described elsewhere.[31,32,36] Vascular ultrasonography of the internal and common carotid arteries was used to determine the intima-media thickness (IMT).[30] The common carotid artery IMT was determined to be the mean of the maximum wall thickness for near and far walls on both the left and right sides. We used the mean of the internal and common carotid IMT for adjustment.

All variables used in analyses were based on the 1997-1998 clinic examination, concurrent with retinal photography, except fasting glucose concentration, diabetes medications, and standing height, which were taken from the 1996-1997 examination, and data on high-density-lipoprotein cholesterol level, CRP level, and internal and common carotid IMT, which were obtained from the 1992-1993 examination.

Table 1. Baseline Characteristics of Study Population According to Retinal Vascular Caliber, Cardiovascular Health Study, 1997-1998 Examination*

Characteristic	Retinal Arteriolar Caliber			Retinal Venular Caliber		
	1st Quartile, Smallest (n = 499)	4th Quartile, Largest (n = 498)	*P* Value†	1st Quartile, Smallest (n = 498)	4th Quartile, Largest (n = 498)	*P* Value†
Age, y	78.9 ± 4.5	77.8 ± 4.1	<.001	79.5 ± 4.5	77.3 ± 3.8	<.001
Men, No. (%)	213 (42.7)	190 (38.2)	.15	194 (39.0)	216 (43.4)	.16
African Americans, No. (%)	68 (13.7)	85 (17.2)	.13	47 (9.5)	130 (26.3)	<.001
Hypertension, No. (%)	319 (64.1)	265 (53.2)	.001	295 (59.2)	297 (59.6)	.90
Blood pressure, mm Hg						
Systolic	134.5 ± 19.4	127.1 ± 18.9	<.001	133.2 ± 20.6	130.1 ± 19.3	.02
Diastolic	68.2 ± 11.1	65.0 ± 11.2	<.001	65.9 ± 10.5	67.3 ± 10.9	.04
Diabetes, No. (%)	69 (14.2)	73 (15.5)	.71	76 (15.8)	88 (18.8)	.30
Glucose, mg/dL	100.9 ± 29.9	102.4 ± 29.8	.43	100.6 ± 28.7	104.9 ± 33.4	.04
Total plasma cholesterol, mg/dL	202.3 ± 38.9	201.9 ± 36.8	.89	199.2 ± 37.8	205.0 ± 38.7	.02
HDL cholesterol, mg/dL	53.4 ± 14.2	52.9 ± 14.1	.58	54.1 ± 14.0	52.7 ± 14.5	.13
Body mass index‡	26.8 ± 4.2	27.3 ± 4.8	.12	26.4 ± 4.2	27.8 ± 4.5	<.001
C-reactive protein level, mg/dL§	2.4 (1.1, 4.8)	2.9 (1.4, 5.6)	.005	2.2 (1.0, 4.8)	2.9 (1.4, 5.9)	<.001
Carotid artery IMT, mm	1.2 ± 0.3	1.2 ± 0.3	.22	1.2 ± 0.3	1.2 ± 0.3	.97
Current cigarette smoker, No. (%)	26 (5.3)	45 (9.1)	.002	24 (4.8)	50 (10.1)	<.001

Abbreviations: HDL, high-density lipoprotein; IMT, intima-media thickness.
SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; to convert cholesterol to millimoles per liter, multiply by 0.0259.
*Data are given as mean ± SD or proportions unless otherwise indicated.
†*P* value represents difference in means or proportions; *t* test for continuous variables, Kruskal-Wallis test for C-reactive protein level, and χ^2 test for categorical variables.
‡Calculated as weight in kilograms divided by height in meters squared.
§Data are given as median (25th percentile, 75th percentile).

STATISTICAL ANALYSIS

Retinal arteriolar and venular calibers were categorized into quartiles. We defined large retinal venular caliber as present if caliber was in the fourth quartile of the population distribution.

We estimated the 5-year cumulative incidence of CHD or stroke, defined as 100 × (1 – Kaplan-Meier cumulative CHD- or stroke-free survival at 5 years). Follow-up time was defined as the number of days from the time of the 1997-1998 clinic visit to the date of the first cardiovascular event of interest (CHD or stroke), death, last contact, or June 30, 2002, whichever occurred first. We used Cox proportional hazards regression to estimate hazard rate ratios and 95% confidence intervals (CIs) for CHD and stroke in association with retinal vascular caliber and generalized retinal venular dilatation. We initially controlled for age, sex, race (white or black), and field center, and, further, for standard cardiovascular risk factors including systolic and diastolic blood pressure (in millimeters of mercury), diabetes (present or absent), fasting plasma glucose concentration (in milligrams per deciliter [millimoles per liter]), cigarette smoking status (never, former, or current), the number of pack-years of smoking, and low-density-lipoprotein and high-density-lipoprotein cholesterol (in milligrams per deciliter [millimoles per liter]) (model 1). We constructed 2 additional multivariable models adjusting for variables in model 1 plus body mass index and CRP level (model 2) and variables in model 1 plus mean common and internal carotid artery IMT (model 3). In these analyses, because retinal calibers were highly correlated ($r = 0.61$), arteriolar and venular calibers were included in the same model.[37] We have shown that this approach accounts for confounding between arterioles and venules and produces fewer biased results.[37] Analyses in which arteriolar and venular calibers were included in separate models were also conducted. Tests for trend across quartiles of retinal vascular diameter were conducted by fitting the grouped linear model; the *P* value was derived from a 2-sided Wald test.

To examine for interaction, analyses were repeated, stratifying the population by age group, sex, and the presence of diabetes and hypertension. All data analyses were performed using STATA version 8.0 (StataCorp, College Station, Tex).

RESULTS

Table 1 gives participant characteristics according to distribution of retinal vascular caliber, comparing first with fourth quartiles of arteriolar and venular caliber. Persons with smaller retinal arteriolar caliber (first quartile) were older; more likely to have hypertension, and higher systolic and diastolic blood pressure; and less likely to be current cigarette smokers. Persons with larger retinal venular caliber (fourth quartile) were younger and more likely to be African American; to have lower systolic but higher diastolic blood pressure, higher fasting glucose concentration, and total cholesterol level; and to be current cigarette smokers. Larger arterioles and venules were both associated with higher CRP levels.

There were 115 incident CHD events. **Table 2** gives the 5-year cumulative incidence and rate ratio of CHD by quartiles of retinal caliber. Participants with larger venular caliber had higher cumulative incidence of CHD (11.7%; 95% CI, 8.7%-15.8%, vs 8.1%; 95% CI, 5.7%-11.6%, comparing largest with smallest venular caliber quartiles). After controlling for age, sex, race, and field center, participants with larger retinal venular caliber were more likely to develop incident CHD (rate ratio, 2.7, comparing largest with smallest venular caliber quartiles). This association was not substantially changed with additional adjustment for standard cardiovascular risk fac-

Table 2. Incidence and Rate Ratio of Coronary Heart Disease in Association With Retinal Vascular Diameter

Retinal Vascular Caliber	No. at Risk	Incident CHD*	Age/Sex/Race/Center Adjusted†	Multivariate Model 1‡	Multivariate Model 2‡	Multivariate Model 3‡
Arteriolar						
1st Quartile (smallest)	379	35 (10.2)	2.0 (1.1-3.7)	2.0 (1.1-3.7)	2.1 (1.1-4.0)	2.0 (1.1-3.8)
2nd Quartile	379	29 (8.2)	1.3 (0.8-2.3)	1.3 (0.7-2.3)	1.3 (0.7-2.4)	1.3 (0.7-2.4)
3rd Quartile	380	25 (7.3)	1.1 (0.6-2.0)	1.1 (0.6-2.0)	1.1 (0.6-2.0)	1.1 (0.6-2.0)
4th Quartile (largest)	377	26 (8.0)	1.0	1.0	1.0	1.0
P_{trend}			.02	.03	.02	.03
Venular						
1st Quartile (smallest)	380	28 (8.1)	1.0	1.0	1.0	1.0
2nd Quartile	378	23 (6.3)	1.1 (0.6-2.0)	1.3 (0.7-2.4)	1.2 (0.7-2.2)	1.3 (0.7-2.4)
3rd Quartile	379	25 (7.7)	1.4 (0.8-2.6)	1.7 (0.9-3.2)	1.6 (0.8-3.0)	1.7 (0.9-3.2)
4th Quartile (largest)	378	39 (11.7)	2.7 (1.5-4.9)	3.0 (1.6-5.7)	2.9 (1.5-5.6)	3.0 (1.6-5.8)
P_{trend}			.001	.001	.001	.001

Abbreviations: CHD, coronary heart disease; CI, confidence interval.
*Data are given as number of CHD events: 5-year cumulative incidence (percent).
†Data are given as rate ratio (95% CI) from Cox models with the following as covariates: arteriolar caliber, venular caliber, age, sex, race, and field center.
‡Data are given as rate ratio (95% CI) from Cox models with the following as covariates: arteriolar caliber, venular caliber, age, sex, race, field center, systolic and diastolic blood pressure, diabetes status, glucose concentration, cigarette smoking status, pack-years of smoking, low-density-lipoprotein and high-density-lipoprotein cholesterol levels (model 1), variables in model 1 plus body mass index and C-reactive protein level (model 2), and variables in model 1 plus mean common and internal carotid artery intima-media thickness (model 3).

Table 3. Incidence and Rate Ratio of Stroke in Association With Retinal Vascular Diameter

Retinal Vascular Caliber	No. at Risk	Incident Stroke*	Age/Sex/Race/Center Adjusted†	Multivariate Model 1‡	Multivariate Model 2‡	Multivariate Model 3‡
Arteriolar						
1st Quartile (smallest)	472	27 (6.2)	1.4 (0.7-2.6)	1.1 (0.5-2.2)	1.1 (0.5-2.3)	1.1 (0.5-2.2)
2nd Quartile	472	30 (7.3)	1.4 (0.8-2.5)	1.4 (0.8-2.6)	1.5 (0.8-2.8)	1.4 (0.8-2.6)
3rd Quartile	473	31 (7.4)	1.4 (0.8-2.5)	1.3 (0.7-2.4)	1.3 (0.7-2.4)	1.3 (0.7-2.3)
4th Quartile (largest)	471	25 (6.1)	1.0	1.0	1.0	1.0
P_{trend}			.35	.73	.63	.74
Venular						
1st Quartile (smallest)	472	25 (5.8)	1.0	1.0	1.0	1.0
2nd Quartile	472	29 (7.0)	1.2 (0.7-2.2)	1.2 (0.7-2.3)	1.3 (0.7-2.4)	1.2 (0.7-2.3)
3rd Quartile	473	25 (5.7)	1.3 (0.7-2.3)	1.3 (0.7-2.6)	1.4 (0.7-2.7)	1.3 (0.7-2.6)
4th Quartile (largest)	471	34 (8.4)	2.1 (1.1-3.8)	2.2 (1.1-4.3)	2.3 (1.1-4.5)	2.2 (1.1-4.3)
P_{trend}			.03	.02	.02	.03

Abbreviation: CI, confidence interval.
*Data are given as number of stroke events: 5-year cumulative incidence (percent).
†Data are given as rate ratio (95% CI) from Cox models with the following as covariates: arteriolar caliber, venular caliber, age, sex, race, and field center.
‡Data are given as rate ratio (95% CI) from Cox models with the following as covariates: arteriolar caliber, venular caliber, age, sex, race, field center, systolic and diastolic blood pressure, diabetes status, glucose concentration, cigarette smoking status, pack-years of smoking, low-density-lipoprotein and high-density-lipoprotein cholesterol (model 1), variables in model 1 plus body mass index and C-reactive protein level (model 2), and variables in model 1 plus mean common and internal carotid artery intima-media thickness (model 3).

tors (rate ratio, 3.0; model 1), body mass index and CRP (rate ratio, 2.9; model 2), or carotid artery IMT (rate ratio, 3.0; model 3). Smaller retinal arteriolar caliber was associated with incident CHD (rate ratio, 2.0, comparing largest with smallest arteriolar caliber quartiles).

There were 113 incident stroke events. **Table 3** shows associations of retinal vascular caliber and incident stroke. Participants with the largest retinal venular caliber had the highest incidence of stroke (8.4%; 95% CI, 6.0%-11.7%, vs 5.8%; 95% CI, 3.9%-8.4%, comparing fourth with first venular caliber quartiles). After controlling for age, sex, race, and field center, participants with larger retinal venular caliber were more likely to develop incident stroke (rate ratio, 2.1, comparing fourth with first venular caliber quartiles), which did not change after additional multivariable adjustment. Retinal arteriolar caliber was not associated with incident stroke.

In analyses in which arteriolar and venular caliber were entered separately in the models, associations of larger venular caliber with incident CHD (rate ratio, 2.0; 95% CI, 1.2-3.5, comparing fourth with first venular caliber quartiles; P_{trend}=.01, adjusting for variables in model 1) and incident stroke (rate ratio, 2.1; 95% CI, 1.2-3.9; P_{trend}=.02) were largely similar. A smaller retinal AVR was also associated with incident CHD (rate ratio, 1.9; 95% CI, 1.1- 3.5, comparing first with fourth AVR quartiles; P_{trend}=.005) and stroke (rate ratio, 1.7; 95% CI, 0.9-3.1; P_{trend}=.06). Focal retinal signs (retinopathy, focal arteriolar narrowing, and arteriovenous nicking) were not associated with incident CHD or stroke (data not shown).

Table 4. Incidence and Rate Ratio of Coronary Heart Disease and Stroke in Association With Large Retinal Venular Caliber,* Stratified by Risk Factors

Characteristic	Incident Coronary Heart Disease			Incident Stroke		
	No. at Risk	Multivariate RR (95% CI)†	*P* Value (Interaction)	No. at Risk	Multivariate RR (95% CI)†	*P* Value (Interaction)
Total cohort	378	2.0 (1.3-3.2)		471	1.7 (1.0-2.7)	
Age, y						
<80	291	1.7 (0.9-3.0)	.40	356	1.6 (0.9-2.8)	.96
≥80	87	2.5 (1.3-5.0)		115	0.7 (0.3-1.6)	
Men	147	2.3 (1.2-4.5)	.42	203	1.2 (0.5-2.6)	.73
Women	231	1.8 (0.9-3.6)		268	1.7 (0.9-3.1)	
Diabetes	64	3.9 (1.4-11.1)	.34	79	2.3 (0.7-7.7)	.61
No diabetes	297	1.8 (1.0-3.0)		363	1.6 (0.9-2.7)	
Hypertension	222	2.6 (1.3-5.3)	.40	278	1.1 (0.5-2.4)	.18
No hypertension	156	3.8 (0.8-17.4)		193	0.5 (0.1-3.1)	

Abbreviations: CI, confidence interval; RR, rate ratio.
*Large venular caliber defined as fourth quartile of venular caliber, the reference exposure category being the other 3 quartiles.
†Data are given as rate ratio (95% CI) from Cox models with the following as covariates: arteriolar caliber, venular caliber, age, sex, race, field center, systolic and diastolic blood pressure, diabetes status, glucose concentration, cigarette smoking status, pack-years of smoking, low-density-lipoprotein and high-density-lipoprotein cholesterol levels, and arteriolar caliber (model 1).

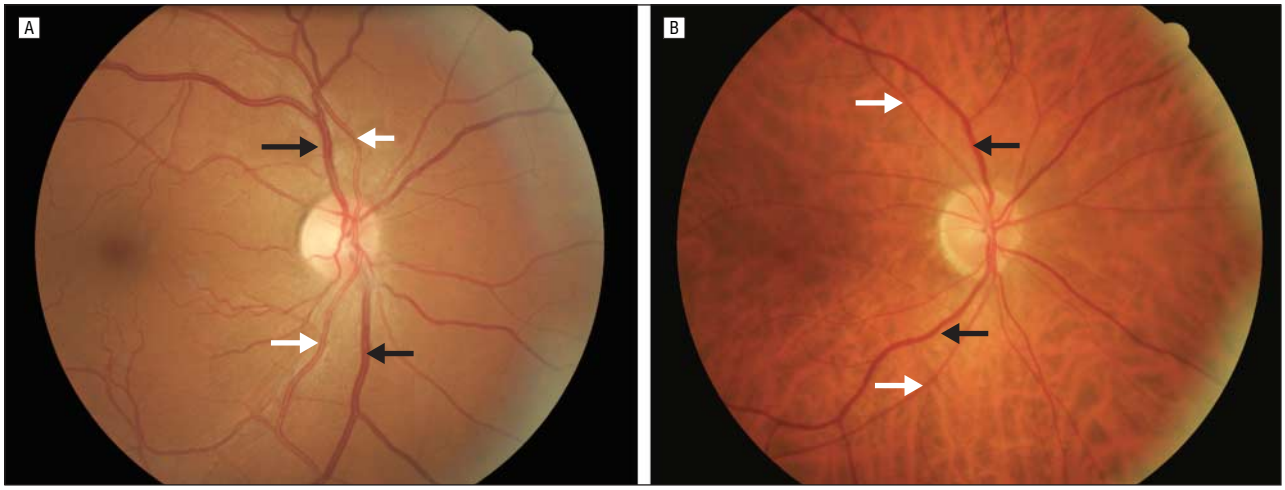

Figure. Retinal photographs. A, Note large retinal venular caliber (black arrows) and normal arteriolar caliber (white arrows). B, Note normal retinal venular caliber (black arrows) and narrowed arteriolar caliber (white arrows).

Table 4 shows the association of large retinal venular caliber (venular caliber in the fourth quartile of the population) with incident CHD and stroke in the total cohort and stratified by age, sex, and diabetes and hypertension status. There were no substantial sex differences in these associations. For incident CHD, somewhat stronger associations were noted in older persons, persons with diabetes, and persons without hypertension. For incident stroke, stronger associations were noted in persons with diabetes and persons with hypertension. None of these interactions were statistically significant.

COMMENT

In this prospective, population-based study in older persons with a mean age of 79 years, we describe an association between larger retinal venular caliber (**Figure**, A), as quantified from retinal photographs, and 5-year risk of CHD and stroke. Participants with larger venular caliber were at higher risk of CHD and stroke, after adjusting for age, sex, race, blood pressure, glucose concentration, cigarette smoking status, low-density-lipoprotein and high-density-lipoprotein cholesterol levels, and other cardiovascular risk factors including CRP and common and internal carotid artery IMT. In addition, smaller retinal arteriolar caliber (Figure, B) was associated with 5-year risk of CHD but not stroke. Focal retinal microvascular signs, however, were not associated with either CHD or stroke.

Prevention of CHD and stroke in older persons requires an improved understanding of pathogenic mechanisms and predictive factors in this age group. Previous studies have principally focused on large vessel atherosclerosis and its risk factors (eg, lipid levels), but our findings, along with other evidence, suggest that a substantial proportion of cardiovascular events in older persons might relate to or share risk factors with changes in the microvasculature.[7-11]

Our findings should be compared with those of other cohort studies that have recently examined the association of retinal vascular caliber, measured from retinal photographs using similar methods, and risk of various cardiovascular diseases. In the middle-aged (51-72 years) population from the ARIC study, a smaller AVR, representing either smaller arteriolar caliber or larger venular caliber, was associated with incident CHD[19] and stroke.[20] In the Beaver Dam Eye Study, a smaller AVR was associated with cardiovascular mortality only in younger (43-74 years) but not older (75-84 years) participants.[21] Similarly, the Blue Mountains Eye Study found an association of larger venular caliber with incident CHD in younger (49-75 years) but not older (>75 years) men and women, and smaller arteriolar caliber with CHD in younger women only.[23] The Rotterdam Study (participant age, >55 years) was the first to demonstrate significant associations of larger venular caliber with incident stroke in an older cohort.[24] The current CHS extends these findings to incident CHD, supports the importance of studying retinal arteriolar and venular caliber separately, and provides further evidence that retinal vascular caliber may also provide predictive information about cardiovascular risk in older persons.

Our initial observations of these associations were interpreted as reflecting ischemic effects of arteriolar disease.[38] In the ARIC study, the association of smaller AVR with CHD[19] and stroke[20] was thought to reflect smaller retinal arterioles, presumably from chronically elevated blood pressure, although associations for arteriolar and venular caliber were not reported separately. The findings from our study and others showing associations of enlarged retinal venules with cardiovascular diseases are not so readily explained on the basis of ischemia. There may be other explanations. Retinal venular dilatation has been hypothesized to reflect the effects of hypoxia and has been associated with inflammation and endothelial dysfunction.[39,40] Animal studies showed that lipid hydroperoxide administration in the vitreous of rats results in infiltration of leukocytes in the retinal microvasculature and an increase in retinal venular but not arteriolar caliber.[39] Dilation of the retinal vessels has been further attributed to increased nitric oxide production and release of cytokines resulting from activated endothelial cells.[40] Recent clinical and epidemiologic studies support these observations, showing that larger venular caliber is associated with systemic biomarkers of inflammation or endothelial dysfunction.[41-44] In the Rotterdam Study,[42] the Beaver Dam Eye Study,[43] and the Multi-Ethnic Study of Atherosclerosis,[44] larger venular caliber was associated with a range of inflammatory markers, including CRP and interleukin 6 concentrations. Thus, inflammation may underlie part of the association of larger venular caliber with CHD and stroke in the CHS. Further research into mechanisms underlying retinal venular dilation will clearly be useful in understanding the importance of these observations.

In the CHS, we found no association of focal retinal signs (retinopathy, focal arteriolar narrowing, and arteriovenous nicking) with either CHD or stroke, whereas other studies have found stronger associations of these focal retinal signs with both subclinical and clinical stroke,[20-22,45] particularly in younger persons.[20,21,45] These differences may be related to selective mortality in the CHS (discussed in the following paragraph), a higher prevalence of comorbid conditions in older persons that may mask the cardiovascular risks associated with retinal signs, or weaker predictive associations of retinal signs in older persons compared with younger persons. However, we found that the association of larger venular caliber and incident CHD was not weaker but stronger in older (≥80 years) compared with younger (<80 years) participants.

The strengths of the CHS include a community-sampled study population, quantitative measurement of retinal vascular caliber, and standardized identification of incident CHD and stroke events. There are several important limitations. First, retinal photography was performed approximately 10 years after the start of the study, and a significant proportion of photographs were ungradeable because of media opacity or poor pupil dilation in this older population. Biases related to nonattendance for photography, ungradeable photographs, and selective mortality may lead to an underestimation of the true risks. For example, the lack of association of retinopathy (eg, microaneurysms and hemorrhages) and incident cardiovascular events may be related to higher mortality among participants with retinopathy at baseline who did not attend subsequent follow-up examinations. Second, although we adjusted for cardiovascular risk factors, residual confounding may still be present because some factors (eg, CRP and high-density-lipoprotein cholesterol levels) were measured 5 years before retinal photography was performed.

Our study has 2 potential clinical applications. First, our findings support the value of specifically targeting the microcirculation in reducing cardiovascular morbidity and mortality in older persons.[7,8,46] There is increasing evidence that some antihypertensive agents (eg, angiotensin-converting enzyme inhibitors) may have direct beneficial effects on microvessel structure and function beyond their primary effect of lowering blood pressure.[46] Such agents may, therefore, have added therapeutic value in preventing and treating cardiovascular disease. Second, the collective data from our study and others suggest that a quantitative measurement of retinal vascular caliber from retinal photographs may provide additional information for cardiovascular risk prediction.

In conclusion, we demonstrate an association of larger venular caliber and future risk of CHD and stroke and of smaller arteriolar caliber with risk of CHD in older persons. It is not known whether similar processes affecting venules occur in the heart and brain, but studying the mechanisms underlying venular dilation may provide important insights into various pathophysiologic processes of CHD and stroke in older persons.

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Author Affiliations: Centre for Eye Research Australia, University of Melbourne and Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore (Dr Wong); Departments of Biostatistics (Ms Kamineni) and Medicine and Epidemiology (Dr Siscovick), University of Washington, Seattle; Department of Ophthalmology, University of Wisconsin, Madison (Drs R. Klein and B. E. Klein); Department of Epidemiology, The

Johns Hopkins Bloomberg School of Public Health, Baltimore, Md (Dr Sharrett); Departments of Medicine and Pathology, University of Vermont, Burlington (Dr Cushman); and Graduate Studies Program in Epidemiology, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (Dr Duncan).
Correspondence: Tien Yin Wong, MD, PhD, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne St, Victoria 3002, Australia (twong@unimelb.edu.au).
Author Contributions: *Study concept and design:* Wong and B. E. Klein. *Acquisition of data:* Wong, R. Klein, Siscovick, and Cushman. *Analysis and interpretation of data:* Wong, Kamineni, Sharrett, Siscovick, and Duncan. *Drafting of the manuscript:* Wong and Kamineni. *Critical revision of the manuscript for important intellectual content*: Wong, Kamineni, R. Klein, Sharrett, B. E. Klein, Siscovick, Cushman, and Duncan. *Statistical analysis:* Wong, Kamineni, and Siscovick. *Obtained funding:* Wong and R. Klein. *Administrative, technical, and material support:* Wong, R. Klein, B. E. Klein, and Cushman. *Epidemologic and conceptually favorable content:* Duncan.
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REFERENCES

1. American Heart Association. *Heart Disease and Stroke Statistics: 2006 Update.* Dallas, Tex: American Heart Association; 2006.
2. Benfante R, Reed D, Frank J. Do coronary heart disease risk factors measured in the elderly have the same predictive roles as in the middle aged: comparisons of relative and attributable risks. *Ann Epidemiol.* 1992;2:273-282.
3. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH. Does the association of risk factors and atherosclerosis change with age: an analysis of the combined ARIC and CHS cohorts. *Stroke.* 1997;28:1693-1701.
4. Denke MA, Winker MA. Cholesterol and coronary heart disease in older adults: no easy answers. *JAMA.* 1995;274:575-577.
5. Kaplan GA, Haan MN, Wallace RB. Understanding changing risk factor associations with increasing age in adults. *Annu Rev Public Health.* 1999;20:89-108.
6. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age: a report based on the Framingham data. *Arch Intern Med.* 1993;153:1065-1073.
7. Marcus ML, Chilian WM, Kanatsuka H, Dellsperger KC, Eastham CL, Lamping KG. Understanding the coronary circulation through studies at the microvascular level. *Circulation.* 1990;82:1-7.
8. Chilian WM. Coronary microcirculation in health and disease: summary of an NHLBI workshop. *Circulation.* 1997;95:522-528.
9. Egashira K, Inou T, Hirooka Y, Yamada A, Urabe Y, Takeshita A. Evidence of impaired endothelium-dependent coronary vasodilatation in patients with angina pectoris and normal coronary angiograms. *N Engl J Med.* 1993;328:1659-1664.
10. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med.* 2002;346:1948-1953.
11. Kaul S, Ito H. Microvasculature in acute myocardial ischemia. Part I, evolving concepts in pathophysiology, diagnosis, and treatment. *Circulation.* 2004;109: 146-149.
12. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke.* 2003;34:1126-1129.
13. Kwa VI, van der Sande JJ, Stam J, Tijmes N, Vrooland JL. Retinal arterial changes correlate with cerebral small-vessel disease. *Neurology.* 2002;59:1536-1540.
14. Goto I, Kimoto K, Katsuki S, Mimatsu T, Ikui H. Pathological studies on the intracerebral and retinal arteries in cerebrovascular and noncerebrovascular diseases. *Stroke.* 1975;6:263-269.
15. Cannon RO III, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary arteries: role of small coronary arteries. *Am J Cardiol.* 1985; 55:50B-60B.
16. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med.* 2000;342:829-835.
17. Wong TY, Klein R, Klein BE, Tielsch JM, Hubbard L, Nieto FJ. Retinal microvascular abnormalities and their relations with hypertension, cardiovascular diseases and mortality. *Surv Ophthalmol.* 2001;46:59-80.
18. Brown SM, Jampol LM. New concepts of regulation of retinal vessel tone. *Arch Ophthalmol.* 1996;114:199-204.
19. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of coronary heart disease in men and women: the Atherosclerosis Risk in Communities Study. *JAMA.* 2002;287:1153-1159.
20. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident strokes: the Atherosclerosis Risk in the Communities Study. *Lancet.* 2001; 358:1134-1140.
21. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and ten-year cardiovascular mortality: a population-based case-control study. *Ophthalmology.* 2003;110:933-940.
22. Mitchell P, Wang JJ, Wong TY, Smith W, Klein R, Leeder SR. Retinal microvascular signs and risk of stroke and stroke mortality. *Neurology.* 2005;65:1005-1009.
23. Wang JJ, Liew G, Wong TY, et al. Retinal vascular calibre and the risk of coronary heart disease–related death. *Heart.* 2006;92:1583-1587.
24. Ikram MK, de Jong FJ, Bos MJ, et al. Retinal vessel diameters and risk of stroke: the Rotterdam Study. *Neurology.* 2006;66:1339-1343.
25. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol.* 2002;86:1007-1013.
26. Wong TY, Klein R, Sharrett AR, et al. The prevalence and risk factors of retinal microvascular abnormalities in older people: the Cardiovascular Health Study. *Ophthalmology.* 2003;110:658-666.
27. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol.* 1991;1:263-276.
28. Tell GS, Fried LP, Hermanson B, Manolio TA, Newman AB, Borhani NO. Recruitment of adults 65 years and older as participants in the Cardiovascular Health Study. *Ann Epidemiol.* 1993;3:358-366.
29. Tell GS, Rutan GH, Kronmal RA, et al; Cardiovascular Health Study (CHS) Collaborative Research Group. Correlates of blood pressure in community-dwelling older adults: the Cardiovascular Health Study. *Hypertension.* 1994;23:59-67.
30. O'Leary DH, Polak JF, Wolfson SK Jr, et al. Use of sonography to evaluate carotid atherosclerosis in the elderly: the Cardiovascular Health Study. *Stroke.* 1991; 22:1155-1163.
31. Robbins J, Wahl P, Savage P, Enright P, Powe N, Lyles M. Hematological and biochemical laboratory values in older Cardiovascular Health Study participants. *J Am Geriatr Soc.* 1995;43:855-859.
32. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem.* 1995; 41:264-270.
33. Hubbard LD, Brothers RJ, King WN, et al. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities (ARIC) Study. *Ophthalmology.* 1999;106:2269-2280.
34. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events: the Cardiovascular Health Study. *Ann Epidemiol.* 1995;5:278-285.
35. Price TR, Psaty B, O'Leary D, Burke G, Gardin S. Assessment of cerebrovascular disease in the Cardiovascular Health Study. *Ann Epidemiol.* 1993;3:504-507.
36. Tracy RP, Lemaitre R, Psaty BM, Cushman M, Meilahn EN, Kuller LH. Relationship of C-reactive protein to risk of cardiovascular disease in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol.* 1997;17:1121-1127.
37. Liew G, Sharrett AR, Kronmal R, et al. Measurement of retinal vascular caliber: issues and alternatives to using the arteriole to venule ratio. *Invest Ophthalmol Vis Sci.* In press.
38. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med.* 2004;351:2310-2317.
39. Tamai K, Matsubara A, Tomida K, et al. Lipid hydroperoxide stimulates leukocyte-endothelium interaction in the retinal microcirculation. *Exp Eye Res.* 2002; 75:69-75.
40. Chester AH, Borland JA, Buttery LD, et al. Induction of nitric oxide synthase in human vascular smooth muscle: interactions between proinflammatory cytokines. *Cardiovasc Res.* 1998;38:814-821.
41. Delles C, Michelson G, Harazny J, Oehmer S, Hilgers KF, Schmieder RE. Impaired endothelial function of the retinal vasculature in hypertensive patients. *Stroke.* 2004;35:1289-1293.
42. Ikram MK, de Jong FJ, Vingerling JR, et al. Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? the Rotterdam Study. *Invest Ophthalmol Vis Sci.* 2004;45:2129-2134.
43. Klein R, Klein BE, Knudtson MD, Wong TY, Tsai MY. Are inflammatory factors related to retinal vessel caliber? the Beaver Dam Eye Study. *Arch Ophthalmol.* 2006;124:87-94.
44. Wong TY, Islam FMA, Klein R, et al. Retinal vascular caliber, cardiovascular risk factors and inflammation: the Multi-Ethnic Study of Atherosclerosis (MESA). *Invest Ophthalmol Vis Sci.* 2006;47:2341-2350.
45. Wong TY, Klein R, Sharrett AR, et al; the ARIC Investigators Arthrosclerosis Risk in the Communities Study. Cerebral white matter lesion, retinopathy and risk of clinical stroke. *JAMA.* 2002;288:67-74.
46. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation.* 2001;104:735-740.