RETINAL EMBOLI AND CARDIOVASCULAR DISEASE: THE BEAVER DAM EYE STUDY

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ABSTRACT

Purpose: To describe the 10-year incidence of retinal emboli, the associated risk factors, and the relationship of retinal emboli to stroke and ischemic heart disease mortality.

Methods: The Beaver Dam Eye Study (n = 4,926) is a population-based study of persons 43 to 86 years of age. Retinal emboli were detected at baseline (1988-1990) and at a 5-year (1993-1995) and a 10-year (1998-2000) follow-up by grading of stereoscopic 30º color fundus photographs using standardized protocols. Cause-specific mortality was determined from death certificates.

Results: The 10-year cumulative incidence of retinal emboli was 1.5%. While adjusting for age and sex, the incidence of retinal emboli was associated with increased pulse pressure (odds ratio [OR] 4th versus 1st quartile range, 2.42; 95% confidence interval (CI), 0.98-5.97; *P* test of trend = .03), higher serum total cholesterol (OR, 2.77; 95% CI, 1.06-7.23; *P* = .03), higher leukocyte count (OR, 2.28; 95% CI, 1.04-4.96; *P* = .05), smoking status (OR current versus never smoker, 4.60; 95% CI, 2.08-10.16; *P*<.001), and a history of coronary artery bypass surgery (OR, 7.17; 95% CI, 3.18-16.18; *P*<.001) at baseline. While controlling for age, sex, and systemic factors, a significantly higher hazard of dying with a mention of stroke on the death certificate was found in people with retinal emboli (hazard ratio, 2.40; 95% CI, 1.16-4.99) compared with those without.

Conclusions: The data show an association of smoking and cardiovascular disease with the incidence of retinal emboli. Also, persons with retinal emboli are at increased risk of stroke-related death.

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INTRODUCTION

The association of retinal arteriolar emboli and increased risk of cerebrovascular disease morbidity and mortality has been well described in the literature.[1-9] Most observations regarding these emboli and their clinical significance have come from clinic-based studies.[1-15] To date, only two population-based epidemiological studies have provided data describing the prevalence and incidence of retinal emboli and associations with risk factors for cardiovascular disease and stroke.[16,17] In Beaver Dam, Wis, we reported a 5-year cumulative incidence of retinal emboli of 0.9%. In that report, we had low power to examine the association of cardiovascular disease and its risk factors with incidence of retinal emboli. The purposes of this report are to (1) describe the 10-year incidence of retinal emboli, (2) examine associated risk factors, and (3) describe the relationship of retinal emboli to stroke and ischemic heart disease mortality in a large population-based cohort in Beaver Dam.

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Bold type indicates AOS member.

METHODS AND MATERIALS

POPULATION

The Beaver Dam Eye Study population has been described in detail in previous reports.[17,18] Briefly, a private census of the population of Beaver Dam, Wis (99% white), was performed from September 15, 1987, to May 4, 1988, to identify all residents in the city or township of Beaver Dam who were 43 to 84 years of age. Of the 5,924 eligible individuals, 4,926 participated in the baseline examination between March 1, 1988, and September 14, 1990. Nonparticipants consisted of 226 persons (3.8%) who had died before the examination, 18 (0.3%) who could not be located, 337 (5.7%) who permitted an interview only (of these, 61 had moved), and 417 (7.0%) who refused to participate (of these, 39 had

moved). Comparisons between participants and nonparticipants at the time of the baseline examination have appeared elsewhere.[18] Of those surviving, 3,684 (81.1%) participated in the 5-year follow-up examination between March 1, 1993, and June 14, 1995, and 2,764 of those surviving (82.9%) participated in the 10-year follow-up examination.[19,20] Persons who were deceased before their scheduled examination for the 10-year follow-up (n = 503) were older at baseline than those who participated (68.3 years versus 58.3 years, $P<.001$). Persons who were alive but did not participate in the 10-year follow-up (n = 418) were older at baseline than those who did (61.2 years versus 58.3 years, $P<.001$). After adjusting for age, those who were alive during the study period and did not participate were more likely to have a history of ever smoking, higher systolic blood pressure, higher pulse pressure, hypertension, higher pulse rate, and higher white blood cell count than persons who participated. After adjusting for age and sex, participants with retinal emboli at baseline were as likely to participate as those in whom retinal emboli were absent (data not shown). Informed consent was obtained for all subjects for all examinations, and the study was approved by the institutional review board.

PROCEDURES

Similar procedures were used at both baseline and follow-up examinations and have been described in detail elsewhere.[17-22] Informed consent was obtained from each participant at the beginning of the examination. The examinations at baseline and follow-up included measuring weight, height, pulse rate, and blood pressure (using a random-zero sphygmomanometer following the Hypertension Detection and Follow-up Program protocol).[23] A standardized questionnaire was administered by the examiners. Nonfasting blood specimens were obtained from participants. Serum total cholesterol,[24] high-density lipoprotein (HDL) cholesterol,[25] and blood glucose levels[26] were determined by enzymatic procedures. Hematocrit values and leukocyte counts were determined by using a Coulter counter method. Blood glycated hemoglobin was determined using affinity chromatography.[27] Stereoscopic 30° color fundus photographs centered on the disc (Diabetic Retinopathy Study [DRS] standard field 1)[28] and macula (DRS standard field 2) and a nonstereoscopic color fundus photograph temporal to but including the fovea of each eye were taken. When retinal emboli or other lesions were seen outside these three fields, additional fundus photographs were taken, if feasible. For purposes of this report, the 4,856 people with at least one eye gradable for retinal emboli are included in the analyses.

Photographs were graded using the Wisconsin Age-Related Maculopathy grading scheme.[22,29] As part of this scheme, all photographic fields of each eye were examined by the graders to detect retinal emboli, lesions that appeared as reflective bright or nonreflective dull; lesions that were rhomboidal, rectangular, or round in shape; and those that were lodged in retinal arterioles, which were classified as not present, questionable, or present.[22] When present, the number of emboli (one, two, or three or more) was counted. In addition, emboli locations were indicated by field in which emboli first appeared, listing an appearance only once if the same embolus appeared in several fields. Different types of emboli were not specified in the grading because of the difficulty in correctly classifying the embolus as cholesterol, fibrin-platelet, or calcific in origin from its appearance on the fundus photographs. Instead, emboli reflectance (dull versus bright, based on a reference standard photograph) was indicated. One of the authors (R.K.) examined all the photographs of persons with questionable or definite retinal emboli.

Retinal microaneurysms, blot hemorrhages, cotton-wool spots, hard exudates, intraretinal microvascular abnormalities, venous beading, arteriovenous nicking, new vessels on the disc and elsewhere, and preretinal and vitreous hemorrhages were graded in a masked fashion using an abbreviation of the modified Airlie House classification scheme.[28] Focal arteriolar narrowing was graded using a standard photograph from the Wisconsin Age-Related Maculopathy Grading protocol, in which focal narrowing of small arterioles in the posterior pole (field 2) involves a total length of 1/3 disc diameter.[22] Arteriolar narrowing was graded as absent, questionable, less than the standard, or greater than or equal to the standard for all arterioles more than 750 μm from the disc margin in all three standard fields. When there were multiple but separate areas of focal arteriolar narrowing, the composite length of involvement was compared with the standard. For purposes of analyses, two categories were used: (1) absent or questionably present and (2) present. Arteriovenous nicking was graded for all arteriovenous crossings that were more than 750 μm from the disc margin in all three fields. Arteriovenous nicking was graded as present if there was a decrease in the diameter of the venule on both sides of the arteriole that was crossing it. The presence of other retinal disease, such as central and branch retinal arterial or venous occlusion, or surface wrinkling retinopathy, was graded using a detailed protocol.[22]

Diameters of retinal vessels were measured after converting the photographs of field 1 to digital images. All arterioles and venules were measured in the area between one-half and one disc diameter from the optic disc margin using a computer-assisted program. Computer-assisted measurements of individual arterioles and venules were

each combined according to formulas developed by Parr and Spears[30,31] and Hubbard and colleagues[32] to provide the average diameters of retinal arterioles (central retinal arteriolar equivalents) and venules (central retinal venular equivalents) in that eye. These were then expressed as an arteriole-to-venule ratio. A ratio of 1.0 indicates that, on average, retinal arteriolar diameters are the same as venular diameters, while a smaller ratio represents narrower arterioles or larger venules.

When two eyes of a participant were discrepant regarding the presence of a lesion, the grade assigned for the participant was that of the more severely involved eye. For example, a participant would be considered to have a retinal embolus if the retinal embolus was present in one eye but not the other. When lesions could not be graded in one eye, and the other eye had no lesions present, the participant's information was set to "missing."

DEFINITIONS

The incidence of retinal emboli was estimated from all persons who had no emboli at the baseline examination and who participated in the follow-up examination(s). Current age was defined as the age at the time of the baseline examination. The mean systolic blood pressure was the average of the two systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the two diastolic blood pressures. The pulse pressure was computed by taking the difference between the mean systolic and the mean diastolic blood pressures. Hypertension was defined as a mean systolic blood pressure ≥160 mm Hg, a mean diastolic blood pressure ≥95 mm Hg, and/or a history of hypertension with use of antihypertensive medication at the time of examination. Uncontrolled hypertension was defined as systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 95 mm Hg or greater. Cardiovascular disease was defined as a history of angina pectoris, myocardial infarction, or stroke or current use of heart medication such as digitalis or nitroglycerin. Cigarette smoking status was defined as follows: subjects were classified as having never smoked if they reported having smoked fewer than 100 cigarettes in their lifetime; as ex-smokers if they had smoked more than this number of cigarettes in their lifetime but had stopped smoking before the examination; and as current smokers if they had not stopped. There were 375 people with a previous history of diabetes mellitus, treated with either insulin, oral hypoglycemic agents, and/or diet. There were also 48 people with newly diagnosed diabetes mellitus.[33]

STATISTICAL METHODS

Because some participants who had not developed retinal emboli by the first follow-up examination did not return for the second follow-up, methods appropriate for censored observations were used. Ten-year cumulative incidence was calculated by the product-limit method.[34] Trends in proportions across categories were tested for significance using the Mantel-Haenszel procedure stratified by observation period.[35] Multivariable models of incidence of retinal emboli were based on the discrete linear logistic model.[36] Generalized estimating equations models were used to assess relationships with data from both eyes when a risk factor was eye-specific (retinopathy, focal retinal arteriolar narrowing, and arteriovenous nicking).[37] The relation of retinal emboli to overall mortality and to mortality in which ischemic heart disease or stroke was listed as a cause of death was examined after age and sex adjustment using the Cox proportional hazards model.[38]

RESULTS

INCIDENCE OF RETINAL EMBOLI

Over the 10 years of follow-up, retinal emboli occurred in 48 of 3,488 at-risk participants for a 10-year cumulative incidence of retinal emboli of 1.5%. The incidence of retinal emboli varied with age and was more likely to occur in men than in women (Table I). Persons who were 65 years of age or older at baseline were 2.4 times as likely (95% CI, 1.2-5.0) to develop a retinal emboli compared with persons 43 to 54 years of age at baseline. The 10-year overall incidence was similar in right and left eyes (0.7% versus 0.9%, respectively). Only 3 people of 48 who developed retinal emboli did so in both eyes. Of those eyes that developed retinal emboli, 1 embolus was found in 83.3% (20/24) of right eyes and 67.9% (19/28) of left eyes, 2 emboli in 12.5% (3/24) of right eyes and 14.3% (4/28) of left eyes, and 3 or more emboli in 4.2% (1/24) of right eyes and 17.9% (5/28) of left eyes. Emboli that developed were described as dull in appearance in 62.5% (15/24) of right eyes and 46.4% (13/28) of left eyes. Only 1 right eye and 4 left eyes developed both dull and bright emboli in the same eye. Emboli disappeared (present at baseline or 5 years, absent at a later examination) in 86.9% of eyes (53/61). In one eye, the emboli disappeared at 5 years and reappeared at 10 years.

The relation of cardiovascular disease and its risk factors to the 10-year incidence of retinal emboli is presented in Table II. While adjusting for age and sex, the incidence of retinal emboli was associated with increased pulse pressure, higher serum total cholesterol, higher serum total cholesterol/HDL cholesterol ratio, increased leukocyte count, history of past and current smoking, a history of angina, and a history of coronary artery bypass at baseline. Although not statistically significant ($P>.05$), odds ratios of greater than 2 for the incidence of retinal emboli were found for current history of heavy alcohol use

TABLE I: THE 10-YEAR INCIDENCE OF RETINAL EMBOLI IN EITHER EYE IN THE BEAVER DAM EYE STUDY

CHARACTERISTICS	NO. AT RISK	INCIDENCE %	*P* VALUE
Age (yr)			
43-54	1,244	1.0	.04*
55-64	1,020	1.5	
65-74	905	2.4	
75+	319	1.3	
Sex			
Female	1,965	1.2	.04
Male	1,523	2.0	
Overall	3,488	1.5	

*Mantel-Haenszel test of trend.

at baseline and a history of diabetes mellitus, myocardial infarction, and carotid artery bypass surgery ascertained at baseline. Systolic and diastolic blood pressure, hypertension, serum HDL cholesterol, hematocrit, platelet count, gross proteinuria, body mass index, aspirin use, hypertension, and history of stroke at baseline were not associated with the 10-year age- and sex-adjusted incidence of retinal emboli. Smoking, a history of coronary artery bypass surgery, and serum total cholesterol remained highly significant when included together with age in a multivariate model (Table III). Table III also shows the effect of substituting other factors for coronary bypass surgery. When this is done, history of angina and myocardial infarction are also significantly associated with incidence of retinal emboli, whereas cardiovascular disease history and aspirin use are not.

In multivariate analyses using the Liang-Zeger method[37] while excluding subjects with diabetes and controlling for age, history of smoking, history of coronary artery bypass surgery, and serum total cholesterol, retinopathy (OR, 1.77; 95% CI, 0.58-5.45; $P = .32$) was not significantly associated with the incidence of retinal arteriolar emboli, nor was focal retinal arteriolar narrowing (OR, 0.75; 95% CI, 0.22-2.50; $P = .64$). Arteriole-to-venule ratio (generalized retinal arteriolar narrowing) at baseline was not associated with incident retinal emboli (data not shown). No eyes with arteriovenous nicking (n = 40) at baseline developed retinal emboli.

RELATIONSHIP OF RETINAL EMBOLI TO CARDIOVASCULAR DISEASE MORTALITY

From the time of the baseline examination (1988 to 1990) through 1999, there were 1,199 total deaths in the cohort. Of those in the cohort who died, 365 persons (30.4%) had ischemic heart disease and 154 persons (12.8%) had stroke listed as one of the causes of death on the death certificate. People with retinal emboli present at baseline (n = 61) had an 11-year age- and sex-adjusted overall survival rate of 74.6% compared with a rate of 82.6% in persons who did not have retinal emboli present (n = 4,795) ($P = .02$); there was no effect of male or female sex on this association.

The relation of retinal emboli status at baseline to stroke and ischemic heart disease death is shown in Table IV. Persons with retinal emboli at baseline have experienced 16.8 deaths per 1,000 person-years of follow-up with stroke mentioned, compared with 3.0 deaths per 1,000 person-years of follow-up in those without emboli ($P<.001$). The corresponding results for any mention of ischemic heart disease are 14.7 and 7.6 deaths per 1,000 person-years of follow-up ($P = .08$). While adjusting for age and sex, persons with retinal emboli at baseline had an increased hazard of dying with stroke mentioned as a cause (hazard ratio, 2.93; 95% CI, 1.43-6.00) compared with those without emboli. This relationship remained after additionally controlling for pulse pressure, hypertension status, pulse rate, diabetes status, body mass index, cardiovascular disease history, and sedentary lifestyle (hazard ratio, 2.40; 95% CI, 1.16-4.99). The number of emboli (1 versus 2 or more) and the type of emboli (bright versus dull) did not appear to have different associations with stroke mortality (data not shown). Additionally, controlling for a history of previous stroke or carotid surgery did not change these relations. The presence of retinal emboli was not related to the incidence of fatal myocardial infarction (data not shown). There were no significant interactions found between retinal emboli and systemic risk factors for stroke mortality (data not shown).

DISCUSSION

Most information about the frequency of retinal emboli has been derived from studies of clinic populations in which patients with severe disease may be overrepre-

TABLE II: AGE- AND SEX-ADJUSTED RELATIONS OF VARIOUS CHARACTERISTICS TO THE 10-YEAR INCIDENCE OF RETINAL EMBOLI IN THE BEAVER DAM EYE STUDY

CHARACTERISTIC	VALUE	N	OR (95% CI)*	P†
Systolic blood pressure, mmHg	71-117	927	1.00	.22
	118-129	896	1.26 (0.51-3.16)	
	130-143	866	1.60 (0.67-3.84)	
	144-248	798	1.67 (0.68-4.08)	
Diastolic blood pressure, mmHg	42-69	726	1.00	.42
	70-76	837	0.82 (0.33-2.04)	
	77-83	940	1.06 (0.46-2.46)	
	84-127	984	1.28 (0.57-2.91)	
Pulse pressure, mmHg	11-41	967	1.00	.03
	42-51	925	0.82 (0.31-2.14)	
	52-65	939	1.35 (0.56-3.24)	
	66-162	656	2.42 (0.98-5.97)	
Serum total cholesterol, mmol/L	2.45-5.25	870	1.00	.03
	5.30-5.95	860	1.89 (0.70-5.12)	
	6.00-6.65	907	2.71 (1.05-6.96)	
	6.70-15.50	842	2.77 (1.06-7.23)	
Serum HDL cholesterol, mmol/L	0.15-0.95	753	1.00	.09
	1.00-1.20	911	0.82 (0.39-1.72)	
	1.25-1.55	855	0.90 (0.41-1.95)	
	1.60-4.10	955	0.38 (0.14-1.02)	
Serum total/HDL ratio	1.46-3.64	899	1.00	.003
	3.65-4.66	896	2.62 (0.83-8.26)	
	4.67-5.97	857	3.05 (0.98-9.45)	
	5.98-39.00	822	4.74 (1.59-14.17)	
Hematocrit, %	22.3-40.6	872	1.00	.27
	40.7-43.1	889	0.88 (0.39-1.96)	
	43.2-45.6	875	0.55 (0.22-1.35)	
	45.7-65.5	843	0.66 (0.26-1.63)	
Leukocyte count, g/L	2.3-5.9	919	1.00	.05
	6.0-7.0	840	1.10 (0.46-2.65)	
	7.1-8.4	900	1.01 (0.42-2.44)	
	8.5-43.7	819	2.28 (1.04-4.96)	
Platelet count, g/L	26-239	830	1.00	.12
	240-280	869	1.64 (0.70-3.80)	
	281-327	898	1.29 (0.52-3.22)	
	328–1133	879	2.20 (0.94-5.16)	
Urine protein	Absent	3,163	1.00	0.86
	Present	83	0.84 (0.11-6.18)	
Body mass index, kg/m^2	14.7-24.4	853	1.00	.75
	24.5-27.4	867	0.95 (0.42-2.19)	
	27.5-30.7	875	1.06 (0.47-2.39)	
	30.8-66.8	881	0.83 (0.35-1.97)	
Smoking status	Never	1,579	1.00	<.001
	Ex	1,234	2.10 (0.97-4.55)	
	Current	674	4.60 (2.08-10.16)	
Heavy drinking status	Never	2,912	1.00	.12
	Ex	488	0.49 (0.17-1.40)	
	Current	76	2.43 (0.72-8.22)	
Aspirin use	No	2,417	1.00	.11
	Yes	1,070	1.60 (0.90-2.86)	
Diabetes	No	3,185	1.00	.06
	Yes	244	2.22 (0.98-5.00)	
Hypertension	Normal	2,309	1.00	.56
	Untreated	215	1.60 (0.56-4.64)	
	Treated, normal	775	1.56 (0.81-2.99)	
	Treated, high	188	1.30 (0.39-4.37)	
Angina	No	3,166	1.00	.04
	Yes	280	2.21 (1.04-4.69)	
Myocardial infarction	No	3,321	1.00	.08
	Yes	162	2.22 (0.90-5.44)	
Coronary artery bypass	No	3,404	1.00	<.001
	Yes	84	7.17 (3.18-16.18)	
Stroke	No	3,409	1.00	.52
	Yes	79	1.60 (0.38-6.89)	
Carotid artery bypass surgery	No	3,462	1.00	.33
	Yes	25	2.72 (0.36-20.37)	

*OR (95% CI) = odds ratio (95% confidence interval).
†Test of trend except for smoking status, heavy drinking status, hypertension, and dichotomous variables.

TABLE III: MULTIVARIATE RELATIONSHIPS BETWEEN VARIOUS CHARACTERISTICS OF THE POPULATION AND INCIDENCE OF RETINAL EMBOLI, THE BEAVER DAM EYE STUDY

CHARACTERISTIC	MODEL 1 OR (95% CI)*	MODEL 2 OR (95% CI)*	MODEL 3 OR (95% CI)*	MODEL 4 OR (95% CI)*	MODEL 5 OR (95% CI)*
Age, per 10 yr	1.59 (1.17-2.16)				
Smoking history					
Former versus never					
Current versus never	2.12 (1.00-4.52)				
	4.77 (2.16-10.51)				
Serum total cholesterol, per 1 mmol/L	1.27 (1.00-1.60)				
Coronary bypass surgery, present versus absent	7.93 (3.55-17.71)				
Angina, present versus absent		2.50 (1.18-5.29)			
Myocardial infarction, present versus absent			2.46 (1.01-6.00)		
Cardiovascular disease, present versus absent				1.71 (0.86-3.42)	
Aspirin use, no versus yes					1.66 (0.93-2.96)

*OR (95% CI) = odds ratio (95% confidence interval).

sented.[1-15] The Beaver Dam Eye Study provides unique data on the long-term incidence of retinal emboli using standardized protocols for the recording and grading of these lesions with stereoscopic color fundus photographs.

We have previously reported a prevalence of retinal emboli in the population of 1.3% and a 5-year cumulative incidence of 0.9%.[17] The 10-year cumulative incidence was 1.5%, varying from 1% in those 43 to 54 years of age to 2.2% in those 65 years of age or older at baseline. On the basis of the Beaver Dam data, we estimate that 460,000 people 65 to 84 years of age will develop at least one detectable embolus. This is probably a significant underestimate of the incidence because of the transient nature of these emboli and because emboli are associated with increased morbidity and mortality.

These data further confirm the association of cardiovascular disease and its risk factors with the incidence of retinal emboli and are consistent with data from previous studies.[4-6,8,9,16,17,39] At the time of the 5-year examination, while controlling for age and sex, only smoking and a history of coronary artery bypass surgery were associated with incident retinal emboli. At the 10-year follow-up, with increased number of outcomes, we now report associations of higher total serum cholesterol, higher leukocyte count, and a history of angina and borderline associations of lower serum HDL cholesterol, diabetes, and a history of myocardial infarction at baseline with a higher incidence of retinal emboli. Persons with carotid artery bypass were nearly three times as likely to develop retinal emboli compared with persons without this surgery; however, owing to the relative infrequency of this procedure in the population, the association was not statistically significant ($P = 0.33$). These associations with cardiovascular disease are not unexpected, because most retinal emboli are thought to originate from mural thrombi in the carotid artery in persons with systemic atherosclerotic disease.[2,40]

The relation of smoking with incident retinal emboli is consistent with previous reports. At baseline in the Blue Mountains Eye Study, those who smoked were 2.6 times as likely to have retinal emboli present compared with those who did not smoke.[16] In a case-control study of 70 men with asymptomatic retinal cholesterol emboli and 21 controls, Bruno and colleagues[8] found a higher prevalence of smoking (56% versus 28%, $P<.001$) in persons with retinal emboli compared with those without retinal emboli.

In Beaver Dam, incident retinal emboli were 2.4

TABLE IV: RELATION OF RETINAL ARTERIOLAR EMBOLI AT BASELINE TO STROKE AND ISCHEMIC HEART DISEASE DEATHS IN THE BEAVER DAM EYE STUDY

VARIABLE	RETINAL ARTERIOLAR EMBOLI* ABSENT	PRESENT
No.	4,795	61
Person-years	45,475.2	476.2
Stroke deaths	136	8
Stroke deaths/1,000 person-years	3.0	16.8
Ischemic heart disease deaths	346	7
Ischemic heart disease deaths/1,000 person-years	7.6	14.7

*There are 10 persons with stroke-related deaths and 12 persons with cardiovascular disease–related deaths in which retinal emboli status at baseline was not known..

times as likely to occur in persons with pulse pressure in the highest quartile range compared with those in the lowest quartile range. This is consistent with our baseline findings.[17] The association is not unexpected, as higher pulse pressure, a marker of increased stiffness of large elastic arteries, is related to carotid artery stenosis,[41] stroke,[42,43] coronary heart disease,[42-44] and congestive heart failure[45] in both persons with and persons without hypertension.

We found no association of hypertension at baseline with incident retinal emboli.[17] We had previously reported that hypertensive persons at baseline were 2.5 times as likely to have prevalent emboli. In the cross-sectional Blue Mountains Eye Study, after controlling for age and sex, hypertension was associated with an odds ratio of 2.2.[16] In a case-control study, hypertension (78% versus 33%, $P<.001$) was more frequent in cases compared with controls.[8,9] The inconsistency of the association of hypertension and prevalent and incident retinal emboli may be due, in part, to the selective survival; that is, persons with uncontrolled hypertension who develop emboli are less likely to survive for a return examination than persons without hypertension who develop emboli.

While adjusting for systemic factors, persons with retinal emboli in Beaver Dam were 2.4 times as likely to have mention of stroke on their death certificate over an 11-year period compared with those without retinal emboli. These findings are consistent with higher mortality in persons with retinal emboli found in Beaver Dam and in other studies.[1-9,17,40] Hollenhorst[1] in his case series reported stroke or transient ischemic attack in 63% of a group, with 34% developing stroke or cerebral transient ischemic attacks during follow-up. In a case-series by Savino and Glaser[6] 6 (38%) of 16 patients with asymptomatic retinal emboli at baseline developed stroke. In a case-control study by Bruno and colleagues,[9] a 10-fold increase in the annual rate of stroke (8.5% versus 0.8% per year in cases versus controls) was found independent of blood pressure and other risk factors. In Beaver Dam, there was no association of retinal emboli at baseline with ischemic heart disease–related mortality.

Conclusions regarding estimates of prevalence and incidence of retinal emboli and associations described herein must be made with caution. These emboli may be of short duration and recurrent and thus may be easily missed, resulting in an underestimate of their prevalence and incidence.[1,15] In addition, it is possible that persons with some risk factors, such as cigarette smoking or hypertension, who developed retinal emboli were more likely to die before follow-up, possibly underestimating the association. Also, the concomitant low frequencies of some risk factors (eg, carotid artery bypass) and the incidence of retinal emboli may limit our ability to detect meaningful relationships.

In summary, the presence of retinal emboli at baseline was associated with a significant increase in the risk of stroke mortality in the cohort. Identification and treatment of modifiable risk factors, such as smoking and hypercholesterolemia, might be of benefit in these individuals.

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DISCUSSION

DR ANDREW K. VINE. This report from the Beaver Dam Eye Study showed a 10-year cumulative incidence of retinal emboli of 1.5%. As expected, retinal emboli are symptomatic of diffuse cardiovascular disease and were associ-

ated with numerous cardiovascular risk factors. Individuals with retinal emboli had a decreased survival rate and a significantly higher risk of dying with the diagnosis of stroke on their death certificate.

The authors correctly suggest that their reported incidence is probably a significant understatement due to the transitory nature of retinal emboli, and individuals were only examined 3 times over a 10-year period.

The use of death certificates to substantiate that an individual died from ischemic heart disease, or stroke may be very inaccurate. In the Collaborative Ocular Melanoma Study,[1] there was only fair agreement (kappa = 0.34) between the determinations of the mortality coding committee and the cause of death reported on the death certificate.

Retinal emboli generally indicate severe cardiovascular disease but the presence of retinal emboli is not a sensitive marker of atherosclerotic cardiovascular disease. Atherosclerosis in now widely accepted to be a chronic inflammatory disorder.[2] Specific markers of inflammation, in particular, high sensitivity C-reactive protein,[3] have been shown to predict incident myocardial infarction,[4] stroke,[5] peripheral arterial disease,[6] and sudden cardiac death[7] in multiple prospective epidemiological trials. A single, non-fasting measurement of C-reactive protein is a strong predicator of future vascular events and is a stronger predictor[8] of cardiovascular disease than low-density lipoprotein cholesterol. Incorporating more sensitive markers of cardiovascular disease would have enhanced this study: C-reactive protein.

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Dr Melvin L. Rubin. What we see in photographs that is often called a retinal embolus is only rarely the crystalline cholesterol embolus itself. The whitish Hollenhorst plaque we see is wider than the column of blood, and so it is probably a reaction of the vessel wall that surrounds something within the vessel that irritates it, such as an embolic cholesterol clump wedged within but not blocking or occluding the blood flow. My point here is that a count of the number plaques will indicate only the minimum number of emboli. There surely must be many more actual emboli being produced that don't embed and create those characteristic plaque-like opacifications.

Dr Brian R. Younge. This is a very important paper because it does have good epidemiological data, and that is needed for studies. This particular embolus is known as the Hollenhorst plaque after one of our members and is very transient and evanescent. Therefore the incidence in this group may be well underestimated, for several reasons that we've already mentioned. One of the things that bothers me a little bit about these is that there's another form of embolus that looks like a cholesterol embolus and is not, and that is a calcific embolus. That is associated more often with blocked arterial flow, and they occur closer to the disk. I'm not sure that you were able to exclude those from your consideration. In Hollenhorst's study, which was a nonepidemiological study, there were over 200 consecutive patients that had emboli and found that their death rate from cardiovascular disease was much higher than the standard population. That's a referral bias in the population too. I think it is a marker of atherosclerotic disease.

Dr Richard P. Mills. Thank you particularly for finding a relationship with cerebrovascular disease. That was always the peculiarity of the Mayo Clinic series, that death rate from cardiovascular disease was really what the bright plaques were markers of. Nowadays we have a new therapy for impending stroke: thrombolysis when performed in a timely way can certainly reduce the morbidity and mortality from stroke. When we see an embolus in our patients now, in addition to asking them to stop smoking and modify their cholesterol, we should inform them that they are at increased risk for stroke. If they develop symptoms of hemiplegia, aphasia, or any sensory defect, they really need to get to the emergency room.

Dr Vinod Lakhanpal. There are certain emboli that are permanent fixtures in the retina that we can see for years in some patients, and some of them are very transitory. Why is that? In your ischemic heart disease patients, were there patients included that had CABG procedure performed? With CABG patients there is a tremendous amount of embolization and that is why there is interest in performing new CABG procedures without the pump.

Dr Ronald Klein. In a further effort to understand the associations of carotid emboli with atherosclerotic disease, we have other more sensitive measures of atherosclerosis (e.g., intima-media wall thickness [IMT] by carotid ultrasound). Because the IMT measurements are still being done we do not have any data regarding the association of this with retinal emboli. In the Beaver Dam Eye Study, inflammation was measured by increased white blood cell. The white blood cell count at baseline was significantly associated with incident retinal emboli in univariate but not in the multivariate analysis suggesting that other factors, associated with inflammation and retinal emboli, such as smoking, may have explained this relation. We do not have C-reactive protein measurements as yet in the population.

A common question is what do you tell the physician and what do you tell the participant when you see these plaques in the eye? We tell them to see their physician for a further work-up and then leave that decision about what to do with the participant's physician.

I thank Mel Rubin for his comment that the appearance of the plaque is, in part, due to a reaction in the retinal blood vessel wall to the emboli. I agree that we are underestimating this, and one reason is that we do not see those emboli that do not become embedded in the arteriolar wall. Only 13 percent of retinal emboli that we had seen at baseline remained at a follow-up examination, so 87 % of them will disappear over the 5-year interval. We're not counting retinal emboli that go through the eye and disappear before examination; those are never detected. A limitation of our study is that we have only 3 standard fields but some of these emboli are found in the periphery and are not detected.

Dr Younge, we did not specifically describe calcific emboli in our grading system, so it was not reported as such. We can reexamine the emboli found for this appearance.

We agree with Dr Lakhanpal, that understanding the epidemiology of retinal emboli is important. We found that those with coronary artery bypass procedure were nearly 8 times more likely to develop retinal emboli. This may affect cognition. The New York Times Science Tuesday this past week reported about "pump" heads, persons who have sustained cognitive decline after this procedure due to emboli associated with it.