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

Methods: The Beaver Dam Eye Study is a large (N=4926) population-based study of persons 43 to 86 years of age at the time of the baseline examination. Retinal emboli were detected at baseline (1988-1990) and at a 5-year (1993-1995) and 10-year (1998-2000) follow-up by grading of stereoscopic 30° 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%. After adjustment for age and sex, the incidence of retinal emboli was associated with increased pulse pressure (odds ratio [OR] [fourth vs first quartile range], 2.42; 95% confidence interval [CI], 0.98-5.97; P = .03, for test of trend), higher serum total cholesterol level (OR, 2.77; 95% CI, 1.06-7.23; P = .03), higher white blood cell count (OR, 2.28; 95% CI, 1.04-4.96; P = .05), smoking status (OR [current vs 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. After 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: We found associations of smoking and cardiovascular disease with the incidence of retinal emboli. Persons with retinal emboli are also at increased risk of stroke-related death.

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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 2 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 the Beaver Dam Eye Study,17 our group 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 the present 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, Wis.

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follow-up examination between March 1, 1993, and June 14, 1995, and 2764 (82.9%) of 3334 survivors participated in the 10-year follow-up examination.2,22 Persons who died before their scheduled examination for the 10-year follow-up (n=502) were older at baseline than those who participated (68.3 years vs 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 participated (61.2 years vs 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 adjustment 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).

PROCEDURES

Similar procedures were used at the baseline and follow-up examinations and have been described in detail elsewhere.17-21 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 examiners. Nonfasting blood specimens were obtained from participants. Total serum cholesterol,24 high-density lipoprotein (HDL) cholesterol,25 and blood glucose26 levels were determined by enzymatic procedures. Hematocrit values and white blood cell counts were determined by using a Coulter counter method. Blood glycosylated hemoglobin was determined using affinity chromatography.27 Stereoscopic 30° color fundus photographs were taken 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 3 fields, additional fundus photographs were taken, if feasible. For this report, the 4856 people with at least 1 eye gradable for retinal emboli are included in the analyses.

Photographs were graded using the Wisconsin Age-Related Maculopathy Grading System.22-32 As part of this system, all photographic fields of each eye were examined by the graders to detect retinal emboli lesions that appeared as reflective bright or nonreflective dull; were rhomboidal, rectangular, or round; and were lodged in retinal arterioles, which were classified as not present, questionable, or present.22 When present, the number of emboli (1, 2, or ≥3) was counted. In addition, emboli locations were indicated by the 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, fibrinplatelet, or calcific in origin from their appearance on the fundus photographs. Instead, emboli reflectance (dull vs 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.

The presence of 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.29 Focal arteriolar narrowing was graded with the use of a standard photograph from the Wisconsin Age-Related Maculopathy Grading System in which focal narrowing of small arterioles in the posterior pole (DRS standard 19) involves a total length of one-third disc diameter.31 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 3 DRS standard fields. When there were multiple but separate areas of focal arteriolar narrowing, the composite length of involvement was compared with the standard. For the analyses, 2 categories were used: absent or questionably present, and present. Arteriovenous nicking was graded for all arteriovenous crossings that were more than 750 µm from the disc margin in all 3 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 and 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 1 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 Spears30,31 and Hubbard et al32 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-venule ratio. An arteriole-venule ratio of 1.0 indicates that, on average, retinal arteriolar diameters are the same as venular diameters, whereas a smaller arteriole-venule ratio represents narrower arterioles or larger venules.

When 2 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 considered 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 2 systolic blood pressure determinations, and the mean diastolic blood pressure was the average of the 2 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 of 160 mm Hg or greater, a mean diastolic blood pressure of 95 mm Hg or greater, and/or 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 a diastolic blood pressure of 95 mm Hg or greater. Cardiovascular disease was defined as a self-report 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. Three hundred seventy-five people had a previous history of diabetes mellitus, treated with insulin, oral hypoglycemic agents,
and/or diet. Forty-eight people had newly diagnosed diabetes mellitus.\(^3\) Data concerning mortality and causes of death were provided by death certificates. All causes listed on the certificates were examined.

### 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.\(^3\) Trends in proportions across categories were tested for significance using the Mantel-Haenszel procedure stratified by observation period.\(^3\) Multivariable models of incidence of retinal emboli were based on the discrete linear logistic model.\(^3\) Generalized estimating equation models were used to assess relationships with data from both eyes when a risk factor was eye specific (retinopathy, focal retinal arterial narrowing, and arteriovenous nicking).\(^3\)

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.\(^3\)

### Results

#### Incidence of Retinal Emboli

During the 10 years of follow-up, retinal emboli occurred in 48 of 3488 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 women (Table 1). Persons who were 65 years or older at baseline were 2.4 times as likely (95% confidence interval [CI], 1.2-5.0) to develop a retinal embolus 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% vs 0.9%, respectively). Only 3 of 48 people who developed retinal emboli did so in both eyes. Of 24 right and 28 left eyes that developed retinal emboli, 1 embolus was found in 20 right eyes (83%) and 19 left eyes (68%), 2 emboli in 3 right eyes (12%) and 4 left eyes (14%), and 3 or more emboli in 1 right eye (4%) and 5 left eyes (18%). Emboli that developed were described as dull in appearance in 15 right eyes (62%) and 13 left eyes (46%). Only 1 right eye and 4 left eyes developed both dull and bright emboli in the same eye. Embolii disappeared (present at baseline or 5 years and absent at a later examination) in 53 (87%) of 61 eyes. In 1 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 2. After adjustment for age and sex, the incidence of retinal emboli was associated with increased pulse pressure, higher serum total cholesterol level, higher serum total cholesterol–HDL cholesterol ratio, increased white blood cell count, and history of past and current smoking, angina, and coronary artery bypass surgery at baseline. Serum HDL cholesterol level was inversely associated with the incidence of retinal emboli, although the association was not statistically significant (\(P = .09\)) Although not statistically significant, odds ratios of greater than 2 for the incidence of retinal emboli were found for current heavy alcohol use at baseline and a history of diabetes mellitus, myocardial infarction, and carotid artery bypass surgery ascertained at baseline. Hypertension, aspirin use, and history of stroke (Table 2) and systolic and diastolic blood pressure, hematocrit value, platelet count, gross proteinuria, and body mass index (data not shown) 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 level remained highly significant when included together with age in a multivariate model (Table 3). Table 3 also shows the effect of substituting other factors for coronary artery 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\(^3\) while excluding subjects with diabetes mellitus and controlling for age, history of smoking, history of coronary artery bypass surgery, and serum total cholesterol level, retinopathy (OR, 1.77; 95% CI, 0.58-5.45; \(P = .32\)) was not significantly associated with the incidence of retinal arterial embolii, nor was focal retinal arterial narrowing (OR, 0.75; 95% CI, 0.22-2.50; \(P = .64\)). Arteriole-venule ratio (generalized retinal arterial 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, Morbidity, and Mortality

From the time of the baseline examination (1988 to 1990) through 1999, there were 1199 deaths in the cohort. Of those, 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 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 (\(P = .02\)); there was no effect of sex.

At baseline, the overall prevalence of retinal arterial emboli was 1.3% (61/4856). Information regarding the prevalence and associated risk factors is found

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**Table 1. The 10-Year Incidence of Retinal Emboli in Either Eye in the Beaver Dam Eye Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. at Risk</th>
<th>Incidence, %</th>
<th>(P) Value</th>
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</tr>
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<tr>
<td>Overall</td>
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<td>1.5</td>
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</tr>
</tbody>
</table>

*Mantel-Haenszel test of trend.

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elsewhere. Persons with retinal emboli at baseline experienced 16.8 deaths per 1000 person-years of follow-up with stroke mentioned compared with 3.0 deaths per 1000 person-years of follow-up in those without emboli \((P<.001)\). The corresponding results for any mention of ischemic heart disease were 14.7 and 7.6 deaths, respectively, per 1000 person-years of follow-up \((P=.08)\). After adjustment 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 mellitus status, body mass index, cardiovascular disease history, and sedentary lifestyle \((hazard\ ratio, 2.40; 95\% CI, 1.16-4.99)\). The number of emboli \((1 vs \geq 2)\) and the type of emboli \((bright vs dull)\) did not appear to have different associations with stroke mortality \(\text{(data not shown)}.\) Additionally controlling for a history of previous stroke or carotid artery bypass surgery did not change these relationships. The presence of retinal emboli was not related to the incidence of fatal myocardial infarction \(\text{(data not shown)}.\) We found no significant interactions between retinal emboli and systemic risk factors for stroke mortality \(\text{(data not shown)}.\)

**COMMENT**

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

Our group previously reported a prevalence of retinal emboli in the population of 1.3% and a 5-year cumulative incidence of 0.9%. The 10-year cumulative incidence was 1.5%, varying from 1.0% in those 43 to 54 years of age to 2.2% in those 65 years or older at baseline. On the basis of the data from the Beaver Dam Eye Study, 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 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. At the time of the 5-year examination, after 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 an increased number of outcomes, we now report associations of higher total serum cholesterol level, higher white blood cell count, and a history of angina and borderline associations of lower serum HDL cholesterol level, diabetes mellitus, and a history of myocardial infarction at baseline with a higher incidence of retinal emboli. Persons who underwent carotid artery bypass surgery were nearly 3 times as likely to develop retinal emboli. 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 mellitus status, body mass index, cardiovascular disease history, and sedentary lifestyle \((hazard\ ratio, 2.40; 95\% CI, 1.16-4.99)\). The number of emboli \((1 vs \geq 2)\) and the type of emboli \((bright vs dull)\) did not appear to have different associations with stroke mortality \(\text{(data not shown)}.\) We found no significant interactions between retinal emboli and systemic risk factors for stroke mortality \(\text{(data not shown)}.\)
In a case-control study, hypertensive persons were associated with the cross-sectional Blue Mountains Eye Study, after controlling for age and sex. Hypertension was associated with baseline were 2.5 as likely to have prevalent emboli. In previously reported that persons with hypertension at baseline with incident retinal emboli. We had wall signs associated with long-standing hypertension at baseline with incident retinal emboli. We had previously reported that persons with hypertension at baseline were 2.5 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. In a case-control study, hypertension (78% vs 33%, P < .001) was more frequent in cases compared with controls. The inconsistency of the association of hypertension or focal and generalized retinal narrowing 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.

When we adjusted for systemic factors, persons with retinal emboli in the Beaver Dam Eye Study were 2.4 times as likely to have mention of stroke on their death certificate during an 11-year period compared with those without retinal emboli. These findings are consistent with higher mortality in persons with retinal emboli found in the Beaver Dam Eye Study and in other studies. In his case series, Hollenhorst reported stroke or transient ischemic attack in 63% of his group, with 34% developing stroke or cerebral transient ischemic attacks during follow-up. In a case series by Savino et al, 6 (38%) of 16 patients with asymptomatic retinal emboli at baseline developed stroke. In a case-control study by Bruno et al, a 10-fold increase in the annual rate of stroke (8.5% vs 0.8% per year in cases vs controls) was found independent of blood pressure and other risk factors. In the Beaver Dam Eye Study, we found 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 underestimation of their prevalence and incidence. 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 surgery) 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 cessation of smoking and treatment for hypercholesterolemia, might be of benefit in these individuals.
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Reprints are not available from the authors.

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REFERENCES