Retinal Arteriolar Emboli and Long-Term Mortality
Pooled Data Analysis From Two Older Populations

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Background and Purpose—To assess the relationship between retinal arteriolar emboli and mortality in older people.

Methods—Pooled data from 2 population-based cohort studies. At baseline, the Beaver Dam Eye Study (BDES) examined 4926 persons 43 to 86 years of age (1988 to 1990), and the Blue Mountains Eye Study (BMES) examined 3654 persons 49 to 97 years of age (1992 to 1994). Retinal arteriolar emboli were assessed by grading retinal photographs using standardized methods. Deaths and causes of death were determined from death certificates or Australian National Death Index. Cox regression models were used to estimate mortality hazard ratios (HRs) associated with emboli, adjusting for age, gender, body mass index, hypertension, diabetes, smoking, serum total cholesterol, high-density lipoprotein cholesterol, study site, and past histories of stroke, angina, and acute myocardial infarct.

Results—Of 8580 baseline participants, 8384 (98%) had retinal photographs available, and 111 showed retinal arteriolar emboli (BDES n=61; BMES n=50). Over 10 to 12 years, 2506 participants (30%) died, including 344 (4%) from stroke-related and 1315 (16%) from cardiovascular causes. The cumulative mortality rates were higher in participants with than without emboli (all-cause 56% versus 30%; stroke-related 12% versus 4.0%; cardiovascular 30% versus 16%). The increased mortality risk associated with emboli was independent of age, gender, other vascular risk factors, and past histories of stroke or heart disease for all-cause (multivariate-adjusted HR, 1.3; CI, 1.0 to 1.8) and stroke-related mortality (HR, 2.0; CI, 1.1 to 3.8) but not for cardiovascular mortality (HR, 1.2; CI, 0.8 to 1.7).

Conclusions—Our pooled data from 2 older populations suggest that retinal emboli predict a modest increase in all-cause and stroke-related mortality independent of cardiovascular risk factors. (Stroke. 2006;37:1833-1836.)

Key Words: epidemiology ■ mortality ■ prognosis ■ stroke

Retinal arteriolar emboli can be detected in 1.3% to 1.4% of individuals >40 years of age1,2 and have a 10-year incidence of 1.5% to 3.0%.3,4 Patients diagnosed with retinal emboli sometimes undergo cardiovascular assessment to determine whether they are at risk of stroke. This clinical practice is largely based on studies showing that retinal emboli are associated with various cardiovascular risk factors3,5 and may confer a higher stroke risk.6-9 However, to date, only the Beaver Dam Eye Study (BDES) has provided population-based evidence linking retinal emboli with 8-year stroke-related mortality.1,3 In this study, we pooled data collected from 2 population-based cohorts and aimed to assess the long-term prognosis of retinal emboli (all-cause, stroke-related, and cardiovascular mortality), and in particular, the consistency and magnitude of the association with mortality over 10 to 12 years.

Materials and Methods
The BDES and Blue Mountains Eye Study (BMES) are population-based studies of eye diseases in older white persons. Both studies, approved by the human ethics committee of their respective universities, were conducted in adherence with the Declaration of Helsinki. Signed informed consent was obtained from all participants.

BDES, conducted from March 1, 1988, to August 30, 1990, in Beaver Dam, Wis, examined 4926 (83.1%) of 5924 eligible residents 43 to 86 years of age. BMES, conducted from March 1, 1992, to December 30, 1994, in the Blue Mountains region of Australia, examined 3654 (82.4%) of 4433 eligible residents ≥49 years of age.

At baseline, all participants had stereoscopic retinal photography of both eyes1,2 using the same type of fundus camera (Zeiss FF3). Photographs were obtained of at least 1 eye in 98% of participants (BDES 4829 of 4926; BMES 3583 of 3654), and complete data were available in 8384 persons (98% of 8580 baseline participants). Retinal emboli were assessed from photographs and confirmed by retinal specialists (R.K., P.M.).1,2

The census cutoff was December 31, 2002, for the BDES and December 31, 2003, for the BMES. Deaths and causes of death were obtained either from death certificates (BDES) or the Australian National Death Index (NDI; BMES). Causes of death in the NDI database were collected from death certificates and recorded using International Classification of Diseases (ICD) codes. Stroke-related
stroke (thrombotic, hemorrhagic) included the following codes from ICD-9 (430.0 to 438.9) and ICD-10 (I60.0 to I69.9). Cardiovascular death included the following codes from ICD-9 (394.9, 402.9, 410.9, 411.9, 414.0, 414.9, 415.1, 420.4, 424.1, 425.4, 426.9, 427.3, 427.4, 427.5, 427.8, 4280, 4281, 4289, 4290, 4291, 4410, 4411, 4413, 4414, 4415, and 4439) and ICD-10 (I09.9, I10, I11.2, I219, I249, I251, I255, I259, I269, I271, I350, I352, I358, I429, I469, I489, I500, I514, I515, I516, I709, and I711). Vascular death was defined to combine cardiovascular and stroke-related death. The sensitivity and specificity of Australian NDI data have been estimated to be 93.7% and 100% for all-cause deaths, and 92.5% and 89.6% for cardiovascular deaths.\textsuperscript{10,11} The validity of death certificates\textsuperscript{12} has also been reported previously. No validity data on stroke-related deaths have been reported previously.

In both the United States and Australia, death is confirmed by certifying physicians (medical certifier) and doctors, as is the cause(s) of death, whether the death occurs in hospital or the community. If the patient had a recent vascular event (stroke or heart attack), this event is routinely included in the causes of death, although it may not be the primary cause. We used any mention of stroke (or cardiovascular event) from the causes of death to include deaths from complications secondary to stroke (or cardiovascular events). The study participants and their doctors might or might not know their retinal emboli diagnosis condition. This would also apply to the doctors who listed the cause(s) of death, although none was aware of the study question addressed in this report.

Baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. Hypertension was defined as SBP \( \geq 140 \) mm Hg or DBP \( \geq 90 \) mm Hg, or use of antihypertensive medications. Current smokers were defined from questionnaire. Diabetes was defined as previous history of diabetes or hyperglycemia, glycosylated hemoglobin \( > 2 \) SDs above the mean for the appropriate age and sex group, a casual blood glucose level \( > 200 \) mg/dL (11.1 mmol/L, BDES), or as fasting blood glucose \( \geq 7.0 \) mmol/L (BMES). Serum total cholesterol and high-density lipoprotein (HDL) cholesterol were measured from casual (BDES) or fasting blood specimen (BMES) using standard procedures.

Cox regression with stepwise procedures (Statistical Analysis System, V9) was used to estimate hazard ratios (HRs) and 95% CIs after adjusting for age, gender, body mass index, hypertension, diabetes, current smoking, total cholesterol, HDL cholesterol, and study site (multivariate-adjusted model 1). We further adjusted for past histories of stroke, angina, and acute myocardial infarct in model 2.

### Results

Retinal arteriolar emboli were detected in 111 baseline participants (BDES \( n=61 \); BMES \( n=50 \)), with an overall prevalence of 1.3%. Table 1 shows baseline characteristics by emboli status of the 2 study populations. Older age and male gender were associated with higher prevalence of retinal emboli in both populations. In the BDES, subjects with retinal emboli had a higher prevalence of hypertension, diabetes, and were more likely to report past history of angina, acute myocardial infarct, or stroke. In the BMES, they were more likely to currently smoke. Total serum cholesterol and HDL cholesterol were not significantly different between participants with and without retinal emboli at baseline (Table 1).

Table 2 shows the association between retinal emboli and all-cause, stroke-related, and cardiovascular mortality. Long-term cumulative all-cause mortality was higher among participants with than without emboli at baseline (56% versus 30%). After adjusting for age and sex, body mass index, hypertension, diabetes, current smoking status, total cholesterol, HDL cholesterol, and study site, there was 40% increased all-cause mortality in participants with retinal emboli detected at baseline (model 1 HR, 1.4; CI, 1.1 to 1.8). This association remained if hypertension was replaced by SBP, DBP, or mean arterial BP in the model or after additionally adjusting for past histories of stroke, angina, and acute myocardial infarct (model 2 HR, 1.3; CI, 1.0 to 1.8). The direction and magnitude of this association was similar in both study samples, although the findings from each individual study did not reach statistical significance (Table 2).

Long-term cumulative stroke-related mortality was nearly 3-fold higher among participants with than without emboli at baseline (12% versus 4%). After adjusting for age and sex, body mass index, hypertension, diabetes, current smoking status, total cholesterol, HDL cholesterol, and study site, there was a doubling of stroke-related mortality in participants with retinal emboli at baseline (model 1 HR, 2.5; CI, 1.4 to 4.4). This association remained if hypertension was replaced by SBP, DBP, or mean arterial BP in the model or after additionally adjusting for past histories of stroke, angina, and acute myocardial infarct (model 2 HR, 2.0; CI, 1.1 to 3.8). The direction and magnitude of this association were similar in both study samples,

### Table 1. Age- and Gender-Specific Prevalence (%) of Retinal Emboli and Baseline Characteristics by Retinal Emboli Status and Study Site

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>BDES Retinal Emboli</th>
<th>BMES Retinal Emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absence (n=4768)</td>
<td>Presence (n=61)</td>
</tr>
<tr>
<td>Mean age in years (95% CI)</td>
<td>61.7 (61.4–62.1)</td>
<td>69.0 (66.5–71.4)</td>
</tr>
<tr>
<td>Mean body mass index (95% CI)</td>
<td>28.8 (28.6–28.9)</td>
<td>28.4 (27.2–29.6)</td>
</tr>
<tr>
<td>Mean serum total cholesterol (mmol/L, SD)</td>
<td>6.04 (1.14)</td>
<td>6.16 (1.02)</td>
</tr>
<tr>
<td>Mean HDL cholesterol (mmol/L, SD)</td>
<td>1.35 (0.46)</td>
<td>1.25 (0.41)</td>
</tr>
<tr>
<td>Men, %</td>
<td>44.0</td>
<td>60.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>50.2</td>
<td>72.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>8.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>19.8</td>
<td>24.6</td>
</tr>
<tr>
<td>Self-reported history of angina, %</td>
<td>10.1</td>
<td>33.3</td>
</tr>
<tr>
<td>History of acute myocardial infarct, %</td>
<td>6.4</td>
<td>21.7</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>3.3</td>
<td>9.8</td>
</tr>
</tbody>
</table>

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although the findings from each individual study did not reach statistical significance (Table 2).

Long-term cumulative cardiovascular mortality was nearly double in participants with than without emboli at baseline (30% versus 16%). After adjusting for age and sex, body mass index, hypertension, diabetes, current smoking status, total cholesterol, HDL cholesterol, and study site, there was no significantly increased cardiovascular mortality in participants with retinal emboli detected (model 1 HR, 1.3; CI, 0.9 to 1.8). Further adjusting for past histories of stroke, angina, and acute myocardial infarct (model 2 HR, 1.2; CI, 0.8 to 1.7) did not alter the findings. The nonsignificance and the magnitude of this association was consistent between the 2 study samples (Table 2).

The association between retinal emboli and vascular death (combined cardiovascular and stroke-related death) was weaker and nonsignificant after adjusting for covariables in model 1 (HR, 1.3; CI, 0.9 to 1.8) or in model 2 (HR, 1.2; CI, 0.8 to 1.7).
Discussion
Pooled data analyses from 2 older populations show that presence of asymptomatic retinal emboli predicts a modestly increased risk of long-term, all-cause mortality independent of age, sex, and vascular risk factors. This increased all-cause mortality risk appears to be partially driven by a higher risk of stroke-related mortality in persons with retinal emboli, which confirms previous observations from a number of studies. Inconsistent with previous reports, we did not find a significant association between retinal emboli and cardiovascular mortality.

Although cardiovascular associations of asymptomatic retinal emboli were explored in previous studies, long-term follow-up data are limited. Because both BDES and BMES used similar study protocols, including standardized retinal photography to document retinal emboli, pooling these data provides an opportunity to study the prognosis of retinal emboli. Apart from age and male gender, most cross-sectional associations between retinal emboli and baseline cardiovascular factors differed between the 2 populations. The associations of retinal emboli and mortality, including all-cause, stroke-related, and cardiovascular mortality, however, were relatively consistent in direction and magnitude across the 2 studies, although findings from each individual study did not reach statistical significance, likely because of limited study power.

Because most retinal emboli are transient, our baseline emboli prevalence is likely to have been underestimated. This could have affected the association in either direction. Our study is also limited by likely low sensitivity and specificity of death certificates in identifying stroke-related causes, which could have led to misclassification of our secondary study outcome. This misclassification on stroke-related causes could have led to biases in the associations found. Although the direction of this bias is unclear, we believe that the misclassification is highly likely to be undifferentiated because our study factor (retinal emboli) was determined using a masked manner, with retinal photographic graders unaware of participants’ vital status. We do not know whether the study outcomes (cause of death) were determined with or without knowledge of the participant’s retinal embolus status. Although it is possible that participants’ doctors could have detected retinal emboli and recorded the finding in the medical record, we consider that this is unlikely, given the difficulty in identifying retinal embolus by clinical examination alone because of their small size. BDES participants were informed after baseline examinations of a finding of retinal emboli, whereas BMES participants were informed after baseline examinations by clinical examination alone because of their small size. BDES participants were informed after baseline examinations of a finding of retinal emboli, whereas BMES participants were not routinely informed of this. Although physicians who listed causes of death might be aware of the retinal embolus status from the medical records, they were unaware of the study question addressed in this report. We do not believe that the knowledge of embolus status could have influenced their determination of causes of death. Findings from the 2 studies were concordant, supporting this conclusion. Undifferentiated misclassification will only bias the associations toward the null, resulting in underestimation of the strength of the associations. We found no significant association between emboli and cardiovascular mortality (excluding stroke-related death) and weaker associations with all-cause mortality (including stroke-related death). This could reflect a degree of specificity for the association of emboli and stroke-related death.

Retinal emboli are usually asymptomatic and detected incidentally during eye examinations. Although many patients found to have retinal emboli may be referred to neurologists and other physicians to assess stroke risk, there are few population-based data available to estimate the magnitude of this increased risk. Our findings indicate a modest increase in the risk of all-cause mortality, particularly stroke-related mortality. Although this could reflect underascertainment attributable to the transient nature of emboli and underestimated magnitude of the mortality risk attributable to likely undifferentiated misclassification of stroke-related death, our findings reinforce the need for clinicians to perform a careful vascular assessment with appropriate investigations in patients with retinal emboli. Future studies should examine whether active preventive strategies could reduce the risk of stroke and stroke-related mortality in patients found to have emboli.

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Disclosures
None.

References
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