Is Diabetic Retinopathy an Independent Risk Factor For Ischemic Stroke?

Ning Cheung, MBBS; Sophie Rogers, Mepi; David J. Couper, PhD; Ronald Klein, MD, MPH; A. Richey Sharrett, MD, DrPH; Tien Y. Wong, MD, PhD

Background and Purpose—The relationship between diabetic retinopathy and ischemic stroke is uncertain and examined in this study.

Methods—A population-based, prospective cohort study of 1617 middle-aged persons with diabetes. Diabetic retinopathy signs were ascertained from retinal photographs, and incident ischemic stroke events were prospectively identified and validated.

Results—Over an average follow-up of 7.8 years, there were 75 ischemic stroke events. After adjustment for age, gender, race, center, 6-year mean arterial blood pressure, anti-hypertensive treatment use, fasting glucose, insulin treatment, duration of diabetes, high-density lipoprotein and low-density lipoprotein cholesterol levels and cigarette smoking status, diabetic retinopathy was associated with an increased risk of ischemic stroke (hazard rate ratio, 2.34; 95% CI, 1.13 to 4.86).

Conclusions—Diabetic retinopathy predicts incident ischemic stroke in people with diabetes, independent of other risk factors. (Stroke. 2007;38:398-401.)

Key Words: diabetic retinopathy ■ ischemic stroke

Individuals with diabetes have higher risk of stroke and stroke mortality than those without diabetes.1,2 Whereas macrovascular disease is the primary cause of ischemic stroke in the general population, microvascular disease may play an important role in diabetic strokes. Individuals with diabetes, for example, are more likely to develop small subcortical infarcts or lacunar strokes than nondiabetic people.

Diabetic retinopathy, a common microvascular manifestation of diabetes, may be a risk marker for cerebral microvascular disease. However, 2 population-based studies have provided inconclusive evidence of whether diabetic retinopathy is related to stroke,3,4 and few other data are available.5–7

The purpose of our study is to determine the independent relation of diabetic retinopathy to incident ischemic stroke.

Methods

Study Population

The Atherosclerosis Risk in Communities study is a population-based cohort study that included 15,792 persons aged 45 to 64 years at recruitment in 1987 to 1989.8 Retinal photographs were first obtained at the third examination (1993 to 1995).9 Of the 12,887 participants who returned for this examination, 2341 had diabetes mellitus, defined as fasting serum glucose levels of $\geq 7.0$ mmol/L, nonfasting levels of $\geq 11.1$ mmol/L, diabetic medications use, or physician diagnosis of diabetes.9 Of these, we excluded those without retinal photographs or ungradable photographs (n=508), without blood pressure measurement (n=5), and with a history of stroke or coronary heart disease at the time of retinal photography (n=211), leaving 1617 participants for this analysis. Persons without gradable photographs were older and more likely blacks, and after controlling for age and race, were more likely to be on insulin treatment and have longer diabetes duration than persons with gradable fundus photographs (data not shown).

Assessment of Diabetic Retinopathy and Stroke

One randomly selected eye was photographed using a 45-degree nonmydriatic camera and evaluated by masked graders according to standardized protocol.9 Retinopathy was defined as absent and present, and also as absent, mild-to-moderate and severe.9 Macular edema was defined separately as absent and present.

Incident stroke events were identified by contacting participants and families annually, and by surveying hospital discharge lists and state death records.10 When a potential stroke was identified, a trained nurse sent hospital records for abstraction. A computer algorithm and a physician independently classified cases, and a second physician adjudicated disagreements. Only ischemic strokes were analyzed in the current study.

Participants underwent standardized evaluations for blood pressure and other cardiovascular risk factors at all examinations.11

Statistical Analysis

Hazard rate ratio for ischemic stroke in relation to diabetic retinopathy was derived using Cox regression, initially controlling for age, gender, race, and center, and then further for 6-year mean arterial
blood pressure (averaged over first 3 examinations), antihypertensive treatment, fasting glucose, insulin use, diabetes duration, high-density lipoprotein and low-density lipoprotein cholesterol levels, and cigarette smoking status. Follow-up time was defined as the number of days from retinal photography to the date of the first ischemic stroke, last contact, or December 31, 2002. We calculated the Kaplan Meier cumulative stroke risk survival among individuals with and without diabetic retinopathy. We compared the unadjusted survival curves by presence versus absence of retinopathy.

Results
Participants with retinopathy were more likely to be blacks, and to have hypertension, higher fasting glucose, and to use insulin than participants without retinopathy (Table 1). Over 7.8 years (standard deviation 1.9) of follow-up, there were 75 ischemic stroke events (81 total strokes).

The Figure shows that individuals with diabetic retinopathy were more likely to have ischemic stroke than those without retinopathy. Table 2 shows that after adjustment for other risk factors, diabetic retinopathy was significantly associated with incident ischemic stroke. Higher risks were also seen for all retinopathy lesions, but were statistically significant only for retinal microaneurysms.

The association of retinopathy and ischemic stroke remained significant with additional adjustment for white blood cell count and plasma fibrinogen (hazard rate ratio, 2.78; 95% CI, 1.29 to 5.95), and for common carotid artery intima-media thickness (hazard rate ratio, 2.90; 95% CI, 1.28 to 6.57) among the subgroup with these measurements (n=983).

Discussion
In this prospective, population-based study, retinopathy was associated with incident ischemic stroke in persons with diabetes. In the Wisconsin Epidemiological Study of Diabetic Retinopathy, proliferative retinopathy was associated with incident stroke (relative risk, 2.9 to 6.0) and stroke mortality (relative risk, 1.9) in participants with type 2 diabetes. However, the Wisconsin Epidemiological Study of Diabetic Retinopathy found no association of mild and moderate retinopathy with incident stroke. In the United Kingdom Prospective Diabetes Study, retinopathy was not a significant risk factor for stroke. There were too few cases in our study to analyze associations with proliferative retinopathy.

The current study extends our previous analyses on the association of hypertensive retinopathy and incident stroke in the general nondiabetic population, and provides
further insights into underlying pathophysiology of diabetic ischemic strokes. Unlike ischemic strokes in nondiabetic individuals, the contribution of large vessel disease to diabetic ischemic stroke may be less important. Autopsy studies indicate that diabetic strokes are commonly related to cerebral microvascular disease. This is in keeping with our findings, which support the importance of microvascular disease in diabetic ischemic strokes.

Limitations of our study should be discussed. First, diabetic retinopathy was graded from a single retinal photograph taken without pharmacological dilation, and many photographs were ungradable. Thus, retinopathy may have been underestimated. Second, selection biases may have distorted associations, because retinal photography was performed only at the third examination. Finally, we did not grade the number of microaneurysms, and whether increasing number correlates with increasing stroke risk is unclear. However, we did not find a dose-dependent association between retinopathy severity and stroke.

In conclusion, we demonstrate an association between diabetic retinopathy and incident ischemic stroke, supporting the importance of microvascular disease as a risk factor for diabetic stroke.

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Disclosures
None.

References
3. Davis TM, Mills H, Stratton IM, Holman RR, Turner RC. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Pro-

### TABLE 2. Incidence and Hazard Rate Ratios of Ischemic Stroke by Presence of Diabetic Retinopathy

<table>
<thead>
<tr>
<th></th>
<th>No. At Risk</th>
<th>N (%) of Events</th>
<th>Age-Gender-Race HR (95% CI)*</th>
<th>Multivariate HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic retinopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1305</td>
<td>51 (3.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>241</td>
<td>24 (10.0)</td>
<td>2.79 (1.52, 5.15)</td>
<td>2.34 (1.13, 4.86)</td>
</tr>
<tr>
<td>Retinopathy grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1305</td>
<td>51 (3.9)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild-Moderate</td>
<td>197</td>
<td>19 (9.6)</td>
<td>2.43 (1.32, 4.50)</td>
<td>2.52 (1.16, 5.48)</td>
</tr>
<tr>
<td>Severe</td>
<td>44</td>
<td>5 (11.4)</td>
<td>2.73 (0.96, 7.73)</td>
<td>1.81 (0.57, 6.40)</td>
</tr>
<tr>
<td>Microaneurysms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1343</td>
<td>54 (4.0)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>206</td>
<td>21 (10.2)</td>
<td>2.81 (1.49, 5.30)</td>
<td>2.25 (1.03, 4.90)</td>
</tr>
<tr>
<td>Retinal hemorrhages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1417</td>
<td>64 (4.5)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>173</td>
<td>15 (8.7)</td>
<td>1.76 (0.87, 3.56)</td>
<td>1.09 (0.48, 2.46)</td>
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<tr>
<td>Cotton wool spots</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1511</td>
<td>64 (4.2)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>92</td>
<td>15 (16.3)</td>
<td>3.15 (1.50, 6.61)</td>
<td>2.10 (0.90, 4.91)</td>
</tr>
<tr>
<td>Hard exudates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1492</td>
<td>68 (4.6)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>78</td>
<td>8 (10.3)</td>
<td>2.63 (1.39, 4.96)</td>
<td>1.45 (0.61, 3.43)</td>
</tr>
<tr>
<td>Macular edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1528</td>
<td>73 (4.8)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>23</td>
<td>2 (8.7)</td>
<td>2.29 (1.08, 4.84)</td>
<td>1.40 (0.54, 3.65)</td>
</tr>
</tbody>
</table>

*Hazard rate ratios (95% CI) of ischemic stroke, adjusted for age, sex, race, and examination center.
†Hazard rate ratios (95% CI) of ischemic stroke, adjusted for age, sex, race, and examination center, 6-year mean arterial blood pressure, use of anti-hypertensive treatment, fasting glucose, use of insulin, duration of diabetes, high-density lipoprotein and low-density lipoprotein cholesterol, and cigarette smoking status.


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