Retinal Signs and Stroke
Revisiting the Link Between the Eye and Brain

Michelle L. Baker, MD; Peter J. Hand, MD, FRACP; Jie Jin Wang, MMed, PhD; Tien Y. Wong, FRANZCO, PhD

Background and Purpose—The retinal and cerebral vasculature share similar anatomic, physiological, and embryological characteristics. We reviewed the literature, focusing particularly on recent population-based studies, to examine the relationship between retinal signs and stroke.

Summary of Review—Hypertensive retinopathy signs (eg, focal retinal arteriolar narrowing, arterio-venous nicking) were associated with prevalent stroke, incident stroke, and stroke mortality, independent of blood pressure and other cerebrovascular risk factors. Diabetic retinopathy signs (eg, microaneurysms, hard exudates) were similarly associated with incident stroke and stroke mortality. Retinal arteriolar emboli were associated with stroke mortality but not incident stroke. There were fewer studies on the association of other retinal signs such as retinal vein occlusion and age-related macular degeneration with stroke, and the results were less consistent.

Conclusion—Many retinal conditions are associated with stroke, reflecting possible concomitant pathophysiological processes affecting both the eye and the brain. However, the incremental value of a retinal examination for prediction of future stroke risk remains to be determined. (Stroke. 2008;39:1371-1379.)

Key Words: stroke ■ mortality ■ hypertensive retinopathy ■ diabetic retinopathy ■ population-based cohort

Stroke is the most common cause of serious disability in adults and is projected to overtake coronary heart disease as the most common cause of death.1 Present stroke risk prediction has several shortcomings. First, a significant proportion of stroke morbidity is not explained by the traditional risk factors, such as hypertension, diabetes, and cigarette smoking, particularly in young people aged <45 years, in which more than one third are diagnosed with cryptogenic stroke.2 Second, the contribution from some of the traditional risk factors to stroke risk is difficult to quantify. Measured blood pressure, for example, is a “snap shot” measurement in time. There is therefore a need for additional biomarkers of stroke risk, which may be particularly useful for persons who do not have traditional risk factors.

The retinal blood vessels share similar anatomic, physiological, and embryological characteristics to the cerebral vessels. The retina is an extension of the diencephalon, and possesses a blood-retinal barrier that is analogous to the blood-brain barrier.3 Changes in the retinal vessels likely reflect similar changes in the cerebral vessels.4 The retinal vasculature, however, is unique in that it can be directly and noninvasively visualized in vivo. Thus, studying retinal signs may provide clues to understanding the pathophysiology of stroke and related cerebrovascular diseases.

The aim of this review is to summarize the present evidence on the association between retinal signs and stroke. We reviewed 6 groups of retinal signs: hypertensive retinopathy signs, retinal vessel diameter, diabetic retinopathy signs, retinal arteriolar emboli, retinal vein occlusion, and age-related macular degeneration, and we concentrated on population-based studies which used retinal photography to document retinal signs.5–8 Among the various studies, 2 were multi-centered studies of cardiovascular diseases in the United States: the Atherosclerosis Risk in Communities Study (ARIC)5 among 15 792 middle-aged subjects aged 45 to 64 years; and the Cardiovascular Health Study (CHS)6 among 5888 older subjects aged 69 to 97 years. Two other studies were conducted in geographically defined areas: The Beaver Dam Eye Study (BDES)7 among 4926 subjects aged 43 to 84 years in Wisconsin, US; and the Blue Mountains Eye Study (BMES)8 among 3654 subjects aged 49 to 97 years in Australia. All 4 population-based studies controlled for multiple cardiovascular risk factors in their analyses. These 4 studies, along with others, are the subject of this review, supported by data from autopsy studies9 and animal models.10

Historical Context of Retinal Signs and Stroke
The ophthalmoscope was invented in 1852. Not long after, Marcus Gunn observed a range of retinal signs including...
cotton-wool spots, flame-shaped and blot-shaped retinal hemorrhages, arterio-venous nicking (AV nicking), focal retinal arteriolar narrowing, generalized arteriolar narrowing and swelling of the optic disc in patients with hypertension and renal disease. He called these signs “hypertensive retinopathy.”

In 1939 Keith, Wagener and Barker showed that these signs were predictors of mortality in patients with hypertension and developed a classification system that divided these retinal signs into 4 categories by a ranking of severity to prognosis. However, the Keith, Wagener, and Barker classification has been limited by poor intra- and interobserver agreement when using ophthalmoscopic examination to detect these signs. Despite many attempts to improve this classification system, no universally accepted or standardized system is established to classify hypertensive retinopathy signs.

New retinal photography and imaging technology, introduced over the past decade, has revolutionized viewing the retina and improved precision in the detection of retinal signs. This includes qualitative grading of retinal photographs to assess retinal signs, and a semiautomated computer program to quantitatively measure retinal vessel diameters. In contrast to the fair intra- and interobserver agreement for the use of mydriatic ophthalmoscopy to detect retinopathy (kappa values of 0.81 to 0.91 for microaneurysms to 0.85 to 0.99 for retinal hemorrhages), there was excellent intra- and interobserver agreement in classifying retinopathy from retinal photographs (kappa values of 0.40 to 0.91 for microaneurysms to 0.85 to 0.99 for retinal hemorrhages). Using retinal photography, there was moderate to excellent agreement for all other retinal signs: retinal arteriolar wall light reflex (κ=0.80 to 0.87); retinal vessel diameters (κ=0.80 to 0.93); retinal vein occlusion and arteriolar emboli (κ=0.76 to 1.00); and age-related macular degeneration (κ=0.55 to 0.92) with the exception of retinal arteriolar wall signs (κ=0.56 to 0.57 for AV nicking and κ=0.18 to 0.62 for focal arteriolar narrowing).

**Hypertensive Retinopathy and Stroke**

**Moderate Hypertensive Retinopathy**

Moderate hypertensive retinopathy signs refer to microaneurysms, cotton-wool spots, retinal hemorrhages, and hard exudates with a prevalence of 7.0% to 11.0% and 5-year cumulative incidence of 6.0% to 9.7%. Histopathologic studies suggest retinopathy is related to small vessel arteriolar sclerosis which involves retinal ischemia and breakdown of the blood-retina barrier.

Table 1 summarizes the association between hypertensive retinopathy signs and stroke. In the ARIC study, participants with hypertensive retinopathy were significantly more likely to have prevalent MRI-detected silent cerebral infarcts (odds ratio [OR] 4.24, 95% CI 1.69 – 10.64) than people without retinopathy. Both ARIC and BMES found higher incidence rates of stroke, and an increased risk of dying from stroke, in those with hypertensive retinopathy. Conversely, in the older CHS cohort, hypertensive retinopathy at base-

**Figure 1.** retinal photograph of hypertensive retinopathy signs demonstrating arteriovenous nicking (box), cotton wool spots (black arrows), and retinal hemorrhage (white arrow).

line was not associated with incident cerebral infarction or hemorrhage, identified by cranial MRI. The authors hypothesized the prognostic significance of the retinopathy signs varied with age, possibly because of selective mortality or alternatively because of a misclassification bias from a higher prevalence of comorbid conditions masking the association with retinal signs.

**Mild Hypertensive Retinopathy or Retinal Arteriolar Wall Signs**

Retinal arteriolar wall signs refer to AV nicking, focal retinal arteriolar narrowing, and an increased arteriolar wall reflex. The combination of these signs, in the absence of microaneurysms, cotton-wool spots, retinal hemorrhages, and hard exudates, is sometimes referred to as mild hypertensive retinopathy. AV nicking describes tapering on both sides of a venule at it crosses under an arteriole. Focal retinal arteriolar narrowing is a localized constricted arteriolar segment (sometimes estimated to be 2/3 the width of distal vessel segments, assessed in arterioles located at least a half a disc diameter away from the optic disc margin). The increased arteriolar wall light reflex is a centralized light reflex from the surface of retinal arterioles also known as copper-wiring or if more severe, silver-wiring. Prevalence of AV nicking and focal retinal arteriolar narrowing increased with age and was between 4.2% to 14.3% for AV nicking and 5.3% to 14.9% for focal retinal arteriolar narrowing. The corresponding 5-year incidence was 6.5% to 9.9%. There was an inverse association between age and prevalence of a mildly increased arteriolar wall light reflex (36.0%, 37.7%, 28.9%, and 18.8% for age groups <60, 60 to 69, 70 to 79, and >80 years, respectively, P for trend<0.001), but this was not observed for a markedly increased reflex.

Population based and histopathologic data have suggested AV nicking is associated with long standing hypertension where the sclerotic arteriolar wall, at points where the arteriole crosses the venule, share a common adventitia covering, which compresses the venular blood column. Focal arteriolar narrowing is associated with present blood
pressure levels, representing an area of localized vasospasm, which may be reversible.\textsuperscript{23,31} Alterations in the arteriolar wall light reflex are associated with uncontrolled or untreated hypertension and represent the sclerotic arteriolar wall.\textsuperscript{20}

The associations between retinal arteriolar signs and stroke are summarized in Table 1. In the ARIC study, the presence of AV nicking and focal retinal arteriolar narrowing was associated with an increased risk of MRI-detected silent cerebral infarcts (OR 1.90; 95% CI 1.25 to 2.88 and OR 1.89; 95% CI 1.22 to 2.92, respectively).\textsuperscript{28} Only AV nicking was associated with incident stroke in the CHS\textsuperscript{29} and the ARIC cohort.\textsuperscript{5} In the BMES\textsuperscript{8} and BDES,\textsuperscript{7} however, both focal retinal arteriolar narrowing and AV nicking at baseline was associated with an increased risk of incident stroke, or stroke mortality. An increased arteriolar wall light reflex was not associated with stroke mortality in the BMES.\textsuperscript{20} Both ARIC\textsuperscript{5} and CHS\textsuperscript{6} used retinal photographs of one eye without pharmacological dilatation, whereas in the BDES\textsuperscript{7} and BMES,\textsuperscript{8} photographs were taken through dilated pupils of both eyes from each study subject, and an underestimation of the prevalence of retinal vessel signs is likely to have occurred in the ARIC and CHS.

**Retinal Vessel Diameter**

The retinal arteriole has a diameter of between 50 and 250 $\mu$m,\textsuperscript{27,32,33} which overlaps the diameters for the small cerebral arteries (ranging from 50 to 400 $\mu$m).\textsuperscript{34} Generalized arteriolar narrowing, traditionally classified as mild hypertensive retinopathy,\textsuperscript{5} is difficult to assess clinically. Apart from hypertension, there is very little prior knowledge of diseases affecting the retinal vessels.\textsuperscript{13} There is now recognition that venular dilatation is one of the earliest responses to hyperglycemia and retinal hypoxia,\textsuperscript{35} whereas narrowing of the retinal arterioles has long been regarded as one of the early features of the hypertensive retinopathy signs.\textsuperscript{36,37}

Using a semiautomated computer system\textsuperscript{38–40} to quantify and summarize retinal vessel calibre from retinal photographs, an arteriole-to-venule ratio (AVR) was initially used to represent the relative narrowing of arterioles in the ARIC study.\textsuperscript{39} The AVR minimizes measurement errors resulting from magnification attributable to refractive errors.\textsuperscript{13} An AVR of 1.0 indicates that arteriolar diameters are, on average, the same as venular diameters, and a smaller AVR indicates either a narrower arteriole, relative to venule, or a wider venule relative to arteriole. The mean AVR in the ARIC population was 0.8444 (SD 0.09).\textsuperscript{41}

The association between retinal vessel diameters and stroke are shown in Table 2. The population-based studies demonstrated only a modestly increased likelihood of incident stroke or MRI detected prevalent stroke or WML for each SD decrease in AVR,\textsuperscript{5,29} with the exception of the BMES, where no such association was observed.\textsuperscript{8} The risk of

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Sample</th>
<th>Methodology</th>
<th>Association With Hypertensive Retinopathy Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent stroke</td>
<td>CHS\textsuperscript{6}</td>
<td>2050</td>
<td>Clinical</td>
<td>Retinopathy: +, 0, 0, 0</td>
</tr>
<tr>
<td></td>
<td>CHS\textsuperscript{29}</td>
<td>1717</td>
<td>MRI</td>
<td>Arteriovenous: +, 0, 0, 0</td>
</tr>
<tr>
<td></td>
<td>ARIC\textsuperscript{28}</td>
<td>1684</td>
<td>MRI</td>
<td>Nicking: +, +, +, +</td>
</tr>
<tr>
<td>Prevalent WML</td>
<td>ARIC\textsuperscript{47}</td>
<td>1684</td>
<td>MRI</td>
<td>Focal Arteriolar Narrowing: +, +, +, +</td>
</tr>
<tr>
<td>Progression WML</td>
<td>ARIC\textsuperscript{28}</td>
<td>1684</td>
<td>MRI</td>
<td>+</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>ARIC\textsuperscript{29}</td>
<td>1717</td>
<td>MRI</td>
<td>0, 0, 0, 0</td>
</tr>
<tr>
<td>5-year</td>
<td>Rotterdam\textsuperscript{43}</td>
<td>490</td>
<td>MRI</td>
<td>+, +, 0, 0</td>
</tr>
<tr>
<td>Progression WML</td>
<td>ARIC\textsuperscript{47}</td>
<td>1684</td>
<td>MRI</td>
<td>0, 0, 0, 0</td>
</tr>
<tr>
<td>Progression WML</td>
<td>CHS\textsuperscript{29}</td>
<td>1717</td>
<td>MRI</td>
<td>0, 0, 0, 0</td>
</tr>
<tr>
<td>Progression WML</td>
<td>ARIC\textsuperscript{28}</td>
<td>1684</td>
<td>MRI</td>
<td>0, 0, 0, 0</td>
</tr>
<tr>
<td>Progression WML</td>
<td>CHS\textsuperscript{29}</td>
<td>1717</td>
<td>MRI</td>
<td>0, 0, 0, 0</td>
</tr>
<tr>
<td>Progression WML</td>
<td>ARIC\textsuperscript{47}</td>
<td>1992</td>
<td>Clinical</td>
<td>0, 0, 0, 0</td>
</tr>
<tr>
<td>Progression WML</td>
<td>BMES\textsuperscript{8}</td>
<td>3654</td>
<td>CT or MRI</td>
<td>+, 0, 0, +</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>BMES\textsuperscript{8}</td>
<td>3654</td>
<td>ANDI</td>
<td>+, +, +, +</td>
</tr>
<tr>
<td>7-year</td>
<td>BDES\textsuperscript{24}</td>
<td>413 cases</td>
<td>Death certificate</td>
<td>+, +, +, +</td>
</tr>
<tr>
<td>10-year</td>
<td>BDES\textsuperscript{24}</td>
<td>413 controls</td>
<td>Death certificate</td>
<td>+, +, +, +</td>
</tr>
</tbody>
</table>

Significant multivariate adjusted associations ($P<0.05$): + positive, 0 null, blank not reported.

CHS indicates Cardiovascular Health Study; ARIC study, Atherosclerosis and Risk in Communities Study; BMES, Blue Mountains Eye Study; BDES, Beaver Dam Eye Study; Rotterdam, Rotterdam Scan Study; WML, white matter lesions; AVR, arteriovenous ratio; ANDI, Australian National Death Index.

*With hypertension; #Without diabetes; ‡Without diabetes or hypertension; §With hypertension, diabetes or both, aged 43 to 74 years.
dying from a stroke was one-and-a-half–fold greater per SD reduction in AVR in the BDES. In a subgroup analysis of the ARIC, the risk of MRI-detected subclinical cerebral infarction was nearly 5-fold greater (OR 4.76, the first versus fifth quintile) in hypertensive persons with smaller as compared with larger AVR.

It should be noted that the AVR measurement does not provide specific information on whether these associations were attributable to arteriolar narrowing, venular dilatation, or both. The Rotterdam Scan Study, a population-based study of 5540 Dutch people aged >55 years, was the first to demonstrate significant associations of larger venular dilatation, rather than arteriolar narrowing, with WML progression (not severity) and incident stroke, independent of other cardiovascular risk factors. Likewise, the CHS found larger venular dilatation was associated with 5-year incident stroke but not arteriolar narrowing. However, there no association for each SD increase in arteriolar diameter, or SD decrease in venular diameter, with either 10- to 12-year incident stroke or stroke mortality from pooled BDES and BMES data.

Diabetic Retinopathy and Stroke

Diabetic retinopathy can be divided into nonproliferative (NPDR) and proliferative (PDR) forms. NPDR refers to microaneurysms, retinal hemorrhages, hard exudates, cotton-wool spots, venous beading, and intraretinal microvascular abnormalities (Figure 2). Progression to the proliferative form is characterized by neovascularization. For any type of diabetes, the prevalence of diabetic retinopathy in people more than 40 years of age was reported to be 40.3% for

Table 2. Retinal Vessel Diameter and Stroke, Population-Based Studies Using Retinal Photography

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Sample</th>
<th>Methodology</th>
<th>Association With Retinal Vessel Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent stroke</td>
<td>CHS6</td>
<td>2050</td>
<td>Clinical</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CHS29</td>
<td>1717</td>
<td>MRI</td>
<td>AVR</td>
</tr>
<tr>
<td></td>
<td>ARIC28</td>
<td>1684</td>
<td>MRI</td>
<td>AVR*</td>
</tr>
<tr>
<td>Prevalent WML</td>
<td>ARIC37</td>
<td>1684</td>
<td>MRI</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>CHS29</td>
<td>1717</td>
<td>MRI</td>
<td>AVR</td>
</tr>
<tr>
<td></td>
<td>Rotterdam43</td>
<td>490</td>
<td>MRI</td>
<td>Venular diameter</td>
</tr>
<tr>
<td>Progression WML</td>
<td>Rotterdam43</td>
<td>490</td>
<td>MRI</td>
<td>Venular diameter</td>
</tr>
<tr>
<td>3.3-year</td>
<td>CHS29</td>
<td>1717</td>
<td>MRI</td>
<td>AVR</td>
</tr>
<tr>
<td>5-year</td>
<td>Rotterdam43</td>
<td>490</td>
<td>MRI</td>
<td>0†</td>
</tr>
<tr>
<td>5-year</td>
<td>ARIC5</td>
<td>10358</td>
<td>Clinical</td>
<td>0</td>
</tr>
<tr>
<td>5-year</td>
<td>CHS29</td>
<td>1717</td>
<td>MRI</td>
<td>AVR</td>
</tr>
<tr>
<td>7-year</td>
<td>Rotterdam43</td>
<td>1992</td>
<td>Clinical</td>
<td>Venular diameter</td>
</tr>
<tr>
<td>7-year</td>
<td>BMES8</td>
<td>3654</td>
<td>CT or MRI</td>
<td>0#</td>
</tr>
<tr>
<td>8.5-year</td>
<td>Rotterdam43</td>
<td>5540</td>
<td>CT or MRI</td>
<td>Venular diameter</td>
</tr>
<tr>
<td>10–12 year</td>
<td>Pooled BDES BMES45</td>
<td>7494</td>
<td>Clinical</td>
<td>0</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>7-year</td>
<td>BMES8</td>
<td>3654</td>
<td>ANDI</td>
</tr>
<tr>
<td>10-year</td>
<td>BMES45</td>
<td>413 cases</td>
<td>Death certificate</td>
<td>AVR§</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>10–12</td>
<td>Pooled BDES BMES45</td>
<td>7494</td>
<td>Death certificate or ANDI</td>
</tr>
</tbody>
</table>

Significant multivariate adjusted associations (P<0.05): + positive, 0 null, blank not reported.

CHS indicates Cardiovascular Health Study; ARIC study, Atherosclerosis and Risk in Communities Study; BMES, Blue Mountains Eye Study; BDES, Beaver Dam Eye Study; Rotterdam, Rotterdam Scan Study; WML, white matter lesions; AVR, arteriovenous ratio; Venular diameter, larger retinal venular diameter; ANDI, Australian National Death Index.

*With hypertension; †Lacunar stroke; #Without diabetes; §With hypertension, diabetes or both, aged 43 to 74 years.

Figure 2. Retinal photograph of diabetic retinopathy signs demonstrating microaneurysms (boxes), hard exudates (black arrow), and retinal hemorrhages (white arrows).
NPDR and 8.2% for PDR. The 3-year incidence of any diabetic retinopathy was 10.3% per year.

Two population-based studies have evaluated the association between diabetic retinopathy and risk of stroke or stroke mortality, and few other data are available. In the ARIC study, the association of diabetic retinopathy with stroke prevalence and incidence was examined. The other population-based study was the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) in persons with type 1 and type 2 diabetes, and assessed the association between diabetic retinopathy and stroke prevalence, incidence and mortality. Table 3 summarizes the association between diabetic retinopathy and stroke. In both studies, prevalent stroke was not associated with any severity of diabetic retinopathy. However, prospective analysis of the ARIC data showed that the risk of incident ischemic stroke was higher (hazard rate ratio [HR] 2.34, 95% CI 1.13 to 4.86) in people with mild NPDR as compared with no retinopathy in the ARIC. There were insufficient numbers of subjects with PDR in the ARIC study to assess the associations with stroke. In the WESDR, the risk of incident stroke was 6-fold higher in people with type 2 diabetes and PDR, and the risk of stroke mortality was 2-fold higher.

Table 3. Diabetic Retinopathy and Stroke, Population-Based Studies Using Retinal Photography

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Sample</th>
<th>Methodology</th>
<th>Association With Diabetic Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent clinical stroke</td>
<td>ARIC51</td>
<td>1600 type 2 diabetes</td>
<td>Self reported stroke</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>WESDR53</td>
<td>2366 type 1 and 2 diabetes</td>
<td>Self reported stroke</td>
<td>0</td>
</tr>
<tr>
<td>Incident clinical stroke</td>
<td>4-year WESDR53</td>
<td>891 type 1 diabetes</td>
<td>Self reported stroke</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>987 type 2 diabetes</td>
<td>PDR*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8-year ARIC52</td>
<td>1617 type 2 diabetes</td>
<td>Self reported stroke</td>
<td>Mild NPDR</td>
</tr>
<tr>
<td>Stroke mortality</td>
<td>16-year WESDR54</td>
<td>663 type 1 diabetes</td>
<td>Death certificate</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>114 type 2 diabetes</td>
<td>PDR</td>
<td></td>
</tr>
</tbody>
</table>

Significant multivariate adjusted associations (P<0.05): + positive, 0 null, blank not reported.

ARIC study indicates Atherosclerosis and Risk in Communities Study; WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy; PDR, Proliferative diabetic retinopathy; NPDR, Nonproliferative diabetic retinopathy.

*Adjusted for age only.

Retinal arteriolar emboli are a transient phenomena, and 1 study showed that up to 90% of emboli that had been detected were absent on review 5 years later. Retinal arteriolar emboli are infrequent in the general population, with a prevalence of 0.2% to 1.4% of adults aged 40 years or older in the general community, rising to 5.5% in those with hypertension who are smokers. The 10-year cumulative incidence was 3.0%. Bilateral retinal arteriolar emboli are rare, although multiple emboli in a single eye have been detected fairly frequently.

Table 4 summarizes the association between retinal arteriolar emboli and stroke. Although retinal arteriolar emboli were not associated with an increased prevalence or incidence of stroke in the BDES, they were associated with a higher risk of stroke-related death: nearly 3-fold greater in participants with retinal emboli over a 5-year and 10-year period in the BDES, or in pooled data from the BDES and BMES.

**Retinal Vein Occlusion and Stroke**

Retinal vein occlusion (RVO) refers to dilated and tortuous veins and the presence of retinal hemorrhages, cotton wool...
spots, and macular and optic disc edema. In central RVO, all 4 quadrants have hemorrhages, whereas in branch RVO these lesions localize in one sector corresponding to that branch area. The pathogenesis is unclear but is likely multifactorial, and postulated causes include thrombosis in the venule resulting from compression by an adjacent atherosclerotic arteriole, local alteration to blood flow from unfavourable physiological characteristics or hematologic abnormalities.65–69 RVO increases with age and prevalence has been reported to be 0.3% to 1.6% in adults aged 40 years and older,60,70–73 and 4.6% in people 80 years and older.70 In the BMES, the 10-year incidence was 1.6%.72 Pooled data from the BDES and BMES72 found the presence of RVO was not associated with stroke mortality (HR 0.9; 95% CI 0.4 to 2.1) in people more than 70 years of age, stratified by gender. However, there were no stroke deaths among persons in the younger group (aged 43 to 69 years) with RVO. This finding is similar to smaller, clinic-based studies which have not demonstrated any consistent association between RVO and stroke.74–78 Pooled data from the ARIC and CHS,60 examining vascular risk factors for RVO, adjusted for age, found carotid artery plaque (defined as an area of focal thickening of the intima-media layer of the right or left coronary artery occluding ≥50% of the lumen) was associated with RVO (OR 5.62; 95% CI 2.6 to 12.2).

### Age-Related Macular Degeneration and Stroke

Age-related macular degeneration (AMD) refers to a degenerative condition affecting the macular or central area of the retina. The main characteristic of early AMD is the presence of soft drusen which are yellow deposits under the retinal pigment epithelium and retinal pigment changes (hyper- and hypopigmentation). Late AMD includes 2 distinct forms, atrophic (dry) AMD or neovascular (wet) AMD (Figure 4). The etiology involves both genetic and environmental factors. All studies showed an exponential increase in AMD prevalence after the age of 70. Early AMD was observed in 15% of persons aged 65 to 74 years and 25% of those 75 years and older, whereas late AMD was seen in 1% and 5%, respectively.79–81 The 15-year cumulative incidence for early AMD was 14.3% and for late AMD was 3.1%, with the latter rising to 8.0% in those 75 years and older.82

There have been a number of studies that have examined a possible association of AMD with stroke, including the CHS,83 and the ARIC study,22,84 among others.85,86 The presence of any AMD was found to be associated with prevalent WML (OR 1.59 95% CI 1.12 to 2.27) in the CHS83 and MRI-detected subclinical stroke (OR 1.64 95% CI 1.15 to 2.35) in the ARIC.22 The presence of early AMD in ARIC was associated with an almost 2-fold risk of 10-year incident stroke (OR 1.85 95% CI 1.19 to 2.87),22 compared to those people without any AMD. However, these 2 studies had insufficient cases to assess the associations with late AMD.

### Implications and Future Directions

Several common themes emerged from these new studies. First, hypertensive retinopathy signs are common findings in the general community and are generally stronger and more consistent predictors of stroke events in persons with or without diabetes, than other retinal conditions such as retinal arteriolar emboli, RVO, and AMD. Some retinopathy lesions are considered signals of a disruption of the blood-tissue barrier, which is thought to be a precursor in the development of cerebrovascular disease. Nonetheless, the extent to which

![Figure 4. Retinal photograph of late age-related macular degeneration with disciform scar.](image-url)
retinopathy and other retinal signs contribute independently to stroke risk remains inconclusive.

Second, the prognostic significance of the retinal signs varied with age. There were weaker associations for hypertensive retinopathy with stroke events in the older BMES (mean age 69.9 years) and the CHS (mean age 78.5 years) populations than in the middle-aged ARIC cohort (mean age 53.6 years). Likewise, in the BDES population, all hypertensive retinopathy signs were associated with stroke mortality in persons aged 43 to 75 years but not in those aged 75 years and older. It is unclear why the association of retinal diseases with stroke is stronger in younger persons, but it has been speculated that the associations observed mainly in younger persons may be reflective of selective mortality, as participants in these studies who manifest retinal diseases, and who are susceptible to the pathological effects associated with these abnormalities (ie, hypertension and diabetes) more likely to die, leaving a group of older participants whose biological and genetic makeup protects them from processes associated with these retinal abnormalities. In addition, a higher prevalence of comorbid conditions in older persons likely overshadowed the associations with retinal signs. Further, older persons were more likely to have cataract, leading to a poor view of retinal images and likely measurement errors that resulted in dilution of the associations.

Third, the combination of retinal signs and cerebral markers of microvascular disease may indicate more severe or extensive cerebral microvascular pathology. For example, in the ARIC, participants with both hypertensive retinopathy signs and WMLs had a stroke risk 18 times higher than persons without either sign.

Finally, the association between retinal arteriolar emboli and stroke mortality raises the question for clinicians to perform careful vascular assessments in patients detected with retinal emboli. How extensive the vascular assessment should be remains elusive, as the usefulness of performing carotid ultrasonography, transthoracic echocardiography, or carotid endarterectomy in people with retinal arteriolar emboli remains controversial.

The strengths of the recent population-based studies were their large sample size, which are representative of the general population, the use of retinal photography and semi-automated measurement for retinal vessel calibre to document the retinal signs, and the adjustment of multiple cardiovascular risk factors in the analyses. However, there were limitations that complicated the comparisons among the studies. In the ARIC and CHS, retinal signs were assessed from a single non stereoscopic retinal photograph of 1 eye without pupil dilation, whereas the BDES used 3 retinal stereoscopic fields, and the BMES used 6 fields of both eyes after pharmacological pupillary dilation. As a result of this, a higher percentage of photographs were upgradeable in the ARIC (27%) and CHS (14.2%) compared to 1% to 3% in the BDES and BMES. Although the quantitative assessment method used by the 4 studies was essentially the same, there was no uniformly accepted standardized grading protocol used across the 4 studies to classify retinal signs. This may account for the fact that the prevalence of AV nicking in the BDES was only 1/3 of the prevalence found in the ARIC, despite more photographic fields available in the BDES.

Retinal photographs were obtained many years after the baseline examination in the ARIC and CHS, in comparison to retinal photographs being taken at baseline in the BDES and BMES. Studies which relied on a self-reported past history of stroke could have contributed to misclassification bias. Undifferentiated misclassification, however, would bias the retinal associations with stroke toward the null, resulting in an underestimation of the associations observed. Finally, different stroke subtypes (eg, ischemic versus hemorrhagic) were rarely analyzed separately in any of the studies because of low numbers.

These population-based studies considered all types of strokes events together as the necessary first step to document whether there was an association between retinal signs and stroke. Future studies should replicate some of these findings in clinical populations for the associations of retinal signs with different stroke subtypes (eg, ischemic versus hemorrhagic). Researchers need to develop a standardized photographic and grading classification system to assess retinal disease, to facilitate comparison and confirmation of findings from different populations. Although retinal signs seem to provide predictive information that is independent of traditional vascular risk factors, their incremental value in stroke risk stratification or stroke prognosis prediction is unknown. Finally, research should assess the impact of specific therapy targeted at the microcirculation on retinal signs, as has been suggested by some experimental work and clinical studies. This could potentially result in retinal photography acting as a surrogate marker of treatment efficacy, which has significant implications for clinical trials.

Conclusion

New data, from population-based studies, suggests that many retinal signs, in particular hypertensive retinopathy signs (eg, focal retinal arteriolar narrowing, arterio-venous nicking), may be markers of stroke risk and mortality, independent of other stroke risk factors. Diabetic retinopathy signs (eg, microaneurysms, hard exudates) are similarly associated with incident stroke and stroke mortality. There are fewer studies on the association of retinal arteriolar emboli, retinal vein occlusion, and age-related macular degeneration with stroke, and the findings have been less consistent. Furthermore, it remains to be seen whether retinal imaging techniques will result in the identification of people at high risk of stroke in clinical settings, and ultimately become part of the routine clinical stroke risk assessment.

Search Strategy and Selection Criteria

Information for this review was identified from a MEDLINE ISI using the terms retinal signs, retinal photographs, retinal microvascular, retinal arteriolar narrowing, retinopathy, AV nicking, AV ratio, arteriovenous ratio, retinal arteriolar emboli, retinal vein occlusion, and age-related macular degeneration or age-related maculopathy, in various combinations and combined with stroke and either observer agreement, observer variability, kappa, prognosis, or mortality up to June 2007. From the articles identified, original investigations and review articles were included. All English articles were read,
and for non-English articles, the English abstracts were reviewed. The reference lists of articles were also searched for additional relevant articles. Bibliographies of these articles provided further references, including books and internet-based data.

Sources of Funding
This work was funded by a Singapore National Medical Research Council (NHMRC) grant (352337) and an Australian National Health and Medical Research Council (NHMRC) grant (5352337).

Disclosures
None.

References
18. Lin DY. The sensitivity and specificity of single-field nonmydriatic monochromatic digital fundus photography with remote image interpre-


Retinal Signs and Stroke: Revisiting the Link Between the Eye and Brain
Michelle L. Baker, Peter J. Hand, Jie Jin Wang and Tien Y. Wong

Stroke. 2008;39:1371-1379; originally published online February 28, 2008;
doi: 10.1161/STROKEAHA.107.496091
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/39/4/1371

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/