Comparison of Risk Factors in Patients With Transient and Prolonged Eye and Brain Ischemic Syndromes

Gillian E. Mead, MD; Stephanie C. Lewis, PhD; Joanna M. Wardlaw, FRCP; Martin S. Dennis, FRCP

Background and Purpose—Patients with ischemic stroke, cerebral transient ischemic attacks (TIAs), retinal artery occlusion (RAO), and amaurosis fugax are thought to have similar risk factors and underlying vascular disease. However, if risk factors are different in patients with eye compared with brain symptoms and in those whose symptoms last <24 hours (transient) compared with those lasting >24 hours (prolonged), more focused prevention strategies are possible in the future.

Methods—All patients with ischemic stroke, cerebral TIA, RAO, and amaurosis fugax presenting to our hospital from 1994 to 1999 were examined by a stroke physician. Risk factors were documented, and patients underwent carotid Doppler ultrasound.

Results—We registered 1491 patients with ischemic stroke, 580 with cerebral TIA, 79 with RAO, and 138 with amaurosis fugax. Atrial fibrillation was more common in brain than eye events, whether prolonged [ischemic stroke versus RAO: odds ratio (OR), 3.6; 95% confidence interval (CI), 1.1 to 12] or transient (cerebral TIA versus amaurosis fugax: OR, 2.9; 95% CI, 0.7 to 13), and more common in prolonged than transient events, whether brain (stroke versus cerebral TIA: OR, 3.3; 95% CI, 2.1 to 5.1) or eye (RAO versus amaurosis fugax: OR, 2.7; 95% CI, 0.4 to 16). Severe ipsilateral carotid disease was less common in brain than eye events, whether prolonged (ischemic stroke versus RAO: OR, 0.6; 95% CI, 0.3 to 1.0) or transient (cerebral TIA versus amaurosis fugax: OR, 0.4; 95% CI, 0.2 to 0.6).

Conclusions—These data suggest that there are pathogenetic differences between transient and permanent eye and brain ischemic syndromes. Improved understanding of these mechanisms could lead to more effective stroke prevention.

Key Words: amaurosis fugax ■ carotid stenosis ■ cerebral infarction ■ cerebral ischemia, transient ■ embolism ■ stroke

It is thought that the risk factors and causes of ischemic stroke, cerebral transient ischemic attacks (TIAs), retinal artery occlusion (RAO), and amaurosis fugax are similar. Therefore, patients with these 4 types of ischemic events often undergo similar investigations, and the strategies used for secondary prevention of ischemic events are broadly similar in the 4 groups. If these 4 syndromes are manifestations of the same underlying disease process, the same approaches to investigation and management are appropriate. However, if the origins and risk factors for the 4 syndromes are different, improved understanding of the pathophysiology of these ischemic events might improve patient investigation and management.

If the 4 syndromes are manifestations of the same underlying disease process, then one would expect to find the same pattern of risk factors. Several studies that compared risk factors in cerebral TIA and ischemic stroke (ie, transient versus prolonged brain symptoms; total n=3249; Table 1) found no consistent difference in risk factors. Five small studies (total n=775) compared the prevalence of risk factors in patients with eye and brain events (Table 2) but did not find consistent differences in the pattern of risk factors between eye and brain events. There are data, however, to suggest that eye and brain events may be distinct. For example, compared with cerebral TIA, the prognosis of amaurosis fugax is better and the benefits of endarterectomy are fewer.

We hypothesized that the pattern of risk factors would differ according to both the site of symptoms (brain compared with eye) and the duration of symptoms (transient versus prolonged). Hence, we compared the pattern of risk factors in a consecutive series of patients with ischemic stroke, cerebral TIA, amaurosis fugax, and RAO.

Methods
From November 1994 to April 1999, several stroke physicians prospectively identified consecutive patients with stroke, cerebral TIA, amaurosis fugax, and RAO who required inpatient care or who were seen at our neurovascular outpatient clinics. The stroke service sees all patients with suspected cerebral or eye ischemic symptoms without restriction in our catchment population of 500,000. It is the

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main referral pathway for carotid endarterectomy for this population. There are no direct referrals from family doctors to vascular surgeons. All diagnoses made by trainees were reviewed by a consultant. All patients diagnosed as having stroke, cerebral TIA, amaurosis fugax, and RAO were entered into the study. Stroke, cerebral TIA, and amaurosis fugax were defined according to previous work. RAO was defined as rapid onset of monocular visual loss (partial or complete) lasting >24 hours that after assessment was considered likely to be due to reduction of flow to the retina or optic nerve as a result of vascular disease.

Risk factors were documented by use of information from history, examination, and routine investigation (age, sex, diabetes mellitus, prior stroke or TIA, ischemic heart disease, valvular heart disease, known atrial fibrillation, peripheral vascular disease, current smoker,

### TABLE 1. Summary of Studies Comparing Risk Factors in Cerebral TIA and Ischemic Stroke

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Population</th>
<th>Patients, n</th>
<th>Carotid Imaging?</th>
<th>Significant Difference in Risk Factors Between 2 Groups?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison and Marshall</td>
<td>Neurology patients undergoing carotid angiography</td>
<td>40 TIA, 44 strokes</td>
<td>Yes</td>
<td>No difference*</td>
</tr>
<tr>
<td>Humphrey and Marshall</td>
<td>Referrals to 2 hospital consultants</td>
<td>117 TIA, 42 RIND</td>
<td>Angiography in ~50%</td>
<td>No difference</td>
</tr>
<tr>
<td>Gambina et al</td>
<td>“Acute cerebrovascular diseases” hospital department</td>
<td>187 TIA, 522 RIND</td>
<td>No</td>
<td>Smoking more common in RIND; hematocrit &gt;45% more common in TIA</td>
</tr>
<tr>
<td>Fritz et al</td>
<td>Referrals to a hospital “cerebrovascular clinic”</td>
<td>388 TIA, 137 minor strokes</td>
<td>Yes but reported in relation to diabetes, not type of ischemic event</td>
<td>Diabetes more common in strokes</td>
</tr>
<tr>
<td>Dennis et al</td>
<td>Oxfordshire Community Stroke Project</td>
<td>184 TIA (including 32 amaurosis fugax), 312 minor stroke</td>
<td>No</td>
<td>No difference</td>
</tr>
<tr>
<td>Errando and Puiggros</td>
<td>Not stated</td>
<td>144 TIA, 110 cerebral infarcts minor sequelae</td>
<td>Not stated</td>
<td>Hypertension less common in TIs</td>
</tr>
<tr>
<td>Falke et al</td>
<td>Hospital based</td>
<td>129 TIA, 80 minor strokes</td>
<td>No</td>
<td>Hypertension more common in TIs</td>
</tr>
<tr>
<td>Iannuzzi et al</td>
<td>Peripheral or carotid atherosclerotic disease referred for noninvasive imaging.</td>
<td>336 TIA, 242 hemispheric strokes</td>
<td>Yes</td>
<td>No difference in presence of ipsilateral plaque or ipsilateral occlusion*</td>
</tr>
<tr>
<td>Sempere et al</td>
<td>Community</td>
<td>103 TIs, 132 minor strokes</td>
<td>Yes in 80%</td>
<td>No difference in vascular risk factors; no difference in large-vessel atherosclerosis as a cause of event*</td>
</tr>
</tbody>
</table>

RIND indicates reversible ischemic neurological deficit.

*Direct comparison was not made by the authors of the original article, but by present authors using $\chi^2$ tests.
previous carotid endarterectomy, cholesterol, and hematocrit). Carotid bruits were noted. Atrial fibrillation was confirmed by 12-lead ECG. Carotid arteries were routinely assessed with color Doppler ultrasound (Acuson 128XP 10V with a 7-MHz multifrequency probe) usually on the same day as the clinical assessment by consultant neuroradiologists blinded to the clinical details. In patients admitted with acute stroke, the Doppler ultrasound was almost always performed within the first week of stroke, but in patients seen as outpatients who might have been referred by their family doctor several weeks after their TIA or amaurosis fugax, we included Doppler results obtained up to 3 months after the initial event. Stenosis severity was assessed by use of standard velocity criteria and lesion appearance. We defined severe disease as including 80% to 99% stenosis and complete occlusion. The carotid ultrasound was routinely audited against intracranial angiography and thus known to be reliable (no patient who had had angiography changed stenosis category between ultrasound and angiography). CT or MR brain imaging was performed routinely in patients with stroke and when clinically indicated in patients with cerebral TIA (eg, multiple or atypical attacks), amaurosis fugax, or RAO. Stroke patients with intracerebral hemorrhage on brain imaging were excluded from analysis.

### TABLE 3. Clinical Risk Factors in the 4 Groups in the Present Study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Ischemic Stroke (n=1491)</th>
<th>Cerebral TIA (n=580)</th>
<th>RAO (n=79)</th>
<th>Amaurosis Fugax (n=138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>68 (13)</td>
<td>67 (11)</td>
<td>65 (11)</td>
<td>65 (9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>800 (54)</td>
<td>328 (57)</td>
<td>47 (59)</td>
<td>89 (64)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>820 (55)</td>
<td>285 (49)</td>
<td>39 (49)</td>
<td>59 (43)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>169 (11)</td>
<td>49 (8)</td>
<td>4 (5)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>534 (36)</td>
<td>197 (34)</td>
<td>34 (43)</td>
<td>62 (45)</td>
</tr>
<tr>
<td>Atrial fibrillation known before event, n (%)</td>
<td>187 (13)</td>
<td>24 (4)</td>
<td>3 (4)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Previous TIA, n (%)</td>
<td>182 (12)</td>
<td>92 (16)</td>
<td>7 (9)</td>
<td>17 (12)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>288 (19)</td>
<td>64 (11)</td>
<td>7 (9)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>365 (24)</td>
<td>163 (28)</td>
<td>22 (28)</td>
<td>37 (27)</td>
</tr>
<tr>
<td>Valvular heart disease, n (%)</td>
<td>150 (10)</td>
<td>57 (10)</td>
<td>11 (14)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>312 (21)</td>
<td>122 (21)</td>
<td>13 (16)</td>
<td>29 (21)</td>
</tr>
<tr>
<td>Previous carotid endarterectomy, n (%)</td>
<td>5 (0.3)</td>
<td>4 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean cholesterol (SD), mmol</td>
<td>5.7 (1.3)</td>
<td>6.0 (1.2)</td>
<td>6.2 (1.5)</td>
<td>5.8 (1.0)</td>
</tr>
<tr>
<td>Mean hematocrit (SD), %</td>
<td>41 (6)</td>
<td>42 (5)</td>
<td>42 (4)</td>
<td>42 (4)</td>
</tr>
<tr>
<td>Aspirin or other antiplatelets at time of event, n (%)</td>
<td>502 (34)</td>
<td>208 (36)</td>
<td>30 (38)</td>
<td>39 (28)</td>
</tr>
<tr>
<td>Anticoagulants at time of event, n (%)</td>
<td>60 (4)</td>
<td>18 (3)</td>
<td>2 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Severe ipsilateral carotid disease (80%–100%), n (%)</td>
<td>164 (15)</td>
<td>63 (14)</td>
<td>17 (22)</td>
<td>39 (30)</td>
</tr>
</tbody>
</table>

For severe ipsilateral carotid disease, data are not relevant for 342 ischemic strokes, 135 cerebral TIAs, 1 RAO, and 8 amaurosis fugax, and the percentages are of the total number of patients who had carotid imaging performed.

*Hypertension was defined as history or treatment at any time or blood pressure >160/90 mm Hg.
†Diabetes mellitus known before stroke.
‡Ischemic heart disease was defined as previous myocardial infarction and/or angina before the current event.
§Peripheral vascular disease was defined as intermittent claudication or history of peripheral vascular surgery or peripheral vascular disease on examination (femoral bruit, absence of both dorsalis pedis and posterior tibial pulses in a foot).
Descriptive statistics were used to compare the risk factor profiles within the 4 groups. We used univariate analysis (odds ratios [ORs] and 95% CIs) to compare stroke with cerebral TIA (ie, prolonged brain versus transient brain), RAO with amaurosis fugax (ie, prolonged eye versus transient eye), stroke with RAO (ie, prolonged brain versus prolonged eye), and cerebral TIA with amaurosis fugax (ie, transient brain versus transient eye) to determine which risk factors predicted the site and duration of symptoms. Results are displayed as ORs and 95% CIs. Only the symptomatic carotid artery was considered in the analysis of percent stenosis and type of ischemic syndrome; thus, patients with nonlateralizing syndromes or posterior circulation events were coded as not relevant (Table 3).

We also compared the presence or absence of an ipsilateral carotid bruit with the presence or absence of a severe carotid disease in each of the 4 groups to investigate whether the referral of patients to our hospital might have been biased by carotid bruits.

**Results**

During the study period, 2498 patients with brain or eye ischemic events were registered. Of these, 210 with >1 syndrome (eg, cerebral TIA and amaurosis fugax) were excluded. Therefore, 1491 patients with ischemic stroke, 580 with cerebral TIA, 79 with RAO, and 138 with amaurosis fugax are the subject of this report.

Table 3 shows the prevalence of risk factors in the 4 groups. There were some differences in risk factors between eye and brain events (Table 4 and Figures 1 and 2). First, atrial fibrillation was more common in brain events than eye events, whether permanent or transient (stroke versus RAO: OR, 3.6; 95% CI, 1.1 to 12; cerebral TIA versus amaurosis fugax: OR, 2.9; 95% CI, 0.7 to 13). Second, severe ipsilateral carotid disease was less common in brain than eye events, whether permanent or transient (stroke versus RAO: OR, 0.6; 95% CI, 0.3 to 1.0; cerebral TIA versus amaurosis fugax: OR, 0.4; 95% CI, 0.2 to 0.6).

The only difference in risk factors between transient and permanent events (Figures 1 and 2) that applied to both brain and eye events was that atrial fibrillation was more common in prolonged than temporary events (stroke versus cerebral TIA: OR, 3.3; 95% CI, 2.1 to 5.1; RAO versus amaurosis fugax: OR, 2.7; 95% CI, 0.4 to 16).

Although our prespecified aim was not to compare risk factors for ischemic stroke with the other 3 subgroups, we also found that there were significant differences in the prevalence of risk factors for stroke compared with both cerebral TIA and RAO. First, a history of prior stroke was thought to be relevant only in the origin of anterior circulation (nonlacunar) events, investigated the effect of removing patients with nonlacunar syndromes or posterior circulation events (both TIA and strokes) and lacunar events (both TIA and strokes) on the prevalence of severe carotid stenosis.

**Definitions for *, †, ‡, §, as in Table 3.**
ORs for both atrial fibrillation and carotid stenosis, and the number is far too small to have biased the results or to be handled separately. Furthermore, this approach was justified by examining the distribution of atrial fibrillation in patients with or without carotid stenosis for the whole cohort and for each ischemic category. For the whole data set of 2288 people, the proportion with atrial fibrillation was 10% for patients with no stenosis, 7% for those with stenosis, and 10% for those in whom the stenosis was not relevant (P=NS). The proportion with atrial fibrillation was similarly equally distributed across the stenosis, no stenosis, and not relevant categories for each of the individual categories of ischemia (all P=NS).

In a sensitivity analysis, with patients with lacunar and posterior circulation events (both cerebral TIA and strokes) excluded, severe carotid disease was still significantly less common in carotid territory cerebral TIA than amaurosis fugax (OR, 0.5; 95% CI, 0.3 to 0.8), but there was no difference between stroke and RAO (OR, 0.9; 95% CI, 0.5 to 1.5). Atrial fibrillation was still more common in carotid territory cerebral TIA than amaurosis fugax (OR, 3.3; 95% CI, 0.7 to 15) and in carotid territory nonlacunar stroke than RAO (OR, 4.7; 95% CI, 1.5 to 15).

The proportion of patients with a bruit on the symptomatic side was 111 of 1257 strokes (9%), 65 of 457 TIA (14%), 16 of 76 RAO (21%), and 36 of 131 amaurosis fugax (27%). The ratio of bruits to severe carotid disease was 0.6 for strokes and 1 for the other subgroups.

### Discussion
This is the largest study to date to compare risk factors in ischemic stroke, cerebral TIA, RAO and amaurosis fugax. Severe ipsilateral carotid stenosis was more common in eye than brain events, and atrial fibrillation was more common in brain than eye events. Atrial fibrillation was more often associated with prolonged (stroke and RAO) than transient (cerebral TIA and amaurosis fugax) symptoms. These data suggest that brain and eye events reflect distinct patterns of vascular disease and risk factors that probably have relevance to the pathophysiology of the event and its prognosis.

Why have these differences in risk factor prevalence not been observed previously (Table 1 and 2)? Previous studies were smaller (the present study is 3 times larger than the largest previous study), included more restricted populations (our study was all patients), looked at only 1 or 2 risk factors (we examined many), and had less complete investigations.

With the assumption that carotid disease and atrial fibrillation cause the syndrome by acting as sources of cerebral emboli, interesting questions arise about pathophysiological mechanisms. Emboli from the internal carotid artery are possibly carried through the ophthalmic arteries in preference to the middle cerebral arteries, whereas emboli from the left atrium are carried through the middle cerebral artery in preference to the ophthalmic artery (Figure 3). Emboli arising from carotid stenosis may be smaller than thrombi arising in the atria (Figure 3). It is possible that high velocities across a tight carotid stenosis displace platelet-fibrin thrombi from the plaque surface early in their formation when they are still small, whereas thrombi developing in the low-velocity environment of the atria could grow much larger before being displaced into the aortic arch. A large thrombus passing up the internal carotid artery is likely to stay in midstream and is mechanically unlikely to pass round the sharp angle into the ophthalmic artery (Figure 4). Platelet-fibrin thrombi from the carotid plaque, being smaller and starting their journey in the lea of a carotid stenosis, might be more likely to drift in the edges of the bloodstream rather than just in the center (boundary layer separation) and to enter the ophthalmic artery. Differential particle flow in streams was used thousands of years ago by Chinese engineers for river manage-
ment to remove large rocks and debris while allowing filtered water with nutrients to irrigate fields (Figure 5). Our data would support the idea that the carotid siphon may act as an important “filter” with just this mechanism. Support for the notion of particle size influencing the position of the particle in a flowing liquid, and for complex patterns of flow at arterial bifurcations, comes from physics models using artificial particles and dyes. Small particles entering the cerebral circulation might be less likely to cause symptoms by being more rapidly cleared spontaneously than larger particles. Small particles blocking small retinal arteries might be more likely to cause symptoms than equivalent particles entering small cerebral vessels in which the rich anastomoses may preserve flow pending spontaneous lysis. In other words, we are not suggesting that small particles do not enter the cerebral circulation but rather that it may take a much larger number of them to cause symptoms than in the eye.

Other less “mechanical” explanations include the hypothesis that because the eyes are constantly in use during waking hours, patients might notice transient loss of vision more readily than functions like language that are used more intermittently. The association between atrial fibrillation and prolonged or transient brain or eye symptoms might be explained by the reduction in cardiac output resulting from the adverse affect of atrial fibrillation on both cerebral and retinal perfusion, thereby rendering both the retina and brain more susceptible to other embolic insults.

What are the limitations of this study? We did not identify all patients with cerebrovascular events occurring in a population at a given time but used referrals to our hospital, raising the possibility of referral bias. For example, patients with a carotid bruit might have been referred more often. It is difficult to estimate the size of any potential bias; although the proportion of patients with a bruit varied in each group, the ratio of bruits to severe stenosis was similar in RAO, amaurosis fugax, and cerebral TIAs, suggesting that the presence of a bruit did not lead to a disproportionate referral of patients with eye symptoms than cerebral TIAs, but we cannot exclude the possibility that patients with RAO, amaurosis fugax, and cerebral TIAs were referred more often than patients with stroke. If patients with cerebral TIAs and strokes with atrial fibrillation had been referred more often

Figure 3. Mechanisms by which cardiac and carotid emboli might preferentially cause prolonged or transient brain or eye symptoms. A, Carotid artery. B, Close-up of a stenosis showing the platelet-fibrin thrombi (P-FT) forming on the surface but being quickly displaced by blood flowing at high velocity to get through the stenosis. Poststenotic turbulent flow causes the emboli to pass into the lea of the stenosis. C, From there, they are carried up the internal carotid artery (ICA) close to the vessel wall so that they easily enter the ophthalmic artery (OA). D, Emboli arising from the heart (cardiac emboli, CE) tend to be larger and have greater momentum by the time they reach the carotid arteries and thus are carried in the center of the flow stream (rather than at the edges), which, together with their larger size, means that they are less likely to enter the ophthalmic artery. ECA indicates external carotid artery; CCA, common carotid artery; MCA, middle cerebral artery; and ACA, anterior cerebral artery.
serve the population on 1 side of our town and because the carotid surgeons work in a different hospital on the other side of town, there are likely to be very few patients with significant carotid disease who bypass the clinic. We therefore feel that any bias is likely to be small and probably will not change our overall conclusion. We also recognize that there are similarities between TIAs and minor strokes in risk factors, but we wanted to take a broader view of the question of whether, in general, there were differences in risk factors between transient and permanent events.

Our hypothesis, based on the results of this study, is that mechanical factors and fluid dynamics may play a more subtle but important role in eye and brain ischemic symptoms than previously recognized. This is not to suggest that the cause of the ischemic syndrome should not be sought in individual patients. Rather, we wish to highlight the fact that these differences in risk factors are likely to reflect differences in pathogenetic mechanisms. If confirmed, this hypothesis may lead to alterations in the ways that patients are stratified in trials of secondary prevention, perhaps to the development of better ways of preventing the consequences of these different types of embolic behavior, and ultimately to focused management of subgroups of patients with different cerebrovascular ischemic symptoms to target stroke prevention more effectively.

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References


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