

Population-based study of capsular warning syndrome and prognosis after early recurrent TIA



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ABSTRACT

Objective: Many guidelines recommend emergency assessment for patients with ≥ 2 TIAs within 7 days, perhaps in recognition of the capsular warning syndrome. However, it is unclear whether all patients with multiple TIAs are at high early risk of stroke and whether treatable underlying pathologies are more prevalent in this group.

Methods: We studied clinical characteristics, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, and risk of stroke in 1,000 consecutive patients with incident and recurrent TIAs in a prospective, population-based study (Oxford Vascular Study).

Results: Of 1,000 patients with TIAs, 170 had a further TIA within 7 days (105 within 24 hours). Multiple TIAs were not associated with carotid stenosis or atrial fibrillation, and much of the 10.6% (95% confidence interval [CI] 6.5–15.9) risk of stroke during the 7 days after the first TIA was due to patients with small-vessel disease (SVD) etiology (10 of 24 vs 8 of 146, odds ratio [OR] = 12.3, 95% CI 3.7–41.9, $p < 0.0001$), particularly those with motor weakness (i.e., capsular warning syndrome) compared with hemisensory events (9 of 15 [60%], 95% CI 35.3–84.7 vs 1 of 9 [11.1%], 95% CI 0–31.7, $p = 0.03$). The 7-day risk of stroke after a recurrent TIA was similar to the risk after a single TIA in patients with non-SVD TIA (8 of 146 [5.5%] vs 76 of 830 [9.2%], OR = 0.58, 95% CI 0.25–1.3, $p = 0.20$). Of the 9 patients with stroke after a capsular warning syndrome, all had the recurrent TIA within 24 hours after the first TIA, and the subsequent stroke occurred within 72 hours of the second TIA in 8. The ABCD2 scores of all preceding TIAs were ≥ 4 in all 9 patients with capsular warning syndrome before stroke.

Conclusions: Capsular warning syndrome is rare (1.5% of TIA presentations) but has a poor prognosis (7-day stroke risk of 60%). Otherwise, recurrent TIA within 7 days is not associated with a greater stroke risk than that after a single TIA. *Neurology*® 2012;79:1356–1362

GLOSSARY

CI = confidence interval; GP = general practitioner; OR = odds ratio; OXVASC = Oxford Vascular Study; SVD = small-vessel disease; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

The risk of stroke after TIA is highest within the first 7 days.^{1–8} Individual risk can be predicted to some extent by the use of clinical scores such as the ABCD2 score.⁹ The occurrence of recurrent or dual TIAs has been proposed as an addition to the ABCD2 score to improve early stroke risk prediction after TIA.¹⁰ Many guidelines also recommend urgent evaluation for patients with ≥ 2 TIAs within 7 days,^{11–17} perhaps in recognition of the capsular warning syndrome. In the classic description of the capsular warning syndrome, multiple, stereotyped motor TIAs precede capsular infarction,^{18,19} probably as a consequence of hemodynamic compromise or thrombosis within a small, single penetrating artery or proximal middle cerebral artery stenosis.^{19–21} It is not certain whether all patients with recurrent TIAs are at high early risk of stroke or whether the capsular warning syndrome mainly accounts for the overall increased risk. Moreover, the prognosis of capsular warning syndrome itself may have changed

CME



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since the original hospital-based studies of patients presenting in the 1980s and 1990s^{18,19} and may also be systematically different in population-based studies. It is also not certain to what extent other treatable underlying pathologic conditions, such as carotid stenosis or atrial fibrillation, are overrepresented in patients with multiple TIAs. We addressed these issues in the first prospective, population-based study of the incidence, prognosis, and outcomes of all incident and recurrent TIAs and strokes in Oxfordshire, UK (Oxford Vascular Study [OXVASC]).

METHODS OXVASC is a prospective, population-based study of all strokes and TIAs in 91,105 individuals of all ages registered with 63 general practitioners (GPs) in Oxfordshire, UK. The study methods have been described elsewhere.^{22,23} In brief, multiple overlapping methods of hot and cold pursuit were used to achieve near-complete ascertainment of all individuals presenting to medical attention with TIA or stroke.^{22–24} These include the following:

1. A 7-day, open-access TIA service to which participating GPs and the local accident and emergency department send all individuals with suspected TIA or minor stroke whom they would not normally admit to the hospital, with emergency provision on weekends supplementing a weekday clinic.
2. Daily searches of admissions to the stroke unit, medical, neurology, and other relevant wards.
3. Daily searches of the local accident and emergency and eye hospital attendance register.
4. Monthly computerized searches of GP diagnostic coding and hospital discharge codes.
5. Monthly searches of all cranial and carotid imaging studies performed in local hospitals.
6. Monthly reviews of all death certificates and coroner reports.

All patients presenting with TIAs were asked about symptoms of TIA within the previous 90 days. Event characteristics and risk factors were recorded, and patients underwent brain imaging with CT or MRI as appropriate. All cases were subsequently reviewed by the study senior neurologist (P.M.R.) and classified as TIA or other condition using standard definitions.^{22,23} We excluded stroke patients in whom it was impossible to obtain a definite history of preceding TIAs because they were aphasic, confused, or unconscious. Patients were followed up face to face at 30 days and 6 months by a study nurse or physician, recurrent symptoms were recorded, and disability was assessed with the modified Rankin scale. All recurrent events that received medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by P.M.R. Etiologic classification of events was performed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification once investigations were complete.²⁵ This article includes the first 1,000 consecutive patients with TIAs from April 1, 2002, to August 15, 2011.

Analysis. We restricted analysis to the risk of recurrent events after the first TIA in the study period (index TIA). We determined the risk of recurrent TIA and stroke within 90 days of the

index TIA, including patients who did not seek medical attention for the initial symptoms but presented after a recurrent TIA or stroke. A recurrent TIA was defined as a new neurologic symptom of less than 24 hours' duration in a patient in whom the initial symptoms had completely resolved. In patients who had multiple recurrent events, the end point was the first recurrence after the index TIA. A recurrent stroke was defined as a new persistent neurologic symptom in a patient in whom the initial symptoms had already substantially or fully resolved. The 7-day risk of stroke after the recurrent TIA was determined in relation to the ABCD2 score and TOAST subtype. A lacunar (or small-vessel disease [SVD]) TIA was diagnosed if the following criteria were fulfilled: 1) the presence of a) unilateral motor or sensory disturbance of at least 2 of 3 body parts (face, arm, leg) in the absence of cortical dysfunction presumed due to subcortical ischemia, b) ataxic hemiparesis, or c) clumsy hand dysarthria syndrome and 2) the presence of lacunar infarct on diffusion-weighted imaging (in patients with symptom duration <4 hours or 3) absence of other TOAST etiologies.

We defined capsular warning syndrome as recurrent, motor lacunar TIAs within 7 days.

Standard protocol approvals, registrations, and patient consents. OXVASC is approved by our local ethics committee. All patients provided written consent and were seen by study physicians as soon as possible after their initial presentation.

RESULTS Complete baseline data and follow-up to 90 days were available for all 1,000 consecutive, first TIAs (table 1). The mean (range) age was 73 (24–99) years with 327 (33%) patients aged older than 80 years. A total of 940 patients were referred to secondary care in Oxford, and 684 (73%) to the TIA clinic (32 patients had their event on holiday and 28 were managed by their GP only). Of 871 patients with cerebral TIAs referred to secondary care, 828 (95%) had brain imaging; the majority had CT (703 [85%]) as first-line imaging, and 125 (15%) had MRI. For those without brain imaging, reasons were patient condition (n = 22), diagnostic uncertainty at initial assessment (n = 12), and patient refusal (n = 9).

A total of 246 (25%) patients had a recurrent event at 7 days (table 2), with the first recurrence being a TIA in 170 patients (17.0%, 95% confidence interval [CI] 14.6–19.4) and stroke in 76 cases (9.2%, 7.2–11.2). Patients with recurrent TIAs were younger ($p = 0.007$) (table 1), less likely to have had a previous stroke ($p = 0.02$) or to be taking antihypertensive drugs ($p = 0.04$), and more likely to have intracranial vascular imaging ($p < 0.001$), but no more likely to have atrial fibrillation or $\geq 50\%$ symptomatic carotid stenosis (17 of 90 vs 186 of 442, $p = 1.0$, in those with carotid territory events) than in those with a single TIA. Of all recurrent TIAs within 7 days, 105 (62%) occurred within 24 hours and 136 (80%) within 48 hours. The second TIA occurred before the patient sought medical attention in 141 patients (83%). TOAST subtype was not associated with a risk of recurrent TIA (table 1).

Table 1 Baseline characteristics of all patients

	Single TIA (n = 830)	Recurrent TIA (n = 170)	p Value
Age, y, mean (SD)	72.8 (13.4)	69.7 (13.7)	0.007
Male sex, n (%)	384 (46.3)	89 (52.4)	0.15
Closest systolic BP after TIA, mm Hg, mean (SD)	151.3 (28.0)	151.7 (23.6)	0.87
Closest diastolic BP after TIA, mm Hg, mean (SD)	82.0 (14.1)	83.3 (12.6)	0.26
Hypertension, n (%)	460 (55.4)	84 (49.4)	0.18
Diabetes, n (%)	107 (12.9)	27 (15.9)	0.32
Angina or myocardial infarction, n (%)	152 (18.3)	29 (17.1)	0.74
Peripheral vascular disease, n (%)	42 (5.1)	5 (2.9)	0.32
Atrial fibrillation, n (%)	131 (15.8)	25 (14.7)	0.82
Current smoker, n (%)	103 (12.4)	23 (13.5)	0.70
Previous TIA, n (%)	110 (13.3)	19 (11.2)	0.53
Previous stroke, n (%)	86 (10.4)	8 (4.7)	0.02
Prior treatment			
Antiplatelet/anticoagulant, n (%)	319 (38.4)	58 (34.1)	0.30
Statin, n (%)	203 (24.5)	45 (26.5)	0.63
Antihypertensive, n (%)	460 (55.4)	79 (46.5)	0.04
Carotid territory, n (%)	513 (61.8)	98 (57.6)	0.31
Carotid imaging, n (%) ^a	716 (86.3)	158 (92.9)	0.02
Intracranial vascular imaging, n (%)	272 (32.8)	88 (51.8)	0.001
TOAST			
CE	136 (16.4)	22 (12.9)	0.30
LAA	106 (12.8)	30 (17.6)	0.11
SVD	85 (10.2)	24 (14.1)	0.09
Undetermined	391 (47.1)	78 (48.9)	0.80
Unknown/multiple/other	16 (9.4)	112 (13.5)	0.17

Abbreviations: BP = blood pressure; CE = cardioembolism; LAA = large artery arteriosclerosis; SVD = small-vessel disease; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

^a Includes patients with vertebrobasilar events.

In those with recurrent TIAs, stroke risk after the first TIA was 5.9% (95% CI 2.4–9.4, n = 10) in the first 48 hours, 10.6% at 7 days (5.9–15.3, n = 18), 14.1% at 30 days (8.8–19.4, n = 24), and 14.7% (9.4–20, n = 25) at 90 days. The 7-day stroke risk after recurrent TIA was similar to the risk after a single TIA (18 of 170 vs 76 of 830, $p = 0.56$), and risks were also similar when stratified by ABCD2 score (table 2). In contrast to the risk of recurrent TIA, which did not vary according to TOAST subtype, the 7 day stroke risk was highest after recurrent TIAs of the SVD subtype (10 of 24 vs 8 of 146, odds ratio [OR] = 12.3, 95% CI 3.7–41.9, $p < 0.0001$). For all other TOAST subtypes, 7-day stroke risk was no different after recurrent TIAs compared with that after a single TIA (8 of 146 [5.5%] vs 76 of 830 [9.2%], OR = 0.58, 0.25–1.3, $p = 0.20$). Thus, recurrent TIAs of the SVD type were associated with a particularly high 7-day stroke risk of 42% (10 of 24, 21.9–61.5), and risks were highest after recurrent motor TIAs than after recurrent sensory TIAs (9

of 15 [60%] vs 1 of 9 [11.1%], $p = 0.03$) (figure 1). However, if strokes due to TIAs of SVD etiology are excluded, the 7-day stroke risk after a recurrent TIA is low (8 of 146 (5.5%), 1.8–9.2) (figure 1). At 30 days, the risk of stroke in those with a recurrent TIA and $\geq 50\%$ symptomatic carotid/vertebral stenosis or atrial fibrillation tended to be higher than that in those non-SVD recurrent TIAs of undetermined etiology (9 of 41 [22.0%], 9.3–34.7 vs 6 of 114 [5.3%], 1.2–9.4, $p = 0.002$) (figure 2). Of 13 patients with non-SVD recurrent TIAs and $\geq 50\%$ symptomatic carotid stenosis, only 1 had a carotid endarterectomy within 7 days.

Of 24 patients with recurrent TIAs of the SVD subtype, the main features were motor weakness in 15 patients (12 with hemiparesis, 2 with ataxic hemiparesis, and 1 with slurred speech) and heminumbness in 9 patients. Of 146 patients with recurrent TIAs of the non-SVD subtype, only 7 had hemiweakness without cortical symptoms; the etiologies in these patients were large artery arteriosclerosis

Table 2 Seven-day stroke risk after single and recurrent TIA stratified by ABCD2 score of the first TIA and TOAST classification

	No. single TIA	No. strokes	7-day stroke risk, % (95% CI)	No. recurrent TIAs	No. strokes	7-day stroke risk, % (95% CI)
ABCD2 score						
0	3	0	0	1	0	0
1	48	3	6.2 (0-13.1)	19	0	0
2	115	7	6.1 (1.8-10.4)	36	3	8.3 (0-17.3)
3	152	10	6.6 (2.7-10.5)	39	3	7.7 (0-16.1)
4	187	14	7.5 (3.8-11.2)	34	3	8.8 (0-18.4)
5	173	14	8.1 (4.0-12.2)	27	5	18.5 (3.8-33.2)
6	133	26	19.5 (12.8-26.2)	11	3	27.3 (1-53.6)
7	19	2	10.5 (0-24.2)	3	1	33.3 (0-86.6)
ABCD score <4	318	20	6.3 (3.6-9.0)	95	6	6.3 (1.4-11.2)
ABCD score ≥4	512	56	10.9 (8.2-13.6)	75	12	16.0 (7.8-24.2)
TOAST						
CE	136	16	11.8 (9.8-13.8)	22	2	9.1 (0-21.12)
LAA	106	13	12.3 (6.0-18.6)	30	3	10.0 (0-20.8)
SVD	85	17	20.0 (11.6-28.4)	24	10	41.7 (21.9-61.5)
Undetermined	391	15	3.8 (1.8-5.8)	78	1	1.3 (0-3.8)
Unknown	74	8	10.8 (3.7-17.9)	6	1	16.7 (0-46.5)
Multiple/other	38	7	18.4 (6.1-30.7)	10	1	10.0 (0-28.6)
Total patients	830	76	9.2 (7.2-11.2)	170	18	10.6 (5.9-15.3)

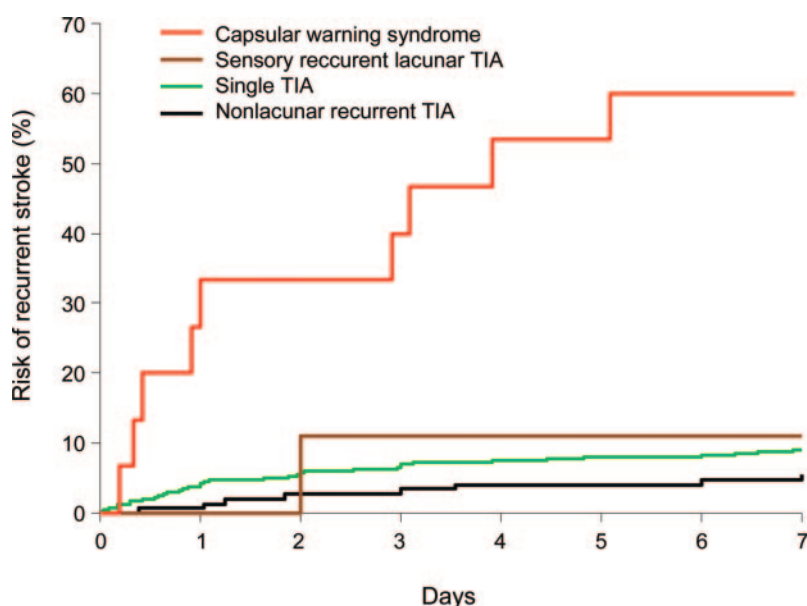
Abbreviations: CE = cardioembolism; CI = confidence interval; LAA = large artery arteriosclerosis; SVD = small-vessel disease; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

(LAA) (n = 3), cardioembolism (n = 2), multiple (n = 1), and other (n = 1). Of 10 patients with stroke after recurrent lacunar SVD TIAs, all had the recurrent TIAs within 24 hours after the first TIA (median time to the recurrent TIA 2.3 hours, SD 9.4).

The subsequent stroke occurred within 24 hours of the second TIA in 5 patients and within 72 hours in 9 patients (median time to stroke 29.5 hours, SD 37.7). Nine of the 10 patients had motor weakness as a feature of the recurrent TIA (8 with hemiparesis and 1 with slurred speech) and only 1 had heminumbness, such that the ABCD2 score of all TIAs before stroke was ≥4 in 9 patients.

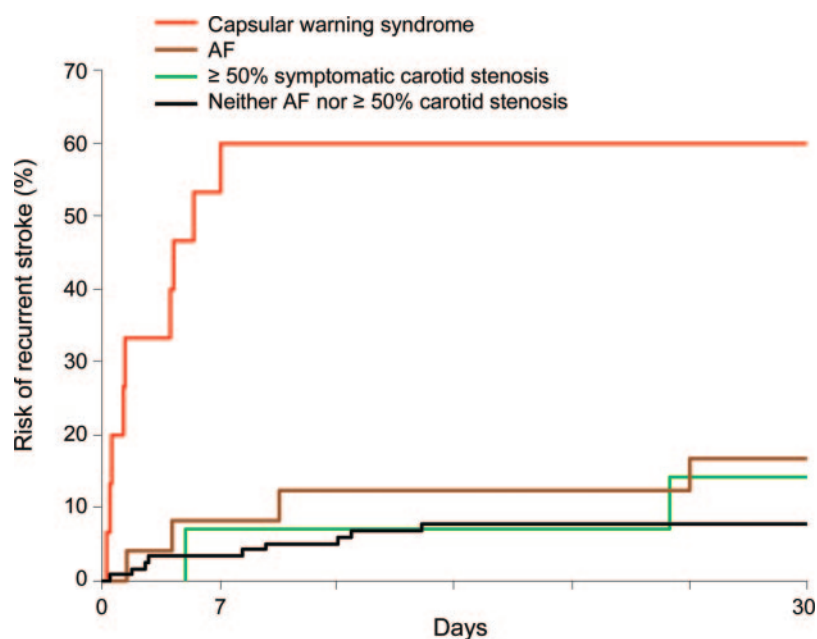
Of 15 patients with recurrent motor lacunar TIAs (capsular warning syndrome), the 7-day stroke risk was 60% (95% CI 35.3–84.7, n = 9), with no strokes at 8–90 days. Ten of 15 patients presented to medical attention before any stroke (5 to GPs, 4 to the accident and emergency department, and 1 to a doctor while on holiday) and 5 presented after a subsequent stroke. Among the 10 patients who presented before any stroke, the risk of progression to stroke appeared to be lower in those given an immediate loading dose of an antiplatelet drug (0 of 4 vs 4 of 6, *p* = 0.08), either starting aspirin (n = 3) or adding clopidogrel to premonitory aspirin (n = 1). Of the 9 patients with capsular warning syndrome stroke, the median modified Rankin scale score at 1 month after stroke was 2 (range 1–4).

Figure 1 Seven-day stroke risk after the first TIA in single and recurrent TIA of lacunar and nonlacunar type



DISCUSSION Recurrent TIA has been incorporated into guidelines as an indication for urgent sec-

Figure 2 Thirty-day stroke risk after the first TIA in those with recurrent TIA and capsular warning syndrome, $\geq 50\%$ symptomatic carotid stenosis, atrial fibrillation (AF), or neither of these etiologies



ondary prevention,^{11–17} and it has been proposed that it should be included as a variable in prognostic scores.¹⁰ However, there are limited published data on whether all those with multiple TIAs are at high risk of recurrent stroke or whether this group differs in terms of treatable underlying pathologies. We have shown the early stroke risk after a recurrent TIA is similar to that after a single TIA in our population, other than in the case of the capsular warning syndrome, and that the prevalence of atrial fibrillation and large-artery stenosis is no greater. Indeed, in patients with multiple non-SVD TIAs, the early risk of stroke tended to be lower than that after a single TIA.

In our study, the 7-day risk of recurrent TIA was high at 17%, which appears to be consistent with previous studies.^{10,26,27} However, reports of the prognostic significance of recurrent TIAs have been less consistent. In an emergency department cohort of 1,707 patients, the 90-day stroke risk after a recurrent TIA was not greater than that after a single TIA.²⁸ In another hospital-based study of 113 patients with TIAs, progression or fluctuation of symptoms was an independent predictor of stroke.²⁶ However, when patients with multiple attacks at presentation were analyzed separately, there was no significant difference in stroke risk.²⁶ In a recent analysis of pooled data from 2,654 patients with TIAs, ≥ 2 TIAs within 7 days occurred in 19.4% and was associated with higher stroke risk (OR = 5.0, 95% CI 2.76–9.06).¹⁰ However, no previous studies have determined the extent to which prognostic significance

is dependent on the underlying etiology of recurrent TIAs.

In our study, early stroke risk was highest after a single or recurrent TIA of SVD etiology. Previous studies have shown that the large-artery stenosis subtype is associated with high recurrent stroke risk after TIA or stroke^{27,29,30} but have tended to underestimate the risk of stroke after SVD events by including patients presenting with lacunar stroke rather than lacunar TIA. Although capsular warning syndrome is rare (only 1.5% of TIA presentations in our study), the early risk of stroke in previous studies has been very high.^{18,19} Our results show that this poor prognosis still applies today. In contrast to capsular warning syndrome, however, the risk of stroke after recurrent TIAs of other etiologies was much lower in our study. The current emphasis in guidelines on greater urgency of assessment of all patients with multiple vs single TIAs may not be justified by their stroke risk.

The emphasis on recurrent TIAs in management guidelines and in prognostic scores could still be justified, however, if they were particularly associated with treatable pathologic conditions. However, we found no excess of atrial fibrillation or carotid stenosis in patients with multiple TIAs. Moreover, specific treatments for capsular warning syndrome are lacking, although thrombolysis, hydration, blood pressure elevation, and dual antiplatelet and anticoagulant treatment have been shown to be beneficial in case reports.^{31–35}

Our results show that despite improvements in processes of care, the prognosis of capsular warning syndrome is similar to that when it was first described in the 1980s. The trend toward a reduced risk of early stroke in patients given an immediate loading dose of antiplatelet drugs is encouraging, and this approach is probably justified despite the lack of trial data.

In our study, less than half of patients with capsular warning syndrome presented to medical attention before recurrent stroke, highlighting the continued need for public education on TIAs. However, we also found that the high risk of stroke persists beyond 48 hours, such that randomized treatment trials might be feasible nevertheless.

Our study had some potential limitations. First, our estimate of stroke risk in the acute phase may not be completely precise because an unknown proportion of patients with TIAs and minor strokes will never seek medical attention. However, this bias is likely to be somewhat smaller after a second event, with patients probably being less likely to ignore 2 events. Second, our analysis of stroke risk after a recurrent TIA was based on only 18 stroke outcomes.

Although this is more than the 12 stroke outcomes after multiple TIAs in the Californian cohort,²⁸ further studies would help confirm or refute our findings. Third, the intensity and timing of secondary prevention may have varied according to treatment setting, causing a difference in the timing of recurrent events. However, 73% of our patients were seen in the EXPRESS clinic,³⁶ in which secondary prevention was initiated at time of assessment, and only 1 patient had a carotid endarterectomy with 7 days; therefore, the effect of treatment setting is likely to be small. Fourth, the low stroke risk after pure sensory lacunar TIAs may be due to events of nonvascular origin, a limitation also present in previous studies of recurrent TIA.²⁸ However, even if many of our patients had nonischemic events, the stroke risk would still be low. Therefore, there would need to be a very high misdiagnosis rate for the stroke risk after sensory events to be similar to that of motor events. Fifth, rates of intracranial vascular imaging in our study were low (36% of patients), and we were not therefore able to identify the subset of patients with capsular warning syndrome due to proximal middle cerebral artery stenosis.^{20,21}

AUTHOR CONTRIBUTIONS

Nicola L.M. Paul: study concept and design, acquisition of data, draft and revision of the manuscript, statistical analysis and interpretation of data. Michela Simoni: revision of the manuscript content, acquisition of data. Arvind Chandratheva: revision of the manuscript content, acquisition of data. Professor Peter M Rothwell: study concept and design, draft and revision of the manuscript, analysis and interpretation of data, study supervision.

DISCLOSURE

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