Patterns and Predictors of Early Risk of Recurrence After Transient Ischemic Attack With Respect to Etiologic Subtypes

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Background and Purpose—The risk of recurrent stroke is highest within the first few weeks after a transient ischemic attack (TIA), and it is likely to be related to the underlying pathology. We sought to study the early risk of recurrent stroke by etiologic subtype.

Methods—We prospectively studied 388 TIA patients. The cause of TIA was classified according to the Trial of ORG 10172 criteria: large-artery atherosclerosis (LAA, n=90), cardioembolism (n=87), small-vessel disease (n=68), undetermined (n=127), and other determined cause (n=16). Patients were followed up at 3 months. Risk factors and clinical symptoms for each subtype were recorded.

Results—The duration of symptoms and clinical symptoms varied significantly among the different subtypes. LAA was associated with recurrent short episodes of weakness, whereas speech impairment and cortical symptoms were associated with cardioembolism (P<0.05). The association of vascular risk factors was highest in LAA (P<0.05). New strokes were recorded in 35 (9%) patients. Recurrent stroke risk varied among subtypes (P<0.001): LAA, 20.0%; cardioembolism, 11.5%; undetermined, 4.7%; small-vessel disease, 1.5%; and other cause, 0%. Cox proportional-hazards multivariate analyses did not identify any independent predictor of further cerebral ischemic events for LAA, cardioembolism, undetermined, or small-vessel disease.

Conclusions—The risk of early recurrent stroke is highest in patients with LAA. This supports the need for urgent carotid and transcranial imaging for identifying those patients at highest risk. Some risk factors and clinical symptoms are related to some etiologic subtypes, but stronger predictors of stroke recurrence are needed to identify those patients with highest risk for each TIA subtype. (Stroke. 2007;38:3225-3229.)

Key Words: etiology ■ outcome ■ risk factors ■ stroke classification ■ transient ischemic attack

Recent studies suggest that the risk of very early recurrent stroke in patients with transient ischemic attack (TIA) has been underestimated and may be as high as 9.5% to 20% at 90 days.1–5 Although many studies attempted to identify independent risk factors for stroke after TIA, like age, weakness, speech impairment, diabetes, blood pressure, and duration of symptoms,5–8 the way these patients are managed is heterogeneous. There is little consensus about which strategy is the most cost-effective.10 Whereas in some hospitals TIA patients are frequently discharged with poor management from the Emergency Department, they are admitted routinely to other institutions.11 The risk of early recurrent stroke is likely to be related to the underlying pathology. Patients who had a hemispheric TIA related to internal carotid artery (ICA) disease had the highest risk of stroke in the first few days after the TIA.2 However, previous studies in TIA patients on the early risk of recurrent stroke by etiologic subtypes are lacking. The evaluation of risk factors for individual subtypes may contribute to more effective prevention of ischemic stroke because the underlying pathogenesis and prognosis seem to differ among subtypes.

In this study, we aimed to determine the early risk of stroke in different etiologic subtypes of TIA according to the Trial of ORG 10172 (TOAST) criteria12 and to evaluate risk factors associated with individual subtypes and stroke recurrence.

Subjects and Methods

Patient Selection and Diagnostic Protocol

We prospectively studied 410 consecutive patients with a transient neurologic deficit attended by a neurologist in the Emergency Department from October 2002 to January 2005. TIA was defined as a reversible episode of neurologic deficit of ischemic origin that...
resolved completely within 24 hours. A total of 22 clinical episodes were attributable to causes other than brain ischemia: epilepsy (5 cases), cerebral tumor (4 cases), hypoglycemia (5 cases), subdural hemorrhage (3 cases), cerebral amyloid angiopathy (4 cases), and cerebral myelopathy (1 case). Finally, 388 patients were included. TIA diagnosis was recorded. Regarding the number of clinical events, TIA was categorized as a single event or a cluster of TIAs (when repeated TIAs occurred within the first week of the index event). Vertebrobasilar TIA was represented by the following symptoms: bilateral or shifting motor or sensory dysfunction, complete or partial loss of vision in both homonymous fields, dizziness, vertigo, or any combination thereof.

Determination of the ABCD² risk score was performed retrospectively (≥60 years = 1 point; systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg = 1 point; unilateral weakness = 2 points; speech disturbance without weakness = 1 point; other symptoms = 0 points; duration of symptoms ≥60 minutes = 2 points, 10 to 59 minutes = 1 point, and <10 minutes = 0 points; and diabetes = 1 point), although the components of the score were prospectively collected. Examinations during admission included medical history; physical examination; routine blood biochemistry; ECG; chest x-ray; transthoracic echocardiography and Holter ECG when indicated; cerebral carotid ultrasound and transcranial Doppler ultrasound; and computed tomography (CT) scan. Transcranial Doppler recordings were performed on admission, within the first 24 hours after symptoms onset, with the use of a Multi-Dop-X transcranial Doppler device (DWL Elektronische Systeme GmbH). Intracranial stenoses were diagnosed when the mean blood flow velocity at a circumscribed insonation depth was >80 cm/s, with side-to-side differences >30 cm/s and signs of disturbed flow. Baseline cerebral ICA atherosclerosis was categorized by echo Doppler as follows: absent; mild, if 1 or both ICAs had <50% stenoses; moderate, when any of the ICAs presented with 50% to 70% stenoses; and severe, if any ICA had >70% stenoses. Cranial CT was performed on a Multislice MX8000 Philips spiral CT scanner with 4 rows of detectors.

Baseline Vascular Risk Factors
Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medications. Cigarette smoking was defined as present if the patient reported smoking cigarettes during the past 5 years. Hypercholesterolemia was defined as a total cholesterol concentration ≥220 mg/dL or current use of lipid-lowering agents. Diabetes mellitus was defined by a history of fasting glucose ≥126 mg/dL or current use of hypoglycemic drugs. History of diagnosed coronary artery disease, intermittent claudication, atrial fibrillation, and valvular heart disease was also recorded.

Classification of Stroke Subtypes and Clinical End Point
TIAs were classified etiologically according to TOAST criteria as due to large-artery occlusive disease (LAA), small-vessel disease (SV), cardioembolism (CE), other cause (OC), or undetermined cause (UND). Patients were followed up by face-to-face interview at 60 years (SV), cardioembolism (CE), other cause (OC), or undetermined cause (UND). Patients were followed up by face-to-face interview at 90 days. Endpoint events included further stroke. Stroke was defined as rapidly developed clinical symptoms of focal disturbance of cerebral function lasting >24 hours with an apparent vascular cause. We also recorded death and any major vascular event other than stroke. A recurrent TIA was considered when it occurred after the first week of the index event.

Statistical Analysis
Analyses were performed with the SPSS statistical package, version 12.0. Statistical significance for intergroup differences was assessed by the χ² test for categorical variables and the Student t and Mann-Whitney U tests for continuous variables. Univariate analysis was performed to detect variables associated with the occurrence of a cerebral ischemic event. Cox proportional-hazards multivariate analyses were used to identify predictors of further cerebral ischemic events in which age, sex, vascular risk factors, and variables showing P<0.1 on univariate testing were included. Finally, cumulative event-free rates for the time to an ischemic event were estimated by the Kaplan-Meier product-limit method. A probability value <0.05 was considered significant. A Bonferroni correction (multiple-comparison correction) was applied to all significant associations to reduce the risk of finding false-positive associations. The study was approved by our local ethics committee. Because it was an observational longitudinal study, written, informed consent from all study participants was not needed.

Results
A total of 388 patients were included in the study. The mean age of all patients was 70.8±12.0 years and 230 (59.3%) were male (Table 1). Hypertension, present in 216 (55.7%) cases, was the main vascular risk factor. Median duration of symptoms was 1 (range, 0.25 to 3) hour. The ABCD² score in 169 (43.6%) patients was 5 or greater. The distribution of TIA subtypes was as follows: LAA n=90, CE n=87, SV n=68, UND n=127, and OC n=16. Two or more competing causes were determined in 8 of the 128 cases of UND. The frequencies of risk factors and clinical features for each subtype are presented in Table 1. The proportion of males (P=0.014), hypertension (P<0.001), previous stroke (P=0.024), diabetes mellitus (P=0.002), peripheral arterial disease (P=0.004), smoking (P=0.001), and heart disease (P<0.001) varied significantly among the different subtypes. LAA was associated with recurrent short episodes of weakness, whereas speech impairment and cortical signs or symptoms were associated with CE (P<0.05). Finally, patients with OC were younger than patients with other etiologies (P=0.001).

Follow-Up End Points
Recurrent strokes occurred in 35 patients (9%) within the first 90 days after the index TIA, 26 (6.7%) at 7 days and 9 (2.3%) at 2 days. New TIAs were recorded in 21 patients at the 90-day follow-up. Six patients (1.5%) had an acute myocardial infarction and 1 patient (0.3%) had an intracranial hemorrhage. Finally, peripheral arterial disease was identified in 2 patients. Six patients (1.5%) died, 5 after cerebral ischemic stroke and 1 after an intracranial hemorrhage.

There was heterogeneity among the different subtypes for the 3-month risk of recurrent stroke (log-rank P<0.001; the Figure). Patients with LAA had the highest risk of further cerebral ischemic events at 3 months (20.0%, 95% CI=11.7 to 28.3 vs 5.7%, 95% CI=4.4 to 7.0 in the rest; P<0.001). Moreover, recurrent stroke risk varied among the degrees of carotid stenosis: absent 5%, mild 25%, moderate 11.1%, and severe 35% (P<0.001). The presence of intracranial stenoses (11.9%) was also associated with stroke risk within the first 7 days after the index TIA (25%, 95% CI=20.7 to 29.3 vs 6.1%, 95% CI=3.7 to 8.5; P=0.026). No recurrence was observed beyond the 7-day follow-up.

Independent Predictors of New Cerebral Ischemic Events
In univariate analyses, after Bonferroni adjustment, only LAA was associated with stroke recurrence at 7 and 90 days after the onset of symptoms. In Cox proportional-hazards multivariate analyses, LAA remained an independent predic-
tor of stroke recurrence at the 7-day follow-up (hazard ratio = 4.07, 95% CI = 1.88 to 8.80, \( P = 0.001 \)) and after 90 days of follow-up (hazard ratio = 3.78, 95% CI = 1.95 to 7.33, \( P = 0.001 \)).

With regard to subtypes of TIA (Table 2), no clinical variables were associated with stroke recurrence. Oral anticoagulants were better than antiaggregants for secondary prevention after CE transient cerebral ischemic events (30.0%, 95% CI = 20.3 to 39.6 vs 77.9%, 95% CI = 69.2 to 86.6; \( P = 0.056 \)). Moreover, early carotid endarterectomy was associated with a low risk of stroke in patients with TIA due to LAA (5.6%, 95% CI = 0.8 to 10.3 vs 25.0%, 95% CI = 16.1 to 33.9; \( P = 0.114 \)) without statistical significance. No discharge treatment was more effective than any other after TIA due to UND or SV.

**Discussion**

To our knowledge, this is the first prospective study with TIA patients that has estimated the incidence of stroke recurrence in terms of etiologies and analyses of risk factors. Among our consecutive patients, UND was the most common subtype (31.7%). We found that patients with LAA had the highest early risk of recurrent stroke compared with other etiologic subgroups, whereas patients with OC had the lowest risk. Moreover, the association of risk vascular factors was higher in LAA. Recurrent short episodes of weakness were associated with LAA, whereas cortical symptoms were more frequent in patients with CE and UND.

These findings are consistent with previous studies. Diagnosis of TIA is a difficult clinical problem because many of the symptoms may have resolved before patients arrive at the hospital, \(^{5,14}\) and there are many different conditions that mimic cerebral ischemic events. \(^{15,16}\) Therefore, TIA patients are mainly classified as the UND subtype compared with ischemic stroke patients. \(^{17}\) On the other hand, it is known that patients who have a hemispheric TIA or stroke related to ICA disease have a high risk of stroke in the first few days after the index event. \(^{2,18}\) Moreover, according to our previous findings, not only TIA patients with moderate to severe extracranial stenoses but also patients with intracranial stenosis have a
higher risk of stroke recurrence. These findings have important implications for targeting stroke prevention. The routine use of combined carotid/transcranial ultrasound testing within the first 24 hours after an index TIA will be useful for identifying those patients at high risk and who might most benefit from aggressive prevention therapies.19,20 Additionally, clinical data are insufficient to distinguish those patients at higher risk.20 Nevertheless, strong predictors within the different subtypes are lacking. Further studies are needed to identify new predictors within the different subgroups. Biomarkers of systemic inflammation that should be higher in patients with an exaggerated inflammatory response and that might accelerate atheroma progression and facilitate plaque instability could be useful.21 Moreover, performing magnetic resonance diffusion-weighted imaging (DWI) in TIA patients could also be useful.22–24 New infarction on the CT scan performed within 48 hours of a clinical event could also be predictive of recurrent stroke.25 During the follow-up, only recurrent ischemic events, and not recurrent TIs, were considered because this outcome is much more relevant to clinicians and patients.

This study has several limitations. Namely, a larger cohort would be necessary to better explore TIA subgroups. A complete diagnostic procedure with transesophageal echocardiography could improve the etiologic classification. It provides a better estimate of left ventricular function and is more sensitive for detecting other potential sources of CE. Transesophageal echocardiography is superior for the detection of atheromatous disease of the thoracic aorta. On the other hand, if DWI magnetic resonance imaging were performed in all patients, some cases would be classified in other ways. In those patients with DWI lesions, the different magnetic resonance imaging patterns of acute ischemic brain lesions can suggest the most likely causative mechanism of infarction.26–28 In addition, the TOAST criteria were meant to be applied to stroke and not to TIA. Patients presenting without cortical symptoms or signs are difficult to classify.

### Table 2. Univariate Analyses of Variables Associated With Stroke Recurrence by Etiologic Subtype of TIA

<table>
<thead>
<tr>
<th>Variable</th>
<th>LAA (n=72)</th>
<th>Yes (n=18)</th>
<th>P</th>
<th>CE (n=10)</th>
<th>Yes (n=4)</th>
<th>P</th>
<th>UND (n=121)</th>
<th>Yes (n=6)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td><strong>Risk factors</strong></td>
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<tr>
<td>Age, mean ± SD, y</td>
<td>71.0 ± 11.0</td>
<td>67.7 ± 12.5</td>
<td>0.277</td>
<td>72.7 ± 12.4</td>
<td>77.6 ± 8.9</td>
<td>0.230</td>
<td>70.6 ± 11.6</td>
<td>79.5 ± 8.7</td>
<td>0.066*</td>
</tr>
<tr>
<td>Male</td>
<td>52 (72.2)</td>
<td>13 (72.2)</td>
<td>1</td>
<td>37 (48.1)</td>
<td>6 (60.0)</td>
<td>0.477</td>
<td>75 (62.0)</td>
<td>4 (66.7)</td>
<td>0.817</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (68.1)</td>
<td>11 (61.1)</td>
<td>0.576</td>
<td>44 (57.1)</td>
<td>7 (70.0)</td>
<td>0.437</td>
<td>45 (37.2)</td>
<td>3 (50.0)</td>
<td>0.672</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>31 (43.1)</td>
<td>4 (22.2)</td>
<td>0.175</td>
<td>20 (26.0)</td>
<td>4 (40.0)</td>
<td>0.351</td>
<td>31 (25.6)</td>
<td>3 (50.0)</td>
<td>0.341</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (29.2)</td>
<td>3 (16.7)</td>
<td>0.379</td>
<td>17 (22.1)</td>
<td>4 (40.0)</td>
<td>0.213</td>
<td>14 (11.6)</td>
<td>2 (33.3)</td>
<td>0.335</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>14 (19.4)</td>
<td>6 (33.3)</td>
<td>0.205</td>
<td>19 (24.7)</td>
<td>3 (30.0)</td>
<td>0.716</td>
<td>20 (16.5)</td>
<td>0 (0)</td>
<td>0.589</td>
</tr>
<tr>
<td>Smoker</td>
<td>22 (30.6)</td>
<td>5 (27.8)</td>
<td>0.818</td>
<td>4 (5.2)</td>
<td>1 (10.0)</td>
<td>0.465</td>
<td>25 (20.7)</td>
<td>1 (16.7)</td>
<td>1</td>
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<tr>
<td>Peripheral arterial disease</td>
<td>13 (18.1)</td>
<td>2 (11.1)</td>
<td>0.726</td>
<td>6 (7.8)</td>
<td>1 (10.0)</td>
<td>0.588</td>
<td>6 (5.0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27 (37.5)</td>
<td>10 (55.6)</td>
<td>0.164</td>
<td>27 (35.1)</td>
<td>3 (30.0)</td>
<td>0.1</td>
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</tr>
<tr>
<td>Congestive heart disease</td>
<td>0 (0)</td>
<td>1 (5.6)</td>
<td>0.200</td>
<td>11 (14.3)</td>
<td>2 (20.0)</td>
<td>0.641</td>
<td>0 (0)</td>
<td>1 (16.7)</td>
<td>0.047*</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
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</tr>
<tr>
<td>Cluster TIA</td>
<td>32 (44.4)</td>
<td>6 (35.3)</td>
<td>0.493</td>
<td>12 (15.6)</td>
<td>3 (20.0)</td>
<td>0.367</td>
<td>29 (24.0)</td>
<td>1 (16.7)</td>
<td>1</td>
</tr>
<tr>
<td>Aphasia</td>
<td>19 (26.4)</td>
<td>9 (50.0)</td>
<td>0.091*</td>
<td>36 (46.8)</td>
<td>6 (60.0)</td>
<td>0.628</td>
<td>50 (41.3)</td>
<td>2 (33.3)</td>
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<tr>
<td>Weakness</td>
<td>47 (65.3)</td>
<td>5 (27.8)</td>
<td>0.011*</td>
<td>29 (37.7)</td>
<td>4 (40.0)</td>
<td>0.1</td>
<td></td>
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</tr>
<tr>
<td>Cortical signs</td>
<td>22 (30.6)</td>
<td>10 (55.6)</td>
<td>0.158</td>
<td>43 (55.8)</td>
<td>6 (60.0)</td>
<td>0.589</td>
<td>58 (47.9)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Vertebrobasilar symptoms</td>
<td>7 (9.7)</td>
<td>1 (5.6)</td>
<td>1</td>
<td>8 (10.4)</td>
<td>0 (0)</td>
<td>0.588</td>
<td>19 (15.7)</td>
<td>1 (16.7)</td>
<td>1</td>
</tr>
<tr>
<td>Duration</td>
<td>0.25 hour</td>
<td>0.33 hour</td>
<td>0.805</td>
<td>1 hour</td>
<td>0.85</td>
<td>0.185</td>
<td>0.75</td>
<td>0.752</td>
<td></td>
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<tr>
<td>ABCD2 ≥ 5</td>
<td>31 (43.1)</td>
<td>6 (33.3)</td>
<td>0.567</td>
<td>34 (44.1)</td>
<td>6 (60.0)</td>
<td>0.693</td>
<td>49 (40.5)</td>
<td>2 (33.3)</td>
<td>1</td>
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<td><strong>Discharge treatment</strong></td>
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<tr>
<td>Aspirin</td>
<td>21 (29.2)</td>
<td>2 (11.1)</td>
<td>0.331</td>
<td>12 (15.6)</td>
<td>1 (10.0)</td>
<td>1</td>
<td>63 (52.1)</td>
<td>0 (0)</td>
<td>0.119</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>25 (34.7)</td>
<td>2 (11.1)</td>
<td>0.128</td>
<td>12 (15.6)</td>
<td>3 (20.0)</td>
<td>0.367</td>
<td>38 (33.0)</td>
<td>4 (66.7)</td>
<td>0.985</td>
</tr>
<tr>
<td>Trifluar</td>
<td>10 (13.9)</td>
<td>2 (11.1)</td>
<td>1</td>
<td>1 (1.3)</td>
<td>2 (20.0)</td>
<td>0.034*</td>
<td>13 (10.7)</td>
<td>2 (33.3)</td>
<td>0.395</td>
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<tr>
<td>Anticoagulation</td>
<td>20 (27.8)</td>
<td>7 (38.9)</td>
<td>0.368</td>
<td>60 (77.9)</td>
<td>5 (30.0)</td>
<td>0.056*</td>
<td>12 (9.9)</td>
<td>1 (16.7)</td>
<td>0.348</td>
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<tr>
<td>Statins</td>
<td>35 (48.6)</td>
<td>6 (33.3)</td>
<td>0.268</td>
<td>21 (27.3)</td>
<td>4 (40.0)</td>
<td>0.458</td>
<td>43 (35.5)</td>
<td>2 (33.3)</td>
<td>1</td>
</tr>
<tr>
<td>Renin-angiotensin system blockers</td>
<td>26 (36.1)</td>
<td>4 (22.2)</td>
<td>0.361</td>
<td>21 (27.3)</td>
<td>3 (30.0)</td>
<td>0.708</td>
<td>24 (20.9)</td>
<td>3 (50.0)</td>
<td>0.197</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>18 (25.0)</td>
<td>1 (5.6)</td>
<td>0.114</td>
<td></td>
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</tbody>
</table>

Percentages are shown in parentheses.

*Not significant after Bonferroni adjustment.
patients with DWI abnormalities could be classified in a different way.

In conclusion, our study confirms that early recurrence rates for stroke due to LAA are higher than those for other subtypes. This supports the need for urgent carotid and transcranial imaging for identifying those patients at highest risk. Some risk factors and clinical symptoms are related to some etiologic subtypes, but stronger predictors of stroke recurrence are needed to identify those patients at highest risk in each TIA subtype.

Disclosures

None.

References

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