Higher Risk of Further Vascular Events Among Transient Ischemic Attack Patients With Diffusion-Weighted Imaging Acute Ischemic Lesions

Francisco Purroy, MD; Joan Montaner, MD, PhD; Álex Rovira, MD; Pilar Delgado, MD; Manuel Quintana; José Álvarez-Sabín, MD, PhD

Background and Purpose—Recently, a new definition of transient ischemic attack (TIA) has been proposed based on the duration of symptoms and diffusion-weighted imaging (DWI) findings. We investigate the value of temporal and neuroimaging data on the prognoses of TIA patients.

Methods—Clinical data, symptom duration, DWI, and ultrasonographic findings were collected in 83 consecutive classical TIA patients attended in the emergency department. Stroke recurrence, myocardial infarction, or any vascular event was recorded at follow-up (mean of 389 days).

Results—A total of 27 (32.5%) patients revealed focal abnormalities on DWI, whereas 37 (44.6%) had symptoms lasting >1 hour. Large-artery disease was detected in 37 (44.6%) patients. Twenty (24.1%) patients experienced an endpoint: 2 (2.4%) myocardial infarctions, 16 (19.3%) cerebral ischemic events, and 2 cases (2.4%) of peripheral arterial disease. Cox proportional hazards multivariate analyses identified the association of symptoms >1 hour with DWI abnormalities as independent predictors of further cerebral ischemic events or any vascular event (hazard ratio [HR], 5.02; CI, 1.37 to 18.30; \( P = 0.015 \); and HR, 3.77; CI, 1.09 to 13.00; \( P = 0.029 \)). Large-artery occlusive disease also remained an independent predictor of both endpoints (HR, 4.22; CI, 1.17 to 15.22; \( P = 0.028 \); and HR, 3.60; CI, 1.14 to 11.39; \( P = 0.0293 \)).

Conclusions—TIA patients with DWI abnormalities associated with duration of symptoms >1 hour and those with large-artery occlusive disease have a higher risk of further vascular events. Routine use of DWI and Doppler ultrasonographic examinations will be useful for identifying TIA patients at high risk to plan aggressive prevention therapies. (Stroke. 2004;35:2313-2319.)

Key Words: cerebral ischemia, transient ■ magnetic resonance imaging, diffusion-weighted ■ outcome ■ ultrasonography, Doppler

Transient ischemic attacks (TIA) are defined classically as reversible episodes of neurologic deficits of vascular origin that resolve completely within 24 hours.\(^1\,^2\) This longstanding definition has been based on the assumption that TIA are associated with a complete resolution of brain ischemia occurring rapidly enough to cause only transient symptoms and no permanent brain injury. After a first TIA, 10.5% of patients have a stroke within the next 90 days, and for 50% of these, the stroke occurs within the first 24 to 48 hours after the event.\(^3\) Consequently, TIA must be considered a medical emergency.

However, only a small number of clinical factors have been found to be weakly associated with an increased risk of stroke after TIA: advanced age, diabetes mellitus, symptoms lasting >10 minutes, weakness, and impaired speech.\(^1\,^4\) Recently, a new definition of a TIA has been proposed, based on the duration of symptoms and imaging data.\(^4\) Most TIA are resolved within 60 minutes, and the likelihood that symptoms will be completely resolved is <15% if symptoms last for >1 hour.\(^4\) New magnetic resonance imaging (MRI) techniques like diffusion-weighted imaging (DWI), which are very sensitive for determining brain ischemia, facilitate the correct diagnosis. Aggregate DWI data from studies performed in the past few years have clearly demonstrated that almost half of all patients with clinical TIA syndrome have a DWI abnormality (range, 35% to 67%), with the probability of DWI positivity increasing with the duration of the symptoms.\(^1\,^5\,^6\) Taking these data into account, TIA may be defined as a brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting <1 hour, and without neuroimaging evidence of acute infarction.\(^5\)
We targeted TIA patients who were attended to within 24 hours by taking into account temporal and differences in the risk of further ischemic events among patients with TIA by using MRI.

Baseline Vascular Risk Factors and Clinical Variables
Hypertension was defined as a systolic blood pressure \( \geq 140 \) mm Hg or diastolic blood pressure \( \geq 90 \) mm Hg or current use of antihypertensive medications. Cigarette smoking was defined as present if the patient reported smoking cigarettes during the last 5 years. Hypercholesterolemia was defined as a total cholesterol concentration \( \geq 220 \) mg/dL or the current use of lipid-lowering agents. Diabetes mellitus was defined by fasting glucose \( \geq 126 \) mg/dL or the current use of hypoglycemic medication. History of diagnosed coronary artery disease, peripheral arterial disease, atrial fibrillation, and valvular heart disease were also recorded.

Ultrasound Protocol
Transcranial Doppler recordings were performed on admission, within 1 day of the onset of symptoms, with the use of a Multi-Doppler X/TCD device (DWL Elektronische Systeme GmbH). Intracranial stenoses were diagnosed if the mean blood flow velocity at a circumscribed isonation depth was \( > 80 \) cm/s, with side-to-side differences \( > 30 \) cm/s and signs of disturbed flow. Attending the velocity values, intracranial stenoses were calculated as follows: mild stenoses (80 to 120 cm/s), moderate stenoses (120 to 140 cm/s), and severe stenoses (\( > 140 \) cm/s).

Baseline cervical internal carotid artery (ICA) atherosclerosis was categorized by echo Doppler as follows: absent; mild, if 1 or both ICA had \( < 50 \)% stenoses; moderate, when any of the ICA presented a moderate \( < 70 \)% stenoses; and severe, if any ICA had a severe stenoses or there was a history of carotid surgery.

Patients were classified as having large-artery occlusive disease if a moderate to severe intracranial or extracranial stenoses was recorded after ultrasonography study.

Electrocardiogram Protocol
An ECG was performed within 1 day of the onset of symptoms. Abnormal ECG findings included any of the following diagnoses: atrial fibrillation, atrioventricular block, left ventricular hypertrophy, T wave abnormality, or Q wave.

MRI Protocol
All patients were evaluated with MRI within 7 days of the onset of symptoms. Eight patients (9.6%) were imaged within the first 2 days after symptom onset, 54 patients (65.1%) between the second and fifth day, and the remaining 21 (25.3%) after the sixth day. In every case, MRI was performed before a new follow-up stroke.

Before the MR examination, all cases had been studied with nonenhanced CT, and patients who presented a nonischemic brain lesion that could explain the acute patient symptoms were excluded.

All MRI was performed with a 1.5-T whole-body imager system with 24-mT/m gradient strength, 300-ms rise time, and an echo-planar-capable receiver equipped with a gradient overdrive (Magnetom Vision Plus; Siemens Medical Systems).

The images obtained included axial T2-weighted turbo spin-echo [(3700/90/2) (TR/TE/excitations)], TI-weighted spin-echo [(1500/14/2)], turbo fluid-attenuated inversion recovery [(9000/110/2)], and echo-planar diffusion images [(6500/120)]. The DWI were obtained with a single-shot spin-echo echo-planar pulse sequence with diffusion gradient b values of 0, 500, and 1000 sec/mm² along all 3 orthogonal axes over 15 axial sections, using 5-mm-thick sections, an interslice gap of 1.5 mm, a field of view of 230 mm, and 96×128 matrix. The acquisition time for the DWI equaled 56 seconds. To minimize the effects of diffusion anisotropy, the diffusion-weighted data were automatically processed to yield standard isotropic DWI.

Tissue abnormality was defined as areas of high signal intensity on isotropic DWI (reflecting decreased water motion) reflecting an acute ischemic lesion. For the study aims, we classified the patients

In this study we aimed to determine whether there were differences in the risk of further ischemic events among patients with TIA by taking into account temporal and neuroimaging data, together with ultrasonographic findings.

### Patients and Methods

#### Patient Selection
We targeted TIA patients who were attended to within 24 hours by the neurologist in the emergency room. In this study, we have prospectively included 87 classical TIA patients who received an MRI as part of the study protocol within 7 days of the onset of symptoms. Four patients were excluded for the following reasons: epilepsy, 2 cases; cerebral tumor, 1 case, and cervical myelopathy, 1 case. Examinations during admission included medical history; physical examination; routine blood biochemistry; electrocardio-

### Table 1. Descriptive Analyses of TIA Patients

<table>
<thead>
<tr>
<th>Past history</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke</td>
<td>15 (18.1)</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>13 (25.3)</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>7 (8.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>9 (10.8)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Risk factor of vascular disease</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (54.2)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (25.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19 (22.9)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27 (32.5)</td>
</tr>
</tbody>
</table>

#### Cause

| Large-artery atherosclerosis      | 30 (36.1) |
| Small-vessel atherosclerosis      | 5 (6.0) |
| Cardioembolic                     | 15 (18.1) |
| Undetermined etiology             | 33 (39.8) |
| ECG abnormalities                 |       |
| Atrialventricular block           | 1 (1.2) |
| Left ventricular hypertrophy      | 6 (7.2) |
| Q wave                            | 6 (7.2) |
| Atrial fibrillation               | 6 (7.2) |
| T wave                            | 5 (6.0) |

#### Discharge treatment

| Any vascular event                | 20 (24.1) |
| Heart ischemic disease            | 2 (2.4) |
| Cerebral ischemic event           | 16 (19.3) |
| Vascular death                    | 2 (2.4) |

Percentages are shown in parentheses as appropriate. ECG indicates electrocardiogram.

#### Electrocardiogram Protocol

An ECG was performed within 1 day of the onset of symptoms. Abnormal ECG findings included any of the following diagnoses: atrial fibrillation, atrioventricular block, left ventricular hypertrophy, T wave abnormality, or Q wave.

#### MRI Protocol

All patients were evaluated with MRI within 7 days of the onset of symptoms. Eight patients (9.6%) were imaged within the first 2 days after symptom onset, 54 patients (65.1%) between the second and fifth day, and the remaining 21 (25.3%) after the sixth day. In every case, MRI was performed before a new follow-up stroke.

Before the MR examination, all cases had been studied with nonenhanced CT, and patients who presented a nonischemic brain lesion that could explain the acute patient symptoms were excluded.

All MRI was performed with a 1.5-T whole-body imager system with 24-mT/m gradient strength, 300-ms rise time, and an echo-planar-capable receiver equipped with a gradient overdrive (Magnetom Vision Plus; Siemens Medical Systems).

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depending on the presence or absence of tissue abnormality on isotropic DWI.

**Classification of Stroke Subtypes and New TIA Definition**

TIA cause was classified prospectively according to the Trial of ORG 10172 as large-artery atherosclerosis, small-vessel stroke, cardioembolic, and inhabitual and undetermined cause.

We classified patients according to the new criteria as follows: patients with the duration of symptoms lasting <60 minutes, patients without DWI abnormalities, and patients with the duration of symptoms lasting <60 minutes and without DWI abnormalities.

**Clinical Endpoints**

Patients were followed-up for a mean of 389 days. Clinical interviews were performed every 3 months during the follow-up. Endpoint events included stroke or classical TIA, coronary ischemic event, peripheral arterial disease, and mortality.

**Statistical Analysis**

Analyses were performed with the SPSS statistical package version 10.0. 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 analyses were performed to detect variables associated with the occurrence of vascular endpoints. Cox proportional hazards multivariate analyses were used to identify predictors for further cerebral ischemic events or any major vascular event, 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 of an ischemic event were estimated by the Kaplan–Meier product limit method, and patients with symptoms lasting for <60 minutes and without DWI abnormalities were compared with patients who did not fulfill the 2 new criteria definition of TIA by the log-rank test. P<0.05 was considered to be significant.

**Results**

A total of 83 patients were included in the study. Table 1 shows baseline characteristics of the study population. Mean age of patients was 66.35±12.42 years and 54.2% of them were male. Forty-five patients (54.2%) had hypertension. Median duration of symptoms was 30 minutes.

New temporal definition of TIA (<60 minutes) was present in 55.4% of TIA, whereas imaging-negative TIA (DWI normality) was identified in 67.5% of patients. The 2 new diagnostic criteria (DWI normality and duration of <60 minutes) were both present in 36.4% of the patients. Carotid territory TIA was defined in 47 patients (56.6%). Embolic cardiac diseases were identified in 18.1% of patients, and 39.8% of TIA had an uncertain cause. Extracranial stenoses were detected in 22 (26.5%) patients; 4 (4.8%) cases were mild, 5 (6.0%) were moderate, and 13 (15.7) were severe. In 32 (38.6%) patients, intracranial stenoses were detected. Large-artery occlusive disease was identified in 22 (36.1%) patients. Cranial CT scan performed within 24 hours of symptom onset showed a chronic ischemic infarct in 18 (21.7%) patients, whereas 27 (32.5%) subjects had a chronic ischemic infarct on cranial MR. DWI demonstrated acute ischemic lesions in 27 (32.5%) patients. Most patients received antiaggregation (72.5%) as secondary prevention treatment.

**Follow-Up Endpoints**

At follow-up, 16 (19.3%) new cerebral ischemic events were recorded. Two patients (2.4%) died: 1 after a cerebral ischemic stroke and the other after an intracranial hemorrhage. Two patients (2.4%) had an acute myocardial infarction. Finally, peripheral arterial disease was identified in 2 patients (2.4%).

Forty-six patients with a short duration of symptoms (<1 hour) presented 6 cerebral ischemic events (14%) and 7 vascular events (16.3%) at follow-up, whereas 8 cerebral ischemic events (14.3%) and 10 vascular events (17.9%) appeared in 56 patients who fulfilled the neuroimaging criteria (DWI normality). Only 3 cerebral ischemic events (10.7%) with no other vascular event were recorded in 28 patients with the duration of symptoms lasting <60 minutes and without positive DWI. In addition, among 10 patients with symptoms lasting for >60 minutes and DWI abnormal-
ities, cerebral ischemic event developed in 4 patients (40%) and 5 cases (50%) had a vascular event during the follow-up (Figure 1).

**Variables Associated With New Cerebral Ischemic and Vascular Events (Univariate Analyses)**

Table 2 shows the univariate analyses of variables associated with cerebral ischemic event and major vascular events occurring during follow-up. Past history of previous stroke, duration of symptoms of >60 minutes associated with DWI abnormality, and large-artery occlusive disease detected by ultrasonographic study were associated with an increased risk of further cerebral ischemic events (all \( P < 0.05 \)).

Age, past history of previous stroke, duration of symptoms for >60 minutes or DWI abnormality, and large-artery occlusive disease were associated with future major vascular events (all \( P < 0.05 \)).

**Independent Predictors of New Cerebral Ischemic or Vascular Events (Multivariate Analyses)**

In Cox proportional hazards multivariate analyses, in which age, sex, vascular risk factors, and variables showing \( P < 0.1 \) on univariate models were included, the association of duration \( \geq 60 \) minutes with DWI abnormality (hazard ratio [HR], 5.02; 95% CI, 1.37 to 18.30; \( P = 0.0146 \)) and large-artery occlusive disease (HR, 4.22; 95% CI, 1.17 to 15.22; \( P = 0.0276 \)) were independent predictors of further cerebral ischemic events and also for any vascular event during the follow-up (HR, 3.77; 95% CI, 1.09 to 13.00; \( P = 0.0293 \); and HR, 3.60; 95% CI, 1.14 to 11.39; \( P = 0.0293 \), respectively).

At short-term follow-up (90 days), the association of symptom duration \( > 1 \) hour with DWI abnormalities was identified as the only independent predictor of further cerebral ischemic events or any vascular event (HR, 5.33; 95% CI, 1.01 to 25.91; \( P = 0.038 \); and HR, 5.63; 95% CI, 1.17 to 27.05; \( P = 0.031 \)) (Table 3). Kaplan–Meier curves are shown in Figures 2 and 3.
Discussion

The present study demonstrates that patients with the duration of symptoms \( \geq 1 \) hour in association with DWI abnormality and moderate to severe extracranial/intracranial stenoses detected by ultrasonographic exploration are at higher risk for new cerebral ischemic and vascular events at short-term and medium-term follow-up. Diagnosis of TIA is a difficult clinical problem because many of the symptoms may have resolved before patients arrive at the hospital\(^4\) and there are many different conditions such as seizure, migraine, cerebral tumor, subdural hematoma, or syncope that mimic cerebral ischemic events.\(^3,7,14\) Some studies have reported clinical characteristics linked with further cerebral ischemic events, like age older than 60 years, diabetes mellitus, the duration of symptoms lasting \( >10 \) minutes, weakness, and speech impairment.\(^3,15\) But none of these was able to apply prognosis variables from one cohort in different cohorts of patients.\(^16,17\)

DWI techniques that are very sensitive in determining cytotoxic edema have become an indispensable tool in the early assessment of acute brain ischemia. In fact, recent observational studies of classical TIA patients have demonstrated that almost one half of all patients have a DWI abnormality, and that the probability of the appearance of DWI lesions increases with the duration of symptoms.\(^1,5,12\) Consequently, in 2002, a new definition of TIA was proposed, based on the duration of symptoms and DWI data.\(^4\) However, previous to our study, there was no trial evaluating the prognostic value of DWI abnormalities. In the same direction as our findings, Douglas et al have demonstrated that new infarct on head CT in TIA patients is associated with an increased short-term risk of stroke.\(^18\)

If we consider a definitive acute ischemic cerebrovascular syndrome as an episode of cerebral ischemia with an evidence-based diagnostic certainty by neuroimaging techniques following Kidwell and Warach’s definition,\(^6,7\) TIA patients with DWI abnormalities will have a definitive acute ischemic cerebrovascular syndrome. They will equally share a similar underlying pathophysiology (brain ischemia). In fact, in our study, this cohort of patients with DWI abnormality, independently of the duration of the symptoms, have an increased risk for cerebral ischemia or any vascular event (29.6%). Therefore, we demonstrate the value of DWI to identify subsets of typical TIA patients with different levels of risk of having a stroke. Patients with symptom duration \( <1 \) hour and without DWI lesions have the lowest risk for further ischemia during the follow-up (10.7%). Patients with symptom duration of any length \( >24 \) hours and with DWI abnormalities have a risk of cerebral ischemia during follow-up of 29.6%, and the highest risk was identified for those patients with symptom duration \( >60 \) minutes and DWI abnormalities (40%).

### Table 3. Multivariate Analyses of Variables Associated With Further Cerebral Ischemic and Vascular Events

<table>
<thead>
<tr>
<th></th>
<th>Cerebral Ischemic Event</th>
<th>Any Vascular Event</th>
<th>Cerebral Ischemic Event</th>
<th>Any Vascular Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90-Day Follow-Up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>5.63</td>
<td>1.17–27.05</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>5.33</td>
<td>1.10–25.90</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td><strong>Complete Follow-Up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>5.02</td>
<td>1.37–18.30</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>4.22</td>
<td>1.17–15.22</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** A, Kaplan–Meier estimates of the proportion of patients remaining free from any cerebral ischemic event \((P=0.0140, \text{log-rank test})\). Dashed line indicates patients with clinical event duration \( \geq 60 \) minutes and DWI abnormality; solid line indicates patients with clinical event duration \( <60 \) minutes and DWI without abnormality. B, Kaplan–Meier estimates of the proportion of patients remaining free from any ischemic event \((P=0.0350, \text{log-rank test})\). Dashed line indicates patients with clinical event duration \( \geq 60 \) minutes and DWI abnormality; solid line indicates patients with clinical event duration \( <60 \) minutes and DWI without abnormality.
Figure 3. A, Kaplan–Meier estimates of the proportion of patients remaining free of any cerebral ischemic event (P=0.0295, log-rank test). Dashed line indicates patients with large-artery occlusive disease detected by Doppler; solid line indicates patients without large-artery disease. B, Kaplan–Meier estimates of the proportion of patients remaining free of any vascular event (P=0.0104, log-rank test). Dashed line indicates patients with large-artery occlusive disease detected by Doppler; solid line indicates patients without large-artery disease.

Patients with DWI normality and symptoms lasting for <1 hour may represent a cohort of cases with probable misdiagnoses of cerebral ischemic syndrome or with low probability of ischemic cause. However, there are also patients with a definitive ischemic source who present events lasting only a few minutes and without lesions in DWI. These patients may have an excellent prognosis because of an effective endogenous fibrinolytic activity or because of a genetic predisposition to clot dissolution. Nevertheless, this cohort of patients at lowest risk still had a high hazard of further ischemic events (10.7%), which means that TIA, per se, is a vascular condition that always needs an urgent and complete neurologic evaluation. Because the relationship between DWI and ischemic event recurrence is already present within the first 90 days after the index TIA, a complete diagnostic and therapeutic protocol should be performed as soon as possible in these patients at high risk.

Ultrasound analyses play an important role in the diagnoses of TIA. Moreover, we have also confirmed that it is an excellent prognosis tool with which to identify patients at high risk for new vascular events. TIA patients with severe extracranial stenoses have a higher risk for stroke during early follow-up.19,20 These patients with large-artery occlusive disease could benefit from early treatment when an ultrasonographic study (or any other vascular imaging method if available) is performed within 24 hours of symptoms onset.

This study has several limitations. First, to improve the power of the study a larger cohort would be necessary. Second, it would be useful to evaluate data collected from a new cerebral MR examination performed during the follow-up. Although it is known that some DWI abnormalities are transient and time-dependent1,21,22 in patients with classical TIA, we do not know if there are any differences between patients with transient DWI abnormalities and patients with definitive cerebral ischemic lesions.

In conclusion, our study confirms the importance of performing DWI techniques and ultrasonographic analyses in patients with transient cerebral events. Patients with DWI abnormalities associated with the duration of symptoms lasting >60 minutes, particularly if large-artery disease is the underlying cause, are at high risk for future ischemic events. Early aggressive therapeutic and preventive strategies should thus be initiated in this subset of TIA patients.

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References


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