Factors Associated With a High Risk of Recurrence in Patients With Transient Ischemic Attack or Minor Stroke

Angel Ois, MD; Meritxell Gomis, MD; Ana Rodríguez-Campello, MD; Elisa Cuadrado-Godia, MD; Jordi Jiménez-Conde, MD; Claustre Pont-Sunyer, MD; Gracia Cuccurella, MD; Jaume Roquer, MD, PhD

Background and Purpose—The aim of our study was to identify factors associated with stroke recurrence after an initial minor stroke or transient ischemic attack (TIA) in a prospective hospital-series.

Methods—Included in the series were 689 patients with NIHSS lower than 4 at hospital admission. The end point was a new neurological event (worsening ≥4 points in the initial NIHSS was considered as recurrence) at 90 days (and additionally at 7 days). Factors based on two previous reported scores (ABCD and SPI-II) were analyzed in relation with stroke recurrence: age, duration of symptoms >1 hour, weakness, speech impairment, initial hypertension, hypertension, diabetes, coronary disease, minor stroke versus TIA, prior stroke, and heart failure. We also analyzed: gender, hyperlipidemia, severe alcohol intake (>60gr/d), current smoking habits, peripheral arterial disease, atrial fibrillation, acute lesion in initial head computed tomography, severe symptomatic extra or intracranial arterial disease (SSAD; arterial stenosis ≥70%), previous TIA, and vertebrobasilar event. Patients were also analyzed separately according to diagnosis of TIA or minor stroke.

Results—90-day recurrence occurred in 111 patients (16.1%), whereas 62 patients had 7-day recurrence (9%). The independent variables associated with 90-day recurrence were: SSAD (OR=4.97), weakness (OR=3.25), speech impairment (OR=1.96), severe alcohol intake (OR=4.18), heart failure (OR=2.41), previous TIA (OR=4.62), and vertebrobasilar events (OR=2.87). SSAD was independently associated with 7-day recurrence (OR=7.73) and also for TIA (OR=3.45) and minor stroke (OR=5.15) patients.

Conclusions—An arterial study to discard SSAD would be necessary, in combination with clinical factors, to improve the identification of patients with a higher risk of 90-day recurrence after an initial minor stroke or TIA. (Stroke. 2008;39: 1717-1721.)

Key Words: acute stroke ■ TIA ■ recurrence

Stroke recurrence in patients with an initial nondisabling acute ischemic stroke (AIS) is one of the most frustrating medical situations. Studies assessing factors for detecting patients with a higher neurological risk have been of increasing relevance in recent years. Nevertheless, stronger predictors of stroke recurrence are needed to enable practitioners to take clinical decisions.1–3

Previous studies4–7 have reported factors related with recurrence after transient ischemic attack (TIA) or nondisabling stroke, for example the Stroke Prognosis Instrument (SPI-II)4 validated in 2000, with 7 factors to predict the risk of stroke or death in the first 2 years. A 6 point score, with only clinical parameters to identify patients at a higher risk for recurrent ischemic stroke during the first 7 days after a TIA, has been recently validated (ABCD score).6–7 Radiological techniques,8 such as diffusion-weighted MRI (DWI-MRI), also help to identify patients at high risk after a TIA9–10 or TIA and mild stroke.11

Most of these studies, however, have been focused on stroke recurrence after TIA. In some cases they were based on data obtained from trials or cohorts in which patients were recruited weeks or months after their initial event and that underestimated early recurrence.12–14 Moreover, other factors also related with a high risk of stroke recurrence, such as the presence of extracranial large vessel disease15–16 and intracranial arterial stenosis,17 were not included in these studies. Therefore, the available evidence, based on a large, prospective, hospital-series of patients with initial nondisabling stroke or TIA and with complete arterial study, is reduced.

The aim of our study was to detect which factors are associated with stroke recurrence after acute minor stroke or TIA during a follow-up period of 3 months.

Patients and Methods

From January 2004 to January 2007, 689 patients with a diagnosis of AIS and an initial neurological severity lower than 4 points in the
National Institutes of Health Stroke Scale (NIHSS), were prospectively evaluated in our hospital. All consecutive patients with acute stroke (n = 1119) were considered for the study. Patients were included in the BasicMar database (grant supported by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III; FIS Number PI051737) an ongoing prospective register of patients with AIS at our hospital. This is the only public hospital serving a population of 300,000 people in 3 districts of Barcelona city. Patients were evaluated at hospital admission by a neurologist who established the initial severity. This cut off point (0 to 3 points in the initial NIHSS) was chosen according to previously reported criteria in similar studies.

End Point
The end point of the study was a new neurological event at 90 days and additionally at 7 days. In patients with symptoms at admission we also considered recurrence as the worsening by at least 4 points in the initial NIHSS punctuation or clearly-defined new symptoms that suggested a new event. All patients with recurrence were submitted to new clinical reassessments and radiological studies. In all cases, the recurrence was validated by a neurologist trained in cerebrovascular pathology. Follow-up data were obtained from direct patient visit at 90 days or by telephone interview (n = 76) if patients failed to attend the visit. All patients with stroke recurrence were attended in our hospital from onset with the exception of 4 cases (3 patients were sent to our hospital from others centers), and in 1 case the patient had a recurrence and died in another hospital. Nevertheless, we had access to all medical data.

Methodology of Care
All patients had a complete medical exploration, blood test, chest radiography, ECG (daily during hospitalization), and head scan (CT) at admission. Patients were clinically monitored during hospitalization at least once a day with NIHSS assessment carried out by a trained neurologist. We performed a strict control of blood pressure, temperature, and serum glucose levels in all patients. In May 2005 we inaugurated the stroke unit in our center and added continuous cardiac monitoring during at least 24 hours in those patients admitted (n = 227). Patients not admitted at stroke unit were admitted at neurological emergency room area or at neurological area. The neurological team that attended these patients was the same using the same protocols. Care differences were just the specialized nursing and the continuous monitoring only available in the Stroke Unit.

Echocardiograph explorations (n = 386), transesophageal (n = 105), and Holter tape (n = 113) were performed and interpreted by a trained cardiologist. Intra- and extracranial Doppler studies of the supra-aortic arteries (Multi-Dop-Portable Doppler System-DWL) were performed by a trained neurologist in ultrasonographic techniques following previously established criteria for arterial stenosis or occlusion. The study was carried out in all patients during the first 24 hours. We performed additional explorations (carotid duplex [n = 497], MR angiography [n = 412], CT angiography [n = 79], and arteriography [n = 47]) to complete the study in patients with abnormalities or inadequate initial ultrasonographic study and in those strokes of unknown origin, posterior circulation strokes, or those of clinical interest. This methodology has demonstrated a good correlation between explorations and interobserver.

Treatment was decided in each case by a neurologist experienced in neurovascular diseases following international consensus. In all cases we started antiplatelet therapy in the acute phase with the exception of those patients with cardioembolic strokes, and in some selected patients with severe arterial disease (patients already pretreated with antiplatelet, crescendo TIA, or progressive stroke after antiplatelet treatment) in whom anticoagulation was initiated. An interventional procedure (5 patients angioplasty + stent; 45 patients endarterectomy) was performed in cases with symptomatic carotid stenosis ≥70% without complete occlusion and in 2 patients with severe basilar stenosis. In all cases we recommended a strict control of vascular risk factors after discharge.

The preexisting conditions and presence of previous TIA were obtained from the patient, relatives, caregivers, or prior medical records following the definitions recommended by the international guidelines and registered in a structured questionnaire (BasicMar) as follows: arterial hypertension (evidence of at least 2 raised blood pressure measurements, systolic >140 mm Hg or diastolic >90 mm Hg, recorded on different days before stroke onset, a physician’s diagnosis, or use of medication); diabetes (a physician’s diagnosis or use of diabetes medication); hyperlipidemia (physician’s diagnosis, use of medication, serum cholesterol concentration >220 mg/dL, LDL-cholesterol >130 mg/dL, or serum triglyceride concentration >150 mg/dL); current smoking habits, severe alcohol intake >60 gr/d, coronary artery disease (documented prior history of angina pectoris or myocardial infarct), peripheral arterial disease (physician’s diagnosis of intermittent claudication or ankle-brachial index <0.90 in either leg), and atrial fibrillation (prior documented history or diagnosis during hospitalization). In our protocol the presence of TIA within the 7 days before stroke onset is specifically registered. At hospital admission we also registered the following clinical variables: duration of symptoms, presence of motor weakness, or speech impairment. Diagnosis of congestive heart failure was established with previous well-documented history or was performed during hospitalization based on standard clinical criteria from the Framingham Study.

Analyzed Factors
Using the ABCD score criteria we analyzed the following variables: weakness (2 points); speech impairment (without weakness 1 point); duration of symptoms ≥1 hour [2 points (1 point: 10 minutes to 1 hour)]; age ≥60 years (1 point); and initial hypertension ≥140 mm Hg (systolic) and/or ≥90 mm Hg (diastolic) (1 point). A similar clinical risk stratification model developed in northern California has been validated which additionally includes diabetes as a factor. Using the Stroke Prognosis Instrument (SPI-II) we analyzed 7 factors: congestive heart failure (3 points); diabetes (3 points); prior stroke (3 points); age >70 years (2 points); non-TIA (the distinction between stroke and TIA was determined by the presence of symptoms lasting >24 hours) (2 points); severe hypertension >180/100 mm Hg (1 point); and coronary artery disease (1 point). The presence of acute ischemic changes in the initial CT was determined by a trained radiologist with access to clinical information, but blinded to posterior outcome. Based on the previously described relationship between this finding and the recurrence risk after TIA, we analyzed the presence of acute stroke signs in initial CT and stroke recurrence in our population. We also analyzed 2 controversial clinical data in relation with the recurrence: prior TIA (in the previous 7 days) and vertebrobasilar events defined according to radiological data or following previously well-defined clinical criteria.

Severe symptomatic extra or intracranial arterial disease (SSAD) was defined by the detection of ipsilateral carotid stenosis ≥70% (a degree of carotid stenosis previously reported with a high risk of recurrence) or symptomatic intracranial stenosis ≥50%. We also analyzed the relationship between recurrence and: hyperlipidemia, peripheral arterial disease, atrial fibrillation, current smoking habits, and severe alcohol consumption.

Ethics
Data for the study was collected following the local ethical guidelines. The identity of the individual patients was completely anonymous. All patients signed an informed consent. There was no delay in any of the therapeutic interventions in order to carry out the present study.

Statistical Analysis
In the first part of the study we detailed the analyzed factors (number of patients and percentages and their relationship with 90-day and 7-day stroke recurrence and, separately, with 90-day recurrence in patients with TIA or minor stroke). Chi² test was used to evaluate differences in univariate analysis.

Multivariable odds ratios (OR) with 95% CI were calculated using a multiple logistic regression model. We introduced all variables
Results

We included 689 patients with a mean age of 71.73 (SD: 11.7) years, ranging from 26 to 97. The median arrival time at the hospital after onset of symptoms was 12.20 (SD: 11.6) hours. The length of stay was mean 4.54 (5.7), range 1 to 41 days. 111 patients (16.1%) had stroke recurrence (4 of them with a hemorrhage event; 16 died). 165 patients had an initial stroke severity of 0 at hospital admission, 30 of which (18.2%) presented stroke recurrence. The absence of symptoms at admission was not related to recurrence (P=0.407; OR=1.21 95% CI [0.76 to 1.93]). Table 1 describes the analyzed factors and their association in the univariate analysis with stroke recurrence at 90 days and 7 days for the whole series, and separately for patients with TIA and minor stroke at 90 days. Because of the number of variables analyzed, we have not included in Table 1 the other cut-off point described in the scores for age and blood pressure. We did not find any association in the univariate analysis with 90-day recurrence, age (≥60 years) (P=0.407; OR=1.21 95% CI [0.76 to 1.93]) or initial blood pressure (>180/100) (P=0.957; OR=1.02 95% CI [0.56 to 1.84]). Neither did we detect any difference with respect to recurrence rate according to patient management and treatment: admission to stroke unit (n=227; 31 patients with recurrence, P=0.219); initial treatment with anticoagulants (n=117; 21 patients with recurrence, P=0.553); or arterial procedures in patients with severe arterial disease (n=52/111; 23 patients with recurrence [one with recurrence after procedure, P=0.344]).

We found an independent association between 90-day recurrence and the following variables: weakness, speech impairment, vertebrobasilar events, previous TIA, severe alcohol intake, heart failure, and SSAD (Table 2). Stroke recurrence within the first 7 days was detected in 62 patients (9%). The variables associated in the multivariable model were: weakness, previous TIA, heart failure, and SSAD. We separately analyzed the factors associated with 90-day stroke recurrence in similar multivariate models for TIA and minor stroke patients (Table 2). In patients with TIA, 90-day

Table 1. Univariate Data of Factors Analyzed in Relation With Recurrence at 90 and 7 Days in the Whole Series, and With 90-Day Recurrence for TIA or Initial Minor Stroke Studied Separately

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole Series</th>
<th>90-Day Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n=689 (%)</td>
<td>At 90 Days n=111 (%)</td>
</tr>
<tr>
<td>Age, &gt;70 years</td>
<td>435 (63.1)</td>
<td>70 (63.1)</td>
</tr>
<tr>
<td>Symptoms, &gt;1 hour</td>
<td>559 (81.1)</td>
<td>93 (83.8)</td>
</tr>
<tr>
<td>Speech impairment</td>
<td>238 (34.5)</td>
<td>50 (45)</td>
</tr>
<tr>
<td>Weakness</td>
<td>208 (30.2)</td>
<td>54 (48.6)</td>
</tr>
<tr>
<td>Hypertension, ≥140/90</td>
<td>256 (37.2)</td>
<td>40 (36)</td>
</tr>
<tr>
<td>Minor stroke vs TIA</td>
<td>468 (67.9)</td>
<td>69 (62.2)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>104 (15.1)</td>
<td>18 (16.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>203 (29.5)</td>
<td>32 (28.8)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>94 (13.6)</td>
<td>17 (15.3)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>37 (5.4)</td>
<td>11 (9.9)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>376 (54.6)</td>
<td>58 (52.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>442 (64.2)</td>
<td>74 (66.7)</td>
</tr>
<tr>
<td>Hypertiglyceridemia</td>
<td>322 (45.8)</td>
<td>57 (51.4)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>167 (24.2)</td>
<td>37 (33.3)*</td>
</tr>
<tr>
<td>Severe alcohol intake</td>
<td>46 (6.7)</td>
<td>17 (15.3)*</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>69 (10)</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>121 (17.6)</td>
<td>15 (13.5)</td>
</tr>
<tr>
<td>Prior TIA</td>
<td>62 (9)</td>
<td>28 (25.2)*</td>
</tr>
<tr>
<td>Acute infarct in CT</td>
<td>55 (8)</td>
<td>9 (8.1)</td>
</tr>
<tr>
<td>Vertebrobasilar event</td>
<td>80 (11.6)</td>
<td>18 (16.2)*</td>
</tr>
<tr>
<td>Severe arterial disease</td>
<td>111 (16.1)</td>
<td>46 (41.4)*</td>
</tr>
</tbody>
</table>

Variables selected for the regression model were those with a P<0.1 in the univariate analysis (*) and all the variables above the line. NA indicates not applicable.

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recurrence was independently associated with weakness, duration of symptoms, previous TIA, and SSAD. In patients with minor stroke, a new event was independently associated with weakness, speech impairment, severe alcohol intake, previous TIA, and SSAD. Finally, among the 111 patients with SSAD, 80 (11.6%) had severe carotid or vertebral disease and 38 (5.5%) presented intracranial disease (7 with simultaneous intra- and extracranial). When dichotomized into intra- and extracranial symptomatic disease, both factors were independently associated with recurrence in a logistic regression model adjusted by the remaining analyzed factors: intracranial, \( P = 0.010 \), adjusted OR = 2.87 95% CI (1.29 to 6.35); extracranial, \( P < 0.001 \), adjusted OR = 4.70 95% CI (2.63 to 8.38).

### Discussion

Our data showed a 7-day and 90-day recurrence rate of 9.3% and 16.1%, respectively, in patients with TIA or initial minor stroke. This fact is congruent with previous reports that estimated a range between 10% and 20% in the ensuing 90 days.\(^2,13,29–31\) There are no models to identify patients with a high risk of 90-day recurrence after TIA or minor stroke. We therefore analyzed the same previously described factors in 2 well-validated scores (ABCD score and SPI-II),\(^4–7\) but with different methodology (different population, follow up, or end points). Because of this different methodology our results cannot be used to validate these models. For a 90-day or 7-day follow-up, 2 clinical factors derived from the ABCD score (motor symptoms and speech impairment) and 1 factor from the SPI-II (heart failure) were associated with recurrence. Age was not associated with recurrence in our population using both 60- and 70-year cut-off points. Moreover, initial blood pressure did not demonstrate any value for predicting a high risk of recurrence in our population. It is possible that the careful monitoring of blood pressure in the acute phase, and the posterior control, might have decreased its deleterious effect on recurrence risk. The inclusion of minor strokes in our study (all with symptoms lasting more than 1 hour) decreased the prognostic value of symptom duration (which has been found for patients with TIA). We did not find any different risk of recurrence between patients with minor stroke compared to patients with TIA. In the SPI-II score, patients with minor stroke were associated with poor prognosis.\(^4\) Nevertheless, because of the relatively low number of events in patients with TIA, a confirmation is needed from a larger cohort. In our population, the presence of ischemic lesions in the initial CT during the acute stroke phase was not associated with recurrence. In a previous report\(^8\) concerning only TIA patients, this relationship was demonstrated in CT studies performed in the first 48 hours from the onset of symptoms. We did not confirm these findings in our patients in spite of the fact that the demonstration of an acute lesion in the CT study depends on the time of onset of symptoms. Finally, other vascular risk factors previously reported in relation with recurrence such as: diabetes, coronary artery disease, or atrial fibrillation, were not associated with recurrence in our series.\(^4,29–31\) These factors might have a higher association with stroke prognosis (in relation with other new cardiovascular events) than with the recurrence risk at a relatively short follow-up period in a hospital admitted population.

We have detected an independent association between 90-day recurrence and the following factors: motor weakness, speech impairment, previous TIA, vertebrobasilar event, severe alcohol intake, heart failure, and SSAD. With 7-day recurrence we obtained the same factors except speech impairment and severe alcohol intake. TIA and minor stroke in vertebrobasilar territory have been traditionally perceived to have a better prognosis than in carotid territory. In spite of the fact that there was a lack of epidemiological data, a recent meta-analysis\(^26\) has shown that these patients have the same risk or even a higher risk in acute phase. Our data suggest a higher recurrence risk for patients with vertebrobasilar events. Severe alcohol intake was another factor related with late recurrence; a possible explanation could be fewer adherence to prescribed treatments for these patients. In our series, a TIA 7 days before admission was clearly associated with the recurrence risk (at 7 and 90 days). This finding could reflect an unstable vascular condition with higher risk. The presence of SSAD is a well-known factor associated with a higher risk of recurrence.\(^15–17\) and was associated with both 7 and 90 days and also for TIA and minor stroke patients analyzed separately. Both extra- and intracranial diseases were associated with recurrence, with a higher OR for severe extracranial disease in the 90-day recurrence.

### Table 2. Independent Factors Associated With 7-Day and 90-Day Recurrence (Additionally Divided Into TIA and Minor Stroke Patients)

<table>
<thead>
<tr>
<th>Symptoms, &gt;1 hour</th>
<th>At 7 Days</th>
<th>At 90 Days</th>
<th>90-Day Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>TIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minor Stroke</td>
</tr>
<tr>
<td>Speech impairment</td>
<td>NS</td>
<td>1.96 (1.20 to 3.18)</td>
<td>2.30 (1.03–5.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>3.14 (1.79 to 5.52)</td>
<td>3.25 (2.01 to 5.28)</td>
<td>3.03 (1.33 to 6.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe alcohol intake</td>
<td>NS</td>
<td>4.18 (1.98 to 8.84)</td>
<td>3.28 (1.82 to 5.92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.66 (1.03 to 6.81)</td>
<td>2.41 (1.04 to 5.56)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior TIA</td>
<td>5.30 (2.72 to 10.34)</td>
<td>4.62 (2.46 to 8.68)</td>
<td>5.17 (2.11 to 12.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verteobasilar event</td>
<td>NS</td>
<td>2.87 (1.47 to 5.59)</td>
<td>5.08 (1.89 to 13.64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe arterial disease</td>
<td>3.16 (1.72 to 5.81)</td>
<td>4.97 (2.98 to 8.27)</td>
<td>3.45 (1.52 to 7.84)</td>
</tr>
</tbody>
</table>

**OR (95% CI). NS indicates nonsignificant.**
Limitations
Our methodology considers as recurrence those patients with a worsening of initial minor symptoms. Our definition was based on restrictive clinical criteria (4 points in NIHSS) which are less influenced by clinical fluctuations. In most cases this fact clearly represents a recurrent event; in lacunar strokes with only 1 acute lesion, however, the concrete pathophysiology of deterioration is unclear.32–33 Our methodology could, therefore, have overestimated the recurrence rate. Nevertheless, we chose this definition in spite of the clinical interest in identifying all events that represent a poor neurological evolution. A second limitation is that we obtained DWI-MRI data in only 427 (62%) patients, and in some cases DWI data were obtained after early recurrence and were, therefore, not included in the statistical analysis. Finally, another limitation is the low number of end-point events after segmenting the series to multivariate analysis.

In conclusion, after an exhaustive study we have found 3 variables showing an independent association with stroke recurrence in all multivariable models: weakness, TIA in the previous 7 days, and the presence of SSAD. We suggest that extra- and intracranial arterial data are useful to identify those patients at high risk of stroke recurrence after TIA or minor stroke.

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Disclosures
None.

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