High Risk of Early Neurological Recurrence in Symptomatic Carotid Stenosis

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Background and Purpose—Few data are available on very early stroke recurrence evaluated within the first hours after onset of symptoms and outcome for unselected patients with first-ever mild stroke or TIA and symptomatic carotid stenosis ≥50%.

Methods—One hundred sixty-three patients with symptomatic carotid stenosis and initial mild stroke (121) or TIA (42) were evaluated within 6 hours from onset of symptoms in a single tertiary hospital. Neurological recurrence (NR) was defined as a clearly defined new neurological event (TIA or stroke) or an increase of 4 points in the initial NIHSS. The NR rate was determined at 72 hours, 7 days, and 14 days. Disability was defined as a score of 3 to 6 on the modified Rankin scale at 14 days.

Results—Forty-five patients (27.6%) had NR, including 6 patients with 2 episodes in different time periods: 34 (20.9%) within the first 72 hours; 11 (6.7%) between 72 hours and 7 days; and 6 (3.7%) at 14 days. Only carotid stenosis ≥70% was associated with NR; diabetes was marginally associated. At 2 weeks, 19 patients (11.7%) had disability; 14 of them experienced NR in the first 72 hours.

Conclusions—Patients with first-ever mild stroke or TIA and symptomatic carotid stenosis are at high risk for NR, especially within the first 72 hours. Our results suggest the necessity of testing pharmacological or interventional strategies for use during the hyperacute stroke phase in these patients. (Stroke. 2009;40:2727-2731.)

Key Words: carotid stenosis ■ prognosis ■ stroke care

The efficacy of carotid endarterectomy for medical treatment, as well as the accepted surgical risk for patients with symptomatic carotid stenosis (SCS), is well-known from the results of 2 large trials: the European Carotid Surgery Trial and the North American Symptomatic Carotid Endarterectomy Trial.1–3 Data from these trials have been used to perform various subanalyses to obtain information concerning various aspects of the clinical evolution of these patients, including early risk of stroke after TIA4 or the relevance of randomization within 2 weeks.4 Both trials, however, recruited patients after a nondisabling ischemic stroke; consequently, it is not possible to know how many patients were noneligible because of early recurrence, and subsequent disability, during the time before randomization.

Recent studies have shown a high recurrence risk in the first days after TIA or TIA and minor stroke.5–11 Moreover, the very high early risk of recurrence has been described in patients with carotid stenosis.11 There are, however, few data about the clinical evolution in the first hours from symptom onset in unselected patients with SCS.

The aim of the present study was to describe the recurrence rate at 72 hours, 7 days, and 14 days, in an unselected series of patients with SCS ≥50% and first-ever nondisabling stroke or TIA evaluated in the first 6 hours from onset of symptoms.

Subjects and Methods

From May 2002 to May 2008, 1151 consecutive patients with first-ever mild acute ischemic stroke (defined as initial neurological severity <7 points on the National Institutes of Health Stroke Scale)12 or TIA were evaluated in our hospital within the first 6 hours from the onset of symptoms. This cut-off point (7 points) was chosen according to previously reported criteria to define mild stroke.11 Patients were prospectively included in the BasicMar database, an ongoing register of patients with acute ischemic stroke at our hospital. This is the only public hospital to our knowledge serving a population of 300 000 people in 3 districts of the city of Barcelona. We selected patients with ipsilateral SCS ≥50% without occlusion. Any patient with advanced age, comorbidity, or concomitant cardiac diseases was excluded in an effort to reflect the clinical evolution of patients with SCS in actual clinical practice. The final study cohort was 163 patients, once all patients whose stroke was not associated with ipsilateral SCS were excluded: 121 cases of mild stroke and 42 cases of TIA, representing 14.1% of total ischemic strokes or TIA. In all cases, the degree of arterial stenosis was confirmed by concordance of high-resolution ultrasonographic studies (duplex) performed by trained physicians and other radiology techniques, either intracranial/extracranial contrast-enhanced magnetic resonance angiography or computer scan angiography, performed and interpreted by trained radiologists following established...
North American Symptomatic Carotid Endarterectomy Trial criteria.\textsuperscript{1,3,14} An arteriography study was performed in those cases with doubtful or discordant results (n=42).

**Methodology of Care**

Cases were directly diagnosed on hospital admission by a neurologist who established the initial neurological severity. Time of stroke onset was registered in all patients. When the onset of the neurological symptoms was unknown, or occurred while sleeping, the stroke onset was established as the last time that the patient was seen free of symptoms. All patients had a complete medical examination, blood test, chest radiography, ECG (daily during hospitalization), and head scan (CT) on admission. Patients were clinically monitored with National Institutes of Health Stroke Scale assessment at least once per day during hospitalization. All patients were assessed in the same way, following the therapeutic and diagnostic protocols. Initially, antiaggregant therapy is started as 300 mg aspirin or other anti-aggregants (clopidogrel or trifusal) for patients with aspirin intolerance; in some patients already receiving aspirin treatment (n=24), 75 mg clopidogrel was added, in consultation with the attending physician. In 14 cases, this initial antiaggregant therapy was a combination of aspirin and clopidogrel. In all cases, treatment was started in the first 6 hours from hospital admission and after the initial examination. High-dose atorvastatin (80 mg) was administrated in hyperacute phase only in the last patients of the series (n=32), when protocols were adjusted to accommodate new evidence. Any previous treatment with statins was withdrawn. Glycemia, blood pressure, and temperature were monitored carefully. Blood pressure was determined each hour (in the stroke unit) or every four hours (in the rest of cases) during at least the first 24 hours. Antihypertensive agents were administered only in patients with heart failure, under current international stroke guidelines, or if the diastolic blood pressure was >120 mm Hg or the systolic blood pressure was >220 mm Hg. Moreover, in selected patients already pretreated with antplatelet drugs who presented with repetition/crescendo TIA (n=6) or patients with an associated high-risk cardioembolic cause, we started anticoagulation with endovenous heparin. In May 2005 we inaugurated the stroke unit in our center and added continuous noninvasive monitoring of admitted patients for at least 24 hours (n=61). The same neurology team attended the patients before and after May 2005, and the same protocols were used. The specialized nursing and continuous monitoring that became available in the new stroke unit were the only differences in care.

In the first 3 hours after stroke onset, endovenous thrombolytic treatment with recombinant tissue plasminogen activator was administered (n=5) based on the European Medicines Evaluation Agency Criteria (SITS-MOST criteria). None of the included patients had surgery in the first 2 weeks. This is because the vascular surgery team in our center considers ≥2 weeks to be the optimal timing for carotid endarterectomy or angioplasty plus stent after ischemic stroke.

**End Points**

Given the standard timing of vascular surgery in our center, the end point of the study was neurological recurrence at 2 weeks. Neurological recurrence (NR) was defined as a new neurological clinical event. In patients with TIA, this was a new TIA or stroke. In patients with mild stroke, NR was a worsening by at least 4 points from the initial National Institutes of Health Stroke Scale score or clearly defined new symptoms that suggested a new neurological event during the follow-up period.

To discard non-neurological causes of deterioration or a possible nonipsilateral NR, all patients with NR were submitted to clinical reassessment or new radiological studies (DWI-MRI in 34 patients and CT in the remaining patients). In all cases, a neurologist trained in neurovascular pathology validated the end point.

NR was divided into 3 time periods: initial 72 hours, from 72 hours up to 7 days, and from 7 days to 14 days. At 14 days, disability was registered as a score of 3 to 6 on the modified Rankin scale. The disability was determined by direct examination by a neurologist.

Forty-five patients were discharged within 2 weeks without disability. In all cases, patients and their family members or caregivers were advised about the risk of NR and received clear instructions about the urgent need for emergency room care in the event of any worsening or any new symptom. Moreover, a neurologist evaluated all patients at 14 to 17 days to discard NR. In all cases, NR in the first 2 weeks was registered, whether the patient was hospitalized.

**Factors Analyzed**

We analyzed the relationship between NR and the following factors: age, gender, initial stroke severity, vascular risk factors, major cardioembolic sources, SCS ≥50% to 69% or ≥70%, presence of significant (≥50%) ipsilateral intracranial stenosis or contralateral arterial carotid stenosis ≥50%, and presentation as a TIA. Those patients with neurological symptoms fully recovered at the initial neurological examination or with symptoms and complete recuperation in the first 24 hours without evidence of acute ischemic lesion in the initial CT study. Vascular risk factors were obtained from the patient, relatives, caregivers, or previous medical records, following the definitions recommended by the international guidelines.\textsuperscript{13} The risk factors were 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 medication); hyperlipidemia (a 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; ischemic heart disease (documented history of angina pectoris or myocardial infarction); and peripheral arterial disease (physician’s diagnosis of intermittent claudication or ankle–brachial index <0.90 in either leg). We also registered previous TIA (based on focused questions concerning neurological symptoms attributable to carotid stenosis in the previous 7 days) and previous treatment with statins or anti-thrombolic drugs (anticoagulants or anti-platelets).

**Statistical Analysis**

Differences in parametric and nonparametric continuous variables were evaluated using the t test and the Mann–Whitney U test, respectively, and the χ² test was used for proportional analysis. The univariate analysis is presented in Table 1 for proportional variables; continuous variables, age and initial severity, are discussed later in this article. Multivariate OR with 95% CI were calculated by a logistic regression model. Variables with a significance of P<0.1 in the univariate analysis were introduced into the logistic regression models. An independent statistician performed regression analysis by the forward method. The variables were cross-tabulated to assess multicollinearity. Statistical significance was determined at α level of 0.05.

**Ethics**

Data for the study were collected following the local ethics guide-lines. Data were anonymous and the identity of the individual patients was completely protected. The study did not delay any therapeutic interventions.

**Results**

The mean age was 71.8 years (SD, 10.4; range 45–92), and the median arrival time to neurological evaluation after onset of symptoms was 3 hours (1st and 3rd quartiles: 2, 4). Seventy-nine patients (48.5%) had stenosis ≥70% without occlusion, and 84 patients (51%) had stenosis ≥50% to 69%. Demographic, clinical, and arterial variables are detailed in Table 1.

Major cardioembolic causes were detected in 25 patients (15.3%): atrial fibrillation (documented history or diagnosis during hospitalization, n=17); left ventricular ejection fraction <35% (n=5); valvular disease (n=1); severe anterior
akinesia (n=1); and left ventricular aneurism with associated thrombus (n=1). We performed echocardiography in 126 patients (77.3%); of the 45 patients with NR, 36 (78%) had an echocardiography study performed.

Neurological Recurrence

During the first two weeks after stroke onset, 45 patients (27.6%) presented with NR. The majority, 34 patients (20.9%), presented NR within the first 72 hours (progressive NR was reported in 22.7% of patients). The majority, 34 patients (77.3%); of the 45 patients with NR, 36 (78%) had an echocardiography study performed.

Table 1. Demographics, Vascular Risk Factors, and Clinical Variables in Relation to Recurrence

<table>
<thead>
<tr>
<th></th>
<th>Total Cases, N=163 (%)</th>
<th>Recurrence, N=45 (%)</th>
<th>No Recurrence, N=118 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>97 (59.5)</td>
<td>24 (53.3)</td>
<td>73 (61.9)</td>
<td>0.321</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>119 (73)</td>
<td>33 (73.3)</td>
<td>86 (72.9)</td>
<td>0.954</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63 (38.7)</td>
<td>22 (48.9)</td>
<td>41 (34.7)</td>
<td>0.097*</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>105 (64.4)</td>
<td>30 (66.7)</td>
<td>75 (63.6)</td>
<td>0.711</td>
</tr>
<tr>
<td>Current smoking</td>
<td>52 (31.9)</td>
<td>12 (26.7)</td>
<td>40 (33.9)</td>
<td>0.376</td>
</tr>
<tr>
<td>Heart ischemic disease</td>
<td>32 (19.6)</td>
<td>11 (24.4)</td>
<td>21 (17.8)</td>
<td>0.339</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>23 (14.1)</td>
<td>5 (11.1)</td>
<td>18 (15.3)</td>
<td>0.497</td>
</tr>
<tr>
<td>Major cardiogenic cause</td>
<td>25 (15.3)</td>
<td>7 (15.6)</td>
<td>18 (15.3)</td>
<td>0.962</td>
</tr>
<tr>
<td>Antithrombotic pretreatment</td>
<td>60 (36.8)</td>
<td>17 (37.8)</td>
<td>43 (36.4)</td>
<td>0.874</td>
</tr>
<tr>
<td>Statin pretreatment</td>
<td>45 (27.6)</td>
<td>10 (22.2)</td>
<td>35 (29.7)</td>
<td>0.342</td>
</tr>
<tr>
<td>Symptomatic carotid stenosis ≥70%</td>
<td>79 (48.5)</td>
<td>29 (64.4)</td>
<td>50 (42.4)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Contralateral carotid stenosis ≥50%</td>
<td>29 (17.8)</td>
<td>10 (22.2)</td>
<td>19 (16.1)</td>
<td>0.361</td>
</tr>
<tr>
<td>Intracranial ipsilateral stenosis</td>
<td>49 (30.1)</td>
<td>11 (24.4)</td>
<td>38 (32.2)</td>
<td>0.334</td>
</tr>
<tr>
<td>TIA as initial symptom</td>
<td>42 (25.8)</td>
<td>10 (22.2)</td>
<td>32 (27.1)</td>
<td>0.523</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>29 (17.8)</td>
<td>12 (26.7)</td>
<td>17 (14.4)</td>
<td>0.067*</td>
</tr>
</tbody>
</table>

Univariate analysis. *Selected for logistic regression analysis.

Disability

At 2 weeks, 19 patients (11.7% of the entire cohort) had disability. Three patients did not experience NR. Of the 16 NR cases, 14 (87.5%) occurred in the first 72 hours and the remaining 2 occurred between 72 hours and 2 weeks of follow-up. Three patients died, with large new ischemic lesions.

Discussion

It is well-known that the risk of recurrence after stroke or TIA has been traditionally underestimated. Recent studies have shown a high recurrence risk in the first days after TIA or TIA and minor stroke. However, few data are available concerning recurrence risk in patients with minor stroke, which generally includes early neurological deterioration, a factor that may often reflect early recurrence. Moreover, no previous series to our knowledge specifically included patients in the first 6 hours from onset of symptoms. We sought to quantify how many patients with mild stroke or TIA and ipsilateral carotid disease experienced a recurrence in a hospital with a trained team of vascular neurologists following standard medical practice. We found a high NR rate of 27.6% (22.7% if recurrent TIA was excluded), mainly in the first 72 hours (only 9.8% of total NR were beyond the first 72 hours). Although there are no similar previously published series to compare with our results, a recent meta-analysis showed a risk of stroke recurrence of 13.4%, and 17.3% at 30

Table 2. Factors Analyzed With Neurological Recurrence in the Logistic Regression Model

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>0.052</td>
<td>2.06</td>
<td>0.99–4.27</td>
</tr>
<tr>
<td>Carotid stenosis ≥70%</td>
<td>0.018</td>
<td>2.44</td>
<td>1.16–5.13</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>0.158</td>
<td>1.88</td>
<td>0.78–4.50</td>
</tr>
</tbody>
</table>
and 90 days, respectively. In 1 population-based study of patients with TIA and minor stroke, the recurrence rate was 11.5% and 15%, respectively. At present, a high recurrence risk is widely accepted in stroke patients with large-artery atherosclerosis. An article focusing on patients with hemispheric TIA and carotid stenosis ≥50% reported a risk of stroke at 2 weeks of 21%, similar to that obtained in our series. Our results confirm the high risk of early NR in patients with SCS. In our center, all patients with carotid stenosis are admitted, independent of severity of initial symptoms, and we immediately start treatments and neurological and clinical monitoring. Recently, new evidence of benefits from starting urgent treatments (single or combined) in patients with TIA or mild stroke to prevent stroke recurrence has been published. However, these studies were not focused on patients with carotid stenosis. We attribute the high figure observed in our series to 4 possible factors: (1) early evaluation after onset of symptoms; (2) the consideration of worsening of symptoms as an end point; (3) exhaustive neurological monitoring; and (4) the inclusion of consecutive patients, including those with concomitant causes of stroke, leading to the possibility that an embolic stroke could cause early recurrence in patients with associated cardiac sources of embolus. One noteworthy finding is the relationship between NR and the degree of carotid disease, especially in patients with stenosis ≥70% who presented with NR in 36.7% of cases. Other factors, such as TIA presentation, ipsilateral arterial disease, or contralateral carotid disease, were not associated with stroke recurrence, and diabetes was the only factor marginally associated. Diabetes mellitus is a relevant risk factor in cerebrovascular patients and its relationship with the risk of early recurrence has been previously described after a TIA, but not in relation to a high risk of early recurrence in patients with carotid disease. We found a borderline statistical relationship, probably because of the small number of cases. With regard to outcome, we found that 11.7% of patients had disability/death at 15 days. Taking into account that all cases were in patients with initially mild stroke or TIA under exhaustive medical control, and were treated with current protocols, this is a considerably high rate. These data confirm the unresolved problem of current stroke management during the first days after onset of symptoms.

Acute medical options such as the combination of antiaggregants, high-dose statins, clopidogrel dose-loading, or other antithrombotics might have a higher protective effect on NR in these patients. However, the consideration of urgent endovascular/surgical procedures (in the first hours) in cerebrovascular disease, clearly accepted in other vascular pathologies such as coronary disease, could be an interesting option to explore because only 2 patients experienced disabling NR beyond the first 72 hours after symptoms onset.

In conclusion, with current medical treatments, patients with first-ever mild stroke or TIA and SCS are at high risk for NR, especially within the first 72 hours. Our results suggest the necessity of testing pharmacological or interventional strategies for use during the hyperacute stroke phase in these patients.

Acknowledgments
The authors appreciate the statistical support of Isaac Subirana. MSc. (Statistician, Unidad de Recerca de Lípidos i Epidemiologia Cardiovascular, Institut Municipal d’Investigació Médica, Barcelona) and the careful review of English grammar and style by Elaine Lilly, PhD (Writer’s First Aid).

Sources of Funding
This study was funded in part by the Ministry of Health, Instituto de Salud Carlos III (Red HERACLES RD06/0009).

Disclosures
None.

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Stroke. 2009;40:2727-2731; originally published online June 4, 2009;
doi: 10.1161/STROKEAHA.109.548032

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