Factors associated with early outcome in patients with large-vessel carotid strokes

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ABSTRACT

Objective To describe the severity and early neurological deterioration (END) in patients with symptomatic carotid stenosis and to analyse the influence of related factors.

Methods Observational cohort study of patients with ischaemic stroke, ipsilateral carotid stenosis and without evidence of cardiac sources of embolism prospectively recorded since January 2003 to January 2012. Initial severity was categorised as mild (NIH stroke scale (NIHSS) ≤7), moderate (NIHSS 8–14) or high (NIHSS >14). Logistic ordinal and regression analyses were performed for stroke severity and END risk.

Results Of 2332 ischaemic strokes attended, 338 patients were included. Stroke severity was mild in 254 (75.1%) cases, moderate in 53 (15.7%) and severe in 31 (9.2%). Adjusted ORs (95% CI) for stroke severity were: degree of carotid stenosis, 2.20 (1.55 to 3.11, p<0.001); intracranial disease, 1.93 (1.18 to 3.17, p=0.009); plasma glucose, 1.01 (1.003 to 1.02, p=0.014); previous TIA (OR 0.37 (0.17 to 0.82, p=0.014). 78 patients (23.1%) had END. Multivariate analysis showed independent association with initial severity are not very well known. Therefore, the aim of our study was to describe the initial severity and END in a prospective cohort of patients with significant carotid atherosclerosis including occlusion and to look for factors associated with worse outcomes.

METHODS

Our tertiary stroke centre is the only public hospital offering round-the-clock acute phase stroke services to a population of 300 000 in three Barcelona city districts. In January 2003 we started a prospective observational register of first-ever atherothrombotic strokes with ipsilateral symptomatic carotid stenosis ≥50% (according to Trial of Org 10172 in acute stroke treatment criteria) in order to study their short-term evolution. For the current study we included patients attended during the first 24 h of symptoms onset, recorded through January 2012.

Methodology of care

Patients were attended in the emergency department during the first 24 h. After April 2005, patients (n=258) were attended in our stroke unit following the same diagnostic and therapeutic protocols. Patients were evaluated at hospital admission and at least twice a day during the first 3 days by a trained neurologist who established initial severity using the NIH stroke scale (NIHSS). All patients had a complete physical examination, blood test, chest radiography, CT brain scan and ECG at admission. Heart rhythm was monitored for at least 24 h in all patients to rule out cardioembolic aetiology. A transthoracic echocardiogram was performed at the discretion of the treating physician (n=263).

Within the first 24 h, all patients had a complete B-mode colour Doppler study of the supra-aortic arteries (Multi-Dop-Portable Doppler System-DWL, Sonosite MicroMaxx) by a neurologist trained in ultrasonography techniques, following established criteria. In all cases, the degree of arterial stenosis was confirmed during hospitalisation with another radiological procedure, either intracranial/extracranial contrast-enhanced MRI angiography or CT scan angiography. All vascular images were interpreted by trained neuroradiologists following the...
Cerebrovascular disease

North American Symptomatic Carotid Endarterectomy Trial criteria\(^5\) for extracranial lesions and the Warfarin–Aspirin Symptomatic Intracranial Disease trial methods for intracranial stenosis.\(^6\) A digital subtraction angiography was performed in those cases with discrepancy between the screening tests in the degree of stenosis (n=44). None of the strokes were related to radiological procedures.

Treatment was decided in each case by a neurologist experienced in neurovascular diseases following international consensus. The treatment protocol has been described previously.\(^5\) Briefly, antplatelet therapy is started in all patients with 300 mg aspirin. Other antplatelet agents (clopidogrel or trifusal) are used in patients whose medical records indicate aspirin intolerance. In some patients already receiving aspirin (n=65), 75 mg clopidogrel was added, in consultation with the attending physician. In 14 cases, this initial antplatelet therapy was a combination of aspirin and clopidogrel. In all cases, treatment was started after the initial examination and within the first 6 h following hospital admission. High-dose atorvastatin (80 mg daily) was administrated in the hyperacute phase in patients included after September 2006 (n=225), when protocols were adjusted to accommodate new evidence. Any previous treatment with statins other than atorvastatin was withdrawn and dosage was adjusted in patients already receiving atorvastatin. Initial glycaemia, blood pressure (BP) and temperature were monitored carefully.

Antihypertensive agents were administered only in patients with heart failure, under current international stroke guidelines, or if the diastolic BP was >120 mm Hg or the systolic BP was >220 mm Hg. Moreover, in selected patients already pretreated with antplatelet drugs who presented with repetition/crescendo TIA (n=15), we started anticoagulation with intravenous heparin (infusion of 1000 units per hour), monitoring the partial thromboplastin time (PTT) ratio every 6 h.

Intravenous thrombolytic therapy with alteplase (tPA) was administrated in 29 (8.6%) cases. Six patients were treated with urgent mechanical thrombectomy followed by angioplasty and stenting, procedures performed in our hospital since October 2009. Carotid endarterectomy was performed in 86 patients and elective angioplasty with stenting was done in eight patients. Median time to surgery was 5 weeks (3 weeks in the last 3 years). None of the patients had surgery in the first 72 h.

The study proposal was approved by our local ethics committee. Written informed consent was obtained from all patients participating in the study (or their relatives).

**Main outcome measures**

END was defined as the worsening by at least four points in the initial NIHSS punctuation and/or clearly defined new symptoms suggestive of a new event (TIA or stroke) within the first 72 h. Patients with deterioration due to other illness (two heart failure and one respiratory infection) were excluded. This methodology has been previously described.\(^5\)\(^\text{11}\)

We analysed the associations between initial stroke severity, END development and numerous variables: age, sex, hypertension, diabetes, hypercholesterolaemia, current smoking, previous cardiovascular events, previous antplatelet agents; statin use, degree of carotid stenosis (categorised into three groups\(^5\): moderate (50–69%), high (≥70% and near-occlusion),\(^5\)\(^\text{12}\) and occlusion), existence of a significant contralateral carotid disease (≥50% stenosis or occlusion), significant ipsilateral intracranial disease (≥50% stenosis or occlusion), and documented TIA during the preceding 3 months. Other variables analysed due to previous association with END were initial plasma glucose levels and initial mean arterial pressure (MAP), calculated with the formula (2/3×diastolic BP+1/3 systolic BP).\(^13\)

**Statistical analysis**

Data are presented as mean±SD or median (Q25–75) for continuous variables and as frequencies and percentages for categorical variables. The t test and analysis of variance were used to evaluate the differences in means for continuous variables, and the χ\(^2\) test was used for categorical variables. Glucose levels and MAP were analysed as continuous variables. Due to a non-normal distribution, initial stroke severity was categorised into three groups according to previous methodology: mild severity (NIHSS ≤7), moderate severity (NIHSS 8–14) and high severity (NIHSS >14).\(^14\) Multivariate ORs with 95% CI for stroke severity were estimated by an ordinal logistic analysis for each category. For END risk, multivariate ORs with 95% CI were calculated with a logistic regression model. Multivariate models were adjusted by variables that obtained a p value <0.1 in the univariate analysis. Two-sided p values <0.05 were considered significant. All statistical analyses were performed by a biostatistician (IS) with SPSS for Windows V.19.

**RESULTS**

Of 2532 ischaemic strokes during the first 24 h, 422 patients met inclusion criteria. After excluding patients with concomitant major cardiac sources of embolism (n=82), incomplete data (n=3) and non-atherosclerotic carotid disease (n=12), the final cohort was 338 patients (67.8% were male and mean age was 70.47±10.57 years). No differences in the main study variables were observed between patients attending before and after the stroke unit opened. Analysed factors are detailed in table 1. Among 155 patients with ≥70% stenosis, 24 (17.7%) had distal internal carotid artery calibre reduction suggestive of near-occlusion.

**Initial severity**

Initial median (p25–p75) NIHSS was 4 (1–7.25). Stroke severity was mild in 254 (75.1%) cases, moderate in 55 (15.7%) and severe in 31 (9.2%). Ninety-six patients (28.4%) had a TIA and 18 patients fulfilled radiological criteria of lacunar stroke (subcortical infarction <15 mm in diameter in the territory of the deep-penetrating arteries). Factors associated with the initial severity were degree of carotid stenosis, higher initial glucose levels, previous TIA and concomitant intracranial disease (table 1). In the multivariate analysis (table 2), adjusted OR (95% CI) for higher stroke severity were the following: degree of carotid stenosis (OR 2.20 (1.55 to 3.11), p<0.0001), intracranial disease (OR 1.93 (1.18 to 3.17), p=0.009), initial glucose levels (OR 1.13 (1.06 to 1.21), p=0.001) for each mmol/l and previous TIA (OR 0.57 (0.17 to 0.82), p=0.014).

**Early neurological deterioration**

A total of 78 patients (23.1%) suffered END, 56 of them (71%) during the first 24 h. In 48 patients, END consisted of a progressive stroke; 30 patients had a stroke recurrence (14 new TIA and 16 new strokes). The rate of END increased with stenosis degree: 14 (17.9%) with <50% stenosis, 33 (42.3%) with ≥70% stenosis and 51 (39.7%) with carotid occlusion. Other variables associated with END in univariate analysis (table 3) were MAP, previous TIA, previous antplatelet use, previous statin use and initial severity according to initial NIHSS. Multivariate analysis (table 4) showed an independent association between END development and degree of carotid stenosis (OR 1.64 (1.14 to 2.34), p=0.007), previous TIA (OR 2.40 (1.25...
Intra- and extra-cranial vessels. Embolic aetiologies; however, they included strokes due to all large-artery atherosclerotic strokes compared with other long-term outcome. Previous studies found a lower severity of main prognostic factor, independently associated with poor initial stroke severity. Initial stroke severity assessment is crucial because it is the key role of arterial stenosis degree in increased severity and END risk.

### Stroke severity

Initial stroke severity assessment is crucial because it is the main prognostic factor, independently associated with poor long-term outcome. Previous studies found a lower severity of large-artery atherosclerotic strokes compared with other embolic aetiologies; however, they included strokes due to all intra- and extra-cranial vessels. In the carotid surgery trials, almost 50% of the patients presented with TIA as the initial event. However, information on patients excluded due to severe strokes is scarce. In our study, two thirds of the strokes were of mild severity and only 9% were severe. Patients with severe strokes had a worse 90-day outcome and almost 55% had carotid occlusions.

The influence of stenosis degree on initial severity has not previously been evaluated. In two large previous studies, stroke severity was higher in patients with carotid occlusion than in those with carotid stenosis, although severity was not specifically analysed. In our study, independent factors associated with stroke severity were the degree of carotid stenosis, the existence of concomitant intracranial stenosis or occlusion, and initial glucose levels. Preceding TIA, within the previous 5 months, was found associated with a lower stroke severity.

Previous studies reported larger lesion volumes in strokes due to carotid occlusion compared with carotid stenosis. Chronic impairment of haemodynamic status might be responsible for the higher volume load and stroke severity in patients with carotid occlusion. Preceding TIA has been associated with lower stroke severity in previous studies, although the pathophysiological explanation for this finding is not well known. The other independent factors affecting stroke severity have been described previously. In large series of patients with symptomatic steno-occlusive disease, intracranial middle cerebral artery occlusions have higher severity than carotid occlusions.

Moreover, in neuroimaging studies, middle cerebral artery (MCA) occlusions alone or MCA occlusions with coexistent carotid occlusion have more extensive infarcts than carotid occlusions. The relationship between initial glucose and stroke severity might be explained by the multilevel deleterious effect of initial hyperglycaemia in acute strokes.

### Table 1 Univariate analysis for initial severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=338)</th>
<th>NIHSS ≤7 (n=254)</th>
<th>NIHSS 8–14 (n=53)</th>
<th>NIHSS &gt;14 (N=31)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>229 (67.8)</td>
<td>175 (68.9)</td>
<td>30 (56.6)</td>
<td>24 (77.4)</td>
<td>0.106</td>
</tr>
<tr>
<td>Age years, mean (SD)</td>
<td>70.47 (10.57)</td>
<td>70.80 (10.48)</td>
<td>69 (11.60)</td>
<td>70.47 (10.57)</td>
<td>0.528</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>244 (72.2)</td>
<td>186 (73.2)</td>
<td>35 (66)</td>
<td>23 (74.2)</td>
<td>0.549</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>127 (37.6)</td>
<td>95 (37.4)</td>
<td>19 (35.8)</td>
<td>13 (41.9)</td>
<td>0.851</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>206 (60.9)</td>
<td>157 (61.8)</td>
<td>28 (58.2)</td>
<td>21 (67.7)</td>
<td>0.342</td>
</tr>
<tr>
<td>Current smoking</td>
<td>134 (39.6)</td>
<td>95 (37.4)</td>
<td>26 (49.1)</td>
<td>13 (41.9)</td>
<td>0.277</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>50 (14.8)</td>
<td>38 (15)</td>
<td>8 (15.1)</td>
<td>4 (12.9)</td>
<td>0.953</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>58 (17.2)</td>
<td>43 (16.9)</td>
<td>9 (17)</td>
<td>6 (19.4)</td>
<td>0.693</td>
</tr>
<tr>
<td>MAP mm Hg, mean (SD)</td>
<td>106.20 (19.80)</td>
<td>106.49 (21.09)</td>
<td>106.52 (16.65)</td>
<td>103.30 (12.66)</td>
<td>0.629</td>
</tr>
<tr>
<td>Glucose mmol/l, mean (SD)</td>
<td>7.70 (3.49)</td>
<td>7.33 (3.00)</td>
<td>8.34 (3.64)</td>
<td>9.69 (5.65)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Contralateral carotid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis ≥50%</td>
<td>80 (23.7)</td>
<td>57 (22.4)</td>
<td>16 (30.2)</td>
<td>7 (22.6)</td>
<td>0.696</td>
</tr>
<tr>
<td>Occlusion</td>
<td>14 (4.14)</td>
<td>12 (4.7)</td>
<td>1 (1.9)</td>
<td>1 (3.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ipsilateral intracranial disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis ≥50%</td>
<td>32 (9.5)</td>
<td>27 (10.6)</td>
<td>2 (3.8)</td>
<td>3 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>11 (3.3)</td>
<td>2 (0.8)</td>
<td>3 (5.7)</td>
<td>6 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Previous TIA</td>
<td>69 (20.4)</td>
<td>60 (23.6)</td>
<td>9 (17.0)</td>
<td>0</td>
<td>0.007*</td>
</tr>
<tr>
<td>Statins</td>
<td>105 (31.1)</td>
<td>80 (31.5)</td>
<td>13 (24.5)</td>
<td>12 (38.7)</td>
<td>0.382</td>
</tr>
<tr>
<td>Antiplatelets</td>
<td>101 (29.9)</td>
<td>76 (29.9)</td>
<td>17 (32.1)</td>
<td>8 (25.8)</td>
<td>0.832</td>
</tr>
<tr>
<td>Degree of carotid stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>50–69%</td>
<td>107 (31.7)</td>
<td>90 (35.4)</td>
<td>13 (24.5)</td>
<td>4 (12.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;70%</td>
<td>135 (39.9)</td>
<td>109 (42.9)</td>
<td>16 (30.2)</td>
<td>10 (32.3)</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>96 (28.4)</td>
<td>55 (21.7)</td>
<td>24 (45.3)</td>
<td>17 (54.8)</td>
<td></td>
</tr>
<tr>
<td>90-day mRS</td>
<td>2 (0–3)</td>
<td>1 (0–2)</td>
<td>3 (2–4)</td>
<td>4 (3–6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results expressed as no. (%), unless indicated otherwise.

*Variables selected for multivariate analysis.

MAP, mean arterial pressure; NIHSS, NIH stroke scale; TIA, transient ischemic attack.

### Table 2 Ordinal logistic regression analysis for initial severity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95%CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of carotid stenosis</td>
<td>2.20 (1.55 to 3.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial disease</td>
<td>1.93 (1.18 to 3.17)</td>
<td>0.009</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>1.13 (1.06 to 1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>0.37 (0.17 to 0.82)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack.
Very few studies have described the END risk in patients with carotid occlusions. To our knowledge, this is the first study to analyse the factors that might influence END development in patients with symptomatic carotid atherosclerosis. In our cohort, the degree of carotid stenosis and the existence of preceding TIA were the main predictive factors. Initial MAP was also independently associated.

Our results are very similar to those from a recent large study that showed a higher rate of neurological worsening/recurrence, in-hospital death and poor functional outcome at discharge in patients with carotid occlusion compared with severe stenosis.6 However, that study did not clearly define neurological worsening or analyse other related factors.

Whereas recurrent emboli are more likely implicated in END of high-risk stenosis, in patients with carotid occlusions the haemodynamic factors that result in infarction of the oligemia tissue may be more crucial.22 Nevertheless, the coexistence of embolic and haemodynamic mechanisms is frequent in this stroke subtype and may have a synergistic effect with delayed washout of microemboli material in patients with haemodynamic failure.23

Recent TIA has been associated with high risk of early stroke, possibly because of repeated emboli, poor collateral circulation or impaired cerebral autoregulation.24 Finally, initial hypertension has been associated with END in previous studies,21,25 as are acute BP drops during the acute phase.26 Elevated BP, a protective mechanism to maintain cerebral perfusion after a stroke,25 might be a marker of haemodynamic failure of other compensatory mechanisms and therefore a predictor of END.

This study has limitations. We did not perform vasoreactivity tests or perfusion imaging in the acute phase to assess the contribution of the haemodynamic status to the development of severe strokes or END. Moreover, the influence of collateral filling on the outcomes could not be determined. BP was registered for each patient only on admission; we did not register BP when patients suffered END to analyse potential changes. We did not analyse acute treatments because of the different strategies used in the study (thrombolysis, thrombectomy, antiplatelets and anticoagulants). Due to the low number of patients we could not assess initial severity and END risk in patients presenting with a high degree of stenosis and near-occlusion. In endarterectomy trials, patients with near-occlusion have shown a lower stroke recurrence risk than patients with a high degree of stenosis without near-occlusion; however, little is known about the acute stroke phase in this subgroup.27 Future studies should focus on this topic.

**CONCLUSIONS**

Although strokes due to significant symptomatic carotid atherosclerosis are generally of mild severity, degree of carotid stenosis, concomitant intracranial occlusions and increased initial glucose levels are associated with higher severity. Preceding TIA is associated with lower severity. Degree of stenosis is also a determining factor in the END that occurs in many patients. Other related factors are previous TIA and initial BP.

Ultra-early assessment of the arterial status helps to select patients that might benefit from very careful monitoring during the first days following stroke.

**Contributors** EC-G is the principal author and corresponding author, and is responsible for ensuring that author contributions and full disclosures appear on the submitted, revised and final accepted manuscript and that the page proofs reflect the author contributions and disclosures listed. SJ has contributed to data.
acquisition, writing for content and study supervision. AO has contributed to study design, analysis and data interpretation, and revising the manuscript. AR-C has contributed to data acquisition. EG-S has contributed to study coordination. CS has contributed to study design, interpretation of data and manuscript revision.

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