Distribution and Outcome of Symptomatic Stenoses and Occlusions in Patients With Acute Cerebral Ischemia

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**Objective:** To describe the distribution of steno-occlusive disease and the associated rate of recurrence in patients with acute cerebral ischemia.

**Design:** An inception cohort was prospectively recruited after an index event and followed up to assess recurrent stroke and death up to 1 year after the event.

**Setting:** Eleven German departments of neurology with acute stroke units.

**Patients:** A total of 4157 patients who experienced an acute ischemic stroke or a transient ischemic attack and had complete cerebrovascular examination results. Follow-up information could be obtained in 85.3% of these patients.

**Results:** Symptomatic vessel occlusions were associated with a high mortality rate and were found most often in the proximal internal carotid artery (6.5% of patients), the M1 segment of the middle cerebral artery (3.7%), and the vertebral artery (3.0%). Symptomatic stenosis of 50% to 99% of the internal carotid artery was found in 308 patients (7.4%), and 272 patients (6.5%) had symptomatic intracranial stenosis. The highest rates of recurrent stroke during the first 3 days occurred in patients with symptomatic carotid and intracranial occlusions. Overall, 82 (8.0%) of 1027 patients with symptomatic cerebrovascular disease experienced a recurrent stroke between day 4 and 1 year, but no significant differences in recurrent stroke rates could be found when comparing different locations of steno-occlusive disease.

**Conclusions:** Our study provides representative data on the distribution and outcome of steno-occlusive disease in patients with acute cerebral ischemia. In contrast to prior studies in more selected populations, the rate of recurrent stroke in patients with symptomatic intracranial stenosis was not elevated compared with that of patients without steno-occlusive disease.

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Since the introduction of noninvasive vascular diagnostic examinations, several observational and interventional studies have investigated risk factors and outcome of symptomatic cerebrovascular steno-occlusive disease. Race and sex could be consistently identified as independent predictors of the location (intracranial vs extracranial) of cerebral arteriosclerosis. Recently, the Warfarin-Aspirin Symptomatic Intracranial Disease study (WASID) showed no advantage of oral anticoagulation over high-dose aspirin in patients with symptomatic intracranial arterial stenosis. Nevertheless, the rate of ischemic stroke in that trial (20.4% in the aspirin group and 17.0% in the warfarin group during a mean follow-up of 1.8 years) was substantially higher than in other trials of secondary prevention of stroke in which aspirin or warfarin was evaluated, suggesting that intracranial stenosis is a high-risk disease for which alternative therapies are needed. Considering the existence of newer antiplatelet agents and fixed antiplatelet combinations and the fast development of intracranial angioplasty with and without stenting as alternatives to medical preventive treatment, knowledge about the natural recurrence rate in patients with intracranial stenosis is of particular interest. However, clinical interventional studies bear an inherent selection bias, and, to our knowledge, only 1 hospital-based study in a Chinese population has compared the outcome of patients with various forms of cerebrovascular steno-occlusive disease. We, therefore, investigated the exact location and outcome of cerebrovascular steno-occlusive lesions in a large, multicenter, hospital-based cohort of patients with acute cerebral ischemia.
This study was part of a prospective validation of prognostic models for acute ischemic stroke that has been previously published. Enrollment of patients started on July 1, 2000, and was terminated on March 15, 2002. The 11 participating neurological departments (a complete list of members of the German Stroke Collaboration appears on page 1290) documented all patients admitted within 24 hours after an acute cerebrovascular ischemic event (ie, an ischemic stroke or a transient ischemic attack [TIA]). After the exclusion of 36 patients without cerebral imaging data to rule out primary intracerebral hemorrhage and other causes mimicking cerebral ischemia, 4637 patients were included in this analysis. Patients or their next of kin were informed about study participation, and informed written consent was obtained to forward personal data to the coordinating center. Data collection and management were approved by the Ethics Committee of the University of Duisburg-Essen, and aspects of data safety were approved by the responsible data protection state representative. Definitions of risk factors and comorbid conditions and data management have been previously described.

A complete cerebrovascular workup included conventional angiography, magnetic resonance angiography, or combined extracranial Doppler/duplex and transcranial Doppler/computed tomographic angiography. The criteria for quantification of stenosis depended on the examination technique and corresponded to frequently used reference values. Occlusion or stenosis of 50% or greater diameter reduction of the vertebral common carotid artery, the proximal internal carotid artery with 3 categories of stenosis (50%-69%, 70%-89%, and 90%-99%), the distal internal carotid artery (from the extracranial skull base to the intracranial bifurcation), the middle cerebral artery (main stem [M1] and proximal [M2 or M3] branches), the anterior cerebral artery, the posterior cerebral artery, or the basilar artery was diagnosed as being symptomatic by the treating neurologist if there was a cerebral infarction on computed tomographic/magnetic resonance imaging or (in the absence of a visible infarction) if clinical symptoms matched the supplied brain territory of the affected artery. According to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, a symptomatic stenosis or occlusion was classified as large-artery atherosclerosis (LAA) when no concurrent stroke causes were found. Early recurrent cerebrovascular ischemia was defined as sudden worsening of neurological deficits with exclusion of intracerebral hemorrhage by cerebral imaging in case of persistent symptoms. In addition, recurrent TIA or stroke was assessed during follow-up performed predominantly via telephone interview by the coordinating center and blinded to baseline status and cerebrovascular pathological features. Follow-up was performed by the admitting hospital, if the patient had not given consent that personal data could be forwarded to the coordinating center. Outcome was assessed using the Barthel Index at 100 days (mean [SD], 107 [21] days) and 1 year (mean [SD], 371 [64] days) after the event or by confirmation of death. If patients self-reported a recurrent TIA or stroke, confirmation was sought from the treating general practitioner. If no follow-up information could be obtained from the patient, relatives, or the treating general practitioner, a query was sent to the local death registry. No complete follow-up information could be obtained from 231 (18.4%) of 1258 patients with steno-occlusive disease, which was mainly because of limited central funding and lack of staff in the participating hospitals. Patients without complete follow-up information were significantly older (P<.001) and had more severe initial neurological deficits (P<.001) than patients with complete follow-up information.

Figure. Patient inclusion chart.
## Table. Baseline Characteristics and Outcomes of Patients With Symptomatic Cerebrovascular Steno-occlusive Disease*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carotid Artery (CCA/ICA) Stenosis</th>
<th>MCA (M1 Segment) Occlusion</th>
<th>Basilar Artery Occlusion</th>
<th>Intracranial Stenosis</th>
<th>Any Steno-occlusive Disease</th>
<th>All Patients With Complete Workup Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of patients</td>
<td>379 (9.1)</td>
<td>366 (8.8)</td>
<td>153 (3.7)</td>
<td>48 (1.2)</td>
<td>272 (6.5)</td>
<td>1258 (30.3)</td>
</tr>
<tr>
<td>Age, mean (median), y</td>
<td>70 (71)‡</td>
<td>66 (65)‖</td>
<td>64 (65)‡</td>
<td>65 (67)</td>
<td>67 (70)</td>
<td>67 (69)</td>
</tr>
<tr>
<td>Female sex</td>
<td>32.7¶</td>
<td>39.1</td>
<td>45.8</td>
<td>39.6</td>
<td>36.0¶</td>
<td>36.4¶</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>72.3</td>
<td>70.5</td>
<td>60.8¶</td>
<td>62.5</td>
<td>70.6</td>
<td>69.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27.2</td>
<td>21.0</td>
<td>14.4‡</td>
<td>25.0</td>
<td>28.3</td>
<td>24.7</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>40.1‡</td>
<td>26.8‡</td>
<td>22.2‡</td>
<td>35.4</td>
<td>30.1</td>
<td>31.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>27.2</td>
<td>33.0‡</td>
<td>24.8</td>
<td>25.5</td>
<td>22.5</td>
<td>25.9</td>
</tr>
<tr>
<td>History of stroke</td>
<td>31.4‡</td>
<td>24.0</td>
<td>14.4‡</td>
<td>18.8</td>
<td>23.9</td>
<td>23.8</td>
</tr>
<tr>
<td>History of coronary disease</td>
<td>29.0¶</td>
<td>26.0</td>
<td>18.3</td>
<td>18.8</td>
<td>28.7¶</td>
<td>26.0¶</td>
</tr>
<tr>
<td>MCA large cortical infarct</td>
<td>44.5¶</td>
<td>66.4¶</td>
<td>76.5¶</td>
<td>4.2¶</td>
<td>35.7¶</td>
<td>44.6¶</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>26.6</td>
<td>7.9‡</td>
<td>1.3¶</td>
<td>10.6</td>
<td>22.5</td>
<td>15.6¶</td>
</tr>
<tr>
<td>NIHSS score at hospital admission, median</td>
<td>4</td>
<td>12‡</td>
<td>16‡</td>
<td>9‡</td>
<td>6‡</td>
<td>7‡</td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>67.8¶</td>
<td>47.3‡</td>
<td>28.8¶</td>
<td>41.7¶</td>
<td>57.4¶</td>
<td>49.2¶</td>
</tr>
<tr>
<td>Cardioembolic cause</td>
<td>6.3¶</td>
<td>19.9¶</td>
<td>42.5¶</td>
<td>14.6¶</td>
<td>15.4¶</td>
<td>18.1¶</td>
</tr>
<tr>
<td>Early recurrent ischemia</td>
<td>4.7</td>
<td>7.4¶</td>
<td>9.8¶</td>
<td>14.6¶</td>
<td>4.4</td>
<td>6.0¶</td>
</tr>
<tr>
<td>BI ≥95 after 100 d‡</td>
<td>46.1</td>
<td>21.6¶</td>
<td>10.5¶</td>
<td>14.0¶</td>
<td>44.6</td>
<td>36.1¶</td>
</tr>
<tr>
<td>Death</td>
<td>5.4</td>
<td>21.2¶</td>
<td>21.4¶</td>
<td>44.7¶</td>
<td>10.1</td>
<td>15.6¶</td>
</tr>
<tr>
<td>Within 100 d§</td>
<td>9.5</td>
<td>21.7¶</td>
<td>21.4¶</td>
<td>44.7¶</td>
<td>10.1</td>
<td>15.6¶</td>
</tr>
<tr>
<td>Within 1 y</td>
<td></td>
<td></td>
<td>13.6</td>
<td>26.5¶</td>
<td>27.4¶</td>
<td>46.8¶</td>
</tr>
<tr>
<td>TIA after 4 d to 1 y¶</td>
<td>5.1</td>
<td>3.8</td>
<td>5.4</td>
<td>3.0</td>
<td>3.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Stroke after 4 d to 1 y¶</td>
<td>6.3</td>
<td>10.0 to 8.0</td>
<td>8.0</td>
<td>9.1</td>
<td>5.3</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Abbreviations: BI, Barthel Index; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

*Data are given as percentage of each group unless otherwise indicated.
†Significant at P<.05 compared with patients without that particular vessel involved.
‡Data for 15.4% of patients were missing.
§Data for 6.8% of patients were missing.
¶Data for 8.0% of patients were missing.
‖Data for 14.7% of patients were missing.

bral artery, 123 patients (3.0%); of the basilar artery, 49 patients (1.2%); and of the posterior cerebral artery, 12 patients (0.3%). Symptomatic stenosis of 50% or greater of the common carotid artery was found in 26 patients (0.6%); of the proximal internal carotid artery, 308 patients (7.4%); of the distal carotid artery, 69 patients (1.7%); of the middle cerebral artery (M1 segment), 93 patients (2.2%); of the middle cerebral artery (M2 segment), 55 patients (1.3%); of the anterior cerebral artery, 2 patients (0.0%); of the basilar artery, 50 patients (1.2%); and of the posterior cerebral artery, 17 patients (0.4%). Stenosis of the internal carotid artery was graded as 50% to 69% in 111 patients (2.7%), as 70% to 89% in 118 patients (2.8%), and as greater than or equal to 90% in 71 patients (1.7%) (no grading was available in 8 patients). Sixty (7.5%) of 795 patients with extracranial steno-occlusive disease had an additional intracranial stenosis, and 90 patients (11.3%) had an additional intracranial vessel occlusion. An additional middle cerebral artery occlusion was present in 10 (2.5%) of 395 patients with carotid artery stenosis of 50% or greater and in 52 (14.2%) of 366 patients with carotid artery occlusion. The distribution of symptomatic steno-occlusive disease and its association with risk factors and baseline characteristics of patients are presented in the Table.

Early recurrent cerebral ischemia during the first 72 hours after hospital admission was observed in 144 patients (3.5%), which was significantly more frequent in patients with basilar (14.6%), middle cerebral (9.8%), and carotid (7.4%) artery occlusion. The overall rate of recurrent stroke between day 4 until 1 year after the event was 8.0% and, like the rate of TIA (3.6%), was not significantly different between patients with various locations or degree of steno-occlusive disease (Table). When we considered only those patients with a classification of symptomatic LAA, the rate of recurrent stroke between day 4 until 1 year after the event was 6.9% in 216 patients with stenosis of the carotid arteries (vs 5.0% in 100 patients with causes other than LAA, P = .62) and 6.1% in 132 patients with symptomatic intracranial stenosis (vs .4% in 95 patients without a classification of LAA, P = .77). Carotid endarterectomy or angioplasty within 1 year after the event was reported by 44.0% of all patients with an internal carotid stenosis of greater than or equal to 70% and by 13.4% of patients with an initial carotid stenosis of 50% to 69%. After 1 year, 230 (19.9%) of 1157 patients with symptomatic cerebrovascular disease had died (no information on the survival status of 101 patients could be obtained). The highest mortality was observed in patients with occlusion of the basilar or middle cerebral artery and the common carotid and internal carotid artery (Table).
The German Stroke Study Collaboration includes the following collaborators, all from neurology departments at their affiliations, all in Germany: Christoph Hagemeister, MD, Krankenanstalten Gilead, Bielefeld; Christoph Kley, MD, Rheinische Kliniken Bonn, Bonn; Panagiotis Kostopoulos, MD, Universitätsklinikum des Saarlandes, Homburg; Vera Willig, MD, Universitätsklinikum Jena, Jena; Michael Goertler, MD, Universitätsklinikum Magdeburg, Magdeburg; Joerg Glahn, MD, Klinikum Minden, Minden; Kai Aulich, MD, Städtisches Krankenhaus Harlaching, München; Antje Kloth, MD, Universitätsklinik Rostock, Rostock; Thomas Mieck, MD, Bürgerhospital, Stuttgart; Matthias Riepe, MD, Universitätsklinikum Ulm, Ulm; Vesna Zegarac, MD, Universitätsklinik Essen, Essen.

In conclusion, to our knowledge, our study provides the first representative distribution and outcome data of extracranial and intracranial steno-occlusive disease in consecutive white patients with acute cerebral ischemia. Although patients with symptomatic vessel occlusion had an elevated mortality, the risk of recurrent stroke cohort, the highest rate of classic cardiovascular risk factors was found in patients with symptomatic carotid artery disease. Compared with patients with symptomatic extracranial or intracranial stenosis, patients with any symptomatic vessel occlusion had a greater initial stroke severity, had a less likely history of a preceding TIA, and were less often classified as having LAA according to TOAST criteria. The highest rate of LAA was supposed in patients with high-grade internal carotid stenosis, of whom 44.0% subsequently underwent carotid endarterectomy or carotid angioplasty with stenting. Because of the short follow-up, no difference in the rate of recurrent stroke could be observed in patients with and without carotid endarterectomy or stenting. Symptomatic intracranial stenosis was found in 6.5% of all patients, which is substantially lower than the percentage reported in Asian populations and comparable to that in racially mixed US populations.2,3,7,17 On the other hand, the rate of combined carotid artery stenosis and intracranial stenosis was higher than that reported from the North American Symptomatic Carotid Endarterectomy Trial (NASCET),18 which observed intracranial artery stenosis of greater than 50% in 0.9% of patients with TIA or minor stroke and symptomatic extracranial carotid artery stenosis.

Early recurrent cerebral ischemia within the first 3 days was significantly more frequent in patients with symptomatic vessel occlusion compared with patients without vessel occlusion, which may reflect hemodynamic insufficiency in vascular borderline territories. In contrast, the recurrence rate between day 4 and 1 year was not significantly different in patients with various steno-occlusive locations and without steno-occlusive disease. Also, in consideration of different imaging modalities and of the predominantly noninvasive imaging in our study, the overall recurrent stroke rates of 4.4% within the first 3 days and 3.3% between day 4 and 1 year in patients with an intracranial stenosis are substantially lower than those reported in the WASID trial and in 2 case series of patients with symptomatic middle cerebral artery stenosis.6,19,20 Even when we considered only patients with symptomatic intracranial stenosis and a classification of LAA, the resulting recurrent stroke rate of 6.1% between day 4 and 1 year remains similar to all patients with complete follow-up information. Unfortunately, we had no information on serum C-reactive protein levels, which have been suggested to predict further cerebral ischemic events in patients with symptomatic intracranial large-artery occlusive disease.21 No effects of differential secondary prevention strategies were investigated because any differences would have been undetectable given the efficacy known from randomized trials. Mortality up to 1 year was highest in patients with basilar artery occlusion, which corresponds well to several case series22-24 but is markedly higher than that reported by the New England Medical Center Posterior Circulation Registry.25

In conclusion, to our knowledge, our study provides the first representative distribution and outcome data of extracranial and intracranial steno-occlusive disease in consecutive white patients with acute cerebral ischemia. Although patients with symptomatic vessel occlusions had an elevated mortality, the risk of recurrent stroke...
in patients with symptomatic intracranial stenosis generally does not seem elevated compared with that of patients without steno-occlusive disease. This should influence decisions about invasive treatment in these patients.

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REFERENCES


Announcement

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