Intracranial Internal Carotid Artery Stenosis:
Longterm Prognosis

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SUMMARY Sixty-six patients with ≥50% stenosis of an intracranial internal carotid artery (IICA) were followed-up for an average of 3.9 years. Eighty patients (27.3%) experienced ischemic events; 8 (12.1%) had isolated TIA and 10 (15.2%) a stroke. The observed stroke rate for patients 35 years and older was 13 times the expected infarction rate for a normal population. Patients with tandem extracranial stenosis had a greater risk of stroke than patients with isolated IICA stenosis. Thirty-three patients (50%) died during follow-up and 55% of all deaths were cardiac related. The observed 5 year survival rate was 60% compared to an expected rate of 87%. Patients with ICA stenosis had a higher risk of stroke and death compared to a previously reported referral population with ICA occlusion. IICA stenosis is a marker of extensive cerebrovascular and systemic atherosclerotic disease, especially coronary artery disease.

EXTRACRANIAL TO INTRACRANIAL (EC/IC) ARTERIAL BYPASS surgery is usually done for one of three angiographic lesions: internal carotid artery (ICA) occlusion, intracranial ICA (IICA) stenosis, or middle cerebral artery (MCA) stenosis/occlusion. While there is some information regarding the long-term risk of stroke in patients with ICA occlusion1 or MCA stenosis,2 the prognosis for atherosclerotic stenosis of the IICA is less clear. Since this information is needed to help evaluate the therapeutic effectiveness of EC/IC arterial bypass surgery, we studied the risk of stroke and death in a population with angiographically proven moderate or severe stenosis of an IICA.

Methods

The cerebral angiographic records of patients seen at the Cleveland Clinic from 1966 through 1977 were reviewed. The angiographic films of all patients with reported stenosis of an IICA were then examined and 69 patients with at least 50% stenosis of an IICA were selected for follow-up. The degree of stenosis was defined as the maximal luminal compromise in any single angiographic plane. Stenoses were localized as follows: intrapetrous (temporal bone to foramen lacerum); intracavernous (foramen lacerum to anterior clinoid); supracavernous (above anterior clinoid). Concomitant stenosis of the extracranial ICA (EICA) and other brain vessels was recorded. Patients with tandem lesions of the EICA were included since isolated IICA stenosis proved too uncommon to permit acquisition of adequate follow-up data.

Follow-up dated from the time of angiography and was accomplished using available Cleveland Clinic records, telephone interviews and/or standardized questionnaires. End points were death, stroke or the performance of EC/IC arterial bypass surgery. Transient ischemic attacks (TIA) or the performance of carotid endarterectomy (CE) were noted but were not sufficient reasons for stopping follow-up. None of the strokes during follow-up were complications of CE. Actuarial methods were used to calculate the net survival during follow-up.3,4 The Kaplan-Meier product limit method,5 in which an estimate is calculated at each unique time of stroke, was used to determine cumulative stroke risk. Original data from a previously reported referral population with ICA occlusion were used for comparing the relative risks of stroke and death for our patients with IICA stenosis.

Results

Follow-up averaged 3.9 years and was achieved in 66 patients (95.7%). The mean age of the 50 males and 16 females at the time of angiography was 61.5 years. The sites of IICA stenosis were: intrapetrous, 14; intracavernous 65; supracavernous, 6. Nineteen patients
had bilateral IICA stenosis. Of the 85 IICA stenoses identified, 53 lesions (36 patients) had tandem EICA stenosis (≥ 50%, 24; < 50%, 29) with or without ulceration, and 32 lesions (30 patients) represented isolated IICA stenosis. Twenty-four patients (36.4%) had mild contralateral IICA disease ranging from diffuse irregularity to stenosis of less than 50%. Other cerebrovascular lesions included: ≥ 50% contralateral EICA stenosis or occlusion, 17 patients (25.8%); moderate MCA stenosis, 2 patients (3%); anterior cerebral artery stenosis or occlusion, 2 patients (3%); known severe unilateral vertebral artery stenosis or occlusion, 5 patients (7.6%); known basilar artery occlusion, 1 patient (1.5%).

Forty-six patients (70%) presented with ischemic symptoms, 24 with TIA alone (17 ICA territory) and 22 with infarction (17 ICA territory). Twenty-seven patients (41% of total population) had ischemic symptoms ipsilateral to an IICA stenosis, 16 with isolated TIA and 11 with an ICA territory infarct. However, among these 27 patients 16 had a tandem EICA stenosis (≥ 50%, 8; < 50%, 8) so that IICA stenosis was the only apparent cause of ischemic symptoms in 11 patients (16.7% of total population). Among the patients presenting with brain infarction, the stroke was severe in one patient and mild or moderate in 21 patients. The median time from stroke to angiography was 11 months. Among patients with TIA, the onset of attacks before angiography ranged from 3 years to 15 days with a median interval of 5 months.

Angiography was done in 20 patients for a variety of other reasons: asymptomatic carotid bruit, 13; encephalopathy, 2; dizziness, 2; seizures, 2; cranial nerve palsies, 1.

A list of associated conditions in our patient population is given in table 1. Thirty-eight patients (57.6%) had severe coronary artery disease. This was documented by coronary angiography in 29 patients. Twenty-one patients had undergone coronary artery bypass surgery and 24 patients had experienced a myocardial infarction.

During the initial hospitalization CE was performed on 21 patients (31.8%). Eleven of these patients had ipsilateral IICA stenosis, 6 of whom had experienced ipsilateral TIA. At the time of discharge 24 patients were receiving antiplatelet therapy (aspirin, 20; aspirin plus dipyridamole, 4) and seven were receiving anticoagulant therapy.

During follow-up 18 patients (27.3%) experienced one or more ischemic events. Eights patients (12.1%) had isolated TIA (all ICA territory) and 10 patients (15.2%) had a stroke (8 ICA territory), presumably an infarct in 4 and definitely so in 6. Six of the patients with stroke during follow-up also experienced TIA, all in the same vascular territory as the stroke. Fifteen of the 18 patients who experienced ischemic symptoms in follow-up had ischemic events prior to angiography, and the pre and post-angiography events occurred in the same vascular territory in 10 of these patients.

Seven of the 8 patients with isolated TIA in follow-up had ipsilateral IICA stenosis on their reference angiogram. Among the 7 patients, 5 had tandem EICA stenosis (≥ 50%, 2; < 50%, 3). One patient with a > 50% tandem EICA lesion had undergone CE. Follow-up angiography 7.5 months later demonstrated recurrent mild IICA stenosis with ulceration which prompted a repeat CE. The 2 patients without tandem EICA lesions had repeat angiography. The EICA was still normal 3.5 years later in one patient; the other had mild EICA disease after 2.8 years; both patients showed mild progression of their IICA stenosis. Hence, in only 1 of the 8 patients with isolated TIA during follow-up was IICA stenosis the only apparent cause of the ischemic symptoms. Five of these 8 patients were receiving medical treatment (antiplatelet, 4; anticoagulation, 1) at the time of their follow-up TIA.

The median time from angiography to stroke was 2.5 years (range, 1 day to 6.6 years). Although the average stroke rate per year was 3.5% at the fourth year, the risk varied greatly by year of follow-up. For example, the average stroke rate was 5.2% per year by the sixth year of follow-up (fig. 1). The observed stroke rate for patients 35 years and older was 13 times the expected infarction rate for a normal population with a similar age and sex distribution (table 2). The difference was most striking in the age group from 35 through 54 years. Of a total of 10 strokes in all distributions, 2 occurred among 30 patients (7%) without tandem EICA stenosis on reference angiography while 8 strokes occurred among 36 patients (22%) with tandem stenosis (p = 0.08). In 5 of the 8 patients with stroke and a tandem lesion the extracranial stenosis was less than 50%.

### Table 1

<table>
<thead>
<tr>
<th>Associated condition</th>
<th>%</th>
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<tbody>
<tr>
<td>Coronary artery disease</td>
<td>57.6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>50.0</td>
</tr>
<tr>
<td>Hypertension (&gt; 150/90)</td>
<td>39.4</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15.2</td>
</tr>
</tbody>
</table>

![Figure 1. Cumulative risk of stroke for 66 patients with ≥ 50% intracranial internal carotid artery stenosis.](http://stroke.ahajournals.org/)
Eight of the 10 patients with stroke in follow-up had ipsilateral IICA stenosis on their reference angiogram and in 6 there was a tandem EICA stenosis (≥ 50%, 2; < 50%, 4). One patient with a mild tandem EICA lesion underwent CE; follow-up angiography 6.8 years later demonstrated occlusion at the previous CE site and progression of contralateral mild EICA stenosis to severe stenosis. One patient had undergone a prior CE and had a normal extracranial intravenous digital subtraction angiogram 4.3 years later. No follow-up angiograms were performed on the 2 patients with isolated IICA stenosis on the reference angiogram. Therefore, IICA stenosis was the only apparent cause for 2 of the 10 strokes occurring in follow-up. Five of the 10 patients were receiving antiplatelet therapy when their follow-up stroke occurred.

There were 33 deaths (50%) during follow-up. The observed 5 year survival rate on an actuarial basis was 60% compared to an expected rate of 87% in a normal population (fig. 2). Eighteen deaths (54.6% of all deaths) had known severe coronary artery disease and 7 had undergone coronary bypass surgery. There were no known stroke deaths.

Except for the first year after angiography, the proportion of patients surviving with IICA stenosis was significantly lower than for a group of previously reported patients with ICA occlusion (table 3). Although the observed stroke rate for patients 35 years and older with IICA stenosis was 13 times the expected rate compared to 8 times for patients with ICA occlusion, this difference is not statistically significant (p = 0.19).

Discussion

In the only previous natural history study of IICA stenosis, Meguro et al found a 38% ipsilateral stroke rate among 21 patients followed for 31 months. They also found a high frequency of ipsilateral TIA (14%) and 4 of 8 deaths were cardiac-related. Our results also suggest that IICA stenosis is associated with a high risk of stroke as well as death from cardiac disease. Patients with tandem EICA disease appear to have the greatest stroke risk which probably reflects more advanced atherosclerotic disease. Since it is often difficult to ascribe a cerebral infarction directly to IICA stenosis due to the high frequency of tandem EICA disease and the lack of follow-up angiography, IICA stenosis is best viewed as a marker of extensive cerebrovascular and systemic atherosclerotic disease, especially coronary artery disease.

In the Joint Study of Extracranial Arterial Occlusion,9 of 4748 patients studied ICA occlusion (extracranial plus intracranial) accounted for 52.5% of the angiographic lesions whereas IICA stenosis accounted for 13.3% of the lesions and MCA stenosis or occlusion for 11.9%. Pathologic studies indicate that intracranial atherosclerosis develops later and is less severe than atherosclerotic disease in the aorta, coronary arteries or extracranial carotid arteries.10,11 Fisher et al found that calcified plaques of the carotid siphon region were common but significant stenosis of the ICA intracranially was rare.

Based on limited data, IICA stenosis appears to carry a greater risk of stroke and death during follow-up than either ICA occlusion or MCA stenosis. Many, but

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**TABLE 2** Incidence of Stroke for 66 Patients with ≥ 50% Intracranial Internal Carotid Artery Stenosis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Patients with stroke</th>
<th>Person years</th>
<th>Per 100,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-54</td>
<td>4</td>
<td>56</td>
<td>7143</td>
</tr>
<tr>
<td>55-64</td>
<td>4</td>
<td>107</td>
<td>3738</td>
</tr>
<tr>
<td>65-74</td>
<td>2</td>
<td>56</td>
<td>3571</td>
</tr>
<tr>
<td>≥ 75</td>
<td>0</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>≥ 35</td>
<td>10</td>
<td>233</td>
<td>4292</td>
</tr>
</tbody>
</table>

*Based on cerebral-infarction rates for population of Rochester, Minnesota, 1955 to 1969.

†p-values based on Poisson distribution.

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**TABLE 3** Cumulative Proportion of Patients Surviving with Intracranial Internal Carotid Artery Stenosis and Internal Carotid Artery Occlusion

<table>
<thead>
<tr>
<th>Years after angiography</th>
<th>Cumulative proportion surviving ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100 ± 0.00</td>
</tr>
<tr>
<td>1</td>
<td>86 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>3</td>
<td>71 ± 6</td>
</tr>
<tr>
<td>4</td>
<td>62 ± 6</td>
</tr>
<tr>
<td>5</td>
<td>60 ± 6</td>
</tr>
<tr>
<td>6</td>
<td>52 ± 7</td>
</tr>
<tr>
<td>7</td>
<td>44 ± 10</td>
</tr>
</tbody>
</table>

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**FIGURE 2.** Probability of survival for 66 patients with ≥ 50% intracranial internal carotid artery stenosis compared to expected survival rates for a matched normal population.
not all, patients with ICA occlusion remain asymptomatic during longterm follow-up. In one group of patients with ICA occlusion, the longterm risk of stroke was 3\% per year and the relative risk of stroke was greatest in young adults with ICA occlusion. The observed stroke rate for patients age 35 years and older with ICA occlusion was 8 times the expected rate in a normal population. Our patients with IICA stenosis had an increased risk of stroke and death compared not only to a normal population but also to this group of patients with ICA occlusion. MCA disease may carry the most benign prognosis of these three angiographic lesions. MCA occlusion is more often embolic than atherothrombotic. Patients with atherosclerotic stenosis of the MCA appear to do well on medical therapy during longterm follow-up.

No conclusions regarding the relative efficacy of various treatments for patients with IICA stenosis can be made from our data. The results of the Cooperative Extracranial to Intracranial Arterial Anastomosis Study should shed further light on the natural history of these angiographic lesions and should determine whether EC/IC arterial bypass surgery has a favorable impact on the longterm stroke and death rates.

Acknowledgment
The authors thank Sarah Forsythe for statistical assistance.

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