Population-Based Study of Symptomatic Internal Carotid Artery Occlusion
Incidence and Long-Term Follow-Up

Matthew L. Flaherty, MD; Kelly D. Flemming, MD; Robyn McClelland, PhD; Neal W. Jorgensen, BS; Robert D. Brown Jr, MD, MPH

Background and Purpose—Internal carotid artery (ICA) occlusion is an important cause of transient ischemic attack (TIA) and cerebral infarction. There are no previous population-based natural history studies evaluating outcome after symptomatic ICA occlusion (SICAO).

Methods—We performed a retrospective, population-based study of SICAO. All Olmsted County (Minnesota) residents with possible SICAO from 1986 to 2000 were identified by cross-referencing appropriate clinical and imaging codes. Inclusion criteria were cerebral infarction or TIA in a carotid distribution and imaging documentation of ipsilateral ICA occlusion <3 months after the index event. Kaplan–Meier estimates were used to calculate the risk of cerebral infarction, myocardial infarction, and death after SICAO.

Results—Seventy-five patients qualified. Annual SICAO incidence was 6 per 100 000 persons (age and gender adjusted to the 2000 US white population). Risk of cerebral infarction during follow-up was 8% at 30 days, 10% at 1 year, and 14% at 5 years. Five of 11 cerebral infarctions occurred within the first week after diagnosis of occlusion. Risk of myocardial infarction was 0% at 30 days, 8% at 1 year, and 24% at 5 years. Risk of death was 7%, 13%, and 29%, respectively.

Conclusions—There may be 15 000 to 20 000 incident cases of SICAO in the United States annually. Risk of cerebral infarction after SICAO is initially high and then stabilizes, whereas risk of myocardial infarction is initially low but gradually increases. Better strategies are needed to reduce early stroke recurrence in this setting. (Stroke. 2004;35:e349-e352.)

Key Words: carotid arteries ■ occlusion ■ cerebral infarction ■ cerebral ischemia, transient

Symptomatic internal carotid artery occlusion (SICAO) is a relatively uncommon but still important cause of transient ischemic attack (TIA) and cerebral infarction. Although SICAO has been the subject of previous studies, most have been limited by referral and selection bias. Furthermore, little data have been provided about the very early (<1 month) risk of adverse events after SICAO. We undertook the first population-based study of SICAO to (1) calculate SICAO incidence rates and (2) determine its natural history in a defined population.

Subjects and Methods

This study was performed under the auspices of the Rochester Epidemiology Project (REP). Most inpatient and outpatient medical care for Olmsted County, Minnesota, residents is provided at either Mayo Medical Center or a non-Mayo-affiliated community hospital and clinic, and virtually all patients in the community have care provided at one of these medical centers during any 3-year period. The medical care data for the few Olmsted County residents receiving some of their medical care at the Veterans Administration Hospital in Minneapolis are also included in the REP database. The comprehensive medical record availability increases the likelihood of essentially complete ascertainment of a specified diagnosis for Olmsted County residents.

We retrospectively identified patients with potential SICAO from 1986 to 2000 by cross-referencing Mayo Clinic radiologic codes for internal carotid artery (ICA) occlusion detected by carotid ultrasound or conventional angiography with all cases of stroke and TIA ascertained in Olmsted County during this period. ICA occlusion identified by magnetic resonance angiography (MRA) was not routinely coded during this period. Although MRA was seldom used independently to diagnose ICA occlusion before 2000, we further cross-referenced clinical codes for TIA, cerebral infarction, and athero-occlusive disease from 1994 to 2000 to identify additional potential patients. All medical records were reviewed by a study physician (M.L.F.).

Study inclusion criteria were cerebral infarction or TIA (hemispheric or retinal) in a carotid distribution and imaging documentation of ipsilateral ICA occlusion <3 months after the index event. Exclusion criteria included iatrogenic ICA occlusion and previously documented ipsilateral ICA occlusion. Among documented risk
factors, coronary artery disease was defined as a history of myocardial infarction (MI), angina, coronary angioplasty, or coronary artery bypass grafting, and dyslipidemia was defined as total cholesterol $>$240, low-density lipoprotein $>$160, high-density lipoprotein $<$40, or pharmacological treatment. In accordance with Joint National Committee 7 guidelines, hypertension was defined as a systolic pressure consistently $>$140 mm Hg or a diastolic pressure consistently $>$90 mm Hg before the index event, or pharmacological treatment. 4

The Kaplan–Meier product limit method was used to estimate the rate of cerebral infarction, MI, death (of any cause), and the combination of cerebral infarction, MI, and death after SICAO. Expected rates of MI were calculated by applying the age- and gender-specific rates observed in the Olmsted County MI cohort to the observed age- and gender-specific person years at risk for the SICAO cohort. 5 Time to recurrent cerebral infarction was compared between the SICAO cohort and the Rochester Stroke and TIA Registry using a Kaplan–Meier plot and accompanying log rank test. 6 The demographic characteristics of Rochester, Minn, and Olmsted County, Minn (which includes Rochester contributing 69% of the county population), are very similar in terms of age, gender, and ethnicity, allowing the valid comparison of relevant incidence rates in Rochester-based studies to those including all Olmsted County residents.

Results

Seventy-five patients met inclusion criteria. Demographic information and baseline risk factors are presented in Table 1. Median follow-up was 4.7 years. The overall incidence rate per 100 000 persons age- and gender-adjusted to the 2000 US white population was 6 (95% CI, 4.6 to 7.3). Age-and gender-specific SICAO incidence rates are presented in Table 2. Kaplan–Meier estimates of adverse outcomes are presented in Table 3. There were 6 ipsilateral and 5 contralateral cerebral infarctions during follow-up. Five of 11 cerebral infarctions occurred within 1 week of imaging confirmation of occlusion.

Kaplan–Meier analysis of cerebral infarction–free survival comparing our SICAO cohort with the Rochester Stroke and TIA Registry showed that recurrence was significantly less common in the SICAO cohort ($P$=0.023 by log rank test). There were 17 MIs during 351 person years of follow-up, a significant excess compared with the 1.8 MIs expected after age and gender matching to the Olmsted County MI incidence cohort ($P<0.001$). 5

Discussion

Given an adjusted incidence rate of 6 per 100 000 persons, one can conservatively attribute 15 000 to 20 000 ischemic events to incident SICAO in the United States annually. This is almost certainly an underestimate because (1) many patients with TIA do not present for medical evaluation, and (2) a sizable minority of patients with cerebral infarction or TIA do not have carotid imaging. 6 The incidence of ischemic stroke caused by large artery stenosis or occlusion in Rochester, Minnesota, is estimated to be 27 per 100 000 persons. 7 Although study methodologies are not directly comparable, our cohort suggests that $\approx 15\%$ of large artery infarctions may as result of ICA occlusion.

The natural history after SICAO in our cohort differs from that of undifferentiated TIA and cerebral infarction patients.

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### Table 1. SICAO Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>66.2 (range 40.4 to 87.6)</td>
</tr>
<tr>
<td>Male/female</td>
<td>55/20 (73/27)</td>
</tr>
</tbody>
</table>

Qualifying event

- Cerebral infarction: 53 (71)
- Cerebral TIA: 11 (15)
- AF: 9 (12)
- AF+cerebral TIA: 2 (3)

Method of diagnosis

- Ultrasound alone: 33 (44)
- Conventional angiography alone: 17 (23)
- >1 modality: 25 (33)
- Diabetes: 16 (21)
- Coronary artery disease: 32 (43)
- Dyslipidemia: 40 (54)
- Prior cerebral infarction: 12 (16)
- Ever smoker: 56 (76)
- Hypertension: 49 (65)
- History of atrial fibrillation: 13 (17)
- Baseline mRS 0–1: 52 (69)
- Baseline mRS 2–3: 23 (31)

AF indicates amaurosis fugax; mRS, modified Rankin score.

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### Table 2. Incidence of SICAO, 1986–2000

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Men</th>
<th>Women</th>
<th>Both Sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population*</td>
<td>Cases</td>
<td>Rate</td>
</tr>
<tr>
<td>0–14</td>
<td>190 423</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>15–24</td>
<td>111 387</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>25–34</td>
<td>149 156</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>35–44</td>
<td>136 490</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>45–54</td>
<td>97 879</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>55–64</td>
<td>64 911</td>
<td>3</td>
<td>4.6</td>
</tr>
<tr>
<td>≥65</td>
<td>104 734</td>
<td>11</td>
<td>10.5</td>
</tr>
<tr>
<td>Total</td>
<td>854 956</td>
<td>20</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Incidence rate per 100 000 persons is adjusted to the 2000 US white population.
Among all TIA patients in Rochester, Minnesota, actuarial risk of cerebral infarction at 1 month, 6 months, 1 year, and 5 years has been estimated to be 7%, 10%, 13%, and 28%, respectively, whereas among cerebral infarction patients, risks were 4%, 9%, 12%, and 29%.8,9 When compared with a cohort of 74 ischemic stroke patients from Rochester with large-vessel etiology (stenosis or occlusion), cerebral infarction risk was lower among SICAO patients (14% versus 40% 5-year risk), whereas mortality was similar (29% versus 32% 5-year mortality).10

Klijn et al have reviewed previous, nonpopulation-based studies of SICAO and calculated a 5.5% annual stroke rate among 1923 patients.1 Many of the studies reviewed excluded patients with major stroke and were conducted when conventional angiography was the only means of SICAO diagnosis. Hankey and Warlow reviewed prospective studies of angiographically proven SICAO, including 1261 patients, and found an average annual cerebral infarction risk of “at least 7%.”22 In our cohort, long-term cerebral infarction risk was lower than reported in most previous SICAO studies. In contrast, the very short-term (<1 week) risk of cerebral infarction after SICAO was considerable.

The cause of recurrent cerebral infarction after SICAO has been the subject of speculation. Recently, attention has focused on hemodynamic failure distal to ICA occlusion. Hemodynamic failure detected by positron-emission tomography (PET) scanning appears to identify a subset of SICAO patients at high risk of subsequent infarction.11 Extracranial-intracranial arterial bypass failed to prevent cerebrovascular insufficiency in SICAO patients studied previously.12 It has been proposed that high risk SICAO patients identified by PET may benefit from bypass.13 Our findings differ from those of Grubb et al, who documented a 19% 2-year cerebral infarction risk among 81 SICAO patients followed prospectively in a trial that provided much of the impetus for the Carotid Occlusion Surgery Study.11 In Grubb’s report, 29.2% of patients with PET-defined hemodynamic failure experienced cerebral infarction during follow-up compared with 5.3% of patients without hemodynamic failure. The lower cerebral infarction risk in our population-based study suggests that the occurrence of hemodynamic failure, with its reported higher cerebral infarction risk, may be less common in the general population than in patients seen at tertiary referral centers.

Our study has several limitations. The population of Olmsted County is nearly 90% white. Although our patient numbers were relatively small, it will be difficult to produce population-based studies with more patients but similar case ascertainment and follow-up, which, in our study, included inpatient and outpatient SICAO and all degrees of stroke severity. Some cases of SICAO (eg, devastating stroke in which no work-up was pursued, patient refusal of testing) will still have been missed. Many of our patients were diagnosed with ICA occlusion by ultrasound. Although very high-grade ICA stenosis cannot always be distinguished from occlusion by duplex ultrasound, these instances should be rare.14

In conclusion, we present the first population-based study of SICAO. Cerebral infarction after SICAO peaks early and then stabilizes. The occurrence of cerebral infarction during follow up is lower than would be expected in a population-based comparison group of patients with all cerebral ischemia mechanisms. MI gradually increased over time, with the occurrence of MI during follow-up being higher than expected. This emphasizes the fact that SICAO is a marker of systemic vascular disease and that attention should be paid to cardiac as well as cerebrovascular screening and risk modification. Management of SICAO patients in the acute setting, when stroke risk is highest, remains unsettled.

Acknowledgments
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References

| TABLE 3. Rates of MI, Stroke, and Death After SICAO |
|----------------|----------------|----------------|----------------|----------------|----------------|
| Event          | Event Ever | 30-Day No. (%) | 6-Month No. (%) | 1-Year No. (%) | 5-Year No. (%) | 5-Year Rates (95% CI) |
| MI             | 17         | 0 (0)           | 3 (4%)          | 5 (8%)         | 13 (24%)       | 11% to 35%         |
| Stroke         | 11         | 6 (8%)          | 7 (10%)         | 7 (10%)        | 9 (14%)        | 5% to 22%          |
| Death          | 31         | 5 (7%)          | 9 (12%)         | 10 (13%)       | 21 (29%)       | 18% to 39%         |
| Combined       | 39         | 9 (12%)         | 16 (21%)        | 18 (24%)       | 32 (45%)       | 32% to 56%         |

All rates are derived from Kaplan–Meier curve of the specified outcome.


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