Long-term Risk of Stroke and Other Vascular Events in Patients With Asymptomatic Carotid Artery Stenosis

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Context: The annual risk of ischemic stroke in patients with asymptomatic carotid artery stenosis is about 2% during the short-term (2-3 years), but the long-term risks of stroke and other vascular events are unknown, although they may affect surgical decision making.

Objective: To evaluate the long-term risk of stroke and other vascular events in patients with asymptomatic carotid artery stenosis.

Design: Cohort study with a median follow-up of 10 years (range, 5-18 years).

Setting: The teaching hospital of the University of Toronto, Toronto, Ontario.

Patients: From the initial cohort of 500 patients, 106 patients with asymptomatic carotid artery stenosis were selected because they had completed at least 5 years of follow-up.

Main Outcome Measures: Ipsilateral stroke, myocardial infarction, and nonstroke vascular death.

Results: The 10- and 15-year actuarial risks of ipsilateral stroke were 5.7% (95% confidence interval [CI], 0%-12%) and 8.7% (95% CI, 1%-17%), respectively, in patients with 0% to 49% internal carotid artery stenosis, and 9.3% (95% CI, 1%-18%) and 16.6% (95% CI, 1%-32%) in patients with 50% to 99% internal carotid artery stenosis. The 10- and 15-year risks of myocardial infarction and nonstroke vascular death were 10.1% (95% CI, 4%-16%) and 24.0% (95% CI, 14%-34%). Age (P = .02), diabetes mellitus (P = .02), and internal carotid artery stenosis of 50% or more (P = .04) were predictive of increased risks of myocardial infarction and nonstroke vascular death. Internal carotid artery stenosis of 50% or more did predict the risk of ipsilateral stroke (P = .003) when all 181 asymptomatic carotid arteries were included.

Conclusions: The annual stroke risk in patients with asymptomatic carotid artery stenosis was low and remained stable during long-term follow-up. Any benefit from carotid surgery is therefore unlikely to increase significantly with long-term follow-up. The high long-term risks of myocardial infarction and nonstroke vascular death suggest that prevention strategies should concentrate on coronary risk more than stroke risk.

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C AROTID ARTERY atherosclerosis is responsible for 20% to 30% of ischemic strokes.1 Recent prospective, randomized multicenter trials have demonstrated the superiority of carotid endarterectomy (CEA) over medical therapy for stroke prevention among patients with previous cerebral ischemic events.2,3 However, the role of CEA in asymptomatic carotid artery stenosis remains controversial, partly because of uncertainty about the natural history of the condition with medical treatment alone.

Endarterectomy reduces the relative risk of ipsilateral stroke and death by about 50%,3,4 but the absolute risk of stroke in patients receiving medical treatment is relatively low. Most natural history studies of asymptomatic carotid artery stenosis have reported an annual risk of ipsilateral stroke of approximately 1% to 2%, depending on the degree of internal carotid artery (ICA) stenosis.5-12 However, follow-up in these studies was usually only 2 to 3 years, and there are few published data on the long-term risks. There are also very few data on the factors that identify asymptomatic patients with a higher-than-average risk of stroke and other vascular outcomes on long-term follow-up who might benefit most from preventive treatment.

To provide more information about long-term risks and risk factors for stroke and other vascular events, we studied pa-
PATIENTS AND METHODS

PATIENTS AND STUDY DESIGN

A total of 106 patients, from an initial cohort of 500 prospectively studied patients, had long-term continuous Doppler follow-up. The study is confined to this subgroup. All patients had annual Doppler and clinical follow-up. This included documentation of putative risk factors for stroke (age, sex, hypertension, diabetes mellitus, and ischemic heart disease). Medications were also recorded, although compliance was not tested. If follow-up visits were missed, patients were telephoned and asked about further clinical events. We recorded the following end points: ipsilateral stroke, ipsilateral transient ischemic attack (TIA), myocardial infarction (MI), CEA, nonstroke vascular death, and nonvascular death. All hospital records were audited at the end of the study. We documented details of all deaths, whenever possible, according to hospital records and autopsy reports. The definition of nonstroke vascular death included death from MI, sudden death, cardiac failure, ruptured aorta, and peripheral vascular disease.

CAROTID ARTERY IMAGING

Patients were examined with 2 generations of Doppler equipment. Both were validated against catheter angiography on an annual basis. Patients enrolled in the study from 1981 through 1991 were examined with continuous-wave carotid Doppler scanning (Dopscan 1050; Carolina Medical Inc, King, NC) using established criteria to estimate the percentage reduction in the cross-sectional area of the carotid arterial lumen. In our laboratory, the technique has a sensitivity of 87% and a specificity of 91% in detecting ICA stenosis of more than 30% compared with conventional angiography. Patients studied from 1991 through 1999 underwent ultrasound testing using a color-coded duplex ultrasound unit (Ultramark-9; ATL Ultrasound, Bothell, Wash), and a high degree of correlation was established between the peak systolic velocity and angiographic measurement of ICA stenosis.

RESULTS

One hundred six patients (44 women; mean±SD age, 64±8 years) were followed for a median of 10 years (range, 5-18 years) for a total of 1010 patient-years of observation. At the end of the study, 1506 Doppler scans were available for analysis. All patients underwent follow-up for 5 years, half for 10 years, 23% for 15 years, and 5% for 18 years. At the baseline, 70% of patients had hypertension, 23% had diabetes, and 11% were smokers.

To determine the differences between patients with complete follow-up (n=106) and those with incomplete follow-up (n=394), we compared the baseline characteristics of the 2 groups (Table 1). The mean age of patients was similar, but there were significantly more men (P=.03) and patients with diabetes (P<.007) in the group with complete follow-up. There were significantly fewer patients with mild (<30%) ICA stenosis but significantly more patients with moderate (30%-74%) and severe (≥75%) stenosis in the group with complete follow-up.

ANALYSIS

In view of the partly retrospective nature of the clinical follow-up, analysis of cerebrovascular outcome events was limited to stroke. Where relevant, the number of recorded TIAs is mentioned in the results, but these events are not included in the formal analyses.

Data were first analyzed for each patient, with each subject categorized according to the most highly stenosed vessel. If the stenoses were identical, the left carotid artery was chosen. To control for events occurring contralateral to the patient's most highly stenosed vessel, and to determine the relationship between plaque progression and ipsilateral stroke, cerebrovascular outcomes for each internal carotid artery were also analyzed separately and event rates were calculated per vessel. Previously symptomatic (ipsilateral stroke or TIA) and/or surgically treated (CEA) arteries were excluded from the analysis. Arteries were censored following the first ipsilateral event (stroke or CEA), but the contralateral asymptomatic artery was still followed.

To study the effect of baseline ICA stenosis on outcome, stenosis was categorized as 0% to 49% or 50% to 99%. Our sample size was insufficient to allow analysis of the degree of stenosis as a continuous variable. Plaque progression was determined according to previously published criteria.

Statistical analysis was performed using SPSS version 10.05 (Statistical Product and Service Solutions Inc, Chicago, Ill). Continuous data were summarized as mean±SD or median (range). We used a t test for comparison of means. In cases when normality and/or equal variance tests failed, the Mann-Whitney test was used. Proportional differences among the groups were evaluated with a χ² test. Event rates over specific follow-up periods were calculated by life-table analysis. Survival curves were calculated by Kaplan-Meier analysis of the time to the first event. Comparison of survival curves was performed with the log-rank test.

ANALYSIS PER PATIENT

The maximum asymptomatic ICA stenosis was less than 30% in 25 patients, 30% to 49% in 23 patients, 50% to 69% in 23 patients, and 70% or more in 33 patients. Eleven strokes occurred during follow-up, all of which were in the carotid territory and 10 of which were ipsilateral to the most stenosed artery. The rate of ipsilateral stroke remained stable up to the maximum follow-up of 18 years (Figure 1). The 10- and 15-year actuarial risks of ipsilateral stroke were 5.7% (95% confidence interval [CI], 0%-12%) and 8.7% (95% CI, 1%-17%), respectively, in patients with 0% to 49% ICA stenosis and 9.3% (95% CI, 1%-18%) and 16.6% (95% CI, 1%-32%) in patients with 50% to 99% ICA stenosis. A TIA occurred in 13 cases, of which 5 were ipsilateral to the most severe stenosis. None
of the clinical risk factors were significant predictors of ipsilateral stroke (Table 2).

Seventeen patients died during follow-up, 2 from stroke and 10 from cardiac causes, and 10 patients had an MI. The 10- and 15-year risks of MI and nonstroke vascular death were 10.1% (95% CI, 4%-16%) and 24.0% (95% CI, 14%-34%), respectively. These risks were higher than the risk of ipsilateral stroke (Figure 1). Nonstroke vascular death were 10.1% (95% CI, 4%-16%) and 24.0% (95% CI, 4%-31%), respectively. These risks were higher than the risk of stroke. Management of patients with asymptomatic carotid artery stenosis should, therefore, concentrate as much on reduction of nonstroke vascular death including age, sex, diabetes, and diabetics of the combined end point of stroke/MI/vascular death.

ANALYSIS PER VESSEL

To increase statistical power and to take into account both carotid arteries, data were reanalyzed calculating the end points for individual arteries. Thirty-one previously symptomatic and/or surgically treated arteries were excluded, leaving 181 arteries in the analysis.

There were 38 CEAs performed, and 29 of these were performed on previously symptomatic arteries initially excluded from the analysis. Therefore, only 9 CEAs were included in our analysis; 2 arteries underwent CEA after TIAs that occurred in asymptomatic vessels during follow-up, and the remaining 7 ICAs were surgically treated for asymptomatic carotid artery stenosis. All 9 CEAs were conducted in arteries with ICA stenosis of more than 60%. Baseline ICA stenosis was 30% or less in 74 arteries, 30% to 49% in 34 arteries, 50% to 69% in 30 arteries, and 70% or more in 43 arteries.

One stroke occurred contralateral to the most severely stenosed asymptomatic ICA. Therefore, there were 11 strokes in the territory of 181 asymptomatic carotid arteries during follow-up. The risk of stroke was significantly higher in arteries with ICA stenosis of 50% to 99% than in those with 0% to 49% stenosis (log-rank=9; \( P = .003 \); Figure 2). For arteries with 50% to 99% stenosis, the 10- and 15-year risks were 8.5% (95% CI, 1%-17%) and 18.0% (95% CI, 4%-31%), respectively. Ipsilateral TIA occurred in the distribution of another 13 ICAs.

Progression of stenosis was documented in 55 ICAs (30%), and stenosis remained stable in 126 arteries. Overall, median baseline ICA stenosis was 35% compared with 50% at the end of follow-up (\( P < .001 \); Mann-Whitney test). Progression of stenosis during the follow-up was not a significant predictor of ipsilateral stroke.

We have shown that the long-term risk of stroke from asymptomatic stenosis is less than 1% per year for stenoses of 50% or more and about 1% per year for stenoses of less than 50%. These results are consistent with previous short-term follow-up studies\(^8\)-\(^13\) and show that the low risk of stroke remains constant with time. This has important implications for surgical treatment because the marginal short-term benefits from CEA do not change during at least the next 10 years, whereas the long-term risks of MI and nonstroke vascular death are greater than the risk of stroke. Management of patients with asymptomatic carotid artery stenosis should, therefore, concentrate as much on reduction of nonstroke vascular risk as on stroke risk.

With the exception of the degree of ipsilateral carotid artery stenosis, baseline clinical characteristics did not predict the risk of stroke on long-term follow-up. The difficulty of predicting the risk of stroke in patients with asymptomatic stenosis has been noted previously.\(^16\) In contrast, and despite similarly small numbers of events, there were several useful predictors of MI and nonstroke vascular death, including age, sex, diabetes, and

### Table 1. Baseline Characteristics of Patients With and Without Complete Follow-up*

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Complete (n = 106)</th>
<th>None (n = 394)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>64</td>
<td>63</td>
<td>.9</td>
</tr>
<tr>
<td>Sex, % F/M</td>
<td>42/58</td>
<td>62/38</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (70)</td>
<td>216 (55)</td>
<td>.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (23)</td>
<td>41 (10)</td>
<td>.007</td>
</tr>
<tr>
<td>ICA stenosis &lt;30%</td>
<td>25 (24)</td>
<td>205 (52)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>ICA stenosis 30%-74%</td>
<td>46 (43)</td>
<td>111 (28)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>ICA stenosis ≥75%</td>
<td>35 (33)</td>
<td>78 (20)</td>
<td>&lt;.001†</td>
</tr>
</tbody>
</table>

*ICA indicates internal carotid artery. Data given as number (percentage) of patients unless otherwise indicated.†A single \( x^2 \) test was conducted across all stenosis categories (\( x^2 = 27.3; P < .001 \)).

![Figure 1. Survival free of ipsilateral stroke (IS) (thick line) and survival free of myocardial infarction (MI) or nonstroke vascular death (NSVD) (thin line) in patients with asymptomatic carotid artery stenosis.](chart1.png)

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the maximum degree of asymptomatic carotid artery stenosis. The predictive value of the severity of asymptomatic carotid artery disease is consistent with our previous report of short-term risk.13

Plaque progression was documented in about one third of our patients. This is higher than reported in other cohorts.11 However, progression of stenosis increases with time,10 and our rate is likely to reflect the long follow-up. In contrast to our previous finding,13 we did not find a relationship between plaque progression and ipsilateral stroke.

Although we consider our results valid, our study population was limited to a subgroup of 106 patients from the initial cohort of 500.13 We selected this group because they had continuous long-term Doppler follow-up, but this may have introduced some degree of selection bias. We cannot exclude the possibility that the risk of stroke and other vascular events was higher in those patients who were not followed up continuously, thereby underestimating the long-term risk. However, baseline risk factor comparison between our cohort and the remainder who had incomplete follow-up shows that patients with complete follow-up were not healthier than those without it. In fact, the higher prevalence of diabetes and the preponderance of men and more severe ICA stenoses in our study cohort produced a bias favoring a poorer prognosis than for those with incomplete follow-up. Therefore, it is less likely that the population of patients without long-term follow-up had higher incidence of stroke, MI, or vascular death.

Also, selection bias is less likely to have had a qualitative effect on risk factor estimates, and these should be more reliable. In some cases, clinical follow-up was obtained retrospectively, so it is possible that we may have missed some minor strokes, which may also have caused underestimation of the stroke risk. These 2 factors that potentially contributed to underestimation of the stroke risk mean that, if anything, more strokes occurred than we calculated. Although our sample size (106 patients with 181 asymptomatic stenoses) was relatively small, and our results must be interpreted with caution, there are currently no other data available on the long-term risks of stroke and other vascular events in patients with asymptomatic carotid artery stenosis.

In the Asymptomatic Carotid Atherosclerosis Study, CEA reduced the relative risk of ipsilateral stroke and operative death by 53% in patients with ICA stenosis of more than 60% with 30-day operative risk of stroke and death of less than 2.3%.7 However, not all centers achieve this low operative risk,19,20 and negative cost-effectiveness is another important consideration.19,21 Our data show that the annual risk of stroke with medical treatment remains consistently low on long-term follow-up, suggesting that any benefit from endarterectomy for asymptomatic carotid artery stenosis is unlikely to increase dramatically with longer follow-up.

The low risk of stroke observed over many years in our patients with asymptomatic carotid artery stenosis, in combination with the continuing long-term risk of MI and nonstroke vascular death, challenges the value of CEA in these patients. Any benefit from carotid surgery is unlikely to increase significantly with long-term follow-up. The high long-term risks of MI and nonstroke vascular death suggest that prevention strategies should concentrate on coronary risk more than stroke risk.

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REFERENCES


