The Case Against Surgery for Asymptomatic Carotid Stenosis

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SUMMARY Asymptomatic cervical bruits with their implication of underlying carotid artery disease, carry an established but low risk of stroke. In spite of the rising numbers of patients subjected to carotid endarterectomy for this condition, there is little evidence that the benefits outweigh the risks.

Outcome data from community studies and the current prospective Toronto study of patients with asymptomatic neck bruits indicate that the annual stroke rate is 1-2%, and the annual cardiac death rate is 2-4%. Published data of the results of carotid surgery suggest that surgical risks outweigh any possible benefits, unless a subgroup with spontaneous stroke risk of at least 5% can be identified.

Although asymptomatic carotid bruits are an established risk factor for ischemic stroke,1,2 the management of asymptomatic patients with carotid bruits and carotid stenosis remains controversial.3,4 Carotid endarterectomy is performed in increasing numbers of patients1 although its efficacy has not been demonstrated convincingly for either asymptomatic or symptomatic disease. Since a requirement of any treatment is that benefits should outweigh risks, the stroke risk reduction after carotid endarterectomy must outweigh the combined hazards of angiography and surgery.

Jonas and Hass5 compared the outcome of patients in operated and unoperated groups of the Extracranial Arterial Occlusion Joint Study,6 and calculated that a stroke complication rate greater than 2.9% is unacceptable for extracranial arterial surgery in symptomatic patients. Since the spontaneous stroke rate in asymptomatic patients with carotid stenosis is less, an even lower surgical complication rate would seem mandatory for successful surgical treatment.

The relatively benign outcome of patients followed in the prospective Toronto Asymptomatic Cervical Bruit (ACB) Study has prompted this evaluation of the factors critical to the efficacy of carotid endarterectomy for asymptomatic carotid stenosis.

Current State of Knowledge

The reported outcome of asymptomatic patients with neck bruits varies widely but the best perspective is obtained from community studies in Evans County1 and Framingham,2 where the overall stroke rates were 2.3% and 1.7% per annum. In addition to increased stroke risk, these patients have an increased cardiac risk, and an overall mortality, from causes other than stroke, of approximately 4% per annum.

The best estimates of the protection afforded by carotid endarterectomy are from studies in patients with transient ischemic attacks (TIAs), figures which may not apply to asymptomatic patients. Both the Extracranial Arterial Occlusion Joint Study6 and the Mayo Clinic7 reported a two-thirds reduction in stroke rates following uncomplicated carotid endarterectomy. The reduced long-term risk is offset by the more immediate complications of surgery. For carotid endarterectomy, surgeons with a high level of expertise achieve peri-operative stroke and/or death rates less than 5% (table 1).8-13 Operative stroke and death occurring with about equal frequency. Angiographic complications should also be considered, but are omitted from further discussion because recent technological refinements have reduced permanent neurological sequelae to well below 1%.14-16

These data are the basis for evaluating the merits of carotid endarterectomy in patients with asymptomatic carotid stenosis.

Selection of Endpoints

If stroke risk alone is considered, the net stroke reduction at three years in the surgical group is 42%, and the 'break-even point' is 13 months (fig. 1). The 'break-even point' is the moment when the number of strokes in each group is equal. A randomized surgical trial would require 1214 patients in each group to achieve a statistically significant result (table 2, trial 1).

If both stroke and death risks are considered (fig. 2), the net (stroke and/or death) risk reduction at three
TABLE 1  Carotid Endarterectomy — Peri-operative Stroke and/or Death Rate

<table>
<thead>
<tr>
<th>Specialised units</th>
<th>Operations</th>
<th>Peri-operative stroke and/or death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleming et al (8)</td>
<td>240</td>
<td>3.2%</td>
</tr>
<tr>
<td>Thompson et al (9)</td>
<td>1286</td>
<td>2.1*</td>
</tr>
<tr>
<td>Ennix et al (10)</td>
<td>1546</td>
<td>4.5</td>
</tr>
<tr>
<td>Allen and Preziosi (11)</td>
<td>154</td>
<td>1.5</td>
</tr>
<tr>
<td>Sundt et al (12)</td>
<td>1145</td>
<td>2.5</td>
</tr>
<tr>
<td>Ferguson (13)</td>
<td>150</td>
<td>2.7</td>
</tr>
<tr>
<td>City-wide experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Springfield, Illinois (17)</td>
<td>228</td>
<td>21.1%</td>
</tr>
<tr>
<td>Cincinnati, Ohio (18)</td>
<td>431</td>
<td>11.4</td>
</tr>
</tbody>
</table>

*Peri-operative mortality only; stroke rate not reported.

years becomes only 6%, the break-even point is 28 months and the required sample size for an endarterectomy trial 3582 in each group (table 2, trial 1). Even if 7000 patients could be recruited, such results would not be clinically important.

The inclusion of mortality in this calculation is debatable as some patients might gamble on their survival to avoid long-term disability from stroke. In an endarterectomy trial fulfilling ethical requirements, deaths must be counted because peri-operative death is a significant hazard. In practice, patients should choose between conservative and surgical treatment on the basis of their personal attitudes toward surgery, stroke and death.

Spontaneous Stroke and Death Risk

Knowledge of the natural history of asymptomatic carotid disease is incomplete. The Evans County1 and Framingham2 studies have determined the overall stroke rate but the relationship between stroke and underlying carotid disease is uncertain. Substantial variation in reported outcome suggests that subgroups do exist within the ACB population. For example,

Cooperman et al17 and Thompson et al10 reported higher spontaneous stroke rates of 3% and 4.3% per annum (respectively), probably because a greater proportion of surgical referrals have carotid stenosis.

Carotid endarterectomy is more acceptable if the spontaneous stroke rate is at least 5% per annum (table 2, trial 2). If the combined risks of stroke and death are considered, the net risk reduction at three years is 26% and the break-even point is 10 months (fig. 3). This effect could produce a dramatic decline in the overall incidence of stroke in the community. A multi-centre randomized trial would require a more feasible total study population of 1206 patients (table 2, trial 2).

Of 500 patients followed for up to 30 months in the Toronto Asymptomatic Cervical Bruit Study, neurological ischemic events have occurred in 28. Twenty-two of 25 patients with carotid events had ipsilateral carotid stenosis. The event rate in patients with internal carotid artery (ICA) stenosis greater than 75% was 15% per annum, compared with 3% per annum in patients with ICA stenosis less than 75% and 2% in patients without carotid stenosis (fig. 4). Patients with progressing lesions had a higher incidence than non-progressors. However, 26 of the 28 patients presented with TIA's and only three of these suffered a stroke. Only two patients presented with stroke without prior

TABLE 2  Predicted Net Risk Reduction from Carotid Endarterectomy for Asymptomatic Carotid Stenosis and Sample Size Requirements for a Randomized Trial* (endarterectomy vs conservative management)

<table>
<thead>
<tr>
<th>Trial No.</th>
<th>Spontaneous event rate (per annum)</th>
<th>Endpoint stroke</th>
<th>Endpoint stroke and/or death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peri-operative complication rate</td>
<td>Surgical stroke risk reduction</td>
<td>3 year net risk reduction</td>
</tr>
<tr>
<td>1</td>
<td>Stroke 2% Death 4%</td>
<td>1.5%</td>
<td>2/3</td>
</tr>
<tr>
<td>2</td>
<td>Stroke 5% Death 4%</td>
<td>1.5%</td>
<td>2/3</td>
</tr>
<tr>
<td>3</td>
<td>Stroke 5% Death 4%</td>
<td>1.5%</td>
<td>1/3</td>
</tr>
<tr>
<td>4</td>
<td>Stroke 5% Death 4%</td>
<td>5.0%</td>
<td>2/3</td>
</tr>
</tbody>
</table>

*Five year study, four year entry, three year mean follow-up, α = 0.05, β = 0.2, two-tailed.

*Surgical group has worse outcome than controls.
TIAs. The risk of cerebral ischemic events was related to the presence, severity and progression of carotid stenosis, but the incidence of stroke, especially unheralded stroke, in our 'high-risk' patients was well below 5% per annum. Cerebral ischemic events were also more frequent in patients with heart disease, males and patients over 65 years. Multivariate analysis demonstrated that the initial severity of carotid stenosis and the presence of heart disease were the best predictors of cerebral ischemic events.

Risk Reduction after Carotid Surgery

A two-thirds reduction in stroke rate may be unduly optimistic and the long-term therapeutic effect of endarterectomy in asymptomatic patients may be less than for symptomatic patients. The overall stroke rate is less and therefore, stroke syndromes less likely to be prevented by endarterectomy, such as cerebral hemorrhage, lacunar infarction and middle cerebral artery thrombosis may assume a greater proportion. Assuming a high-risk subgroup exists, if the stroke risk reduction from carotid endarterectomy is only one-third (table 1, trial 3), the net surgical stroke and/or death risk reduction is only 7%, and again of doubtful clinical importance.

Risks of Carotid Surgery

Although the reported peri-operative complication rates in major referral centres are less than 5%, city-wide audits in Springfield, Illinois and Cincinnati, Ohio have shown alarmingly high stroke and/or death rates, 21.1% and 11.4% respectively (table 1). The complication rate of 16.7% in 24 patients withdrawn from the Toronto Asymptomatic Carotid Bruit Study following endarterectomy was also significantly higher.

A peri-operative stroke and/or death rate around 15% places the surgical group at a clear disadvantage (table 2, trial 4 and figure 3), while a lesser rate of 10% confers no advantage to either group. Although rates between 5% and 10% result in a small benefit to the surgical group, the large sample required to achieve statistical significance would preclude a randomized trial.

Conclusion

The efficacy of carotid endarterectomy is extremely responsive to the choice of endpoint and variations in the spontaneous stroke rate, the risk reduction from surgery and the peri-operative complication rate. The role of carotid endarterectomy in asymptomatic patients has not yet been clearly defined. A randomized trial should be deferred until a subgroup is identified with at least a 5% per annum stroke risk. Only those
surgical units with a documented peri-operative complication rate of less than 5% should participate.

References
The case against surgery for asymptomatic carotid stenosis.
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Stroke. 1984;15:964-967
doi: 10.1161/01.STR.15.6.964

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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