Risk of stroke in the distribution of an asymptomatic carotid artery

The European Carotid Surgery Trialists Collaborative Group*

Summary
Screening and carotid endarterectomy have been advocated for asymptomatic carotid stenosis. However, the risk of stroke without treatment has not been adequately defined.

We investigated the risk of stroke in the distribution of the asymptomatic carotid artery in 2295 patients randomised in the European Carotid Surgery Trial. During a mean follow-up of 4-5 years, there were 69 carotid territory strokes, nine of which were fatal, giving three year Kaplan-Meier risks of stroke and fatal stroke of 2.1% (95% CI, 1.5-2.8) and 0.3% (95% CI, 0.06-0.56) respectively. The stroke risk in the 127 patients with severe (70-99%) carotid stenosis was 5.7% (95% CI, 1.5-9.8).

Given these low stroke risks, the potential benefit of endarterectomy for asymptomatic carotid stenosis is small. Population screening is not justified and endarterectomy for asymptomatic carotid stenosis should only be performed in the context of well organised randomised controlled trials.

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Introduction
Patients with a recent carotid distribution transient ischaemic attack or non-disabling ischaemic stroke, and a severe stenosis of the relevant carotid artery, can benefit from carotid endarterectomy.1-3 Although endarterectomy for asymptomatic carotid stenosis has been advocated,1-3 there is no clear evidence of benefit. Between 5 and 10% of the general population over 65 years of age8-9 and between 20 and 30% of patients attending hospital because of ischaemic heart disease or peripheral vascular disease10,11 have more than 50% stenosis of one carotid artery. A policy of surgery for asymptomatic carotid stenosis would therefore have major public health implications.

There is a mortality risk of about 1% and a stroke risk of between 5 and 10% in patients who have had endarterectomy for symptomatic stenosis,1-2 and so the risk of stroke in the distribution of an asymptomatic stenosis needs to be substantial to justify surgery. As yet this risk has not been adequately determined and reported annual stroke risks vary from less than 1%12 to 18%.13 Much of the existing data were gathered retrospectively, and none of the prospective studies were large enough to give stroke risks with narrow confidence intervals for different degrees of carotid stenosis.12,14-19 Moreover, the most important outcome—disability due to stroke—has not been studied.

The European Carotid Surgery Trial (ECST) was set up to examine the efficacy of carotid endarterectomy in patients who had symptomatic carotid stenosis. 3026 patients were randomised; most had unilateral cerebrovascular symptoms but had had bilateral carotid angiography. These patients had an angiographically defined asymptomatic carotid artery (ie, one that was not associated with any symptoms), and were followed up regularly by a neurologist, with all strokes and related disability recorded. Our results enabled us to study the risk of stroke in patients with asymptomatic carotid arteries who received standard medical therapy.

Patients and methods
Patients were randomised if they had had a carotid-distribution transient ischaemic attack, a minor ischaemic stroke, a non-disabling major ischaemic stroke, or a retinal infarction within the previous 6 months, and if the neurologist and surgeon were uncertain whether to recommend carotid endarterectomy after the patient had had a carotid angiogram. Patients came from over 100 centres in 14 European countries and were randomised to "immediate surgery" (60%) or to "avoid immediate surgery" (40%). Clinicians ensured that both groups had "best medical treatment" which usually included aspirin or another anti-platelet drug, treatment of hypertension, and advice to stop smoking. When patients were randomised certain baseline clinical data

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Table 1: Baseline characteristics of 2295 patients studied

were recorded (table 1) and sent to the main trial centre along with the pre-randomisation carotid angiogram, a pre-randomisation computed tomographic (CT) brain scan (if abnormal), an electrocardiogram, and details of the nature and outcome of any carotid surgery. The degree of stenosis in both internal carotid arteries was measured by one observer on the angiogram by the ECST method as previously described.123

Follow-up was done at 4 and 12 months after randomisation (then annually) by the neurologist. At each follow-up visit the neurologist recorded any strokes or myocardial infarctions that had occurred since the previous visit, any further carotid surgery, and blood pressure and current medications. For all deaths, non-fatal strokes and myocardial infarctions occurring after randomisation, clinical details, including CT scan and necropsy reports were sent to the main trial centre for classification by a neurologist and then by a blinded clinical audit committee. For each stroke during follow-up, the local neurologist recorded the actual or expected disability on the Rankin scale21 6 months afterwards.

Our study was confined to the 2695 patients randomised in the ECST prior to January 1992, so that baseline data were complete and all patients had at least one year of follow-up. We excluded 205 patients because of a history of transient ischaemic attacks or strokes in the territory of both carotid arteries. We also excluded a further 15 patients, randomised to surgery, who had bilateral endarterectomy shortly after randomisation, and 180 patients with an absent or inadequate angiographic view of the asymptomatic carotid artery. Thus 2295 patients were eligible for the study. At least 1 year of follow-up data were available in 2252 patients (98%). The main outcomes was first stroke, haemorrhage, or infarct, in the distribution of asymptomatic carotid artery, which was fatal or lasted more than 7 days. For

<table>
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<th>Characteristic</th>
<th>Degree of symptomless stenosis (%)</th>
<th>Total</th>
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<tr>
<td></td>
<td>0-29</td>
<td>30-69</td>
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<td>Mean age (yr)</td>
<td>61.5</td>
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<td>71.2</td>
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<td>Peripheral vascular disease (%)</td>
<td>13.2</td>
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<td>Diabetic (%)</td>
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<td>Mean obesity index (kg/m2)</td>
<td>25.1</td>
<td>25.4</td>
</tr>
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</table>

*% for linear trend=21.4, p=0.001. ** linear trend=38.2, p=0.001. †Regression analysis for trend, p=0.014.

Figure 1: Actuarial analysis of survival free from stroke lasting longer than 7 days in the distribution of an asymptomatic artery

comparison the risk of stroke, defined in the same way, in the distribution of the symptomatic carotid artery was analysed in the same 2295 patients.

Statistical analysis
We used life-table methods and logrank tests for formal analyses of time from randomisation to first stroke, censoring for non-stroke death.

Results
Mean duration of follow-up was 4-5 years (range 1-11.4). The prevalence of ischaemic heart disease and peripheral vascular disease and mean systolic blood pressure increased with the degree of asymptomatic stenosis, but there were no other significant differences between patients with mild (0-29%), moderate (30-69%) or severe (70-99%) asymptomatic stenosis (table 1). 480 patients had a stenosis of less than 10%.

Five strokes in the distribution of the asymptomatic artery occurred within 30 days of carotid endarterectomy performed on the symptomatic artery. Of the 37 patients who had endarterectomy on the asymptomatic artery at some stage during follow-up, seven had a stroke in the vessels supplied by operated artery within 30 days of surgery (table 2). The reason given for endarterectomy on the asymptomatic side was development of a transient ischaemic attack or stroke in 19 cases (stenosis: 4 mild; 7 moderate; 8 severe), but in 11 cases endarterectomy was done specifically for asymptomatic stenosis (stenosis: 2 moderate; 9 severe), and in 7 cases (stenosis: 2 moderate; 5 severe) the reason for surgery was unknown. All surgical strokes were included in the analysis of stroke risk. Overall, 69 patients had a first stroke lasting longer than 7 days in distribution of the asymptomatic carotid artery during follow-up. This gave an overall Kaplan-Meier estimate of stroke risk at 3 years of 2.1% (95% CI: 1.5-2.8). The stroke risk was almost identical in patients with mild and moderate stenosis (table 2 and figure 1), but the 3 year risk increased to 9.8% (95% CI: 0.6-21) in patients with 80-89% stenosis, and to 14.4% (95% CI: 5-38) in patients with 90-99% stenosis (figure 2). However, neither these risks, nor the 5.7% risk in patients with 70-99% stenosis as a whole, were statistically significantly greater than the stroke risk in the rest of the group. The 30-day case fatality of stroke was 13%, giving a Kaplan-Meier three-year risk of fatal stroke of 0.3%
Figure 2: Kaplan-Meier 3-year estimates (95% CI) of risk of stroke lasting longer than 7 days in distribution of asymptomatic artery
Number above error bar indicates number of patients in each stenosis group.

(0.06–0.56). A Rankin disability score was available in 50 (83%) of the 60 non-fatal strokes (table 2). Of these, 14 (28%) were disabling (Rankin >2) at 6 months. If the strokes in which degree of disability was unknown are regarded as disabling the Kaplan-Meier three-year risk of a disabling or fatal stroke was 1.0% (0.3–1.8). The risk of stroke on the asymptomatic side did not differ significantly with treatment allocated for the symptomatic stenosis (surgery: 40/1390 [2.9%] compared with no surgery: 29/905 [3.2%]).

Figure 3 shows the Kaplan-Meier curves derived from our analysis of follow-up. The three-year risk of carotid distribution stroke ipsilateral to a severe symptom-free stenosis (5.7%, CI: 1.5–9.8) was significantly less than the same risk ipsilateral to a severe symptomatic stenosis with medical treatment (17.1%, 13.3–20.1), and was not significantly greater than the risk ipsilateral to a severe asymptomatic stenosis after successful endarterectomy (3.1%, 1.4–4.4).

Discussion
In patients with symptomatic carotid stenosis, the degree of stenosis is the most important predictor of stroke risk in the territory of the symptomatic artery.24 Because of the increasing interest in carotid endarterectomy for patients with asymptomatic stenosis, the relation between the degree of stenosis and stroke risk with medical treatment should be determined accurately. Our study is the largest study of risk of stroke in patients with an asymptomatic carotid artery. All stenoses were imaged with angiography, which allows the degree of stenosis to be measured accurately and reproducibly.22 Ultrasound imaging, used in previous studies,14 is less reproducible.23 The overall 2.1% 3-year risk of stroke in the distribution of asymptomatic stenoses is low, but is unlikely to be an underestimate. Follow-up was done regularly by experienced neurologists, and was complete in over 98% of cases. All strokes were counted, including those caused by surgery on the symptomatic or asymptomatic artery. The patients studied had all had symptoms arising from the contralateral carotid stenosis, had a high frequency of diabetes, ischaemic heart disease, and peripheral vascular disease, and over half were cigarette smokers. However, endarterectomy performed on the asymptomatic artery may have prevented a small number of strokes in a few patients. We did not include patients whose symptoms of stroke lasted less than 7 days.

The low risk of stroke in our study concurs with ultrasound-based studies of risk of stroke in the distribution of asymptomatic carotid arteries. Chambers and Norris followed up patients with asymptomatic stenosis for a mean of 2 years,15 and reported 6 strokes in 113 patients with 75–100% stenosis. Hennerici et al12 followed up 235 patients with more than 50% asymptomatic stenosis for a mean of 32 months and reported 7 strokes. Bogousslavsky et al14 followed up 38 patients with 90–99% asymptomatic stenosis for a mean of 4 years and reported 3 ischaemic strokes.

Each year 5–20% of patients with a previously asymptomatic carotid stenosis are said to have neurological events or cerebral ischaemic events.13,15,16,24 A clinical trial of carotid endarterectomy for asymptomatic stenosis reported a significant reduction in cerebral ischaemic events in the treated group, although there was no significant effect on the risk of stroke or death.26 In all these studies, most events were transient ischaemic attacks. Although from a pathophysiological point of view, it can be argued that the distinction between transient ischaemic attacks and stroke is arbitrary, an outcome which gives equal weight to transient events that do not cause lasting disability and major strokes that cause death or lifelong dependency, is too broad to have any real clinical meaning. Furthermore, it is misleading to compare the risk of such events with the quoted risks of carotid endarterectomy, which only include stroke or death.24 In order that patients should not be inadvertently misinformed about the balance of risks and benefits of surgery for asymptomatic stenosis we did not analyse the risk of transient ischaemic attacks during follow-up.

The burden of disability that results from stroke in the distribution of asymptomatic carotid stenosis has not been measured previously. Although stroke is less heterogeneous than the term cerebral ischaemic events, there is still variation in the severity of stroke, ranging from minor sensory disturbance to devastating permanent
hemiparesis with aphasia or neglect. Therefore we should categorise strokes as non-disabling, disabling, or fatal. The case fatality of stroke in this study was 13%. In over 70% of the non-fatal strokes for which a Rankin score was available, there was no significant disability 6 months later.

The risks of stroke in patients with 80–90% and 90–99% stenosis were based on small numbers of patients with very few outcome events, and the confidence intervals were therefore extremely wide. The overall risk in patients with 70–99% stenosis was lower, but was based on a larger number of patients and therefore has greater validity. What might be gained from endarterectomy performed for severe asymptomatic stenosis? The background risk of carotid distribution stroke after successful endarterectomy, which are probably largely caused by lacunar and cardio-embolic strokes, should be accounted for. The risk of stroke in the distribution of the asymptomatic artery may be somewhat greater than the background risk of ipsilateral carotid distribution stroke after successful endarterectomy for symptomatic stenosis (figure 3). However, this difference in risk was not statistically significant.

Surgical morality and morbidity will have to be considerably lower than in trials of endarterectomy in symptomatic patients if surgery for asymptomatic stenosis is to be beneficial. Indeed, even the stringent 3% limit on risk of stroke and death recommended by the American Heart Association for surgeons operating on asymptomatic stenoses would probably nullify any benefit. Even with complication-free surgery, the cost effectiveness of the procedure must be in doubt: about five strokes prevented over five years following successful endarterectomy in 127 patients with severe asymptomatic stenosis (figure 3).

The risks of fatal, disabling, and non-disabling stroke in the distribution of the asymptomatic carotid artery in patients receiving medical treatment are low. Screening with a view to prophylactic endarterectomy would be undermined by the prevention paradox: most strokes (54 out of 69 patients) occurred in low-risk patients with mild or moderate stenosis, with only a small proportion in patients with severe stenosis (table 2). Prognostic modelling may identify patients at high risk of stroke, but in the meantime endarterectomy cannot be justified for asymptomatic carotid stenosis without a randomised controlled trial. Since the cost-effectiveness and public health impact of the procedure are likely to be marginal, on the available evidence population screening is not warranted.

Writing Committee:
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References

1 European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. Lancet 1991; 337: 1235–43.


