MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis

EUROPEAN CAROTID SURGERY TRIALISTS' COLLABORATIVE GROUP

The European Carotid Surgery Trial is a multicentre trial of carotid endarterectomy for patients who, after a carotid territory non-disabling ischaemic stroke, transient ischaemic attack, or retinal infarct, are found to have a stenotic lesion in the relevant (ipsilateral) carotid artery. Over the past 10 years 2518 patients have been randomised, and the mean follow-up is now almost 3 years among the 2200 thus far available for analysis of the incidence of strokes that lasted more than 7 days. For the patients with "moderate" (30-69%) stenosis on their pre-randomisation angiogram the balance of surgical risk and eventual benefit remains uncertain, and full recruitment continues. For 374 patients with only "mild" (0-29%) stenosis there was little 3-year risk of ipsilateral ischaemic stroke, even in the absence of surgery, so any 3-year benefits of surgery were small, and were outweighed by its early risks. For 778 patients with "severe" (70-99%) stenosis, however, the risks of surgery were significantly outweighed by the later benefits: although 7.5% had a stroke (or died) within 30 days of surgery, during the next 3 years the risks of ipsilateral ischaemic stroke were (by life-table analysis) an extra 2.8% for surgery-allocated and 16.8% for control patients (a sixfold reduction, $p<0.0001$). There was also a small reduction in other strokes, and at 3 years the total risk of surgical death, surgical stroke, ipsilateral ischaemic stroke, or any other stroke was 12.3% for surgery and 21.9% for control (overall difference 9.6% SD 2.3, $2p<0.05$). The main concern was to avoid disabling or fatal events, and, among severe stenosis patients, 3.7% had a disabling stroke (or died) within 30 days of surgery, an extra 1.1% surgery versus 8.4% control ($p<0.0001$) had a disabling or fatal ipsilateral ischaemic stroke by 3 years, and the total 3-year risk of any disabling or fatal stroke (or surgical death) was 6.0% surgery versus 11.0% control (overall difference 5.0% SD 2.3, $2p<0.05$); but, for disabling or fatal stroke the control risks seemed to diminish after the first year, so delay of surgery by just a few months after clinical presentation might make this overall difference non-significant.


Introduction

The left internal carotid, right internal carotid, and vertebrobasilar arteries provide different routes of arterial blood flow to the circle of Willis, and thence to the brain. Therefore, even complete occlusion of just one of these arteries may not cause cerebral ischaemia if there is sufficient collateral blood flow. However, partial occlusion of an internal carotid artery by an atherothrombotic lesion may produce emboli that lodge in arteries distal to the circle of Willis, causing an ipsilateral "carotid-territory" ischaemic stroke (ie, a stroke in those parts of the brain principally supplied by branches of that internal carotid artery). The likelihood of a future stroke may be substantial if there has in the past been one or more non-disabling ischaemic stroke, transient ischaemic attack, or retinal infarct. Among patients who have had such a non-disabling carotid-territory ischaemic event, angiography of the relevant (ie, "symptomatic") carotid artery may reveal stenosis, which is almost always atherothrombotic, at or near the bifurcation of the common carotid artery into the external and internal carotid arteries. The degree of stenosis, expressed as the maximum percentage reduction in the diameter of the relevant carotid artery, may then be mild (here defined as under 30%), moderate (30-69%), or severe (70-99%). Soon after an influential report of carotid reconstruction by Eastcott and colleagues, the related surgical procedure of carotid endarterectomy was introduced in the 1950s, the aim...
In patients where both carotid arteries are symptomatic: (a) If only one carotid artery is patent then that is on the "relevant" side; else (b) if one patent carotid artery is more stenosed than the other then that is on the particularly in the territory of the operated artery. By the subsequent incidence of fatal or disabling stroke, were taking place, chiefly in North America. Unfortunately few percent of causing death or a disabling stroke while the operation itself, as currently performed, carries a risk of a preoperative angiography—which will be undergone 1980s well over 100,000 carotid endarterectomies a year adds a further risk of at least a few per thousand.8 (If surgery, particularly if ultrasound imaging is unavailable—diagnostically by more patients than eventually undergoes.) Hence, with long-term support provided by the UK Medical Research Council (MRC), the European Carotid Surgery Trial (ECST) began in 1981 to randomise symptomatic patients with carotid stenosis between the management policies of recommending "immediate surgery" and of recommending "no immediate surgery". The present report is of the interim results of this comparison.

From the outset it was expected that some types of patient would benefit much more than others from "apparently successful" surgery—ie, surgery after which the patient survives at least 30 days without having a stroke. (Even such apparently successful surgery does not, of course, completely guarantee the achievement or maintenance of arterial patency.) Likewise, it was expected that some types of patients would be at greater risk than others of "surgery-associated events"—ie, stroke or death within 30 days of surgery. Hence, the main aim of the trial was to subdivide the patients into various categories, particularly with respect to the degree of carotid stenosis on the pre-randomisation angiogram, and to assess the risk and benefits in each category separately. This implied the need for very large numbers of patients to be randomised (so that at least the main categories would be large enough to be informative) and the need for the patients randomised to be heterogeneous (so that the key question of who needs treatment could be addressed more directly than would be possible in a more homogeneous trial).

If the patient was prepared at least to consider surgery, then to maximise both the size and the heterogeneity of the study, and to avoid any ethical problems, eligibility was determined chiefly by the "uncertainty principle" (fig 1). This meant three things for the neurologist and surgeon responsible for an individual patient, once they had considered in their own way whatever medical, personal, or other factors seemed to them to be relevant.

(a) If they were then reasonably certain, for any reason, that they did wish to recommend immediate surgery, then that patient was ineligible.
(b) If they were reasonably certain, for any reason, that they did not wish to recommend immediate surgery, then that patient was likewise ineligible.
(c) If, but only if, they were substantially uncertain what to recommend, then that patient was eligible for randomisation between immediate versus no immediate surgery, with all patients receiving whatever their doctors judged to be the best available medical care (which generally included advice to stop smoking, treatment of any hypertension, and, in recent years, the use of aspirin as an antithrombotic drug).

There were substantial differences between doctors in the patients they wished to randomise—in the severity of carotid stenosis, and in various other characteristics. This guaranteed that no category—mild, moderate, or severe stenosis—would be wholly excluded, and hence that the trial would yield at least some direct evidence in each.

The chief aim of the trial is to provide separate answers in each of three separate categories—mild, moderate, or severe stenosis—to three main questions:

1. Surgery-associated death or stroke—What, for these particular surgeons in the 1980s and early 1990s, are the 30-day risks of death or disabling stroke associated with carotid surgery?
2. Other strokes—What, among patients who survive surgery for at least 30 days without a disabling stroke, are the long-term (eg, 10 years or more) effects on the incidence of disabling or fatal stroke of having undergone carotid surgery?
3. When the evidence on any risks and on any benefits is combined in a life-table analysis, what difference does carotid surgery by these particular surgeons make to the eventual overall duration of non-disabled survival among these particular patients?

These three questions are separated partly because there may be considerable differences of opinion as to how big the benefits should be to justify the risks, and partly because the risk/benefit ratio may be different for other patients operated on by other surgeons. In future, the risks of surgery at a given centre might be thought to be substantially larger (or smaller) than they are in the present collaborative group. Moreover, the absolute benefit expected even from "apparently successful" surgery will depend on how likely a particular carotid lesion would be, if not operated on, to cause a disabling or fatal stroke, and that
may well vary greatly from one category of patient to another.

The ECST data monitoring committee periodically reviews the accumulating evidence for mild (0–29%), moderate (30–69%), and severe (70% or more) stenosis patients, and in January, 1991, it was decided that the principal investigators should be informed of the main results both in the severe stenosis category and in the mild stenosis category, but not in the moderate stenosis category. These main analyses of disabling or fatal strokes are now presented. For patients in the mild stenosis and in the severe stenosis categories, ancillary analyses are also presented of all strokes (disabling or not) that lasted more than 7 days, of ipsilateral ischaemic strokes (ie, in the vascular territory of the relevant or “symptomatic” carotid artery and, therefore, the type most likely to be prevented by apparently successful surgery), and of other types of stroke.

Methods

Patients with a carotid territory non-disabling ischaemic stroke, transient ischaemic attack, or retinal infarction during the previous 6 months were eligible if, after a carotid angiogram, the local neurologist and local surgeon were “substantially uncertain” whether to recommend carotid endarterectomy for the relevant artery (fig 1). The proportion of angiogrammed patients in each centre who actually entered the trial was not recorded but would have become greater as the years went by because of the gradual introduction of ultrasound technology to screen out from subsequent angiography patients with normal carotid arteries. Patients were randomised from a total of 80 centres in 14 European countries by telephone to the MRC/Imperial Cancer Research Fund Clinical Trial Service Unit (CTSU) at the University of Oxford. During the telephone call enough information to identify the centre, the doctor, and the patient was entered into the CTSU computer. As soon as this entry was complete, a treatment allocation to “immediate surgery” or to “no immediate surgery” was displayed, and that patient was then irrevocably in the trial, to be followed up until death. The telephone call ended with the doctor being informed of the treatment allocation. Clinicians were asked to ensure that patients in the two groups received similar and appropriate medical treatment: this usually included aspirin, treatment of any definite hypertension, and advice to stop smoking. Any surgery was supposed to take place promptly, but could be deliberately delayed for 4–6 weeks after a recent stroke. Follow-up was due at 4 months and at 12 months after randomisation and annually thereafter. Patients who lapsed from their hospital clinic
follow-up were followed through their family doctor, or in any other feasible way. At each follow-up visit a note was made of any possible symptoms that lasted more than 7 days, irrespective of long-term disability (and all surgery-associated deaths).

The "ischaemic" events also include strokes of uncertain pathology

TABLE I—MAIN OUTCOME EVENTS

<table>
<thead>
<tr>
<th>Type of outcome event</th>
<th>Definition</th>
<th>70-99% (severe)</th>
<th>0-29% (mild)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. &quot;Unclassified&quot; death</td>
<td>All non-stroke deaths except those occurring within 30 days of carotid surgery</td>
<td>455</td>
<td>219</td>
</tr>
<tr>
<td>1. Surgery-associated death or stroke</td>
<td>Either death from any cause within 30 days of surgery, or stroke of any pathology or site within those 30 days</td>
<td>455</td>
<td>206</td>
</tr>
<tr>
<td>2. Haemorrhagic stroke</td>
<td>All strokes (except those associated with surgery) classified by CT scan, lumbar puncture, or necropsy as definitely or probably primary intracranial haemorrhage or spontaneous subarachnoid haemorrhage</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>3. Verteobasilar ischaemic stroke</td>
<td>All other strokes that were definitely in the verteobasilar arterial distribution</td>
<td>17 (3.7%)</td>
<td>5 (2.3%)</td>
</tr>
<tr>
<td>4. Contralateral ischaemic stroke</td>
<td>All other strokes that were definitely contralateral to the &quot;relevant&quot; (i.e., symptomatic) carotid artery</td>
<td>34 (7.5%)</td>
<td>10 (46%)</td>
</tr>
<tr>
<td>5. Ipsilateral ischaemic stroke</td>
<td>All strokes that were ipsilateral to the relevant carotid artery (plus any of uncertain territory)</td>
<td>34 (7.5%)</td>
<td>10 (46%)</td>
</tr>
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Main analysis of "death or disability" ignores all except the surgery-associated deaths and the "disabling or fatal" strokes. "Disabling" strokes were those that, 6 months after the event, still involved substantial stroke disability (modified Rankin grades 3, 4, or 5). If the patient died a non-stroke death less than 6 months after the stroke, or follow-up had not yet reached 6 months, then the predicted disability was used.

Ancillary analyses of "any events" ignores unrelated events, transient ischaemic attacks, and strokes that lasted less than a week, but otherwise includes all strokes with symptoms that lasted more than 7 days, irrespective of long-term disability (and all surgery-associated deaths). The "ischaemic" events also include strokes of uncertain pathology.

include the few events that occurred after randomisation but before surgery. Although any strokes within 30 days after surgery were counted as "surgery-associated" events, and so were removed from the subsequent stroke analyses, no formal attempt has been made to remove 30 days of risk from the group who were allocated no immediate surgery.

Sometimes there was a delay between the time when a stroke or death was first reported to the trial centre and the time when central clinical review of it (which often involved much correspondence, with some doctors not directly involved in the trial) was complete. But, when definite information was eventually reviewed, the final reports were generally confirmed in their assessment of whether a stroke had occurred (and, if so, whether it was likely to have been disabling or not, ipsilateral or not, and ischaemic or not). Hence, the

The analyses of surgery-associated risks include all deaths (from any cause) within 30 days of surgery and all strokes within this same 30-day period. This definition of "surgery-associated death or stroke" (table 1) avoids attribution of causality to specific events; it turned out, however, that the large majority were within 3 days of surgery, so almost all were presumably due to surgery.

Some analyses of possible surgical benefits involved the "ipsilateral ischaemic strokes" since these are the most likely to be prevented, whereas others also involved the smaller numbers of strokes with a different site or pathology (table 1).

The main analyses are concerned only with fatal or disabling strokes or with surgery-associated deaths, but ancillary analyses include, in addition, all non-disabling strokes that lasted more than 7 days. The analyses are by allocated treatment, and therefore
analyses presented are of all unrefuted reports available at Jan 1, 1991, of strokes, or of surgery-associated (30-day) events. For all analyses patients were kept in their originally allocated treatment group irrespective of whether surgery was or was not performed.

Statistical methods

For surgery-associated death or stroke, simple analyses of proportions suffice. For long-term benefit among those who survived surgery without such an event, life-table methods and logrank tests were used for analyses of time from randomisation to first subsequent stroke (as recommended in the 1976/1977 statistical report to the MRC Leukaemia Committee,10 we censored any non-stroke deaths and ignored any selective biases due to the non-random removal of the few killed or disabled by surgery). The occurrence of one of the outcomes in table I prevents any subsequent outcome of another type from occurring first, and so the logrank analyses for two or more of the specific types of stroke (type 2 to 5 in table I) can simply be added together. For the combination of risk and benefit (type 1 to 5 in table I), however, life-table methods were again used, together with estimates of the standard deviations 3 years after randomisation of those life-tables (since logrank tests would not have been appropriate for comparing life-tables that might be expected first to diverge and then to converge).

Results

Surgery-associated events (table ii)

3.7% of patients with severe stenosis and 2.3% of patients with mild stenosis died or had a disabling stroke within 30 days of carotid surgery. These proportions are not significantly different. If all strokes that produced symptoms for more than 7 days are included then both proportions are doubled, but the difference between them

Patients

Between Oct 14, 1981, and Jan 1, 1991, a total of 2518 patients were randomised, always in the ratio 60% immediate surgery to 40% no immediate surgery. This asymmetrical but unbiased allocation allowed slightly more extensive study of the adverse effects of surgery but it must be borne in mind whenever absolute numbers of events are tabulated. Recruitment is currently about 400 patients per year but in the first half of the trial it was about 100 per year, so overall the mean follow-up thus far is less than 3 years. When this preliminary report was being prepared, follow-up was more than 1 year overdue for only 32 patients, and it is expected that most of these will eventually be found. The present report is restricted to the 2200 whose computerised record in January, 1991, included details of a pre-randomisation carotid angiogram and at least one follow-up, and among them the mean duration of follow-up is currently 2-7 years. 96% (1254/1312) of the surgery group had at least one carotid operation, and 3% have had a subsequent operation (5 to the same and 38 to the opposite carotid artery). 4% (40/888) of the group allocated no immediate surgery have had at least one operation (31 ipsilateral to the originally relevant artery, 6 contralateral, and 3 bilateral: total 43 operations). Among those operated on in the surgery-allocated group the median time from randomisation to surgery was 12 days: 79% were operated on within 1 month, 94% within 2 months, and 99% within 4 months of randomisation.

Of the 2200 available patients almost half had moderate stenosis (30-69%) and, as recommended by the data monitoring committee, the results in these are not yet to be reported (fig 1). This paper is therefore further restricted to the 1152 patients whose pre-randomisation angiogram showed either mild stenosis (0-29%; 219 surgery versus 155 no-surgery) or severe stenosis (70-99%; 455 surgery versus 323 no-surgery) of the relevant (ie, "symptomatic") carotid artery. Various patient characteristics, their balance with respect to allocated treatment, and their relevance to the main measures of outcome will be described at the end of the main results.

Deaths from stroke, and deaths within 30 days of carotid surgery, were few, and will be analysed along with non-fatal strokes (see below). If such deaths are omitted, then (as expected) there was no significant difference in "intercurrent" deaths from any other cause, which affected a total of 8-5% (36 severe stenosis + 20 mild stenosis) of those allocated immediate surgery, and 8.6% (31 severe stenosis + 10 mild stenosis) of the remainder. Irrespective of whether the various differences in effective duration of exposure to risk are allowed for, these intercurrent mortality rates (each of which is about 0.3% per month) do not differ significantly from each other.

Patients with severe (70-99%) carotid stenosis on pre-randomisation angiogram

"Disabling or fatal" strokes (or surgery-associated deaths)—Analyses are presented in fig 2 and in table IV of the outcome among patients with severe carotid stenosis. After "apparently successful" surgery there was about an eightfold reduction in ipsilateral ischaemic strokes (fig 2a) (5455 versus 273; or by a logrank test, 5 observed versus 0 expected) among those allocated surgery, were few, and will be analysed along with non-fatal strokes (see below). If such deaths are omitted, then (as expected) there was no significant difference in "intercurrent" deaths from any other cause, which affected a total of 8.5% (36 severe stenosis + 20 mild stenosis) of those allocated immediate surgery, and 8.6% (31 severe stenosis + 10 mild stenosis) of the remainder. Irrespective of whether the various differences in effective duration of exposure to risk are allowed for, these intercurrent mortality rates (each of which is about 0.3% per month) do not differ significantly from each other.
elimination of this would leave about a tenfold odds ratio. The effects on other strokes (fig 2b) was also slightly favourable, though not statistically significantly so. The overall results (fig 2c) indicate a net advantage to surgery but the standard deviation for the absolute difference was quite large (absolute difference 5.0%, SD 1.3, 2p < 0.05), so it is possible that the net benefit is only small. Perhaps further follow-up for several more years will eventually indicate much larger absolute benefits, but perhaps it will not, for fig 2a suggests that the main excess of disabling or fatal ipsilateral ischaemic strokes may be limited to the first year or so (in which case delay of surgery by just a few months after clinical presentation might make the overall difference non-significant).

Strokes lasting more than 7 days (or surgery-associated deaths) — Analyses are presented in fig 2 and in table IV of the outcome among patients with severe carotid stenosis. The general pattern is the same as in the analyses of disabling or fatal strokes but the absolute risks and benefits are both about twice as large. Table I has shown the immediate risks associated with allocation to carotid surgery and fig 2d shows the main benefit: the incidence of ipsilateral ischaemic stroke was reduced by about sixfold (9/455 versus 44/323; logrank test: 9 observed versus 31.8 expected among those allocated surgery, a difference of 6.4 standard deviations; 2p < 0.001). Fig 2e shows that surgery was, if anything, also associated with a lower incidence of the other types of stroke, but the difference was only marginally significant (9 observed versus 14.3 expected, a difference of 2.3 standard deviations; 2p = 0.03) and was due partly (table IV) to a shortfall in vertebrobasilar strokes and primary intracranial haemorrhage, so it may largely have been due to the play of chance. Fig 2f combines the surgery-associated events (table I) and all strokes (figs 2d, 2e), and shows the 3-year effects of the treatment allocation (absolute difference of 9.6%, SD 3.3, 2p < 0.01). The number of patients followed up beyond 3 years is still small, so the results become progressively less reliable after that point.

Patients with mild (0–29%) carotid stenosis on pre-randomisation angiogram

Neither for the small number of ipsilateral ischaemic strokes that lasted more than 7 days, nor for the even smaller number of disabling or fatal ipsilateral ischaemic strokes,
The aim in NASCET was to randomise only patients with 30–99% stenosis, and to monitor separately those with 30–69% and 70–99% stenosis. After randomising over 1000 patients between surgery and no-surgery with a mean follow-up of about 2 years, statistically definite results have emerged from NASCET for patients with 70–99% stenosis, among whom (as in ECST) surgery involved a 30-day risk of a few percent, followed by avoidance of the large majority of all ipsilateral carotid-territory ischaemic strokes. In NASCET, as in ECST, the results for patients with only 30–69% stenosis on their pre-randomisation angiongram remain unclear, so in both studies randomisation of such patients continues.

For patients with severe (70–99%) carotid artery stenosis, there is a substantial risk of an ipsilateral ischaemic stroke over the next few years, and ECST and NASCET have shown that the large majority of these strokes can be avoided by “apparently successful” carotid endarterectomy of the symptomatic artery. For ipsilateral ischaemic stroke, the proportional (relative) risk reduction is so extreme that it can be generalised with a considerable degree of confidence to other populations with severe carotid stenosis—including, perhaps, even patients who have not yet had a carotid territory ischaemic event, although neither trial randomised such patients. (Trials among such patients are in progress.)

The general implications of the ECST and NASCET results are therefore that, in patients with severe carotid stenosis, (1) a large proportion of ischaemic ipsilateral strokes over the next few years are due to atherothrombosis at the carotid bifurcation with complicating embolism and/or low flow, and (2) that the large majority of them can be prevented by “apparently successful” carotid endarterectomy. Hence, among patients with severe carotid stenosis the chief determinant of the absolute benefits of “apparently successful” surgery is simply the absolute likelihood of experiencing an ipsilateral carotid ischaemic stroke over the next few years without surgery. In principle this could be determined by epidemiological study of large populations, but in practice this may be unhelpful, for in the present study almost none of the factors recorded at entry apart from carotid artery stenosis and evidence of past stroke were significantly related to those allocated surgery even after 3 years of follow-up (figs 3c, 3f). Further follow-up may clarify whether the apparent slight trend against surgery is real or not.

Characteristics of the randomised patients (table v) and their relation with the risk of ipsilateral ischaemic stroke and the risk of surgery-associated events

The patients were aged about 60, some 70% were male, more than half had experienced an episode of transient cerebral or monocular ischaemia while about a half had had a stroke, and there was a high prevalence of vascular disease and risk factors. There were no statistically significant or substantial differences between the immediate and no-immediate surgery groups (data available on request). In patients allocated no-surgery a logrank analysis of time to ipsilateral ischaemic stroke revealed three interrelated adverse prognostic factors, other than the degree of carotid stenosis—a history of stroke, residual neurological signs, and infarction on the pre-randomisation CT scan. The factors that were not significantly related to this risk in the first few years of the present study included sex, age, obesity, blood pressure, cholesterol, smoking, diabetes, peripheral vascular disease, cardiomegaly or other heart abnormalities, haematocrit, heart rate, and number of ischaemic episodes before randomisation. Among those allocated surgery the chief factors that predicted an adverse 30-day outcome were high blood pressure (systolic >160 mm Hg) and rapid surgery (less than one hour).

Discussion

The European Carotid Surgery Trial is already the largest randomised trial of any surgical procedure to date, and recruitment of patients with moderate (30–69%) carotid stenosis is continuing. After a mean follow-up of almost 3 years, interim results are now reported in patients with mild (0–29%) and with severe (70–99%) carotid stenosis.

Results very similar to those in the ECST have been made public in a “clinical alert” from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).
risk the more this risk will be worth taking. These conclusions are of some direct value, although, without reliable knowledge of local surgical risks, which ideally requires prospective independent audit, great uncertainties will remain. The qualitative conclusions are also of some indirect value, for they may encourage further research into ways of minimising surgical risks, or into other medical or surgical ways of limiting the risks of stroke from the carotid lesion itself. In closely related circumstances the treatment of hypertension reduces the risk of stroke, as does the use of aspirin, and perhaps other drugs will also be found to be protective—for example, hydroxymethylglutaryl CoA reductase inhibitors produce such large cholesterol reductions that appreciable regression of atheroma may occur. Carotid angioplasty is another option that requires proper evaluation, for although it may restore patency it may not prevent emboli as effectively as endarterectomy appears to do.

For patients with moderate (30-69%) carotid stenosis, full-scale randomisation will continue, perhaps for several more years, in both ECST and NASCET; as yet, the balance of surgical risk and benefit remains unclear.

For patients with mild (0-20%) carotid stenosis, this trial provides no direct support for carotid surgery. Not only is there no apparent benefit from the procedure but, more importantly, there are almost no ipsilateral ischaemic strokes over the next few years to be prevented. There may, of course, be particular patients with some special type of carotid lesion (or some other special feature) who do have an appreciable risk of a stroke due to carotid artery disease that involves only mild stenosis, but in general the risks of surgery for patients with only mild stenosis seem to outweigh any likely benefits, at least within the first few years. More information will become available from further analysis of the strokes which presumably will occur over the next several years during the continuing follow-up of this group of patients.

Validity of the qualitative conclusions

The two main conclusions from the ECST and NASCET are that surgery involves definite increased risks (of 30-day surgery associated death or stroke) and definite decreased risks (of ipsilateral ischaemic stroke) in patients with severe carotid stenosis. These fundamental conclusions are based on such extreme risk ratios that they cannot be materially affected by any minor biases. Hence, it is of little importance that the patients included were most certainly not a representative sample of any definable population, that the stenosis assessment was relatively crude, that the treatment was (inevitably) not blind, that the assessment of outcome was only partly blind, that patients who died from unrelated causes were thereafter “censored” from the analyses, and that interim trial results may somewhat exaggerate the net treatment effect.

Long-term balance of risk and benefit

This study has produced clear evidence about the short-term (30-day) risks of surgery and about the medium-term (3-year) benefits of surgery, but not about the long-term (10+ year) benefits of surgery. For severe stenosis patients in the ECST, fig 2c suggests that for disabling or fatal strokes the main benefit may be in the first year or so (and provides no statistically significant evidence that offering surgery to those already allocated no-surgery would improve their prognosis), whereas fig 2f suggests that for non-disabling strokes the main benefit extends over at least the first 2 years. Only with further follow-up, however, will really reliable evidence emerge of the size of the absolute risk in each successive year, and of the extent to which these risks can be avoided by technically successful surgery. If little or no further advantage accumulates after the first few years then fig 2c suggests that 20 endarterectomies might cause one death or disabling stroke while preventing two. The confidence limits on this net benefit are, however, wide; and, more importantly, long-term follow-up may well show that the eventual net benefit (and hence the “cost-effectiveness” of surgery) is substantially better than these interim results.

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REFERENCES


