Articles

# Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST)

*European Carotid Surgery Trialists' Collaborative Group**


## Summary

**Background** Our objective was to assess the risks and benefits of carotid endarterectomy, primarily in terms of stroke prevention, in patients with recently symptomatic carotid stenosis.

**Methods** This multicentre, randomised controlled trial enrolled 3024 patients. We enrolled men and women of any age, with some degree of carotid stenosis, who within the previous 6 months had had at least one transient or mild symptomatic ischaemic vascular event in the distribution of one or both carotid arteries. Between 1981 and 1994, we allocated 1811 (60%) patients to surgery and 1213 (40%) to control (surgery to be avoided for as long as possible). Follow-up was until the end of 1995 (mean 6·1 years), and the main analyses were by intention to treat.

**Findings** The overall outcome (major stroke or death) occurred in 669 (37·0%) surgery-group patients and 442 (36·5%) control-group patients. The risk of major stroke or death complicating surgery (7·0%) did not vary substantially with severity of stenosis. On the other hand, the risk of major ischaemic stroke ipsilateral to the unoperated symptomatic carotid artery increased with severity of stenosis, particularly above about 70–80% of the original luminal diameter, but only for 2–3 years after randomisation. On average, the immediate risk of surgery was worth trading off against the long-term risk of stroke without surgery when the stenosis was greater than about 80% diameter; the Kaplan-Meier estimate of the frequency of a major stroke or death at 3 years was 26·5% for the control group and 14·9% for the surgery group, an absolute benefit from surgery of 11·6%. However, consideration of variations in risk with age and sex modified this simple rule based on stenosis severity. We present a graphical procedure that should improve the selection of patients for surgery.

**Interpretation** Carotid endarterectomy is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the symptomatic stenosis is greater than about 80%. Age and sex should also be taken into account in decisions on whether to operate.


*Lancet* 1998; **351:** 1379–87
*See Commentary page XXXX*

*Writing committee, study organisation, and participants given at end of paper

**Correspondence to:** Prof Charles Warlow, Department of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK (e-mail: cpw@skull.dcn.ed.ac.uk)

## Introduction

We designed the European Carotid Surgery Trial (ECST) as a randomised comparison of "carotid endarterectomy as soon as possible" with "avoid surgery if at all possible, for as long as possible" (ie, surgery versus control) in patients with one or more carotid-territory ischaemic episodes within the previous 6 months and with some degree of stenosis near the origin of the symptomatic internal carotid artery (ICA). From the outset we expected that the balance of surgical risk and benefit, in terms of the prevention of stroke, would vary among categories of patients, and in particular with severity of stenosis. This expectation was borne out by the interim results.[1,2] Now that trial recruitment and follow-up are complete, we can report in detail on the balance of surgical risk and benefit.

## Methods

We carried out the trial in 97 centres in 12 European countries and one centre in Australia and described much of the methodology in our first report.[1] Ethical approval was obtained in all centres. Informed consent was obtained from each patient in accordance with the requirements of the local ethics committee.

### *Eligibility*

Eligible patients had experienced, in the previous 6 months, one or more carotid-territory ischaemic events in the brain or eye, which were either transient (symptoms lasting minutes, hours, or days) or permanent but did not cause any serious disability. We excluded patients who were likely to have had embolism from the heart to the brain or eye, and patients who had more severe disease of the distal than of the proximal ICA.

After contrast angiography of the symptomatic artery, with whatever technique was in use at the time in the local centre, the physicians and surgeons enrolled patients for randomisation when they were "substantially uncertain" whether or not to recommend endarterectomy of the affected artery. The anatomical extent, technique, and quality of angiography varied widely between centres but at the very least we required visualisation of the symptomatic carotid bifurcation. A few patients with occlusion of the symptomatic carotid artery, although not eligible, were assigned randomised treatment in error. This error usually came to light at central review of the angiograms, but these ineligible patients were included in trial follow-up and analysis.

### *Measurement of carotid stenosis and definition of the symptomatic side*

We collected the angiograms in the trials office, and a single observer measured the percentage diameter stenosis on the best angiographic view of the point of maximum narrowing, using as the denominator an estimate of the original width of the artery at this narrowest point and bearing in mind the slight widening of

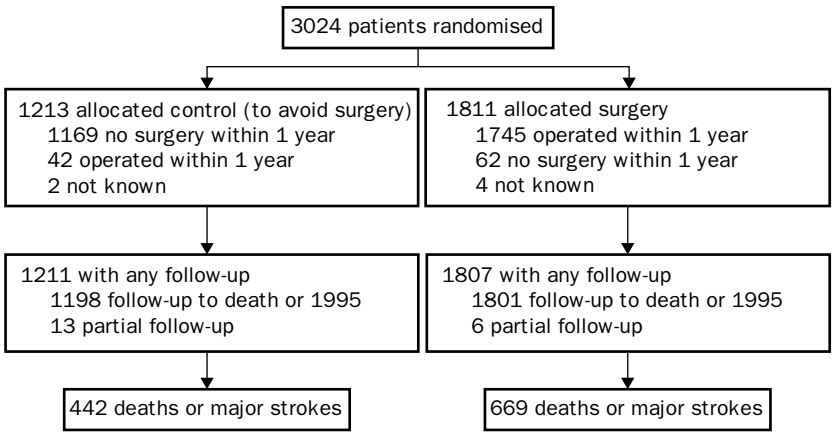



Figure 1: **Trial profile**

the normal ICA origin which is where most of the stenoses were found.[3] If only one artery had been symptomatic, this was, naturally, defined as the symptomatic artery, and it defined the side for classification of any cerebral or ocular ischaemic outcome events as ipsilateral or contralateral to that artery. If both carotid arteries had been symptomatic, we defined the symptomatic artery, and side, as that with the most recent symptoms. If the symptoms had occurred at more or less the same time on each side, the most stenosed artery defined the symptomatic artery, and side, unless it was clear that the ICA on this side was occluded or had been operated on electively before randomisation.

### *Randomisation and follow-up*

We randomised the first patient on Oct 14, 1981, and the last on March 31, 1994, by telephone to the Clinical Trial Service Unit in Oxford. A computer program generated the randomisation schedule, stratified by centre, making it impossible for the local investigators to know whether the next allocation was going to be to surgery (60% of the patients) or control (40% of the patients). Irrespective of trial treatment allocation, all patients received what was judged to be the best medical treatment. Although this treatment varied somewhat between centres and over the years, it usually consisted of advice against smoking, treatment of raised blood pressure, and antiplatelet drugs. From the moment of randomisation, we expected follow-up information for every randomised patient at 4 months, at 12 months, and then annually until the end of 1995. We planned to follow-up every patient for at least a year, mostly in neurology clinics, but if necessary via the patient's family doctor.

### *Trial treatment*

When we allocated a patient to surgery we expected the operation to be carried out within a reasonable time. For the purpose of analysis, we defined trial treatment as the first carotid endarterectomy within a year of randomisation and any subsequent endarterectomy on the same artery, also within a year. We designated as cross-overs to the control group any patients allocated surgery who were not operated on within a year of randomisation. Likewise, we classified as cross-overs to the surgery group any control patients who were operated on within a year of randomisation. The side on which the operation was to be done was left to the judgment of the surgeon; in just 26 (1·5%) of 1745 cases this was different from what we had designated as the trial symptomatic side. The protocol allowed an endarterectomy before randomisation but only if the intent was then to assign randomised treatment for the other carotid artery, which must have been symptomatic within the previous 6 months. Patients assigned to surgery could have a bilateral carotid endarterectomy if clinically appropriate, but we expected that surgery on either side would be avoided for patients assigned to control.

### *Recording of outcome events*

We collected the clinical details of all deaths and of any possible non-fatal strokes after randomisation, prepared a summary for agreement by the collaborating physician, and then sent the summary, with treatment allocation concealed, to the clinical audit committee for their final approval. We resolved any disagreements by discussion. We classified the outcome events in various ways, with emphasis on major strokes, and whether any death was due to stroke, some non-stroke vascular cause, or a clearly non-vascular cause.

*Stroke* was defined as a clinical syndrome characterised by rapidly developing symptoms and/or signs of focal and at times global (applied to patients in deep coma and those with subarachnoid haemorrhage), loss of cerebral function lasting longer than 24 h or leading to death, with no apparent cause other than that of vascular origin.

*Major stroke* was a stroke, as defined above, with symptoms lasting longer than 7 days.

*Disabling stroke* was a stroke that after 6 months was associated with disability as recorded on the modified Rankin scale of 3,4, or 5.[4] If the patient died of a cause other than stroke within the 6 months after the stroke, or if there had been a further stroke in that period, we used an intelligent clinical estimate of the likely future disability from the original stroke. After a disabling stroke, a patient was classified as permanently disabled, hence only one such event was possible in each patient.

*Fatal stroke* was that deemed by the clinical audit committee to have caused the death of the patient, either directly by the brain damage or indirectly by some non-neurological complication, at any stage after the stroke.

*Surgical events* were all strokes lasting longer than 7 days and all deaths occurring within 30 days of trial surgery (in surgery or control patients).

*Ipsilateral major ischaemic stroke* was any major stroke in the distribution of the symptomatic (at the time of randomisation) carotid artery, or of uncertain vascular distribution, and which was not definitely haemorrhagic in origin, and which was not a surgical event.

*Haemorrhagic major stroke* was any major stroke classified by computed tomography, magnetic resonance imaging, lumbar puncture, or necropsy as definitely due to primary intracerebral or subarachnoid haemorrhage.

*Other major stroke* was any major stroke that was not a surgical event or an ipsilateral major ischaemic stroke (ie, strokes that were haemorrhagic, in the vertebrobasilar distribution, or in the distribution of the contralateral carotid artery).

*Non-stroke vascular death* was any death that was due to vascular disease but not stroke, and which did not occur within 30 days of trial surgery. This category included sudden deaths and those due to the complications of cardiac disease and ruptured aortic aneurysm.

*Non-vascular death* was any death definitely due to non-vascular causes such as cancer.

*Unknown cause of death* was all deaths not otherwise classified.

### *Trial outcomes*

Each patient could experience several adverse outcomes during follow-up, which might differ in severity and in likely relevance to the surgical treatment. It was difficult to choose a main trial outcome that summarised all the important outcome information but did not reflect too narrow a prejudice about the likely effect of carotid endarterectomy. For this reason we focused the main

| | Surgery (n=1807) | Control (n=1211) |
|---|---|---|
| **Demography** | | |
| Male/female | 1299 (72%)/508 (28%) | 869 (72%)/342 (28%) |
| Mean (SD) age in years | 62·5 (8·1) | 62·3 (8·0) |
| **Ischaemic events** | | |
| Any cerebral transient ischaemic attack | 895 (50%) | 595 (49%) |
| Any amaurosis fugax | 452 (25%) | 318 (26%) |
| Any minor stroke (symptoms <7 days) | 408 (23%) | 253 (21%) |
| Any major stroke | 491 (27%) | 340 (28%) |
| Any retinal infarction | 113 (6%) | 73 (6%) |
| Infarct visible on CT scan on symptomatic side | 456 (25%) | 295 (24%) |
| Residual neurological signs | 535 (30%) | 346 (29%) |
| Mean (SD) days from last symptoms | 62·3 (53·4) | 62·3 (52·7) |
| **History** | | |
| Hypertension* | 839/1614 (52%) | 504/1078 (47%) |
| Mean (SD) systolic blood pressure (mm Hg) | 151 (22·3) | 150·2 (21·3) |
| Mean (SD) diastolic blood pressure (mm Hg) | 86·2 (11·4) | 86·3 (10·8) |
| Ischaemic heart disease | 443 (24%) | 258 (21%) |
| Peripheral vascular disease | 292 (16%) | 203 (17%) |
| Diabetes | 208 (12%) | 145 (12%) |
| Current cigarette smoking* | 844/1604 (53%) | 557/1077 (52%) |
| Previous carotid endarterectomy* | 29/1614 (2%) | 23/1081 (2%) |
| **Laboratory data** | | |
| Mean blood cholesterol (mmol/L)* | 6·4 (13·5) | 6·4 (13·8) |
| Mean (SD) packed-cell volume (%)* | 43·3 (6·6) | 43·8 (6·9) |
| **Stenosis of symptomatic carotid artery** | | |
| 0–29% | 240 (13%) | 179 (15%) |
| 30–49% | 390 (22%) | 261 (22%) |
| 50–69% | 582 (32%) | 377 (31%) |
| 70–99% | 586 (32%) | 389 (32%) |
| Occluded | 9 (0·5%) | 5 (0·4%) |
| **Stenosis of contralateral carotid artery** | | |
| 0–29% | 894 (53%) | 569 (51%) |
| 30–49% | 379 (22%) | 261 (23%) |
| 50–69% | 264 (16%) | 176 (16%) |
| 70–99% | 107 (6%) | 67 (6%) |
| Occluded | 49 (3%) | 49 (4%) |
| Missing (no views available) | 114 (6%) | 89 (7%) |

*Variables not collected beyond January, 1992: for cholesterol n=1573 surgery, 1059 control; for packed-cell volume n=1614, 1081.

Table 1: **Baseline characteristics of all analysed patients**

analysis on the most important clinical question—the effect of surgery on stroke. Because carotid endarterectomy may cause stroke within a matter of days, but generally not later, the relative risk of stroke changes with the length of follow-up and so analysis at a single time point would not fully describe the balance of risk and benefit from surgery. To overcome this difficulty, we not only looked at the treatment effect at 3 years, a data-derived cut-off point when the excess risk of ipsilateral ischaemic stroke seemed to have disappeared in the control patients, but also estimated the gain in stroke-free life expectancy.

To restrict attention to the compound outcome of stroke or death might suggest that all strokes are comparable to death. Therefore, we have shown several ways of viewing trial outcomes disaggregated into several clinically sensible parts: death; major stroke or death within 30 days of trial treatment (ie, surgical events, the vast majority of which occurred within 5 days of surgery and were, therefore, in some way almost certainly caused by surgery); and major stroke not associated with trial surgery. We further split this last category into stroke ipsilateral to the symptomatic artery and not identified as definitely haemorrhagic (ie, ipsilateral major ischaemic strokes) and all other strokes (ie, all known haemorrhages, vertebrobasilar or contralateral carotid ischaemic strokes). These outcomes were not mutually exclusive, so some tables include some patients twice. However, the survival curves of compound events were based on only the first major stroke or death for each patient. All analyses, unless otherwise stated, were of all outcome events occurring between the moment of randomisation and the final follow-up for each patient and by allocated treatment (ie, intention to treat). Even if some patients allocated surgery never underwent endarterectomy, they were analysed in the surgery group. Similarly, patients allocated control who underwent endarterectomy within the 12-month time limit for trial surgery or later were analysed in the control group. Thus, some patients in the group allocated control treatment could have a surgical event after trial surgery.

### *Statistical methods*

The primary objective of our analysis was to estimate the range of stenosis within which carotid endarterectomy confers statistically proven benefit. For this purpose we had to estimate treatment effect as a function of stenosis, which required a regression model. Since our primary outcome was time to recurrent major stroke or death, a survival model is appropriate. We used the Cox proportional-hazards technique. As might be expected with a surgical intervention, the model had to take into account a short period of excess risk immediately after surgery and a diminution of treatment effect after some years. We found that these effects were adequately modelled by a 5-day postoperative period of high risk and a constant long-term treatment effect falling to zero at 3 years. Thus, these terms were included as time-dependent covariates.

We chose stroke-free life expectancy as the main trial outcome because the immediate hazard of surgery means that treatment failures occur sooner, on average, with surgery than without. Examination of the surviving proportions at a chosen point in time would not have reflected this early penalty. As with simple life expectancy, this outcome is strongly affected by age and sex. We therefore included age and sex in the regression model to ensure that their true effect was assessed at each stage in the calculation. Other factors that may affect surgical risk,[5] or risk without surgery,[6] were not included. Since no treatment effect was found beyond 3 years, life expectancies were assumed to be equal in stroke-free survivors in each treatment group beyond this time and estimated from another study (unpublished). Further details of this calculation and other features such as implementation of the intention-to-treat principle with time-dependent treatment risk, development of the model, steps to minimise bias due to data-dependent model selection, justification of duration of time-dependent model terms, and estimation of baseline hazards are available from the investigators. The Cox model was estimated with the programme TDA (version 5.5) and simulations used Minitab (version 9.2).

## Results

3024 patients received randomised treatment allocation—1811 surgery and 1213 control (figure 1). The mean follow-up was 6·1 years (mean 6·1 years in the control group, 6·0 years in the surgery group; maximum 13·8 years). We lost only 25 patients (0·83%) to follow-up, six because of emigration. Because 19 of these 25 had at least some follow-up (mean 3·0 years for controls; 3·2 years for surgery group) we were able to include them in the analysis up until the time we lost them. Therefore, 3018 (99·8%) patients were included in the trial analysis, 1807 in the surgery group and 1211 in the control group. There were some small baseline differences between the groups, particularly in the prevalence of hypertension and ischaemic heart disease (table 1), but these were unlikely to have been clinically relevant.

62 (3·4%) of the 1807 patients allocated surgery did not undergo carotid endarterectomy within a year of randomisation. Of the 1745 patients who received surgery as allocated, 50% were operated on within 14 days of randomisation and 95% within 70 days. Five patients had a major stroke while awaiting surgery. Not surprisingly, a higher proportion (143 [11·8%]) of the 1211 patients allocated control did not adhere to the allocation and

| | 0–19% | | 20–29% | | 30–39% | | 40–49% | | 50–59% | |
|---|---|---|---|---|---|---|---|---|---|---|
| | S (n=78) | C (n=62) | S (n=162) | C (n=117) | S (n=200) | C (n=139) | S (n=190) | C (n=122) | S (n=350) | C (n=240) |
| **Major-stroke/surgical death** | | | | | | | | | | |
| Within 30 days of trial surgery | 5 (6·4%) | 0 | 3 (1·9%) | 0 | 14 (7·0%) | 0 | 18 (9·5%) | 0 | 22 (6·3%) | 0 |
| Ipsilateral major ischaemic stroke not within 30 days | 6 (7·7%) | 4 (6·5%) | 13 (8·0%) | 6 (5·1%) | 16 (8·0%) | 9 (6·5%) | 11 (5·8%) | 8 (6·6%) | 18 (5·1%) | 26 (10·8%) |
| Other major stroke not within 30 days | 3 (3·8%) | 5 (8·1%) | 16 (9·9%) | 9 (7·7%) | 13 (6·5%) | 6 (4·3%) | 11 (5·8%) | 11 (9·0%) | 24 (6·9%) | 12 (5·0%) |
| All major stroke or surgical death | 12 (15·4%) | 9 (14·5%) | 29 (17·9%) | 14 (12·0%) | 38 (19·0%) | 14 (10·1%) | 38 (20·0%) | 16 (13·1%) | 59 (16·9%) | 36 (15·0%) |
| **Any major stroke** | 12 (15·4%) | 9 (14·5%) | 29 (17·9%) | 14 (12·0%) | 37 (18·5%) | 14 (10·1%) | 38 (20·0%) | 16 (13·1%) | 57 (16·3%) | 36 (15·0%) |
| **Death from any cause** | 21 (26·9%) | 12 (19·4%) | 47 (29·0%) | 30 (25·6%) | 56 (28·0%) | 40 (28·8%) | 46 (24·2%) | 24 (19·7%) | 94 (26·9%) | 66 (27·5%) |
| **Any major stroke or death** | 28 (35·9%) | 16 (25·8%) | 60 (37·0%) | 39 (33·3%) | 78 (39·0%) | 46 (33·1%) | 65 (34·2%) | 32 (26·2%) | 126 (36·0%) | 86 (35·8%) |
| **Disabling/fatal stroke or surgical death** | | | | | | | | | | |
| Disabling stroke or death within 30 days | 2 (2·6%) | 0 | 2 (1·2%) | 0 | 5 (2·5%) | 0 | 8 (4·2%) | 0 | 11 (3·1%) | 0 |
| Fatal/disabling ipsilateral ischaemic stroke not within 30 days | 2 (2·6%) | 3 (4·8%) | 4 (2·5%) | 1 (0·9%) | 8 (4·0%) | 4 (2·9%) | 6 (3·2%) | 6 (4·9%) | 8 (2·3%) | 13 (5·4%) |
| Other fatal/disabling stroke not within 30 days | 2 (2·6%) | 2 (3·2%) | 9 (5·6%) | 4 (3·4%) | 8 (4·0%) | 4 (2·9%) | 7 (3·7%) | 3 (2·5%) | 15 (4·3%) | 6 (2·5%) |
| All disabling/fatal stroke or surgical death | 6 (7·7%) | 5 (8·1%) | 15 (9·3%) | 5 (4·3%) | 21 (10·5%) | 8 (5·8%) | 21 (11·1%) | 9 (7·4%) | 34 (9·7%) | 19 (7·9%) |
| **Fatal stroke or surgical death** | | | | | | | | | | |
| Fatal stroke/other death within 30 days of trial surgery | 1 (1·3%) | 0 | 1 (0·6%) | 0 | 2 (1·0%) | 0 | 2 (1·1%) | 0 | 4 (1·1%) | 0 |
| Fatal ipsilateral ischaemic stroke not within 30 days | 1 (1·3%) | 1 (1·6%) | 2 (1·2%) | 0 | 2 (1·0%) | 1 (0·7%) | 2 (1·1%) | 2 (1·6%) | 2 (0·6%) | 5 (2·1%) |
| Other fatal stroke not within 30 days | 0 | 1 (1·6%) | 5 (3·1%) | 1 (0·9%) | 3 (1·5%) | 2 (1·4%) | 2 (1·1%) | 3 (2·5%) | 6 (1·7%) | 3 (1·2%)) |
| All fatal stroke or surgical death | 2 (2·6%) | 2 (3·2%) | 8 (4·9%) | 1 (0·9%) | 7 (3·5%) | 3 (2·2%) | 6 (3·2%) | 5 (4·1%) | 12 (3·4%) | 8 (3·3%) |

S=surgery, C=control.

Table 2: **Number of patients with each important outcome by degree of stenosis and treatment allocation**

underwent carotid endarterectomy at some stage during the trial, mostly because of recurrent symptoms; 42 (3·5%) were operated on within a year of randomisation and thus were classified as cross-overs. As expected, the severity of symptomatic stenosis varied widely (tables 1 and 2).

### *Non-trial treatments likely to influence prognosis*

A greater proportion of patients allocated control than of those allocated surgery were recorded as taking aspirin at randomisation (58·7 *vs* 54·7%, p<0·05). The use of other antiplatelet drugs, anticoagulants, and lipid-lowering drugs was similar in the two groups. During follow-up there was a tendency for control patients to be treated somewhat more aggressively. The proportions of control and surgery patients recorded as receiving treatment on 50% or more of their follow-up forms were: aspirin (79% *vs* 77%, p=0·25), other antiplatelet drugs (18% *vs* 16%, p=0·38), anticoagulants (8% *vs* 6%, p=0·09), lipid-lowering drugs (8% *vs* 6%, p=0·09), and any of these preceding drugs (86% *vs* 82%, p=0·003). These differences might have reduced any apparent benefit of surgery.

### *Important outcome events by severity of symptomatic carotid stenosis*

Table 2 shows the numbers of patients with various events within categories of stenosis severity for various important outcomes. The major ischaemic strokes involved those regions of the brain most likely to be supplied by the symptomatic artery (ipsilateral major ischaemic strokes), and those in other regions. All strokes known to be haemorrhagic were counted with the other major strokes. Causes of deaths are shown in table 3; there were no significant differences between the groups.

| | Surgery (n=1807) | Control (n=1211) |
|---|---|---|
| **Fatal stroke or surgical death** | | |
| Death within 30 days of trial surgery | 17 (n=1745) | 0 (n=42) |
| Other ipsilateral ischaemic stroke | 21 | 18 |
| Other stroke | 30 | 30 |
| All fatal stroke or surgical death | 68 (3·8%) | 48 (4·0%) |
| **Other deaths*** | | |
| Non-stroke vascular or unknown | 286 (15·8%) | 186 (15·4%) |
| Non-vascular | 144 (8·0%) | 88 (7·3%) |
| **Total deaths** | 498 (27·6%) | 322 (26·6%) |

*Not within 30 days of trial surgery.

Table 3: **Causes of death**

### *Stroke and death within 30 days of surgery*

Among the 1745 patients who were allocated and received surgery, there were 122 non-fatal major strokes or deaths (table 4). The overall risk of non-fatal major stroke or death was 7·0% (95% CI 5·8–8·3). The risk was slightly greater in the middle than in the outer ranges of stenosis ($\chi^2$ test for heterogeneity p=0·05, figure 2A). Of the 122 patients, 61 had non-disabling major strokes, 40 non-fatal disabling major strokes, 15 fatal strokes (ten of whom died within 30 days of trial surgery and so were counted as surgical deaths), and seven non-stroke deaths (one after a disabling stroke; table 4). The overall surgical risk among the patients allocated control treatment who crossed over and underwent carotid endarterectomy was 4·8% (95% CI 0·6–16·2; 2 of 42 patients).

The risk of major stroke or death associated with non-trial operations (with the exclusion of operations within 30 days of trial surgery, because any adverse events during this period were attributed to that trial treatment) was slightly higher than that associated with trial operations (5/61, 8·2% [2·7–18·1]) in patients allocated surgery and 9/101, 8·9% [4·2–16·2] in control patients).

### *Risk of ipsilateral ischaemic stroke after successful surgery*

In the control group the risk of major stroke was clearly related to the severity of carotid stenosis, but only within the first 2–3 years after randomisation. Thereafter, there was no relation between stroke risk and severity of stenosis (figure 3). A qualitatively similar picture was obtained when we restricted the analysis to patients who survived 5 years; thus the reduction in stroke risk with

| 60–69% | | 70–79% | | 80–89% | | 90–99% | | 100% | | All | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| S (n=232) | C (n=137) | S (n=231) | C (n=170) | S (n=251) | C (n=159) | S (n=104) | C (n=60) | S (n=9) | C (n=5) | S (n=1807) | C (n=1211) |
| 22 (9·5%) | 1 (0·7%) | 21 (9·1%) | 1 (0·6%) | 12 (4·8%) | 0 | 4 (3·8%) | 0 | 1 (11%) | 0 | 122 (6·8%) | 2 (0·2%) |
| 14 (6·0%) | 14 (10·2%) | 13 (5·6%) | 15 (8·8%) | 13 (5·2%) | 34 (21·4%) | 5 (4·8%) | 19 (31·7%) | 0 | 1 (20%) | 109 (6·0%) | 136 (11·2%) |
| 16 (6·9%) | 11 (8·0%) | 16 (6·9%) | 21 (12·4%) | 15 (6·0%) | 12 (7·5%) | 6 (5·8%) | 7 (11·7%) | 1 (11%) | 2 (40%) | 121 (6·7%) | 96 (7·9%) |
| 48 (20·7%) | 23 (16·8%) | 46 (19·9%) | 33 (19·4%) | 39 (15·1%) | 44 (27·7%) | 11 (10·6%) | 24 (40·0%) | 2 (22%) | 3 (60%) | 321 (17·8%) | 216 (17·8%) |
| 47 (20·3%) | 23 (16·8%) | 44 (19·0%) | 33 (19·4%) | 38 (15·1%) | 44 (27·7%) | 11 (10·6%) | 24 (40·0%) | 2 (22%) | 3 (60%) | 315 (17·4%) | 216 (17·8%) |
| 58 (25·0%) | 32 (23·4%) | 63 (27·3%) | 51 (30·0%) | 76 (30·2%) | 48 (30·2%) | 34 (32·7%) | 17 (28·3%) | 3 (33%) | 2 (40%) | 498 (27·6%) | 322 (26·6%) |
| 82 (35·3%) | 48 (35·0%) | 89 (38·5%) | 69 (40·6%) | 98 (39·0%) | 71 (44·7%) | 39 (37·5%) | 31 (51·7%) | 4 (44%) | 4 (80%) | 669 (37·0%) | 442 (36·5%) |
| 11 (4·7%) | 0 | 11 (4·8%) | 1 (0·6%) | 6 (2·4%) | 0 | 4 (3·8%) | 0 | 1 (11%) | 0 | 61 (3·4%) | 1 (0·1%) |
| 4 (1·7%) | 8 (5·8%) | 4 (1·7%) | 7 (4·1%) | 7 (2·8%) | 18 (11·3%) | 3 (2·9%) | 10 (16·7%) | 0 | 0 | 46 (2·5%) | 70 (5·8%) |
| 9 (3·9%) | 5 (3·6%) | 5 (2·2%) | 13 (7·6%) | 9 (3·6%) | 6 (3·8%) | 3 (2·9%) | 3 (5·0%) | 0 | 1 (20%) | 67 (3·7%) | 47 (3·9%) |
| 24 (10·3%) | 13 (9·5%) | 20 (8·7%) | 21 (12·4%) | 22 (8·8%) | 24 (15·1%) | 10 (9·6%) | 13 (21·7%) | 1 (11%) | 1 (20%) | 174 (9·6%) | 118 (9·7%) |
| 5 (2·2%) | 0 | 4 (1·7%) | 0 | 1 (0·4%) | 0 | 1 (1·0%) | 0 | 1 (11%) | 0 | 22 (1·2%) | 0 |
| 3 (1·3%) | 0 | 1 (0·4%) | 2 (1·2%) | 4 (1·6%) | 3 (1·9%) | 2 (1·9%) | 4 (6·7%) | 0 | 0 | 19 (1·1%) | 18 (1·5%) |
| 5 (2·2%) | 5 (3·6%) | 2 (0·9%) | 7 (4·1%) | 1 (0·4%) | 6 (3·8%) | 3 (2·9%) | 2 (3·3%) | 0 | 0 | 27 (1·5%) | 30 (2·5%) |
| 13 (5·6%) | 5 (3·6%) | 7 (3·0%) | 9 (5·3%) | 6 (2·4%) | 9 (5·7%) | 6 (5·8%) | 6 (10·0%) | 1 (11%) | 0 | 68 (3·8%) | 48 (4·0%) |

Table 2: **Continued**

time in patients with severe stenosis could not be attributed to early mortality in high-risk patients. This finding led us to compare the balance of risk and benefit of surgery at 3 years. The effect of successful trial surgery (ie, not counting any surgical strokes or deaths) on the 3-year risk of ipsilateral major ischaemic stroke in deciles of stenosis severity (with the first two deciles combined because very few patients had 0–10% stenosis), showed a clear advantage above about 80% stenosis (test of trend in treatment effect $p<0·001$, figure 2B).

### *Effect of surgery on other major strokes*

As expected, surgery had less effect on other types of stroke (ie, haemorrhagic, vertebrobasilar, and contralateral carotid ischaemic strokes) than on ischaemic stroke (test of trend in treatment effect $p=0·071$, figure 2C). Because it was difficult to differentiate some stroke types, and we were not completely unaware of treatment allocation, the overall analysis that follows minimised observer bias by combining all the strokes.

### *Overall results*

For the combined outcome of surgical events, ipsilateral major ischaemic strokes, and other major strokes, there was no overall effect below about 70–80% stenosis (figure 2D). The clear downward trend in the benefit of surgery ($p<0·001$) from the 90–100% to 80–89% categories of stenosis is likely to be continued into the 70–79% category, which suggests that the value of stenosis above which the surgical effect is beneficial, on average, lies somewhere in this range of 70–79% stenosis. As an illustration of the survival curves, we calculated Kaplan-Meier estimates within the subgroup with 80–99% stenosis; the early risk of surgery, the benefit over the next 2–3 years, and the lack of any definite benefit thereafter were clear (figure 4). The absolute difference at 3 years was 139 events avoided per 1000 patients treated by surgery.

The predicted proportion of patients with each of the various outcomes at 3 years is shown in table 5. The absolute benefit in terms of major strokes and all deaths was 11·6%—that is, 116 major strokes or deaths from any cause might be avoided per 1000 patients treated by surgery. Thus about nine patients must be treated by surgery for one more patient to be alive and free of major stroke at 3 years. If the analysis is restricted to disabling strokes, the number needed to treat is 18.

### *Estimation of major-stroke-free survival*

We have shown how treatment effect at 3 years varies with stenosis, the contribution from the short-term risk of surgery and the long-term prevention of stroke after surgery, and also the size of benefit that might be achieved if the treatment decision was based on a stenosis of 80% or above. However, these 3-year risks obscure the fact that patients allocated surgery tended to have strokes earlier than those allocated control. This disadvantage of surgery is directly reflected in stroke-free life expectancy, which thus seems a more appropriate measure of benefit. In our Cox proportional-hazards model on which our estimation of stroke-free life expectancy was based, we

| | Surgery (n=1807) | Control (n=1211) |
|---|---|---|
| **Operations** | | |
| Patients receiving trial surgery | 1745 (97%) | 42 (3%) |
| Patients receiving first* surgery more than 1 year after randomisation | 3 | 101 |
| Patients with operations to both ICAs during trial | 68 | 11 |
| Patients with repeat surgery to one ICA during trial | 9 | 0 |
| **Surgical events within 30 days of trial surgery** | | |
| Total major stroke | 116 (6·6%) | 2 (4·8%) |
| Non-disabling major stroke | 61 | 1 |
| Non-fatal disabling stroke | 40 | 1 |
| Fatal stroke† | 15 | 0 |
| Total non-stroke death | 7 | 0 |
| Non-stroke vascular death | 5 | 0 |
| Non-vascular death | 2 | 0 |
| All major stroke or death | 122 (7·0%)‡ | 2 (4·8%) |

*First beyond date of trial entry.
†10 of these resulted in death within 30 days of trial surgery.
‡1 non-vascular death followed a major stroke, hence total is not sum of categories.

Table 4: **Surgical operations and adverse events from trial surgery**

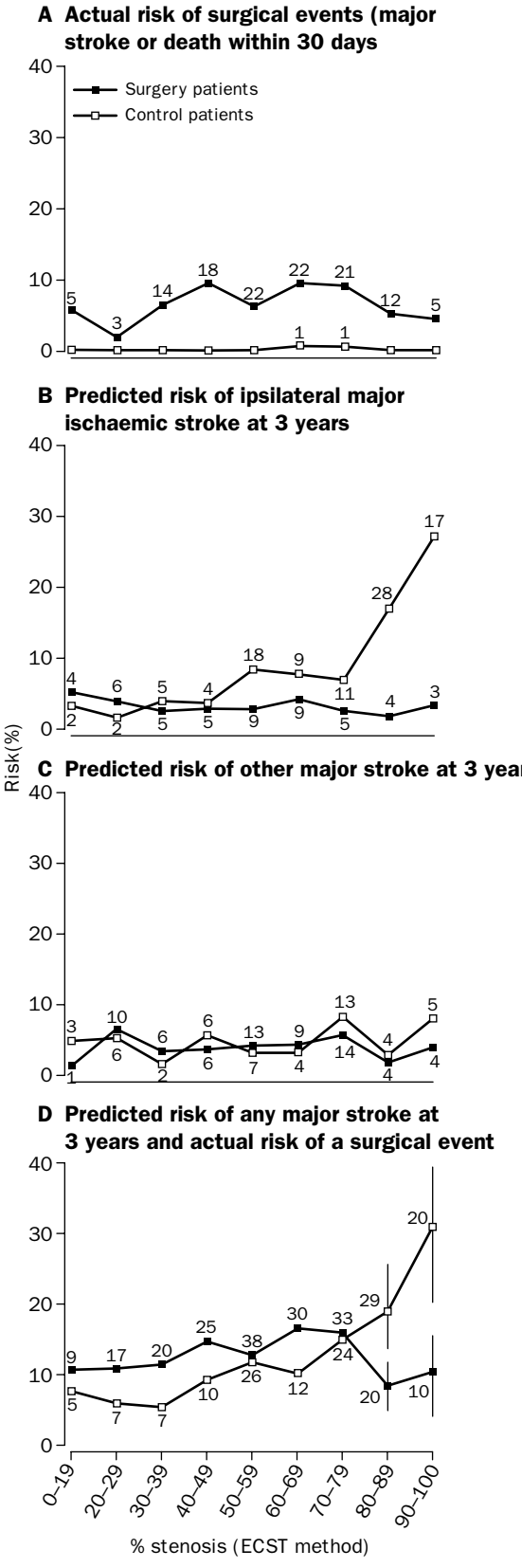



Figure 2: **Risks of outcome events by treatment group and severity of symptomatic carotid stenosis**
For surgical events, the actual risk is plotted. For ipsilateral major ischaemic stroke and other major strokes, the predicted risk at 3 years is plotted. The combined outcome is predicted risk of any major stroke at 3 years and actual risk of a surgical event.
Numbers above curves=numbers of patients with event.
Vertical bars=95% CI.

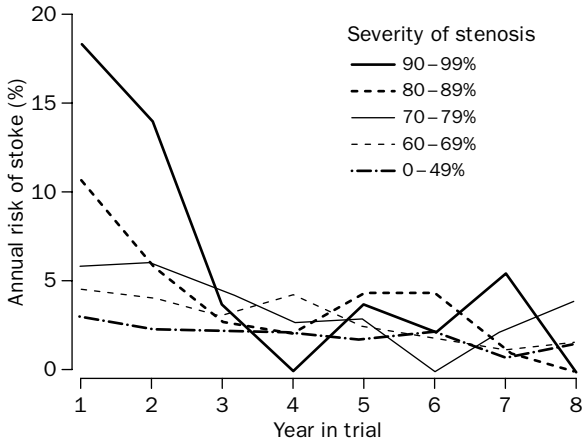
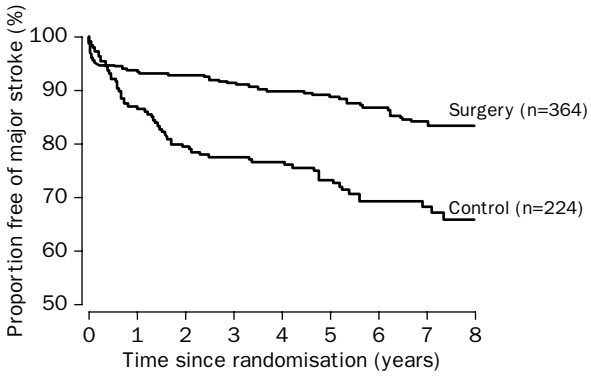



Figure 3: **Risk of any major stroke (first or subsequent) in control patients by severity of stenosis and in each of the 8 years after randomisation**

analysed time to death or major stroke using not only treatment allocation and stenosis severity, but also age and sex. We included these variables partly because increasing age is associated with an increased risk of stroke after transient ischaemic attacks,[6] and female sex with an increased risk of stroke complicating carotid endarterectomy,[5] and also because it makes clinical sense that life expectancy will actually depend on these additional variables (table 6). Age and sex had a highly significant effect on this combined outcome of major stroke or death, similar for control patients and surgery patients beyond the 5-day high-surgical-risk period; for example, women were 29% less likely than men to have a major stroke or die. Risk soon after surgery was greatly increased in a manner dependent on a complex function of stenosis and was also higher in women than in men. However, the age effect soon after surgery exactly cancelled the age effect applying to all other patients in the model, which suggests that immediate surgical risk was not related to age. Surgery patients beyond the end of the 5-day high-risk period and up to 3 years were at significantly lower risk than control patients, but this effect did not vary with age, sex, or severity of stenosis. This observation fits well with the hypothesis that stenosis severity is the major determinant of risk and that its removal leaves all patients in a similar state. Risk in the




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Surgery | 364 | 335 | 326 | 306 | 286 | 249 | 195 | 143 | 100 |
| Control | 224 | 189 | 172 | 165 | 158 | 128 | 92 | 63 | 43 |

Figure 4: **Kaplan-Meier survival curves to show survival free of major stroke (with non-stroke deaths occurring more than 30 days after surgery censored) in surgery and control patients with 80–99% stenosis of symptomatic carotid artery**

| | Surgery (n=356) | Control (n=220) | Absolute difference | 2p |
|---|---|---|---|---|
| Surgical events | 4·8 | 0 | −4·8 | . . |
| Ipsilateral major stroke excluding surgical events | 2·0 | 20·6 | 18·6 | <0·0001 |
| Ipsilateral major stroke including surgical events | 6·8 | 20·6 | 13·8 | <0·0001 |
| Other major strokes | 2·9 | 3·4 | 0·5 | 0·74 |
| Any major stroke or surgical death | 8·5 | 22·4 | 13·9 | <0·0001 |
| Death | 8·8 | 10·5 | 1·7 | 0·50 |
| Any major stroke or death | 14·9 | 26·5 | 11·6 | 0·001 |

Kaplan-Meier estimates at 3 years.

Table 5: **Frequency (%) of major outcome events among patients with 80–100% symptomatic carotid stenosis**

control group was described by a linear term in stenosis (ie, an exponential effect in the Cox model). This model predicted well the Kaplan-Meier estimates of risk at 3 years for the surgery and control groups within deciles of stenosis and the observed risks of death or stroke in the 5-day high-surgical-risk period (data available from the investigators).

The model's predictions of the difference in total major-stroke-free life expectancy between surgery and control groups are presented as a function of age and of stenosis, and by sex in figure 5. These graphs can be used in decisions on whether to offer surgery to a particular patient, by plotting his or her age and severity of stenosis on the appropriate graph. Men derived rather more benefit from surgery than did women, there was more benefit with increasing severity of stenosis, and younger patients showed definite benefit over a narrower range of severe stenosis than did older patients. For example, a man aged 70, with 80% stenosis, might gain about 8 months of major-stroke-free survival from surgery but there would be less certainty for a woman with the same characteristics.

54% of the major strokes were disabling. Although this proportion did not vary between treatment groups, with severity of stenosis, or by sex, more strokes in older patients were disabling: under 60 the proportion was 47%; for those of 60–69, 54%; and for those of 70 and over, 64%. There were too few disabling strokes for precise inferences of treatment effects to be made but

| | Hazard ratio | p for difference in hazard ratio from 1 |
|---|---|---|
| **Hazards for all patients at all times** | | |
| Age in years at randomisation | 1·042* | <0·0001 |
| Female sex | 0·71 | <0·0001 |
| **Patients from 0–5 days after trial surgery** | | |
| Treatment effect | 735 | <0·0001 |
| Female sex | 2·39 | <0·0001 |
| Age in years at randomisation | 0·959* | 0·0007 |
| Linear term in normalised stenosis (ie {Stenosis%−50}/50) | 1·28† | 0·012 |
| Square term in normalised stenosis | 0·952‡ | 0·024 |
| Cubic term in normalised stenosis | 0·982‡ | 0·038 |
| Occluded symptomatic carotid artery at randomisation | 12·77 | 0·042 |
| **Patients from 5 days to 3 years after trial surgery** | | |
| Treatment effect | 0·78 | 0·01 |
| **Control patients and surgery patients before trial surgery** | | |
| Linear term in normalised stenosis | 1·104† | <0·0001 |

*Per year of age.
†Per 10% stenosis.
‡Calculated for a change of stenosis from 50% to 60%.

Table 6: **Results from Cox proportional-hazards model of major stroke or death from any cause**

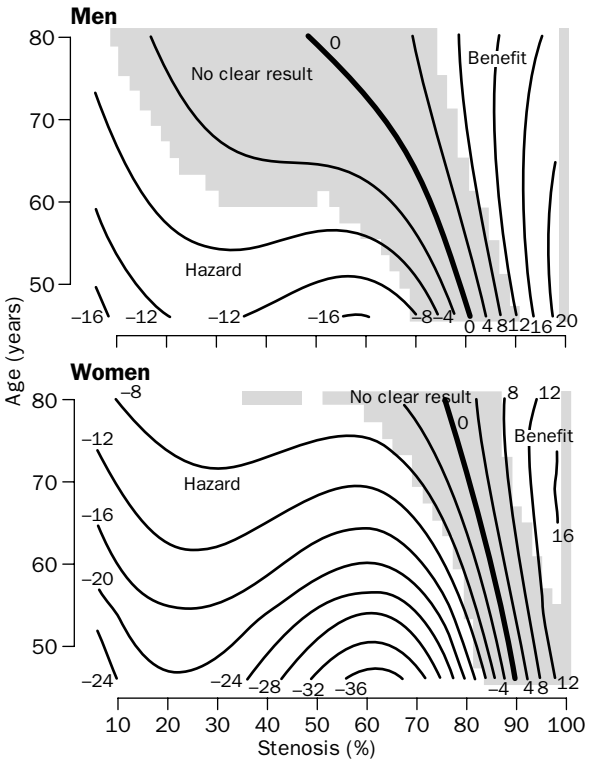



Figure 5: **Estimated change in total major-stroke-free life expectancy in months for men and women depending on their age and severity of symptomatic carotid stenosis**
Curved lines connect points of equal months of major-stroke-free life expectancy; numbers adjacent to these lines represent number of such months, either positive favouring surgery or negative against surgery. Hatched areas represent uncertainty. To the left of these areas there is definite hazard from surgery (p<0·05), and to the right definite benefit (p<0·05). The hatched vertical bar on the right of each graph excludes occluded arteries from the region of definite benefit.

rough estimates can be obtained by halving the gain in major-stroke-free life expectancy obtained from figure 5.

## Discussion

The ECST has shown that for patients with recently symptomatic carotid stenosis, carotid endarterectomy carries a small but serious risk of stroke or death; that without surgery there is a substantial risk of stroke ipsilateral to a severely stenosed carotid artery, particularly in the first 2–3 years; and that most of the risk of ipsilateral stroke is abolished by successful surgery, so most of these strokes must be caused by embolism from, or low flow distal to, severe carotid stenosis. These qualitative conclusions are based on extreme risk ratios, and are supported by the accumulating results of the parallel North American Symptomatic Carotid Endarterectomy Trial (NASCET).[7] They are most unlikely, therefore, to have been affected substantially by any minor biases in our trial; for example, the outcome assessment of stroke could not be completely masked, the measurement of stenosis was crude, and the trial was stopped early for patients with severe and mild carotid stenosis.[1]

In clinical practice, surgical risk depends on the type of patients operated on, the technique used, and the skill of the operating team. Risk may therefore differ from that reported in this trial, or in any other trial or case series. Therefore, our reported risk cannot easily be applied to the practice of an individual clinician. On the other hand,

there may be no option but to use this estimate of risk because local institutional surgical risks are rarely measured prospectively. Even if surgical risks are assessed properly, up-to-date and precise estimates of risk are all but impossible because the numbers of operated patients in the previous 1–2 years are usually so small, and the proportion of patients harmed by surgery is so low. Therefore, when considering the surgical risks in individual patients, most institutions will probably have to use the sort of risks that we and the NASCET have reported.

These risks are at least reasonably representative of what good European and North American surgeons achieved in the 1980s and 1990s. No doubt surgical risks will fall with time, and allowance can be made for this effect, perhaps by shifting downwards the severity of carotid stenosis above which surgery is indicated. On the other hand, the outlook without surgery for these patients may also improve with time as a result, perhaps, of better antiplatelet drugs, better control of raised blood pressure, and more effective cholesterol-lowering drugs. Such changes will have the effect of shifting upwards the severity of stenosis below which the risk of surgery is not worth trading off against the prognosis for stroke without surgery.

This final report adds to our interim results[1,2] and to what is so far available from the NASCET.[7] We can now refine the treatment decision for individual patients. In particular, we now know more about the severity of carotid stenosis at which the immediate risk of surgery is worth taking for future benefit in terms of long-term stroke prevention, while taking into account life expectancy. The balance of risk and benefit is definitely in favour of surgery with extreme degrees of stenosis, and definitely against surgery for mild stenosis. On the other hand, where the cut-off point for stenosis should lie, and how this might be in part determined by the life expectancy of the individual patient being considered for surgery has not been at all clear until now.

Our initial analysis here suggests that on average this cut-off point should be at about 80% stenosis (which is equivalent to about 70% stenosis in the NASCET).[3] But this approach takes no account of the patients' life expectancy and so for how long they might enjoy the advantages of surgery—in other words, for how long they might live without a stroke, particularly ipsilateral to the symptomatic carotid stenosis. Furthermore, surgery itself seems to be riskier in women than in men, not just in our study but also in a systematic review of other series.[5] The decision point for severity of stenosis will therefore be higher in women. That is why we have tried to model age and sex, as well as the severity of the stenosis, and to present the results in terms of months of major-stroke-free survival. Figure 5 shows that men derive rather more benefit than women, and that in general it is only definitely worth operating at above about 90% stenosis in women and above about 80% in men. An extra year or two of major-stroke-free survival is achievable in men, and about an extra year in women.

The success of any decision to operate based on stenosis severity alone, without taking into account age and sex, is small when assessed in the ECST population with stenosis above 70%, the previously recommended cut-off point for surgery. With our model as the gold standard, although the sensitivity of stenosis alone as the deciding factor for surgery was high (97% for men and 100% for women), the specificity was poor (69% for men and 87% for women) and would have resulted in 131 (33%) of 392 inappropriate operations among the men and 37 (70%) of 53 among the women. Of course, these inappropriate operations are all in patients for whom we still have insufficient evidence to recommend either surgery or no surgery with confidence (ie, we are not talking about patients for whom surgery is definitely not worthwhile). But, even with our better model based on age and sex as well as stenosis, there are still quite large areas of uncertainty and there are, conceivably, patients with moderate stenosis who should receive surgery, if only we knew who they were (in some sense they will be those at lowest risk with surgery and highest risk of ipsilateral stroke without surgery).

Some of our uncertainty is the result of quite small numbers in some groups of patients—for example, women aged 55 with more than 90% stenosis and men aged 80 with 30% stenosis. This must not be taken to imply that the balance of risk and benefit favours surgery, or indeed no surgery, but merely that we still do not know exactly where that balance really lies in groups such as these. This uncertainty will be reduced when we have the final results of the NASCET and can do a pooled analysis of all the individual patients' data from both trials, and also when we can refine and validate much better models to estimate baseline risk of ipsilateral ischaemic stroke in patients not treated by surgery (using not just stenosis severity, age, and sex but other prognostic factors that may be important such as eye *vs* brain ischaemia)[8] and also better models of surgical risk. Another factor that might tip the balance in favour of surgery in an individual patient is the timing of surgery. On average, we were able to achieve surgery 2–3 months after the last cerebrovascular symptoms, but earlier surgery might have a greater relative benefit because the risk of stroke without surgery decreases rapidly in patients with severe carotid stenosis (figure 3). Perhaps this decreasing risk is due to some kind of healing of an unstable atheromatous plaque or the development of better collaterals distal to the stenosis.

It is important not to lose sight of other less serious complications of surgery that we have not reported on (particularly damage to motor nerves in the operation field), as well as of the general fear and discomfort of surgery, which in some patients may well weigh against the decision to go for surgery, even at quite high degrees of stenosis. Furthermore, many centres are still not satisfied that non-invasive evaluation of the severity of carotid stenosis is sufficiently accurate to replace catheter angiography. Therefore, the inevitable but small risk of an angiographic stroke must be taken into account when advising patients whose ultrasonographic examination suggests severe stenosis whether to have an angiogram with a view to later surgery if severe stenosis is confirmed.

*ECST organisation*
*Writing Committee*—B Farrell, A Fraser, P Sandercock, J Slattery, C P Warlow.
*Policy and Monitoring Committee*—H Barnett, M Baum, R Doll (chairman), C Hill, R Peto, H Van Crevel.
*Trial Office, Department of Clinical Neurosciences, Edinburgh (1987–96)*—S Anderson, R Bland, A Bowie, Y Davidson, B Farrell, A Fraser, H Fraser, C Freir, J Halliday, A Honeymoon, T Lindsay, M Livingstone, J MacKenzie, L Maclean, R McGowan, G Moody, P Rothwell, L Scott, J Slattery, B M Smith, H Taylor, F Waddell, C P Warlow.
*Trial Office, Department of Clinical Neurology, Oxford (1981–87)*—Y Bailey, B Farrell, M Goulding, A Lawson, K McPherson, J Ratcliff, H Storey, C P Warlow.

*Clinical Trial Service Unit, Oxford*—V Boag, J Burrett, R Clack, R Collins, A Daniels, J Godwin, B Hafner, S Knight, G Mead, R Peto, A Radley, S Richards, R Ripley.
*Clinical Audit Committee*—D De Bono, M J G Harrison, A Mansfield.
*Radiological Review*—M Hourihan, P Rothwell, C P Warlow.

### Collaborators

*Australia* (1 patient): Perth (M A Goodman, G Hankey)
*Belgium* (98 patients): Brugge (M D'Hooghe, J De Letter, I Dehaene, M Lanckneus, A Lecluyse, M M B Marchau, A Rocher, M Van Zandijcke; Bruxelles (S Blecic, J P Dereume, J Hildebrand); Dendermonde (M Bosiers, E Van Buggenhout); Gent (J J De Reuck, J De Roose, D Decoo; Leuven (L Herroelen, R Suy, P Verdru); Mons (J Fastrez, P Indekeu).
*Denmark* (65 patients): Aalborg (J Christensen, K Egeblad, H H Hinge, R Jelnes, I Magnussen, J Marquardsen, J H Nehen, A M Nehen; Aarhus (T S Jensen, B S Jensen); Copenhagen (P Arlien-Soborg, G Boysen, H C Engell, T Schroeder).
*England* (762 patients): Birmingham/Coventry (J D Hamer, G Jamieson); Derby/Nottingham (K C Callum, D T Hope, D Jefferson, A Whiteley); East Berkshire (J Wade); Exeter (W B Campbell, R Hardie, J F Thompson); Leicester (P R F Bell, B Kendall, P Millac, I F Pye); Liverpool (P Harris, P Humphrey); London Middlesex/UCH (M Adiseshiah, C Bishop, M J G Harrison); London Charing Cross (R Greenhalgh, G Perkin): London St George's (M M Brown, R S Taylor); London St Mary's (H H G Eastcott, J R Kenyon, A Mansfield, A N Nicolaides, D Thomas, J H N Wolfe); Manchester North (C Bannister, D Shepherd); Manchester South (D Charlesworth, C McCollum, P O'Neill); Newcastle upon Tyne (D Bates, N Cartlidge, P Cleland, D Lambert, A D Mendelow, R Sengupta); Oxford (R Greenhall, A Molyneux, P Morris); Plymouth (B Bliss, J Gibson, D Jennings, D Thrush); Romford (L Findley); Sheffield (J Beard, U Bergvall, T Powell, G Venables, C L Welsh); Sussex (J Rees, C Strachan); Truro (B N McLean, P Smith); Wakefield (G J Brown, L Loizou).
*Finland* (141 patients): Jyvaskyla (R Fogelholm, E Hurskainen, A Rissanen); Kuopio (P Hartikainen, K Koivisto, I Oksala, P Riekkinen, J Sivenius).
*France* (271 patients): Bordeaux (J P Castel, J M Orgogozo, J J Pere); Caen (V De la Sayette, J M Derlon, F Viader); Grenoble (H Guidicelli, M Hommel, J L Magne); Meaux (F Chedru, F Gigou); Montpellier (J M Blard, P A Chaptal); Paris Henri Mondor (J P Becquemin, P Cesaro); Paris Lariboisière (B George, M Haguenau, A Rey, F Woimant); Paris Salpétrière/Saint Antoine (M-G Bousser, E Kieffer, C Petitjean, D Rougemont, P-J Touboul); Rennes (M Bihel-Schleich, A Cardon, Y Kerdiles, J F Pinel): Rouen (B Mihout, J Watelet); Toulouse (G Gilles Geraud, Y Glock, V Larrue); Tours (A Autret, F Lapierre).
*Germany* (196 patients): Berlin (R Häring, P Marx); Freiburg (A Hetzel, C H Lücking, V Schlosser, G Spillner, G M Von Reutern, M G Wernz); Giessen (C Hornig, H W Pia); Heidelberg (J R Allenberg, H Eckstein, N Maeder, R Reuther, R Winter); Mainz (G Kramer, K Nagel, G Rothacher, W Schmiedt, B Tettenborn); Minden (O Busse, H Griese, J Gronninger, I Kunze).
*Italy* (264 patients): Ancona (F Alo, L Carbonari, G Ceravolo, L Provinciala); Aosta (E Bottacchi, G D'Alessandro, D Palombo, F Peinetti, C Porta); Bergamo (G Bonaldi, M Camerlingo, L Casto, G M Losapio, A Mamoli, M Selti); Bologna (A Andreoli, E Pozzati, R Zoni); Brescia (P Anzola, M Floriani, S Giulini); Firenze (C Baruffi, D Bertini, D Inzitari, P Nencini, C Pratesi); Milano Niguarda (O Arena, G Bottini, M Collice, R Sterzi); Milano Policlinico (E Cella, G Landi); Padova/Venezia (G P Deriu, M Haefele, A Saia); Perugia (E Biasini, E Boschetti, P Cao, N Caputo, M G Celani, A Del Favero, L Moggi, G Nenci, S Ricci, U Senin, F Simoncini, E Signorini); Torino (C Buffa, M Conforti, F Ponzio, C Ravetti); Trieste (R Adovasio, L Antonutti, N Carraro, G Cazzato, F Chiodo Grandi, G Mase, M Pasqua, M Zorzon).
*Netherlands* (458 patients): Amsterdam (M Limburg, H Speelman); Eindhoven (J N Berendes, J Buth); Enschede (P J A M Brouwers, P De Smit, J Hoogendam, E N H Jansen, J Nihom, F G Roozenboom, R J Van Det); Heerlen (E C Bollen, C L Franke, H Van Houtte); Maastricht (P Kitslaar, J Lodder); Nijmegen (A Keyser, B P M Schulte); Rotterdam (N A J J DuBois, P Koudstaal, M Van Gemert, H Van Urk, M Vermeulen); The Hague Leyenburg (L J Endtz, R E M Hekster, J C Sier, A R Wattendorf); The Hague Westeinde (A C De Vries, J T J Tans, V Van Kasteel); Tilburg (A A W Op de Coul, R Schellens, C C Tijssen, D Van Berghe Henegouwen); Utrecht (B C Eikelboom, L J Kappelle, J Van Gijn, T Van Vroonhoven); Venlo (M G M H Barwegen, B J Meems, T G Segeren, G D M Van Hellemondt).
*Norway* (76 patients): Oslo Aker Sykehus (T Dahl, A Kroese, P M Sandset); Oslo Akershus (T Broyn, B Hoivik, O Rosjo).
*Portugal* (51 patients): Lisboa (J Campos, M Crespo, A Damiao, J Fernandes, J M Ferro, T P Melo, V Oliveira).
*Scotland* (308 patients): Aberdeen (J Engeset, J Hern, R S G Knight); Dundee (D L W Davidson, R Roberts, T R K Varma, J Winton McNab); Edinburgh (R Cull, A Jenkins, V Ruckley, P A G Sandercock, R Sellar, C P Warlow); Glasgow (I Bone, M Calvert, R Carter, W F Durward, D Gilmour, P Leiberman, R Quin, E Teasdale).
*Spain* (129 patients): Barcelona-Bellvitge (J Arruga, M Calopa, J M Capdevilla, J L Monfort, F Rubio, R Vila, M A de Miguel); Barcelona Del Mar (S Alfonso, M Cairols, C Oliveras); Bilbao (A G Alfageme, J Larracoechea); Madrid (C Ricart, J G Uria); Madrid La Paz (P Barreiro, E Diez-Tejedor, A Frank, P Magallon, L Saez); Majorca (G Amer, C Corominas, A Gimenez-Gaibar, J Julia, P Lozano, M Palomar); Sevilla (R Alberca, J L Garcia-Rodriguez, A Gil-Peralta, J R Gonzalez-Marcos, A Mayol); Tarragona (R Mares, R Martin-Paredoro).
*Sweden* (177 patients): Goteborg (C Blomstrand, J Holm, L Kjallman, T Lundh); Helsingborg (S Bornhov, G Plate, P Ovarfordt); Kalmar (L Brattstrom, S Kallero); Linkoping/Norrkoping (A Alm, J Elfstrom, I Johansson, F Lundgren, J Radberg, L Skoglund, V Zbornikova); Orebro (N Rudback, M Samuelsson, B Stenburg); Stockholm, (H-G Hardemark, P Konrad, V Kostulas, M Lindqvist, P Olofsson, C E Soderstrom, J Swedenborg, R Takolander, M Von Arbin, N G Wahlgren).
*Wales* (21 patients): Cardiff (A Compston, K Frazer); Llandough (J Harvey, J H Lazarus).

### Acknowledgments

The trial was principally funded by the UK Medical Research Council, the European Union Biomed 1 programme, and the University of Oxford ICRF/MRC Clinical Trial Service Unit. The Netherlands Heart Foundation, the French INSERM, Sandoz, Bayer, European Aspirin Foundation, Pfizer, and Boehringer Ingelheim all helped with the collaborators' meetings and with travel. The design, conduct, analysis, and reporting of the trial were independent of all sponsors.

### 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.
2 European Carotid Surgery Trialists' Collaborative Group. Endarterectomy for moderate symptomatic carotid stenosis: interim results from the MRC European Carotid Surgery Trial. *Lancet* 1996; **347:** 1591–93.
3 Rothwell PM, Gibson RJ, Slattery J, Sellar RJ, Warlow CP, for the European Carotid Surgery Trialists' Collaborative Group. Equivalence of measurements of carotid stenosis: a comparison of three methods on 1001 angiograms. *Stroke* 1994; **25:** 2435–39.
4 Bamford JM, Sandercock PAG, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; **20:** 828.
5 Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death due to carotid endarterectomy. *BMJ* 1997; **315:** 1571–77.
6 Hankey GJ, Warlow CP. Transient ischaemic attacks of the brain and eye. London: WB Saunders, 1994.
7 North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991; **325:** 445–53.
8 Streifler JY, Eliasziw M, Benavente RO, et al, for the North American Symptomatic Carotid Endarterectomy Trial. The risk of stroke in patients with first-ever retinal vs hemispheric transient ischaemic attacks and high-grade carotid stenosis. *Arch Neurol* 1995; **52:** 246–49.