Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis

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Summary

Background Endarterectomy reduces risk of stroke in certain patients with recently symptomatic internal carotid stenosis. However, investigators have made different recommendations about the degree of stenosis above which surgery is effective, partly because of differences between trials in the methods of measurement of stenosis. To accurately assess the overall effect of surgery, and to increase power for secondary analyses, we pooled trial data and reassessed carotid angiograms.

Methods We pooled data from the European Carotid Surgery Trial (ECST), North American Symptomatic Carotid Endarterectomy Trial, and Veterans Affairs trial 309 from the original electronic data files. Outcome events were re-defined, if necessary, to achieve comparability. Pre-randomisation carotid angiograms from ECST were re-measured by the method used in the other two trials.

Results Risks of main outcomes in both treatment groups and effects of surgery did not differ between trials. Data for 6092 patients, with 35 000 patient-years of follow-up, were therefore pooled. Surgery increased the 5-year risk of ipsilateral ischaemic stroke in patients with less than 30% stenosis (n=1746, absolute risk reduction −2·2%, p=0·05), had no effect in patients with 30–49% stenosis (1429, 3·2%, p=0·6), was of marginal benefit in those with 50–69% stenosis (1549, 4·6%, p=0·04), and was highly beneficial in those with 70% stenosis or greater without near-occlusion (1095, 16·0%, p<0·001). There was a trend towards benefit from surgery in patients with near-occlusion at 2 years' follow-up (262, 5·6%, p=0·19), but no benefit at 5 years (–1·7%, p=0·9).

Interpretation Re-analysis of the trials with the same measurements and definitions yielded highly consistent results. Surgery is of some benefit for patients with 50–69% symptomatic stenosis, and highly beneficial for those with 70% symptomatic stenosis or greater but without near-occlusion. Benefit in patients with carotid near-occlusion is marginal in the short-term and uncertain in the long-term.

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Introduction

In the USA, the rate of carotid endarterectomy has more than doubled since the publication of positive results from large randomised controlled trials.[1–3] Roughly 150 000 operations were done in 1998, about half of which were for recently symptomatic carotid stenosis.[4,5] Rates of endartectomy have also risen in Europe.[6]

There have been five randomised trials of endarterectomy for recently symptomatic carotid stenosis.[1,2,7–9] The first two were small, were done more than 20 years ago, included a high proportion of patients with non-carotid symptoms, and did not stratify results by severity of stenosis.[8,9] In 1991, the Veterans Affairs trial (VA309) reported a non-significant trend in favour of surgery,[7] but was stopped early when the initial results of the two largest trials, the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), were reported.[10,11] The final results of these trials were published in 1998.[1,2] The ECST investigators reported benefit from surgery only in patients with 80% stenosis or greater, and in women with 90% stenosis or greater.[1] Clinical guidelines in Europe are based on these results.[6,12] By contrast, the NASCET findings showed significant benefit from surgery in patients with 50% stenosis or greater,[2] and North American guidelines are based on these results.[13,14]

The differences between the trial results are partly due to differences in the methods of measurement of the degree of carotid stenosis on the prerandomisation catheter angiograms;[15] the method used in ECST produces higher values than that used in NASCET and VA309 (figure 1).[16,17] The definitions of outcome events also differed. Meta-analyses of the overall trial results have been reported,[18,19] but these took no account of the differences between the trials. Only by detailed re-analysis of the individual patient data and reassessment of the original angiograms can the results be properly compared or combined.

Our aim was to determine with as much precision as possible the effectiveness and durability of endarterectomy by degree of carotid stenosis. We therefore pooled data for individual patients from the three trials, reassessed the original angiograms, and did analyses with the same method of measurement of stenosis and the same definitions of outcomes.

Methods

Searches for randomised controlled trials of endarterectomy plus medical treatment versus medical treatment alone for symptomatic carotid stenosis[18–20] identified only five trials.[1,2,7–9] Since the two small, early trials no longer accord with current clinical practice,[8,9] data from the three most recent trials (ECST, NASCET, and VA309) were used.[1,2,7] These data consisted of all patients randomised in the past 20 years, which were more than 95% of patients ever randomised.

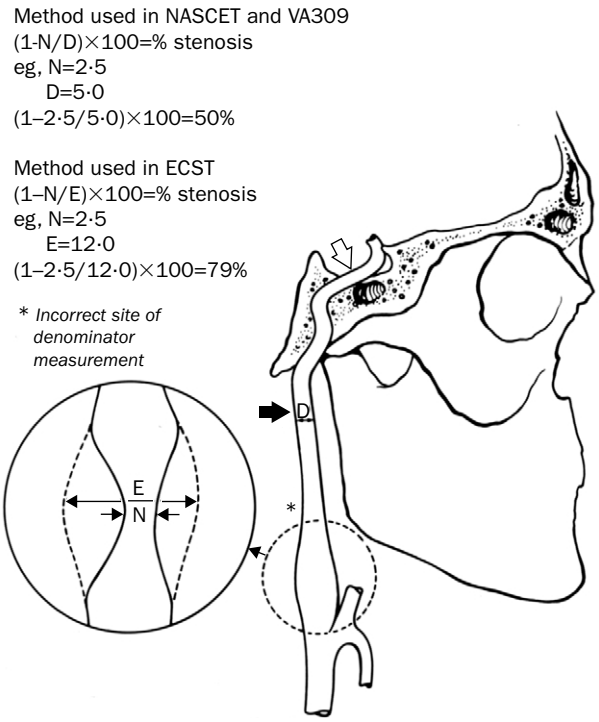

Figure 1: **Schematic diagram of carotid bifurcation and internal carotid artery, showing methods of measurement of the degree of carotid stenosis on an arterial angiogram**

Comparability of trial designs

The methods of the three trials were very similar, and have been reported and compared in detail.[18–22] Briefly, patients were recruited if they had had a recent carotid distribution transient ischaemic attack, non-disabling ischaemic stroke, or a retinal infarction, and had a stenosis of the ipsilateral (symptomatic) carotid artery. Before randomisation in all trials patients were required to be seen by a neurologist or a stroke physician to confirm their eligibility, and the symptomatic carotid artery (and preferably the contralateral carotid artery and intracranial circulation) had to be imaged by angiography (usually selective catheter angiography). Treatment (immediate carotid endarterectomy plus best medical treatment *vs* best medical treatment alone) was allocated by central telephone randomisation stratified by centre. A neurologist or a stroke physician followed-up the patients at prespecified intervals.

In ECST recruitment was from 100 centres in 14 European countries, in the NASCET from 106 centres mainly in the USA and Canada, but including some in Europe, Israel, South Africa, and Australia; and VA309 from 16 Veterans Affairs medical centres in the USA. Although the trial designs were similar, there were some differences in methods between ECST and NASCET and between these trials and VA309. (1) VA309 included only men; ECST and NASCET included both sexes. (2) Time from last cerebrovascular event to randomisation had to be less than 4 months in VA309 and in NASCET (changed to 6 months after 1991), and less than 6 months in ECST. (3) In ECST, inclusion and exclusion were based on the uncertainty principle,[10] whereas NASCET and VA309 had specified criteria.[7,11] Thus, patients with any degree of carotid stenosis could be randomised or treated outside the trial at the discretion of the physician in ECST, whereas NASCET and VA309 intended only to recruit patients with stenosis greater than 30% and 50%, respectively. (4) Patients were randomised in a 50/50 ratio in NASCET and VA309, and in a 60 (surgery) to 40 (no surgery) ratio in ECST. (5) The recommended dose of aspirin was 1300 mg in NASCET, 325 mg in VA309, and unspecified in ECST. (6) Follow-up was at 1, 3, 6, 9, and 12 months, and every 4 months thereafter in NASCET; at 4 and 12 months and yearly thereafter in ECST; and at 1 and 3 months, and every 6 months thereafter in VA309.

Pooling of individual patient data

The original individual patient data were obtained for the three trials. Data on presenting events, baseline clinical, brain imaging, and angiographic characteristics, surgical and anaesthetic techniques, and follow-up were merged into a single composite database. Detailed consideration was given to the definitions of each variable used in the original trials. When definitions were identical, comparable data were merged. If possible, differences in definitions of variables between studies were resolved by reconstruction of definitions to achieve comparability.

Reassessment of carotid angiograms and identification of near-occlusions

All ECST and NASCET pre-randomisation angiograms had been obtained and reviewed centrally. So that analyses could be consistently stratified by degree of symptomatic carotid stenosis, the 3018 ECST angiograms were remeasured by one observer (PMR), who was unaware of outcome events, and the degree of stenosis re-calculated by the method used in NASCET and VA309. The NASCET method is based on measurement of the minimum residual lumen at the point of maximum stenosis and the diameter of the normal internal carotid artery well beyond the carotid bulb at a point where the walls of the artery are parallel. Observer agreement between PMR and the NASCET principal neuroradiologist (AJF) was assessed with 120 randomly selected angiograms (60 from ECST and 60 from NASCET).

The degree of stenosis cannot be calculated by the method used in NASCET and VA309 on angiograms in which the post-stenotic internal carotid artery (ICA) is narrowed to the point of near-occlusion (figure 2). In the original NASCET reports, these near-occlusions were identified and assigned as 95% stenosis for the analysis.[17,23] Near-occlusions were therefore identified during the

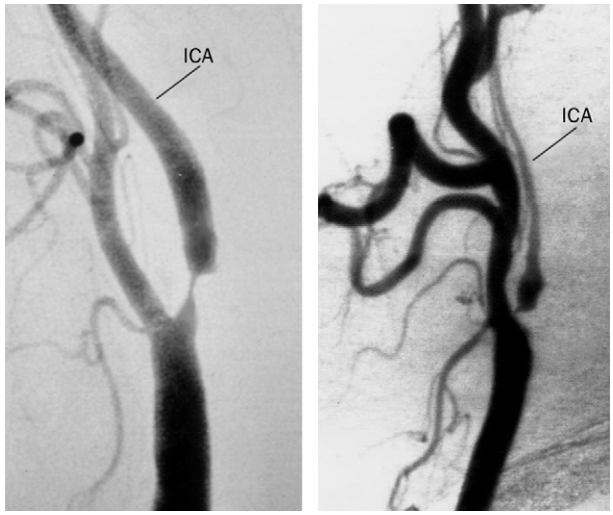

Figure 2: **Arterial angiograms of carotid bifurcation showing 85% stenosis by method of measurement used in NASCET and VA309 (left) and near-occlusion (right)**
ICA=internal carotid artery.

reassessment of ECST angiograms for our study. The previously reported NASCET angiographic criteria for near-occlusion were used: severe stenosis with evidence of reduced flow in the distal ICA (delayed arrival of contrast into the distal ICA, or evidence of collateral flow of contrast towards the symptomatic cerebral hemisphere from other arterial territories, or both) and evidence of narrowing of the poststenotic ICA (lumen diameter similar to, or less than, the ipsilateral external carotid artery and less than the contralateral ICA).[23–25] To ensure comparability with NASCET, the NASCET principal neuroradiologist (AJF) assessed all potential near-occlusions identified in the ECST. The VA309 trial angiograms were not available for further review, and were not included in the analysis of near-occlusions. For the analysis, all VA309 angiograms with 70% stenosis or greater were categorised as 70% stenosis or greater without near-occlusion.

Redefinition of outcome events

In NASCET and VA309, a stroke outcome was defined as a cerebrovascular event with symptoms lasting longer than 24 h. In ECST, investigators had recorded all such events, but had restricted analysis to events with symptoms that lasted for at least 7 days. In NASCET and VA309, retinal infarcts were included as stroke outcomes. In ECST, they were not, although they were recorded. For the combined analyses, stroke was defined as any cerebral or retinal event with symptoms lasting longer than 24 h.

In ECST and NASCET, investigators used the modified Rankin scale to define disabling stroke; [26] in VA309 an equivalent in-house scale was used. Disability was defined 3 months after stroke in the NASCET, at 6 months in ECST, and at the next routine follow-up assessment in VA309. For the combined analysis, disabling stroke was defined as a stroke that resulted in a Rankin score of three or more, or equivalent, at these points of follow-up.

Analysis

All patients included in the final analysis of the results of the original trials were included in the combined analysis. The main analyses were stratified according to the stenosis groups that were used in NASCET (<30%, 30–49%, 50–69%, ⩾70%),[2] with near-occlusions analysed separately. Outcomes defined for analysis of the effectiveness of surgery were: (1) time to any first stroke or operative death; (2) time to first ipsilateral ischaemic stroke in the territory of the symptomatic carotid artery, and any stroke or death that occurred within 30 days of trial surgery; and (3) time to first ipsilateral disabling or fatal ischaemic stroke in the territory of the symptomatic carotid artery, and any disabling stroke or death that occurred within 30 days of trial surgery.

Trial surgery was defined as the first carotid endarterectomy done in patients who were randomised to surgery. Operative risk was defined as any stroke or death that occurred within 30 days of trial surgery. Surgical death included all deaths within 30 days of trial surgery. The symptomatic carotid artery was defined as in the original trials.[1,2,7]

	ECST[1]	NASCET[2]	VA309[7]	Total
General				
Patients	3018	2885	189	6092
Sex				
Male	2168 (72%)	2012 (70%)	189 (100%)	4369 (72%)
Female	850 (28%)	873 (30%)	0 (0%)	1723 (28%)
Age (years)				
<65	1744 (58%)	1161 (40%)	90 (48%)	2995 (49%)
65–74	1098 (36%)	1315 (46%)	83 (44%)	2496 (41%)
⩾75	176 (6%)	409 (14%)	16 (9%)	601 (10%)
Presenting event				
Stroke	1274 (42%)	1301 (45%)	50 (27%)	2625 (43%)
Ocular events only	568 (19%)	546 (19%)	53 (28%)	1167 (19%)
Carotid territory				
Left	1620 (54%)	1514 (53%)	103 (55%)	3237 (53%)
Right	1398 (46%)	1371 (48%)	86 (46%)	2855 (47%)
Time since last symptoms				
0–1 month	1087 (35%)	1284 (45%)	115 (61%)	2486 (41%)
2–3 months	1160 (38%)	1047 (36%)	61 (32%)	2268 (37%)
⩾4 months	771 (26%)	554 (19%)	13 (7%)	1338 (22%)
Angiography				
Symptomatic carotid stenosis				
<30%	1321 (44%)	425 (15%)	0 (0%)	1746 (29%)
30–49%	487 (16%)	942 (33%)	0 (0%)	1429 (24%)
50–69%	646 (22%)	856 (30%)	47 (25%)	1549 (25%)
⩾70%	429 (14%)	525 (18%)	141 (75%)	1095 (18%)
Near-occlusion	125 (4%)	137 (5%)	NA	262 (3%)
Occlusion	9 (0%)	0 (0%)	0 (0%)	9 (0%)
Missing data	1 (0%)	0 (0%)	1 (1%)	2 (0%)
Total	3018 (100%)	2885 (100%)	189 (100%)	6092 (100%)
Contralateral ICA occlusion	97 (3%)	155 (5%)	14 (7%)	266 (4%)
Medical history				
Previous stroke	181 (6%)	435 (15%)	17 (9%)	633 (10%)
Myocardial infarction	362 (12%)	571 (20%)	68 (36%)	1001 (16%)
Angina	510 (17%)	775 (27%)	86 (46%)	1371 (23%)
Coronary artery surgery	72 (2%)	341 (12%)	36 (19%)	449 (7%)
Peripheral vascular disease	516 (17%)	436 (15%)	79 (42%)	1031 (17%)
Cardiac failure	46 (2%)	71 (3%)	7 (4%)	124 (2%)
Treated diabetes	354 (12%)	622 (22%)	57 (30%)	1033 (17%)
Current smoking	1400 (46%)	1218 (42%)	172 (91%)	2790 (46%)

NA=not available. Data are number (% of number in trial) patients.

Table 1: **Baseline clinical and angiographic characteristics of patients according to source trial**

Trial	ECST		NASCET		VA309		Total		p*
Outcome									
Stroke or death									
<50%	73/1044	6·9% (5·4–8·6)	43/663	6·5% (4·7–8·6)	0/0	..	116/1707	6·7% (5·6–8·0)	0·52
50–69%	37/371	10·0% (6·9–13·1)	30/421	7·1% (4·8–10·0)	2/20	10·0% (1·2–3·2)	69/812	8·4% (6·6–10·5)	0·16
⩾70%	17/249	6·8% (4·0–10·7)	14/261	5·4% (3·0–8·8)	5/71	7·0% (2·3–15·7)	36/581	6·2% (4·4–8·5)	0·58
Near-occlusion	3/78	3·8% (0·8–10·8)	5/70	7·1% (2·4–15·0)	0/0	..	8/148	5·4% (2·4 –10·4)	0·48
Total	130/1742	7·5% (6·3–8·8)	92/1415	6·5% (5·3–7·9)	7/91	7·7% (3·1–15·2)	229/3248	7·1% (6·3–8·1)	0·30
Death									
<50%	10/1044	0·9% (0·5–1·7)	7/663	1·1% (0·4–2·2)	0/0	..	17/1707	1·0% (0·6–1·6)	0·80
50–69%	6/371	1·5% (0·6–3·3)	6/421	1·4% (0·5–3·1)	0/20	0% (0–16·8)	12/812	1·4% (0·8–2·5)	0·83
⩾70%	1/249	0·4% (0–12·2)	1/261	0·4% (0–2·1)	3/71	4·2% (0·8–11·9)	5/581	0·9% (0·3–2·0)	0·97
Near-occlusion	0/78	0% (0–4·6)	1/70	1·4% (0–7·7)	0/0	..	1/148	0·7% (0–3·7)	0·29
Total	17/1742	1·0% (0·6–1·6)	15/1415	1·1% (0·6–1·7)	3/91	3·3% (0·7–9·3)	35/3248	1·1% (0·8–1·5)	0·86

Data are number/events/number/patients, and percentage risk (95% CI). *Heterogeneity.

Table 2: **Risks/death and stroke or death within 30 days/surgery in patients who underwent trial surgery by degree/symptomatic carotid stenosis**

In randomised controlled trials of carotid endarterectomy, the cumulative risk of outcome events is different in the two treatment groups. The risk of stroke and death is high immediately after endarterectomy in patients randomised to surgery, but is low thereafter, whereas the cumulative risk increases gradually over time in patients randomised to medical treatment. Consequently, surgery has harmful effects during early follow-up, but might be beneficial with longer follow-up. The qualitative change in the effect of treatment over time means that neither standard meta-analytic techniques nor Cox proportional hazards models are appropriate methods for derivation of estimates of overall treatment effects. An alternative, if the hazard rates and treatment effects are similar across the trials, is to pool data for individual patients and to do Kaplan-Meier analyses of event-free survival on the pooled data, with stratification by trial where necessary.

To establish whether analyses of pooled data might be inappropriate, we attempted to identify within each stenosis group any differences between the trials in the risks of the three main outcome events within each treatment group, and in the effect of the randomised treatment allocation on the absolute and relative risks of the three main outcomes at 3, 5, and 8 years' follow-up. Analyses of the pooled data were done only if there was no significant heterogeneity between the trials. Significance of heterogeneity (p_{het}) between trials in the relative risk reduction with surgery was calculated with Woolf's χ^2 test.[27]

All analyses of the effect of surgery were done on an intention-to-treat basis according to the randomised treatment allocation. Significance of differences between treatment groups was assessed by the log rank test, stratified by study.[28] Estimates of the absolute treatment effect (and 95% CIs) at 3, 5, and 8 years follow-up were calculated from the Kaplan-Meier event-free survival curves. Significance of differences in baseline data between trials and treatment groups was tested by χ^2 test or t test, as appropriate. All analyses were done with SPSS for Windows (version 10.0).

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Because of remeasurements of the degree of carotid stenosis and specific other baseline clinical characteristics, and changes in definitions of outcome events, the data we obtained differ slightly from those in the original trial reports. Individual patient data were available for all 6092 patients randomised and included in the final analysis of the three original trials (table 1). Of these, one VA309 patient had no follow-up data at the time the trial was stopped, nine ECST patients had an occlusion of the symptomatic carotid artery on the prerandomisation angiogram, and the degree of stenosis was unknown in one further ECST patient. These cases were not included in analyses of the effect of surgery by stenosis group. Thus, 6081 (99·8%) patients were included in analyses of the effect of surgery stratified into the prespecified stenosis groups. Mean follow-up was 65 months (SD 34, range 1 day–167 months), giving a total of 35 000 patient-years of follow-up, with 1711 stroke outcomes in 1265 patients.

Reassessment of carotid angiograms showed that the relation between ECST and NASCET/VA309 measurements was linear for stenosis of greater than 30% and they were highly correlated (r=0·94, p<0·00001), but the ECST method produced higher values than the method used in the other two trials. For example, on average, 50% and 70% stenosis by the NASCET/VA309 method were equivalent to 65% and 82% stenosis, respectively, by the ECST method. Near-occlusion with poststenotic narrowing of the ICA was present in 262 patients (125 in ECST and 137 in NASCET). Inter-observer agreement between the ECST and NASCET radiologists in the allocation of the degree of stenosis into the standard categories was good (κ=0·70, 95% CI 0·59–0·83, p<0·0001), and there was no systematic bias between the two observers.

Table 1 shows the characteristics of the patients in every trial. Some differences arose because of variation in inclusion criteria. For example, patients in VA309 were all male and all had at least 50% symptomatic carotid stenosis. However, they were also less likely to have had a stroke as the presenting event than those in the other two trials, and they tended to have more vascular risk factors than patients in ECST and NASCET. There were also some differences between the ECST and NASCET. For example, NASCET had more elderly patients, and the median time from last symptoms to randomisation was less than in the ECST. However, the trial populations were otherwise broadly similar.

Of the patients who were randomised to surgery, 1742 of 1807 underwent trial surgery in ECST, 1415 of 1436 in NASCET, and 91 of 91 in VA309. The median time from randomisation to trial surgery was 2 days in VA309, 3 days in NASCET, and 14 days in ECST. Table 2 shows the risks of stroke or death within 30 days of trial surgery. Operative risk of stroke and death did not differ between the trials (χ^2=1·1, df=2, p=0·6). There was a non-significant trend towards higher operative stroke

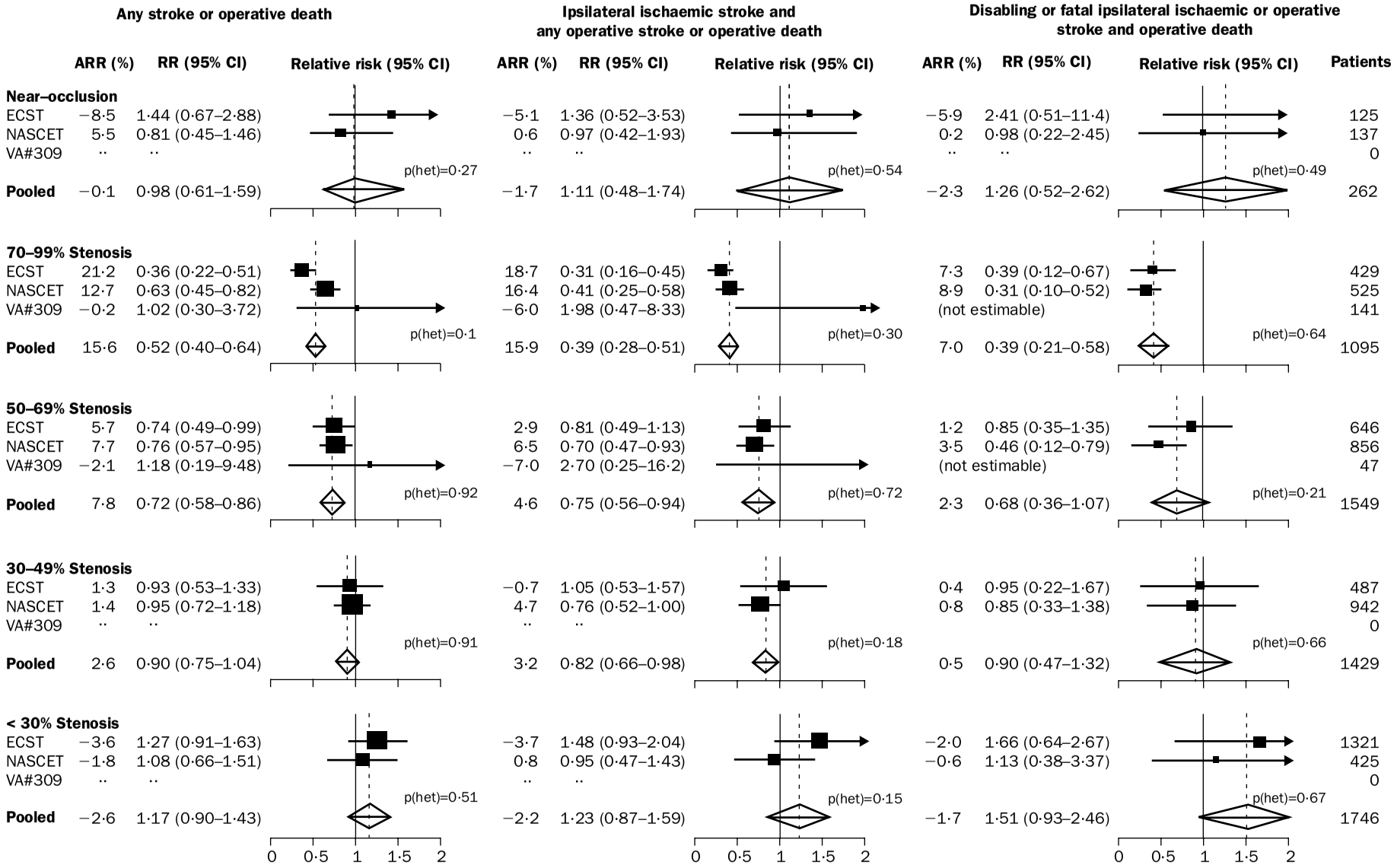

Figure 3: **Relative (RR) and absolute (ARR) reductions in risk of main trial outcomes in the surgery group by degree of symptomatic carotid stenosis**
Analyses are based on 5-year follow-up in ECST and NASCET, and 2-year follow-up in the VA309 trial. p(het)=significance of any differences between trials in relative risk with surgery.

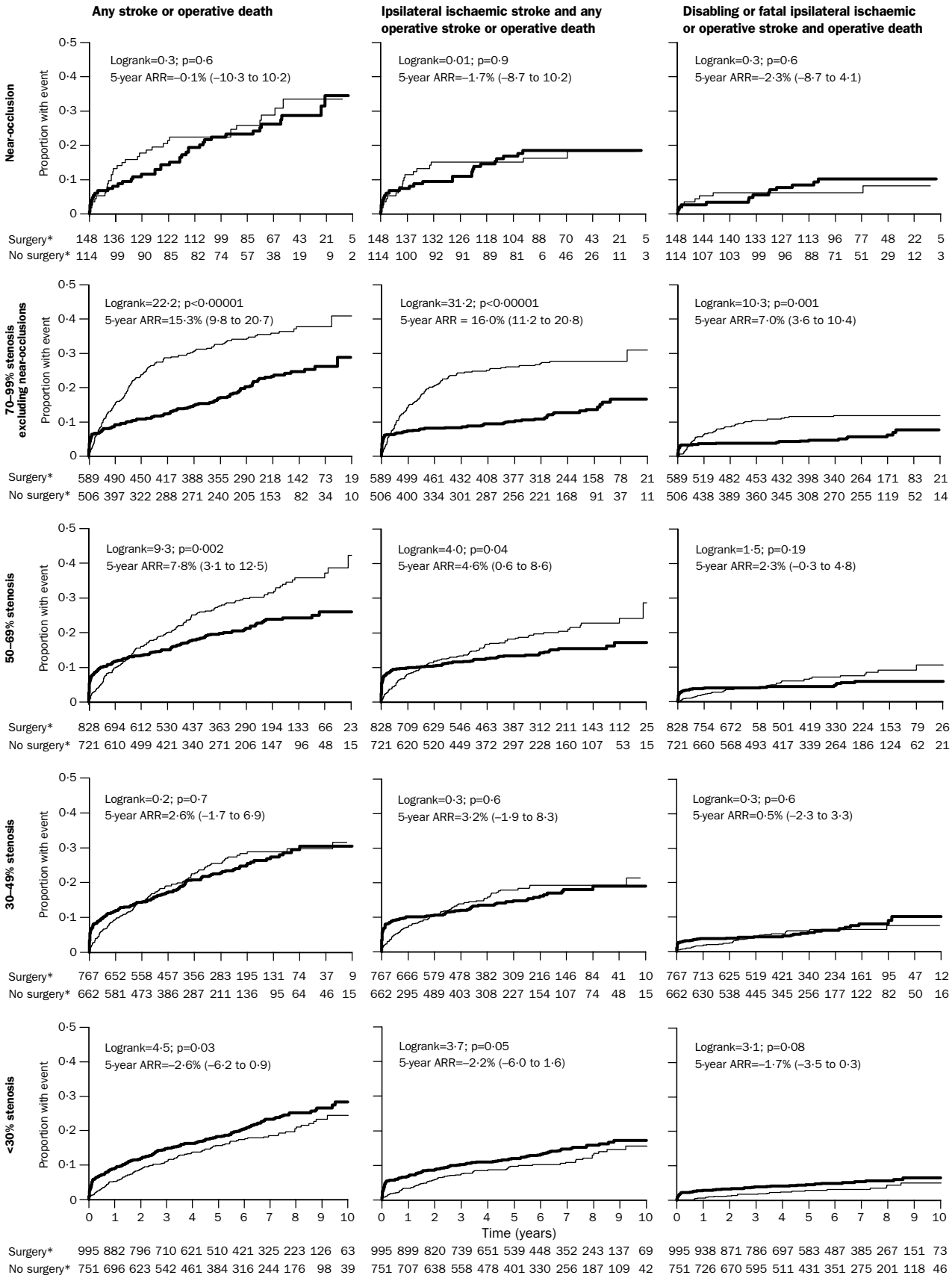

Figure 4: **Effects of surgery on main study outcomes by degree of symptomatic carotid stenosis in analysis of pooled data from ECST, NASCET, and VA309**

*Numbers at risk. Thick line is surgical treatment; thin line is medical treatment. Analysis was by intention-to-treat.

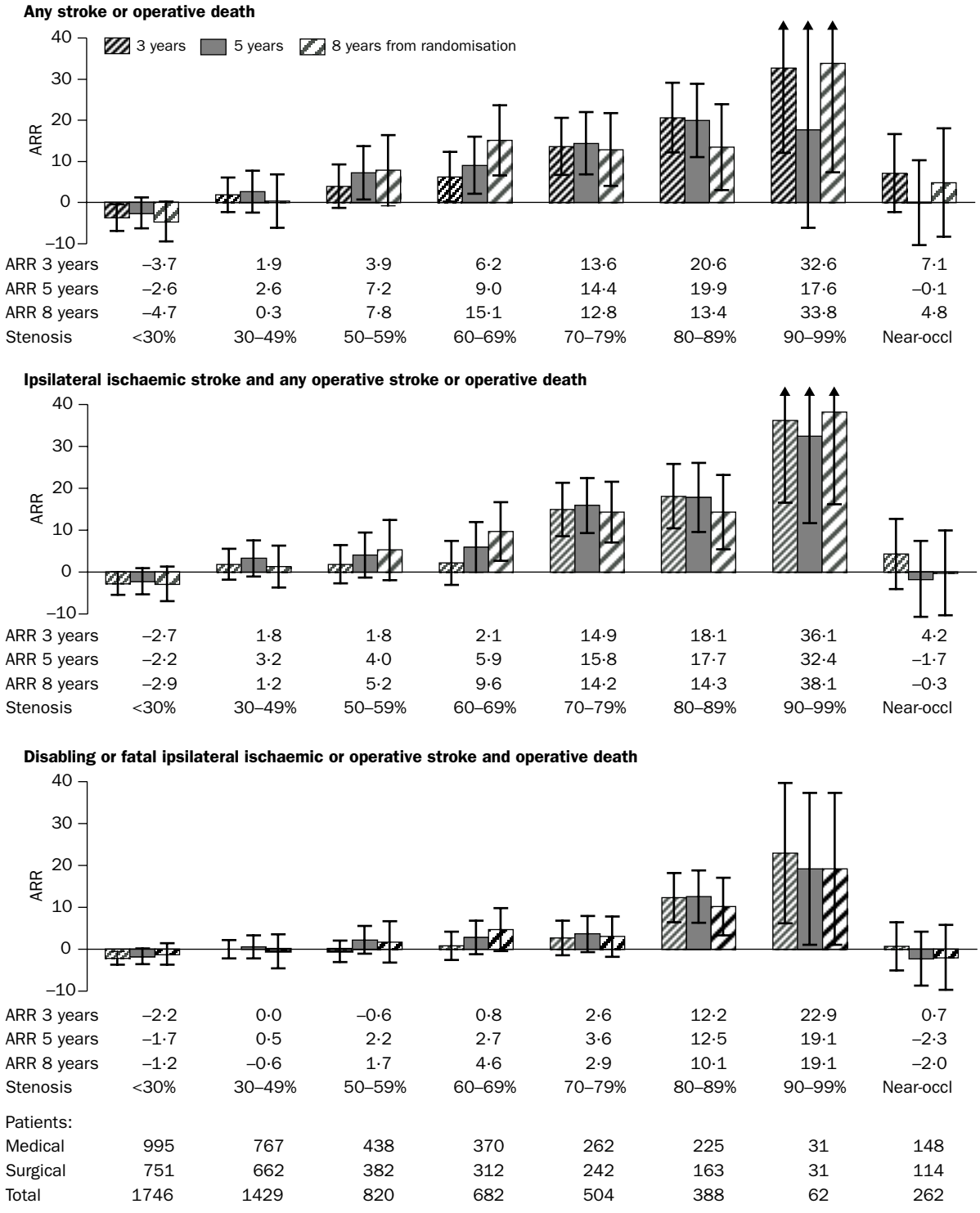

Figure 5: **Effect of surgery on absolute risk of main trial outcomes at 3, 5, and 8 years' follow-up by degree of symptomatic carotid stenosis, in analysis of pooled data from ECST and NASCET**

Exact absolute risk reductions (ARR) with surgery are given below each graph. Near-occl=near-occlusion. Analysis was by intention-to-treat. See Results, 5th paragraph, for details of crossovers. Bars are 95% CI. The upper 95% CIs of the 90–99% stenosis group are 53·2%, 41·5%, and 60·2% for any stroke or operative death at 3, 5, and 8 years, respectively, and 55·7%, 53·1%, and 60·1%, respectively, for ipsilateral ischaemic stroke and any operative stroke or operative death.

morbidity in patients with 50–69% stenosis in ECST and VA309 compared with NASCET, but operative mortality did not differ.

In all the trials, some of the patients who were randomised to medical treatment had endarterectomy of the symptomatic carotid artery during follow-up. This situation arose in 458 patients: 118 of 1211 (10%) in ECST, 331 of 1449 (23%) in NASCET, and nine of 98 (9%) in VA309. The median time from randomisation to such surgery was 536 (IQR 162–975) days in ECST, 555 (217–963) days in NASCET, and 79 (4–182) days in VA309. Surgery was done mostly in patients who had severe stenosis at randomisation: 33 of 114 (29%) with near-occlusions; 161 of 506 (32%) with 70% stenosis or

greater without near-occlusion; 132/721 (18%) with 50–69% stenosis; 87 of 662 (13%) with 30–49% stenosis; 44 of 751 (6%) with less than 30% stenosis. Most of these crossovers happened after the announcement of benefit from surgery in patients with 70% stenosis or greater by the investigators of ECST and NASCET in 1991,[10,11] and most patients who had more than 70% stenosis at baseline and who subsequently had operations had stenosis of 70% or greater by the time of surgery.

We noted no differences between the trials in the risks of the main outcomes, when stratified by stenosis group and treatment group. Neither was there any significant heterogeneity between the trials in the effect of the randomised treatment allocation on the relative risks of any of the main outcomes in any of the stenosis groups. Figure 3 shows the effect of surgery on the relative risks of the main outcomes at 5 years' follow-up, along with the corresponding absolute risk reductions, by degree of stenosis for ECST and NASCET. The results of VA309 are also included in figure 3, but are calculated at 2 years because the trial was stopped early before follow-up was complete. The seeming absence of benefit from surgery in VA309 compared with ECST and NACSET indicates the low risk of stroke in the medical treatment group at this early stage of follow-up. The trend towards greater harm from surgery in the group with less than 30% stenosis in ECST than in NASCET is attributable to a higher proportion of patients in this group in ECST having very mild (<10%) stenosis (62% *vs* 27%). However, since surgery was not beneficial in the group with less than 30% stenosis as a whole, further subdivision was not done.

Since there were no significant differences between the trials either in the risks of the study outcomes during follow-up in the medical or surgical groups, or in the effects of surgery, analyses were done on the pooled data. There were no imbalances in baseline characteristics between the surgery and medical groups in the original trials, and none were introduced when the trials were pooled.

Of the 3334 patients who were randomised to surgery, 3248 (98%) underwent trial surgery (table 2). The median time from randomisation to trial surgery was 6 days. Overall, 7·1% of patients had strokes or died within 30 days of surgery (95% CI 6·3–8·1). Operative risk did not differ between the stenosis groups. The risk of death within 30 days of endarterectomy was 1·1% (35 of 3248, 95% CI 0·8–1·5), and the 30 day case-fatality for operative strokes was 9·6% (20 of 209, 95% CI 5·9–14·4).

Surgery had no significant effect on risk of death during follow-up in any of the stenosis groups, either in the individual trials or in the pooled data. Figure 3 shows the relative risks of all the main study outcomes at 5 years' follow-up, derived from the pooled data. The effect of surgery on survival free of these outcomes is shown for individual stenosis groups in figure 4. Surgery tended to be harmful in patients with less than 30% stenosis. In patients with 30–49% stenosis, the risks for all the main outcomes were higher in the surgery group for the first 2 years of follow-up. Thereafter, the risks were similar in both treatment groups, with no significant benefit from surgery for any of the main outcomes (figure 4).

In patients with 50–69% stenosis, surgery was also associated with a higher risk of all the main outcomes for the first 2 years of follow-up (figure 4), but this trend reversed during subsequent follow-up, resulting in significant benefit from surgery for any stroke or operative death (number needed to treat to prevent one event at 5 years [NNT]=13, 95% CI 8–28) and ipsilateral carotid territory ischaemic stroke and operative stroke or death (NNT=22, 12–80). Benefit was not significant for disabling or fatal ipsilateral ischaemic stroke or operative stroke and operative death.

In patients with 70% stenosis or greater without near-occlusion, there was a highly significant reduction in the surgery group in the risks of all the main outcomes (figure 4). Benefit was apparent during the first year of follow-up, reached a maximum by 3 years, and was still present at 8 years. Number needed to treat was six (95% CI 5–9) for ipsilateral carotid territory ischaemic stroke and operative stroke or death and 14 (8–35) for disabling or fatal ipsilateral ischaemic stroke or operative stroke and operative death.

The results for patients with near-occlusion were difficult to interpret because numbers of patients and outcome events were small. However, although a trend towards benefit from surgery was recorded in patients with near-occlusion at 2 years' follow-up (absolute reduction in risk of ipsilateral ischaemic stroke 5.6%, p=0.19), this trend was no longer evident on further follow-up (figures 3 and 4). The difference in the effectiveness of surgery between patients with near-occlusion and patients with 70% stenosis or greater without near-occlusion was significant for all outcomes: any stroke or operative death (χ^2_H=4·1, p=0·04), ipsilateral carotid territory ischaemic stroke and operative stroke or death (χ^2_H=7·9, p=0·005), and disabling or fatal ipsilateral ischaemic stroke or operative stroke and operative death (χ^2_H=5·4, p=0·02).

Figure 5 shows the absolute risk reductions with surgery at 3, 5, and 8 years in patients with less than 30% stenosis, 30–49% stenosis, 50% stenosis or greater by decile, and in near-occlusions. Measurements of stenosis by decile were not available for VA309. This analysis was therefore confined to ECST and NASCET. For each of the main outcomes benefit from surgery increased steadily from 50–59% stenosis to 90% stenosis or greater (without near-occlusion). In patients with 50–59% and 60–69% stenosis, the benefit was small at 3 years' follow-up, but rose with time. In patients with 60–69% stenosis, benefit was similar to that in patients with 70–79% stenosis by 8 years. However, benefit from surgery in respect of disabling or fatal ipsilateral ischaemic stroke or operative stroke and operative death was only seen in patients with 80–89% and 90% or greater stenosis (without near-occlusion).

Discussion

Analysis of individual patient data has advantages over meta-analysis of overall trial results, and was essential for the endarterectomy trials. Differences between the trials in the method of measurement of carotid stenosis and in the definition of outcome events made tabular results impossible to combine satisfactorily. By re-analysis of the individual patient data and reassessment of the carotid angiograms we have shown that the results of ECST and NASCET were consistent, removing the uncertainty that was generated by the disparities between the originally reported results of the trials.

The results of the pooled analyses have important implications for clinical practice. With the exception of near-occlusions, the degree of stenosis above which surgery is beneficial was 50% (by the measurement technique used in NASCET and VA309—equivalent to about 65% stenosis by the method used in ECST). Benefit in patients with 50–69% stenosis is modest, but increases with time. Absence of benefit for moderate stenosis in the original ECST report[1] is not inconsistent with this finding, but is explained by the differences between the analyses in the measurement of stenosis, and the definition of outcome events. This re-analysis has shown that the effects of surgery in the ECST and

NASCET in patients with 50–69% stenosis were consistent.

Surgery was highly effective in patients with 70% stenosis or greater without near-occlusion. The absolute benefit was greater than reported in the original trials because of the identification and exclusion of near-occlusions. Analysis by decile of stenosis showed that benefit increased within the 70–99% range of stenosis. For disabling or fatal ipsilateral ischaemic stroke or operative stroke and operative death, surgery resulted in clinically important benefit only in patients with 80–99% stenosis.

The risk of stroke for medically-treated patients with near-occlusion was lower than in patients with severe stenosis without near-occlusion; this lowered risk is probably due to good collateral circulation,[24,28,29] but the effect of endarterectomy has not been established. Our analysis of the long-term effect of surgery in this group showed no significant benefit.

Our intention-to-treat analysis might have underestimated the benefit of endarterectomy in patients with near-occlusions, because of the high rate of endarterectomy during follow-up in the medical treatment group in NASCET. However, the rate of endarterectomy was the same in patients with 70–99% stenosis without near-occlusion, and yet there was substantial benefit by intention-to-treat analysis in this group. Moreover, there was no benefit from surgery in the near-occlusion group in ECST, in which the rate of endarterectomy in the medical group was lower than in NASCET. The confidence intervals around our estimates of treatment effect in the near-occlusions were wide, but the difference in the effect of surgery between this group and patients with 70% stenosis or greater without near-occlusion was significant for all three main outcomes. Some patients might still wish to undergo surgery, especially if they have recurrent transient ischaemic attacks, but they should be informed that benefit from endarterectomy in prevention of stroke is likely to be small in the short-term and unknown in the long-term.

The 7% operative risk of stroke and death within 30 days of endarterectomy included any stroke (ocular or cerebral) with symptoms lasting longer than 24 h. This risk is consistent with surgical case-series in which patients were also assessed postoperatively by a neurologist.[30] The benefits of surgery outlined above will only be obtained in routine clinical practice if the operative risk is similarly low. The risks reported in NASCET should serve as a guide to best practice. Since minor strokes are probably often missed in routine clinical practice outside strictly organised clinical trials, audit of operative risk should be done by an independent neurologist or stroke physician.[30,31] The 30-day case-fatality for operative stroke in the pooled analysis was 9·6% (95% CI 5·9–14·4) and the ratio of non-fatal to fatal operative strokes was 10 to 1. The possibility that non-fatal strokes have been missed should be considered in any surgical audit in which the ratio of non-fatal to fatal outcomes is lower than 10 to 1.

The pooled results draw attention to the extent to which benefit from endarterectomy is dependent on the degree of carotid stenosis. Measurement should be accurate and reliable. Our analysis was based on the measurement of the degree of stenosis by the method that was used in the NASCET and VA309 trials. In view of the confusion caused by the use of different methods in the original trials, we suggest that this method be adopted as the standard. Additionally, since inclusion of patients in the trials of endarterectomy for symptomatic carotid stenosis required a pre-randomisation arterial angiogram, care should be taken if the results reported here are applied to routine clinical practice with non-invasive techniques of imaging. If such techniques are used to select patients for surgery, then they must be properly validated against catheter angiography within individual centres.[32–34] More work is required to assess the accuracy of non-invasive methods for the detection of near-occlusion.

In conclusion, although other factors also determine the effect of endarterectomy,[35,36] the degree of carotid stenosis is the single most important factor. Reanalysis of the original trials with standardised definitions of outcomes and methods of measurement of stenosis yielded highly consistent results. The degree of stenosis above which surgery is beneficial is 50%, although benefit in patients with 50–69% stenosis is substantially less than in those with 70% stenosis or greater. Patients with carotid near-occlusion are distinct from patients with 70% or greater stenosis without near occlusion, and have a lower risk of stroke on medical treatment. The evidence suggests that benefit from endarterectomy in such patients is marginal.

Contributors

P M Rothwell was a co-investigator on ECST, remeasured the ECST angiograms, pooled individual patient data, did analyses, and wrote the manuscript. M Eliasziw was a co-principal investigator and data manager of NASCET, and commented on the analyses and manuscript. S A Gutnikov pooled individual patient data, did analyses, and commented on the manuscript. A J Fox was the chief neuroradiological investigator of NASCET, identified near-occlusions in the ECST and NASCET angiograms, and commented on the manuscript. M R Mayberg was the principal investigator of the VA309 trial, and commented on the manuscript. W Taylor was co-principal investigator (biostatistics and epidemiology) of NASCET, and commented on the manuscript. C P Warlow was the principal investigator of ECST, and commented on the manuscript. H J M Barnett was the principal investigator of NASCET, provided access to the complete NASCET database, and commented on the manuscript.

Conflict of interest statement

None declared.

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