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REVIEW

Overview of the Principal Results and Secondary Analyses from the European and North American Randomised Trials of Endarterectomy for Symptomatic Carotid Stenosis

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Objectives: *Review of the primary results and secondary analyses from the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET).*
Design: *Review of 48 ECST and NASCET papers.*
Results: *The simple assumption that all patients with a symptomatic stenosis >70% benefit from CEA is untenable. Approximately 70–75% will not have a stroke if treated medically. The ECST and NASCET have identified subgroups that should have expedited investigation and surgery (male sex, age >75 years, 90–99% stenosis, irregular plaque, hemispheric symptoms, recurrent events for >6 months, contralateral occlusion, multiple co-morbidity). Accordingly development of local protocols for patient selection/exclusion should involve surgeons and physicians and take account of the local operative risk. The ECST and NASCET have also shown that the ubiquitous "string sign" is not associated with a high risk of stroke, and emergency CEA is unnecessary.*
Conclusions: *Surgeons must quote their own results and be aware that a high operative risk reduces long-term benefit. Accordingly, in those centres with a higher operative death/stroke rate, some "lower risk" patients should probably be considered for best medical therapy alone. It is hoped that pooling of the ECST and NASCET databases will enable more definitive guidelines to be developed regarding who benefits most from CEA.*

Key Words: Carotid endarterectomy; ECST; NASCET.

Introduction

Within three decades of its introduction, carotid endarterectomy (CEA) became the most commonly performed arterial procedure in the world. However, concerns about case selection and effectiveness[1,2] led to a reduction in the number of operations performed world-wide and became a catalyst for the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET). ECST and NASCET published data on the benefit of surgery for recently symptomatic severe carotid disease in 1991.[3,4] The ECST also showed that surgery was harmful in patients with only mild stenosis.[3] The role of surgery for moderate stenosis was clarified later.[5,6] For many, this signalled an end to the debate. However, a number of controversies remain, fuelled in part by the emergence of angioplasty as an alternative to endarterectomy, improvements in "best medical therapy" (BMT) and questions about the generalisability of the results of large international trials to routine practice. Similarly confusing has been the "drip feed" of secondary analyses, particularly from NASCET, which may have influenced management decisions in a manner that was not intended. The ECST has not published any single variable subgroup analyses, but NASCET has published several papers reporting single variable subgroup analyses based on small numbers of patients and outcome events. Overall, ECST and NASCET have now published 48 papers (ECST = 16, NASCET = 32) in 12 journals over a 12-year period.[3–50] Even for those interested in stroke prevention, it can be difficult to keep abreast of the literature. The aims of this paper are therefore two-fold. Firstly, to summarise the principal results from the trials. Secondly, to review the secondary analyses

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which have been reported and determine their implications for surgical practice. Both aims require the inclusion of some previously unreported data from the ECST. With this information, each unit can thereafter review local practice and modify protocols for fast-track investigation and/or case selection as appropriate.

Data presentation

Readers will already be aware of the potential for confusion regarding data interpretation in ECST and NASCET. This not only applies to methods for measuring stenosis, but also to the definition of stroke, small sub-group analyses and varying periods of follow-up. For example, NASCET defined operative stroke as being present if the deficit persisted for >24 h. ECST only included patients with a deficit persisting beyond seven days. NASCET has always reported the long-term *ipsilateral* stroke/death rate, while ECST usually quotes the *any* stroke/death rate.

In this review, the ipsilateral stroke/death rate is listed where possible. Surgical or medical risk is the risk of ipsilateral stroke and operative stroke or death at the specified time period. The operative risk is the 30-day death and/or *any* stroke rate. Absolute risk reduction (ARR) is the difference between medical and surgical risks. Relative risk reduction (RRR) is the proportional reduction in stroke risk conferred by surgery over best medical therapy. The "number needed to treat" to prevent one stroke (NNT) is obtained by dividing 100 by the ARR. The number of strokes prevented by performing 1000 CEAs is calculated by dividing 1000 by the NNT. The latter parameters enable readers to gauge the "relative" effectiveness of CEA in different clinical situations. The actual numbers should not be taken too literally, and appropriate allowance should be made when estimates are based on a small numbers of end-points.

The International Trials

Methodology

The U.K. Medical Research Council sponsored the ECST. Between 1981–1994, 3024 patients with symptomatic carotid disease were randomised to best medical therapy (BMT) or CEA plus BMT. The National Institute of Neurological Disease and Stroke funded NASCET. Between 1987–1996, 2885 patients with ipsilateral carotid symptoms were randomised. The ECST recruited from 100 centres in 14 European countries, the NASCET from 106 centres mainly in the U.S.A. and Canada.

The methods of the ECST and NASCET were similar. 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. Each trial required that patients were seen by a neurologist or a stroke physician prior to randomisation to confirm their eligibility. Each trial also required that the symptomatic carotid artery (and preferably the contralateral carotid artery and intracranial circulation) was imaged using angiography (ideally selective catheter angiography). However, strokes or deaths due to pre-randomisation angiography were not recorded and were not included in the analysis in those cases that were subsequently randomised. Degree of stenosis of the symptomatic internal carotid artery (ICA) was quantified centrally, although randomisation was made on the basis of each centre's interpretation of disease severity. In both trials, treatment was allocated by central telephone randomisation stratified by centre. Surgeons were only permitted to randomise patients following review of their recent "track record". CEA was performed as soon as possible after randomisation. The peri-operative period extended from the date of randomisation until 30 days after surgery. Follow-up was performed at set intervals by a neurologist or a stroke physician. The main differences in methods between the trials were as follows:

(1) Patients with any degree of carotid stenosis could be randomised in the ECST, whereas the NASCET aimed to include only patients with >30% stenoses. Analyses of the effect of treatment were pre-specified according to severity of stenosis as mild (0–29%), moderate (30–69%) or severe (70–99%) in the ECST, and as moderate (30–69%) or severe (70–99%) in NASCET.
(2) Time from last symptoms to randomisation had to be less than 4 months in the NASCET (changed to 6 months after 1991) and less than 6 months in the ECST.
(3) There was a difference between ECST and NASCET in the manner of selection and exclusion from the trials. In the ECST, inclusion and exclusion were based on the "uncertainty principle" (i.e. if both the patient and clinicians were uncertain about whether or not to recommend surgery then the patient was eligible), whereas the NASCET had more strictly specified eligibility criteria.[19]
(4) Patients were randomised in a 50:50 ratio in the NASCET, and in a 60 (surgery):40 (no surgery) ratio in the ECST.

(5) The recommended dose of aspirin was 1300 mg in the NASCET, and unspecified in the ECST.
(6) Follow-up was performed at 1, 3, 6, 9 and 12 months, and 4 monthly thereafter in the NASCET, and at 4 and 12 months and annually thereafter in the ECST.
(7) In the ECST, a follow-up stroke was defined as a focal neurological deficit lasting >7 days, but did *not* include retinal ischaemic events. In NASCET, stroke was defined as any neurological or retinal ischaemic deficit persisting beyond 24 h. In both trials, stroke severity was scored following neurological assessment at 6 months using the modified Rankin classification.[51]

Measurement of stenosis

Both trials used the minimum residual luminal diameter as the numerator in the calculation of the degree of carotid stenosis. In ECST, the denominator was the estimated artery diameter at the same point, usually the carotid bulb (Fig. 1). In NASCET, the denominator was the diameter of a disease free point in the ICA above the stenosis where the walls of the vessel are parallel. These different methods produce different values for the same "stenosis". For example, a NASCET 60% stenosis is roughly equivalent to an ECST 80% stenosis.[8] Neither trial used the common carotid (CCA) method in which the denominator is the diameter of common carotid artery proximal to the bifurcation.[8]

The different methods of measuring the degree of stenosis are each of similar predictive value for stroke risk on medical treatment, but the CCA method is slightly more reproducible than the others.[7] ECST observed that the relationship between the stenosis measurements derived from the different methods were almost linear, thus enabling conversion from one to another.[8] ECST concluded that the CCA method was preferable for use in future trials. NASCET found that the relationship was non-linear at very mild degrees of stenosis, and did not support the use of the CCA method.[27] ECST also studied the reproducibility of measurement of stenosis according to the technique of angiography.[11] Inter-observer agreement was good for division into mild, moderate or severe disease using selective angiography (=0.68) and arch angiography (=0.64), but was poor for intravenous DSA (=0.29).

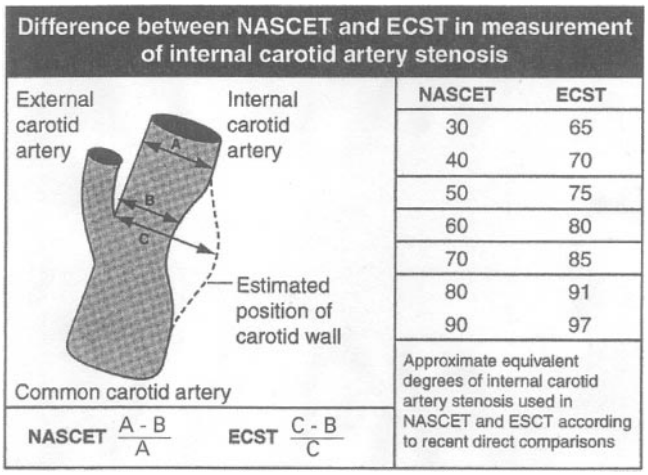

Fig. 1. ECST and NASCET methods for measuring stenosis. Reproduced by permission of *The Lancet*.[65]

Principal Results from ECST & NASCET

Late ipsilateral stroke/death

Both trials observed significant benefit for CEA in patients with 70–99% stenoses (Table 1). ECST found no evidence of benefit for CEA in patients with mild disease. NASCET showed that patients with 50–69% stenoses gained a small but significant benefit from CEA. This group is equivalent to those patients with 70–79% stenoses in the ECST.[12] In NASCET patients with 50–69% stenoses, CEA conferred maximal benefit in (i) males, (ii) patients presenting with stroke and (iii) those with hemispheric as opposed to retinal

Table 1. Long term risk of ipsilateral stroke *(including peri-operative stroke or death).*

Stenosis (%)	Surgical risk (%)	Medical risk (%)	ARR (%)	RRR (%)	NNT	Strokes prevented per 1000 CEAs
ECST						
<30	9.8 at 5 years	3.9 at 5 years	−5.9	n/a	n/a	n/a
30–49	10.2 at 5 years	8.2 at 5 years	−2.0	n/a	n/a	n/a
50–69	15.0 at 5 years	12.1 at 5 years	−2.9	n/a	n/a	n/a
70–99	10.5 at 5 years	19.0 at 5 years	8.5	45	12	83 at 5 years
NASCET						
30–49	14.9 at 5 years	18.7 at 5 years	3.8	20	26	38 at 5 years
50–69	15.7 at 3 years	22.2 at 3 years	6.5	29	15	67 at 3 years
70–99	8.9 at 3 years	28.3 at 3 years	19.4	69	5	200 at 3 years

ARR = absolute risk reduction, RRR = relative risk reduction, NNT = number of CEAs to prevent one ipsilateral stroke, n/a = not applicable.

symptoms.[6] Twelve CEAs in male patients with 50–69% stenoses were required to prevent one ipsilateral stroke compared with 67 in women and 16 CEAs were required to prevent one disabling stroke in men as compared with 125 in women.[6]

Operative risk

The 30-day risk of death/stroke was unrelated to stenosis severity (Table 2). In ECST, the highest risk (9.5%) was observed in patients with moderate stenoses. The lowest operative risk (3.8%) occurred in those with 90–99% stenoses.[12,49,50] One third of strokes/deaths in NASCET were apparent upon recovery from anaesthesia and one third occurred on the first post-operative day. The rest were distributed over the next 29 days, but 86% had occurred within 7 days of surgery.[39] The same temporal pattern was observed in the ECST. Of the 122 operative strokes or deaths, 85 (70%) were evident by the first post-operative day, and 115 (94%) by the end of the first week (unpublished data).

Factors predictive of increased operative risk in the ECST[14,50] included; (i) female gender (10.4% vs 5.8%, $p = 0.0001$, hazard ratio = 2.05), (ii) peripheral vascular disease (12.0% vs 6.1%, $p < 0.0001$, hazard ratio = 2.48); (iii) systolic blood pressure (<120 mmHg = 3.4%; 121–159 = 6.5%; 160–180 = 7.7%; >180 = 13.0%; $p = 0.04$, hazard ratio = 2.21), and the nature of the presenting cerebrovascular event (retinal events only = 3.2%; hemispheric stroke = 6.3%, hemispheric TIA only = 9.1%; $p < 0.006$). All of these factors remained statistically significant after correction for other baseline clinical characteristics in a multiple regression analysis.[50] Only 1/147 surgeons undertaking CEA in ECST had an operative risk outwith the upper 95th confidence interval (95% CI 2.0–8.0%). However, once the data were corrected for case mix, this excess risk disappeared.[13]

Factors predictive of a significantly higher operative risk in NASCET[39] included: (i) hemispheric as opposed to retinal events (6.3% vs 2.7%, hazard ratio = 2.3), (ii) left vs right CEA (6.7% vs 3.0%, hazard ratio = 2.3), (iii) contralateral occlusion (9.4% vs 4.4%, hazard ratio = 2.2), (iv) ipsilateral CT/MR infarct (6.3% vs 3.5%, hazard ratio = 1.8), and (v) irregular as opposed to smooth plaque (5.5% vs 3.7%, hazard ratio 1.5). NASCET observed no association between age and operative risk (<65 years = 7.9%, 65–74 years = 5.5%, >75 years = 5.2%).[48] There was a trend towards increasing risk with age in ECST (<55 years = 5.6%, 55–65 = 6.4%, >65 = 8.7%), but this was not statistically significant ($p = 0.16$), but the operative risk was lowest (4.4%) in patients aged >75 years.

NASCET noted that CEA patients taking aspirin doses of <650 mg daily were significantly more likely to suffer a peri-operative stroke.[6] However, a large randomised trial involving 2849 patients thereafter showed the converse to be true.[52] The available evidence suggests that low dose aspirin (75–300 mg) is effective in reducing early cardiovascular morbidity/mortality, whilst avoiding the adverse side effects associated with higher dose therapy. This dose range was used in virtually all patients in the ECST.

It is often difficult for a surgeon to gauge how his/her operative risk actually influences the long-term benefit of CEA. Table 3 presents a reanalysis of the ECST data in patients with either a 70–99% or an 80–99% stenosis according to the initial risk. Thus for a unit with a 2% operative risk when operating upon patients with a 70–99% stenosis, the relative risk reduction is 73%, 112 ipsilateral strokes will be prevented per 1000 CEAs and only 9 CEAs are required to prevent one ipsilateral stroke. If the operative risk increases to 10% (as in the recent CAVATAS study[53]), the relative risk reduction at three years falls to 21% and 32 CEAs are now necessary to prevent one stroke. ECST has suggested that CEA should be reserved for patients with 80–99% stenoses.[12] Table 3 suggests that such a policy would greatly increase the overall effectiveness of the procedure in units with a higher operative risk. Even if a surgeon had a 10% operative risk, the relative risk reduction at three years would still be 42%.

Peri-operative medical complications

Ten percent of CEA patients in NASCET suffered a medical complication in the peri-operative period as compared with 3.4% of medical patients in the first

Table 2. Peri-operative surgical risk.

	ECST			NASCET	
	<30% ($n = 138$)	30–69% ($n = 913$)	70–99% ($n = 750$)	30–69% ($n = 1087$)	70–99% ($n = 328$)
Operative mortality	1.5%	1.1%	0.9%	1.2%	0.6%
Death +/− disabling stroke	2.3%	3.8%	3.7%	2.8%	2.1%
Death +/− any stroke	4.6%	7.9%	7.5%	6.7%	5.8%

Table 3. Effect of 30 day operative risk on 3 year rate of ipsilateral stroke in patients with 70–99% or 80–99% ECST stenosis.

Operative risk (%) *	Surgery		Medical									
	Risk of ipsilateral CVA/death at 3 years		Risk of ipsilateral CVA/death at 3 years		Absolute risk reduction		Relative risk reduction		No of ipsilateral CVA/death prevented per 1000 CEAs		No of CEAs to prevent 1 ipsilateral CVA/death	
	70–99%	80–99%	70–99%	80–99%	70–99%	80–99%	70–99%	80–99%	70–99%	80–99%	70–99%	80–99%
0	2.2	2.0	15.3	20.8	13.1	18.8	86	90	132	188	8	5
2	4.2	4.0	15.3	20.8	11.1	16.8	73	81	112	168	9	6
4	6.2	6.0	15.3	20.8	9.1	14.8	60	71	92	148	11	7
6	8.2	8.0	15.3	20.8	7.1	12.8	47	61	72	128	14	8
8	10.2	10.0	15.3	20.8	5.1	10.8	34	52	52	108	19	9
10	12.2	12.0	15.3	20.8	3.1	8.8	21	42	32	88	32	11

*Operative risk = *any* stroke or death within 30 days after CEA, 70–99% = patients undergoing CEA with a 70–99% ECST stenosis, 80–99% = patients undergoing CEA with an 80–99% ECST stenosis.

30 days after randomisation.[38] The commonest were cardiovascular (CEA = 8.1%, medical = 1.2%) and respiratory (CEA = 0.8%, medical = 0.5%). However, 70% of medical morbidity in CEA patients were classed as mild, while 27% were moderately severe. Only 0.3% (5/1415) of CEA patients suffered a major complication (all myocardial infarction) and no surgical patient suffered a pulmonary embolus. In ECST, there were four patients (0.2%) with myocardial infarction within 30 days of surgery, and two patients (0.1%) with pulmonary embolism.[50]

Peri-operative wound and cranial nerve morbidity

One hundred and thirty-two surgical patients in NASCET (9.3%) suffered a wound complication (haematoma, infection etc.), but in only 0.3% of patients was this considered severe.[39] Cranial nerve injuries were documented in 8.6%. Almost all were classified as mild with full recovery within 30 days. None suffered a major cranial nerve injury. The commonest nerves to be injured were the hypoglossal (3.7%), vagus (2.5%) and mandibular branch of the facial nerve (2.2%). No NASCET patient suffered glossopharyngeal nerve palsy, reflecting the exclusion of patients with high carotid disease from the trial.[19] In ECST, 111 patients (6.4%) suffered a cranial nerve palsy, 53 patients (3.1%) had a neck haematoma requiring re-operation, and four patients developed a significant wound infection.[50] Of the patients with cranial nerve injury, symptoms had resolved by the time of hospital discharge in 37, and in only 9 cases were the symptoms permanent (unpublished data).

Causes of late death and stroke

The principal causes of late death within the trials were myocardial infarction, cancer then stroke.[4,6,7] In NASCET, there were 1039 strokes (ischaemic ($n = 1021$), haemorrhagic ($n = 17$), subarachnoid haemorrhage ($n = 1$)) in 749 (26% of 2885) patients during follow-up.[41] Of the 1021 ischaemic strokes, 112 (10.8%) were classed as cardio-embolic, 211 (20.3%) were lacunar, while 698 (67.2%) were considered large vessel in origin. Cardioembolic strokes were responsible for the highest proportion of late disabling strokes. Lacunar strokes were the least disabling. In ECST, there were 728 strokes in 555 patients, 317 patients had a disabling or fatal stroke, and there were a total of 820 deaths during follow-up (unpublished data).

Secondary Analyses

NASCET has published several papers reporting the effect of CEA, usually in the 70–99% stenosis patients, stratified according to a single baseline variable, such as intracranial disease. The ECST has not published any single variable subgroup analyses, but has used multiple regression analyses to predict the risks of stroke on medical treatment and the operative risk.[14,50] The secondary analyses from NASCET have stimulated debate about who benefits most from CEA, but must be interpreted with caution until they can be independently validated. They can be difficult to interpret because NASCET was not specifically powered to look at small subgroups. Until the NASCET observations are assessed in the ECST, it would seem sensible to use the NASCET secondary analyses only very cautiously in clinical practice. It is probably more reasonable to use secondary analyses to determine who should be fast-tracked for investigation and surgical treatment, rather than who should not be considered for surgery.

Do elderly patients benefit from carotid surgery?

There has been a tendency to avoid CEA in elderly patients because it is perceived that a higher operative risk may nullify any long-term benefit. NASCET found that the long-term benefit of CEA increased significantly in older patients, without increasing the operative risk.[54] Table 4 presents the two-year risk of ipsilateral stroke relative to age and degree of stenosis. Patients aged >75 years consistently derived a better outcome following CEA, particularly in those with severe disease. This secondary analysis therefore suggests that biological (as opposed to chronological age) should be the basis for referral. As was observed in an accompanying editorial,[55] the average life expectancy of an 85-year-old living in the U.S.A. is six years! Exactly the same trend towards increasing benefit from surgery with age was observed in the ECST, and also when the data from both trials were combined.[55]

Do patients with subocclusion require urgent endarterectomy?

There has been much controversy regarding the significance of the "string sign". NASCET analysed the 30-day and 1-year risks of ipsilateral stroke relative to stenosis severity and whether or not the "string sign" was present (Table 5). Near occlusion with string sign was defined as a 95–99% stenosis with underfilling/non-visualisation or collapse of the distal ICA. Near occlusion with no string implied that the distal ICA opened into a normal calibre vessel. The one-year risk of ipsilateral stroke in medically treated patients increased from 12.8% (70–79% stenosis) to 18.5% (80–89% stenosis), peaking at 35.1% for 90–94% stenoses.[34] The one-year risk fell to 18.3% in the presence of near occlusion and no string sign. The 1-year risk was lowest in those with angiographic evidence of a string sign (11%).

When compared with the surgical group (Table 5), two observations emerge. First, the patient with near occlusion (with or without the string sign) does not appear to have an increased risk of stroke within the next 30 days (medical risk = 0.0%, surgical risk = 6.7%). Second, the ARR in ipsilateral stroke at 1 year for those with near occlusion and a string sign was only 4.4%. This is significantly less than for any other sub-group and equates to 23 CEAs being necessary to prevent one ipsilateral stroke. This compares with four CEAs in those with 90–94% stenoses.

Support also comes from the ECST who used objective data to measure the degree of post-stenotic narrowing.[15] Post-stenotic narrowing was defined as an ICA/CCA ratio < 0.42, which represented two standard deviations below the mean of ICA and CCA diameters in 2966 carotid arteries with 0–49% stenoses. Post-stenotic narrowing was not observed until the stenosis exceeded 70% and was evident in 18% of patients with 80–99% stenoses.[15] The 5-year risk of stroke in patients with no distal narrowing was 22 and 32% for 80–89% and 90–99% stenoses respectively. This contrasted with an 8% 5-year risk in those with post-stenotic narrowing.

These data suggest that patients with sub-occlusion and the string sign do not require expedited surgery. There is time for more discriminating investigation and risk profiling. In the past, suspicion of a string sign with trickle flow on Duplex has prompted formal angiography with its attendant risks. Because the stroke risk appears to be low in patients with the string sign, it might now be reasonable to consider a more conservative approach in patients (especially female) presenting with a single ischaemic event (especially amaurosis fugax). Patients with recurring ipsilateral events should undergo contrast angiography.

Table 4. Effect of age on 2 year risk of ipsilateral stroke.*

Age (years)	Degree of stenosis in randomised artery					
	<50%		50–69%		70–99%	
	ARR (%)	NNT	ARR (%)	NNT	ARR (%)	NNT
>75	7.3	14	17.3	6	28.9	3
65–74	1.1	91	5.3	19	15.1	7
<65	1.4	71	−1.2	n/a	9.7	10

* Adapted from Alamowitch *et al.* on behalf of NASCET.[48]

Table 5. 30 day and 1 year risk of ipsilateral stroke relative to degree of stenosis and presence of string sign.*

Degree of stenosis (/− string)	Surgical risk (%)		Medical risk (%)		ARR (%)	RRR (%)	NNT	CVA prevented per 1000 CEAs
	30 days	12 months	30 days	12 months				
70–79%	3.9	4.6	1.4	12.8	+8.2	64	12	83
80–89%	6.3	8.7	6.4	18.5	+9.8	53	10	100
90–94%	8.7	8.7	4.6	35.1	+26.4	75	4	250
95–99% + no string	6.1	9.1	2.3	18.3	+9.2	50	11	91
95–99% + string sign	6.7	6.7	0.0	11.1	+4.4	40	23	43

* Adapted from Morgenstern *et al.* on behalf of NASCET.[34]

How long should CEA be deferred after a completed stroke?

In the 1960s, "emergency" CEA after acute stroke was associated with a 60% risk of haemorrhagic transformation of the infarct.[56] Accordingly, not only was CEA avoided in patients with stroke due to ICA thrombosis, but it became customary to defer CEA for 6–8 weeks in *all* patients, irrespective of severity. Improvements in case selection, risk factor control and ITU/HDU facilities have prompted a reappraisal of this stance.[58] In NASCET, 4.9% of medically treated patients presenting with stroke and a severe ICA stenosis suffered a recurrent stroke within 30 days of randomisation.[26] NASCET analysed outcomes in 100 randomised stroke patients with severe disease.[26] Although patients in whom CEA was deferred for >30 days were more likely to have an abnormal CT, there was no difference in the mean diameter of the infarcts and no difference in the peri-operative risk (<30 days = 4.8%, >30 days = 5.2%). In particular, the operative risk was not higher in patients with an infarct on CT scan (<30 days = 0.0%, >30 days = 5.4%). Both surgical groups had a 12% risk of ipsilateral stroke at 18 months.[26]

The numbers are relatively small but suggest that fear of haemorrhagic transformation should not be the only consideration when planning the timing of CEA after stroke. Expedited surgery (<4 weeks) should be considered in patients who make a rapid recovery and who have relatively small infarction volumes on CT.[58] Patients under consideration for CEA with larger infarcts and significant residual neurological disability should have surgery deferred for 6–8 weeks as before.

Does multiple co-morbidity reduce the benefit of CEA?

NASCET analysed the two-year risk of ipsilateral stroke relative to cumulative risk factors including; age > 70, stroke on presentation, male sex, 80–99% stenosis, systolic BP > 160 mmHg, diastolic BP > 90 mmHg, ulceration on angiography, a cerebral event within the preceding 30 days and a history of congestive cardiac failure, diabetes, current smoking, claudication, myocardial infarction, hypertension and hyper-lipidaemia.[4] In medically treated patients, the 2-year risk of ipsilateral stroke increased from 17% for those with <5 factors to 23% in those with 6 factors and 39% in patients with 7+ risk factors. More important, the number of risk factors had *no* influence on outcome following CEA (9% ipsilateral stroke risk at two years irrespective of concurrent disease). This data supports the intuitively held view that the patient with increasing cardiovascular co-morbidity has a very high risk of stroke if treated medically. These high-risk patients can be considered for surgery without otherwise compromising safety. Similar conclusions can be drawn from the risk modelling work in the ECST[14] – the higher the risk of stroke on medical treatment, the higher the benefit from surgery, with relatively little correlation between medical risk and surgical risk. The only proviso in routine clinical practice is that randomised controlled trials tend to include relatively healthy patients. NASCET, in particular, had stringent exclusion criteria relating to severe comorbidity.

Should CEA be performed outside the 6 month threshold?

To qualify for the trials, patients had to have suffered an ipsilateral, carotid territory event within the preceding 6 months. This was somewhat arbitrary, but since the trials demonstrated that CEA conferred a significant benefit in this group, the threshold of 6 months has persisted. However, there are some data to suggest that the 6-month threshold might be extended in selected patients with very severe disease[6,12] and other risk factors for stroke. Figure 2 shows the annual risk of stroke in medically treated patients in the ECST. The annual risk never exceeded 6% for patients with a 70–79% stenosis. The risk for 80–89% stenoses was 11% in the first year and 6% in the second. The highest risk was observed in those with a 90–99% stenosis (18% first year risk, 14% in the second). After 2 years, the annual stroke risk

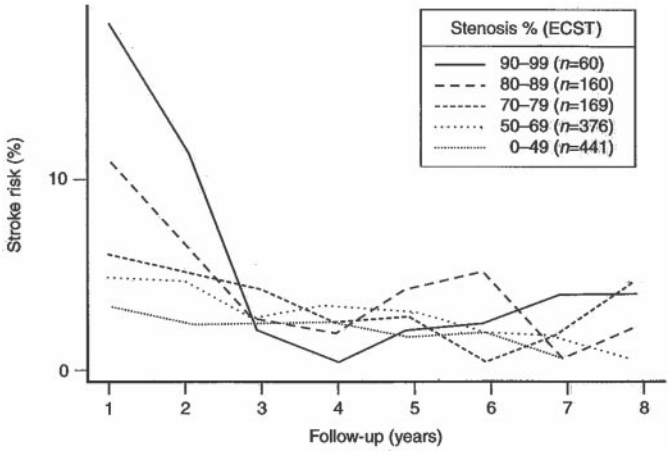

Fig. 2. Annual risk of stroke in ECST patients randomised to best medical therapy relative to degree of stenosis at the time of randomisation. Reproduced by permission of *The Lancet*.[12]

never exceeded 3% in any stenosis group. However, the high stroke risk in the second year of follow-up in patients with 90–99% stenosis does suggest that this group might still benefit from surgery after the 6 month threshold.

Following publication of the principal results of NASCET, the investigators suggested that patients with severe disease who had been randomised to medical therapy should now be offered CEA. They subsequently observed that 25% had already progressed to carotid occlusion, of whom 31.7% had suffered a stroke as a consequence.[46] Overall, 21% of medical patients with 70–84% stenoses progressed to occlusion, increasing to 32% in those with 85–99% stenoses. The 3-year risk of ipsilateral stroke in medically treated patients who underwent *delayed* CEA was 7.9%. This compared with 15.0% in those maintained on BMT. However, this is, of course, a non-randomised comparison, and it is quite possible that the patients who declined surgery, or who were not offered surgery, were at higher risk because of more severe comorbidity or other factors, and that those patients who had surgery might also have done better had they had BMT only.

On balance, the 6-month threshold should definitely be retained for patients with 70–79% ECST stenoses. However, it would now seem reasonable to consider surgery for up to 12 months after the last event in *selected* patients. Depending on the operative risk of the surgeon, these might include certain patients with 80–99% stenoses (especially 90–99% but excluding near-occlusion), who exhibit one or more important risk factors for stroke on BMT (e.g., male sex, ulcerated plaque, multiple concurrent risk factors, hemispheric as opposed to retinal symptoms, recurring events and contralateral occlusion, etc). This should definitely not be seen as a reason to extend the time threshold in all patients. Centres with an operative risk >7% should probably retain the 6-month threshold for all patients.

Do patients with recurrent symptoms require expedited assessment?

NASCET compared the risk of late stroke[33] in 164 patients with severe disease who reported a history of carotid territory events over a >6 month period (recurrent group) with 444 who described onset of symptoms within the preceding 6 months (recent group). The 2-year risk of ipsilateral stroke was 18.6% in medically treated "recent onset" patients, compared with 7.8% in patients subjected to CEA (ARR = 10.8%, RRR = 58%, NNT = 9). However, the 2 year risk of ipsilateral stroke in medically treated patients with recurrent cerebral events was 41.2%, compared to 10.8% in the surgical group (ARR = 30.4%, RRR = 59%, NNT = 3). This analysis suggests that expedited investigation and CEA is sensible in patients reporting recurrent symptoms over a >6 month time period.

Should patients with retinal TIAs still be offered carotid surgery?

Both trials analysed outcome according to whether the patient presented with hemispheric symptoms (hemiparesis, hemisensory signs, dysphasia, etc) or retinal events (amaurosis fugax, central retinal artery occlusion). In ECST,[14] patients with hemispheric symptoms were more than twice as likely to suffer a late stroke than patients with ocular events (odds ratio 2.5 (95%CI 1.1–3.7). In NASCET patients with severe stenosis, the 2-year risk of ipsilateral stroke was 16.6% for retinal events as compared with 43.5% in those describing hemispheric symptoms.[30]

These data suggest that patients with severe disease and hemispheric symptoms should be allocated a high priority for rapid investigation and management. NASCET continues to recommend CEA for patients with amaurosis fugax.[30] Centres with a high operative risk (7%) might, however, favour medical therapy (especially in female patients) in those with retinal symptoms in association with a 70–79% stenosis. On the other hand, the operative risk in patients with retinal events only is certainly lower than that in patients with hemispheric events.[59]

Do TIA patients with infarcts on CT scan have a worse long-term prognosis?

NASCET hypothesised that patients presenting with TIA, 70–99% stenoses and ipsilateral infarction on CT scan might have a worse prognosis compared with similar patients with normal CT scans.[29] Of the 114 TIA patients with severe disease randomised to medical therapy, 50 (28%) had CT evidence of ipsilateral infarction. TIA patients with CT evidence of infarction were significantly more likely to be older and have more risk factors for stroke (hypertension, ulcerated plaques, recent symptoms) than TIA patients with no infarction. Univariate analysis indicated that the presence of infarction doubled the risk of ipsilateral stroke over a 16-month period. However, once a multi-variate analysis corrected for other variables, the excess risk disappeared. Similar conclusions can be drawn from the risk modelling in the medical treatment group in the ECST.[14]

Does the status of the contralateral ICA influence outcome?

NASCET examined the risk of ipsilateral stroke (i.e., ipsilateral to the *treated* stenosis, not the non-operated side) relative to the degree of disease in the contralateral ICA (Table 6).[32] The 30-day risk of stroke/death after CEA was significantly higher in patients with a severe symptomatic stenosis and contralateral occlusion (14.3%) as compared to patients with contralateral severe (4%) or mild/moderate stenoses (5.1%). The higher operative risk in patients with contralateral occlusion was also found in the ECST, and is highly consistent across published surgical case-series.[59] However, despite the higher operative risk, CEA still conferred a highly significant reduction in the 2-year risk of ipsilateral stroke in NASCET patients with severe carotid stenosis and contralateral carotid occlusion (ARR = 47.3%, RRR = 68%, NNT = 2). Patients with symptomatic severe disease and contralateral occlusion should therefore be allocated a high priority for expedited investigation and CEA. They should also be warned that surgery carries a higher perioperative risk.

Do patients presenting with lacunar stroke benefit from CEA?

This remains a contentious issue. The concern, on the part of some stroke physicians and neurologists, is based on the premise that lacunar infarction follows occlusion of a deep perforating artery, rather than thrombo-embolism from the ICA. It is an important question to answer as up to 40% of hemispheric strokes or CT ve infarcts in the trials were possibly or probably lacunar in origin.[10,43] NASCET analysed the type of recurrent stroke during follow-up[43] and observed that patients presenting with lacunar stroke were three times more likely to suffer another lacunar stroke during follow-up (9.2% vs 2.9%). ECST noted a non-significant excess risk of late stroke in non-operated, non-lacunar as opposed to non-operated lacunar patients.[10] However, ECST concluded that small numbers (43 lacunar patients with severe carotid disease) prevented conclusions being made as to whether CEA was less beneficial.[10]

NASCET analysed the 3-year risk of ipsilateral stroke in 1158 patients presenting with stroke.[43] These were classified as non-lacunar ($n = 665$), possibly lacunar ($n = 283$) or probably lacunar ($n = 210$) on the basis of symptoms/signs or CT findings. Table 7 presents the outcome in stroke patients who had a 50–99% ipsilateral stenosis. CEA conferred maximum benefit in patients with non-lacunar strokes (ARR = 15.2%, RRR = 61% NNT = 7). CEA had less benefit in those classed as "possibly" or "probably" lacunar, but still achieved an ARR of 9% at 3 years.[43] One explanation for CEA being beneficial in lacunar stroke is that by improving inflow, the subsequent risk of thrombotic occlusion in the diseased perforating arteries is reduced. It would have been interesting, therefore, to see the effect of surgery in patients with lacunar stroke in NASCET patients with 70–99% stenosis; the group in which haemodynamic factors would be most likely to be important. It is unclear why, in contrast to all their previous papers, NASCET did not stratify their findings by degree of stenosis in this paper.

The currently available evidence suggests that patients with cortical stroke should be accorded a high priority for investigation and surgery. However, it was still appropriate to offer CEA to patients with lacunar stroke and a severe stenosis. Centres with a high operative risk should probably not operate on patients with lacunar stroke with a moderate stenosis (50–69% NASCET, 70–79% ECST).

Should CEA be avoided in patients with tandem intracranial disease?

As with increasing age and multiple co-morbidity, there is a perception that the presence of tandem intracranial disease (ICD) is a relative contra-indication to CEA. NASCET analysed 2885 carotid angiograms and defined ICD as being mild (wall irregularities,

Table 6. Effect of contralateral disease on 2 year risk of stroke ipsilateral to the operated or medically treated severe carotid stenosis.*

Status of contralateral ICA	2 year ipsilateral stroke		ARR (%)	RRR (%)	NNT
	Medical ($n = 331$)	Surgical ($n = 328$)			
<70% stenosis ($n = 559$)	26.2	8.3	17.9	68	6
70–99% stenosis ($n = 57$)	29.3	9.3	20.0	68	5
Occlusion ($n = 43$)	69.4	22.1	47.3	68	2

* Adapted from Gasecki *et al*. on behalf of NASCET.[32]

Table 7. 3 year risk of ipsilateral stroke in patients presenting with a stroke and 50–99% stenosis: effect of stroke subtype on late risk.*

Type of stroke at presentation	3 year ipsilateral stroke risk		ARR (%)	RRR (%)	NNT
	Medical (%)	Surgical (%)			
Non-lacunar	24.9	9.7	15.2	61	7
Possibly lacunar	16.1	7.6	8.5	53	12
Probably lacunar	25.5	16.5	9.0	35	11

* Adapted from Inzitari *et al*. on behalf of NASCET.[43]

no stenosis), moderate (<50% stenosis) or severe (50–99% or occlusion) in the infra-clinoid ICA, the supra-clinoid ICA and the anterior cerebral/middle cerebral arteries.[37] Overall, 67% had no ICD. Intracranial disease was mild in 27%, moderate in 6% and severe in 0.5%. Factors associated with an increased incidence of ICD included black patients, ulcerated plaques, severe extracranial disease and a history of smoking, hypertension, diabetes, claudication and ischaemic heart disease.

All subgroups of ICD severity were combined and outcomes compared with patients with no ICD. The presence of tandem ICD did not increase the operative risk following CEA (6.1% vs 6.7%). However, the presence of ICD conferred an incrementally greater risk of ipsilateral stroke at three years in *medically* treated patients, irrespective of the degree of extracranial disease (Table 8). The highest risk was observed in medically treated patients with ICD and an 85–99% stenosis in whom CEA conferred a 37.1% ARR. Note that the presence of ICD had no influence on late stroke risk in surgically treated patients.[37]

There is currently no evidence that tandem disease confers increased risk. However, patients with severe distal ICA disease were probably not randomised in the trials. Accordingly, if Duplex ultrasound or MRA does not show evidence of significant abnormalities in the distal waveform or anatomy, there is no evidence that routine angiographic visualisation of the intracranial circulation will alter either the early or late risk in surgical patients.

Should CEA be avoided in patients with intracranial aneurysm?

It has been speculated that untreated intra-cranial aneurysms (ICAN) contribute towards an increased risk of peri-operative and late stroke (presumably haemorrhagic) and that they are a relative contra-indication to surgery. NASCET observed that 90/2885 patients (3.1%) had 99 intracranial aneurysms.[45] The majority (83%) were <5 mm. The incidence of ICAN >10 mm (i.e., considered for neurosurgical intervention) was 0.3%. The available evidence suggests that ICAN does not influence outcome. The 5-year risk of ipsilateral stroke was 10% in CEA patients with a non-repaired ICAN as compared to 14.8% in those with no aneurysm. This compares with a 5-year risk of ipsilateral stroke of 22.7% in medically treated patients with a non-repaired ICAN vs 22.5% in those with no aneurysm. The available evidence suggests that small non-repaired intracranial aneurysms do not confer an increased early or late risk of stroke after CEA.

Does knowledge of intracranial collaterals influence outcome after CEA?

NASCET correlated stroke risk with recruitment of intracranial collaterals.[40] Recruitment of collaterals was defined as angiographic evidence of flow through the ipsilateral anterior cerebral, posterior cerebral or ophthalmic arteries towards the symptomatic ICA. Of the 2885 patients, 280 (9.7%) had evidence of collateral recruitment. The commonest pattern was reversed flow in the ipsilateral anterior cerebral (70%), 9% recruited via the posterior-communicating artery, while 20% had multiple pathways. Only five (0.2%) had retrograde flow in the ophthalmic artery.[40] Collateralisation was present in 0.5% with an ICA stenosis <50%, 3% in patients with a 50–69% stenosis, 25% in those with a 70–84% stenosis and 43% in those with 85–99% stenoses. The highest prevalence was observed in those with near occlusion and distal ICA collapse (64%).

Table 9 details the 2-year risk of ipsilateral stroke relative to mode of treatment, degree of stenosis and the presence or absence of collateralisation. With the exception of patients with near occlusion and distal ICA collapse, the absence of intracranial collaterals

Table 8. Effect of intracranial disease on the 3 year risk of ipsilateral stroke. *

Stenosis degree	Intracranial disease	Medical risk (%)	Surgical risk (%)	ARR (%)	RRR (%)	NNT	CVA/ 1000CEA
<50%	No	13.8	12.5	1.3	9	77	13
	Yes	18.0	13.4	4.6	26	22	45
50–69%	No	14.7	10.5	4.2	29	24	42
	Yes	19.4	11.8	7.6	39	13	77
70–84%	No	23.5	10.1	13.4	57	7	143
	Yes	28.8	6.1	22.7	79	4	250
85–99%	No	25.3	10.0	15.3	60	7	143
	Yes	45.7	8.6	37.1	82	3	333

* Adapted from Kappelle *et al*. on behalf of NASCET.[37]

Table 9. Influence of intracranial collateral recruitment on 2 year risk of ipsilateral stroke. *

Stenosis degree	Intracranial collaterals	Surgical risk (%)	Medical risk (%)	ARR (%)	RRR (%)	NNT
70–84%	None	7.1	25.4	18.3	72	5
70–84%	Yes	3.8	8.0	4.2	53	24
85–99%	None	12.3	43.7	31.4	72	3
85–99%	Yes	2.7	16.4	13.7	84	7
Distal ICA collapse	None	10.4	5.3	−5.1	n/a	n/a
Distal ICA collapse	Yes	11.1	10.9	−0.2	n/a	n/a

* Adapted from Henderson *et al*. on behalf of NASCET.[40]

incrementally increased the two-year risk of ipsilateral stroke in medically treated patients with increasingly severe extracranial disease. Conversely, the presence of intracranial collaterals had no effect on the late stroke risk in surgical patients. Note, however, that the risk of late stroke fell dramatically in those with near occlusion and no collateralisation and that surgery conferred no apparent benefit.[40]

Knowledge about recruitment of intracranial collateral pathways does not influence early or late outcome after CEA.

Is plaque surface irregularity associated with an increased risk of stroke?

There has been much debate whether plaque irregularity/ulceration increases the risk of stroke in medically treated patients. NASCET observed no association between degree of carotid stenosis and plaque ulceration, although only patients with 70–99% stenosis were reported. However, the presence of ulceration was associated with a significantly higher incidence of contralateral severe disease.[22] ECST found that the prevalence of plaque irregularity increased from 10% in patients with a stenosis $<10\%$, to 70% in those with 90–99% stenoses. The proportion of patients with adherent thrombus increased from 12% in patients with $<20\%$ stenoses to 45% in patients with 90–99% stenoses.[16] The NASCET-ACAS plaque project observed that intra-plaque haemorrhage was not associated with either aspirin usage or neovascularity, but was more prevalent in severely stenosed plaques.[21]

Both trials found that the presence of plaque "irregularity" or "ulceration" increased the risk of late, ipsilateral stroke on medical treatment. In the ECST, the 2-year risk of ipsilateral stroke in medically treated patients with an irregular 80–89% stenosis was 26% vs 15% for smooth lesions. Similar statistics for patients with irregular 90–99% stenoses were 31% vs 20% respectively.[16] Table 10 presents parallel data from NASCET. As can be seen, plaque irregularity increased the 2-year risk of ipsilateral stroke relative to the degree of stenosis. The highest stroke risk was observed in patients with 95% stenoses and ulceration (73.2% at 2 years) in whom CEA conferred a 54% ARR (RRR = 74%, NNT = 2). Plaque irregularity had no effect on outcome in surgically treated patients. The ECST have also shown that patients with evidence of plaque irregularity were significantly more likely to have suffered a myocardial infarction in the past and were significantly more likely to suffer an MI or sudden cardiac death in the future.[17] This observation supports the prevailing view that systemic factors may be important in mediating acute cardiovascular events.

Table 10. 2 year risk of ipsilateral stroke in patients with severe carotid disease and plaque ulceration. *

Stenosis (%)	Plaque ulcer	Surgical risk (%)	Medical risk (%)	ARR (%)	RRR (%)	NNT
75	No	10.6	21.2	10.6	50	9
75	Yes	6.9	26.3	19.4	74	5
85	No	10.6	21.3	10.7	50	9
85	Yes	11.5	43.9	32.4	74	3
95	No	10.7	21.3	10.6	50	9
95	Yes	19.2	73.2	54.0	74	2

* Adapted from Eliasziw *et al*. on behalf of NASCET.[22]

However, these results relate to angiographic ulceration and not directly to plaque histology. In the ECST, 1066 angiograms were considered "irregular", but the operating surgeon only scored 779 of these (73%) as being macroscopically ulcerated.[16] Conversely, 605 plaques were considered smooth on angiography, but 252 (42%) were later classed as macroscopically ulcerated by the surgeon. In NASCET, the sensitivity for diagnosing an ulcerated plaque on angiography was 46%, with a specificity of 74%.[24] However, in practical terms, plaque irregularity on angiography (and probably also on Duplex) confers an increased stroke risk on medical treatment (hence the need for expedited investigation), and should also alert the investigating clinician to screen for potential ischaemic heart disease.

What is the risk of stroke in the asymptomatic contralateral hemisphere?

In the ECST, 2295 asymptomatic contralateral carotid arteries were followed up for a mean of 4.5 years.[9] Of the 69 late ipsilateral strokes observed, only 13 (19%) occurred in the territory supplied by a 70–99% stenosis. Fifty-four (78%) were ipsilateral to mild or moderate ICA stenoses, while two (3%) were ipsilateral to an ICA occlusion. The annual risk of ischaemic stroke distal to an asymptomatic 70–99% stenosis was approximately 2%.[9] Thus, an asymptomatic contralateral stenosis in a recently symptomatic patient does not appear to be associated with a higher risk of stroke than asymptomatic stenoses in truly asymptomatic patients.

Up to 24% of "asymptomatic contralateral hemispheres" in NASCET had CT evidence of ischaemic infarction.[44] NASCET analysed the 5-year stroke risk in the asymptomatic hemisphere contralateral to that randomised in the trial, relative to the degree of

stenosis. The 5-year risk increased from 7.8% (>50% stenosis) to 12.9% (50–59%), 14.8% (60–74%) and 18.5% (75–94%). Interestingly, the 5-year risk fell to 14.7% in those with near occlusion. The lowest 5-year risk (9.4%) was observed in patients known to have carotid occlusion from the outset. In NASCET, approximately 50% of all strokes in the territory of an asymptomatic, contralateral 60–99% ICA stenosis were not considered to be of large artery origin.[41]

Are there any models that predict the late stroke risk?

The large trials have shown that CEA confers a major reduction in the risk of stroke as compared with BMT alone in patients with a 70–99% stenosis. However, it is also clear that the majority (approximately 75%) of patients with 70–99% stenosis will not suffer a stroke during follow-up with BMT alone. There has therefore been interest in identifying which individuals are at highest risk of stroke, and most likely therefore to benefit from CEA.

In order to derive a model that could be tested in the 70–99% stenosis patients, the ECST undertook a multivariate analysis in the 857 medically treated patients with a 0–69% stenosis to identify factors significantly predictive of late ipsilateral stroke.[13] Three factors (Table 11) were identified; (i) hemispheric as opposed to ocular events (OR 2.5 (95%CI 1.1–3.7)), (ii) irregular vs smooth plaques (OR 2.1 (95%CI 1.2–3.6)) and (iii) events in the preceding 2 months (OR 1.8 (95%CI 1.02–3.2)). Each was assigned a score of one. Thereafter an allowance was made for increasing degrees of stenosis above 70% (70–79% scored 0, 80–89% scored 1 point and 90–99% scored 2). Thus the maximum score for predicting late stroke risk in medically treated patients was 5. Next, a correction was made to account for the operative risk. A similar multivariate analysis identified factors predictive of an increased risk of operative stroke in 1203 surgical patients with 0–69% stenosis. Three were identified (Table 11); (i) female sex (OR 2.05 (95%CI 1.3–3.2)), (ii) history of claudication (OR 2.5 (95%CI 1.4–4.1)) and (iii) systolic blood pressure >180 mmHg (OR 2.2 (95% CI 1.3–3.8)). Each was assigned a score of 0.5 and the "surgical" total subtracted from the medical score.

The investigators thereafter applied this scoring system to the medically and surgically treated ECST patients with 70–99% stenoses. They demonstrated that patients with a score of ≤3.5 had a 12% 5 year risk of ipsilateral stroke if treated medically (Table 12) as opposed to 11% in the surgical group (ARR 1% over 5 years, RRR = 8.3%, NNT = 100). However, medically treated patients with a score ≥4 had a 40% 5-year risk of stroke as compared with 7% for the surgical group (ARR = 33%, RRR = 83%, NNT = 3). If this scoring system were applied to current surgical practice (i.e., only operate on patients with a score ≥4), fewer than 20% of patients currently considered for CEA would require surgery.[13]

This is the first attempt to develop an evidence-based scoring system to target CEA towards the highest risk patients. This method is currently being tested on the NASCET database to see if it can be applied to other populations of patients.

Table 11. ECST scoring system for predicting risk of late ipsilateral stroke. *

Predictive risk factor	Odds ratio	*95%CI*	Score
Medical risk †			
Cerebral versus ocular	2.5	1.1–3.7	1
Plaque surface irregularity	2.1	1.2–3.6	1
Events in preceding 2 months	1.8	1.02–3.2	1
Degree of ICA stenosis	1.3	1.1–1.4	0 for 70–79% 1 for 80–89% 2 for 90–99%
Surgical risk †			*(Subtract)*
Female	2.05	1.3–3.2	0.5
Claudication	2.5	1.5–4.1	0.5
Systolic BP >180 mmHg	2.2	1.3–3.8	0.5

* Adapted from Rothwell *et al.* on behalf of ECST.[14]
† Thus a female patient with two hemispheric TIAs within the preceding 2 months and who had a 90–99% irregular stenosis on angiography and a past history of claudication would score 5 on the medical risk scale but would have 1.0 deducted (the surgical risk scale) for being female and having a history of claudication. The overall score would be 4.

Generalisability of the Trial Results

Strictly speaking, the ECST and NASCET results apply only to those centres and surgeons who participated in the studies. However, it is increasingly assumed that the trial results are generalisable to routine clinical practice. However, less than 0.5% of

Table 12. 5 year risk of stroke using the ECST prognostic scoring system. *

Risk score	Actuarial predicted 5 year risk †				
	Surgery (%)	Medical (%)	ARR (%)	RRR (%)	NNT
0–3.5	11	12	1	8.3	100
4–5	7	40	33	82.5	3

* Adapted from Rothwell *et al.* on behalf of ECST.[14]
† Thus the patient example described in Table 11 scored 4 and would be predicted to have a 40% risk of stroke in the next 5 years.

patients undergoing CEA in North America between 1988–1989 were actually randomised into NASCET.[20] Second, it is argued that only the "best" surgeons participated in the studies and their results may not reflect actual practice. Although data are unavailable for the ECST and NASCET, ACAS rejected 40% of surgeon applicants following review of their "track record".[60] That surgical practice can vary has been evident for decades. While NASCET was underway, Hsai simultaneously audited mortality following CEA in Medicare beneficiaries.[61] The operative mortality was five times higher than in NASCET (3.0% vs 0.6%). When repeated in 1998, mortality was still two times higher.[62] Non-NASCET centres currently perform 94% of all CEAs in the U.S.A. with a mortality rate significantly higher than that observed in NASCET centres.[63,64] Evidence for worse outcomes than the ECST in Europe include the 9.9% death/stroke rate in the CAVATAS trial.[53] The evidence indicates that patient and surgeon selection can significantly influence the effectiveness of CEA, and that clinicians must take this into account when applying the results of the trials to their own practice. Accordingly, the conclusions regarding clinical practice given in this review will not apply to centres whose operative risk is outside that reported in the trials.

Conclusions

- The simple assumption that ALL patients with a symptomatic stenosis >70% will benefit from CEA is untenable. Approximately 75% will not have a stroke if treated medically.
- Development of local protocols for patient selection (or exclusion) should involve surgeons and physicians and should take local operative risk into account.
- There is anecdotal evidence that the investigation and referral of patients for CEA is taking too long. The ECST and NASCET have identified subgroups who should have expedited investigation and surgery (male sex, 90–99% stenosis, hemispheric symptoms, recurrent events for >6 months, contralateral occlusion, multiple risk factors).
- Surgeons must quote their own results and be aware that a high operative risk reduces long-term benefit. Accordingly, in those centres with higher operative death/stroke rate, certain "lower risk" patients should probably be considered for best medical therapy alone.
- The ECST and NASCET have shown that the ubiquitous string sign is not associated with a high risk of stroke, and emergency endarterectomy is unnecessary.
- It is hoped that pooling of the ECST and NASCET databases will enable more definitive guidelines to be developed regarding who benefits most from CEA.

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