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# Reanalysis of the Final Results of the European Carotid Surgery Trial

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for the European Carotid Surgery Trialists' Collaboration

**Background and Purpose**—The European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) have shown that endarterectomy reduces the risk of stroke in certain patients with recently symptomatic carotid stenosis. However, they differed in the degree of stenosis above which surgery was reported to be effective. This disparity has led to inconsistent clinical recommendations but may have been due to differences between the trials in the methods of measurement of carotid stenosis and definitions of outcome events.

**Methods**—To allow direct comparison of analyses from ECST and NASCET, we remeasured the prerandomization ECST carotid angiograms and redefined the outcome events the same way as in NASCET.

**Results**—We randomized 3018 patients and followed them up for a mean of 73 months. Surgery reduced the 5-year risk of any stroke or surgical death by 5.7% (95% CI, 0 to 11.6) in patients with 50% to 69% stenosis ( $n=646$ ,  $P=0.05$ ) and by 21.2% (95% CI, 12.9 to 29.4) in patients with 70% to 99% stenosis without “near occlusion” ( $n=429$ ,  $P<0.0001$ ). These benefits were maintained at the 10-year follow-up. However, surgery was of no benefit in patients ( $n=125$ ) with near occlusion. The effect of surgery in this group was highly significantly different from that in patients with 70% to 99% stenosis without near occlusion ( $P=0.002$ ). Surgery was harmful in patients with  $<30\%$  stenosis ( $n=1321$ ,  $P=0.007$ ) and of no benefit in patients with 30% to 49% stenosis ( $n=478$ ,  $P=0.6$ ).

**Conclusions**—Results of the ECST and NASCET were consistent when analyzed in the same way. In ECST, surgery was highly beneficial for 70% to 99% stenosis and moderately beneficial for 50% to 69% stenosis. However, contrary to clinical recommendations and current practice, surgery was of little benefit in patients with carotid near occlusion. (*Stroke*. 2003;34:514-523.)

**Key Words:** carotid endarterectomy ■ randomized controlled trials ■ stroke prevention

Since the publication of positive results from large randomized controlled trials,<sup>1-3</sup> the number of carotid endarterectomies performed in the United States and Europe has doubled.<sup>4-6</sup> Approximately 150 000 operations are performed each year in the United States, about half of which are for recently symptomatic carotid stenosis.<sup>4,5</sup> Rates are lower in Europe, but the proportion of operations for symptomatic stenosis is higher than in the United States.<sup>6</sup>

Two randomized controlled trials of endarterectomy versus medical treatment for symptomatic carotid stenosis were published in the 1970s<sup>7,8</sup> but were too small to provide reliable estimates of the balance of risk and benefit from surgery. A third trial, the Veterans Affairs Trial,<sup>9</sup> was stopped early when 2 large trials, the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), reported their initial results in 1991.<sup>10,11</sup> ECST and NASCET published their final results in 1998.<sup>1,2</sup> NASCET reported significant benefit from surgery in patients with  $\geq 50\%$  stenosis,<sup>2</sup> and

North American guidelines are based on these results.<sup>12,13</sup> However, ECST reported that surgery was beneficial only in patients with  $\geq 80\%$  stenosis,<sup>1</sup> and clinical guidelines in Europe are based on these results.<sup>6,14</sup> These disparities have caused confusion, and it is important that they are properly understood.

The designs of ECST and NASCET were similar, but there were a number of important differences in the methods of analysis. First, the 2 trials used different methods of measurement of the degree of carotid stenosis on the prerandomization catheter angiograms (Figure 1).<sup>15</sup> The method used in NASCET produces lower values for stenosis than the method used in ECST.<sup>16,17</sup> Second, there were differences between the trials in the definitions of outcome events (see below). It is possible that these differences in the methods of analysis in ECST and NASCET account for the apparent differences in their results.

To properly compare the results of the ECST and NASCET, we remeasured the original ECST angiograms by

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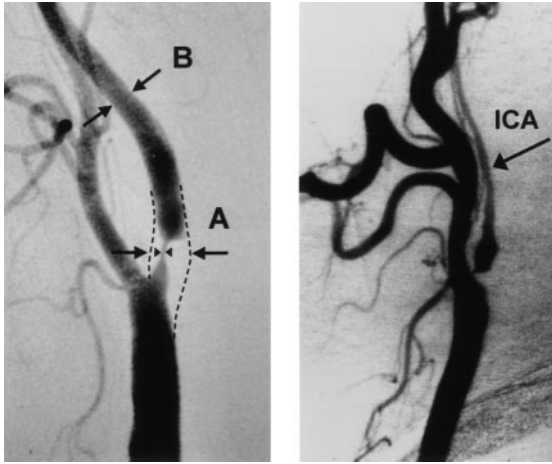
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**Figure 1.** Selective arterial angiograms of carotid bifurcation showing 85% stenosis without near occlusion by the NASCET method of measurement (left) and near occlusion (severe stenosis with narrowing of the distal ICA) (right). To calculate the degree of stenosis, the lumen diameter at the point of maximum stenosis (A) was measured as the numerator in both ECST and NASCET. However, NASCET used the lumen diameter of the distal ICA (B) as the denominator, whereas the ECST used the estimated normal lumen diameter (dotted lines) at the point of maximum stenosis.

the method used in NASCET and redefined the outcome events in the same way.

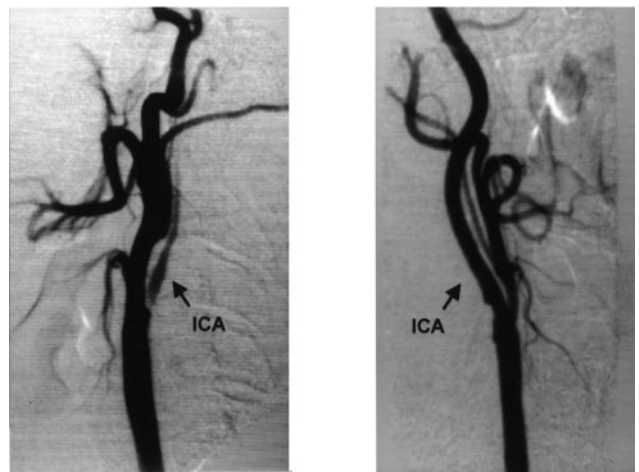
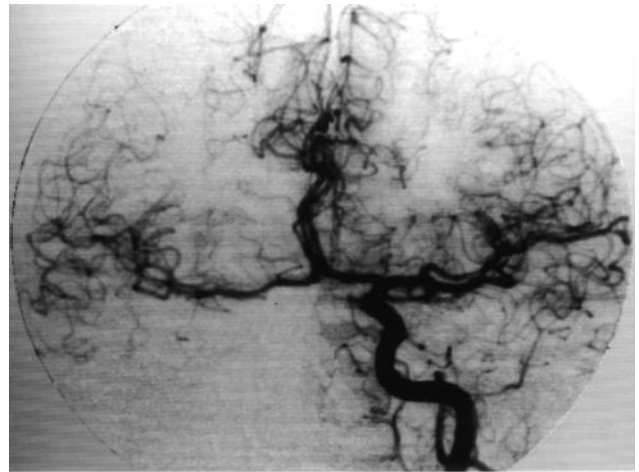
## Methods

The methods of ECST and NASCET have been reported previously.<sup>18–20</sup> In both trials, patients were recruited if, after assessment by a neurologist or a stroke physician, they were thought to have had a recent carotid distribution transient ischemic attack, nondisabling ischemic stroke, or a retinal infarction and had a stenosis of the ipsilateral (symptomatic) carotid artery. Both trials required that the symptomatic carotid artery (and preferably the contralateral carotid artery and intracranial circulation) be imaged with angiography (ideally selective catheter angiography) before randomization. Patients were randomized to immediate carotid endarterectomy plus best medical treatment or best medical treatment alone via a central telephone randomization service. In both trials, randomization was stratified by center. ECST recruited from 100 centers in 14 European countries; NASCET recruited from 106 centers, mainly in North America. In both trials, follow-up was performed at set intervals by a neurologist or a stroke physician.

Although the methods of ECST and NASCET were fundamentally similar, there were some important differences. Inclusion of patients in the ECST was based on the “uncertainty principle,”<sup>10</sup> whereas NASCET had more detailed inclusion and exclusion criteria.<sup>11</sup> One consequence was that patients with any degree of carotid stenosis could be randomized in ECST, whereas NASCET aimed to include only patients with >30% stenosis. Time from last symptoms to randomization had to be <4 months in NASCET (changed to 6 months after 1991), whereas a period of 6 months was allowed in ECST. Patients were randomized in a 50:50 ratio in NASCET and in a 60:40 (surgery:no surgery) ratio in ECST. The dose of aspirin recommended in NASCET was 1300 mg, whereas no specific dose was recommended in ECST. Follow-up was performed at 1, 3, 6, 9, and 12 months and at 4-month intervals thereafter in NASCET and at 4 and 12 months and annually thereafter in the ECST.

## Reassessment of Carotid Angiograms

So that analyses could be stratified by the degree of stenosis of the symptomatic carotid artery, the 3018 ECST prerandomization angiograms were remeasured by 1 observer (P.M.R.) who was blinded to



**Figure 2.** Selective arterial angiograms of both carotid circulations in a patient with a recently symptomatic carotid near occlusion (left) and a mild stenosis at the contralateral carotid bifurcation (right). The nearly occluded ICA is markedly narrowed, and flow of contrast into the distal ICA is delayed. After selective injection of contrast into the contralateral carotid artery, significant collateral flow can be seen across the anterior communicating arteries with filling of the middle cerebral artery of the symptomatic hemisphere (top).

outcome events, and the degree of stenosis was recalculated by the method used in NASCET (Figure 1). Observer agreement with the NASCET principal neuroradiologist for allocation of cases into the stenosis categories used in NASCET (<30%, 30% to 49%, 50% to 69%, 70% to 99%) had been assessed on 120 angiograms and was good ( $\kappa=0.70$ ,  $P<0.001$ ).<sup>21</sup> Intraobserver agreement on 100 consecutive angiograms for the observer was good for both the ECST method ( $\kappa=0.76$ ,  $P<0.001$ ) and the NASCET method ( $\kappa=0.82$ ,  $P<0.001$ ).

The degree of stenosis cannot be calculated by the method used in NASCET on angiograms in which the poststenotic internal carotid artery (ICA) is narrowed (Figures 1 and 2). In the original NASCET reports, some of these “near occlusions” had been identified and arbitrarily defined as 95% stenosis for the purpose of analysis.<sup>17,22</sup> For the purpose of this reanalysis, all ECST angiograms were reassessed to identify near occlusions by the definition used in NASCET. Near occlusions were identified by use of the previously reported angiographic criteria<sup>22</sup>: severe stenosis with evidence of reduced flow in the distal ICA (delayed arrival of contrast into the distal ICA and evidence of collateral flow of contrast toward the symptomatic cerebral hemisphere from other arterial territories) and evidence of narrowing of the poststenotic ICA.<sup>22</sup> Evidence of ICA narrowing by the NASCET criteria requires that the poststenotic ICA

be similar to or smaller than the ipsilateral external carotid artery and/or clearly smaller than the contralateral ICA. An example is shown in Figure 2.

Cases with near occlusion had been identified originally in ECST, but they had not been categorized separately because the method of calculation of the degree of stenosis in ECST did not require measurement of the lumen diameter of the poststenotic ICA.<sup>16</sup> Indeed, the ECST method of measurement of stenosis was used primarily because of the problem of narrowing of the distal ICA beyond a severe stenosis.<sup>16</sup> The degree of narrowing of the distal ICA had been quantified in ECST as the ratio of the lumen diameter of the distal ICA to the lumen diameter of the common carotid artery (CCA),<sup>23</sup> and it had been shown that there was no reduction in the mean ICA:CCA ratio until the degree of stenosis exceeded 70% by the ECST method of measurement of stenosis.<sup>16</sup> In ECST patients with <50% stenosis (<30% by the NASCET method), the lower limit of normal (2 SD below the mean) for the ICA:CCA ratio was 0.42.<sup>23</sup> Abnormal poststenotic narrowing of the distal ICA was therefore defined as a severe carotid stenosis with an ICA:CCA ratio of <0.42. This definition has subsequently been used in NASCET.<sup>24</sup> It has since been shown that the lower limit of normal of the ICA:CCA ratio differs between men and women (0.40 in men, 0.45 in women) because of systematic sex differences in normal carotid bifurcation anatomy.<sup>25</sup> For the purposes of this article, severe stenosis with narrowing of the ICA was defined as a severe carotid stenosis (70% to 99% by the ECST method) with an ICA:CCA ratio of <0.40 in men and <0.45 in women.

### Definition of Stroke

ECST and NASCET used different definitions of stroke outcomes. In NASCET, a stroke was defined as an event with symptoms lasting >24 hours, whereas ECST required that symptoms last  $\geq 7$  days. The NASCET definition of stroke included retinal infarcts; the ECST definition did not. However, strokes with symptoms lasting <7 days and retinal events were recorded in ECST. It was therefore possible to redefine the ECST outcomes. For the purpose of this reanalysis of ECST, stroke was defined as any cerebral or retinal event with symptoms lasting >24 hours. Both the ECST and NASCET used Rankin score to define disabling stroke.<sup>26</sup> For the purposes of this reanalysis of ECST, disabling stroke was defined the same way as in NASCET, ie, as stroke that resulted in a Rankin score of  $\geq 3$  at the 6-month follow-up.

### Statistical Analysis

All patients who were included in the original ECST analysis were included in the reanalysis. The analysis was stratified into the following groups on the basis of the NASCET method of measurement of stenosis of the symptomatic carotid artery: <30%, 30% to 49%, 50% to 69%, 70% to 99% without near occlusion, and near occlusion. Additional analyses were also performed in patients with severe stenosis with narrowing of the ICA based on the ECST definition given above and in patients with 70% to 99% stenosis by the NASCET method without narrowing of the ICA.

The primary outcome used for analysis of the effect of surgery was any first stroke or surgical death. Two additional outcomes are also reported: first ischemic stroke in the territory of the symptomatic carotid artery and any stroke or death that occurred within 30 days of trial surgery, and first disabling or fatal ischemic 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 performed in patients who were randomized 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 trial.<sup>1</sup>

Analyses of the efficacy of surgery were based on intention to treat. Statistical significance of differences between the Kaplan-Meier event-free survival curves for the treatment groups was assessed by the log-rank test. Estimates of the absolute treatment effect (and 95% CIs) were determined at the 5-year follow-up from Kaplan-Meier event-free survival curves. Statistical significance of

**TABLE 1. Baseline Clinical and Angiographic Characteristics of the ECST Patients**

	Surgery	No Surgery	Total
<b>General</b>			
<b>Sex</b>			
Male	1299 (71.9)	869 (71.8)	2168 (71.8)
Female	508 (28.1)	342 (28.2)	850 (28.2)
<b>Age</b>			
<65	1032 (51.7)	712 (58.8)	1744 (57.8)
65–74	664 (36.7)	434 (35.8)	1098 (36.4)
75+	111 (6.1)	65 (5.4)	176 (5.8)
<b>Presenting event</b>			
Stroke	767 (42.4)	507 (41.9)	1274 (42.2)
Ocular events only	337 (18.6)	231 (19.1)	568 (18.8)
<b>Carotid territory</b>			
Left	986 (54.6)	634 (52.4)	1620 (53.7)
Right	821 (45.4)	577 (47.6)	1398 (46.3)
<b>Time since last symptoms</b>			
0–1 month	670 (37.1)	417 (34.4)	1087 (34.9)
2–3 months	672 (37.2)	488 (40.3)	1160 (38.4)
4+ months	465 (25.7)	306 (25.3)	771 (25.6)
<b>Angiographic data</b>			
<b>Symptomatic carotid stenosis</b>			
<30%	783 (43.4)	538 (44.4)	1321 (43.8)
30–49%	302 (16.7)	185 (15.3)	487 (16.1)
50–69%	380 (21.0)	266 (22.0)	646 (21.5)
70–99%	257 (14.2)	172 (14.2)	429 (14.2)
Near-occlusion*	78 (4.3)	47 (3.9)	125 (4.1)
Occlusion	6 (0.3)	3 (0.2)	9 (0.3)
Missing data	0	1 (0.1)	1 (0.1)
Total	1806 (100)	1212 (100)	3018 (100)
Contralateral ICA occlusion	49 (2.7)	48 (4.0)	97 (3.2)
<b>Medical history</b>			
Previous stroke	103 (5.7)	78 (6.4)	181 (6.0)
Myocardial infarction	226 (12.5)	136 (11.2)	362 (12.0)
Angina	320 (17.7)	190 (15.7)	510 (16.9)
Coronary artery surgery	49 (2.7)	23 (1.9)	72 (2.4)
Peripheral vascular disease	306 (16.9)	210 (17.3)	516 (17.1)
Cardiac failure	30 (1.7)	16 (1.3)	46 (1.5)
Treated diabetes	209 (11.6)	145 (12.0)	354 (11.7)
Current smoking	844 (46.7)	556 (45.9)	1400 (46.4)

\*Near occlusion defined using NASCET criteria.

Values in parentheses are percentages.

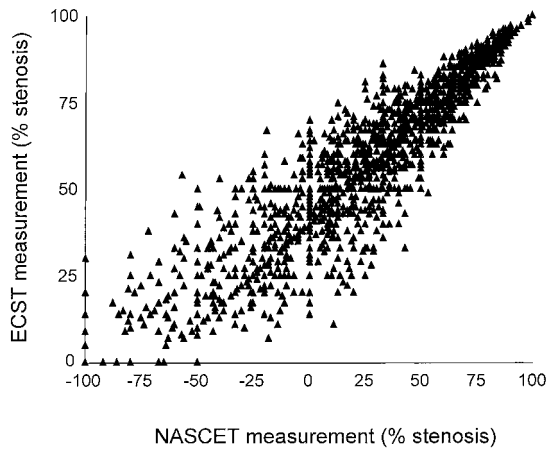
comparisons of baseline data between treatment groups was tested by the  $\chi^2$  test or Student's *t* test when appropriate. All analyses were performed with SPSS for Windows (version 10.0).

### Results

Clinical records and electronic data files were available for all 3018 patients randomized and included in the original final analysis of the ECST (Table 1). Mean follow-up was 73 months (SD=35; range, 1 day to 167 months).

The prerandomization carotid angiogram was unavailable for remeasurement in 1 patient, and 9 patients had an





**Figure 3.** Measurement of degree of stenosis of the symptomatic carotid artery on angiograms from 2892 ECST patients by the method used in ECST and the method used in NASCET. Measurements were made by the same observer, and angiograms showing near occlusions were excluded.

occlusion of the carotid artery that was defined as symptomatic. Thus, 3008 patients (99.7%) were included in analyses of the efficacy of surgery by stenosis group. The degree of carotid stenosis was remeasured by the method used in NASCET on the prerandomization angiogram in each case. The relationship between the ECST and NASCET measurements was linear, and the measurements were highly correlated ( $r=0.94$ ,  $P<0.00001$ ), but the ECST method produced higher values (Figure 3). For example, on average, 50% and 70% stenoses by the NASCET method were equivalent to 65% and 82% stenoses, respectively, by the ECST method.

Near occlusion by the NASCET criteria was present in 125 cases. Severe stenosis with narrowing of the ICA (by the ECST criteria) was present in 108 cases. These groups were highly significantly interrelated ( $P<0.0001$ ) and overlapped in 102 cases (Table 2). In 6 cases, the ICA:CCA ratio suggested that there was poststenotic narrowing of the ICA, but they were not definite near occlusions. In 1 of these, the narrow ICA was due to recanalization after an ICA occlusion; in 2 cases, there was definite poststenotic narrowing of the ICA, but there were insufficient intracranial views to demonstrate the collateral flow necessary to define near occlusion. In 23 cases, there was sufficient evidence to classify the angiographic appearances as near occlusion, but the degree of ICA narrowing was insufficient for the ICA:CCA ratio to fall

**TABLE 2. The Interrelation Between the Angiographic Categories of Near Occlusion (as Used in the NASCET) and the ECST Definition of Severe Stenosis With Narrowing of the Internal Carotid Artery (ICA) Among the 3017 Patients in the ECST With a Prerandomization Angiogram**

	Near Occlusion		Total
	Yes	No	
Narrowing of the ICA			
Yes	102	6	108
No	23	2886	2909
Total	125	2892	3017

**TABLE 3. The Risk (95% CI) of Major Outcome Events Within 30 Days of Surgery According to the Degree of Stenosis of the Operated Artery in 1742 Patients Who Underwent Trial Surgery**

Outcome	Events/Operations	Risk (95% CI)
Any stroke or death		
<30%	46/752	6.1% (4.5–8.1)
30–49%	27/292	9.3% (6.2–13.2)
50–69%	37/371	10.0% (6.9–13.1)
70–99% without near occlusion	17/249	6.8% (4.0–10.7)
Near occlusion†	3/78	3.8% (0.8–10.8)
Total	130/1742	7.5% (6.3–8.8)
Disabling stroke or death		
<30%	20/752	2.7% (1.6–4.1)
30–49%	11/292	3.8% (1.9–6.6)
50–69%	19/371	5.1% (3.1–7.9)
70–99% without near occlusion	10/249	4.0% (1.9–7.2)
Near occlusion†	2/78	2.6% (0.3–9.4)
Total	62/1742	3.6% (2.7–4.5)
Death		
<30%	8/752	1.1% (0.5–2.1)
30–49%	2/292	0.7% (0.1–2.5)
50–69%	6/371	1.5% (0.6–3.3)
70–99% without near occlusion	1/249	0.4% (0–2.2)
Near occlusion†	0/78	0% (0–4.6)
Total	17/1742	1.0% (0.6–1.6)

\*Three patients who had occlusion of the symptomatic carotid artery and who underwent endarterectomy of the contralateral carotid artery are excluded.

†Near occlusion defined using NASCET criteria.

below the lower limit of normal. However, in most of these cases, the angiographic evidence of near occlusion was more subtle than in those cases with definite narrowing of the ICA. Overall, the mean and median ICA:CCA ratios in the 125 near occlusions were 0.32 (SD=0.07) and 0.33 (interquartile range, 0.22 to 0.38), respectively, in men and 0.35 (SD=0.07) and 0.37 (interquartile range, 0.25 to 0.40) in women.

Of the 1807 patients who were randomized to surgery, 1742 (97%) underwent trial surgery. The median time from randomization to trial surgery was 14 days. There were 130 strokes or deaths within 30 days of surgery (7.5%; 95% CI, 6.3 to 8.8). There were no significant differences in operative risk across the stenosis groups ( $\chi^2=8.15$ ,  $df=4$ ,  $P=0.09$ ; Table 3). The risk of death within 30 days of endarterectomy was 1.0% (17 of 1742; 95% CI, 0.6 to 1.6). Thirty-day case fatality for operative strokes was 8.3% (10 of 120; 95% CI, 4.1 to 14.8).

The absolute reductions in the 5-year risk of the main study outcomes with surgery are shown for each of the stenosis groups in Table 4. Surgery was harmful in patients with <30% stenosis, with an increased risk of any stroke or surgical death (log rank=7.2,  $P=0.007$ ) and ipsilateral carotid territory ischemic stroke and surgical stroke or death (log rank=7.6,  $P=0.005$ ). This was maintained out to the 10-year follow-up (Figure 4). There was also a trend toward harm from surgery for disabling or fatal ipsilateral carotid

**TABLE 4. The Effect of Surgery on the Risk of the 3 Main Trial Outcome Events\***

Outcome	Absolute Risk Reduction (95% CI)	Log Rank†
Any stroke or surgical death		
<30%	-3.6% (-7.8-0.5)	p=0.007
30-49%	1.3% (-6.5-9.1)	p=0.6
50-69%	5.7% (0-12.2)	p=0.05
≥70% without near occlusion	21.2% (12.9-29.4)	p<0.0001
Near occlusion‡	-8.5% (-22.0-5.1)	p=0.7
Ipsilateral ischaemic stroke and surgical stroke or death		
<30%	-3.7% (-8.0--0.5)	p=0.005
30-49%	-0.7% (-8.6-6.7)	p=0.30
50-69%	2.9% (-3.0-9.1)	p=0.43
≥70% without near occlusion	18.7% (11.1-26.7)	p<0.0001
Near occlusion‡	-5.1% (-19.2-7.4)	p=0.47
Disabling or fatal ipsilateral ischaemic stroke and disabling surgical stroke or death		
<30%	-2.0% (-5.0-1.0)	p=0.08
30-49%	0.4% (-6.9-7.1)	p=0.3
50-69%	1.2% (-4.5-6.4)	p=0.5
≥70% without near occlusion	7.3% (0.7-14.3)	p=0.04
Near occlusion‡	-5.9% (-12.5-1.3)	p=0.1

\*Absolute risk reductions are calculated at five years follow-up.

†Log-rank test based on full duration of follow-up.

‡Near occlusion defined using NASCET criteria.

territory ischemic stroke and disabling surgical stroke or surgical death (log rank=3.0,  $P=0.08$ ). There was no effect of surgery on any outcome in patients with 30% to 49% stenosis (Table 4 and Figure 4).

There was some evidence of benefit from surgery in patients with 50% to 69% stenosis (Table 4 and Figure 5), with a borderline statistically significant reduction in the risk of any stroke or surgical death (log rank=3.9,  $P=0.05$ ). However, there was no reduction in the risk of ipsilateral carotid territory ischemic stroke and surgical stroke or death (log rank=0.6,  $P=0.43$ ) or in the risk of disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death (log rank=0.5,  $P=0.5$ ).

In patients with 70% to 99% stenosis without near occlusion, there was a highly significant reduction in the surgery group in risks of all outcomes (Table 4 and Figure 5). Benefit was apparent by the end of the first year of follow-up, reached a maximum by 3 years, and was still apparent at 10 years. The number needed to treat to prevent 1 event was 5 (95% CI, 3 to 8) for any stroke or surgical death and 10 (95% CI, 6 to 37) for disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death. The results were very similar (Figure 6) in patients with 70% to 99% stenosis without narrowing of the ICA (by ECST criteria).

In contrast to the 70% to 99% stenosis group, there was no clear evidence of benefit from surgery for any of the

outcomes in patients with near occlusion in the ECST, and there was a nonsignificant trend toward harm for disabling or fatal events (Table 4 and Figure 5). The difference in the effect of surgery between the near occlusions and the 70% to 99% stenosis group was statistically significant for the 5-year risks of any stroke or surgical death ( $P=0.002$ ), ipsilateral carotid territory ischemic stroke and operative stroke or death ( $P=0.0016$ ), and disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death ( $P=0.0018$ ). The same differences were found between the effect of surgery in patients with 70% to 99% stenosis without ICA narrowing and those with the ECST definition of severe stenosis with ICA narrowing (ICA:CCA ratio of <0.40 in men and <0.45 in women):  $P=0.008$ ,  $P=0.008$ , and  $P=0.002$ , respectively. Figure 6 shows the effect of surgery on any stroke or surgical death and disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death in these groups. As expected, given the considerable overlap between the near occlusion group and the severe stenosis with ICA narrowing group, the survival curves are very similar to those in Figure 5.

Surgery did reduce the 5-year risk of transient ischemic attack during follow-up in patients with near occlusion (absolute risk reduction, 15%;  $P=0.007$ ) and in patients with severe stenosis and narrowing of the ICA (absolute risk reduction, 13%;  $P=0.03$ ).

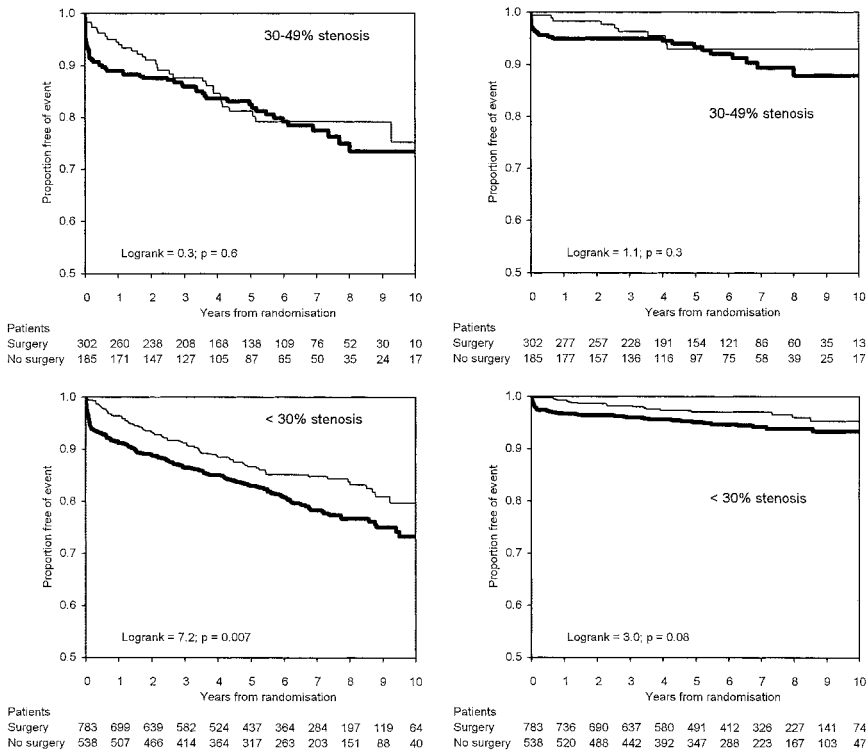
## Discussion

These results remove the uncertainty generated by the apparent disparities between the original results of ECST and the results of NASCET and have several important implications for clinical practice.

### Surgery for Severe Stenosis

The original final results of the ECST reported that surgery was effective only in patients with 80% to 99% stenosis. This reanalysis shows that surgery is highly effective in patients with 70% to 99% stenosis measured by the method used in NASCET. The 21.2% (95% CI, 12.9 to 29.4) reduction in the 5-year absolute risk of any stroke or surgical death with surgery in the ECST in patients with 70% to 99% stenosis without near occlusion is comparable to the 15.0% (15.0% CI, 7.4 to 22.6) absolute risk reduction at 2 years originally reported in NASCET.<sup>11</sup> The greater benefit in ECST may be due in part to the inclusion of near occlusions in the severe stenosis group in the original NASCET article.

The ECST data also demonstrate that the benefit from surgery for severe stenosis is still present at the 10-year follow-up. This significant observation highlights the importance of prolonged follow-up in any future trials comparing endarterectomy with alternative treatments. Assessment of the long-term effectiveness of surgery was possible in ECST because the crossover rate from medical to surgical treatment was very low. In NASCET, there was a high rate of crossovers ( $\approx 50\%$ ) from the medical group to the surgery group shortly after the announcement of benefit from surgery for 70% to 99% stenosis in 1991. ECST announced a similar benefit at the same time, but the ECST coordinating center did not make a specific recommendation about whether



**Figure 4.** Kaplan-Meier curves in patients with <30% stenosis and 30% to 49% stenosis showing the effect of surgery on survival free of any stroke or surgical death (left) and disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death (right). Thick line represents surgical treatment; thin line, medical treatment.

patients who had been randomized to medical treatment should undergo endarterectomy. The subsequent crossover rate in the ECST was <1%. This was considered to be acceptable because the vast majority of patients had been asymptomatic for several months, and most for several years, at the time the results were announced. It was clear from the analysis of the ECST data at that time that the risk of stroke distal to a severe carotid stenosis fell rapidly with time since the last symptomatic event and that the balance of risks and benefits of surgery in patients who had been asymptomatic for several months or years was uncertain.

**Surgery for Near Occlusion**

We did not find any benefit from surgery in patients with near occlusion by the NASCET criteria or in patients with severe stenosis with narrowing of the ICA by the ECST criteria. These were not posthoc subgroup analyses. Rather, they were necessary because the degree of stenosis was not measurable by the method used in NASCET in these cases (Figure 1). The lack of benefit from surgery is an important finding and is contrary to the current clinical consensus. In both the United States and Europe, these cases are considered by many surgeons to require urgent surgery.<sup>6,27</sup>

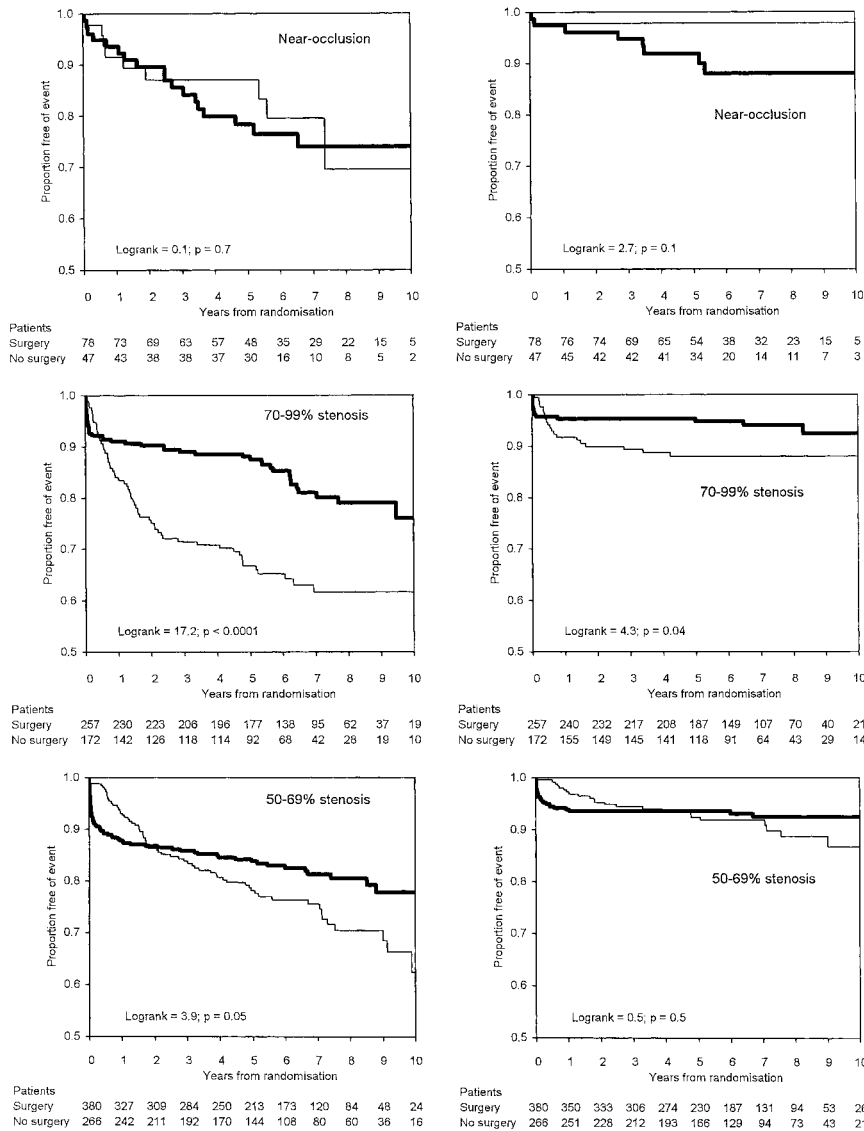
The number of cases with near occlusion or severe stenosis with narrowing of the ICA was relatively small; therefore, the CIs around the treatment estimates in these groups were wide. However, the difference in the effect of surgery between patients with near occlusion and patients with 70% to 99% stenosis without near occlusion and the difference between patients with severe stenosis with narrowing of the ICA and patients with 70% to 99% stenosis without narrowing were statistically significant for all 3 main trial outcomes. The low risk of stroke on medical treatment has been reported previ-

ously in patients with near occlusion in NASCET<sup>28</sup> and in patients with severe stenosis with narrowing of the ICA in both ECST<sup>23</sup> and NASCET.<sup>24</sup> The good prognosis on medical treatment in these patients is most likely due to the presence of good collateral circulation, which is visible on angiography in most patients with narrowing of the ICA distal to a severe stenosis.<sup>23,24,28</sup>

More precise estimates of the risks and benefits of surgery in near occlusions will be available from a pooled analysis of individual patient data from all available randomized trials of carotid endarterectomy for symptomatic carotid stenosis.<sup>29</sup> In the meantime, patients with near occlusion or severe stenosis with narrowing of the ICA should be informed that endarterectomy has not been shown to prevent recurrent stroke. However, some patients may still wish to undergo surgery, particularly if they experience recurrent transient ischemic attacks. Whether clinicians base their decisions on the criteria for near occlusion or the criteria for severe stenosis with narrowing of the ICA will depend on the imaging technique that they use in routine clinical practice (see below).

**Surgery for Moderate Stenosis**

The original ECST analysis of the effect of surgery for moderate stenosis showed no benefit for surgery<sup>30</sup> and was inconsistent with the subsequent NASCET results. Our re-analysis of the ECST data has shown that the effect of surgery in the ECST in patients with 50% to 69% stenosis by the NASCET method of measurement is consistent with that reported by NASCET. There was a modest reduction in the risk of any stroke or surgical death in the surgical group in the ECST. The 5-year absolute risk reduction with surgery (5.7%; 95% CI, -0.8 to 12.2) is well within the 95% CI of the equivalent result in NASCET (8.4%; 95% CI, 1.4 to 15.4).<sup>2</sup>



**Figure 5.** Kaplan-Meier curves in patients with near occlusion (by NASCET criteria), 70% to 99% stenosis without near occlusion, and 50% to 69% stenosis showing the effect of surgery on survival free of any stroke or surgical death (left) and disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death (right). Thick line represents surgical treatment; thin line, medical treatment.

Similarly, although there was no statistically significant benefit from surgery for ipsilateral ischemic stroke alone or for disabling ipsilateral ischemic stroke in ECST, the 95% CIs of the absolute risk reductions with surgery at 5 years (Table 4) still encompass the estimates of the effect of surgery in NASCET.<sup>2</sup> There are therefore no significant differences between the reanalyzed results of the ECST and the results of NASCET.

**Operative Risk**

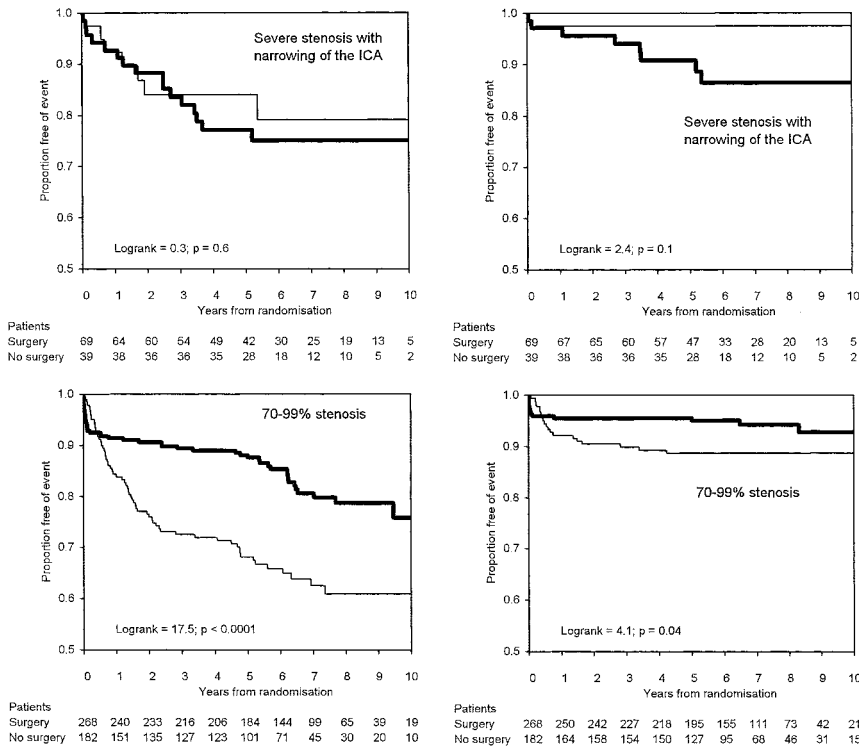
The 7.5% operative risk of stroke and death within 30 days of endarterectomy risk is consistent with surgical case series in which patients were also assessed postoperatively by a neurologist<sup>31</sup> and with the 6.5% (95% CI, 5.3 to 7.9) risk in NASCET. It is likely that some minor operative strokes are missed in normal clinical practice unless postoperative assessments are performed by neurologists or stroke physicians, who should ideally be independent of the operating surgical team.<sup>31,32</sup> It is also important to note that the 30-day case fatality for operative stroke was only 8.3% (10 of 120; 95%

CI, 4.1 to 14.8) and that the ratio of nonfatal strokes to total operative deaths was 6:1. In any surgical audit in which the proportion of fatal outcomes is significantly higher than this, the possibility that some nonfatal strokes have been missed should be seriously considered.

**Implications for Imaging and Measurement of Carotid Stenosis**

Although the severity of carotid stenosis is not the only factor that determines the effectiveness of endarterectomy for symptomatic carotid stenosis,<sup>33</sup> benefit from surgery is still highly dependent on the degree of carotid stenosis. Measurement must therefore be accurate and reliable. This reanalysis was based on the measurement of degree of carotid stenosis by the method used in NASCET. Given the confusion generated by the use of different methods in the original trials, we suggest that this method be adopted as the standard in the future. Arterial angiography (usually conventional selective) was used in the vast majority of cases in ECST. If noninvasive techniques of imaging are used to select patients for surgery,





**Figure 6.** Kaplan-Meier curves in patients with 70% to 99% stenosis without narrowing of the ICA and in patients with severe stenosis with narrowing of the ICA (by ECST criteria) showing the effect of surgery on survival free of any stroke or surgical death (left) and disabling or fatal ipsilateral carotid territory ischemic stroke and disabling surgical stroke or surgical death (right). Thick line represents surgical treatment; thin line, medical treatment.

then they must be properly validated against catheter angiography within individual centers.<sup>34,35</sup>

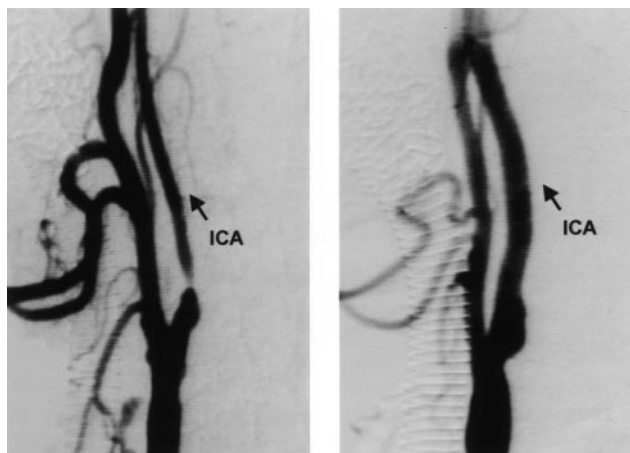
Clinicians who routinely use selective injection contrast arterial angiography will be able to identify near occlusion cases with the NACSET criteria.<sup>22</sup> However, the finding of no obvious benefit from surgery in patients with near occlusion does have implications for clinicians who currently practice using noninvasive methods of carotid imaging. In particular, because these patients have low flow across the stenosis and into the distal ICA, as can be seen on conventional angiography (Figures 1 and 2), they are sometimes misdiagnosed as complete occlusions by noninvasive methods of imaging.<sup>36,37</sup> The lack of obvious benefit from surgery in this group reduces the importance of this shortcoming of noninvasive imaging. Nevertheless, further research is required to assess the sensitivity and specificity of noninvasive methods of imaging in the detection of near occlusion in those cases that are not misdiagnosed as complete occlusions. However, because the near occlusion criteria require the demonstration of collateral flow toward the symptomatic hemisphere (usually seen as flow across the anterior communicating artery after injection of contrast into the contralateral carotid system [Figure 2]),<sup>22,24</sup> noninvasive imaging techniques currently used in routine clinical practice will not be able to apply the criteria directly.

There are several arguments in favor of the continued use of selective arterial angiography in the selection of patients for endarterectomy.<sup>38,39</sup> However, many clinicians now practice with noninvasive imaging alone. One advantage of the ECST criteria for severe stenosis with narrowing of the ICA over the near occlusion definition in identifying patients with severe stenosis who may not benefit from endarterectomy is that it can potentially be derived from noninvasive methods

of carotid imaging. Indeed, ultrasound imaging has been used to demonstrate the return of the ICA lumen diameter to normal after endarterectomy.<sup>36,37</sup> Clinicians who currently practice using noninvasive methods of imaging alone will therefore be able to identify some low-risk severe stenosis patients using the ECST criteria. However, it is important to consider that the data on the ICA:CCA ratio were derived from angiographic images. Further work is necessary to check whether the same cut points should be used to define narrowing of the ICA using other modalities of imaging.

The ECST definition of an abnormally narrow ICA as 2 SD below the population's mean ICA:CCA ratio<sup>23</sup> is, of course, arbitrary. By definition, 2.5% of patients with no stenosis have a sufficiently narrow ICA to be 2 SD below the population mean. The ECST criteria will therefore have a false-positive rate (and a false-negative rate) for the identification of near occlusions. However, given that normal carotid anatomy varies considerably between individuals and between the 2 carotid bifurcations within individuals,<sup>40</sup> it is not possible to identify a cut point for the ICA:CCA ratio that will have no false-positive cases without sacrificing sensitivity. However, the 82% sensitivity and very high specificity of the suggested criteria for ICA narrowing in identifying near occlusions in ECST (Table 2) are likely to prove useful in clinical practice. Moreover, the clinical usefulness of the ECST definition is evident in Figure 6.

It is also important to note that although some patients with severe stenosis with narrowing of the ICA and near occlusion have almost complete collapse of the ICA, as in Figures 1 and 2, others are more subtle. Figure 7 shows angiograms of the carotid arteries of a woman with severe stenosis on the left that satisfies the criteria for severe stenosis with narrowing of the ICA and near occlusion but in whom the ICA is less



**Figure 7.** Arterial angiograms of carotid arteries of a woman with severe stenosis on the left that satisfies the criteria for severe stenosis with narrowing of the ICA and near occlusion but in whom the ICA is only partially narrowed. ICA:CCA ratio is  $<0.45$  on the side of the stenosis (left) compared with 0.6 on the contralateral side (right), and the poststenotic ICA is narrower than the ipsilateral external carotid artery.

completely collapsed than in the cases shown in Figures 1 and 2. Nevertheless, the ICA:CCA ratio is  $<0.45$  on the side of the stenosis compared with 0.6 on the contralateral side, and the poststenotic ICA is narrower than the ipsilateral external carotid artery. In cases in which there is uncertainty, conventional arterial angiography may be necessary to determine whether there is collateral flow toward the symptomatic cerebral hemisphere.

## Conclusions

Reanalysis of the ECST trial using the same definitions of outcomes and the same method of measurement of stenosis used in the NASCET yielded very similar results to those reported in NASCET. There was some evidence of benefit from surgery in patients with 50% to 69% stenosis, although this was not statistically significant for all the main trial outcomes. There was major benefit from surgery in patients with 70% to 99% stenosis without near occlusion and in those with 70% to 99% stenosis without ICA narrowing. However, contrary to current clinical practice, surgery was ineffective in patients with near occlusion or severe stenosis with narrowing of the ICA. More precise estimates of the risks and benefits of surgery will be available from a pooled analysis of individual patient data from all of the available randomized trials of carotid endarterectomy for symptomatic carotid stenosis (Carotid Endarterectomy Trialists' Collaboration).<sup>27,41</sup>

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