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JOURNAL OF THE AMERICAN HEART ASSOCIATION

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*Stroke* 2004;35;2855-2861; originally published online Oct 28, 2004;

DOI: 10.1161/01.STR.0000147040.20446.f6

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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# Sex Difference in the Effect of Time From Symptoms to Surgery on Benefit From Carotid Endarterectomy for Transient Ischemic Attack and Nondisabling Stroke

P.M. Rothwell, PhD; M. Eliasziw, PhD; S.A. Gutnikov, DPhil; C.P. Warlow, MD; H.J.M. Barnett, MD

**Background and Purpose**—Early studies showed that carotid endarterectomy (CEA) carried a high risk if performed within days after a large ischemic stroke. Therefore, many surgeons delay CEA for 4 to 6 weeks after any stroke. To determine the effect of delay to CEA on operative risk and benefit, we pooled data from the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial.

**Methods**—Risk of ipsilateral ischemic stroke in the medical group, operative risk of stroke and death, and overall benefit from surgery were determined in relation to the time from the last symptomatic event to randomization. Operative risk of stroke and death was also determined in relation to the time to surgery. Analyses were stratified by sex and type of presenting event.

**Results**—The 30-day perioperative risk of stroke and death was unrelated to the time since the last symptomatic event and was not increased in patients operated <2 weeks after nondisabling stroke. In contrast, the risk of ipsilateral ischemic stroke in the medical group fell rapidly with time since event ( $P<0.001$ ), as did the absolute benefit from surgery ( $P=0.001$ ). This decline in benefit with time was unrelated to the type of presenting event but was more pronounced in women than men (difference  $P<0.001$ ). Benefit in women was confined to those randomized <2 weeks after their last event, irrespective of severity of stenosis.

**Conclusions**—CEA can be performed safely within 2 weeks of nondisabling ischemic stroke. Benefit from endarterectomy declines rapidly with increasing delay, particularly in women. (*Stroke*. 2004;35:2855-2861.)

**Key Words:** carotid endarterectomy ■ stroke prevention

Carotid endarterectomy (CEA) is highly effective in preventing stroke in patients with recently symptomatic severe stenosis and of lesser benefit in patients with moderate symptomatic stenosis.<sup>1-3</sup> Early studies showed that CEA carries a high risk, particularly of intracranial hemorrhage, if performed within hours or days after a large cerebral infarction.<sup>4-6</sup> Although such severe stroke patients rarely undergo CEA today, many surgeons still delay CEA for 4 to 6 weeks after nondisabling stroke. Yet a previous analysis of data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) suggested that operative risk was not increased in patients operated within 30 days of a nondisabling stroke,<sup>7</sup> and a recent systematic review of surgical case series has confirmed this.<sup>8</sup>

If early CEA is not associated with an increased operative risk after nondisabling stroke, any delay is likely to lead to reduced benefit because of the risk of stroke before surgery. As was first shown by Whisnant et al in the 1960s,<sup>9</sup> and has been confirmed more recently,<sup>10-13</sup> the risk of stroke after a transient ischemic attack (TIA) or nondisabling ischemic

stroke is highest in the first few weeks after the presenting event. In the European Carotid Surgery Trial (ECST) and NASCET, the risk of stroke after randomization of patients in the medical arm fell rapidly during the first year.<sup>1,2</sup> However, current clinical guidelines in North America and Europe simply state that surgery should be performed within 6 months of last symptoms.<sup>14-16</sup>

Subgroup analysis of pooled individual patient data from ECST and NASCET showed that the absolute reduction in risk of ipsilateral ischemic stroke with CEA fell significantly with increasing time from last symptomatic event to randomization,<sup>17</sup> but more detailed analyses are required to guide recommendations about the timing of CEA in routine clinical practice. Therefore, we further analyzed the pooled data from ECST and NASCET.

## Methods

The criteria for inclusion of trials in the Carotid Endarterectomy Trialists Collaboration have been published previously.<sup>3</sup> The analyses in this article were confined to ECST and NASCET because

Received June 7, 2004; final revision received August 3, 2004; accepted September 16, 2004.

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Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000147040.20446.f6

relevant data were not recorded in the Veterans' Affairs 309 trial. The methods of the trials were similar and have been compared previously.<sup>3,18</sup> Briefly, patients were recruited if they had had a recent carotid distribution TIA, nondisabling hemispheric ischemic stroke, or a retinal infarction in the territory of a stenosed carotid artery. Before randomization, patients were seen by a neurologist or stroke physician to confirm their eligibility, and the symptomatic carotid artery was imaged by selective catheter angiography. Patients were assigned to immediate CEA plus best medical treatment versus best medical treatment alone by central telephone randomization. Follow-up was performed at prespecified intervals by a neurologist or stroke physician.

The methods of pooling the individual patient data from the trials have been reported previously.<sup>3</sup> The ECST angiograms were remeasured by the method of measurement of the degree of stenosis that was used in the NASCET, and subsequent reanalysis of ECST, using the definition of stroke as any cerebral or retinal event with symptoms lasting >24 hours, yielded results that were comparable to those of NASCET.<sup>19</sup> No imbalances in baseline characteristics between the surgery and medical groups were introduced by pooling the data from the 2 trials.<sup>3</sup>

### Analysis

The time interval in weeks from most recent symptomatic event to randomization was categorized as <2, 2 to 4, 4 to 12, or >12.<sup>17</sup> The risk of ipsilateral (in the territory of the symptomatic carotid artery) ischemic stroke in patients randomized to medical treatment (medical risk) and the risk of any operative stroke or death (perioperative risk) in patients randomized to surgical treatment were calculated for each time category. Stroke was defined as any cerebral or retinal event with symptoms lasting >24 hours. The perioperative risk was also calculated according to the total time from last event to surgery (ie, the time from last event to randomization plus the time from randomization to surgery) using the same categories. This relationship between perioperative risk and the total time from last event to surgery was also assessed separately for patients presenting with nondisabling hemispheric stroke without complete recovery by the time of randomization versus patients with complete recovery at randomization, and for patients with only a retinal ischemic event or a hemispheric TIA. It should be noted that patients with progressing stroke or major disabling stroke were excluded from the trials.

The primary outcome for analyses of the effect of surgery was time to first ipsilateral ischemic stroke and any perioperative (occurred within 30 days after trial surgery) stroke or death. Benefit from surgery was determined separately in patients with 50% to 69% stenosis,  $\geq 70\%$  stenosis (excluding near-occlusion), and near-occlusion. There were too few patients with near-occlusions to allow separate analysis in each of the 4 time intervals, and so the effect of CEA was assessed with the time intervals collapsed to <4 weeks versus  $\geq 4$  weeks. All analyses of the effect of CEA were performed on an intention-to-treat basis according to the randomized treatment allocation.

To maximize the statistical power needed to detect heterogeneity of the effect of CEA according to time from last event to randomization, and to allow adjustment for the degree of stenosis of the symptomatic carotid artery, analysis of the statistical significance of the timing by treatment interaction was performed across all degrees of stenosis. We performed 2 tests to determine the significance of any treatment effect modification: a Cox proportional hazards model with a timing-by-treatment allocation interaction term, the degree of symptomatic carotid stenosis and the source study, and a test of heterogeneity of the absolute risk reduction at the 5-year follow-up on the basis of risk estimates obtained from life table analysis. Analyses of the effect of surgery in relation to the time from last symptomatic ischemic event to randomization were also performed using any stroke or operative death and any disabling ipsilateral ischemic stroke and disabling operative stroke or death.

In view of the statistically significant interaction between sex and benefit from CEA observed previously,<sup>17</sup> the relationship between benefit from CEA and time since last event was

compared in men versus women. In view of the concern that early CEA might not be indicated in patients who have had a recent stroke, the relationship was compared in patients who had had an ipsilateral hemispheric ischemic stroke during the 6 months before randomization versus those who had had a TIA (hemispheric or retinal) or retinal infarct only. All analyses were done with SPSS for Windows (version 10.0).

### Results

Individual patient data were available for all 5893 patients in the pooled analysis of ECST and NASCET.<sup>17</sup> Mean follow-up was 66 months (SD 34; range 1 day to 166 months; 33 000 patient years). The median time from the last ischemic

**TABLE 1. The Median Time From Last Symptomatic Ischemic Event to Randomization According to Baseline Clinical Characteristics**

Subgroup	No.	Median Days Since Event	P
Degree of symptomatic stenosis			
<30%	1746	44	<0.001
30–49%	1429	47	
50–69%	1502	44	
$\geq 70\%$	954	35	
Near-occlusion	262	30	
Sex			
Male	4175	43	0.32
Female	1718	39	
Age			
<65 years	2900	40	0.03
65–74 years	2408	44	
$\geq 75$ years	585	41	
Primary symptomatic event			
Stroke	2616	45	<0.001
Cerebral TIA	2112	36	
Ocular event	1165	45	
Diabetes			
Yes	974	37	0.001
No	4919	43	
Plaque surface*			
Smooth	2503	38	0.008
Irregular/ulcer	3374	39	
Contralateral internal carotid artery occlusion			
Yes	252	44	0.57
No	5641	42	
Myocardial infarction			
Yes	932	44	0.55
No	4961	42	
Angina			
Yes	1280	42	0.41
No	4613	42	
Treated hypertension			
Yes	2741	41	0.09
No	3152	43	

\*Data available on 5877 (99.7%) of patients.

**TABLE 2. The Operative Risk (95% CI) Attributable to Trial Surgery in Relation to Time Between Last Symptomatic Ischemic Event and Surgery in ECST Compared With NASCET**

	Time Between Last Symptomatic Ischemic Event and Surgery								
	<2 weeks		2–4 weeks		4–12 weeks		>12 weeks		<i>P</i> (Het)
Any stroke or death within 30 days after trial surgery									
ECST	5/77	6.5% (1.0–12.0)	16/249	6.4% (3.4–9.5)	56/756	7.4% (5.5–9.3)	53/660	8.0% (5.9–10.0)	0.86
NASCET	20/283	7.1% (4.1–10.1)	14/281	5.0% (2.4–7.5)	36/555	6.5% (4.4–8.4)	22/296	7.4% (4.4–10.4)	0.64
Total	25/360	6.9% (4.5–10.1)	30/530	5.7% (3.9–8.0)	92/1311	7.0% (5.7–8.5)	75/956	7.8% (6.2–9.7)	0.48
Disabling operative stroke or death within 30 days after trial surgery									
ECST	2/77	2.6% (0.3–9.1)	6/249	2.4% (0.9–5.2)	31/756	4.1% (2.8–5.8)	23/660	3.5% (2.2–5.2)	0.61
NASCET	9/283	3.2% (1.5–6.0)	7/281	2.5% (1.0–5.1)	9/555	1.6% (0.7–3.1)	3/296	1.0% (0.2–2.9)	0.23
Total	11/360	3.1% (1.5–5.4)	13/530	2.5% (1.3–4.2)	40/1311	3.1% (2.2–4.1)	26/956	2.7% (1.8–4.0)	0.89

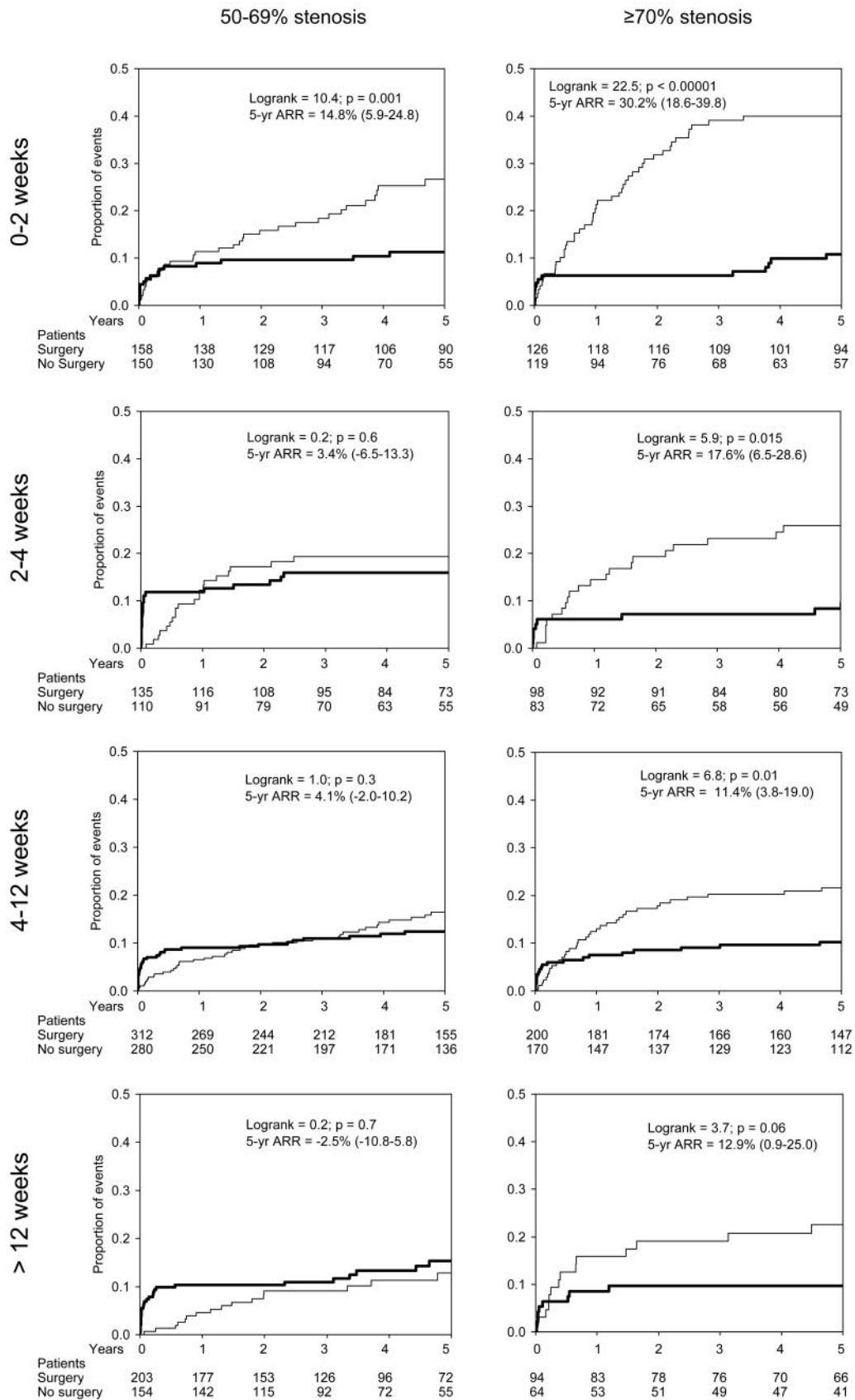
event to randomization was 36 days in NASCET and 45 days in ECST. Where appropriate, analyses were therefore adjusted for source trial. The proportion of patients in each of the timing intervals in ECST and NASCET, respectively, was: <2 weeks 437 (14.5%) and 746 (25.9%); 2 to 4 weeks 574 (19.1%) and 480 (16.6%); 4 to 12 weeks 1214 (40.4%) and 1098 (38.1%); >12 weeks 783 (26.0%) and 561 (19.4%). The median delay between last event and randomization was 7 days in the <2 weeks category, 20 days in the 2 to 4 weeks category, 52 days in the 4 to 12 weeks category, and 122 days in the >12 weeks category, but differed depending on the degree of symptomatic carotid stenosis (Table 1). Therefore, where appropriate, analyses were adjusted for degree of stenosis as well as the source trial. The delay was also related to other baseline characteristics, but differences were relatively small (Table 1). It should be noted that the above timing intervals do not include the time from randomization to CEA itself in those patients who were randomized to surgery. Overall, the median (interquartile range) delay from randomization to surgery was 6 days.<sup>2–18</sup> In patients randomized within 2 weeks of a symptomatic event, the delay was 2 days<sup>1–4</sup> in NASCET and 7 days<sup>3–18</sup> in ECST.

Of the 3157 patients who underwent trial surgery, there were 222 strokes or deaths (7.0%; 95% CI, 6.2 to 8.0) and 90 disabling strokes or deaths (2.9%; 95% CI, 2.3 to 3.5) within 30 days of surgery. Analyses of operative risk were stratified according to the total time from last event to surgery (ie, the time from last event to randomization plus the time from randomization to surgery). There was no association between operative risk and time since event (Table 2). Moreover, there was no statistically significant difference in risk between the time periods in patients with hemispheric stroke with incomplete recovery at randomization: <2 weeks 8 of 77, 10.4% (95% CI, 3.6 to 17.2); 2 to 4 weeks 6 of 137, 4.4% (95% CI, 1.0 to 7.8); 4 to 12 weeks 34 of 426, 8.0% (95% CI, 5.4 to 10.6); and >12 weeks 20 of 276, 7.2% (95% CI, 4.2 to 10.3); *P*=0.39. The findings were similar in patients operated after TIA only, or a stroke with full recovery: <2 weeks 17 of 283, 6.0% (95% CI, 3.5 to 9.4); 2 to 4 weeks 24 of 393, 6.1% (95% CI, 4.0 to 9.0); 4 to 12 weeks 58 of 885, 6.6% (95% CI, 5.0 to 8.4); and >12 weeks 55 of 680, 8.1% (95% CI, 6.2 to 10.4); *P*=0.55. Further subdivision did not reveal any

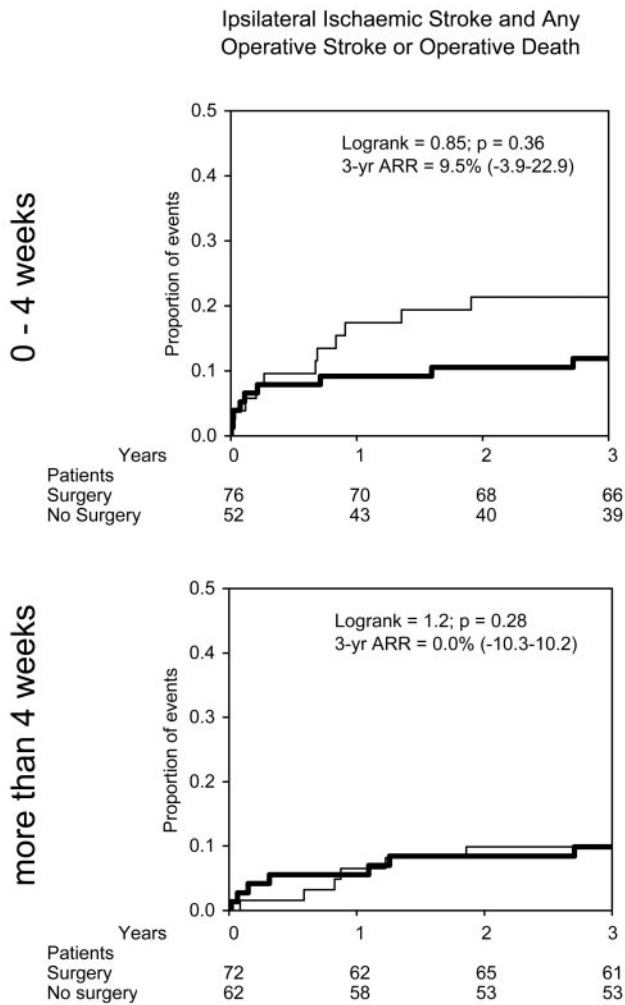
significant difference (*P*=0.52) between the operative risk of stroke and death in patients operated within 1 week of the event (10 of 122; 8.2%; 95% CI, 4.0 to 14.6) and those operated 1 to 2 weeks after the event (15 of 238; 6.3%; 95% CI, 3.6 to 10.2), although the number operated within 1 week of a hemispheric stroke with incomplete recovery was too small to allow reliable estimation of risk.

The risk of ipsilateral ischemic stroke in the medical group decreased with time from last event to randomization (*P*<0.001) in a Cox proportional hazards model, including source study and the degree of symptomatic carotid stenosis. Similar trends were seen for the risk of any stroke (*P*=0.001) and disabling ipsilateral ischemic stroke (*P*=0.03). There was no similar relationship with the time from last event to randomization for operative risk of any stroke or death (*P*=0.33) or disabling stroke or death (*P*=0.54).

The effectiveness of CEA cannot be stratified by time from last event to surgery because there is no medical comparison group for such an analysis. Figure 1 shows the effect of CEA on the risk of ipsilateral ischemic stroke and operative stroke or death by time from last symptomatic ischemic event to randomization in patients with 50% to 69% stenosis and patients with ≥70% stenosis (excluding near-occlusions). Benefit decreased with delay to randomization in both groups. In patients with ≥70% stenosis, the 5-year absolute risk reduction in ipsilateral ischemic stroke and operative stroke or death with CEA in patients randomized within 2 weeks of their last event was 30.2% (number of patients who needed to undergo surgery [NNT] to prevent 1 ipsilateral stroke=3). This benefit was reduced by half in patients randomized 2 to 4 weeks after their last event (NNT=6), and further in patients randomized after 4 weeks (NNT=9). CEA was only beneficial (NNT=7) in patients with 50% to 69% stenosis randomized within 2 weeks of their last symptomatic event. We have shown previously that this trend was present in ECST and NASCET.<sup>17</sup> The same trends were seen for the effect of surgery on the risk any stroke or operative death and on the risk disabling ipsilateral ischemic stroke and disabling operative stroke or death. Figure 2 shows the same analysis in patients with near-occlusion stratified according to whether the time from last symptomatic ischemic event to



**Figure 1.** Kaplan-Meier curves showing the effect of CEA on the risk of ipsilateral ischemic stroke and any operative stroke or death in the pooled data from ECST and NASCET in patients with 50% to 69% stenosis and  $\geq 70\%$  stenosis excluding near-occlusions stratified according to the time from last symptomatic ischemic event to randomization. The thick line represents patients randomized to CEA, and the thin line represents patients randomized to medical treatment. ARR indicates absolute risk reduction.



**Figure 2.** Kaplan–Meier curves showing the effect of CEA on the risk of ipsilateral ischemic stroke and any operative stroke or death in the pooled data from ECST and NASCET in patients with near-occlusions stratified according to the time from last symptomatic ischemic event to randomization. ARR indicates absolute risk reduction.

randomization was <4 weeks or ≥4 weeks, with a trend toward benefit in patients operated early.

The interaction between the time to randomization and benefit from CEA was statistically significant for ipsilateral ischemic stroke and operative stroke or death with the Cox model ( $P=0.02$  for heterogeneity;  $P=0.001$  for trend) and with the test for heterogeneity in the absolute risk reduction with surgery at 5-year follow-up ( $P=0.009$ ). The corresponding  $P$  values for the effect of CEA on the risk of any stroke or operative death were  $P=0.03$  for heterogeneity and  $P=0.004$  for trend with the Cox model, and  $P=0.04$  for the test for heterogeneity in the absolute risk reduction. The corresponding  $P$  values for the effect of CEA risk of disabling ipsilateral ischemic stroke or disabling operative stroke or death were  $P=0.2$  for heterogeneity and  $P=0.07$  for trend with the Cox model, and  $P=0.09$  for the test for heterogeneity in the absolute risk reduction.

Figure 3 shows the relationship between the effect of CEA on ipsilateral ischemic stroke and operative stroke or

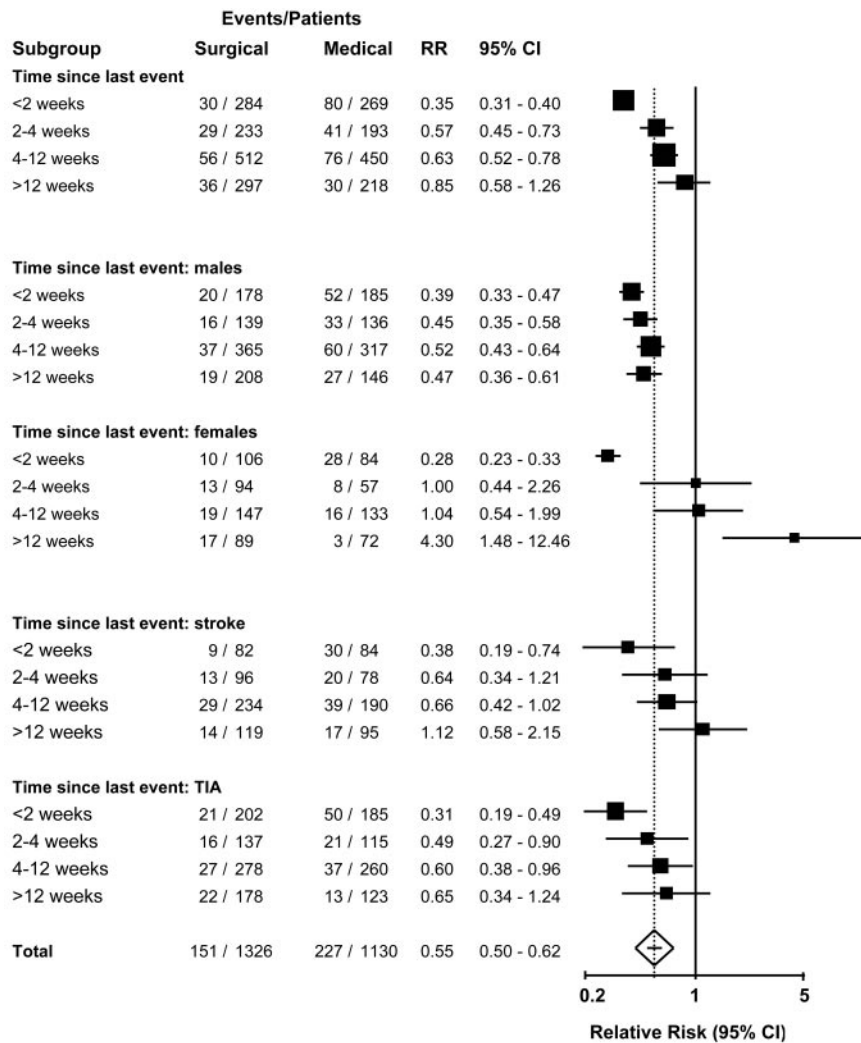
death and the time between the last symptomatic ischemic event and randomization in patients with 50% to 99% stenosis separately for men and women, and for those presenting with hemispheric stroke during the 6 months before randomization versus those who had a TIA (hemispheric or retinal) or retinal infarct only. The trend toward reducing benefit from CEA with time was unrelated to the type of presenting event ( $P=0.68$ ) but differed between the sexes ( $P<0.001$ ). Benefit from CEA diminished significantly with increasing time from last event to randomization in women ( $P<0.001$ ) but not in men ( $P=0.74$ ). The difference between these trends was not accounted for by sex differences in other measured characteristics that influence benefit from CEA. There was no sex difference in the relationship between operative risk and time since last event, but the decline in risk of ipsilateral ischemic stroke with time since last event in the medical group was more rapid in women ( $P<0.0001$ ) than in men ( $P=0.03$ ).

The absolute benefit from CEA in relation to time from last symptomatic event to randomization is shown for men and women separately for 50% to 69% stenosis and ≥70% stenosis in Figure 4. In women, benefit from CEA for ≥70% stenosis was only clear-cut in patients randomized <2 weeks after their last symptomatic event. Surgery for ≥70% stenosis remained beneficial in men randomized >12 weeks after their last event. In both sexes, surgery for 50% to 69% stenosis was only of significant benefit in those randomized <2 weeks after their last event.

### Discussion

The pooled data show that endarterectomy within 2 weeks of a nondisabling hemispheric stroke is not associated with an increased operative risk. This result is consistent with a recent systematic review of surgical case series,<sup>8</sup> which showed very high operative risks in patients operated as an emergency for progressing syndromes but no increase in operative risk in patients operated within the first few weeks of a nondisabling completed stroke versus those in whom surgery was delayed. However, it is very important to note that patients with disabling stroke or extensive infarction with brain swelling were not eligible for randomization in ECST or NASCET and that our conclusions do not apply to such patients, in whom the risks of early CEA are known to be high.<sup>4–6</sup>

Therefore, the main concern in relation to the timing of CEA should be the risk of stroke on medical treatment before surgery. There is now increasing evidence that the risk of stroke in the first few days and weeks after a TIA or minor stroke is particularly high,<sup>9–12</sup> especially in patients with carotid stenosis.<sup>13,20</sup> The early risk of stroke in patients with symptomatic severe carotid stenosis was highlighted by a recent report of 143 consecutive patients identified at a mean of 9.6 days after their last symptomatic event that reported 8 disabling strokes during a median time to surgery of 19 days.<sup>20</sup> Patients randomized in the ECST and NASCET soon after the presenting event would have been at higher risk of stroke during medical treatment than those who had survived the high-risk period without further events and were randomized later, and benefit from endarterectomy would be expected to fall with increasing time from last symptomatic



**Figure 3.** The effect of time from last symptomatic event to randomization on the 5-year relative risk (RR) of ipsilateral ischemic stroke and any operative stroke or death with CEA in the pooled data from ECST and NASCET stratified by sex and the type of presenting event.

event. Our results confirm this for the risk of ipsilateral ischemic stroke and the risk of any stroke during follow-up. The same trend was seen for the effect of surgery on the risk of disabling ipsilateral stroke.

We found that the decline in benefit from CEA with increasing time from last symptomatic ischemic event to randomization was more rapid in women than in men. The numbers of women in the analysis was smaller than the number of men, but the difference between the sexes in the effect of time from last event on benefit from CEA was highly statistically significant ( $P < 0.001$ ). The main determinant of this sex difference was a more rapid fall with time in the risk of stroke in the medical group in women than in men. This observation is consistent with known sex differences in the pathology of symptomatic atherosclerotic plaque, with a greater frequency of transient endothelial erosion than plaque rupture in women.<sup>21-23</sup> Our results are also consistent with the fact that benefit from CEA for asymptomatic stenosis has been demonstrated reliably in men but is uncertain and possibly absent in women.<sup>24</sup>

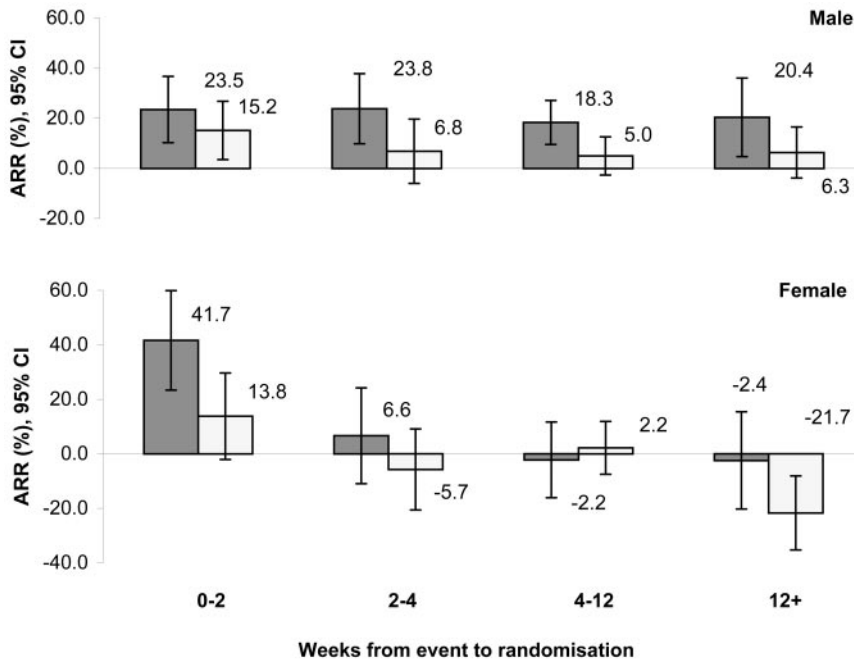
Although overall benefit from CEA for symptomatic carotid stenosis has been shown to be lower in women than in men,<sup>17</sup> it is important to note that our results show that

benefit was similar to that in men in patients randomized within 2 weeks of their last symptomatic event. Whether women presenting late should be considered for CEA should depend on other risk factors identified previously in ECST and NASCET.<sup>17</sup>

In conclusion, the pooled data show that endarterectomy within 2 weeks of a nondisabling hemispheric stroke was not associated with an increased operative risk. Benefit from CEA for symptomatic stenosis fell rapidly during the first few weeks after a TIA or stroke, particularly in women. Benefit from CEA in women was only apparent in those randomized within 2 weeks of their last symptomatic ischemic event. Current clinical guidelines in Europe<sup>14</sup> and North America,<sup>15,16</sup> which state only that CEA should be performed within 6 months of last symptoms, should be amended in light of these results.

### Acknowledgments

S.A.G. is funded by a grant from the UK Stroke Association (grant 8/99). P.M.R. is funded by the UK Medical Research Council (G116/112). M.E. was funded by grant R01-NS-24456 from the National Institute of Neurological Disorders and Stroke and by a senior health scholarship from the Alberta Heritage Foundation for Medical Research. ECST was funded by the UK Medical Research



**Figure 4.** The absolute reduction with surgery in the 5-year risk of each of the 3 main trial outcomes in patients with 50% to 69% stenosis (light bars) and ≥70% stenosis without near-occlusion (dark bars) stratified by the time from last symptomatic event to randomization and sex. The numbers adjacent to the bars indicate the exact absolute risk reduction (ARR).

Council. NASCET was funded by grant R01-NS-24456 from the National Institute of Neurological Disorders and Stroke. We thank all of the collaborators in the original trials.

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