Articles

# Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery

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## Summary

**Background** Carotid endarterectomy reduces the risk of stroke in patients with recently symptomatic stenosis. Benefit depends on the degree of stenosis, and we aimed to see whether it might also depend on other clinical and angiographic characteristics, and on the timing of surgery.

**Methods** We analysed pooled data from the European Carotid Surgery Trial and North American Symptomatic Carotid Endarterectomy Trial. The risk of ipsilateral ischaemic stroke for patients on medical treatment, the perioperative risk of stroke and death, and the overall benefit from surgery were determined in relation to seven predefined and seven post hoc subgroups.

**Results** 5893 patients with 33 000 patient-years of follow-up were analysed. Sex (p=0·003), age (p=0·03), and time from the last symptomatic event to randomisation (p=0·009) modified the effectiveness of surgery. Benefit from surgery was greatest in men, patients aged 75 years or older, and those randomised within 2 weeks after their last ischaemic event, and fell rapidly with increasing delay. For patients with 50% or higher stenosis, the number of patients needed to undergo surgery (ie, number needed to treat) to prevent one ipsilateral stroke in 5 years was nine for men versus 36 for women, five for age 75 years or older versus 18 for younger than 65 years, and five for those randomised within 2 weeks after their last ischaemic event, versus 125 for patients randomised after more than 12 weeks. These results were consistent across the individual trials.

**Interpretation**: Benefit from endarterectomy depends not only on the degree of carotid stenosis, but also on several other clinical characteristics such as delay to surgery after the presenting event. Ideally, the procedure should be done within 2 weeks of the patient's last symptoms.

*Lancet* 2004; **363:** 915–24

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## Introduction

Carotid endarterectomy is one of the most common vascular surgical procedures,[1–3] and it reduced the risk of ischaemic stroke in patients with recently symptomatic carotid stenosis in two large randomised controlled trials.[4,5] A smaller trial, the Veterans Affairs trial (VA309)[6] was stopped early when investigators in the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported their initial findings.[7,8] In 1998, the final results of the ECST and NASCET were reported, and the investigators made different recommendations about the degree of stenosis above which surgery was effective.[1,2] However, there were important differences between the trials in the method of measurement of carotid stenosis on the prerandomisation angiograms and in the definitions of outcome events.[9–11] Subsequent analysis after remeasurement of the ECST angiograms by the method used in NASCET, and use of the definition of stroke as any cerebral or retinal event with symptoms lasting longer than 24 h, yielded results that were highly consistent with NASCET.[12]

A recent meta-analysis of individual patients' data from the ECST, NASCET, and VA309, using the same method of measurement of stenosis and definitions of outcome events, showed that surgery was harmful in patients with less than 30% stenosis, of no benefit in those with 30–49% stenosis, of some benefit for 50–69% stenosis, and highly beneficial for those with 70% or more stenosis without near-occlusion.[13] However, there are several other factors that might affect the risks and benefits of surgery, including the delay between presentation of symptoms and surgery, and specific clinical and angiographic characteristics,[14–21] but neither ECST nor NASCET had high enough statistical power to determine the effect of surgery in subgroups. We therefore analysed pooled individual patients' data from these two trials to determine the effect of surgery in relation to seven predefined and seven post hoc clinical and angiographical subgroups.

## Methods

### Eligibility criteria

Criteria for inclusion of trials, and methods of data pooling and analysis have been reported previously.[13] Two small early trials were excluded because the methods were not consistent with current clinical practice.[22,23] VA309 was not included in the present study because the trial was confined to men, and several other subgroup variables were unavailable for analysis. The remaining large trials ECST and NASCET included 95% of patients ever randomised to endarterectomy versus medical treatment for symptomatic carotid stenosis. The methods of the two trials were very similar, and have been reported and compared in detail previously.[13,24,25]

| | ECST | NASCET | Total |
|---|---|---|---|
| Patients | 3008 | 2885 | 5893 |
| **Predefined patient subgroups** | | | |
| Sex | | | |
| Male | 2163 (71·9%) | 2012 (69·7%) | 4175 (70·8%) |
| Female | 845 (28·1%) | 873 (30·3%) | 1718 (29·2%) |
| Age (years) | | | |
| <65 | 1739 (57·8%) | 1161 (40·2%) | 2900 (49·2%) |
| 65–74 | 1093 (36·3%) | 1315 (45·6%) | 2408 (40·9%) |
| ⩾75 | 176 (5·9%) | 409 (14·2%) | 585 (9·9%) |
| Time since last symptoms (weeks) | | | |
| <2 | 437 (14·5%) | 746 (25·9%) | 1183 (20·1%) |
| 2–4 | 574 (19·1%) | 480 (16·6%) | 1054 (17·9%) |
| 4–12 | 1214 (40·4%) | 1098 (38·1%) | 2312 (39·2%) |
| >12 | 783 (26·0%) | 561 (19·4%) | 1344 (22·8%) |
| Primary symptomatic event | | | |
| Ocular only | 619 (20·6%) | 546 (18·9%) | 1165 (19·8%) |
| Cerebral TIA | 1079 (35·9%) | 1033 (35·8%) | 2112 (35·8%) |
| Stroke | 1310 (43·5%) | 1306 (45·3%) | 2616 (44·4%) |
| Diabetes | 352 (11·7%) | 622 (21·6%) | 974 (16·5%) |
| Irregular or ulcerated plaque* | 1934 (64·6%) | 1440 (49·9%) | 3374 (57·3%) |
| Contralateral ICA occlusion | 97 (3·2%) | 155 (5·4%) | 252 (4·3%) |
| **Post hoc patient subgroups** | | | |
| Duration of cerebral TIA | | | |
| TIA ⩽1 h | 788 (26·2%) | 776 (26·9%) | 1564 (26·5%) |
| TIA >1 h | 291 (9·7%) | 257 (8·9%) | 548 (9·3%) |
| Previous TIA or stroke | 821 (27·3%) | 987 (34·2%) | 1808 (30·7%) |
| Myocardial infarction | 361 (12·0%) | 571 (19·8%) | 932 (15·8%) |
| Angina | 505 (16·8%) | 775 (26·9%) | 1280 (21·7%) |
| Treated hypertension | 1164(38·7%) | 1577 (54·7%) | 2741 (46·5%) |
| Treated hyperlipidaemia | 257 (8·5%) | 991 (34·4%) | 1248 (21·2%) |
| Smoking | 1393 (46·3%) | 1218 (42·4%) | 2611 (44·3%) |

Data are number (%) unless otherwise indicated. TIA=transient ischaemic attack. ICA=internal carotid artery. *Plaque surface not adequately visible in one patient in NASCET and 15 patients in ECST.

Table 1: **Baseline clinical and angiographic subgroup variable frequencies by source trial**

Patients were recruited if they had had a recent carotid distribution transient ischaemic attack, non-disabling ischaemic stroke, or a retinal infarction, in the territory of a stenosed carotid artery. Before randomisation, patients were seen by a neurologist or stroke physician to confirm their eligibility, and that the symptomatic carotid artery was imaged by selective catheter angiography. Participants were assigned by central telephone randomisation to immediate carotid endarterectomy plus best medical treatment versus best medical treatment alone. Follow-up was done at prespecified intervals by a neurologist or stroke physician.

Methods of pooling of individual patients' data have been reported previously.[13] Data for presenting events; clinical, brain imaging, and angiographic characteristics at baseline; surgical and anaesthetic technique; and follow-up were merged into one database. Consideration was given to the definitions of variables used in the original trials, and similar data were merged.

### Selection of subgroups

To reduce the risk of chance findings, a restricted number of subgroups was predefined on the basis of potential clinical importance and availability in both trials at a meeting of collaborators in 1999 before the pooling of data. These subgroups were derived from the risk factors that had been predefined at the beginning of NASCET.[8] The following subgroup analyses were specified: (1) men versus women (2) age younger than 65 versus 65–74 versus 75 years or older; (3) time from most recent symptomatic ischaemic event to randomisation less than 2 weeks, 2–4 weeks, 4–12 weeks, and more than 12 weeks; (4) primary ischaemic event in the territory of the stenosed artery during the 6 months before randomisation, which was defined in a hierarchical manner as hemispheric stroke versus hemispheric transient ischaemic attack but no stroke versus retinal event only; (5) diabetes versus no diabetes; (6) irregular or ulcerated symptomatic carotid plaque versus smooth plaque on the prerandomisation angiogram (details of the assessment have been published previously);[26,27] and (7) contralateral carotid occlusion versus no occlusion.

To identify any important but unexpected treatment effect modifiers, seven post hoc subgroup variables were identified on the basis that comparable baseline data were available from the two trials: (1) duration of cerebral transient ischaemic attack (⩽1 h *vs* >1 h); (2) previous transient ischaemic attack or stroke (ie, events before the 6-month eligibility period as well as recent events); (3) previous myocardial infarction; (4) previous angina; (5) treated hypertension (defined as that needing a blood-pressure-lowering drug); (6) treated hyperlipidaemia (defined as that needing a dietary change or cholesterol-lowering drug); and (7) regular smoking during the previous year.

| | N | Mean (SD)% stenosis | p |
|---|---|---|---|
| **Predefined patient subgroups** | | | |
| Sex | | | |
| Male | 4175 | 40·2 (34·1) | 0·02 |
| Female | 1718 | 42·5 (32·2) | |
| Age (years) | | | |
| <65 | 2900 | 37·1 (37·3) | <0·0001 |
| 65–74 | 2408 | 44·1 (29·7) | |
| ⩾75 | 585 | 45·9 (25·6) | |
| Time since last event (weeks) | | | |
| <2 | 1183 | 46·8 (32·5) | <0·0001 |
| 2–4 | 1054 | 38·6 (36·5) | |
| 4–12 | 2312 | 40·7 (33·7) | |
| >12 | 1344 | 37·5 (31·2) | |
| Primary symptomatic event | | | |
| Ocular only | 1165 | 48·4 (32·6) | <0·0001 |
| Cerebral TIA | 2112 | 40·2 (33·0) | |
| Stroke | 2616 | 38·0 (34·0) | |
| Diabetes | | | |
| Yes | 974 | 45·2 (28·0) | <0·0001 |
| No | 4919 | 40·0 (34·5) | |
| Plaque surface† | | | |
| Smooth | 2503 | 37·1 (36·5) | <0·0001 |
| Irregular or ulcerated | 3374 | 43·8 (31·0) | |
| Contralateral ICA occlusion | | | |
| Yes | 252 | 52·3 (24·9) | <0·0001 |
| No | 5641 | 40·3 (33·8) | |
| **Post hoc patient subgroups** | | | |
| Duration of cerebral TIA | | | |
| TIA ⩽1 h | 1564 | 42·0 (32·9) | <0·0001 |
| TIA >1 h | 548 | 35·1 (32·6) | |
| Previous TIA or stroke | | | |
| Yes | 1808 | 43·7 (32·2) | <0·0001 |
| No | 4085 | 39·6 (34·1) | |
| Myocardial infarction | | | |
| Yes | 932 | 45·4 (28·4) | <0·0001 |
| No | 4961 | 40·0 (34·4) | |
| Angina | | | |
| Yes | 1280 | 46·7 (27·3) | <0·0001 |
| No | 4613 | 39·2 (34·9) | |
| Treated hypertension | | | |
| Yes | 2741 | 43·7 (31·2) | <0·0001 |
| No | 3152 | 38·4 (35·3) | |
| Treated hyperlipidaemia | | | |
| Yes | 1248 | 47·3 (27·1) | <0·0001 |
| No | 4645 | 39·1 (34·9) | |
| Smoking | | | |
| Yes | 2611 | 40·9 (36·4) | 0·88 |
| No | 3282 | 40·8 (31·1) | |

*Based on available data from 5893 patients, unless otherwise indicated.
†Data available for 5877 (99·7%) patients.

Table 2: **Degree of symptomatic carotid stenosis stratified according to subgroup variables***

| | Ipsilateral ischaemic stroke | p | Perioperative stroke or death | p |
|---|---|---|---|---|
| **Predefined patient subgroups** | | | | |
| Sex | | | | |
| Women *vs* Men | 0·79 (0·64–0·97) | 0·03 | 1·50 (1·14–1·97) | 0·004 |
| Age (years) | | | | |
| <65 | 1·00 | 0·001 | 1·00 | 0·78 |
| 65–74 | 1·23 (1·00–1·51) | | 0·99 (0·76–1·32) | |
| ⩾75 | 1·70 (1·28–2·56) | | 0·83 (0·49–1·41) | |
| Time since last event (weeks) | | | | |
| <2 | 1·00 | 0·003 | 1·00 | 0·69 |
| 2–4 | 0·80 (0·61–1·06) | | 1·22 (0·78–1·90) | |
| 4–12 | 0·69 (0·55–0·88) | | 1·14 (0·77–1·68) | |
| >12 | 0·61 (0·46–0·82) | | 1·28 (0·84–1·95) | |
| Primary symptomatic event | | | | |
| Ocular only | 1·00 | <0·0001 | 1·00 | <0·0001 |
| Cerebral TIA | 1·88 (1·38–2·55) | | 2·62 (1·68–4·09) | |
| Stroke | 2·33 (1·74–3·13) | | 1·91 (1·22–3·01) | |
| Diabetes | 1·31 (1·05–1·65) | 0·02 | 1·45 (1·05–2·02) | 0·03 |
| Irregular or ulcerated plaque | 1·35 (1·11–1·64) | 0·003 | 1·37 (1·03–1·82) | 0·03 |
| Contralateral ICA occlusion | 1·30 (0·90–1·88) | 0·16 | 2·21 (1·33–3·67) | 0·002 |
| **Post hoc patient subgroups** | | | | |
| Duration of cerebral TIA | | | | |
| TIA ⩽1 h | 1·00 | | 1·00 | |
| TIA >1 h | 1·45 (1·03–2·04) | 0·03 | 1·24 (0·81–1·92) | 0·33 |
| Previous TIA or stroke | 1·20 (0·99–1·46) | 0·07 | 1·59 (1·21–2·09) | 0·001 |
| Myocardial infarction | 1·40 (1·11–1·77) | 0·004 | 0·87 (0·59–1·27) | 0·46 |
| Angina | 1·26 (1·02–1·56) | 0·03 | 0·67 (0·47–0·97) | 0·03 |
| Treated hypertension | 1·39 (1·15–1·68) | 0·001 | 1·33 (1·02–1·74) | 0·04 |
| Treated hyperlipidaemia | 0·78 (0·62–0·98) | 0·03 | 1·06 (0·74–1·51) | 0·75 |
| Smoking | 0·96 (0·80–1·16) | 0·70 | 0·97 (0·74–1·27) | 0·81 |

Data are hazard ratio (95% CIs) unless otherwise indicated. Hazard ratios were derived from a Cox proportional hazards model including the subgroup variable, source study, and the degree of symptomatic carotid stenosis.

Table 3: **Relation between subgroup variables and risk of each main element of the primary outcome measure**

## Data analysis

All patients included in the final analysis of the original trials were included in the pooled analyses, and all analyses were done on an intention-to-treat basis according to the randomised treatment allocation. Stroke was defined as any cerebral or retinal event with symptoms lasting longer than 24 h. As in the original trials, the primary outcome for analyses of the effect of surgery was time to first ipsilateral ischaemic stroke in the territory of the symptomatic carotid artery, and any stroke or death that occurred within 30 days after trial surgery. The symptomatic carotid artery was defined as in the original trials.[4–6] Trial surgery was defined as the first carotid endarterectomy in patients who were randomised to surgery.

We first assessed the relation between every subgroup variable and: (1) risk of ipsilateral carotid territory ischaemic stroke in patients randomised to medical treatment (medical risk); (2) any stroke or death that occurred within 30 days after trial surgery (perioperative risk). The 5-year cumulative risks of ipsilateral ischaemic stroke were determined in relation to every subgroup variable. The associations were also determined in a Cox proportional hazards model with adjustment for source trial and degree of carotid stenosis.

In randomised controlled trials of carotid endarterectomy, the cumulative risk of outcome events is different in the two treatment groups. The risk of stroke and death is high immediately after carotid endarterectomy in patients randomised to surgery, but is low thereafter, whereas the cumulative risk increases gradually with time in those randomised to medical treatment. Consequently, surgery is harmful during early follow-up, but might be beneficial with longer follow-up. The qualitative change in the effect of treatment over time means that standard meta-analytical techniques are not appropriate for derivation of estimates of overall treatment effects.

An alternative, if hazard rates and treatment effects are similar across the trials, is to pool the individual patients' data and to undertake Kaplan-Meier analyses of event-free survival for the pooled data. We showed previously that trials did not differ significantly in either the risks of the study outcomes during follow-up in the medical or surgical groups, or in the effects of surgery.[13] We also showed that no imbalances in baseline characteristics between the surgery and medical groups were introduced by pooling the trial data.[13] Analyses of the effect of subgroup variables on the benefit from surgery were therefore done on the pooled data. Any significant treatment effect modifiers were then assessed separately in the ECST and NASCET to measure consistency.

Determination of the significance of treatment effect modification by subgroup is confounded by the differential changes in event rate with time in the two treatment groups. Nevertheless, we initially analysed data in a Cox proportional hazards model with treatment allocation, a source study term, degree of stenosis, a subgroup×treatment allocation interaction term, and a stenosis×treatment allocation interaction term. An additional test for trend was also done for the analysis of the effects of age and time from last event to randomisation. To obtain maximum statistical power to detect treatment effect modification by subgroup, these analyses of subgroup by treatment interaction were done for all degrees of stenosis. We believed that the direction of any treatment effect modification by subgroup was unlikely to differ qualitatively with degree of stenosis. However, we did a further Cox model to test the significance of the three-way interaction between stenosis, subgroup, and treatment allocation.

In view of the non-proportionality of the event rate in the two treatment groups, we also tested heterogeneity of the relative risk reduction at 5 years follow-up based on risk estimates obtained from life table analysis. The absolute reductions in 5-year risk of stroke were also determined for each subgroup by life tables for patients with 50–69% stenosis, those with 70% or more stenosis (based on the method of measurement of stenosis used in the NASCET trial),[5] and for all patients. The significance of the difference between subgroups in the 5-year absolute risk reduction with carotid endarterectomy was determined from life table analysis. Predefined subgroup treatment effect modifiers were regarded as significant at $p<0·05$ and post hoc subgroup treatment effect modifiers at $p<0·01$. Effect modifiers were judged robust if they were significant according to all three tests. There were too few patients with carotid near-occlusions to allow subclassification by subgroups. For this investigation, these patients were analysed together with the group that had 70% or more stenosis. All analyses were done with SPSS for Windows (version 10.0).

## Role of funding source

None of the funding organisations had any input into the design of the collaborative study, data collection, analysis of data, data interpretation, or preparation of the manuscript.

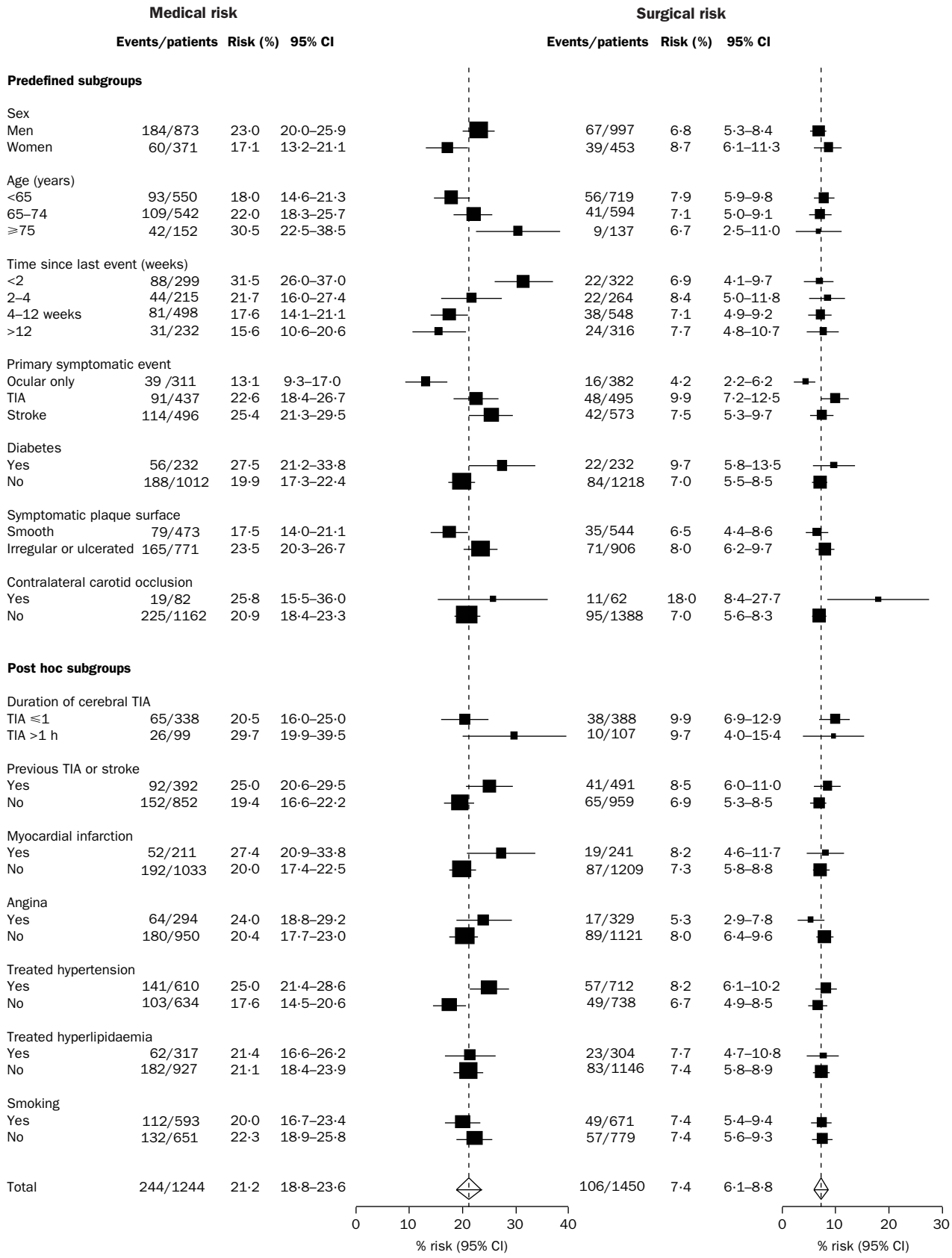


Figure 1: **Relation, in patients with ⩾50% carotid stenosis, between predefined subgroup variables and 5-year cumulative risk of ipsilateral carotid ischaemic stroke in the medical group (medical risk) and risk of any stroke or death within 30 days after trial surgery (surgical risk)**

TIA=transient ischaemic attack.

## Results

Data for individual patients were available for all 5903 patients included in the final analysis of the ECST and NASCET. Of these, nine ECST patients had an occlusion of the symptomatic carotid artery on the prerandomisation angiogram, and the degree of stenosis was unknown in one ECST patient. These cases were excluded from our analyses, leaving 5893 (99·8%) patients. Mean follow-up was 66 months (SD 34, range 1 day to 166 months), giving a total of 33 000 patient-years of follow-up.

Table 1 shows data for subgroup variables. There were significant differences in the degree of stenosis between all of the subgroup variables except smoking (table 2). Analyses of risk in relation to subgroup variables were therefore adjusted for degree of stenosis as well as the source trial.

The risk of ipsilateral stroke in the medical group was significantly related to all subgroup variables apart from occlusion of contralateral internal carotid artery and smoking (table 3). In predefined subgroups, the risk of ipsilateral ischaemic stroke fell with time since last event, rose with age, and was higher in men than in women, higher in patients presenting with hemispheric events than retinal events, in diabetics, and in patients with irregular or ulcerated plaques. Figure 1 shows the effect of every subgroup variable on the 5-year absolute risk of ipsilateral ischaemic stroke for patients with greater than 50% stenosis. The subgroup trends in this clinically relevant range of stenosis are the same as those shown in table 3.

Of the 3157 patients who underwent trial surgery, there were 222 operative strokes or deaths (7·0%, 95% CI 6·2–8·0). In the predefined subgroups, the perioperative risk of stroke or death was higher in women than in men, in patients with hemispheric events, diabetes, contralateral carotid occlusion and irregular or ulcerated plaques (table 3). In the post hoc subgroups, perioperative risk was reduced in patients with angina and increased in those with hypertension and with a previous transient ischaemic attack or stroke. The same patterns were evident in the unadjusted analysis of only patients with greater than 50% stenosis (figure 1).

Table 4 shows the significance of the tests of subgroup treatment effect modification in relative and absolute reductions in the risk of the primary outcome with surgery. In the predefined subgroups there was significant heterogeneity of risk reduction by each of the different tests in relation to sex, age, and time since last event (table 4). The effect of surgery on the 5-year absolute risk of ipsilateral ischaemic stroke is shown in figure 2 by subgroup for all patients, and those with 50–69% and 70% or more stenosis. Overall patterns in treatment effect were consistent across the stenosis categories. For example, benefit from carotid endarterectomy in patients with 50–69% stenosis was significantly less in women (p=0·04), fell significantly with increasing time since last event (p=0·009), and tended to increase with age (p=0·23).

The three-way interaction terms in the Cox model did not identify significant relations between treatment effect by subgroup interaction and degree of stenosis for any subgroup, although there were non-significant trends for the effect of irregular plaque (p=0·09) and primary symptomatic event (p=0·08) on treatment effect to be greater at higher degrees of stenosis. Figure 2 shows that benefit tended to be greatest in patients with stroke and to progressively decline in individuals with cerebral transient ischaemic attack and retinal events in both the 50–69% and 70% or more stenosis groups, and also shows a trend towards greater benefit in patients with irregular plaque than a smooth plaque in both stenosis groups. However, these treatment effects×subgroup interactions were still not significant when the analysis was restricted to patients with 50% or more stenosis: p=0·06 for irregular plaque and p=0·1 for primary symptomatic event.

| | Effect of surgery on the risk of the primary outcome | | |
|---|---|---|---|
| | Relative risk reduction | | Absolute reduction in 5-year actuarial risk |
| | Cox model | 5-year actuarial risk | |
| **Predefined patient subgroups** | | | |
| Sex | 0·007 | 0·008 | 0·003 |
| Age groups | 0·09<br>0·05 (trend) | 0·04 | 0·03 |
| Time since last event groups | 0·04<br>0·006 (trend) | 0·05 | 0·009 |
| Primary symptomatic event | 0·21 | 0·30 | 0·16 |
| Diabetes | 0·51 | 0·85 | 0·63 |
| Irregular or ulcerated plaque | 0·58 | 0·23 | 0·10 |
| Contralateral ICA occlusion | 0·30 | 0·34 | 0·25 |
| **Post hoc subgroups** | | | |
| Duration of cerebral TIA | 0·44 | 0·47 | 0·42 |
| Previous TIA or stroke | 0·08 | 0·23 | 0·50 |
| Myocardial infarction | 0·06 | 0·02 | 0·01 |
| Angina | 0·08 | 0·11 | 0·06 |
| Treated hypertension | 0·19 | 0·29 | 0·09 |
| Treated hyperlipidaemia | 0·63 | 0·85 | 0·85 |
| Smoking | 0·40 | 0·40 | 0·38 |

Table 4: **Significance of treatment-effect modifiers for relative and absolute treatment effect for subgroup variables**

No subgroup-treatment effect interaction term was significant at the p<0·01 threshold for the post hoc subgroups. There was a trend towards increased benefit in patients with a previous myocardial infarction (table 4). The effect of surgery on the 5-year absolute risk reduction of ipsilateral ischaemic stroke and any perioperative stroke or death is shown for all posthoc subgroups for all patients and those with 50–69% and 70% or more stenosis in figure 3.

To assess the consistency of the effects of sex, age, and time since last event on the benefit from carotid endarterectomy, the ECST and NASCET were analysed separately for patients with 50% or more stenosis. Both trials showed the same patterns (figure 4). For patients with 50% or more stenosis, estimates of the number of patients needed to undergo surgery (NNT) to prevent one ipsilateral stroke in 5 years from the pooled data were nine for men versus 36 for women, five for age 75 years or older versus 18 for age younger than 65 years, and five for patients randomised within 2 weeks versus 125 for those randomised after more than 12 weeks.

The absolute risk reduction with surgery in the 70% or more stenosis group is reduced by inclusion of patients with near-occlusion, in whom surgery is less effective.[13] By exclusion of such individuals, figure 5 shows what could potentially be achieved by timely surgery in patients with 70% or more (but not near-occluded) stenosis. The 30·2% reduction in absolute risk of stroke with carotid endarterectomy in patients randomised within 2 weeks of their last event was reduced to nearly a third in patients randomised more than 4 weeks after their last event. For patients with 50–69% stenosis, clinically important benefit was only seen for those patients randomised within 2 weeks of their last event.

## Discussion

We found three significant and clinically important subgroup treatment effect modifiers in the predefined subgroup variables. Benefit from surgery was greater in

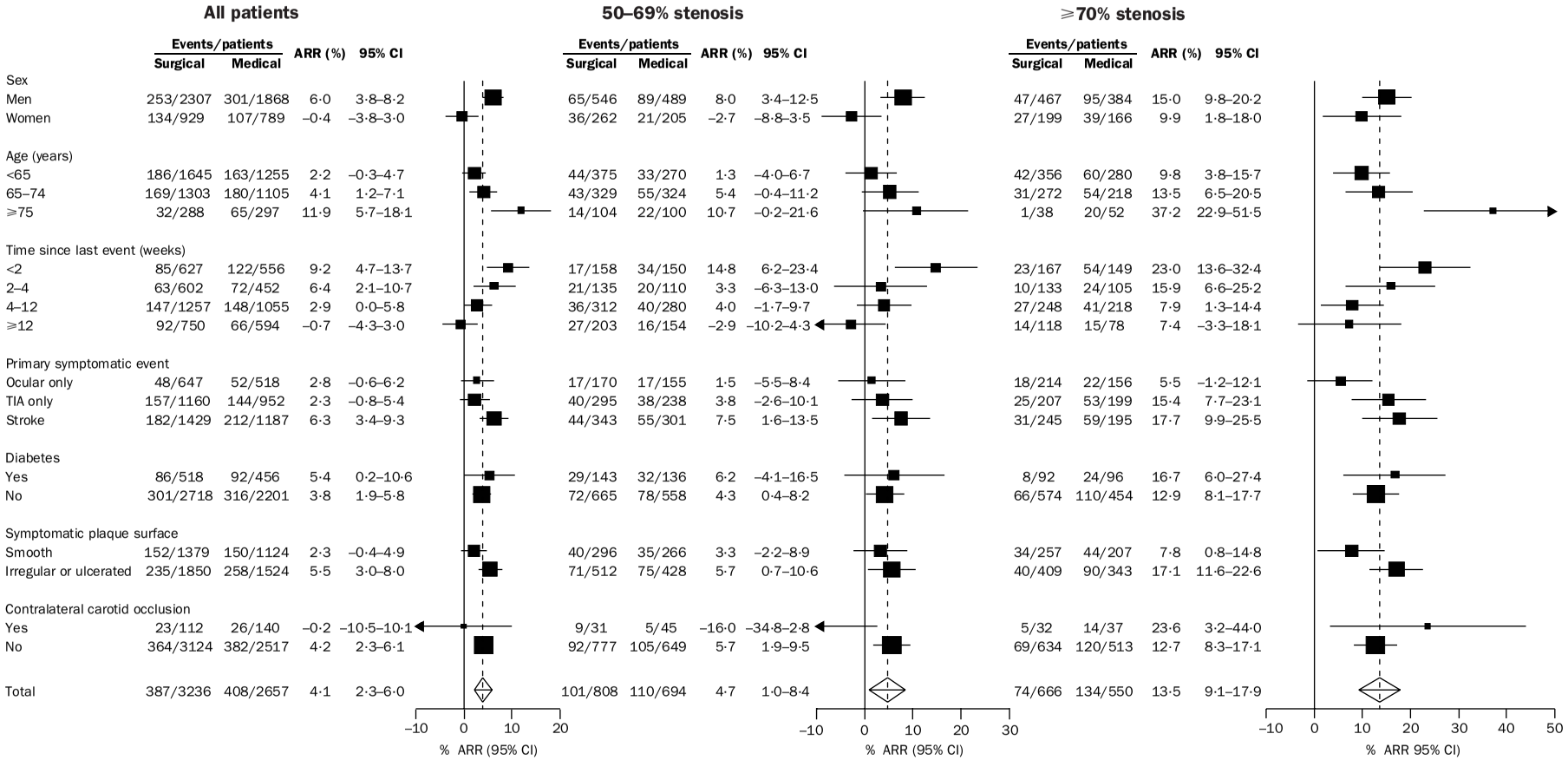


Figure 2: **Absolute reduction with surgery in 5-year actuarial risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery according to predefined subgroup variables in all patients; individuals with 50–69% stenosis; and those with ⩾70% stenosis.**
ARR=absolute risk reduction. Size of squares representing point estimates is reduced by 75% in A.

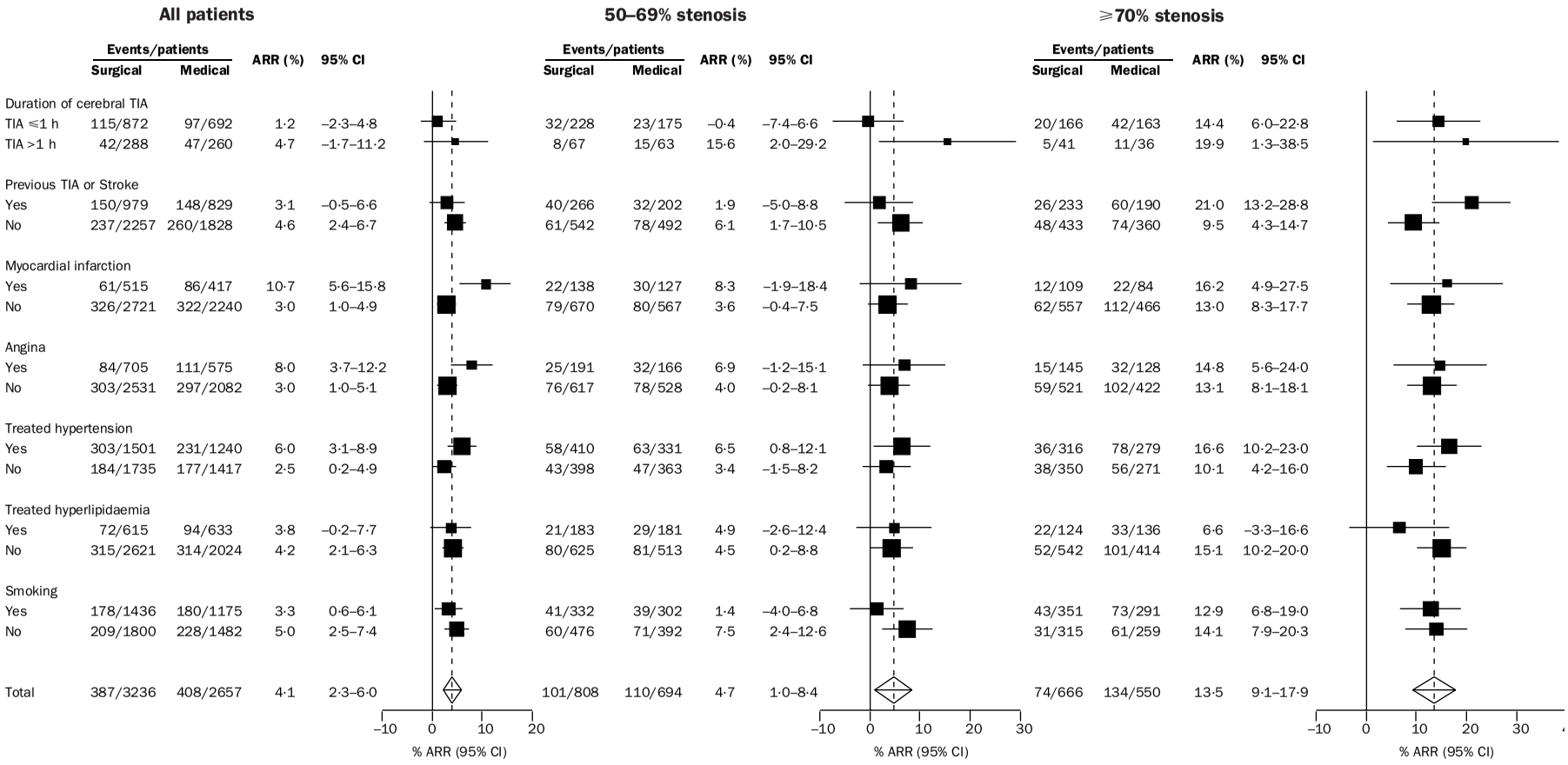


Figure 3: **Absolute reduction with surgery in 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery according to the post hoc subgroup variables in all patients; individuals with 50–69% stenosis; and those with ⩾70% stenosis**
Size of squares representing point estimates is reduced by 75% in all patients.

| | Events / Patients | | ARR (%) | 95% CI |
|---|---|---|---|---|
| | Surgical | Medical | | |
| **Subgroup** | | | | |
| **Sex** | | | | |
| Men | 47/504 | 60/333 | 9·8 | 4·9–14·8 |
| | 65/509 | 124/540 | 10·7 | 5·9–15·5 |
| | 112/1013 | 184/873 | 11·0 | 7·6–14·4 |
| Women | 32/211 | 22/152 | –0·4 | –7·9–7·1 |
| | 31/250 | 38/219 | 5·2 | –1·5–11·9 |
| | 63/461 | 60/371 | 2·8 | –2·2–7·8 |
| **Age (years)** | | | | |
| <65 | 40/385 | 45/274 | 6·6 | 1·1–12·0 |
| | 46/346 | 48/276 | 4·3 | –1·6–10·1 |
| | 86/731 | 93/550 | 5·6 | 1·6–9·6 |
| 65–74 | 33/283 | 28/180 | 4·8 | –1·8–11·5 |
| | 41/318 | 81/362 | 9·7 | 3·8–15·7 |
| | 74/601 | 109/542 | 8·6 | 4·2–13·0 |
| ⩾75 years | 6/47 | 9/31 | 19·1 | 0·1–38·1 |
| | 9/95 | 33/121 | 19·2 | 8·9–29·5 |
| | 15/142 | 42/152 | 19·2 | 10·2–28·2 |
| **Time since last event (weeks)** | | | | |
| <2 | 13/112 | 26/75 | 24·7 | 12·3–37·1 |
| | 27/213 | 62/224 | 15·9 | 8·3–23·5 |
| | 40/325 | 88/299 | 18·5 | 12·1–24·9 |
| 2–4 | 17/136 | 13/81 | 4·4 | –5·5–14·2 |
| | 14/132 | 31/134 | 13·1 | 4·0–22·2 |
| | 31/268 | 44/215 | 9·8 | 3·0–16·5 |
| 4–12 | 29/271 | 31/216 | 4·1 | –2·0–10·2 |
| | 34/289 | 50/282 | 6·4 | 0·4–12·5 |
| | 63/560 | 81/498 | 5·5 | 1·2–9·8 |
| >12 | 20/196 | 12/113 | 0·7 | –6·5–8·0 |
| | 21/125 | 19/119 | –3·1 | –13·3–7·2 |
| | 41/321 | 31/232 | 0·8 | –5·2–6·8 |
| Total | 175/1474 | 244/1244 | 8·5 | 5·6–11·3 |

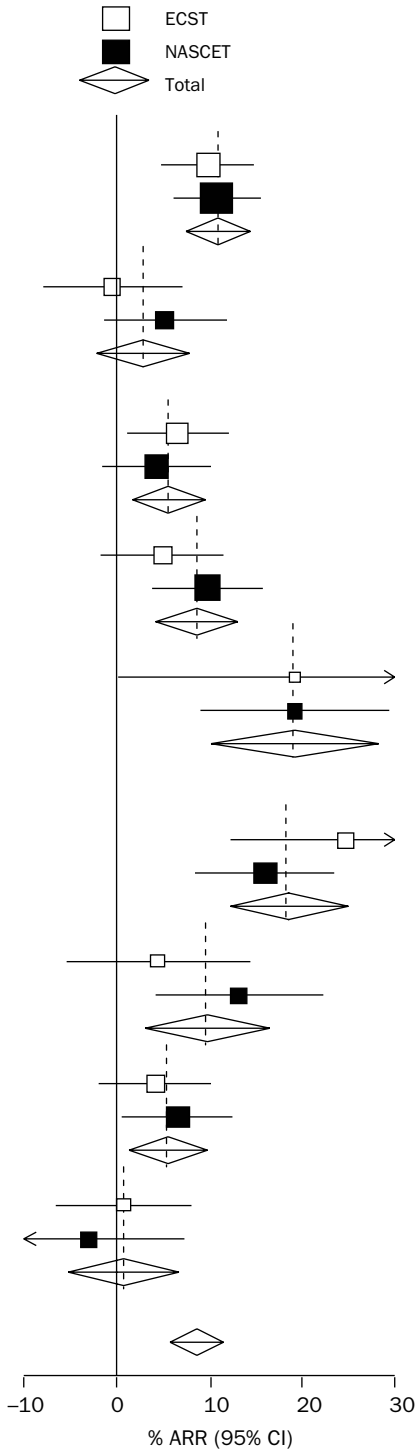


Figure 4: **Absolute reduction with surgery in the 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery according to three variables in patients with ⩾50% carotid stenosis in ECST and NASCET**

men than in women, and in the elderly, and benefit decreased with time since last symptoms. These observations were consistent across the 50–69% and 70% or more stenosis groups and across the two trials. Taken with other evidence discussed later, we feel that these subgroup observations are sufficiently robust to be used to guide the use of carotid endarterectomy in routine clinical practice. Several other variables could not be studied in the pooled data because they were not obtained in the ECST. However, NASCET have published separate reports about leucoariosis on brain imaging,[28] ipsilateral intracranial stenosis of the internal carotid artery,[29] and angiographic collateral flow towards the symptomatic hemisphere.[30]

In most trials of treatments for vascular disease, such as trials of blood-pressure lowering or lipid lowering, the effects of risk factors on the main outcome events are qualitatively similar in treatment and control groups. The analysis of subgroup effects in carotid endarterectomy is more difficult because the overall effect of surgery is

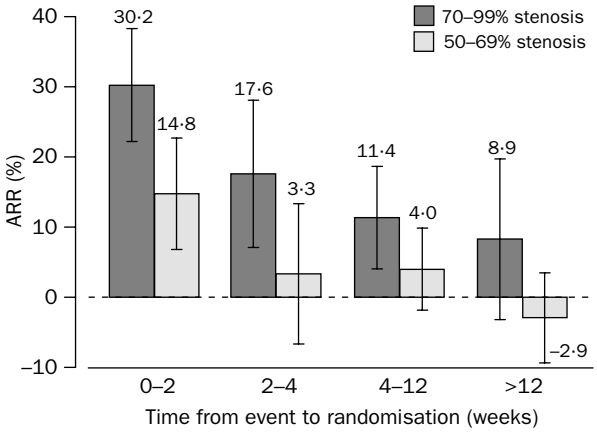


Figure 5: **Absolute reduction with surgery in the 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery in patients with 50–69% stenosis and ⩾70% stenosis without near-occlusion stratified by the time from last symptomatic event to randomisation**

Numbers above bars indicate actual absolute risk reduction. Vertical bars are 95% CIs.

determined by the balance of two different outcomes (ipsilateral carotid territory ischaemic stroke on medical treatment versus the perioperative risk of stroke or death within 30 days of carotid endarterectomy), which have very different mechanisms. Specific risk factors might therefore have qualitatively different effects on the two outcomes, which was the case in our analysis for sex, increasing age, and decreasing time from last event to randomisation.

Women had a lower risk of ipsilateral ischaemic stroke on medical treatment and a higher operative risk than did men. The same patterns were also shown in a large trial of carotid endarterectomy for asymptomatic stenosis.[31] Consequently, this procedure for asymptomatic stenosis was beneficial in men but not in women. We have shown that carotid endarterectomy is clearly beneficial in women with 70% or more symptomatic stenosis, but not in those with 50–69% stenosis. Whether surgery is still indicated in individual women will depend on the balance of their other risk factors.[14,32]

Arguably, the increased benefit from surgery in patients older than 75 years might not be generalisable to routine clinical practice because participants in trials generally have a good outlook,[33] and elderly patients might have a greater operative risk in clinical practice. There is some evidence of a higher operative risk in administrative database studies, especially for patients older than 85 years,[34] but in a recent systematic review of published surgical case-series, researchers reported pooled odds of stroke and death of 1·2 (95% CI 1·0–1·4, p=0·08, 19 studies) for patients older than 75 years versus younger people, and 1·2 (0·9–1·5, p=0·19, 11 studies) for patients older than 80 years versus younger individuals (Rothwell, unpublished data). There is therefore no justification for withholding carotid endarterectomy for patients older than 75 years who are deemed medically fit to undergo surgery. Our analysis indicates that benefit is likely to be greatest in this group because of their high risk of stroke on medical treatment, although it is noteworthy that the trials included very few patients older than 80 years.

The urgency with which carotid endarterectomy should be done has been much debated.[35,36] The risk of stroke on medical treatment after a transient ischaemic attack or minor stroke falls rapidly over the subsequent year, possibly because of the healing of the unstable atheromatous plaque or an increase in collateral blood flow to the symptomatic hemisphere, but there have been no reliable data for the extent to which the effectiveness of carotid endarterectomy also falls with time. There has been concern that the operative risk might be increased if surgery is done early, especially in patients with major cerebral infarction or stroke-in-evolution.[38–40] For neurologically-stable individuals, such as those enrolled in the trials, benefit from the operation was greatest in patients randomised within 2 weeks of their last event and fell rapidly with increasing delay. However, most patients who undergo carotid endarterectomy for symptomatic stenosis in Europe and North America are being operated on more than 2 weeks after their presenting event, and many are operated on more than 12 weeks after the event, when benefit is considerably reduced in individuals with 70% or more stenosis and absent in those with 50–69% stenosis.

Clinical guidelines merely state that patients should be operated on within 6 months of their presenting event,[41–43] and should now be revised on the basis of these results. We need to establish whether the reduction in benefit from carotid endarterectomy with time from the presenting event is dependent on the type of presenting event or other factors, but our overall findings have major implications for the urgency with which health services should assess and investigate patients with transient ischaemic attack and stroke.

The drawbacks of subgroup analysis, particularly the selective reporting of multiple post hoc analyses, are well documented.[44,45] However, we believe that our results are reliable. Our predefined analyses were chosen before pooling trial data, and we have reported all of the analyses that were done. We reported the significance of only the overall interaction of the subgroup variable with the treatment effect, rather than the significance of the treatment effect within each subgroup category. Statistical tests of subgroup-treatment effect interaction terms are conservative and a p value less than 0·1 is generally regarded as significant. However, to reduce the risk of chance findings we specified significance as $p<0·05$ for predefined subgroups and $p<0·01$ for post hoc subgroups. We were also fortunate to have two major trials with very similar methods and were therefore able to assess the consistency of observations in two independent studies. Indeed, the consistency in the subgroup effects between the trials is more convincing than the significance of the overall effects.

The degree of symptomatic carotid stenosis is the most important determinant of benefit from carotid endarterectomy, but other factors, particularly the timeliness of surgery, are also important. The procedure should ideally be done within 2 weeks of the patient's last symptoms. The results of our analyses should be useful in identification of patients who are most likely to benefit from carotid endarterectomy, especially those with 50–69% stenosis, but the effects of combinations of these variables in individual patients is yet to be established.

*Contributors*

P M Rothwell worked on the ECST trial from 1992, remeasured the ECST angiograms by the method used in the NASCET study, restructured baseline variables and outcomes in the individual trials to achieve comparability, pooled the data, did the analyses, and wrote the manuscript. S A Gutnikov did the computer programming necessary to prepare and pool the data from the individual trials, and analysed the data. M Eliaszw worked on the NASCET trial, advised on pooling of the data, and commented on analyses and successive drafts of the manuscript. C P Warlow was the principal investigator on the ECST, and commented on analyses and successive drafts of the manuscript. H J M Barnett was the principal investigator in the NASCET trial, and commented on analyses and successive drafts of the manuscript.

*Conflict of interest statement*
None declared.

*Acknowledgments*
We thank the collaborators in the original trials. Their names are listed in the relevant final results reports.[4,5] S A Gutnikov is funded by a grant from the UK Stroke Association (grant 8/99). P M Rothwell is funded by the UK Medical Research Council (G116/112). M Eliasziw 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 Council. NASCET was funded by the National Institute of Neurological Disorders and Stroke (grant R01-NS-24456). Salary support for some of the researchers involved in this study was provided by the UK Medical Research Council, which also funded the ECST; the UK Stroke Association; and the National Institute of Neurological Disorders and Stroke, which also funded NASCET.

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