REVIEW

# With what to trea with recently syn carotid stenosis?

**Peter M. Rothwell**
Professor of Clinical Neurology, Stroke Prevention Research Unit, University Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE; E-mail: peter.rothwell@clinical-neurology.ox.ac.uk
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## INTRODUCTION

Carotid endarterectomy is the most frequently performed vascular surgical procedure in the USA, and the rates are rising in Europe (Tu *et al*. 1998; Hsia *et al*. 1998). About half of ischaemic strokes are caused by atherothrombo-embolism (Sandercock *et al*. 2003), the majority related to atheroma in the extracranial arteries in white people, often at the origin of the internal carotid artery (ICA). The risk of stroke is relatively low distal to an *asymptomatic* carotid stenosis (Rothwell *et al*. 1995), but is markedly increased, at least for a few years, in patients who present with a transient ischaemic attack (TIA) or minor ischaemic stroke in the territory of a stenosed carotid artery.

Most of the strokes that occur within the first few years after a TIA or minor ischaemic stroke in patients with carotid stenosis are ischaemic and in the territory of the symptomatic artery – i.e. ipsilateral ischaemic stroke. The risk increases with the degree of stenosis and is time dependent, being highest in the few weeks after the presenting event, fairly high for the first year, and falling quickly thereafter (European Carotid Surgery Trialists' Collaborative Group 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991; Rothwell *et al*. 2000). That carotid stenosis definitely causes stroke was shown by the reduction in risk of ipsilateral ischaemic stroke in the randomized trials of endarterectomy (European Carotid Surgery Trialists' Collaborative Group 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991).

There are three main mechanisms by which carotid stenosis causes ischaemic stroke:

- Thrombi may form on the atheromatous lesion and cause local occlusion of the ICA.
- Embolization of plaque debris or thrombus may block a more distal vessel (Fig. 1). The high initial stroke risk is probably caused by a plaque that has become 'activated'; although atheromatous plaques are typically slow

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growing, they may develop ruptures, fissures, or endothelial erosions, which trigger platelet aggregation and thrombus formation (Torvik & Svindland 1989; Ogata *et al*. 1990).

- Severe ICA stenosis may lead to hypoperfusion of distal brain regions, particularly in arterial boundary zones, and thus to 'boundary zone infarction'.

All patients with recently symptomatic carotid stenosis require treatment to reduce their risk of stroke, and vascular events in other arterial territories. Some treatments are required in all patients, others should be targeted at certain specific groups and individuals. The need for targeting is discussed below for each of the main medical treatments, and for carotid surgery.

## ANTIPLATELET DRUGS – ALL PATIENTS

Antiplatelet drug therapy reduces the risk of recurrent stroke, myocardial infarction and vascular death in patients with TIA or ischaemic stroke (Antithrombotic Trialists' Collaboration 2002). Randomised controlled trials (RCTs) have not distinguished between subtypes of ischaemic stroke at baseline, but it is unlikely

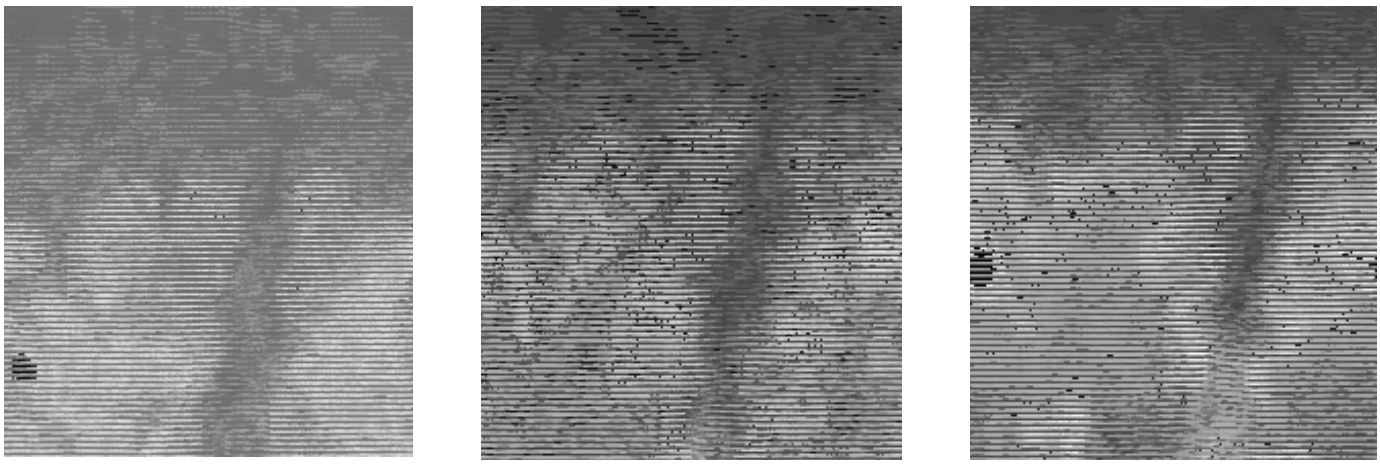

**Figure 1** A diffusion-weighted MR brain scan showing the typical appearance of multiple small cerebral infarcts (high signal), predominantly in the internal and external borderzones of the right cerebral hemisphere, in a patient with a recently symptomatic right carotid stenosis.

that antiplatelet drugs are ineffective in patients with carotid disease. Indeed, a meta-analysis of 6 trials of aspirin after carotid endarterectomy, although involving only 907 patients, identified a significant reduction in the risk of stroke during follow-up (OR = 0.58, $P = 0.04$) (Engelter & Lyrer 2003). In the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), 60% and 84% of the patients, respectively, were on an antiplatelet drug at randomization (most commonly aspirin alone), and the vast majority went onto treatment during follow-up. Aspirin should currently still be the first-line drug. Other antiplatelet regimes such as clopidogrel (Caprie Steering Committee 1996), and modified-release dipyridamole plus aspirin (Sivenius *et al*. 1991), are also effective. The combination of aspirin plus clopidogrel is not effective in the long term after TIA or ischaemic stroke in comparison to clopidogrel alone because the risk of bleeding outweighs any benefit in reduction of ischaemic events (Diener *et al*. 2004). However, there is preliminary evidence that a short period of treatment with aspirin and clopidogrel, for perhaps a month, might be more effective than aspirin alone during the acute phase when patients with symptomatic carotid stenosis are at highest risk of recurrent ischaemic stroke (Markus & Ringelstein 2004; Payne *et al*. 2004). Further trials are ongoing (Hankey 2004).

## ANTICOAGULATION – VERY FEW PATIENTS

There is no evidence to support the use of anticoagulation in patients with recently symptomatic carotid stenosis who are in sinus rhythm. Warfarin with a target International Normalized Ratio (INR) of 3–4.5 was harmful in the SPIRIT trial (Algra *et al*. 1997), and there was no additional benefit compared with aspirin from warfarin at a mean INR of 1.8 (target INR 1.4–2.8) in the WARSS trial (Warfarin Aspirin Recurrent Stroke Study Group 2001). In fact carotid stenosis (> 50%) was an exclusion criterion in the WARSS trial, and no other trial has looked at warfarin vs. aspirin specifically in patients with carotid disease, but there is no good reason to suspect that the effect of warfarin is likely to be qualitatively any different. Problems arise in clinical practice, however, in patients with TIA or ischaemic stroke who have *both* an apparently symptomatic carotid stenosis *and* atrial fibrillation (Kanter *et al*. 1994). Warfarin is usually indicated in patients with TIA or ischaemic stroke in AF (European Atrial Fibrillation Trial & Study Group 1993), but the need for anticoagulation and/or endarterectomy in this situation depends to some extent on whether the recent TIA or stroke was cardioembolic or due to carotid thromboembolism. Echocardiography may reveal left atrial thrombus or atrial enlargement, in which case anticoagulation is probably sensible. Alternatively, echocardiography may be normal and the pattern of ischaemic lesions on brain imaging suggestive of carotid thromboembolism (Fig. 1), in which case endarterectomy alone may be sensible. Occasionally, brain imaging – most usefully diffusion weighted MR imaging – shows asymptomatic recent infarction in several arterial territories, suggesting that cardioembolism is the underlying cause.

## STATINS – ALL PATIENTS

Although observational studies have not suggested a strong association between cholesterol and ischaemic stroke (Prospective Studies Collaboration 1995), trials of statins have shown convincing reductions in the risk of stroke as well as of coronary events in patients with vascular disease (Heart Protection Study Collaborative Group 2002), and slowing of atheroma progression in patients with carotid plaque (Mercuri *et al*. 1996). These benefits were evident even in patients with 'normal' cholesterol levels. However, there is still no convincing evidence of a reduction in the risk of recurrent *stroke* with statin treatment after a TIA or stroke, but there is a clinically important reduction in subsequent coronary events (Collins *et al*. 2004). Moreover, the 50% reduction in the risk of carotid endarterectomy during follow-up in the statin group in the Heart Protection Study (Heart Protection Study Collaborative Group 2002; Collins *et al*. 2004) suggests that statins do very probably reduce the risk of recurrent stroke in the subgroup of patients with carotid disease. Treatment with a statin is therefore indicated where possible in all patients with symptomatic carotid stenosis. The major reduction in stroke risk following treatment with statins in the acute phase in patients with acute coronary syndromes (Waters *et al*. 2002), suggests that treatment should start as soon as possible. Statins were the one current medical treatment that was not widely used during the RCTs of endarterectomy: 34% of the patients in the NASCET and only 9% of those in the ECST were on a lipid-lowering drug at randomization, although their use would have increased during follow-up.

## BLOOD PRESSURE LOWERING – MOST PATIENTS

Blood pressure lowering is effective for secondary prevention of stroke (Progress Collaborative Group 2001), although the effect in different aetiological subtypes of ischaemic stroke at baseline is unknown. However, it is likely that patients with large-artery atherosclerosis will benefit. Many physicians are, however, cautious about lowering blood pressure, particularly in patients with severe bilateral carotid stenosis or occlusion. These patients often also have disease of the vertebral arteries, the carotid siphon, and the cerebral arteries (Thiele *et al*. 1980; Gorelick 1993) and have a particularly high risk of recurrent stroke (Spence 2000). Loss of the normal autoregulatory capacity of the cerebral circulation, such that cerebral blood flow is directly dependent on systemic blood pressure, is common (Van der Grond *et al*. 1995; Grubb *et al*. 1998), and there has been natural concern that blood pressure lowering may reduce cerebral perfusion and increase the risk of stroke.

Surprisingly, there is no mention of carotid disease in hypertension treatment guidelines, and no data on carotid disease were recorded in the trials of blood pressure lowering after stroke or TIA. However, some conclusions can be drawn from an analysis of the risk of stroke in various categories of systolic blood pressure (SBP) stratified according to the presence or absence of flow-limiting (□ 70%) carotid stenosis in patients randomised to *no surgery* in ECST and NASCET (Table 1) (Rothwell *et al*. 2003c). Major increases in stroke risk were seen in association with bilateral flow-limiting stenosis in patients with SBP < 130 and SBP = 130–149, but not in patients with higher SBP. The five-year risk of stroke in patients with bilateral □ 70% stenosis was 64% in those with SBP < 150 mmHg vs. 24% at higher blood pressures ($P$ = 0.002). This difference in risk was not present in those who had had an endarterectomy (13% vs. 18%) suggesting a causal effect in the no surgery group and indicating that aggressive lowering of SBP before endarterectomy might well be harmful in patients with bilateral severe carotid stenosis, or severe symptomatic stenosis and contralateral occlusion.

Unless SBP is less than 130 mm Hg, the relationship between blood pressure and stroke risk is positive in patients with unilateral □ 70% stenosis (Rothwell *et al*. 2003c), suggesting that blood pressure lowering is likely to be safe and beneficial in this group, and following endarterectomy on one side in patients with bilateral severe carotid stenosis or severe symptomatic stenosis with contralateral occlusion.

## CAROTID ENDARTERECTOMY – SOME PATIENTS

### How much stenosis?

To target carotid endarterectomy appropriately, one must first determine as precisely as possible how the overall effect of surgery relates to the degree of carotid stenosis. There have been five RCTs of endarterectomy for symptomatic carotid stenosis. The first two were small and no longer reflect current practice (Fields *et al*. 1970; Shaw *et al*. 1984). The larger VA trial (VA#309) (Mayberg *et al*. 1991) reported a non-significant trend in favour of surgery, but was stopped early when the two largest trials, ECST (European Carotid Surgery Trialists' Collaborative Group 1991) and NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991), reported their initial results. The analyses of these trials have been stratified by the severity of stenosis of the symptomatic carotid artery, but different methods of measurement of the degree of stenosis on prerandomization angiograms were used (Fig. 2), the NASCET method 'underestimating' stenosis as compared with the ECST method. Stenoses of 70–99% in the NASCET are equivalent to 82–99% by the ECST method, and stenoses of 70–99% by the

**Table 1** Hazard ratios (95% CI) for the risk of stroke in patients randomised to medical treatment alone in the ECST and NASCET categorized according to the severity of carotid disease within blood pressure groups (Rothwell *et al*. 2003c)

| | Systolic blood pressure (mmHg) | | | |
|---|---|---|---|---|
| Stenosis group | < 130 | 130–149 | 150–169 | □ 170 |
| Bilateral < 70% | 1.0 | 1.0 | 1.0 | 1.0 |
| Unilateral □ 70% | 1.90 (1.24–2.89) | 1.18 (0.92–1.51) | 1.27 (0.99–1.64) | 1.64 (1.15–2.33) |
| Bilateral □ 70% | 5.97 (2.43–14.68) | 2.54 (1.47–4.39) | 0.97 (0.4–2.35) | 1.13 (0.50–2.54) |

The hazard ratios are derived from a Cox proportional hazards model, stratified by trial, and adjusted for age, sex and previous coronary heart disease. Patients with bilateral < 70% stenosis are allocated a hazard of 1.0.

Some patients with near occlusion may still wish to undergo surgery, particularly if they experience recurrent TIAs, but they should be informed that endarterectomy does not necessarily prevent stroke.

ECST are 55–99% by the NASCET method (Rothwell *et al*. 1994).

In 1998, the ECST (European Carotid Surgery Trialists' Collaborative Group 1998) showed there was no benefit from surgery in patients with $^{ECST}$30–49% stenosis or $^{ECST}$50–69% stenosis, but that there was major benefit in patients with $^{ECST}$70–99% stenosis. When the results of the ECST were stratified by decile of stenosis, endarterectomy was only beneficial in patients with $^{ECST}$80–99% stenosis. The 12% absolute reduction in risk (ARR) of major stroke or surgical death at 3 years was consistent with the 10% reduction in stroke or surgical death at 2 years reported in the NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1998) in patients with $^{NASCET}$70–99% stenosis. However, in contrast to the ECST (European Carotid Surgery Trialists' Collaborative Group 1998), the NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1998) reported a 7% absolute reduction in risk of disabling stroke or surgical death in patients with $^{NASCET}$50–69% stenosis ($^{ECST}$65–82% stenosis).

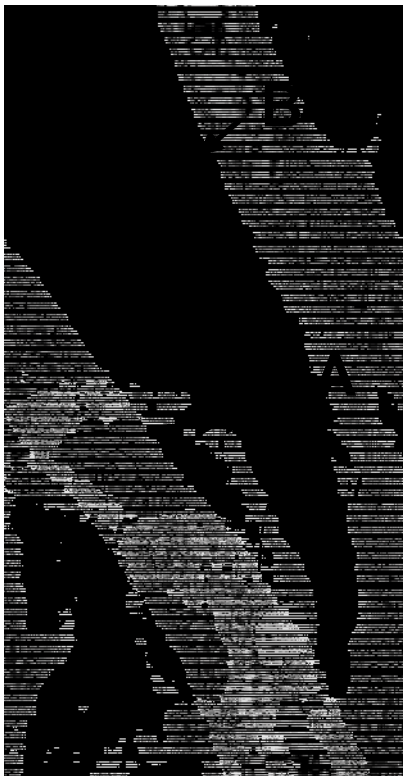

**Figure 2** A selective catheter angiogram of the carotid bifurcation showing a 90% stenosis. To calculate the degree of stenosis, the lumen diameter at the point of maximum stenosis (A) was measured as the numerator in both the ECST and NASCET. However, the NASCET used the lumen diameter of the distal internal carotid artery (B) as the denominator, whereas the ECST used the estimated normal lumen diameter (dotted lines) at the point of maximum stenosis.

Given this apparent disparity between the results of the two trials, the ECST group re-measured all their angiograms by the NASCET method, and the outcome events were re-defined to be comparable to the NASCET. Re-analysis of the ECST (Rothwell *et al*. 2003b) then showed that endarterectomy reduced the 5-year absolute risk of *any stroke or surgical death* by 6% in patients with $^{NASCET}$50–69% stenosis and by 21% in patients with $^{NASCET}$70–99% stenosis without 'near occlusion'. Surgery was harmful in patients with < 30% stenosis and of no benefit in patients with 30–49% stenosis. Thus, the results of the two trials were very consistent when analysed in the same way. This allowed a pooled analysis of data from the ECST, NASCET and VA#309 trials, which included over 95% of patients with symptomatic carotid stenosis ever randomized to endarterectomy vs. medical treatment alone (Rothwell *et al*. 2003a).

The pooled analysis showed that there was no statistically significant heterogeneity between the trials in the effect of surgery on the relative risks of any of the main outcomes in any of the stenosis groups. Data were therefore merged on 6092 patients with 35 000 patient years of follow-up. The overall operative mortality was 1.1% (95% CI 0.8–1.5), and the operative risk of stroke and death was 7.1% (95% CI 6.3–8.1). The effect of surgery on the risks of the main trial outcomes is shown by stenosis group in Fig. 3. Endarterectomy reduced the 5-year absolute risk of *any stroke or surgical death* in patients with $^{NASCET}$50–69% stenosis (ARR, 8%) and was highly beneficial in patients with $^{NASCET}$70–99% stenosis (ARR, 15%), but was of no benefit in patients with near occlusion. Qualitatively similar results were seen for disabling stroke The confidence intervals around the estimates of treatment effect in the near occlusions were wide, but the difference in the effect of surgery between this group and patients with □ 70% stenosis without near occlusion was statistically highly significant for each of the outcomes.

The results of these pooled analyses show that, with the exception of near occlusions, the degree of stenosis above which surgery is beneficial is $^{NASCET}$50% (equivalent to about $^{ECST}$65%

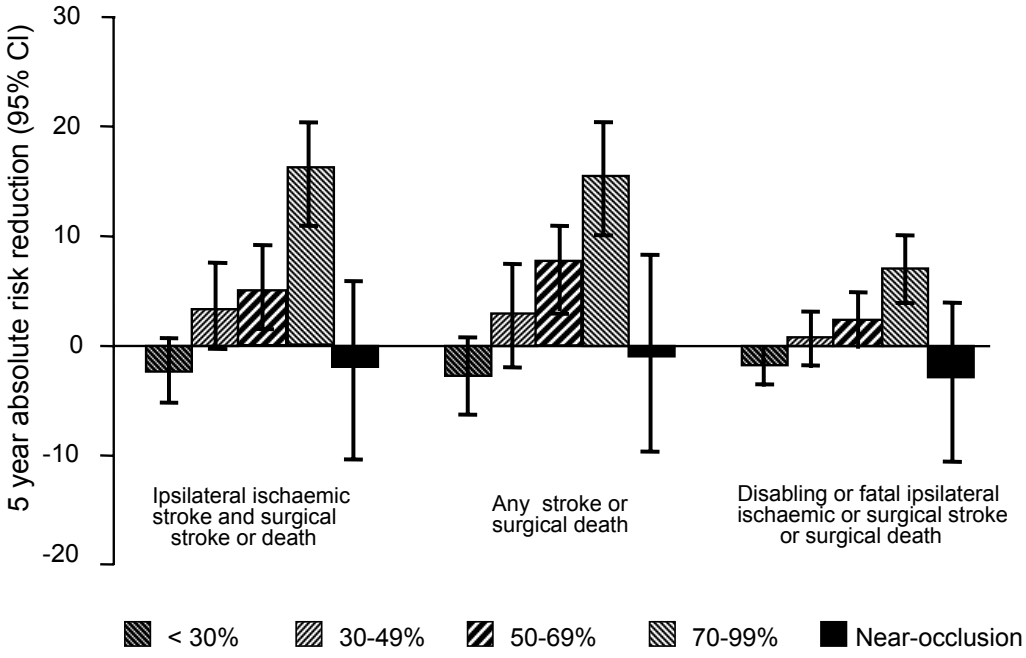


**Figure 3** The effect of endarterectomy on the 5-year absolute risks of each of the main trial outcomes in patients with < 30% stenosis, 30–49% stenosis, □ 70% stenosis without near-occlusion, and in near-occlusions, in an analysis of pooled data from the ECST, NASCET, and VA#309 trials.

stenosis). Given the confusion generated by the use of different methods of measurement of stenosis in the original trials, it has been suggested that the NASCET method be adopted as the standard in future (Rothwell *et al*. 2003a). Although there are several arguments in favour of the continued use of selective arterial angiography in the selection of patients for endarterectomy, there is a small and yet unacceptable risk of stroke, and so nowadays non-invasive methods are used in most patients (Johnston 2001; Norris 2001). However, these non-invasive techniques must be properly validated against catheter angiography within individual centres (Rothwell *et al*. 2000). More work is also required to assess the accuracy of non-invasive methods of carotid imaging in detecting near occlusion (Bermann *et al*. 1995; Ascher *et al*. 2002).

## What about near-occlusions?

Near occlusions (Fig. 4) were identified in the NASCET because it was not possible to measure the degree of stenosis using their method when the poststenotic ICA was narrowed or collapsed due to markedly reduced poststenotic blood flow (Morgenstern *et al*. 1997). Patients with 'abnormal poststenotic narrowing' of the ICA were also identified in the ECST (Rothwell *et al*. 2000). In both trials, these patients had a paradoxically low risk of stroke without surgery (Morgenstern *et al*. 1997; Rothwell *et al*. 2000). The low risk of stroke is most likely due to the presence of a good collateral circulation, visible on angiography in the vast majority of the patients with narrowing of the ICA distal to a severe stenosis (Fig. 4). The benefit from surgery in near occlusions in the NASCET (Morgenstern *et al*. 1997) was minimal, and both the re-analysis of the ECST (Rothwell *et al*. 2003b) and the pooled analysis (Rothwell *et al*. 2003a) suggested no benefit at all in this group in terms of preventing stroke. However, in the re-analysis of the ECST (Rothwell *et al*. 2003b), endarterectomy did reduce the risk of recurrent TIA (absolute risk reduction 15%). Therefore, some patients with near occlusion may still wish to undergo surgery, particularly if they experience recurrent TIAs, but they should be informed that endarterectomy does not necessarily prevent stroke.

## Which other subgroups benefit most?

The overall trial results are of only limited help to patients and clinicians in making decisions about surgery. Although endarterectomy reduces the relative risk of stroke by about 50% over the next 3 years in patients with a recently symptomatic severe stenosis, only 20% of such patients actually have a stroke on medical treatment alone. The operation is of no value in the other 80% of patients who, despite having a symptomatic stenosis, are destined to remain stroke free without surgery and can only be harmed by surgery. It would therefore be useful to be able to identify in advance, and operate on, only those patients with a very high risk of

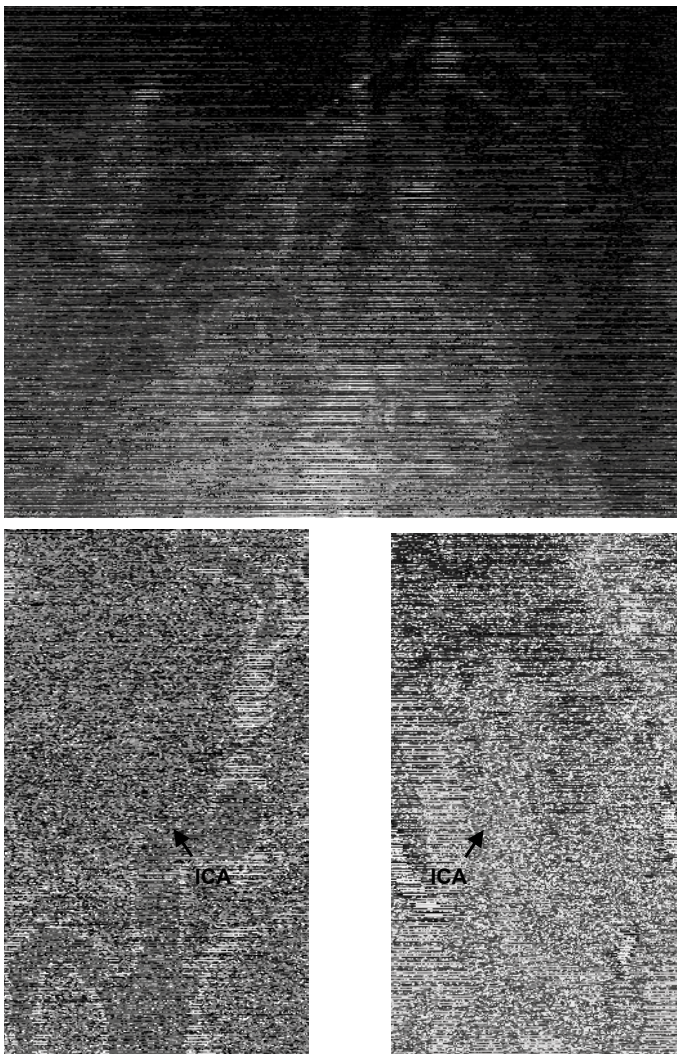


**Figure 4** Selective catheter angiograms of both carotid circulations in a patient with a recently symptomatic carotid 'near-occlusion' (left), and a mild stenosis at the contralateral carotid bifurcation (right). The near-occluded internal carotid artery (ICA) is markedly narrowed, and flow of contrast into the distal ICA is delayed. After selective injection of contrast into the contralateral right carotid artery significant collateral flow can be seen across the anterior communicating arteries with filling of the middle cerebral artery of the symptomatic left hemisphere (top).

stroke on medical treatment alone, but a relatively low operative risk. The degree of stenosis is of course a major determinant of benefit from endarterectomy, but there are several *other* clinical and angiographic characteristics that might influence the risks and benefits of surgery, including the delay between symptoms and surgery (Rothwell & Warlow 1999).

NASCET (Morgenstern *et al*. 1997; Alamowitch *et al*. 2001; Benavente *et al*. 2001; Paddock-Eliasziw *et al*. 1996; Inzitari *et al*. 2000; Streifler *et al*. 2002; Eliasziw *et al*. 1994; Fox 1993; Kappelle *et al*. 1999; Henderson *et al*. 2000; Kappelle *et al*. 2000; Gasecki *et al*. 1995) has published 11 reports of various univariate subgroup analyses. Although interesting, the results are difficult to interpret because several of the subgroups contained only a few tens of patients, with some of the estimates of the effect of surgery based on only one or two outcome events in each treatment group; the 95% confidence intervals around the absolute risk reductions in each subgroup have generally not been given; and there have been no formal tests of the interaction between the subgroup variable and the treatment effect. It is therefore impossible to be certain whether differences in the effect of surgery between subgroups are real or due to chance.

Subgroup analyses of pooled data from ECST and NASCET have had greater power to determine subgroup–treatment interactions reliably and several clinically important interactions have been recently reported (Rothwell *et al*. 2004). Sex ($P = 0.003$), age ($P = 0.03$), and time from the last symptomatic event to randomization ($P = 0.009$) modify the effectiveness of surgery (Fig. 5). Benefit from surgery was greatest in men, patients aged □ 75 years, and patients randomised within 2 weeks after their last ischaemic event, but fell rapidly with increasing delay. For patients with □ 50% stenosis, the number of patients needed to treat (NNT) (i.e. undergo surgery) to prevent one ipsilateral stroke in 5 years was 9 for men vs. 36 for women, 5 for age □ 75 vs. 18 for age < 65 years, and 5 for patients randomised within 2 weeks after their last ischaemic event vs. 125 for patients randomised > 12 weeks. These observations were consistent across the 50–69% and □ 70% stenosis groups and similar trends were present in *both* ECST and NASCET.

Women had a lower risk of ipsilateral ischaemic stroke on medical treatment and a higher operative risk in comparison to men. For recently symptomatic carotid stenosis, surgery is very clearly beneficial in women with □ 70% stenosis, but not in women with 50–69% stenosis (Fig. 5). In contrast, surgery reduced the 5-year absolute risk of stroke by 8.0% in men with 50–69% stenosis. This sex difference was statistically significant even when the analysis of the interaction was confined to the 50–69% stenosis group. These same patterns were also shown in both of the large published trials of endarterectomy for *asymptomatic* carotid stenosis (Fig. 6) (Asymptomatic Carotid Atherosclerosis Study Group 1995; Halliday *et al*. 2004).

Benefit from surgery increased with age in the pooled analysis of trials in patients with recently symptomatic stenosis, particularly in patients over 75 years old (Fig. 5). Although patients randomised in trials generally have a good prognosis (Stiller 1994), and there is some evidence of an increased operative mortality in elderly patients in routine clinical practice, particularly in those aged over 85 (Wennberg *et al*. 1998), our recent systematic review of all published surgical case-series reported no increase in the operative risk of stroke and death in older age groups (Rothwell, unpublished data). There is therefore no justification for withholding surgery in patients aged over 75 years who are deemed to be medically fit to undergo surgery. The evidence suggests that benefit is likely to be greatest in this group because of their high risk of stroke on medical treatment without surgery.

Benefit from surgery is probably also greatest in patients with stroke, intermediate in those with cerebral TIA and lowest in those with retinal events (Fig. 5). In addition there was a trend in

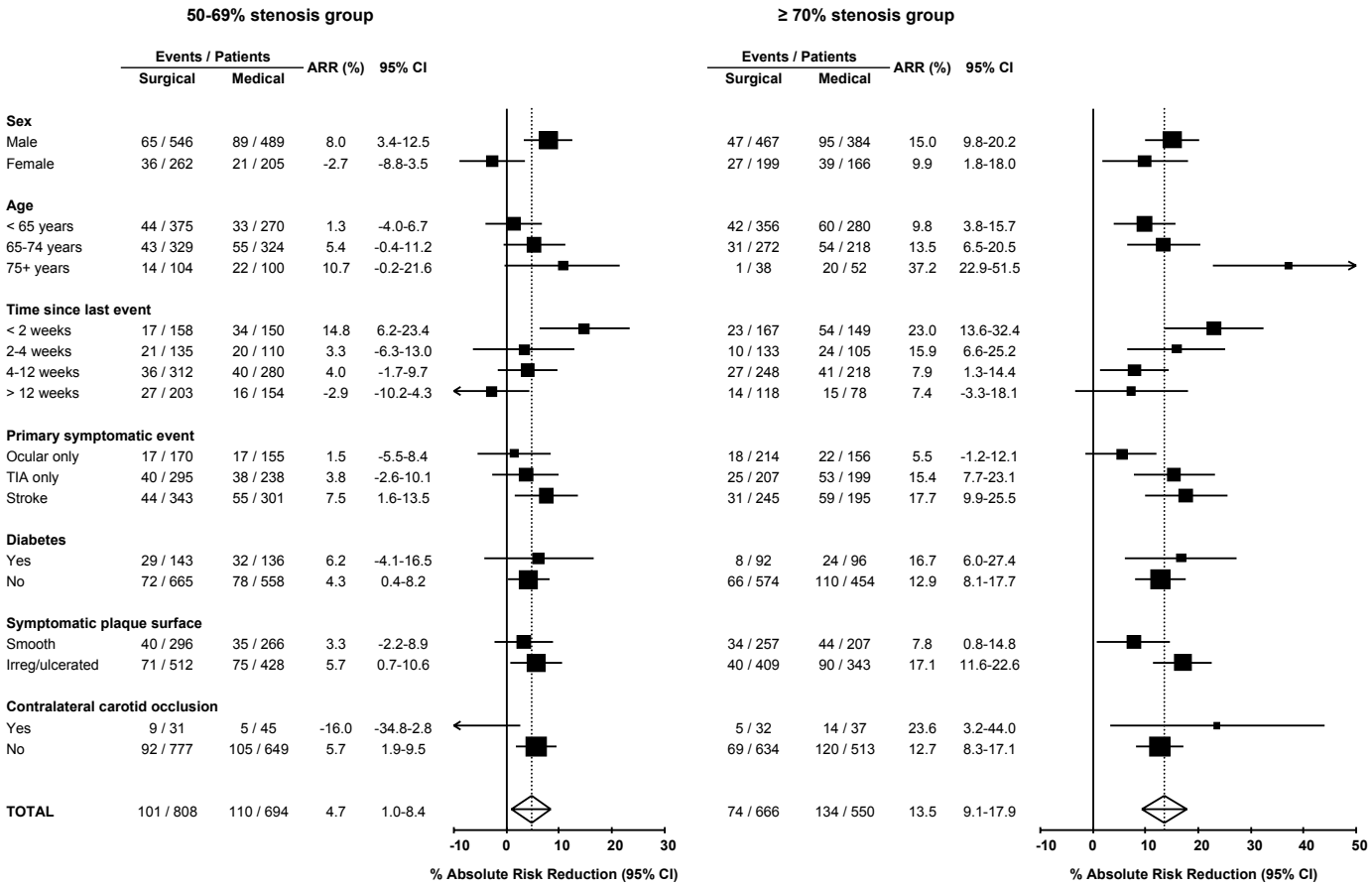


**Figure 5** Absolute risk reduction (ARR) with surgery in the 5-year risk of ipsilateral carotid territory ischaemic stroke and any stroke or death within 30 days after trial surgery according to predefined subgroup variables in (a) patients with 50–69% stenosis and (b) patients with □ 70% stenosis.

the trials towards greater benefit in patients with irregular plaque than a smooth plaque.

## How soon should surgery be performed?

The urgency with which endarterectomy should be performed has been much debated (Pritz 1997; Golledge *et al.* 1996). The risk of stroke on just medical treatment after a TIA or minor stroke is highest during the first few days and weeks (Lovett *et al.* 2003; 2004), particularly in patients with carotid stenosis (Lovett *et al.* 2004). However, the risk falls rapidly over the subsequent year (Rothwell *et al.* 2000; European Carotid Surgery Trialists' Collaborative Group 1998; North American Symptomatic Carotid Endarterectomy Trial Collaborators 1998), possibly because of the 'healing' of the unstable atheromatous plaque or an increase in collateral blood flow to the symptomatic hemisphere. But until recently there have been no reliable data on the extent to which the effectiveness of endarterectomy also falls with time. Indeed, there has been concern that the operative risk may be increased if surgery is performed early, particularly in patients with major cerebral infarction or stroke-in-evolution (Blaisdell *et al.* 1969; Brandl *et al.* 2001). However, for neurologically stable patients, such as those enrolled in the trials, there was no evidence of any increase in operative risk in patients operated within 2 weeks of their last event (Rothwell *et al.* 2004). Moreover, in a systematic review of surgical case series, early surgery in neurologically stable patients was not associated with any increased operative risk (Bond *et al.* 2003), although emergency surgery for stroke-in-evolution or crescendo TIA was and is not advised.

Given the high early risk of stroke on medical treatment alone after a TIA or minor stroke in patients with carotid disease, and the lack of any increased operative risk in neurologically stable patients, early surgery is likely to be particularly effective. The pooled analysis of data from the trials confirms this, showing that benefit is greatest in patients randomised within 2 weeks of their last event (Figs 5 and 7). This was particularly important in patients with 50–69% stenosis, where the reduction in the 5-year risk of stroke with surgery was considerable in those randomized within 2 weeks of their last event (14%), but minimal in patients randomized later. Clinical guidelines currently state that patients should be operated within 6 months of their presenting event (The Intercollegiate Working Party for Stroke 2000; Biller *et al.* 1998) and many patients wait several months for surgery; clearly much more urgent intervention and surgery is required.

## Which individuals benefit most?

There are some clinically useful subgroup observations in the pooled analysis of the endarterectomy trials, but individual patients frequently have several important risk factors, each of which

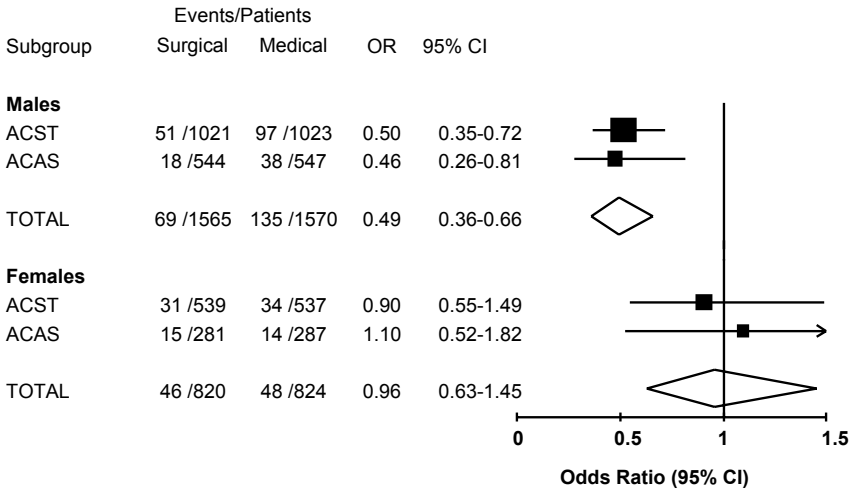


**Figure 6** The effect of endarterectomy for *asymptomatic* carotid stenosis on the relative odds of any stroke and operative death by sex in the Asymptomatic Carotid Surgery Trial (ACST) (Halliday *et al*. 2004) and the Asymptomatic Carotid Artery Study (ACAS) (Asymptomatic Carotid Atherosclerosis Study Group 1995).

interacts in ways that cannot be described using univariate subgroup analysis, and all of which should be taken into account to determine the likely balance of risk and benefit from surgery (Rothwell & Warlow 1999). For example, what would be the likely benefit from surgery in a 78-year-old (increased benefit) female (reduced benefit) with 70% stenosis who presented within 2 weeks (increased benefit) of an ocular ischaemic event (reduced benefit) and was found to have an ulcerated carotid plaque (increased benefit)?

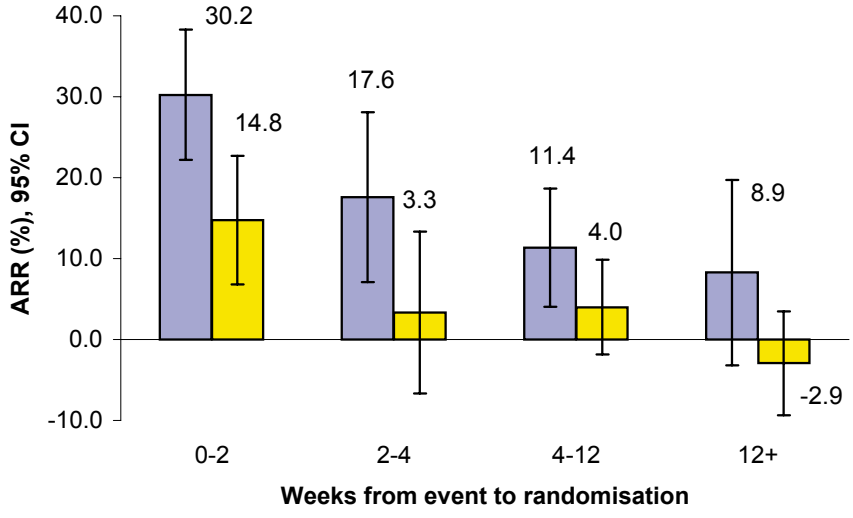


**Figure 7** Absolute risk reduction (ARR) with surgery in the 5-year risk of ipsilateral carotid territory ischaemic stroke and any stroke or death within 30 days after trial surgery in patients with 50–69% stenosis (yellow bars) and □70% stenosis (blue bars) without near-occlusion stratified by the time from last symptomatic event to randomization. The numbers above the bars indicate the actual absolute risk reduction.

One way in which clinicians can weigh the often-conflicting effects of the important characteristics of an individual patient on the likely benefit from treatment is to base decisions on the predicted absolute risks of a poor outcome with each treatment option using prognostic models (Rothwell & Warlow 1999; Rothwell 1995). Properly validated models are available to predict the risk of stroke in the general population (Nanchahal *et al*. 2002), in patients with non-rheumatic atrial fibrillation (Laupacis *et al*. 1994; Pearce *et al*. 2000), and in patients presenting with TIAs (Hankey & Slattery 1992; Kernan *et al*. 2000). A model for prediction of the risk of stroke on *medical* treatment in patients with recently symptomatic carotid stenosis has been derived from the ECST (Rothwell & Warlow 1999; Rothwell *et al*. 2005) (Table 2). This model was validated using independent data from the NASCET and showed very good agreement between predicted and observed medical risk, reliably distinguishing between individuals with a 10% risk of ipsilateral ischaemic stroke after 5-years follow-up and individuals with a risk of over 40% (Fig. 8). Importantly, Fig. 8 also shows that the operative risk of stroke and death in patients who were randomised to surgery in NASCET was unrelated to the medical risk. Thus, when the operative risk and the small additional residual risk of stroke

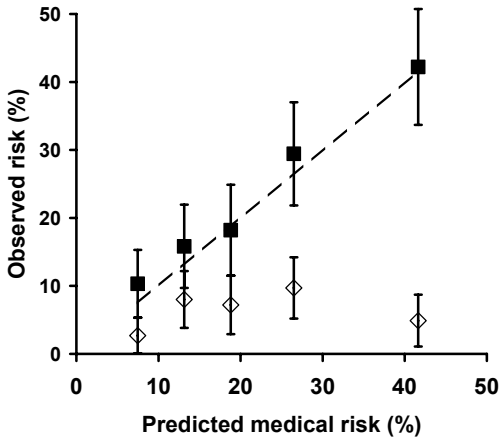


**Figure 8** Validation of the ECST model (Table 2) (Rothwell & Warlow 1999) for the 5-year risk of stroke on medical treatment in patients with 50–99% stenosis in NASCET (Rothwell *et al*. 2005). Predicted medical risk in quintiles is plotted against observed risk of stroke in patients randomised to medical treatment in NASCET (squares) and against the observed operative risk of stroke and death in patients randomised to surgical treatment (diamonds). Error bars represent 95% confidence intervals.

**Table 2** A Cox model for the 5-year risk of ipsilateral ischaemic stroke on medical treatment in patients with recently symptomatic carotid stenosis, derived from the ECST.

| MODEL | | SCORING SYSTEM | | |
|---|---|---|---|---|
| Risk factor | HR (95%CI) | Risk factor | Score | EXAMPLE |
| Stenosis (per 10%) | 1.18 (1.10–1.25) | Stenosis (%) | | |
| | | 50–59 | 2.4 | 2.4 |
| | | 60–69 | 2.8 | |
| | | 70–79 | 3.3 | |
| | | 80–89 | 3.9 | |
| | | 90–99 | 4.6 | |
| Near occlusion | 0.49 (0.19–1.24) | Near occlusion | 0.5 | No |
| Male sex | 1.19 (0.81–1.75) | Male sex | 1.2 | No |
| Age (per 10 years) | 1.12 (0.89–1.39) | Age (years) | | |
| | | 31–40 | 1.1 | |
| | | 41–50 | 1.2 | |
| | | 51–60 | 1.3 | |
| | | 61–70 | 1.5 | 1.5 |
| | | 71–80 | 1.6 | |
| | | 81–90 | 1.8 | |
| Time since last event (per 7 days) | 0.96 (0.93–0.99) | Days since last event | | |
| | | 0–13 | 8.7 | 8.7 |
| | | 14–28 | 8.0 | |
| | | 29–89 | 6.3 | |
| | | 90–365 | 2.3 | |
| Presenting event | | Presenting event | | |
| Ocular | 1.0 | Ocular | 1.0 | |
| Single cerebral TIA | 1.41 (0.75–2.66) | Single cerebral TIA | 1.4 | |
| Multiple cerebral TIAs | 2.05 (1.16–3.60) | Multiple cerebral TIAs | 2.0 | |
| Minor stroke | 1.82 (0.99–3.34) | Minor stroke | 1.8 | |
| Major stroke | 2.54 (1.48–4.35) | Major stroke | 2.5 | 2.5 |
| Diabetes | 1.35 (0.86–2.11) | Diabetes | 1.4 | 1.4 |
| Previous myocardial infarction | 1.57 (1.01–2.45) | Previous MI | 1.6 | No |
| Peripheral vascular disease | 1.18 (0.78–1.77) | Peripheral vascular disease | 1.2 | No |
| Treated hypertension | 1.24 (0.88–1.75) | Treated hypertension | 1.2 | 1.2 |
| Irregular/ulcerated plaque | 2.03 (1.31–3.14) | Irregular/ulcerated plaque | 2.0 | 2.0 |
| TOTAL RISK SCORE | | | | 263 |
| PREDICTED MEDICAL RISK USING NOMOGRAM (using Fig. 9) | | | | 37% |

The model differs slightly from the one previously published (Rothwell & Warlow 1999) in that the degree of stenosis and the definition of the outcome event are based on those used in the NASCET trial. Hazard ratios (HR) derived from the model are used for the scoring system. The score for the 5-year risk of stroke is the product of the individual scores for each of the risk factors present. The score is converted into a risk with the graphic in Fig. 9. An example is shown in the right hand column of the table. The 'presenting event' should be taken as the most severe ipsilateral event (ocular events are least severe and major stroke is most severe) in the previous six months. In patients with near-occlusion, the degree of stenosis should be entered as 85%.

Risk tables allow a relatively small number of important variables to be considered with the major advantage that they do not require the calculation of any score by the clinician or patient.

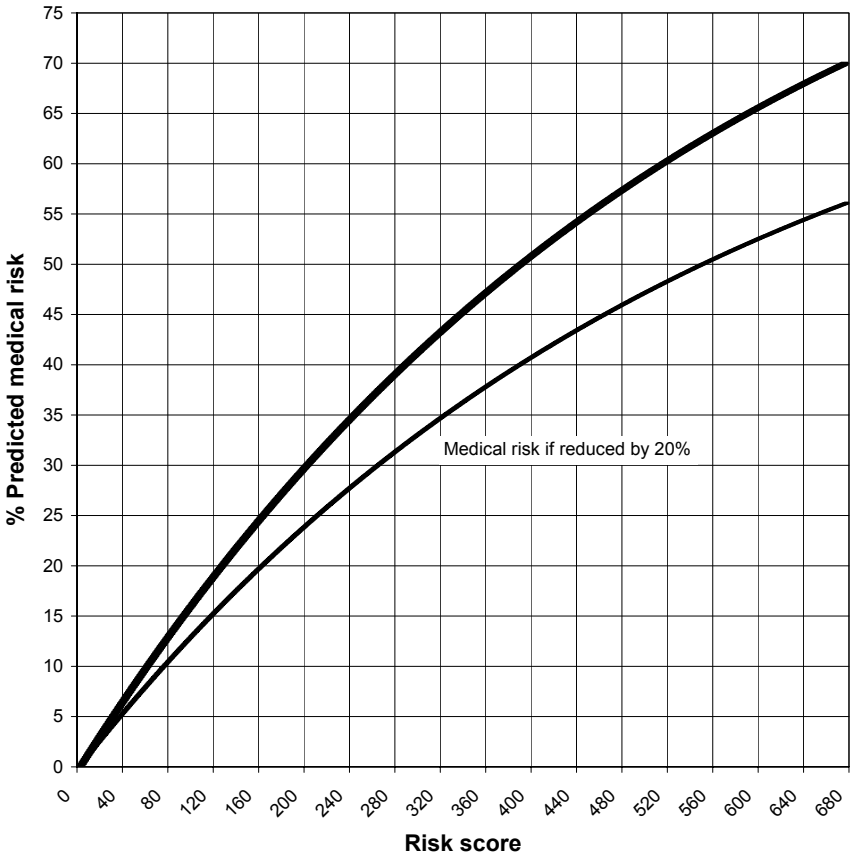


**Figure 9** A plot of the total risk score derived from Table 2 against the 5-year predicted risk of ipsilateral carotid territory ischaemic stroke derived from the full model in Table 2 in patients in the ECST (thick line). This should be used as a nomogram for the conversion of the score into a prediction of the percentage risk. The thin line represents a 20% reduction in risk as might be seen with more intensive medical treatment than was available during the ECST in the late 1980s and 1990s.



following successful endarterectomy are taken into account, benefit from endarterectomy at 5 years varied significantly across the quintiles ($P = 0.001$), with no benefit in patients in the lower three quintiles of predicted medical risk (ARR, 0–2%), moderate benefit in the fourth quintile (ARR; 11%), and substantial benefit in the highest quintile (ARR, 32%).

Prediction of risk using models requires a computer, a pocket calculator with an *exponential* function, or internet-access (the ECST model can be found at http://www.stroke.ox.ac.uk). As an alternative, a simplified risk score based on the hazard ratios derived from the relevant risk model can be derived. Table 2 shows a score for the 5-year risk of stroke on medical treatment in patients with recently symptomatic carotid stenosis derived from the ECST model. As is shown in the example in Table 2, the total risk score is the product of the scores for each risk factor. Figure 9 shows a plot of the total risk score against the 5-year predicted risk of ipsilateral carotid territory ischaemic stroke derived from the full model, and is used as a nomogram for the conversion of the score into a risk prediction.

Alternatively, risk tables allow a relatively small number of important variables to be considered with the major advantage that they do not require the calculation of any score by the clinician or patient. Figure 10 shows such a table for the 5-year risk of ipsilateral ischaemic stroke in patients with recently symptomatic carotid stenosis on medical treatment derived from the ECST model. This table is based on the five variables that were both significant predictors of risk in the ECST model (Table 2) and yielded clinically important subgroup–treatment effect interactions in the analysis of pooled data from the relevant trials (sex, age, time since last symptomatic event, type of presenting event(s) and carotid plaque surface morphology).

One potential problem with the ECST risk model is that it might over-estimate risk in current patients because of improvements in medical treatment, such as the increased use of statins. However, such improvements in treatment pose more problems for interpretation of the overall trial results than for the risk model-

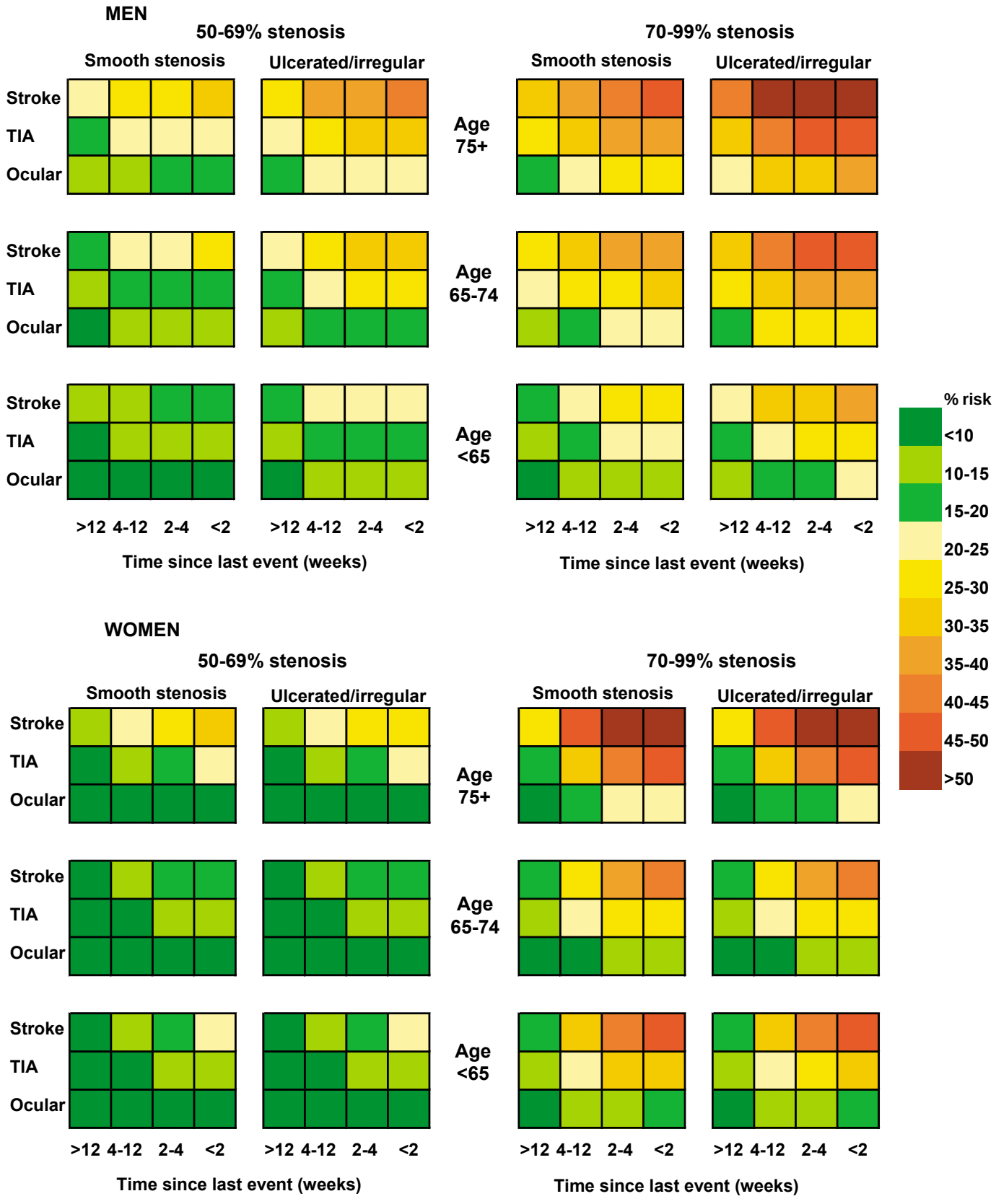


**Figure 10** A table of the predicted absolute five-year risk of ipsilateral ischaemic stroke on medical treatment in ECST patients with recently symptomatic carotid stenosis derived from a Cox model based on six clinically important patient characteristics (Rothwell *et al.* 2005).

ling approach. For example, it would take only a relatively modest improvement in the effectiveness of medical treatment to erode the overall benefit of endarterectomy in patients with 50–69% stenosis. In contrast, very major improvements in medical treatment would be required to significantly reduce the benefit from surgery in patients in the high predicted-risk quintile in Fig. 8. Thus, the likelihood that medical treatments have improved, and are likely to continue to improve, is an argument in favour of a risk-based approach to targeting treatment. However, it would be reasonable in a patient on treatment with a statin, for example, to reduce the risks derived from the risk model by 20% in relative terms (Fig. 9).

## CAROTID ANGIOPLASTY AND STENTING

Transluminal angioplasty was first used in the limbs in the 1960s (Dotter *et al*. 1967) and then subsequently in the renal and coronary arteries. Angioplasty was introduced cautiously in the cerebral circulation because of fears of plaque rupture and embolism causing stroke, but during the past 10 years angioplasty and/or stenting at the carotid bifurcation has increased in popularity and is under investigation as a potential alternative to endarterectomy. Thus far, there have been five small RCTs (CAVATAS Group 2001; Naylor & London 1997; Alberts 2001; Brooks *et al*. 2001; Yadav *et al*. 2002). Taken together, they suggest that angioplasty and/or stenting is associated with a slightly higher procedural risk than endarterectomy and a higher rate of re-stenosis. However, improvements in cerebral protection devices may reduce the procedural risks (Reimers *et al*. 2001), and several further trials are currently ongoing. The use of angioplasty is likely to increase, but whether it will be confined to cases in which endarterectomy is technically difficult – as is currently the case – will depend on the results of the trials. Whichever intervention is used, the main determinant of benefit will continue to be the likely risk of stroke on medical treatment.

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Angioplasty and/or stenting is associated with a slightly higher procedural risk than endarterectomy and a higher rate of re-stenosis.

## CONCLUSIONS

- Patients with recently symptomatic carotid stenosis are at very high risk of early recurrent stroke and require urgent investigation and treatment.
- Medical treatment should include antiplatelet agent(s) (almost always), a statin (almost always) and blood pressure lowering (usually), but anticoagulation is not indicated.
- Blood pressure should not be lowered aggressively in patients with bilateral severe carotid disease prior to endarterectomy.
- Carotid endarterectomy (or possibly angioplasty) should be considered in some patients with 50–69% stenosis and in most patients with □ 70% stenosis, but is of less benefit in near-occlusions.
- Consideration of the need for endarterectomy should take into account age, sex, time since last symptomatic event, type of symptomatic event(s) and – where it has been imaged reliably – plaque surface morphology.
- The most important consideration is time since last symptomatic event because the risk of stroke on medical treatment falls quickly with time. Delays in surgery lead to reduced or no benefit in patients who are eventually operated, and there is a high risk of preventable stroke prior to surgery.
- Given the need to consider multiple factors in making a decision about endarterectomy, risk models or risk tables detailing the likely risk of stroke on medical treatment alone are useful tools with which to guide decision making and to explain decisions to patients.
- Ongoing trials will determine whether carotid angioplasty and stenting are acceptable alternatives to endarterectomy.
- Benefit from angioplasty/stenting will also depend mainly on the risk of stroke without treatment and so on the same factors and risk models that determine benefit from endarterectomy.

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