Carotid endarterectomy for recently symptomatic carotid stenosis: consistent results from two large randomized controlled trials

Atherothrombotic stenosis at or around the carotid bifurcation is associated with an increased risk of ipsilateral carotid territory ischaemic stroke. This risk is reduced, in certain patients, by carotid endarterectomy. Approximately 140 000 operations are now performed each year in the U.S.A.[1], and rates continue to rise in Europe. Two large randomized controlled trials of carotid endarterectomy plus best medical treatment vs best medical treatment alone have recently reported final results[2,3]. Although there were some methodological differences between the trials, the overall results were remarkably similar. Broadly speaking, clinically important benefit from carotid endarterectomy appears to be limited to patients with severe carotid stenosis: 80–99% stenosis by the method of measurement used in the European Carotid Surgery Trial (ECST) and 50–99% by the method of measurement used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Whether or not endarterectomy is beneficial is determined by the balance between the risk of ipsilateral ischaemic stroke without surgery and the risk of stroke and death due to the operation itself. Patients at greatest risk of stroke on medical treatment are likely to have the most to gain from surgery. The analyses of the recent randomized controlled trials of endarterectomy were therefore stratified by the degree of stenosis of the symptomatic carotid artery; a powerful predictor of stroke risk on medical treatment. However, comparison of the trial results is complicated by the use of different methods of measurement of the degree of stenosis on pre-randomization angiograms; the NASCET method underestimating stenosis compared to the ECST method. Stenoses reported to be 70–99% in the NASCET trial were equivalent to 80–99% by the ECST method, and stenoses reported to be 70–99% by the ECST trialists were 50–99% by the NASCET method[4].

There have, in fact, been five randomized controlled trials of endarterectomy in patients with recently symptomatic carotid stenosis[2,3,5–7]. The first two were small and did not produce clear results[5,6], and the larger VA trial (VA #309) reported a non-significant trend in favour of surgery[7]. In 1991, the ECST demonstrated a significant reduction in the overall risk of stroke in operated patients with ECST 70–99% stenosis[8]. At more or less the same time the NASCET trial reported similar results in patients with NASCET 70–99% (ECST 80–99% stenosis)[9]. The ECST also reported that surgery was harmful in patients with mild stenosis (ECST 0–29%), in whom the risk of stroke on medical treatment was too low to offset the operative risks[8]. Both trials continued to randomize patients with moderate stenosis. In 1996, the ECST showed that there was no benefit from surgery in patients with either ECST 30–49% stenosis or ECST 50–69% stenosis[10]. The final results of the trials, both published this year[2,3], are remarkable for the similarity of the major findings:

(1) The operative risks of stroke and death within 30 days of carotid endarterectomy were 6·8% (95% CI=5·6%–8·0) in ECST and 6·7% (5·3–8·4%) in NASCET[2,3]. These risks are higher than those reported in many surgical case series[11], but they are not subject to publication bias, and they are likely to be reliable guides to good clinical practice. The operative risk in the ECST was significantly higher in women (hazard ratio=2·39, P<0·0001), although this difference was not seen in NASCET.

(2) In the final ECST analysis, statistically significant benefit from endarterectomy was confined to patients with ECST 80–99% stenosis (NASCET 70–99% stenosis). The absolute reduction in risk of major stroke or death at 3 years was 11·6% (P=0·01) for patients with NASCET 70–99% stenosis[9]. This is consistent with the 10·1% (P<0·01) reduction in major stroke or death at 2 years reported for patients with NASCET 70–99% stenosis[9]. NASCET also demonstrated a 6·9% (P=0·03) absolute reduction in risk of disabling stroke or death in patients with NASCET 50–69% stenosis (ECST 70–80% stenosis)[3]. This benefit was not seen in ECST[2]. However, the 95% confidence intervals of the
treatment effects in the two trials widely overlap for this range of stenosis and so there is no evidence of any genuine heterogeneity.

(3) In both trials, the risk of carotid territory ipsilateral ischaemic stroke on medical treatment fell rapidly with time from randomization. In ECST, the risks in patients with ECST 80–99% stenosis were approximately 12% in year 1, 8% in year 2, 3% in year 3 and 2–3% annually thereafter[5]. Almost exactly the same risks were reported in NASCET[3]. Clearly, therefore, maximum benefit from endarterectomy requires that the operation is performed within the first few months after the last ischaemic symptoms.

(4) The risk of carotid territory ipsilateral ischaemic stroke after the immediate postoperative period in patients randomized to surgery was remarkably low in both trials: approximately 1% per year in patients with severe pre-operative stenosis. This shows that the carotid plaque must play a role in the aetiology of the vast majority of ischaemic strokes which occur distal to the stenosis on medical treatment alone, and that re-stenosis is not a clinically important problem following endarterectomy.

There is still work to be done to properly evaluate the place of endarterectomy in the management of symptomatic carotid stenosis. A formal meta-analysis of individual patient data from all available randomized controlled trials is currently underway. This will define the overall treatment effect more precisely at the different levels of stenosis, and will allow more complex analyses which aim to better apply the results of the trials to individual patients. Endarterectomy is of overall benefit in patients with recently symptomatic NASCET 50–99% stenosis or ECST equivalent. However, the clinician has to decide whether or not an individual patient is likely to benefit. Only about 30% of patients with a recently symptomatic severe carotid stenosis actually suffer a stroke on medical treatment alone. Endarterectomy would be of no value in the 70% of patients who are destined to remain stroke-free without surgery. Indeed, as a group, these patients would be harmed by surgery because of the morbidity and mortality of the operation. Extrapolation of the overall results of the large randomized controlled trials of endarterectomy directly to clinical practice assumes that we cannot identify which patients are at high and low risk of stroke at the outset. However, this is not the case. There are several clinical and angiographic characteristics, in addition to the degree of stenosis, which identify patients at high risk of stroke and other vascular outcomes on medical treatment alone[12], and there are several risk factors for the operative risk of stroke and death due to endarterectomy[13]. All of these characteristics could potentially influence the effectiveness of endarterectomy and should be taken into account when considering surgery. Ideally, only those individuals at high risk of stroke on medical treatment and a relatively low operative risk should undergo operation[14]. A preliminary analysis of the ECST, using prognostic models to predict the risk of ipsilateral carotid territory ischaemic stroke on medical treatment and the risk of stroke and death within 30 days of carotid endarterectomy, suggests that benefit from surgery is confined to a subgroup of about 20% of patients with ECST 70–99% stenosis[15]. In other words, up to 80% of patients may currently be being operated on unnecessarily. It is planned to test these observations on data from the NASCET trial. In summary, therefore, ECST and NASCET have defined the overall benefit of endarterectomy in patients with symptomatic carotid stenosis, and now provide the opportunity to determine which individual patients are most likely to benefit from surgery.

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References


