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[Intervention Review]

Carotid endarterectomy for asymptomatic carotid stenosis

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ABSTRACT

Background

Carotid endarterectomy (CEA) is of proven benefit in recently-symptomatic patients with severe carotid stenosis. Its role in asymptomatic stenosis is still debated. The Asymptomatic Carotid Surgery Trial (ACST) more than doubled the number of patients randomised to CEA trials. This revised review incorporates the recently published ACST results.

Objectives

To determine the effects of CEA for patients with asymptomatic carotid stenosis.

Search methods

We searched the Cochrane Stroke Group Trials Register (searched May 2004), MEDLINE (1966 to May 2004), EMBASE (1980 to June 2004), Current Contents (1995 to January 1997), and reference lists of relevant articles. We contacted researchers in the field to identify additional published and unpublished studies.

Selection criteria

All completed randomised trials comparing CEA to medical treatment in patients with asymptomatic carotid stenosis.

Data collection and analysis

Two reviewers extracted data and assessed trial quality. Attempts were made to contact investigators to obtain missing information.

Main results

Three trials with a total of 5223 patients were included. In these trials, the overall net excess of operation-related perioperative stroke or death was 2.9%. For the primary outcome of perioperative stroke or death or any subsequent stroke, patients undergoing CEA fared better than those treated medically (relative risk (RR) 0.69, 95% confidence interval (CI) 0.57 to 0.83). Similarly, for the outcome of perioperative stroke or death or subsequent ipsilateral stroke, there was benefit for the surgical group (RR 0.71, 95% CI 0.55 to 0.90). For the outcome of any stroke or death, there was a non-significant trend towards fewer events in the surgical group (RR 0.92, 95% CI 0.83 to 1.02). Subgroup analyses were performed for the outcome of perioperative stroke or death or subsequent carotid stroke. CEA appeared more beneficial in men than in women and more beneficial in younger patients than in older patients although the data for age effect were inconclusive. There was no statistically significant difference between the treatment effect estimates in patients with different grades of stenosis but the data were insufficient.

Authors' conclusions

Despite about a 3% perioperative stroke or death rate, CEA for asymptomatic carotid stenosis reduces the risk of ipsilateral stroke, and any stroke, by approximately 30% over three years. However, the absolute risk reduction is small (approximately 1% per annum over the first few years of follow up in the two largest and most recent trials) but it could be higher with longer follow up.

PLAIN LANGUAGE SUMMARY**Carotid endarterectomy for asymptomatic carotid stenosis**

For most people with a narrowing of the carotid artery which is not causing symptoms a surgical operation to remove the narrowing carries a risk and has little benefit. Carotid stenosis is a narrowing of a major artery in the neck taking blood to the brain. This can cause a stroke. If the narrowing is severe and has caused symptoms, surgery to remove the narrowing (carotid endarterectomy) reduces the risk of stroke. However, if the narrowing has not caused any symptoms the risk of stroke is not very high. Although this low risk can be lowered further by surgery, the surgery itself can sometimes cause a stroke or death. The overall effect of surgery is a small benefit.

BACKGROUND

Whilst carotid endarterectomy (CEA) is of proven benefit in recently symptomatic patients with severe carotid stenosis (ECST; NASCET) the role of CEA in preventing stroke in patients with asymptomatic carotid stenosis is still debated. Natural history studies indicate an annual risk of unheralded stroke of 1% to 3% (Abbott 2005; Chambers 1986; Norris 1991). Even so, the number of asymptomatic stenosis patients undergoing CEA appears to be increasing in some countries (Barnett 1996). More alarming is the trend to perform carotid angioplasty and stenting despite no evidence of efficacy. The Asymptomatic Carotid Surgery Trial (ACST) more than doubled the number of patients randomised to CEA trials. This revised review incorporates the recently published ACST results.

OBJECTIVES

To determine the effects of CEA for patients with asymptomatic carotid stenosis. Our hypotheses were that CEA reduces overall rates of ipsilateral stroke, any stroke, and any stroke or death, despite some cases of perioperative stroke or death.

METHODS

Criteria for considering studies for this review

Types of studies

Truly randomised unconfounded controlled trials comparing CEA with medical management.

Types of participants

All trials involving patients with asymptomatic carotid stenosis were considered, irrespective of degree of stenosis or the method of determining the degree of stenosis, except where trials were performed in the context of coronary artery bypass and other sorts of surgery. Patients with no history at all of cerebrovascular symptoms, remote (more than six months) carotid territory symptoms, prior symptoms in the vertebrobasilar circulation, and prior carotid territory symptoms or a history of CEA on the contralateral side were deemed asymptomatic.

Types of interventions

Carotid endarterectomy was the only intervention evaluated. Specific surgical techniques, type of anaesthesia, and whether the surgery was unilateral or bilateral were not addressed. Antiplatelet therapy was recognised as a potential confounder since in some trials patients in medical and surgical groups could be given antiplatelet therapy whereas in others only medical patients received antiplatelet therapy. We decided to exclude trials in which surgical patients did not receive antiplatelet therapy.

Types of outcome measures

We aimed to extract from each trial the number of patients originally allocated to each group to allow an intention-to-treat analysis. Within each treatment group we then extracted the number of patients with the following outcomes.

(1) Perioperative stroke (of any territory or type) or death (from any cause), including the interval from randomisation to surgery and 30 days after surgery. In medical patients, an equivalent period from randomisation was used for comparison.

(2) Perioperative stroke or death or ipsilateral carotid territory stroke of any pathological type during subsequent follow up.
(3) Perioperative stroke or death, or stroke of any territory or type during follow up. We chose this as the primary outcome measure.
(4) Any stroke or death during the perioperative period and subsequent follow up.

Transient ischaemic attack (TIA) was not included as an outcome. All strokes were counted, regardless of severity, provided the duration of neurological deficit was greater than 24 hours. It was not possible to extract data for the outcomes major stroke, vascular death, long-term disability, or quality of life from the available studies. These data should be reported in future studies.

Search methods for identification of studies

See: 'Specialized register' section in [Cochrane Stroke Group](#)

(1) We searched the Cochrane Stroke Group Trials Register, which was last searched by the Review Group Co-ordinator on 27 May 2004 using a search strategy designed to identify all relevant trials.

(2) We searched MEDLINE (1966 to May 2004) (Appendix 1) and EMBASE (1980 to June 2004) (Appendix 2).

(3) For the previous version of this review we searched Current Contents - Medicine (1995 to January 1997), and the University of Melbourne on-line Ovid version using the terms 'asymptomatic carotid stenosis' and 'carotid endarterectomy'. The program's vocabulary mapping function automatically selects appropriate keywords and text words. These two searches were combined using the 'and' operator with a keyword search for 'randomized controlled trials'.

(4) Experts in the field were questioned at scientific meetings in an effort to identify further published and unpublished studies.

Data collection and analysis

One author (BRC) selected the trials to be included in the review, based on four criteria: study design (randomised trial); target population (patients with asymptomatic carotid stenosis); therapeutic intervention (CEA versus medical treatment); and outcome assignment. Two authors (BRC and GAD) independently extracted data and assessed trial quality. There was agreement for all outcome measures.

We performed data synthesis and statistical analysis using The Cochrane Collaboration's Review Manager software, RevMan 4.2. We used fixed-effect meta-analysis and computed relative risk (RR) with 95% confidence interval (CI), and relative risk reduction (RRR) for all outcomes.

We performed subgroup analyses, using the method of Deeks et al (Deeks 2001), testing the effect of gender, age and degree of stenosis.

Heterogeneity across all studies was assessed using the I^2 statistic (Higgins 2003) computed by RevMan.

RESULTS

Description of studies

Seven trials were identified but four were excluded from our analysis on methodological grounds. The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (*CASANOVA*) study was excluded because of a complicated randomisation process, precluding direct comparison of the results with the other studies. The investigators were unable to supply data for those patients with unilateral carotid stenosis who were truly randomised to CEA or medical management. The Association Universitaire de Recherche en Chirurgie (*AURC*) study was conducted between 1983 and 1989 but the results of the trial were never formally published and the methodology was uncertain. Data derived by personal contact with the principal investigator were inconsistent with the little published material about this trial. It is suspected that outcomes included TIA but the principal investigator did not respond to a request for clarification. The Walter Reed Army Medical Centre Study (*WRAMC*), and the Mayo Asymptomatic Carotid Endarterectomy Study (*MACE*) were small trials comparing CEA with aspirin. *MACE* was terminated prematurely because of an excess of myocardial infarction and TIA in the surgical group attributed to aspirin being withheld. Although these trials were included in our original review, we excluded them from the updated review because they were confounded by the fact that CEA or lack of aspirin could cause the difference in outcome between the medical and surgical groups.

The three studies included in our analysis were the Veterans Affairs Cooperative Study (*VA*), the Asymptomatic Carotid Atherosclerosis Study (*ACAS*) and the Asymptomatic Carotid Surgery Trial (*ACST*). These randomised 5223 patients (3579 males and 1644 females) in total. *VA* was restricted to males. The mean age was about 67 years. *ACAS* excluded patients 80 years of age and over.

The method of angiographic measurement of degree of stenosis was as for *NASCET* in *VA* and *ACAS*, and as for *ECST* in *ACST*. In *ACAS* and *ACST*, patients were randomised on the basis of 60% to 99% stenosis by carotid duplex ultrasound alone (*ACST*) or either ultrasound or angiography (*ACAS*). A few patients in *ACST* also had angiography. In *ACAS*, angiography was then performed in those randomised to surgery who had not previously undergone angiography. In *VA*, all patients underwent angiography prior to randomisation, and were randomised if there was 50% to 99% carotid stenosis.

Antiplatelet therapy, usually aspirin, was administered to medical and surgical groups.

In *VA* and *ACAS*, patients randomised to surgery were required to undergo CEA within 10 days and 14 days respectively. In *VA*, patients in the medical group who developed symptoms could cross over to surgery but it is not certain if they were censored at this point. In *ACAS*, crossovers from medical to surgical treatment occurred but subsequent outcomes were counted. In *ACST* only half the patients allocated immediate surgery had CEA within one month of randomisation and 88% by one year. Patients in the medical (deferred surgery) group underwent surgery if they developed symptoms, and subsequent outcomes were counted according to intention to treat.

Approximately one-quarter to one-third of the patients had a history of prior symptoms or CEA on the contralateral side. Twelve per cent of patients in *ACST* had had ipsilateral symptoms more than six months prior to randomisation.

The mean duration of follow up varied from 2.7 to 4.0 years. Overall, there were 17037 person-years follow up, with mean follow up 3.3 years per patient.

Risk of bias in included studies

Randomisation in each of the three studies was performed by a central co-ordinating centre. In *VA*, randomisation was stratified by the clinical centre and previous contralateral symptoms or CEA. In *ACAS*, patients were randomised using the permuted block method with at least three different block sizes determined randomly, and stratified according to clinical centre, gender, number of eligible arteries, and previous contralateral CEA. In *ACST*, minimised randomisation was performed to balance demographic and potential prognostic variables. In each study, clinical centres could not predict or reject treatment allocation.

Outcomes were assessed by a neurologist and adjudicated by a blinded review committee in all three trials.

Three patients (0.2%) in *ACAS* were lost after randomisation and excluded from the analysis. In *VA*, 35 patients (20 in the surgical group; 15 in the medical group; 7.9% overall) withdrew or were lost to follow up, but substantial follow-up data were available for these patients. In *ACST*, 68 (2.2%) patients were lost to follow up.

In *VA*, 8 (3.8%) patients randomised to surgery did not undergo CEA. It is uncertain if there were crossovers to surgery in the medical group before the development of symptoms. Once patients in the medical group had a TIA they were permitted to cross over to surgical treatment. The number of patients doing so is uncertain. In *ACAS*, 101 (12.2%) patients in the surgical group did not have CEA and 45 (5.4%) in the medical group had CEA without prior ipsilateral TIA or stroke. In *ACST*, about 10% of surgical (immediate surgery) patients did not have ipsilateral CEA, and about 10% of medical (deferred surgery) patients had ipsilateral CEA.

Data from each of the trials were presented in such a way as to permit intention-to-treat analysis, that is, treatment crossovers were analysed by their original allocated treatment.

Effects of interventions

Analyses of primary and secondary outcomes

The three trials included in our review involved 5223 patients and 17,037 person-years follow up.

(1) Perioperative stroke or death

In *VA* and *ACAS*, the overall perioperative complication rate was 3.0% but over the same period there were also events in medical patients (0.5%) giving a net excess of perioperative stroke or death of 2.5% (RR 6.49, 95% CI 2.53 to 16.61, P value < 0.0001). These figures include complications from any angiography done after, but not before, randomisation. In *ACST*, because there was a more leisurely approach to performing CEA after randomisation, data were presented differently. The operation-related 30-day rate of stroke or death was 3.1%. Combining data from all three trials revealed an overall operation-related complication rate of 2.9%.

(2) Perioperative stroke or death or subsequent ipsilateral stroke

There was a 29% relative risk reduction (RRR) from CEA (RR 0.71, 95% CI 0.55 to 0.90, P value 0.005).

(3) Perioperative stroke or death or any subsequent stroke (primary outcome)

The RRR from CEA was 31% (RR 0.69, CI 0.57 to 0.83, P value < 0.0001). The absolute risk reduction (ARR) in VA was 1.0% over mean follow up of 4.0 years, in ACAS 3.0% over 2.7 years and in ACST 3.1% over 3.4 years.

(4) Any stroke or death

Higher event rates in VA (44.2% medical versus 41.2% surgical) are probably explained by the longer duration of follow up (mean 47.9 months). There was an 8% RRR from CEA which did not achieve statistical significance (RR 0.92, 95% CI 0.83 to 1.02, P value 0.09).

There was no significant heterogeneity across the studies for these outcomes ($I^2 = 0$).

Subgroup Analyses

Only ACAS and ACST provided subgroup data. Perioperative complications in ACST were obtained from a web table and added to data from the Lancet publication. We performed subgroup analyses for the outcome of perioperative stroke or death or subsequent carotid stroke. In ACAS carotid stroke refers to ipsilateral, whilst in ACST it refers to all carotid (since there were a large number of uncertain laterality carotid strokes).

For men the RRR from surgery was 51% (RR 0.49, 95% CI 0.36 to 0.66), and for women it was 4% (RR 0.96, CI 0.64 to 1.44). This difference was statistically significant ($Q_{int} = 7.08$, P value 0.008). For men the ARR in ACAS was 3.6% and in ACST it was 4.2%.

In ACAS age 68 was used to distinguish younger and older patients and in ACST age 75. We combined patients from ACAS and ACST, dividing them into younger and older groups, despite the two studies using different age thresholds. For younger patients, the RRR from surgery was 50% (RR 0.50, 95% CI 0.37 to 0.68), and for older patients 9% (RR 0.91, 95% CI 0.61 to 1.36). This difference was statistically significant ($Q_{int} = 5.54$, P value 0.02). However, there was mild heterogeneity between the two studies ($I^2 = 27.6\%$) for patients in the older age category, there being a trend for benefit with CEA in ACAS and the opposite trend in ACST. For younger patients in ACAS the ARR was 2.7% and in ACST it was 4.0%.

In ACAS grades of stenosis were defined (according to NASCET) as 60% to 69%, 70% to 79%, and 80% to 99%, but only in patients who underwent angiography prior to randomisation. In ACST grades of stenosis were defined (according to ECST) as 60% to 79%, 80% to 89%, and 90% to 99%. We combined patients from ACAS and ACST using the three grades of increasing severity (designated as grades 1 to 3) despite the slight variation in grading between the two studies. In these trials, only 58 outcome events occurred in patients with the most severe grade of stenosis and hence the estimate of effect between the different categories of stenosis was imprecise. There was no evidence of a difference in treatment effect between the different categories of stenosis ($Q_{int} = 3.66$, P value 0.16) but the analysis is underpowered.

DISCUSSION

Carotid endarterectomy reduces the overall risk of ipsilateral stroke and any stroke, even taking into consideration those strokes and deaths directly attributable to angiography and surgery. However, the absolute risk reduction is small: about 3% over three years for the outcome of any stroke. Since ARR is reduced by up-front perioperative complications one would expect the ARR to improve with longer follow up. The decision to extend follow up in ACST will provide valuable long-term data.

Although the three studies included in our analysis were methodologically sound, yielding data which we consider of good quality, only 5223 patients were randomised compared with more than 100,000 patients randomised to trials of antiplatelet agents in the secondary prevention of stroke. Given that the two treatments have similar purported efficacy in stroke prevention some caution must be exercised in interpreting the CEA results.

It is possible that the studies included in this review are biased against surgery since patients in the medical arm were allowed to cross over to CEA after TIA.

The 2.9% net excess of operation-related stroke or death is lower than reported in trials of CEA for symptomatic stenosis (ECST 7%; NASCET 5.4%), consistent with the view that operative risk is less for asymptomatic carotid stenosis. The trials were performed in centres of excellence where the risks of surgery would be expected to be less than in institutions where there is less expertise with CEA. Complication rates slightly higher than those reported would reverse the result.

One-quarter to one-third of randomised patients had a history of contralateral symptoms or CEA. Twelve per cent of patients in ACST had ipsilateral symptoms more than six months prior to randomisation. In ACAS and ACST medical patients who had previous contralateral symptoms or CEA had higher stroke rates than those who did not. In ACST medical patients with remote ipsilateral symptoms had a higher stroke rate than those who did not. Moreover, patients with prior contralateral symptoms or CEA seemed to benefit more from CEA of the study artery.

In VA and ACAS 33% overall of eligible patients were not randomised. We do not know how many eligible patients were not randomised in ACST. Whether this introduces bias is uncertain. However, the external validity is questionable. It is possible that some patients were considered to be at higher risk and operated on rather than randomised, while on the other hand, only patients in good general medical health with reasonable life expectancy were randomised.

Provided the excess stroke risk of unoperated asymptomatic carotid stenosis continues, the longer a patient survives after CEA the greater the potential benefit since the adverse consequences of surgery are limited to the perioperative period.

For the type of patients entered in the included trials who were at low absolute risk of stroke over the period of follow up the net gain from surgery was small. Operating on a population whose absolute risk of stroke is much higher may improve the utility of the procedure.

If CEA is to be a worthwhile treatment for asymptomatic carotid disease it is imperative that better risk stratification be achieved

to identify patients at high enough risk to justify surgery. Gender, age, degree of stenosis, plaque morphology, number of risk factors, measures of intracranial haemodynamic insufficiency, microembolic signals detected by transcranial Doppler in the middle cerebral artery, and CT evidence of silent cerebral infarction are some of the parameters under evaluation but there is no clear consensus as to the best method yet.

Cost effectiveness of CEA for asymptomatic carotid stenosis is an important consideration. In Australia in 1997 it was estimated that the cost of preventing one stroke by CEA, over five years of follow up, is AUD\$210,760 for asymptomatic stenosis compared with AUD\$14,230 for symptomatic stenosis, over two years of follow up (NHMRC).

The public health impact of operating on all patients with asymptomatic disease is likely to be small. In Australia it has been calculated that if all eligible patients with 60% or greater carotid stenosis underwent CEA, only 1290 strokes would be prevented, representing 4.6% of the 28,000 first-ever strokes occurring each year (NHMRC). Thereafter, with the pool of eligible patients exhausted, and a relatively low incidence of asymptomatic 60% to 99% stenosis, there would only be a small number of patients being operated on each year.

Subgroup analyses suggest that women may not benefit in the short to medium term. This is consistent with previous observations. Women have a higher surgical complication rate than men due to technical difficulty handling smaller arteries. The spontaneous stroke rate in women with asymptomatic carotid disease is less than in men. There is a case for more women to be randomised in CEA trials to ensure this possible lack of efficacy is not due to Type II error. It is also possible women will benefit with longer follow up.

There is limited evidence on the effects of CEA among older people. The underpowered subgroup analyses suggest that there may be no benefit from CEA in older people with asymptomatic stenosis. This runs counter to the evidence of greater benefit from surgery for symptomatic stenosis among older compared with younger patients (Rothwell 2004). Again, with only a small number of events among older patients there is a possibility of Type II error.

The data are insufficient to examine whether there is a gradient of increasing benefit from surgery with increasing degree of stenosis. Hence, it is unclear whether the apparent difference in effects in different categories of stenosis (with less apparent benefit in the most severe category) is real or merely due to the play of chance. The subgroup analyses of the effect of surgery in patients with symptomatic stenosis are more robust and provide clear evidence that benefit increases substantially with degree of stenosis, excepting the most severe category of stenosis or near-occlusion, where there is no benefit from surgery (Rothwell 2004). The longer-term data from ACST may help to resolve this question.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that in patients with asymptomatic carotid stenosis, despite about a 3% perioperative stroke or death rate, CEA reduces the risk of ipsilateral stroke, and any stroke, by approximately 30% over three years. However, the absolute risk reduction is small (approximately 1% per annum over the first few years of follow up in the two largest and most recent trials) but it could be higher with longer follow up. Any benefit would be negated by a higher perioperative complication rate and only those centres with complication rates of 3% or less should contemplate performing CEA in asymptomatic patients. Whilst there is clear benefit for men, CEA did not appear to help women but it is possible that there could be a positive effect with longer follow up. At present, there is insufficient evidence on whether the surgical outcomes are different in older and younger people, and in patients with different degrees of stenosis. Longer follow up of patients in existing trials or recruitment of additional patients should help clarify these points.

Implications for research

For CEA to become a more cost-effective and clinically-relevant treatment option in patients with asymptomatic carotid stenosis, higher-risk patients must be reliably targeted. Clinical issues which must be resolved by randomisation of more patients and longer follow-up are:

- whether there is a gradient of benefit with increasing degrees of stenosis, as seen for symptomatic carotid disease;
- whether the benefit in women is definitely different to that in men;
- whether there is a different degree of benefit in older patients compared with younger patients.

Other issues which may be resolved by meta-analysis of individual patient source data are:

- whether the benefits of surgery are greater for those with more vascular risk factors;
- whether the benefits of surgery can be related to an expected survival instrument based on age, sex and risk factor criteria.

Other approaches to identify high-risk patients are necessary, such as:

- improved characterisation of plaque morphology;
- detection of microembolic signals by transcranial Doppler.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ACAS

Methods	Randomisation by co-ordinating centre. Stratification by centre, gender, number of eligible arteries, and previous contralateral CEA.
Participants	North American; 39 centres. 1662 patients (66% male; mean age 67 years) were randomised but 3 patients were lost following randomisation and excluded from analysis. Asymptomatic carotid artery stenosis of 60% or greater reduction in diameter determined by non-invasive tests or angiography. Medical and surgical groups comparable in terms of age, gender, race, risk factors, contralateral symptoms or CEA, contralateral occlusion, and infarct on CT. Median follow up 2.7 years.
Interventions	(1) Surgical group: angiography if not performed prior to randomisation, carotid endarterectomy, aspirin 325 mg daily. (2) Medical group: aspirin 325 mg daily.
Outcomes	Primary: ipsilateral stroke or any perioperative stroke or death. Secondary: ipsilateral TIA; any stroke; major ipsilateral stroke; any major stroke; death. Perioperative period was defined as 30 days after CEA in the surgical group and 42 days after randomisation in the medical group.
Notes	Generalisability: 683 non-randomised but likely eligible patients underwent CEA by ACAS surgeons during the trial period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

ACST

Methods	Minimised randomisation by Clinical Trial Service Unit, Oxford, UK.
Participants	International, mainly European; 126 centres. 3120 patients (66% male; mean age 68 years) were randomised to 'immediate surgery' (surgical) and 'deferred surgery' (medical) groups. Asymptomatic carotid artery stenosis of 60% or greater reduction in diameter determined by non-invasive tests or angiography. There were no significant differences between the initial characteristics of medical and surgical groups. Mean follow up 3.4 years.
Interventions	(1) Surgical group: CEA as soon as possible, standard medical treatment including antiplatelet drugs.

ACST (Continued)

(2) Medical group: no CEA unless symptoms occurred, standard medical treatment including antiplatelet drugs.

Outcomes	Primary: perioperative stroke or death; non-perioperative stroke. Secondary: non-perioperative fatal or disabling stroke; non-perioperative carotid territory ischaemic stroke.
Notes	Generalisability: unknown number of eligible patients not randomised. In surgical group only half had CEA within 1 month and 88% by one year. In medical group 6% had CEA after 1 year, and 18% by 5 years, because of symptoms in about half. 68 (2.2%) patients lost to follow up. Unknown laterality of 6/30 (20%) surgical and 8/105 (7.6%) medical patients experiencing carotid strokes. Patients in medical group who had CEA continued to be followed. Hence this is a trial of immediate surgery versus deferred surgery. Authors presented results of sub-group analyses excluding perioperative complications. These are published in a web table. See Footnotes for reference.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

VA

Methods	Randomisation performed by co-ordinating centre. Stratification by clinical centre and previous contralateral symptoms or CEA. Independent assessment of outcomes.
Participants	North American; 11 centres. 444 male veterans. Mean age 64.5 years. 50-99% diameter stenosis. All patients underwent angiography prior to randomisation. Medical and surgical groups comparable for age, race, previous contralateral symptoms, and risk factors. Mean follow up 4.0 years.
Interventions	(1) Surgical group: carotid endarterectomy; aspirin 650 mg bd. (2) Medical treatment group: aspirin 650 mg bd.
Outcomes	Primary: ipsilateral neurological events (TIA, amaurosis, stroke). Secondary: any stroke; death.
Notes	Generalisability: 281 eligible patients refused randomisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

ACAS: Asymptomatic Carotid Atherosclerosis Study

bd: twice a day

CEA: carotid endarterectomy

Carotid endarterectomy for asymptomatic carotid stenosis (Review)

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CT: computerised tomography

Reference to ACST web table: <http://image.thelancet.com/extras/04art3083webtable.pdf>

TIA: transient ischaemic attack

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
AURC	The Association Universitaire de Recherche en Chirurgie (AURC) study was conducted between 1983 and 1989, but the trial was never published and the methodology was uncertain. Data derived by personal contact with the principal investigator were inconsistent with the little published material about this trial. It is suspected that outcomes included TIA but the principal investigator did not respond to a request for clarification. Data from this trial were included in our original review.
CASANOVA	The Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin (CASANOVA) study was excluded because of a complicated randomisation process, precluding direct comparison of the results with the other studies. In CASANOVA, patients with 50% to 90% carotid stenosis were randomised into two groups: those in Group A had CEA for all eligible vessels; in Group B, those patients with unilateral lesions were treated medically whilst those with bilateral lesions had the worst affected side operated on and the other treated medically. Contact with the investigators to obtain additional data for inclusion in this analysis was unfruitful.
MACE	The Mayo Asymptomatic Carotid Endarterectomy Study (MACE) was a small trial comparing CEA with aspirin. MACE was terminated prematurely because of an excess of myocardial infarction and TIA in the surgical group, attributed to aspirin being withheld. Although included in our original review, we excluded this trial from the updated review because it was confounded by the fact that CEA or lack of aspirin could cause the difference in outcome between the medical and surgical groups.
WRAMC	The Walter Reed Army Medical Centre Study (WRAMC) was a small trial comparing CEA with aspirin. Although included in our original review, we excluded this trial from the updated review because it was confounded by the fact that CEA or lack of aspirin could cause the difference in outcome between the medical and surgical groups.

CEA: carotid endarterectomy

TIA: transient ischaemic attack

DATA AND ANALYSES

Comparison 1. Carotid endarterectomy versus medical treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Perioperative stroke or death	2	2103	Risk Ratio (M-H, Fixed, 95% CI)	6.49 [2.53, 16.61]
2 Perioperative stroke or death or subsequent ipsilateral stroke	3	5223	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.55, 0.90]
3 Perioperative stroke or death or any subsequent stroke	3	5223	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.57, 0.83]
4 Any stroke or death	3	5223	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]

Carotid endarterectomy for asymptomatic carotid stenosis (Review)

Analysis 1.1. Comparison 1 Carotid endarterectomy versus medical treatment, Outcome 1 Perioperative stroke or death.

Analysis 1.2. Comparison 1 Carotid endarterectomy versus medical treatment, Outcome 2 Perioperative stroke or death or subsequent ipsilateral stroke.

Analysis 1.3. Comparison 1 Carotid endarterectomy versus medical treatment, Outcome 3 Perioperative stroke or death or any subsequent stroke.

Analysis 1.4. Comparison 1 Carotid endarterectomy versus medical treatment, Outcome 4 Any stroke or death.

Comparison 2. Subgroup analysis

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 Gender	2	4779	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.48, 0.78]
1.1 Men	2	3135	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.36, 0.66]
1.2 Women	2	1644	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.64, 1.44]
2 Age	2	4779	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.49, 0.78]
2.1 Younger	2	3272	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.37, 0.68]
2.2 Older	2	1507	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.36]
3 Stenosis	2	3762	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.47, 0.80]
3.1 Grade 1 - least severe	2	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.35, 0.83]
3.2 Grade 2 - intermediate severity	2	1063	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.81]
3.3 Grade 3 - most severe	2	1147	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.56, 1.53]

Analysis 2.1. Comparison 2 Subgroup analysis, Outcome 1 Gender.

Analysis 2.2. Comparison 2 Subgroup analysis, Outcome 2 Age.

Analysis 2.3. Comparison 2 Subgroup analysis, Outcome 3 Stenosis.

APPENDICES

Appendix 1. MEDLINE search strategy

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1 carotid stenosis/
2 carotid artery diseases/
3 carotid arteries/
4 carotid artery, common/
5 carotid artery, internal/
6 (carotid adj (arter$ or stenosis)).tw
7 1 or 2 or 3 or 4 or 5 or 6
8 endarterectomy, carotid/
9 endarterectomy/
10 (carotid adj5 endarterectomy).tw
11 8 or 9 or 10
12 randomized controlled trials/
13 controlled clinical trials/
14 clinical trials/
15 random$.tw
16 ((clin$ or controlled) adj5 trial$).tw

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17 12 or 13 or 14 or 15 or 16
18 7 and 11 and 17
19 asymptomatic.tw
20 18 and 19

Appendix 2. EMBASE search strategy

1. exp carotid artery obstruction/
2. carotid artery disease/
3. exp carotid artery/
4. (carotid adj5 (arter\$ or athero\$ or steno\$ or narrow\$ or obstruct\$ or thrombo\$ or occlus\$ or plaque or bruit\$)).tw.
5. 1 or 2 or 3 or 4
6. carotid endarterectomy/
7. carotid artery surgery/
8. exp carotid artery disease/su
9. 2 or 3
10. endarterectomy/ or artery surgery/ or vascular surgery/ or surgery/
11. 9 and 10
12. (carotid adj5 (endarterectomy or surgery)).tw.
13. 6 or 7 or 8 or 11 or 12
14. 5 and 13
15. asymptomatic.tw. and 14
16. clinical trial/
17. randomized controlled trial/
18. controlled study/
19. randomization/
20. random\$.tw.
21. versus.tw.
22. types of study/
23. comparative study/
24. Controls.tw.
25. (controlled adj5 (stud\$ or trial)).tw.
26. ((control or intervention or experiment\$ or surg\$) adj5 (group\$ or patients)).tw.
27. (clin\$ adj10 trial\$).tw.
28. or/16-27
29. 15 and 28

WHAT'S NEW

Date	Event	Description
23 July 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 1999

Review first published: Issue 4, 1999

Date	Event	Description
2 June 2005	New citation required and conclusions have changed	Substantive amendment. Change of authorship
4 November 2004	New search has been performed	This major revision was undertaken because of the publication of the Asymptomatic Carotid Surgery Trial (ACST) results in May 2004, more than doubling the number of patients randomised.

Date	Event	Description
		<p>In the original review, Association Universitaire de Recherche en Chirurgie (AURC) data were included in a supplementary analysis. In this review AURC was excluded because of its methodological shortcomings and the substantive data obtainable from other included studies.</p> <p>In this revision, the Walter Reed Army Medical Center (WRAMC) and Mayo Asymptomatic Carotid Endarterectomy (MACE) studies were excluded because surgical patients did not receive aspirin, thereby confounding the effect of carotid endarterectomy. Data from these studies were included in the original review. There were too few patients to test for aspirin effect.</p> <p>The effect of gender, age, and degree of stenosis have been analysed in this update.</p>

CONTRIBUTIONS OF AUTHORS

Brian Chambers: selected the trials to be included in the review, determined the important outcome measures, extracted data from selected trials, corresponded with investigators, and prepared the manuscript.

Geoffrey Donnan: proposed the review be performed, independently extracted data from the selected trials, and checked the manuscript prior to submission.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

*Endarterectomy, Carotid [adverse effects]; Carotid Stenosis [*surgery]; Randomized Controlled Trials as Topic; Risk Assessment; Stroke [*prevention & control]

MeSH check words

Humans