Percutaneous transluminal angioplasty and stenting for carotid artery stenosis (Review)

Ederle J, Featherstone RL, Brown MM

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ABSTRACT

Background
Endovascular treatment by transluminal balloon angioplasty or stent insertion may be a useful alternative to carotid endarterectomy.

Objectives
To assess the benefits and risks of endovascular treatment compared with carotid endarterectomy or medical therapy.

Search strategy
We searched the Cochrane Stroke Group trials register (last searched 14 March 2007) and the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1, 2007), MEDLINE (1950 to March 2007), EMBASE (1980 to March 2007) and Science Citation Index (1945 to March 2007). We also contacted researchers in the field.

Selection criteria
We selected randomised trials of endovascular treatment compared with endarterectomy or medical therapy for carotid artery stenosis.

Data collection and analysis
One review author independently applied the inclusion criteria, extracted data and assessed trial quality. Search results were validated by a second review author.

Main results
Data were available from 12 trials (3227 patients) but not all contributed to each analysis. The primary outcome comparison of any stroke or death within 30 days of treatment favoured surgery (odds ratio (OR) 1.39, P = 0.02, not significant (NS) in the random-effects model). The following outcome comparisons favoured endovascular treatment over surgery: cranial neuropathy (OR 0.07, P < 0.01); 30 day neurological complication or death (OR 0.62, P = 0.004, NS in the random-effects model, with significant heterogeneity). The following outcome comparisons showed little difference between endovascular treatment and surgery: 30 day stroke, myocardial infarction or death (OR 1.11, P = 0.57 with significant heterogeneity); stroke during long-term follow up (OR 1.00). Comparison between endovascular treatment with or without protection device showed no significant difference in 30 day stroke or death (OR 0.77, P = 0.42 with significant heterogeneity). Analysis of stroke or death within 30 days of the procedure in asymptomatic carotid stenosis showed no difference (OR 1.06, P = 0.96). In patients not suitable for surgery, there was no significant difference in 30 day stroke or death (OR 0.39, P = 0.09 with significant heterogeneity).

Authors' conclusions
The data are difficult to interpret because the trials are heterogeneous (different patients, endovascular procedures, and duration of follow up) and five trials were stopped early, perhaps leading to an over-estimate of the risks of endovascular treatment. The pattern of effects on different outcomes does not support a change in clinical practice away from recommending carotid endarterectomy as the treatment of choice for suitable carotid artery stenosis.

PLAIN LANGUAGE SUMMARY

Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Carotid stenosis, or narrowing of one of the major arteries which carries blood to the brain, can cause a stroke. The standard treatment is to remove the narrowing by a surgical operation (carotid endarterectomy). The narrowing can also be treated by percutaneous transluminal balloon angioplasty. This involves passing a fine tube (catheter) through the skin (percutaneously) into the arterial system. The catheter has a small balloon at its tip. The catheter is moved through the arterial system until the balloon reaches the point of arterial narrowing in the carotid artery in the neck. The balloon is briefly inflated. This stretches the artery (angioplasty), and reduces the degree of narrowing. More recently a metal scaffolding (stent) is placed inside the artery to prevent it narrowing down again after the catheter is removed. Angioplasty and stenting are called endovascular treatment. This review, which included 12 trials involving 3227 participants, showed that surgery might be better than endovascular treatment in preventing early stroke or death, but there were fewer immediate neurological complications with endovascular treatment than with surgery. However, during follow up, the risk of stroke or death was similar after endarterectomy compared to endovascular treatment. Treated arteries may be more likely to narrow down after endovascular treatment than after carotid endarterectomy. Further randomised trials are needed to see which treatment yields the best chance of long-term freedom from disabling stroke or death.

BACKGROUND

Carotid stenosis is traditionally treated by carotid endarterectomy. Multicentre randomised controlled trials have shown that surgery significantly reduces the risk of ipsilateral stroke in patients with severe symptomatic carotid stenosis. The European Carotid Surgery Trial (ECST) showed a reduction in ipsilateral stroke in the surgically treated patients at three-year follow up from 21.9% to 9.6% ($P < 0.01$) (ECST 1998). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) showed a reduction from 27.6% to 12.6% at two-year follow up ($P < 0.001$) (NASCET 1998). In the Asymptomatic Carotid Atherosclerosis Study (ACAS), surgery for asymptomatic carotid stenosis was shown to significantly reduce the overall five-year risk of ipsilateral stroke or any perioperative stroke or death from 11% to 5.1% ($P = 0.004$), but not the risk of major ipsilateral stroke or any perioperative stroke or death (6.5% in medical group, 3.4% in surgical group $P = 0.12$) (ACAS 1995). The Asymptomatic Carotid Surgery Trial (ACST) showed a significant reduction in the five-year risk of perioperative fatal stroke from 4.2% to 2.1% ($P = 0.006$) (Halliday 2004). Endovascular techniques for treating carotid stenosis have been developed over recent years. Initially, percutaneous transluminal balloon angioplasty was used. Later stents were invented and have been used in the carotid artery either with or without initial balloon angioplasty. These treatments have the potential of being a useful alternative to carotid endarterectomy. The advantages include avoidance of general anaesthesia, an incision in the neck and the risk of cranial and cutaneous nerve damage from the surgical incision. Surgically inaccessible lesions can be treated and both the procedure and admission time are usually shorter than for surgery, therefore reducing some costs. On the other hand, devices used for endovascular treatment are more expensive.

Some evidence on the risks and benefits of endovascular treatment comes from non-randomised case series, non-randomised trials and registries. In total, we have identified well over 500 cases undergoing a carotid endovascular procedure reported in the literature (Brockenheimer 1983; Cao 2006; Dietrich 1996; Eckert 1996; Ecker 2007; Eskandari 2005; Ferguson 1993; Freitag 1987; Gil-Peralta 1996; Halabi 2006; Henry 1998; Iyer 1996; Kachel 1991; Mathias 1994; Mathur 1998; Munari 1992; Roubin 2001; Theiss 2004; Theron 1987; Theron 1990; Theron 1996; Tsai 1986; Waigland 1998; Wholey 1997; Wiggli 1983; Yadav 1997; White 2005). Primary stenting has replaced balloon angioplasty as the endovascular treatment most often used in clinical practice. Most major strokes after carotid percutaneous transluminal balloon angioplasty are the result of dissection of the carotid artery at the time of balloon inflation with subsequent thromboembolism. Stenting might be safer in experienced hands than simple balloon angioplasty, because dissection and occlusion of the carotid artery are less likely to occur (Dietrich 1996; Roubin 2001). The adverse consequences of dissection are minimised, because the stent maintains laminar flow across the stenosis and seals the site of dissection, preventing a free intimal flap. Superior dilation achieved by stenting compared with balloon angioplasty may also reduce the rate of stroke in the early post-treatment period. In the coronary circulation, stenting has been shown to produce superior outcomes compared with balloon angioplasty (Fischman 1994; Serruys 1996).

The rate of stroke or death within 30 days reported in these case series ranged from 2% to 9%, with an average rate of 4.7%. Thus in these non-randomised case series, the complication rate of endovascular intervention appears to be less than that of carotid endarterectomy in ECST (7.5% stroke rate within 30 days of surgery, 12.3% stroke rate at three year follow up), similar to that seen in NASCET (5.5% stroke rate within 30 days of surgery, 12.6% stroke rate at two year follow up) but greater than in ACAS (2.3% risk of stroke or death within 30 days of randomisation, 5.1% risk at 2.7 year follow up, although this included a 1.2% stroke risk

from arteriography pre surgery) and ACST (2.8% risk of perioperative risk of stroke or death) (ACAS 1995; ECST 1998; Halliday 2004; NASCET 1998). This would seem to suggest that balloon angioplasty carries an early risk no greater than that of surgery. However, the lesions and patients may have been highly selected, thereby reducing the complication rate in some series. For example, asymptomatic lesions were included in some series, as were stenoses less than 70%. Moreover, few of the large series have included independent verification of outcome or long term outcome data.

Concern regarding distal embolisation of debris during carotid artery stenting resulting in neurological deficit has led to the introduction and increasing use of cerebral protection devices. This concept was first described in the series by Theron 1996. There are now many case series in the literature reporting experience of endovascular treatment with temporary cerebral protection (Bonaldi 2002; Bush 2005; Gray 2006; Gray 2007; Guimaraens 2002; Reimers 2001; Reimers 2004; Safian 2006; White 2006). Reported complication rates range from 1% to 9%. In a comparison of symptomatic and asymptomatic patients stented with and without protection, stroke or death occurred in 1.8% and 5.6% (chi squared 19.7, $P < 0.001$), respectively with a calculated threefold increased risk of any stroke or death within 30 days of carotid stenting without protection compared with protection (Kastrup 2003). However, the concept of protective filter devices increasing safety is not accepted by all.

The main aim of treating carotid stenosis is the prevention of stroke in the long term. Carotid endarterectomy has been shown to be effective at preventing ipsilateral stroke over long-term follow-up periods as long as 13 years (ECST 1998). To provide an effective alternative, carotid stenting needs to have similar long-term effectiveness.

A particular concern about endovascular treatment has been that restenosis will limit the efficacy of the procedure in the medium to long term. Restenosis after coronary angioplasty occurs in 25% to 35% of patients (McBride 1988) and causes a recurrence of angina in a significant percentage of patients. However, this is related to the high demands of the coronary circulation for haemodynamic increases in flow and restenosis is less likely to be a problem in the cerebral circulation unless it leads to emboli.

We aim to systematically review all randomised controlled trials comparing carotid angioplasty and stenting with carotid endarterectomy or medical care.

OBJECTIVES

The overall objective of this review was to determine whether endovascular treatment of internal carotid artery stenosis might be an effective and safe alternative to carotid endarterectomy in patients suitable for surgery or to medical treatment in patients unsuitable for surgery. We have added individual objectives to the original protocol to reflect changes in technology and treatment approach. New objectives are marked with an asterisk. We felt it was important to test two primary hypotheses as we were interested in both the safety and efficacy of endovascular treatment compared with surgery.

(1) To determine whether endovascular treatment for carotid artery stenosis has a significantly different risk of periprocedure stroke or death compared with surgery.

(2) To determine whether endovascular treatment for carotid artery stenosis is effective in preventing stroke ipsilateral to the procedure and in other territories.

Additionally, we planned the following secondary analyses to examine whether:

(1) endovascular treatment reduces the risk of cranial neuropathy;

(2) the rates of other vascular complications (myocardial infarction, pulmonary embolism, haematoma) differ between endovascular treatment and surgery;

(3) there is any significant difference in the restenosis rates following endovascular or surgical treatment and whether restenosis leads to recurrent stroke;

(4) in patients unsuitable for surgery, carotid angioplasty and stenting is more effective in preventing stroke compared with medical care;

(5) there is a learning curve, that is, whether the event rate changes over time within trials and from trial to trial*;

(6) endarterectomy or the endovascular treatment arm is responsible for heterogeneity between the trials*;

(7) stenting with cerebral protection devices has a lower rate of treatment-related ischaemic events than stenting without cerebral protection devices*;

(8) endovascular treatment is as safe as surgery in asymptomatic patients*.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We attempted to identify all unconfounded truly randomised trials comparing carotid angioplasty or stenting or both with conventional carotid endarterectomy or trials comparing endovascular treatment with medical therapy alone. We included trials in which the exact method of randomisation was still uncertain after communication with the authors.

Types of participants

We considered trials including patients of any age or sex with symptomatic or asymptomatic carotid stenosis eligible for inclusion in the review.

Types of intervention

We reviewed trials which allowed any acceptable technique for carotid endarterectomy (for example use of a shunt or not, patching or not, local or general anaesthesia) and which allowed any acceptable endovascular technique for treatment of carotid stenosis (for example use of a simple balloon catheter or cerebral protection balloon, use of a stent or not) as well as trials which specified which technique was used. We included patients who had bilateral as well as unilateral procedures. We intended to compare:
(1) endovascular treatment with surgery;
(2) endovascular treatment with medical treatment in patients unsuitable for surgery;
(3) individual endovascular techniques (for example stent versus simple balloon angioplasty).

Types of outcome measures

We planned to analyse outcomes with intention to treat, extracting from each trial the number of patients originally allocated to each treatment group and the outcome of all patients randomised. We planned to look at symptomatic and asymptomatic stenoses separately, and then to consider the following (some outcome measures are changed from the original manuscript and marked with an asterisk).
(1) Periprocedural death or stroke within 30 days of procedure. Strokes were classified, if possible, as: (a) disabling stroke; (b) non-disabling stroke, that is with a score of less than three on the modified Rankin scale.
(2) Subsequent ipsilateral carotid territory stroke: (a) disabling; (b) non-disabling.
(3) Subsequent stroke in any arterial territory: (a) disabling; (b) non-disabling.
(4) Subsequent death of any cause.*
(5) Any death within 30 days of procedure.*
(6) Any stroke within 30 days of procedure.*
(7) Periprocedural cranial neuropathy noted within 30 days of procedure.
(8) Other complications of the procedure which were classified as: (a) myocardial infarction; (b) major, requiring additional therapy or prolonging admission or which were fatal; (c) minor.
(9) The combined outcome of death and neurological complications (stroke and cranial neuropathy) within 30 days of treatment.*
(10) The combined outcome death, neurological complications and vascular complications within 30 days of treatment.*
(11) Restenosis rate resulting in a recurrent carotid stenosis equivalent to greater than 70% by the NASCET method (NASCET 1998), determined by Doppler, catheter angiography, or magnetic resonance angiography at defined intervals. Restenoses were classified as: (a) symptomatic; (b) asymptomatic.
(12) In patients unsuitable for surgery, stroke in any territory during follow up after the initial 30-day period: (a) disabling; (b) non-disabling.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Stroke Group trials register, which was last searched by the Review Group Co-ordinator in March 2007. In addition, we searched the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 1, 2007), MEDLINE (1950 to March 2007), EMBASE (1980 to March 2007) and Science Citation Index (1945 to March 2007). We used the following search strategy for MEDLINE (Ovid) and adapted it for the other databases.

1. carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/
2. carotid arteries/ or carotid artery, common/ or carotid artery, external/ or carotid artery, internal/
3. constriction, pathologic/
4. 2 and 3
5. (carotid adj5 (stenosis or thrombo$ or disease$ or narrow$ or plaque$ or arterioscler$ or atheroscler$)).tw.
6. 1 or 4 or 5
7. angioplasty/ or angioplasty, balloon/ or angioplasty, balloon, laser-assisted/
8. Balloon Dilatation/
9. Stents/
10. (angioplasty or stent$ or endovascular).tw.
11. (balloon adj5 (dilat$ or catheter$)).tw.
12. ((endoluminal or transluminal) adj5 repair$).tw.
13. 7 or 8 or 9 or 10 or 11 or 12
14. 6 and 13
15. Randomized Controlled Trials/
16. random allocation/
17. Controlled Clinical Trials/
18. control groups/
19. clinical trials/ or clinical trials, phase i/ or clinical trials, phase ii/ or clinical trials, phase iii/ or clinical trials, phase iv/
20. double-blind method/
21. single-blind method/
22. Therapies, Investigational/
23. Research Design/
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. clinical trial.pt.
27. random$.tw.
28. (controlled adj5 (trial$ or stud$)).tw.
29. (clinical$ adj5 trial$).tw.
30. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)).tw.
31. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.

32. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
33. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
34. (coin adj5 (flip or flipped or toss$)).tw.
35. latin square.tw.
36. versus.tw.
37. controls.tw.
38. or/15-37
39. 14 and 38
40. limit 39 to humans

In an effort to identify further published, unpublished and ongoing trials we searched reference lists of relevant articles, and contacted individuals active in the field.

METHODS OF THE REVIEW

We identified and assessed published and unpublished trials; one review author (JE) selected trials for inclusion and one review author double checked the extracted data (RF). We identified data in published articles and sought additional information from the principal investigators of the included trials.

We planned to extract the following data:
(1) the method of randomisation and whether the randomising doctor was blinded to the treatment allocated;
(2) the number of patients originally allocated to each treatment group to allow an intention-to-treat analysis;
(3) the method of measuring outcome and whether outcome assessment was independent or blinded or both;
(4) the number of exclusions and losses to follow up;
(5) intervention characteristics;
(6) outcome measures as defined above.

We also intended to extract the following data to allow a number of subgroup analyses:
(1) the number of patients given antiplatelet or anticoagulant drugs within the treatment period;
(2) the proportion of symptomatic versus asymptomatic patients in each treatment group;
(3) the degree of baseline stenosis in each treatment group;
(4) stents versus no stents and the use of protection device versus no protection device.

We tested heterogeneity among trial results using a standard chi-squared test and we chose P = 0.1 as the level of significance. We reported the results as odds ratios (OR) (that is, the odds of an unfavourable outcome in patients treated by endovascular intervention compared to the corresponding odds in patients treated surgically or medically) with a 95% confidence interval (CI), which we calculated using the Peto fixed-effect method. In view of expected heterogeneity between trials, we also calculated the odds ratio using the Mantel-Haenszel random-effects model. We chose P = 0.05 as the level of significance.

DESCRIPTION OF STUDIES

To date we have found seven completed randomised controlled trials comparing endovascular treatment of carotid stenosis with surgery or with medical care, involving 941 patients, that fulfilled the inclusion criteria (BACASS 2006; Beijing 2003; CAVATAS-CEA 2001; CAVATAS-MED 2007; Kentucky 2001; Kentucky 2004; TESCAS-C 2006). In addition, there were five further randomised trials comparing carotid angioplasty and stenting with surgery which were stopped early and included 2286 patients (EVA-3S 2006; Leicester 1998; SAPPHIRE 2004; SPACE 2006; Wallstent 2001).

The Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS) finished randomising patients in July 1997, having enrolled 550 patients. Analysis of the data on 505 patients with carotid artery stenosis suitable for surgery was published in 2001 (CAVATAS-CEA 2001). The results of endovascular compared to medical treatment in 40 patients with carotid stenosis not suitable for surgery were presented in 2007 (CAVATAS-MED 2007).

A single centre trial comparing carotid endarterectomy with carotid angioplasty and stenting in symptomatic patients randomised 104 patients between the two treatment arms, and data from the study were published in 2001 (Kentucky 2001), and from the same group a single centre trial comparing endarterectomy with stenting in asymptomatic patients randomised 85 patients between the two treatment arms (Kentucky 2004).

A single centre trial conducted in China compared carotid stenting with medical care in patients with high grade bilateral carotid stenosis and enrolled 21 patients. The results were published in 2003 (Beijing 2003).

A singe centre trial from Basel, Switzerland, randomised a total of 20 patients to compare carotid endarterectomy and endovascular treatment (BACASS 2006).

A multicentre trial from China reported the results of 166 patients randomised between carotid stenting and surgery for symptomatic carotid artery stenosis in 2006 (TESCAS-C 2006).

A trial of endovascular treatment versus surgery was started at Leicester Royal Infirmary, UK, but was stopped after 23 patients had been randomised to treatment. Only 17 of the randomised patients had received their allocated treatment at the time the trial was suspended (Leicester 1998). Ten carotid endarterectomies proceeded without complication but five of the seven patients who underwent endovascular treatment had a stroke. Three patients were excluded from the trial after randomisation (one patient, due to receive surgery, occluded the carotid artery asymptomatically before

admission and two patients, one each for endovascular treatment and surgery, refused to undergo their allocated treatment after admission. The final three patients (all for endovascular treatment) were awaiting admission when the trial was stopped.

A multicentre randomised trial of carotid stenting versus endarterectomy in the USA was also stopped early after enrolling 219 patients. In an abstract from the 2001 International Stroke Conference, the 30-day periprocedure complication rate (any stroke or death) was reported to be significantly higher in the stented group than in those that underwent carotid endarterectomy (12.1% versus 4.5%, P = 0.049) (Wallstent 2001). Further results from this trial have not been published to date.

A randomised study of carotid stenting, with an Angioguard XP emboli protection guidewire, versus surgery for carotid artery stenosis has enrolled 334 high-surgical-risk patients and published its results in 2004 (SAPPHIRE 2004). The trial was terminated early because of a drop in recruitment numbers in 2002.

A multicentre trial comparing carotid endarterectomy and stenting randomised 1183 patients. The results of the 30-day post-treatment period were published in 2006 (SPACE 2006). The trial stopped randomisation after a futility analysis.

A multicentre trial comparing carotid endarterectomy to carotid stenting was started in France. The trial was stopped after 527 patients had been enrolled due to safety and futility concerns. The Safety Committee recommended stopping the trial, because the 30-day risk of any stroke or death was significantly higher after stenting (9.6%) than after endarterectomy (3.9%) (EVA-3S 2006).

We are aware of two trials of endovascular treatment versus endarterectomy in symptomatic patients that are in progress, one in the USA (CREST) and one recruiting worldwide (ICSS). CREST is also enrolling asymptomatic patients. We are aware of two trials of endovascular treatment versus endarterectomy in asymptomatic patients in progress (ACT I; Agostoni). A third trial in asymptomatic patients is about to start (Asymptomatic Carotid Stenosis Trial-2) (ACST-2), and a fourth trial in asymptomatic patients is being planned in Germany (Link 2000).

METHODOLOGICAL QUALITY

Twelve trials have been included, dating from 1998 to 2007. Due to study design and the nature of the interventions, health workers, patients and assessors were not blinded to treatment or outcome in any of the trials. Moreover, patients treated by carotid endarterectomy are often managed post-operatively on surgical wards where minor neurological events may be missed or misinterpreted. Analyses restricted to disabling stroke or death are likely to be the least affected by this bias. Transient ischaemic attacks were excluded from the analysis because they are likely to be the most affected by this bias.

Centre and patient requirements

CAVATAS is an international multicentre study and incorporated two separate trials of the treatment of carotid stenosis. Long-term follow up (more than five years) continued up to 2007. Each centre had to have a neurologist or physician interested in vascular disease to follow up patients, an experienced vascular surgeon to perform all endarterectomies and either a vascular radiologist with angioplasty experience or an interventional neuroradiologist to perform carotid angioplasty and stenting (CAVATAS-CEA 2001). In the first trial (CAVATAS-CEA 2001), patients with symptomatic or asymptomatic carotid stenosis with any degree of stenosis who were equally suitable for endovascular treatment or surgery and provided the clinician was substantially uncertain about best treatment could be randomised. Surgery could be done using any acceptable technique (e.g. local or general anaesthetic, shunt or no shunt). All endovascular techniques were allowed (e.g. balloon angioplasty or stenting).

If the patient was unsuitable for surgery (for example because of unacceptably high anaesthetic risk factors) randomisation in the second trial (CAVATAS-MED 2007) was between endovascular treatment and medical care. The number of patients randomised in this arm was small and the data were presented in 2007 (CAVATAS-MED 2007).

The Kentucky study was a single centre randomised trial comparing carotid angioplasty and stenting with carotid endarterectomy (Kentucky 2001). It included patients experiencing symptoms or signs or both of cerebral ischaemia confined to the ipsilateral carotid artery within the previous three months and with an ipsilateral stenosis of greater than 70%.

Conducted by the same group, the second Kentucky study was also a single centre randomised trial comparing carotid angioplasty and stenting with carotid endarterectomy in asymptomatic patients (Kentucky 2004). The stenosis had to be more than 80%, documented by digital subtraction angiography.

Patients with severe carotid stenosis on one side and contralateral occlusion as demonstrated on duplex ultrasound or cerebral angiography were eligible to join the single centre study from China (Beijing 2003). No further details on centre or patient requirements were provided.

TESCAS-C 2006, also from China, enrolled patients with severe symptomatic or asymptomatic carotid artery stenosis. No further details were provided. The original study was published in Chinese with only the abstract available in English. Data were extracted from the abstract, details of the trial were not available because the authors of the review were unable to obtain a translation of the article in time for this review.

The single centre BACASS trial randomised patients with symptomatic carotid stenosis greater 70% and suitable for both surgery and stenting, who were willing to participate and available for at least two years of follow up to undergo either surgery or stenting

(BACASS 2006). The results have been presented at a Swiss conference and await publication.

In the single centre Leicester study, all patients with a symptomatic severe internal carotid artery stenosis (greater than 70%) who consented to be included in the study were randomised (Leicester 1998). Surgery was performed by a consultant vascular surgeon, using a standardised operative technique. Endovascular treatment of the stenosis was performed by a single consultant vascular radiologist, using a stent in all cases.

Another multicentre trial randomised patients with symptomatic internal carotid artery stenosis (transient ischaemic attack or completed stroke within 120 days of randomisation, with at least 60% stenosis) to either stenting or carotid endarterectomy (Wallstent 2001). The study was designed to demonstrate the safety and efficacy of endovascular treatment versus carotid endarterectomy. Each participating centre had to demonstrate that it had the personnel, technical experience and infrastructure to support the study, including an interventionalist, surgeon, neurologist, experienced ultrasonographer and study co-ordinator.

A multicentre randomised trial based in the USA compared stenting with cerebral protection to endarterectomy in high surgical risk patients (SAPPHIRE 2004). Patients had to have a greater than 50% symptomatic stenosis (or greater than 80% asymptomatic stenosis) plus one or more comorbidity conditions (e.g. congestive heart failure, left ventricular dysfunction, recent myocardial infarction or severe pulmonary disease). A consensus was reached by a team consisting of a neurologist, surgeon and interventionalist as to whether the patient should be randomised between stenting and surgery (334 patients randomised). Patients who were refused by the surgeon were entered in to a stenting registry (406 patients) and those refused by the interventionalist were entered in to a surgical registry (seven patients).

Patients in the multicentre randomised trial EVA-3S 2006 had to be symptomatic within 120 days before enrolment with a stenosis of 60% to 99%, using the NASCET criteria (NASCET 1998). Patients were excluded from the study if they had made no useful recovery from their stroke as expressed by a modified Rankin score of three or more. Vascular surgeons had to have performed at least 25 endarterectomies in the year before joining the trial, the interventional physician had to have performed at least 12 carotid stenting procedures or at least 35 stenting procedures of the supra-aortic trunks including five carotid stents. Less-experienced interventional physicians were still allowed to join but had to perform all procedures under supervision until sufficient numbers of procedures according to the predefined protocol had been achieved. The trial briefly interrupted randomisation and the compulsory use of cerebrovascular protection devices in the endovascular arm was introduced.

SPACE 2006 is another European multicentre randomised trial. All centres had a multidisciplinary team of neurologists, vascular surgeons, and interventionalists in place. Interventionalists had to show proof of at least 25 successful consecutive percutaneous transluminal angioplasty or stent procedures. Vascular surgeons had to provide documented proof of 25 consecutive carotid endarterectomy procedures and provide mortality and morbidity rates for those procedures. Patients were eligible if they had neurological or ocular symptoms such as amaurosis fugax, hemispherical transient ischaemic attack, or complete stroke in the previous 180 days and ipsilateral carotid stenosis greater than 70% on duplex ultrasound.

Randomisation method

The method of randomisation was given for nine trials (BACASS 2006; Beijing 2003; CAVATAS-CEA 2001; CAVATAS-MED 2007; EVA-3S 2006; Leicester 1998; SAPPHIRE 2004; SPACE 2006; Wallstent 2001). For each of these nine trials, allocation concealment was judged to be adequate. In two trials, patients were randomly assigned treatment by telephone call or fax to the randomisation centre at the Clinical Trial Service Unit in Oxford UK (CAVATAS-CEA 2001; CAVATAS-MED 2007). Patients were randomly assigned by computer with a minimisation algorithm, taking account of centre and timing of symptoms. In the Wallstent 2001 study, randomisation of patients was performed using a computerised number generator. Assignment was provided in sequentially-numbered sealed envelopes. Each centre was assigned its own randomisation sequence. One trial allocated treatment on a consecutive basis from 300 random treatment methods numbered and sealed in opaque envelopes (Leicester 1998). BACASS 2006 also used a sealed envelope method for randomising patients. One trial used a random number table for randomisation but it is not clear from the paper if allocation was concealed (Beijing 2003). One trial used a pseudo-random number generator, distributed by an automated, centralised telephone response system (SAPPHIRE 2004). In one trial a computer-generated sequence involving randomised blocks of two, four, or six patients (EVA-3S 2006) was used and one trial used a computer-generated random allocation schedule (SPACE 2006).

We were unable to obtain detailed information regarding method of randomisation from the authors of three trials (Kentucky 2001; Kentucky 2004; TESCAS-C 2006) and therefore allocation concealment was judged to be unclear.

Follow up

In two trials, patients were followed up one month after treatment and then again at six months, 12 months and yearly following randomisation by the independent participating neurologist or clinician who was not directly involved in treatment (CAVATAS-CEA 2001; CAVATAS-MED 2007). The mean duration of follow up was 1.95 years at the time the data on endovascular treatment versus surgery was published (CAVATAS-CEA 2001) and 4.3 years for the data on endovascular versus medical treatment (CAVATAS-MED 2007). BACASS 2006 followed up patients one month, six months, 12 months after treatment, and yearly thereafter. The mean duration of follow up was given as 48.1 months for the

stenting arm and 43.5 months for the surgery arm of the trial. In the Leicester 1998 study, patients were re-examined by a consultant neurologist 24 hours after intervention. The neurologist re-assessed all patients at 30 days. Patients were followed up for two years. In one trial, patients were assessed by an independent neurologist at 24 hours post procedure and again at one, three, six, 12 and 24 months (Kentucky 2001). Kentucky 2004 followed patients up at 48 hours post procedure and again at one, three, six, 12, 24, and 48 months by an independent neurologist. Patients had a neurological assessment (National Institutes of Health Stroke Scale: NIHSS) performed 24 hours post procedure, then again at six and 12 months, then annually in the Wallstent 2001 trial. Follow up in the SAPPHIRE trial was at 30 days, six months, and at one year (SAPPHIRE 2004). Follow up in the EVA-3S trial was at 48 hours, 30 days, six months after treatment and every six months thereafter (EVA-3S 2006). In the SPACE trial follow up was scheduled after seven and 30 days and six, 12, and 24 months after treatment (SPACE 2006). In one study, follow up was conducted at 30 days and one year after treatment (TESCAS-C 2006). In another study from China, results at 1.5 years after treatment were reported (Beijing 2003).

Assessment of functional outcome

The assessment of functional outcome was by the Oxford Handicap Stroke score in Leicester 1998. Two trials used more than one scale to measure outcome: in Wallstent 2001 the Barthel, Rankin and NIHSS scores were used, and in Kentucky 2001 the Barthel and modified Rankin scores were used. BACASS 2006 used the NIHSS to assess functional outcome and classify cerebrovascular events. In CAVATAS-CEA 2001, strokes were only counted if they lasted more than seven days, CAVATAS-MED 2007 included strokes of any duration. Strokes were classified as disabling if the patient required help undertaking activities of daily living for more than 30 days and non-disabling if help was not required at 30 days. Method of assessment of functional outcome in Beijing 2003, EVA-3S 2006, Kentucky 2004, SAPPHIRE 2004, SPACE 2006, and TESCAS-C 2006 was unspecified.

Analysis of data

Four trials specified that analysis was by intention to treat (BACASS 2006; CAVATAS-CEA 2001; CAVATAS-MED 2007; SPACE 2006), one trial analysed 30-day results on an 'on treatment' basis and six months results on an intention-to-treat basis (EVA-3S 2006). One trial reported results from patients who underwent treatment only (Leicester 1998). It was possible to perform intention-to-treat analysis on all trials as the number of patients originally allocated to each treatment was extracted and the outcome of all patients (including those who did not undergo treatment within the trial) was known. Although SAPPHIRE also included asymptomatic patients and reported a cumulative incidence of the primary endpoint in these patients, an analysis of this group was not possible since the details of outcome events in asymptomatic patients were not provided (SAPPHIRE 2004).

RESULTS

Please see 'Analyses'. Note that in each figure, the overall odds ratio appears at the bottom. Except where stated, the analysis was performed combining treatment of both symptomatic and asymptomatic stenosis.

01: Endovascular treatment or carotid endarterectomy

Comparisons 01.01 and 01.02: Death or any stroke within 30 days of procedure

Data on death or stroke occurring within the first 30 days following the procedure were available for eight included studies, with no significant heterogeneity among trials (chi squared 11.81, P = 0.11). There was a significant excess of death or strokes in the carotid stenting group, fixed-effect OR (endovascular:surgery) 1.39, 95% CI 1.05 to 1.84, P = 0.02. When the random-effects model was used, the excess of death or strokes in the stenting group was not statistically significant, OR (endovascular:surgery) was 1.44, 95% CI 0.91 to 2.26, P = 0.12.

Comparisons 01.03 and 01.04: Death or disabling stroke within 30 days of procedure

Seven trials distinguished among disabling and non-disabling stroke. There was no significant heterogeneity between trials (chi squared 5.16, P = 0.40). There was no significant excess of death or disabling stroke in patients treated endovascularly or with surgery (fixed-effect OR 1.22, 95% CI 0.83 to 1.79, P = 0.31. The random-effects model also showed no significant excess of death or disabling stroke in patients treated either endovascularly or with surgery (random-effects OR 1.20, 95% CI 0.80 to 1.80, P = 0.39).

Comparisons 01.05 and 01.06: Death within 30 days of procedure

No significant heterogeneity among trials was detected (chi squared 2.27, P = 0.69). The effect for death within 30 days of treatment was similar in both groups. (fixed-effect OR 0.99, 95% CI 0.50 to 1.97, P = 0.98, random-effects OR 1.00, 95 % CI 0.49 to 2.04, P = 0.99).

Comparisons 01.07 and 01.08: Stroke within 30 days of procedure

Heterogeneity among trials was significant (chi squared 10.65, P = 0.06). In the fixed-effect model, the effect for stroke within 30 days of treatment favoured surgery significantly (OR 1.40, 95% CI 1.02 to 1.91, P = 0.04). In the random-effects model, however, this significance disappeared (OR 1.47, 95% CI 0.81 to 2.67, P = 0.20).

Comparisons 01.09 and 01.10: Cranial neuropathy within 30 days of procedure

Data are available for six trials with no significant heterogeneity among the trials (chi squared 1.87, P = 0.60). As expected, there was a significant difference in the rate of cranial neuropathy in patients treated endovascularly compared with those treated surgically, (fixed-effect OR 0.07 95% CI 0.03 to 0.20, P < 0.00001,

random-effects OR (endovascular:surgery) 0.09, 95% CI 0.04 to 0.25, P < 0.00001).

Comparisons 01.11 and 01.12: Death or neurological complication within 30 days of procedure

Data are available for six trials with significant heterogeneity among the trials (chi squared 11.06, P = 0.05). There was a significant excess of events in the surgery group using the fixed-effect model (OR 0.62, 95% CI 0.45 to 0.86, P = 0.05). However, in the random-effects model there was no significant difference between the groups (OR 0.60, 95% CI 0.31 to 1.17, P = 0.13).

Comparisons 01.13 and 01.14: Death or stroke or myocardial infarction within 30 days of procedure

Data are available from six studies. One trial (SAPPHIRE 2004) included Q wave and non-Q wave myocardial infarctions in the analysis. The chi-squared test revealed significant heterogeneity among the trials (chi squared 12.90, P = 0.02). There was no significant difference in the rate of death or stroke or myocardial infarction using the fixed-effect model (OR 1.11, 95% CI 0.77 to 1.60, P = 0.57) or the random-effects model (OR (endovascular:surgery) 1.06, 95% CI 0.48 to 2.38, P = 0.88).

Comparisons 01.15 and 01.16: Death or neurological complications or vascular complications within 30 days of procedure

Combined analysis of death, neurological, or vascular complications was possible in six studies, with significant heterogeneity among the trials (chi squared 41.46, P < 0.00001). In the fixed-effect model, endovascular treatment was similar to surgery (OR (endovascular:surgery) 0.87, 95% CI 0.67 to 1.14, P = 0.32) as well as in the random-effects model (OR (endovascular:surgery) 1.16, 95% CI 0.41 to 3.24, P = 0.78)

Comparisons 01.17 and 01.18: Death or any stroke during follow up (including the initial 30-day post-treatment phase)

Data are available from six trials, but events are given for different time points. Two trials presented six months' results, two trials presented outcome events at 12 months after randomisation, and one trial each at two years and three years of follow up. There was significant heterogeneity among the trials (chi squared 14.05, P = 0.02). Overall, there was no significant excess in deaths or any strokes in long-term follow up in the endovascular group, fixed-effect OR (endovascular:surgery) 1.13, 95% CI 0.81 to 1.58, P = 0.47. The random-effects OR was 1.18, 95% CI 0.61 to 2.28, P = 0.62.

Comparisons 01.19 and 01.20: Death during follow up (excluding the initial 30-day post-treatment phase)

There was no significant heterogeneity among the three trials included in this analysis (chi squared 1.27, P = 0.53). Overall, the effect for death during follow up was not significantly different comparing endovascular treatment and surgery (fixed-effect OR 0.58, 95 % CI 0.30 to 1.13, P = 0.11, random-effects OR 0.57, 95% CI 0.29 to 1.12, P = 0.53).

Comparisons 01:21 and 01.22: Stroke during follow up (excluding the initial 30-day post-treatment phase)

In this analysis including the same three trials, heterogeneity among trials was not significant (chi squared 0.82, P = 0.36). The effect for stroke during follow up was similar (fixed-effect OR 1.00, 95% CI 0.47 to 2.14, P = 0.99, random-effects OR 0.99, 95% CI 0.46 to 2.14).

02: Endovascular treatment or medical care

Comparisons 02.01 and 02.02: Death or any stroke after 30 days of the procedure/randomisation

Data are only available from two very small studies (Beijing 2003; CAVATAS-MED 2007). There was significant heterogeneity between the trials (chi squared 3.30 P = 0.07). There was no significant difference in the occurrence of stroke or death after at least 31 days of follow up in the fixed-effect model (OR (endovascular:medical care) 0.39, 95% CI 0.14 to 1.14, P = 0.09) and the random-effects model (OR (endovascular:medical) 0.28, 95% CI 0.02 to 3.23, P = 0.30).

03: Endovascular treatment with or without protection

Comparisons 03.01 and 03.02: Death or any stroke within 30 days of procedure

Data from two trials are available, with significant heterogeneity between trials (chi squared 4.53, P = 0.03). There was no significant difference in death or any stroke between endovascular treatment with or without cerebral protection in the fixed-effect model (OR (protection:no protection) 0.77, 95% CI 0.41 to 1.46, P = 0.43). In the random-effects model, OR (protection:no protection) was 0.57, 95% CI 0.14 to 2.33, P = 0.43.

04: Endovascular treatment or carotid endarterectomy in asymptomatic patients

Comparisons 04.01 and 04.02: Stroke or death within 30 days of procedure

Data are available for two trials only. One trial did not report any stroke or death within 30 days and the test for heterogeneity was not applicable. The fixed-effect model showed no significant difference, fixed-effect and random-effects OR (endovascular:surgery) 1.06, 95% CI 0.16 to 6.94, P = 0.96.

We planned to analyse restenosis rates. However, data on the degree of residual stenosis or restenosis at one year was only available from two studies (BACASS 2006; CAVATAS-CEA 2001). In CAVATAS, one year after treatment, ipsilateral carotid stenosis of 70% to 99% was more common after endovascular treatment than carotid endarterectomy (14% compared to 4%, P < 0.001) but no difference in the rate of ipsilateral stroke was noted in survival analysis up to three years after randomisation (CAVATAS-CEA 2001). In BACASS, one patient in both treatment arms showed a stenosis between 30% and 49% and one patient in the surgery arm showed a stenosis between 50% and 69% at two-year follow up (BACASS 2006). In the Kentucky 2001 study it was reported that the patency of treated arteries remained 'acceptable' after two years in both treatment groups and the average post angioplasty

and stenting stenosis decreased from a mean baseline stenosis of 82.4 +/- 7.1% to a mean of 5.0 +/- 2.7% (range 0% to 10%) (Kentucky 2001).

We planned to analyse the cause of heterogeneity between the trials. Unfortunately, not enough individual patient data was available for this review and there were too few trials to justify a further dividing into subgroups of the trials.

We planned to analyse whether there is a learning curve in carotid stenting. Since individual patient data were not available this was not possible. Instead we plotted the event rate for each trial over time. There appears to be no improvement in the event rate from trial to trial over time (Figure 01).

We planned to analyse subsequent ipsilateral stroke. It was not possible to extract this particular information from the publications and therefore, this analysis was not done.

DISCUSSION

Randomised controlled trials have shown that the addition of carotid endarterectomy to medical therapy is effective in reducing the risk of stroke among patients with carotid stenosis. Data from non-randomised studies suggest that carotid angioplasty and stenting may be performed with comparable risks and benefits. The purpose of this review was to determine whether evidence from randomised trials has shown that endovascular treatment of internal carotid artery stenosis might be an effective alternative to carotid endarterectomy.

Has endovascular treatment for carotid artery stenosis a significantly different risk of periprocedure stroke or death compared with surgery?

The meta-analysis showed that there was a significant difference in the risk of stroke or death between patients treated endovascularly and those treated with surgery using the fixed-effect model favouring surgery. The confidence interval for this result was wide. Calculating the odds ratio using a random-effects model, the statistical significance disappeared and the confidence interval increased even further. This reduces the weight that can be placed on these findings and suggest that the data are not very robust.

No significant difference in the risk of death or disabling stroke within 30 days of either procedure was found and again, the confidence intervals surrounding these results were wide. The effect for stroke within 30 days of procedure was significantly in favour of surgery using the fixed-effect model. In the random-effects model the significance disappeared, leaving the result less robust and less reliable. The effect for death within 30 days of treatment was similar in both groups.

Centres which took part in the trials had a specific interest in secondary prevention of stroke and care must be taken when extrapolating the data into routine clinical practice in less specialist centres. Furthermore, three included trials had been stopped early because of an excess event rate in the endovascular treatment group. Therefore, the overall result might be biased because of this and needs to be interpreted with caution.

The meta-analysis showed that there was a significant reduction in periprocedural cranial neuropathy in patients treated endovascularly compared with those who underwent carotid endarterectomy. Because cranial neuropathy can have potentially devastating consequences for the patient with problems swallowing and difficulties with speech, which could make artificial feeding necessary, the authors analysed a combined outcome of death and neurological complications within 30 days of procedure. In the fixed-effect model the estimated effect for this combined outcome significantly favoured endovascular treatment, but this was associated with significant heterogeneity and the statistical significance of the estimate changed from significant to non-significant when the random-effects model was used.

In their report, the authors of CAVATAS-CEA 2001 did not recommend that endovascular treatment should replace endarterectomy, since interpretation of the data is complicated by the wide 95% confidence intervals surrounding the 10% risk of stroke or death within 30 days of either procedure. The authors of Kentucky 2001 acknowledge that the study is limited by being single centre with a selected team experienced in management of cerebrovascular disease and performing endovascular procedures. Therefore they did not advocate that endovascular treatment replace carotid endarterectomy as a primary revascularisation procedure in patients with symptomatic carotid stenosis (Kentucky 2001). In SAPPHIRE 2004, the authors concluded that carotid artery stenting with cerebral protection devices was not inferior to carotid endarterectomy in high-risk patients. The authors of the Wallstent 2001 study conclude that carotid stenting was not equivalent to carotid endarterectomy in patients with symptomatic carotid artery stenosis. Leicester 1998 and BACASS 2006 constitute too small a sample to draw any firm conclusions in their own right but contribute to the meta-analysis.

The authors of SPACE 2006 concluded that equivalence of periprocedural risk of treating symptomatic carotid artery stenosis with endarterectomy and stenting remains unproven and the widespread use of carotid stenting was not justified. In EVA-3S 2006 it was concluded that in patients with symptomatic carotid artery stenosis greater than 60%, endarterectomy results in lower rates of stroke or death at 30 days and six months than stenting.

Is endovascular treatment for carotid artery stenosis as effective as surgery in preventing stroke in the long term?

At least one-year follow up data was only available from four trials (BACASS 2006; CAVATAS-CEA 2001; SAPPHIRE 2004; Wallstent 2001) and showed that there was no significant difference between the treatments in preventing death or neurological complications, but again the confidence interval is wide and there is significant heterogeneity between the trials. The effects for stroke

during follow up and death during follow up were similar in both groups.

Do the rates of vascular complications (myocardial infarction, pulmonary embolism, haematoma) differ between endovascular treatment and surgery?

There was no significant difference between endovascular treatment and surgery in terms of risk of any stroke, death or myocardial infarction at 30 days following the procedure. However, again the confidence interval was wide.

Since neurological complications of the intervention can lead to devastating consequences for the patients similar to vascular complications, an analysis was performed combining death, neurological or vascular complications within 30 days of procedure. This analysis showed that endovascular treatment was not significantly different from surgery in preventing these complications, but there was significant heterogeneity between the trials.

Does stenting with cerebral protection devices have a lower rate of treatment-related ischaemic events than stenting without cerebral protection devices?

Only two trials included data regarding the use of cerebral protection devices in their respective publication. It has to be noted that the use of protection devices was not allocated strictly randomly and selection bias may be operating. This may bias the assessment of the effect of protection devices and the authors refrain from drawing any conclusions from this subgroup analysis.

Is endovascular treatment safe in asymptomatic patients?

Only two trials allowed for analysing death or stroke within 30 days of treatment and numbers available for analysis were very small. No conclusion can be drawn from this analysis.

For each of the estimates of effect on each of the major clinical outcomes (with the exception of cranial neuropathy, this clearly showed a benefit of endovascular treatment) one cannot exclude a moderately large advantage or a moderately large disadvantage of endovascular over surgical treatment. Hence, further larger scale trials are justified to provide more precise estimates.

There are several possible reasons for the heterogeneity of data between trials. Firstly the endovascular technique used was not the same for all the trials. We have included in the meta-analysis results obtained at the early stage of development of a technique using devices no longer in widespread use and without cerebral protection (CAVATAS-CEA 2001; Kentucky 2001; Leicester 1998; Wallstent 2001). The results in the endovascular arm of SAPPHIRE were significantly better than those in the other studies and this may reflect improved technique and the use of a protection device. There is evidence from CAVATAS and case series that the 30-day morbidity rates improve with experience and the use of protection devices (Brown 2003; Roubin 2001).

There may also be significant heterogeneity between the baseline characteristics of the patients in the trials. In CAVATAS, 12% of patients in the endovascular group and 9% in the surgical group had no symptoms ipsilateral to the carotid artery stenosis within six months of randomisation (CAVATAS-CEA 2001). In SAPPHIRE, only 32% of patients in the stent group and 29% in the surgery group were symptomatic (SAPPHIRE 2004). The other trials only included symptomatic patients. In addition, patients were specifically selected if they were at high surgical risk in SAPPHIRE (SAPPHIRE 2004). Although the CAVATAS protocol did not specify high risk as an inclusion criterion, analysis of the baseline characteristics suggests that CAVATAS also selected a higher proportion of patients at high surgical risk compared to ECST and NASCET (CAVATAS-CEA 2001; ECST 1998; NASCET 1998).

Heterogeneity may arise because we have analysed completed and stopped trials. Three of the included studies were stopped prematurely because of concerns over the safety of stenting. One trial was stopped after a total of 219 patients had been enrolled (Wallstent 2001). In this study the primary end point was the cumulative occurrence of ipsilateral stroke, procedure-related death or vascular death within one year. It was reported that the primary endpoint rate after approximately one year was 12.1% in the stent group and 3.6% in the endarterectomy group (P = 0.022) and that the 30-day periprocedure complication (stroke or death) rate was 12.1% for stenting and 4.4% for endarterectomy (P = 0.049). The decision to terminate the study was based on the data and a futility analysis (Wallstent 2001). However, it has been reported that at a meeting of the American Stroke Association, the trial was criticised firstly because it was stopped by the sponsor, rather than by the Data Safety and Monitoring Board, even though the outcome in all patients had not been validated, and secondly because the competence and experience of those undertaking stenting was questioned (Am Stroke Assoc). As we have not yet obtained detailed data for this study we can make no further assessment of its quality at this time. Leicester 1998 was suspended after referral to the Data Monitoring Committee who invoked the stopping rule. A total of 17 patients had received their allotted treatment. Five of the seven patients undergoing endovascular treatment had strokes (three of which were disabling at 30 days) compared to 10 uncomplicated carotid endarterectomies (P = 0.0034). No patients in either group suffered cranial neuropathy. The investigators subsequently felt that the trial could not be restarted even in an amended form primarily because of difficulties with informed consent.

No evidence on long-term efficacy is available from any of the studies, but given at least similar safety and the potential advantages outlined previously, it seems ethical that randomised trials comparing angioplasty and stenting with surgery should continue to recruit patients. The trials should seek to resolve current uncertainties, including whether the high restenosis rate quoted in CAVATAS-CEA 2001 following endovascular treatment is generally representative, and whether restenosis leads to recurrent stroke. This is especially important with conflicting results from the published literature and the fact that five trials contributing to the meta-analysis have been terminated early.

Published results from three randomised trial were found concerning the risks and benefits of carotid angioplasty and stenting compared to carotid endarterectomy in asymptomatic patients. In asymptomatic patients, endovascular treatment had significantly fewer deaths, strokes and myocardial infarctions within 30 days of procedure and ipsilateral strokes or deaths from any neurological cause during follow up. However, this subgroup analysis is based on a small number of patients and the results are not very robust with a wide confidence interval.

Only two very small trials were identified comparing carotid stenting with best medical care in patients not well enough to undergo surgery. Although presented here, these results do not justify any conclusion.

AUTHORS' CONCLUSIONS

Implications for practice

The data available are limited and conflicting. The overall estimates of effect were both imprecise and difficult to interpret because of substantial heterogeneity among the trials, probably because of different patients, endovascular procedures, and duration of follow up. The data are therefore insufficient to support a change from routine clinical practice in the types of patient for which carotid endarterectomy is the current standard treatment.

Implications for research

The data support the continuing inclusion of patients within randomised clinical trials between endovascular and surgical treatment for carotid artery stenosis. Randomisation should continue in the ongoing trials and centres not participating in the large multicentre trials should be encouraged to randomise suitable patients locally. This could contribute to any future meta-analysis.

POTENTIAL CONFLICT OF INTEREST

The review authors are involved with two completed trials (CAVATAS-CEA 2001; CAVATAS-MED 2007) and one on-going trial (ICSS) included in this systematic review.

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**Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**BACASS 2006**
Methods	Single centre, randomised by sealed envelopes Follow up at 1, 6, 12 months and yearly thereafter Conducted between 1998 and 2002
Participants	20 patients with symptomatic carotid stenosis > 70% Patients were excluded if they were unwilling to participate, unavailable for at least 2 years for follow up, or presented with ICA occlusion or free floating thrombus
Interventions	Patients were assigned to either stenting or CEA
Outcomes	Primary outcome measures were periprocedural stroke, death or MI Secondary outcome measures were peri-interventional TIA, haematoma, cranial nerve paralysis and LOS For the follow up, secondary outcome measures were patency of the treated vessel and stroke prevention related to the treated side
Notes	
Allocation concealment	A – Adequate

Study	**Beijing 2003**
Methods	Single centre, randomised by random number table Follow up at 1.5 years after treatment
Participants	21 patients with severe bilateral carotid stenosis
Interventions	Patients assigned to carotid stenting or medical care alone
Outcomes	Cerebrovascular symptoms since start of treatment
Notes	
Allocation concealment	B – Unclear

Study	**CAVATAS-CEA 2001**
Methods	Multicentre, central telephone randomisation Follow up at 1, 6, 12 months then annually by independent neurologist Intention-to-treat analysis
Participants	505 patients of any age with symptomatic or asymptomatic carotid artery stenosis suitable for surgery or endovascular treatment

Characteristics of included studies (*Continued*)

	Patients unsuitable for surgery because of medical or surgical risk factors, who were unable to give informed consent, unwilling to undergo either procedure or if they had a disabling stroke with no useful recovery of function within the region supplied by the treatable artery were excluded 40 patients with carotid artery stenosis who were not suitable for surgery were randomised to receive best medical treatment alone or in combination with endovascular treatment (see CAVATAS-MED 2007)
Interventions	Patients fit for surgery assigned to endovascular treatment or CEA Those unfit for surgery assigned to endovascular treatment or medical care Patients in the endovascular group given minimum 150 mg aspirin daily for at least 24 hours prior to the procedure Heparin given at the time of procedure and for the following 24 hours
Outcomes	The primary outcome was specified as disabling stroke or death within 30 days of treatment The secondary outcome measure was ipsilateral stroke lasting more than 7 days
Notes	
Allocation concealment	A – Adequate

Study	**CAVATAS-MED 2007**
Methods	Trial methods were the same as in CAVATAS-CEA 2001
Participants	40 patients with carotid artery stenosis who were not suitable for surgery were randomised to receive best medical treatment alone or in combination with endovascular treatment
Interventions	Patients were assigned to receive either endovascular or medical treatment Patients in the endovascular group given minimum 150 mg aspirin daily for at least 24 hours prior to the procedure Heparin given at the time of procedure and for the following 24 hours
Outcomes	The primary outcome was specified as disabling stroke or death within 30 days of treatment The secondary outcome measure was ipsilateral stroke lasting more than 7 days
Notes	
Allocation concealment	A – Adequate

Study	**EVA-3S 2006**
Methods	Multicentre, randomisation by computer-generated sequence, involving randomised blocks of 2, 4, or 6 patients stratified by centre and degree of stenosis Follow up at 48 hours, 30 days and 6 months after treatment
Participants	527 patients with symptomatic carotid stenosis between 60% and 99% within 120 days before enrolment Patients had to be fit to undergo either surgery or stenting Patients with Rankin score > 3, severe tandem lesions, previous revascularisation of the symptomatic stenosis were excluded
Interventions	Patients assigned to stenting or surgery After the study was started, use of cerebral protection devices became mandatory in the stenting group It was recommended to use between 100 mg and 300 mg of aspirin daily in all patients, and 75 mg clopidogrel or 500 mg ticlopidine for 3 days before and 30 days after stenting
Outcomes	Any stroke or death within 30 days after treatment MI, TIA, cranial nerve injury, major local complications, and systemic complications within 30 days after treatment Any stroke or death within 30 days of treatment plus ipsilateral stroke, any stroke, or any stroke or death within 31 days through end of follow up
Notes	Study terminated prematurely due to safety and futility concerns
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Kentucky 2001**
Methods	Single centre, randomised (method not known) Follow up at 1, 3, 6, 12 and 24 months
Participants	104 patients with symptomatic carotid stenosis > 70% (events within 3 months of evaluation) Patients with NIH score > 4, cardiac arrhythmia, sensitivity to aspirin, other antiplatelets or heparin or with recent intracranial haemorrhage were excluded
Interventions	Patients assigned to carotid angioplasty and stenting or surgery All patients received 325 mg aspirin and 75 mg clopidogrel before the procedure and patients in the endovascular group received heparin at the time of the procedure
Outcomes	Death and stroke following the procedure Secondary measures: restenosis rate, length of hospital stay, and relative costs of each procedure
Notes	
Allocation concealment	B – Unclear

Study	**Kentucky 2004**
Methods	Single centre, randomised (method not known) Follow up at 1, 3, 6, 12, 24, and 48 months
Participants	85 patients with asymptomatic carotid stenosis > 80% documented by digital subtraction angiography
Interventions	Patients assigned to carotid angioplasty and stenting or surgery All patients received 325 mg aspirin and 75 mg clopidogrel before the procedure and patients in the endovascular group received heparin at the time of the procedure
Outcomes	Death and stroke following the procedure Secondary measures: perception of perioperative pain, length of hospital stay, and relative costs of each procedure
Notes	
Allocation concealment	B – Unclear

Study	**Leicester 1998**
Methods	Single centre, randomisation by sequentially numbered sealed opaque envelopes containing treatment methods 2 patients randomised in the surgical arm were not included in the analysis: 1 patient spontaneously occluded the relevant ICA, the other patient refused to undergo treatment after admission 4 patients in the endovascular group were not included in the analysis: 1 refused treatment after admission, the other 3 were waiting admission for treatment when the trial was suspended Follow up at 24 hours and 30 days
Participants	23 patients with symptomatic carotid stenosis of 70% to 99% assigned to optimal medical treatment with either CEA or carotid angioplasty and stenting Patients with asymptomatic disease, symptomatic 0% to 69% stenosis, crescendo TIA or stroke in evolution and vertebrobasilar or non-hemispheric symptoms were excluded
Interventions	Patients assigned to CEA or carotid angioplasty and stenting Aspirin therapy was not stopped before treatment All patients received intravenous heparin at the time of the procedure In addition, any patient with evidence of more than 25 emboli during any 10 minute period of transcranial doppler monitoring was given an incremental intravenous infusion of dextran 40
Outcomes	Death and ipsilateral stroke at 30 days post procedure Secondary outcome included median number of cerebral emboli detected on transcranial doppler
Notes	Terminated prematurely due to safety concerns

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**SAPPHIRE 2004**
Methods	Multicentre, randomisation by pseudo-random-number generator and distributed by an automated, centralised telephone response system
Participants	334 patients with > 50% symptomatic carotid stenosis with one or more comorbidity criteria (i.e. high surgical risk group)
Interventions	Patients assigned to CEA or carotid stenting with cerebral protection All patients received aspirin prior to and following treatment In addition, the stented group received clopidogrel pre and post procedure All patients were given heparin during the procedure
Outcomes	Death, any stroke, and MI within 30 days of procedure Death of ipsilateral stroke between 31 days and 1 year post procedure plus 30 day major adverse clinical event rate
Notes	Terminated prematurely due to a drop in randomisation
Allocation concealment	A – Adequate

Study	**SPACE 2006**
Methods	Multicentre, randomised by computer-generated random allocation schedule Follow up at 7 and 30 days, and after 6, 12, and 24 months
Participants	1183 patients with symptomatic carotid stenosis > 70% on duplex ultrasound in the previous 180 days of enrolment Patients had to be older than 50 years
Interventions	Patients assigned to stenting or CEA, patients had to be treated within 14 days of randomisation All patients in the stenting group had to be given 100 mg aspirin plus 75 mg clopidogrel daily for 3 days before and 30 days after treatment CEA patients had to be given 100 mg aspirin before, during, and after surgery
Outcomes	Ipsilateral stroke or death of any cause between randomisation and 30 days after treatment Disabling ipsilateral stroke or death from any cause since randomisation Any stroke up to days after treatment Procedural failure including inability to treat with allocated technique, remaining stenosis > 50% or vessel occlusion assessed up to 30 days after treatment
Notes	Terminated prematurely after futility analysis
Allocation concealment	A – Adequate

Study	**TESCAS-C 2006**
Methods	Multicentre, randomised (method not known) Follow up at 1 and 6 months
Participants	166 patients with severe symptomatic or asymptomatic carotid stenosis
Interventions	Patients assigned to carotid stenting or CEA
Outcomes	Death, stroke or MI at 30 days after treatment Death or ipsilateral stroke between 31 days and 6 months after treatment
Notes	Publication in Chinese with English abstract only Data presented in review taken from abstract
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	Wallstent 2001
Methods	Multicentre, randomisation performed using a computerised random number generator, assignment by sequentially-numbered sealed envelopes; each centre assigned its own sequence
Participants	219 patients aged > 18 years with symptomatic (> 60%) ICA stenosis with events in the last 120 days were included Patients with ipsilateral arterial stenosis greater than the target lesion, NIH score > 15, Rankin score > 2, Barthel score < 60, AF, LV thrombus, endocarditis, heparin sensitivity, not suitable for surgery, moderate or severe dementia, bleeding diathesis or coagulopathy, history of intracranial haemorrhage were excluded
Interventions	Patients assigned to CEA or endovascular treatment All patients in the endovascular group given aspirin 325 mg bd and ticlopidine 250 mg bd for 3 days prior to treatment Following carotid angioplasty and stenting all patients treated with aspirin and ticlopidine for 4 weeks then aspirin only (325 mg bd) For the CEA group use of ticlopidine was optional All surgical patients were treated with aspirin 325 mg bd following the procedure for the duration of the study
Outcomes	The primary endpoint for the study was the cumulative occurrence of any ipsilateral stroke, periprocedure death within 30 days or vascular death within one year of treatment Secondary outcomes included time to major stroke, patency of the treated artery, time to contralateral stroke, time to death, and the occurrence of a TIA
Notes	Terminated prematurely by the sponsor
Allocation concealment	A – Adequate

AF: atrial fibrillation
bd: twice daily
CEA: carotid endarterectomy
ICA: internal carotid artery
LOS: low output syndrome
LV: left ventricular
MI: myocardial infarction
NIH: National Institutes of Health
TIA: transient ischaemic attack

Characteristics of ongoing studies

Study	ACST-2
Trial name or title	Asymptomatic Carotid Surgery Trial 2
Participants	Planned sample size 5000 Patients with significant coronary artery stenosis appropriate for CEA or CAS, fit and willing to have surgery, and where both doctor and patient are substantially uncertain whether to stent or have surgery
Interventions	Carotid endarterectomy versus carotid artery stenting
Outcomes	Primary outcomes are periprocedural hazards (within 30 days) stroke, MI, and death, and long-term hazards (after 30 days) stroke and death Secondary outcome is cost-effectiveness of carotid endarterectomy and carotid artery stenting
Starting date	2006
Contact information	Dr Alison Halliday acst@sgul.ac.uk
Notes	

Characteristics of ongoing studies (*Continued*)

Study	**ACT I**
Trial name or title	Carotid stenting versus endarterectomy to treat severe carotid disease in patients without symptoms
Participants	Planned sample size 1858 Patients with severe carotid artery disease with no related symptoms in the previous 180 days and able to undergo either an interventional stenting or surgical procedure
Interventions	Carotid endarterectomy versus carotid artery stenting for the prevention of stroke
Outcomes	Primary outcome is occurrence of major adverse events 30 days following procedure, and occurrence of ipsilateral strokes between 31 and 365 days post procedure Secondary outcome is acute device success and procedural success
Starting date	March 2005
Contact information	Dana Fletcher dana.fletcher@abbott.com
Notes	

Study	**Agostoni**
Trial name or title	Early invasive treatment of carotid stenosis
Participants	Planned sample size 400 Patients with TIA, minor stroke and with ipsilateral carotid stenosis > 50%
Interventions	Carotid endarterectomy versus carotid angioplasty with stenting performed in the first month after a TIA or minor stroke
Outcomes	Primary endpoints are cumulative incidence of TIA and/or stroke and/or death at 2 years; MI at 1 month Secondary endpoints are cumulative incidence of TIA and/or stroke and/or death at 30 days, cumulative incidence of TIA and/or stroke at 2 years, cumulative incidence of procedure-related adverse events, mean overall hospital stay, and overall procedure-related costs
Starting date	Unknown
Contact information	E Agostoni, Stroke Unit, Clinica Neurologica, Universita Milano-Bicocca, Milan, Italy Email: e.agostoni@libero.it
Notes	

Study	**CREST**
Trial name or title	Carotid revascularisation endarterectomy versus stenting trial (CREST)
Participants	Planned sample size 2500 Patients with TIA, amaurosis fugax or non-disabling stroke within 180 days of randomisation and ipsilateral carotid stenosis of > 50%
Interventions	Carotid artery stenting with cerebral protection versus carotid endarterectomy
Outcomes	Primary endpoints are cumulative occurrence of stroke, MI, or death within 30 days of treatment and stroke ipsilateral to the study artery after 30 days
Starting date	December 2000
Contact information	Professor Robert W Hobson MD University of Medicine and Dentistry of New Jersey, Newark, New Jersey, USA
Notes	

Study	**ICSS**
Trial name or title	International Carotid Stenting Study (ICSS)
Participants	Planned sample size 1500

	Patients aged > 40 years with recently symptomatic severe carotid artery stenosis (> 70%) suitable for stenting and surgery
Interventions	Carotid artery stenting with or without cerebral protection device or carotid endarterectomy In the endovascular group premedication is discretionary but intraprocedural heparin is mandatory
Outcomes	Any stroke or death, TIA, or MI within 30 days of treatment, cranial nerve palsy within 30 days of treatment, local haematoma, stenosis > 70% or occlusion during follow up, quality of life health status and health service costs
Starting date	May 2001
Contact information	Professor Martin M Brown, Box 6, The National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG m.brown@ion.ucl.ac.uk
Notes	

Study	**Link 2000**
Trial name or title	Carotid endarterectomy and carotid stenting: pilot study of a prospective, randomized and controlled comparison
Participants	Planned sample size 200 Patients aged > 40 years with symptomatic carotid stenosis > 70% Patients aged > 80 years will be excluded Patients with symptomatic or asymptomatic contralateral carotid stenosis > 70% will also be excluded
Interventions	Carotid artery stenting or carotid endarterectomy All patients are to receive 300 mg clopidogrel on the day before treatment and 75 mg clopidogrel daily after treatment for 30 days plus 300 mg aspirin daily for life Patients in the stenting group will receive 500 mg aspirin iv and heparin before treatment, patients in the surgery group will receive low-molecular-weight heparin before surgery
Outcomes	Cerebral ischaemia, MI or death within 30 days of treatment Cerebral ischaemia or death within 12 months of treatment Restenosis > 70% or occlusion within 12 months of treatment Re-intervention within 12 months of treatment Technical failure
Starting date	August 1999
Contact information	J Link, Univ Klinikum Regensburg, Inst Rontgendiagnostik, Franz Josef Strauss Allee 11, D-93053 Regensburg, Germany
Notes	

iv: intravenous
MI: myocardial infarction
TIA: transient ischaemic attack

ANALYSES

Comparison 01. Endovascular treatment or carotid endarterectomy

Outcome title	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
01 Death or any stroke within 30 days of procedure (fixed-effect)	8	2915	Odds Ratio (Fixed) 95% CI	1.39 [1.05, 1.84]
02 Death or any stroke within 30 days of procedure (random-effects)	8	2915	Odds Ratio (Random) 95% CI	1.44 [0.91, 2.26]

03 Death or disabling stroke within 30 days of procedure (fixed-effect)	7	2696	Odds Ratio (Fixed) 95% CI	1.22 [0.83, 1.79]
04 Death or disabling stroke within 30 days of procedure (random-effects)	7	2696	Odds Ratio (Random) 95% CI	1.20 [0.80, 1.80]
05 Death within 30 days of procedure (fixed-effect)	7	2696	Odds Ratio (Fixed) 95% CI	0.99 [0.50, 1.97]
06 Death within 30 days of procedure (random-effects)	7	2696	Odds Ratio (Random) 95% CI	1.00 [0.49, 2.04]
07 Stroke within 30 days of procedure (fixed-effect)	7	2698	Odds Ratio (Fixed) 95% CI	1.40 [1.02, 1.91]
08 Stroke within 30 days of procedure (random-effects)	7	2698	Odds Ratio (Random) 95% CI	1.47 [0.81, 2.67]
09 Cranial neuropathy within 30 days of procedure (fixed-effect)	6	1513	Odds Ratio (Fixed) 95% CI	0.07 [0.03, 0.20]
10 Cranial neuropathy within 30 days of procedure (random-effects)	6	1513	Odds Ratio (Random) 95% CI	0.09 [0.04, 0.25]
11 Death or neurological complication within 30 days of procedure (fixed-effect)	6	1513	Odds Ratio (Fixed) 95% CI	0.62 [0.45, 0.86]
12 Death or neurological complication within 30 days of procedure (random-effects)	6	1513	Odds Ratio (Random) 95% CI	0.60 [0.31, 1.17]
13 Death or stroke or myocardial infarction within 30 days of procedure (fixed-effect)	6	1513	Odds Ratio (Fixed) 95% CI	1.11 [0.77, 1.60]
14 Death or stroke or myocardial infarction within 30 days of procedure (random-effects)	6	1513	Odds Ratio (Random) 95% CI	1.06 [0.48, 2.38]
15 Death or neurological complications or vascular complications within 30 days of procedure (fixed-effect)	6	1513	Odds Ratio (Fixed) 95% CI	0.87 [0.67, 1.14]
16 Death or neurological complications or vascular complications within 30 days of procedure (random-effects)	6	1513	Odds Ratio (Random) 95% CI	1.16 [0.41, 3.24]
17 Death or any stroke during follow up (fixed-effect)	6	1770	Odds Ratio (Fixed) 95% CI	1.13 [0.81, 1.58]
18 Death or any stroke during follow up (random-effects)	6	1770	Odds Ratio (Random) 95% CI	1.18 [0.61, 2.28]
19 Death during follow up (fixed-effect)	3	880	Odds Ratio (Fixed) 95% CI	0.58 [0.30, 1.13]
20 Death during follow up (random-effects)	3	880	Odds Ratio (Random) 95% CI	0.57 [0.29, 1.12]
21 Stroke during follow up (fixed-effect)	3	880	Odds Ratio (Fixed) 95% CI	1.00 [0.47, 2.14]
22 Stroke during follow up (random-effects)	3	880	Odds Ratio (Random) 95% CI	0.99 [0.46, 2.14]

Comparison 02. Endovascular treatment or medical care

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death or any stroke after 30 days of procedure/ randomisation (fixed-effect)	2	61	Odds Ratio (Fixed) 95% CI	0.39 [0.14, 1.14]
02 Death or any stroke after 30 days of procedure/ randomisation (random-effects)	2	61	Odds Ratio (Random) 95% CI	0.28 [0.02, 3.23]

Comparison 03. Endovascular treatment with or without protection

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death or any stroke within 30 days of procedure (fixed-effect)	2	814	Odds Ratio (Fixed) 95% CI	0.77 [0.41, 1.46]
02 Death or any stroke within 30 days of procedure (random-effects)	2	814	Odds Ratio (Random) 95% CI	0.57 [0.14, 2.33]

Comparison 04. Endovascular treatment or carotid endarterectomy in asymptomatic patients

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Stroke or death within 30 days of procedure (fixed-effect)	2	136	Odds Ratio (Fixed) 95% CI	1.06 [0.16, 6.94]
02 Stroke or death within 30 days of procedure (random-effects)	2	136	Odds Ratio (Random) 95% CI	1.06 [0.16, 6.94]

INDEX TERMS

Medical Subject Headings (MeSH)

*Angioplasty, Balloon; *Carotid Artery, Internal; Carotid Stenosis [*therapy]; Randomized Controlled Trials; *Stents

MeSH check words

Humans

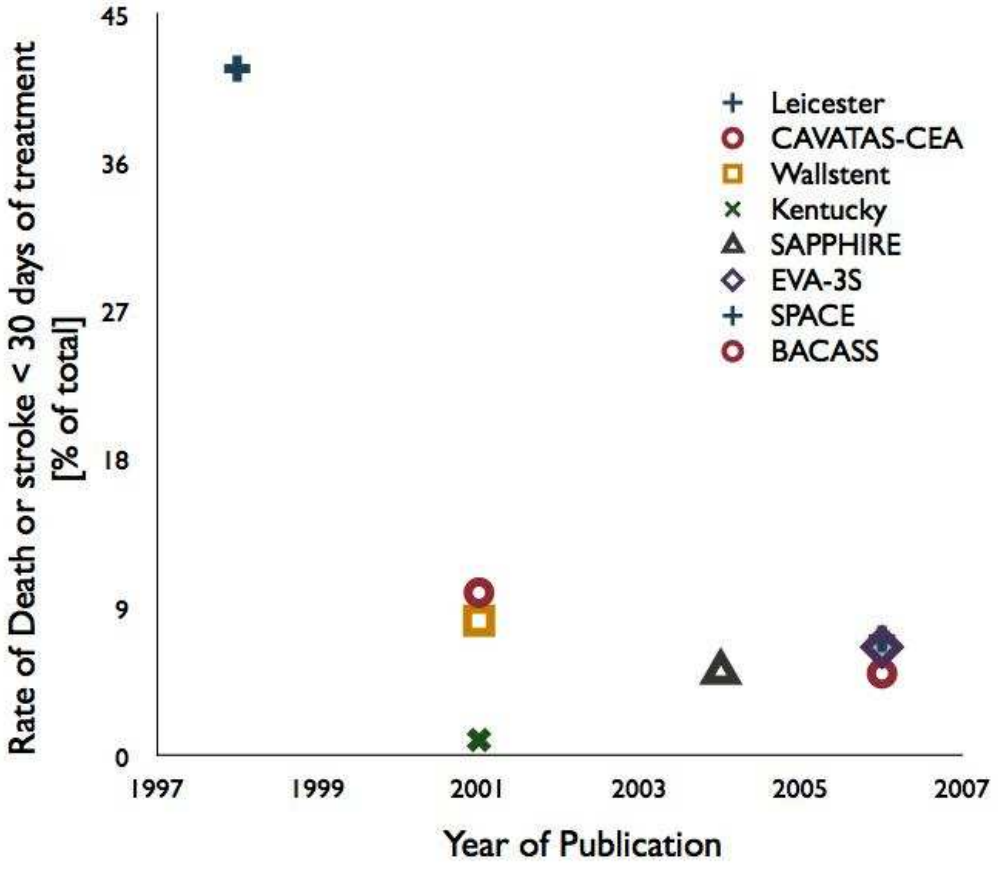
COVER SHEET

Title	Percutaneous transluminal angioplasty and stenting for carotid artery stenosis
Authors	Ederle J, Featherstone RL, Brown MM
Contribution of author(s)	All review authors contributed to the collection and interpretation of data. JE drafted the review. MMB contributed to the critical revision of the review and gave final approval of the version to be published.
Issue protocol first published	1997/4
Review first published	1997/4
Date of most recent amendment	14 August 2007

Date of most recent SUBSTANTIVE amendment	14 August 2007
What's New	For the 2007 update of this review, two trials cited in the previous version as ongoing studies have been included (EVA-3S 2006; SPACE 2006) and five new studies have been identified and included (BACASS 2006; Beijing 2003; Kentucky 2004; TESCAS-C 2006; Wallstent 2001). The results of one trial have been updated with the final published data (SAPPHIRE 2004). A total of 3227 patients were treated within the 12 included trials. The 'Description of studies', 'Methodological quality of included studies', 'Results' and 'Discussion' sections have been substantially revised to incorporate the data from the new included studies. The objectives of the review have been amended to reflect improving knowledge and technology since the previous version. The conclusion of the review is that some analyses favour surgery and others favour endovascular treatment. Results have to be interpreted with great caution since there was significant heterogeneity between the trials and much of the evidence comes from trials that were terminated early.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	02 April 2007
Date authors' conclusions section amended	04 July 2007
Contact address	Prof Martin Brown Professor of Stroke Medicine Department of Brain Repair & Rehabilitation UCL Institute of Neurology Box 6, The National Hospital Queen Square London WC1N 3BG UK E-mail: m.brown@ion.ucl.ac.uk Tel: +44 20 7829 8753 Fax: +44 20 7833 8613
DOI	10.1002/14651858.CD000515.pub3
Cochrane Library number	CD000515
Editorial group	Cochrane Stroke Group
Editorial group code	HM-STROKE

GRAPHS AND OTHER TABLES

Figure 01.



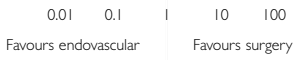
Analysis 01.01. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 01 Death or any stroke within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 01 Death or any stroke within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgical n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
CAVATAS-CEA 2001	25/252	25/253		27.0	1.00 [0.56, 1.80]
Kentucky 2001	0/53	1/51		1.8	0.31 [0.01, 7.90]
Leicester 1998	5/11	0/12		0.3	21.15 [1.01, 445.00]
Wallstent 2001	13/107	5/112		5.2	2.96 [1.02, 8.61]
SAPPHIRE 2004	8/167	9/167		10.3	0.88 [0.33, 2.35]
EVA-3S 2006	25/265	10/262		11.0	2.63 [1.23, 5.58]
SPACE 2006	46/599	38/584		42.7	1.20 [0.77, 1.87]
BACASS 2006	0/10	1/10		1.7	0.30 [0.01, 8.33]
Total (95% CI)	1464	1451		100.0	1.39 [1.05, 1.84]
Total events: 122 (Endovascular), 89 (Surgical)					
Test for heterogeneity chi-square=11.81 df=7 p=0.11 I^2 =40.7%					
Test for overall effect z=2.30 p=0.02					



Analysis 01.02. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 02 Death or any stroke within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

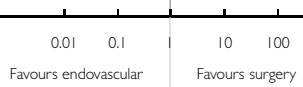
Outcome: 02 Death or any stroke within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
BACASS 2006	0/10	1/10		1.8	0.30 [0.01, 8.33]
Leicester 1998	5/11	0/12		2.1	21.15 [1.01, 445.00]
CAVATAS-CEA 2001	25/252	25/253		22.9	1.00 [0.56, 1.80]
Kentucky 2001	0/53	1/51		1.9	0.31 [0.01, 7.90]
Wallstent 2001	13/107	5/112		12.1	2.96 [1.02, 8.61]
SAPPHIRE 2004	8/167	9/167		13.6	0.88 [0.33, 2.35]
SPACE 2006	46/599	38/584		27.3	1.20 [0.77, 1.87]
EVA-3S 2006	25/265	10/262		18.3	2.63 [1.23, 5.58]
Total (95% CI)	1464	1451		100.0	1.44 [0.91, 2.26]

Total events: 122 (Endovascular), 89 (Surgery)

Test for heterogeneity chi-square=11.81 df=7 p=0.11 I^2 =40.7%

Test for overall effect z=1.56 p=0.1



Analysis 01.03. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 03 Death or disabling stroke within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 03 Death or disabling stroke within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
CAVATAS-CEA 2001	16/252	15/253		29.3	1.08 [0.52, 2.23]
Kentucky 2001	0/53	1/51		3.2	0.31 [0.01, 7.90]
Leicester 1998	3/11	0/12		0.7	10.29 [0.47, 225.93]
SAPPHIRE 2004	4/167	7/167		14.3	0.56 [0.16, 1.95]
EVA-3S 2006	9/265	4/262		8.1	2.27 [0.69, 7.46]
SPACE 2006	28/599	22/584		44.4	1.25 [0.71, 2.22]
× BACASS 2006	0/10	0/10		0.0	Not estimable
Total (95% CI)	1357	1339		100.0	1.22 [0.83, 1.79]

Total events: 60 (Endovascular), 49 (Surgery)

Test for heterogeneity chi-square=5.16 df=5 p=0.40 I^2 =3.2%

Test for overall effect z=1.02 p=0.3

Analysis 01.04. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 04 Death or disabling stroke within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

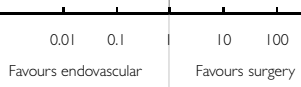
Outcome: 04 Death or disabling stroke within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
× BACASS 2006	0/10	0/10		0.0	Not estimable
CAVATAS-CEA 2001	16/252	15/253		29.3	1.08 [0.52, 2.23]
EVA-3S 2006	9/265	4/262		11.4	2.27 [0.69, 7.46]
Kentucky 2001	0/53	1/51		1.6	0.31 [0.01, 7.90]
Leicester 1998	3/11	0/12		1.7	10.29 [0.47, 225.93]
SAPPHIRE 2004	4/167	7/167		10.4	0.56 [0.16, 1.95]
SPACE 2006	28/599	22/584		45.6	1.25 [0.71, 2.22]
Total (95% CI)	1357	1339		100.0	1.20 [0.80, 1.80]

Total events: 60 (Endovascular), 49 (Surgery)

Test for heterogeneity chi-square=5.16 df=5 p=0.40 I^2 =3.2%

Test for overall effect z=0.86 p=0.4



Analysis 01.05. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 05 Death within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 05 Death within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
× Leicester 1998	0/11	0/12		0.0	Not estimable
CAVATAS-CEA 2001	7/252	4/253		23.7	1.78 [0.51, 6.15]
Kentucky 2001	0/53	1/51		9.3	0.31 [0.01, 7.90]
SAPPHIRE 2004	2/167	4/167		24.2	0.49 [0.09, 2.73]
× BACASS 2006	0/10	0/10		0.0	Not estimable
EVA-3S 2006	2/265	3/262		18.3	0.66 [0.11, 3.96]
SPACE 2006	5/599	4/584		24.6	1.22 [0.33, 4.57]
Total (95% CI)	1357	1339		100.0	0.99 [0.50, 1.97]

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Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Total events: 16 (Endovascular), 16 (Surgery)					
Test for heterogeneity chi-square=2.27 df=4 p=0.69 I^2 =0.0%					
Test for overall effect z=0.03 p=1					

Analysis 01.06. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 06 Death within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 06 Death within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
× BACASS 2006	0/10	0/10		0.0	Not estimable
CAVATAS-CEA 2001	7/252	4/253		32.9	1.78 [0.51, 6.15]
EVA-3S 2006	2/265	3/262		15.7	0.66 [0.11, 3.96]
Kentucky 2001	0/53	1/51		4.9	0.31 [0.01, 7.90]
× Leicester 1998	0/11	0/12		0.0	Not estimable
SAPPHIRE 2004	2/167	4/167		17.3	0.49 [0.09, 2.73]
SPACE 2006	5/599	4/584		29.1	1.22 [0.33, 4.57]
Total (95% CI)	1357	1339		100.0	1.00 [0.49, 2.04]
Total events: 16 (Endovascular), 16 (Surgery)					
Test for heterogeneity chi-square=2.27 df=4 p=0.69 I^2 =0.0%					
Test for overall effect z=0.01 p=1					

Analysis 01.07. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 07 Stroke within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 07 Stroke within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
BACASS 2006	0/10	1/10		2.2	0.30 [0.01, 8.33]
CAVATAS-CEA 2001	18/252	21/253		29.4	0.85 [0.44, 1.64]
EVA-3S 2006	23/265	7/262		9.7	3.46 [1.46, 8.22]
× Kentucky 2001	0/53	0/53		0.0	Not estimable
Leicester 1998	5/11	0/12		0.4	21.15 [1.01, 445.00]
SAPPHIRE 2004	6/167	5/167		7.3	1.21 [0.36, 4.04]
SPACE 2006	45/599	36/584		51.0	1.24 [0.79, 1.95]
Total (95% CI)	1357	1341		100.0	1.40 [1.02, 1.91]

Total events: 97 (Endovascular), 70 (Surgery)

Test for heterogeneity chi-square=10.65 df=5 p=0.06 I^2 =53.1%

Test for overall effect z=2.07 p=0.04

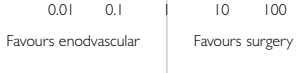
Analysis 01.08. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 08 Stroke within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 08 Stroke within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
BACASS 2006	0/10	1/10		3.0	0.30 [0.01, 8.33]
CAVATAS-CEA 2001	18/252	21/253		26.2	0.85 [0.44, 1.64]
EVA-3S 2006	23/265	7/262		21.2	3.46 [1.46, 8.22]
× Kentucky 2001	0/53	0/53		0.0	Not estimable
Leicester 1998	5/11	0/12		3.5	21.15 [1.01, 445.00]
SAPPHIRE 2004	6/167	5/167		14.9	1.21 [0.36, 4.04]
SPACE 2006	45/599	36/584		31.3	1.24 [0.79, 1.95]
Total (95% CI)	1357	1341		100.0	1.47 [0.81, 2.67]



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Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
Total events: 97 (Endovascular), 70 (Surgery)					
Test for heterogeneity chi-square=10.65 df=5 p=0.06 I^2 =53.1%					
Test for overall effect z=1.27 p=0.2					

Analysis 01.09. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 09 Cranial neuropathy within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 09 Cranial neuropathy within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
CAVATAS-CEA 2001	0/252	22/253		40.5	0.02 [0.00, 0.34]
Kentucky 2001	0/53	4/51		8.2	0.10 [0.01, 1.88]
× Leicester 1998	0/11	0/12		0.0	Not estimable
SAPPHIRE 2004	0/167	8/167		15.3	0.06 [0.00, 0.98]
EVA-3S 2006	3/265	20/262		36.0	0.14 [0.04, 0.47]
× BACASS 2006	0/10	0/10		0.0	Not estimable
Total (95% CI)	758	755		100.0	0.07 [0.03, 0.20]
Total events: 3 (Endovascular), 54 (Surgery)					
Test for heterogeneity chi-square=1.87 df=3 p=0.60 I^2 =0.0%					
Test for overall effect z=5.26 p<0.00001					

Analysis 01.10. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 10 Cranial neuropathy within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

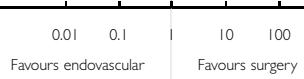
Outcome: 10 Cranial neuropathy within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
× BACASS 2006	0/10	0/10		0.0	Not estimable
CAVATAS-CEA 2001	0/252	22/253		12.3	0.02 [0.00, 0.34]
EVA-3S 2006	3/265	20/262		64.6	0.14 [0.04, 0.47]
Kentucky 2001	0/53	4/51		11.2	0.10 [0.01, 1.88]
× Leicester 1998	0/11	0/12		0.0	Not estimable
SAPPHIRE 2004	0/167	8/167		11.9	0.06 [0.00, 0.98]
Total (95% CI)	758	755		100.0	0.09 [0.04, 0.25]

Total events: 3 (Endovascular), 54 (Surgery)

Test for heterogeneity chi-square=1.87 df=3 p=0.60 I^2 =0.0%

Test for overall effect z=4.69 p<0.00001



Analysis 01.11. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 11 Death or neurological complication within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

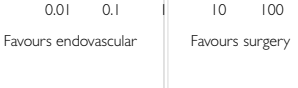
Outcome: 11 Death or neurological complication within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Leicester 1998	5/11	0/12		0.3	21.15 [1.01, 445.00]
CAVATAS-CEA 2001	25/252	49/253		46.6	0.46 [0.27, 0.77]
Kentucky 2001	0/53	5/51		5.9	0.08 [0.00, 1.47]
SAPPHIRE 2004	8/167	17/167		17.1	0.44 [0.19, 1.06]
BACASS 2006	0/10	1/10		1.5	0.30 [0.01, 8.33]
EVA-3S 2006	28/265	30/262		28.6	0.91 [0.53, 1.58]
Total (95% CI)	758	755		100.0	0.62 [0.45, 0.86]

Total events: 66 (Endovascular), 102 (Surgery)

Test for heterogeneity chi-square=11.06 df=5 p=0.05 I^2 =54.8%

Test for overall effect z=2.90 p=0.004



Analysis 01.12. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 12 Death or neurological complication within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 12 Death or neurological complication within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
BACASS 2006	0/10	1/10		3.6	0.30 [0.01, 8.33]
CAVATAS-CEA 2001	25/252	49/253		32.3	0.46 [0.27, 0.77]
EVA-3S 2006	28/265	30/262		31.6	0.91 [0.53, 1.58]
Kentucky 2001	0/53	5/51		4.5	0.08 [0.00, 1.47]
Leicester 1998	5/11	0/12		4.2	21.15 [1.01, 445.00]
SAPPHIRE 2004	8/167	17/167		23.7	0.44 [0.19, 1.06]
Total (95% CI)	758	755		100.0	0.60 [0.31, 1.17]

Total events: 66 (Endovascular), 102 (Surgery)

Test for heterogeneity chi-square=11.06 df=5 p=0.05 I^2 =54.8%

Test for overall effect z=1.50 p=0.1

Analysis 01.13. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 13 Death or stroke or myocardial infarction within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 13 Death or stroke or myocardial infarction within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
CAVATAS-CEA 2001	25/252	28/253		46.2	0.88 [0.50, 1.56]
Kentucky 2001	0/53	1/51		2.8	0.31 [0.01, 7.90]
Leicester 1998	5/11	0/12		0.5	21.15 [1.01, 445.00]
SAPPHIRE 2004	8/167	16/167		28.0	0.47 [0.20, 1.14]
EVA-3S 2006	26/265	12/262		20.0	2.27 [1.12, 4.59]
BACASS 2006	0/10	1/10		2.6	0.30 [0.01, 8.33]
Total (95% CI)	758	755		100.0	1.11 [0.77, 1.60]

Total events: 64 (Endovascular), 58 (Surgery)

Test for heterogeneity chi-square=12.90 df=5 p=0.02 I^2 =61.3%

Test for overall effect z=0.57 p=0.6

Analysis 01.14. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 14 Death or stroke or myocardial infarction within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 14 Death or stroke or myocardial infarction within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
BACASS 2006	0/10	1/10		5.0	0.30 [0.01, 8.33]
CAVATAS-CEA 2001	25/252	28/253		30.5	0.88 [0.50, 1.56]
EVA-3S 2006	26/265	12/262		28.2	2.27 [1.12, 4.59]
Kentucky 2001	0/53	1/51		5.3	0.31 [0.01, 7.90]
Leicester 1998	5/11	0/12		5.8	21.15 [1.01, 445.00]
SAPPHIRE 2004	8/167	16/167		25.2	0.47 [0.20, 1.14]
Total (95% CI)	758	755		100.0	1.06 [0.48, 2.38]

Total events: 64 (Endovascular), 58 (Surgery)

Test for heterogeneity chi-square=12.90 df=5 p=0.02 I^2 =61.3%

Test for overall effect z=0.15 p=0.9

Analysis 01.15. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 15 Death or neurological complications or vascular complications within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 15 Death or neurological complications or vascular complications within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Leicester 1998	5/11	0/12		0.2	21.15 [1.01, 445.00]
CAVATAS-CEA 2001	28/252	73/253		56.7	0.31 [0.19, 0.50]
Kentucky 2001	23/53	9/51		4.5	3.58 [1.45, 8.82]
SAPPHIRE 2004	10/167	17/167		14.0	0.56 [0.25, 1.27]
BACASS 2006	0/10	1/10		1.3	0.30 [0.01, 8.33]
EVA-3S 2006	53/265	33/262		23.3	1.73 [1.08, 2.78]
Total (95% CI)	758	755		100.0	0.87 [0.67, 1.14]

Total events: 119 (Endovascular), 133 (Surgery)

Test for heterogeneity chi-square=41.46 df=5 p=<0.0001 I^2 =87.9%

Test for overall effect z=1.00 p=0.3

Analysis 01.16. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 16 Death or neurological complications or vascular complications within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 16 Death or neurological complications or vascular complications within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
BACASS 2006	0/10	1/10		6.8	0.30 [0.01, 8.33]
CAVATAS-CEA 2001	28/252	73/253		22.5	0.31 [0.19, 0.50]
EVA-3S 2006	53/265	33/262		22.5	1.73 [1.08, 2.78]
Kentucky 2004	23/53	9/51		20.0	3.58 [1.45, 8.82]
Leicester 1998	5/11	0/12		7.7	21.15 [1.01, 445.00]
SAPPHIRE 2004	10/167	17/167		20.6	0.56 [0.25, 1.27]
Total (95% CI)	758	755		100.0	1.16 [0.41, 3.24]
Total events: 119 (Endovascular), 133 (Surgery)					
Test for heterogeneity chi-square=41.46 df=5 p=<0.0001 I^2 =87.9%					
Test for overall effect z=0.28 p=0.8					

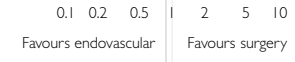
Analysis 01.17. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 17 Death or any stroke during follow up (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 17 Death or any stroke during follow up (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 events at 6 months					
TESCAS-C 2006	8/82	10/84		13.6	0.80 [0.30, 2.14]
EVA-3S 2006	31/265	16/262		21.7	2.04 [1.09, 3.82]
Subtotal (95% CI)	347	346		35.4	1.56 [0.93, 2.62]
Total events: 39 (Endovascular), 26 (Surgery)					
Test for heterogeneity chi-square=2.46 df=1 p=0.12 I^2 =59.3%					
Test for overall effect z=1.68 p=0.09					
02 events at 12 months					
Wallstent 2001	13/107	4/112		5.3	3.73 [1.18, 11.84]
SAPPHIRE 2004	22/167	33/167		43.8	0.62 [0.34, 1.11]



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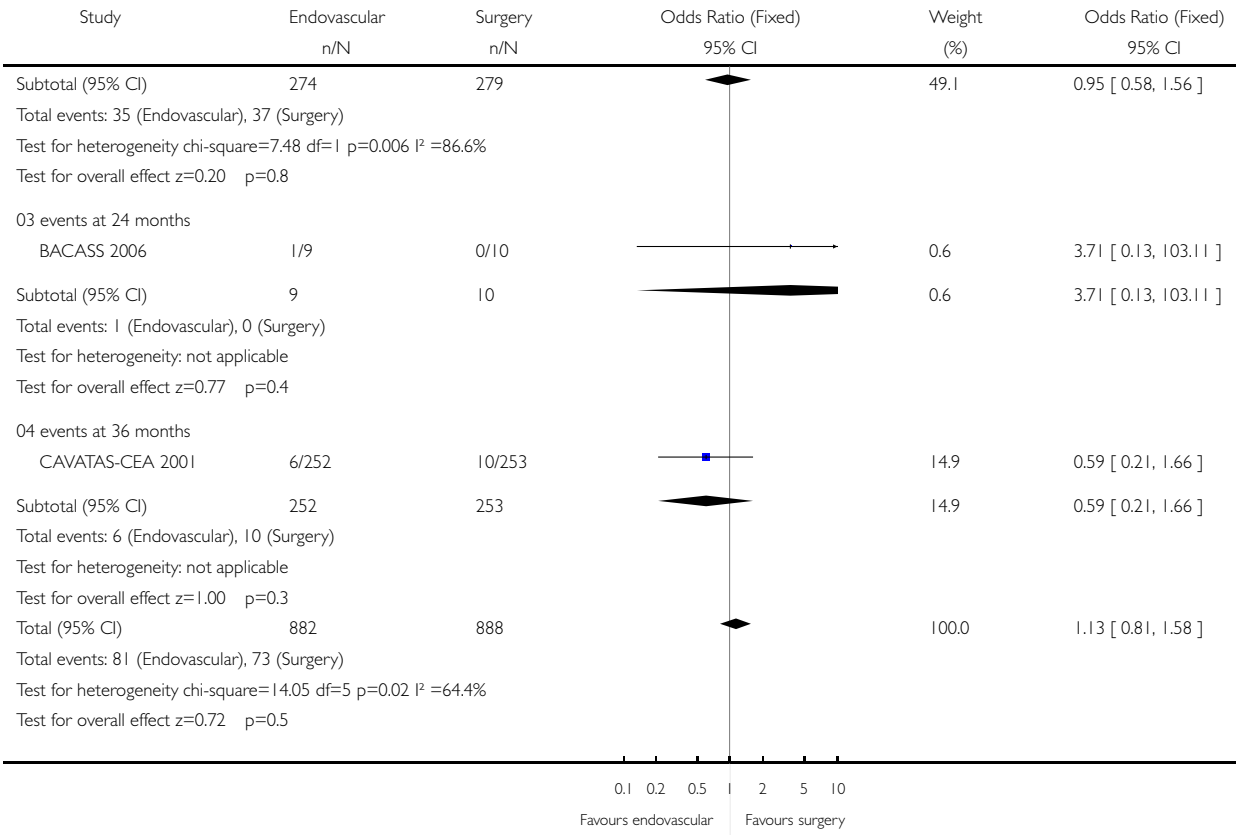


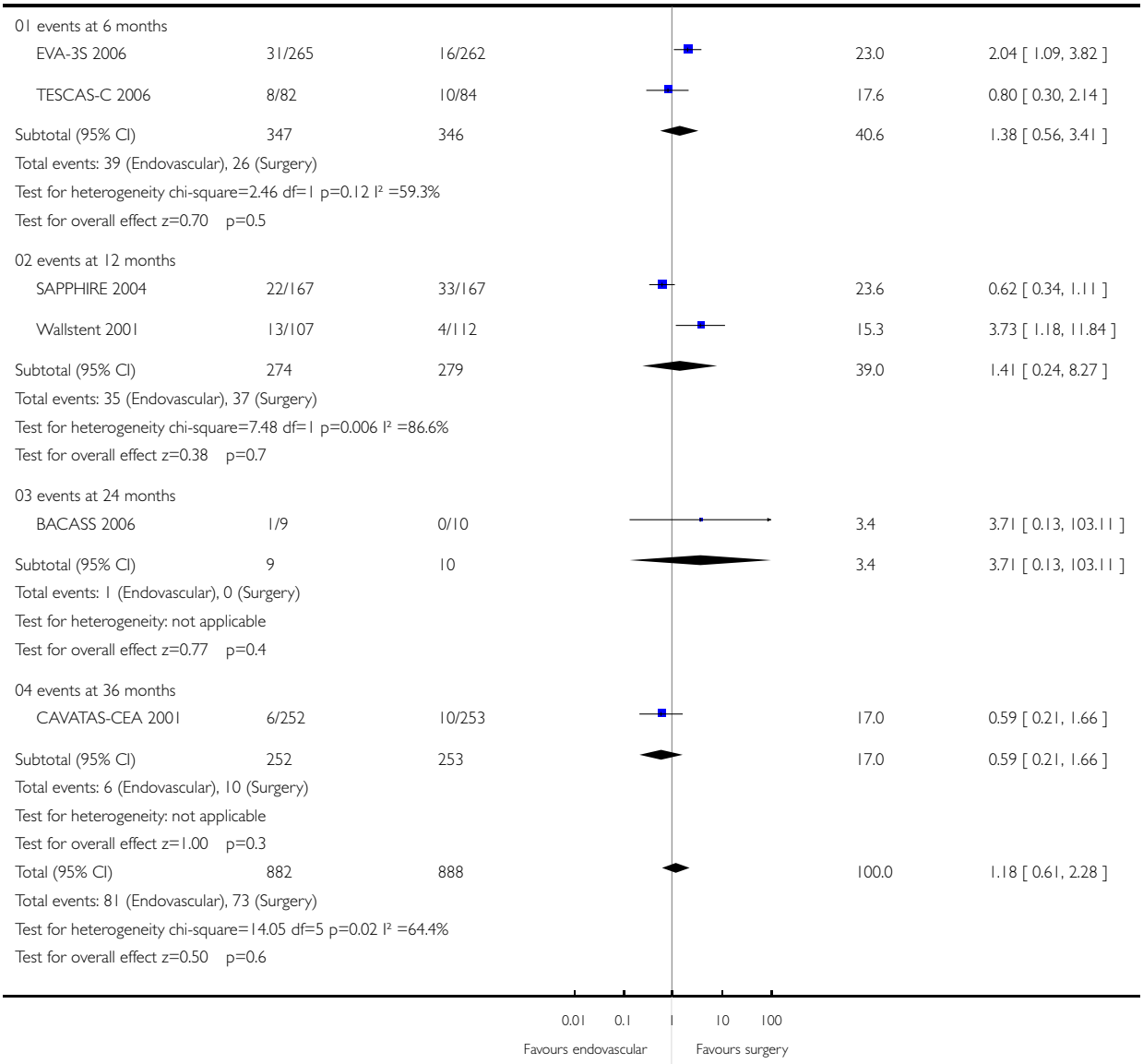
Analysis 01.18. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 18 Death or any stroke during follow up (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 18 Death or any stroke during follow up (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
01 events at 6 months					
EVA-3S 2006	31/265	16/262		23.0	2.04 [1.09, 3.82]
TESCAS-C 2006	8/82	10/84		17.6	0.80 [0.30, 2.14]
Subtotal (95% CI)	347	346		40.6	1.38 [0.56, 3.41]
Total events: 39 (Endovascular), 26 (Surgery)					
Test for heterogeneity chi-square=2.46 df=1 p=0.12 I^2 =59.3%					
Test for overall effect z=0.70 p=0.5					
02 events at 12 months					
SAPPHIRE 2004	22/167	33/167		23.6	0.62 [0.34, 1.11]
Wallstent 2001	13/107	4/112		15.3	3.73 [1.18, 11.84]
Subtotal (95% CI)	274	279		39.0	1.41 [0.24, 8.27]
Total events: 35 (Endovascular), 37 (Surgery)					
Test for heterogeneity chi-square=7.48 df=1 p=0.006 I^2 =86.6%					
Test for overall effect z=0.38 p=0.7					
03 events at 24 months					
BACASS 2006	1/9	0/10		3.4	3.71 [0.13, 103.11]
Subtotal (95% CI)	9	10		3.4	3.71 [0.13, 103.11]
Total events: 1 (Endovascular), 0 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.77 p=0.4					
04 events at 36 months					
CAVATAS-CEA 2001	6/252	10/253		17.0	0.59 [0.21, 1.66]
Subtotal (95% CI)	252	253		17.0	0.59 [0.21, 1.66]
Total events: 6 (Endovascular), 10 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.00 p=0.3					
Total (95% CI)	882	888		100.0	1.18 [0.61, 2.28]
Total events: 81 (Endovascular), 73 (Surgery)					
Test for heterogeneity chi-square=14.05 df=5 p=0.02 I^2 =64.4%					
Test for overall effect z=0.50 p=0.6					



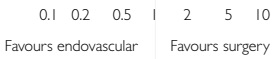
Analysis 01.19. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 19 Death during follow up (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 19 Death during follow up (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 events at 6 months					
EVA-3S 2006	2/265	4/262		16.7	0.49 [0.09, 2.70]
Subtotal (95% CI)	265	262		16.7	0.49 [0.09, 2.70]
Total events: 2 (Endovascular), 4 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.82 p=0.4					
02 events at 12 months					
SAPPHIRE 2004	12/167	21/167		81.6	0.54 [0.26, 1.13]
Subtotal (95% CI)	167	167		81.6	0.54 [0.26, 1.13]
Total events: 12 (Endovascular), 21 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					
03 events at 24 months					
BACASS 2006	1/9	0/10		1.7	3.71 [0.13, 103.11]
Subtotal (95% CI)	9	10		1.7	3.71 [0.13, 103.11]
Total events: 1 (Endovascular), 0 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.77 p=0.4					
Total (95% CI)	441	439		100.0	0.58 [0.30, 1.13]
Total events: 15 (Endovascular), 25 (Surgery)					
Test for heterogeneity chi-square=1.27 df=2 p=0.53 I^2 =0.0%					
Test for overall effect z=1.60 p=0.1					

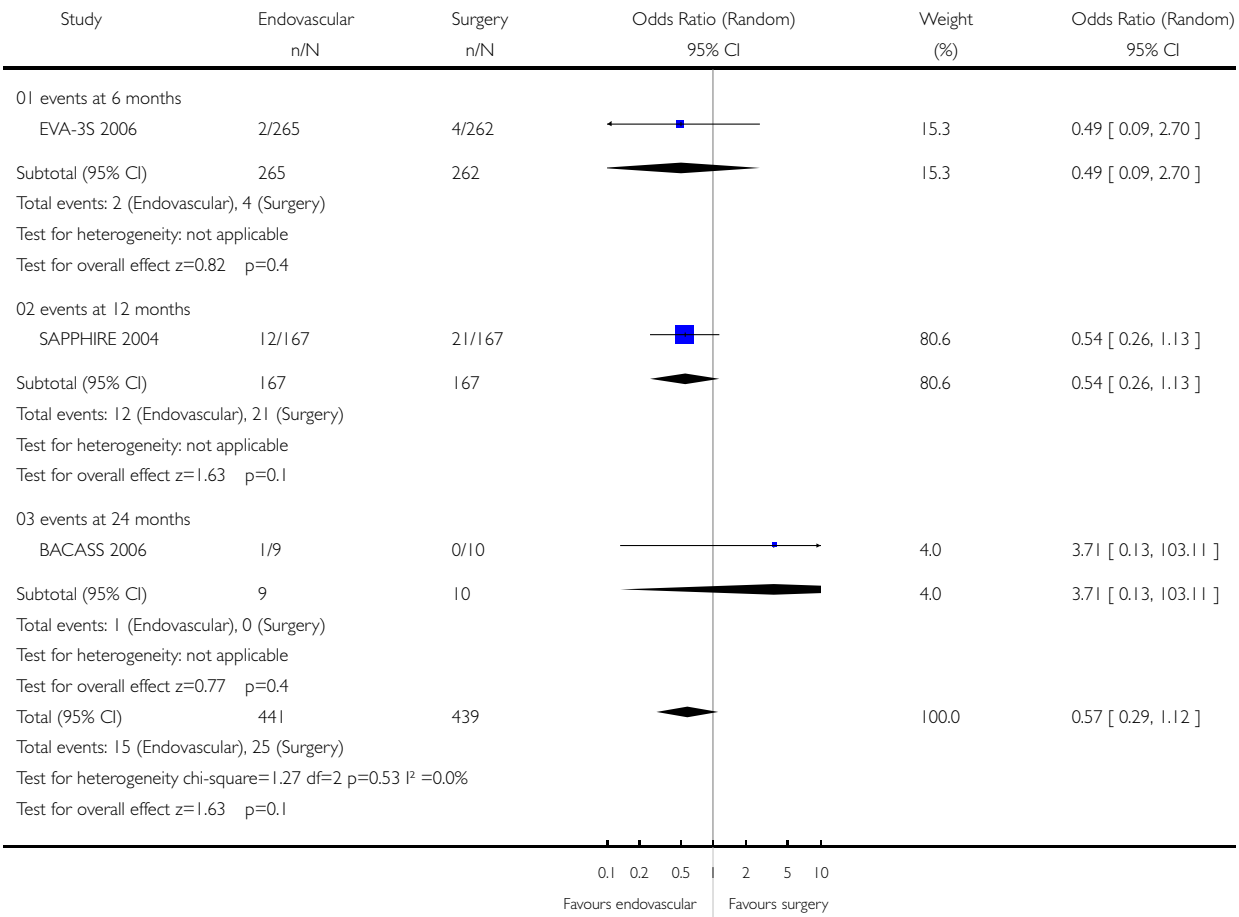


Analysis 01.20. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 20 Death during follow up (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 20 Death during follow up (random-effects)

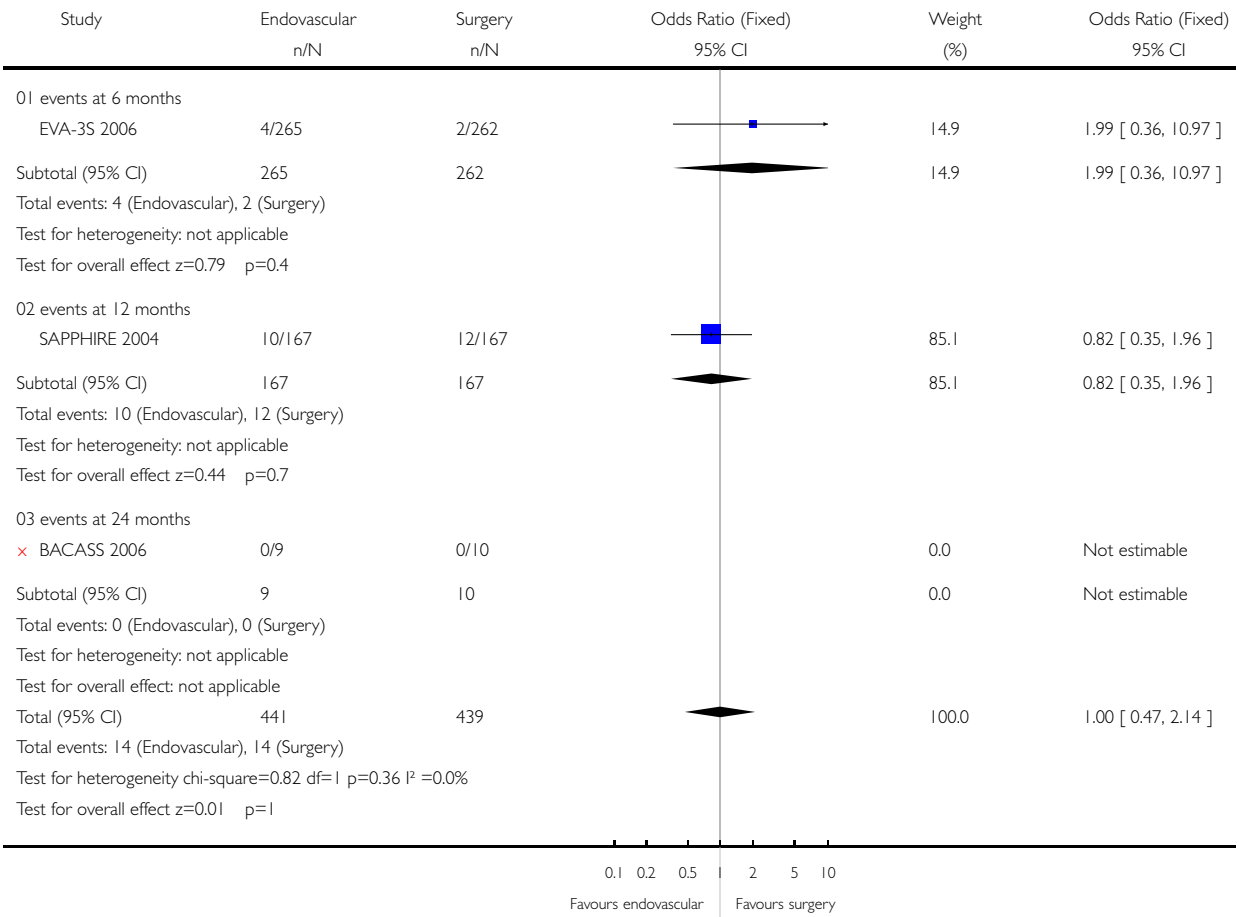


Analysis 01.21. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 21 Stroke during follow up (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 21 Stroke during follow up (fixed-effect)

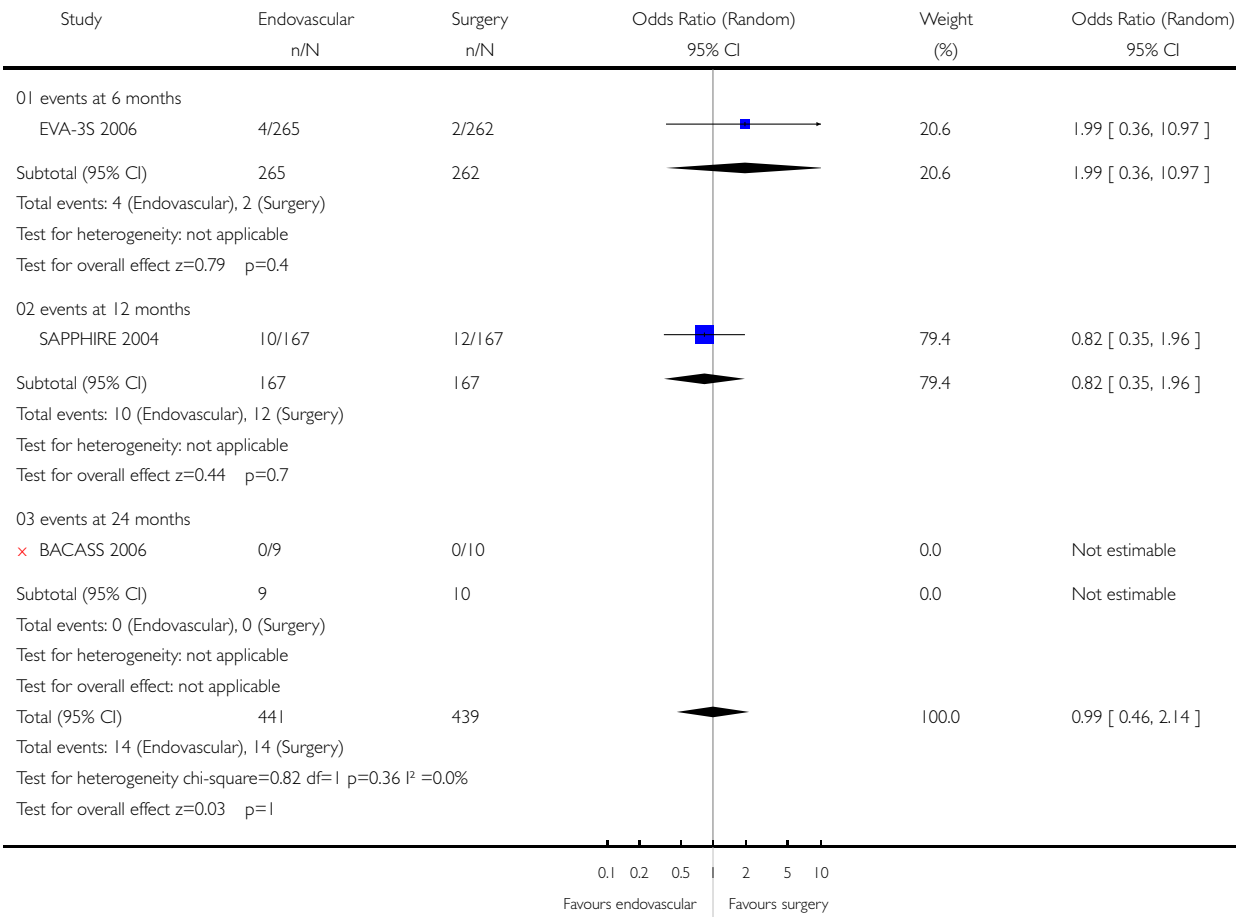


Analysis 01.22. Comparison 01 Endovascular treatment or carotid endarterectomy, Outcome 22 Stroke during follow up (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 01 Endovascular treatment or carotid endarterectomy

Outcome: 22 Stroke during follow up (random-effects)



Analysis 02.01. Comparison 02 Endovascular treatment or medical care, Outcome 01 Death or any stroke after 30 days of procedure/randomisation (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 02 Endovascular treatment or medical care

Outcome: 01 Death or any stroke after 30 days of procedure/randomisation (fixed-effect)

Study	Endovascular n/N	Medical n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Beijing 2003	1/8	9/13		55.0	0.06 [0.01, 0.70]
CAVATAS-MED 2007	6/20	7/20		45.0	0.80 [0.21, 3.00]
Total (95% CI)	28	33		100.0	0.39 [0.14, 1.14]
Total events: 7 (Endovascular), 16 (Medical)					
Test for heterogeneity chi-square=3.30 df=1 p=0.07 I^2 =69.7%					
Test for overall effect z=1.72 p=0.09					

Analysis 02.02. Comparison 02 Endovascular treatment or medical care, Outcome 02 Death or any stroke after 30 days of procedure/randomisation (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 02 Endovascular treatment or medical care

Outcome: 02 Death or any stroke after 30 days of procedure/randomisation (random-effects)

Study	Endovascular n/N	Medical n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
Beijing 2003	1/8	9/13		41.9	0.06 [0.01, 0.70]
CAVATAS-MED 2007	6/20	7/20		58.1	0.80 [0.21, 3.00]
Total (95% CI)	28	33		100.0	0.28 [0.02, 3.23]
Total events: 7 (Endovascular), 16 (Medical)					
Test for heterogeneity chi-square=3.30 df=1 p=0.07 I^2 =69.7%					
Test for overall effect z=1.03 p=0.3					

Analysis 03.01. Comparison 03 Endovascular treatment with or without protection, Outcome 01 Death or any stroke within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 03 Endovascular treatment with or without protection

Outcome: 01 Death or any stroke within 30 days of procedure (fixed-effect)

Study	Protection n/N	No protection n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
EVA-3S 2006	18/227	5/20		38.0	0.26 [0.08, 0.79]
SPACE 2006	11/151	28/416		62.0	1.09 [0.53, 2.25]
Total (95% CI)	378	436		100.0	0.77 [0.41, 1.46]

Total events: 29 (Protection), 33 (No protection)

Test for heterogeneity chi-square=4.53 df=1 p=0.03 I^2 =77.9%

Test for overall effect z=0.79 p=0.4

Analysis 03.02. Comparison 03 Endovascular treatment with or without protection, Outcome 02 Death or any stroke within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 03 Endovascular treatment with or without protection

Outcome: 02 Death or any stroke within 30 days of procedure (random-effects)

Study	Protection n/N	No protection n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
EVA-3S 2006	18/227	5/20		45.5	0.26 [0.08, 0.79]
SPACE 2006	11/151	28/416		54.5	1.09 [0.53, 2.25]
Total (95% CI)	378	436		100.0	0.57 [0.14, 2.33]

Total events: 29 (Protection), 33 (No protection)

Test for heterogeneity chi-square=4.53 df=1 p=0.03 I^2 =77.9%

Test for overall effect z=0.79 p=0.4

Analysis 04.01. Comparison 04 Endovascular treatment or carotid endarterectomy in asymptomatic patients, Outcome 01 Stroke or death within 30 days of procedure (fixed-effect)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 04 Endovascular treatment or carotid endarterectomy in asymptomatic patients

Outcome: 01 Stroke or death within 30 days of procedure (fixed-effect)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
CAVATAS-CEA 2001	3/30	2/21		100.0	1.06 [0.16, 6.94]
× Kentucky 2004	0/43	0/42		0.0	Not estimable
Total (95% CI)	73	63		100.0	1.06 [0.16, 6.94]
Total events: 3 (Endovascular), 2 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1					

Analysis 04.02. Comparison 04 Endovascular treatment or carotid endarterectomy in asymptomatic patients, Outcome 02 Stroke or death within 30 days of procedure (random-effects)

Review: Percutaneous transluminal angioplasty and stenting for carotid artery stenosis

Comparison: 04 Endovascular treatment or carotid endarterectomy in asymptomatic patients

Outcome: 02 Stroke or death within 30 days of procedure (random-effects)

Study	Endovascular n/N	Surgery n/N	Odds Ratio (Random) 95% CI	Weight (%)	Odds Ratio (Random) 95% CI
CAVATAS-CEA 2001	3/30	2/21		100.0	1.06 [0.16, 6.94]
× Kentucky 2004	0/43	0/42		0.0	Not estimable
Total (95% CI)	73	63		100.0	1.06 [0.16, 6.94]
Total events: 3 (Endovascular), 2 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.06 p=1