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[Intervention Review]

Eversion versus conventional carotid endarterectomy for preventing stroke

Piergiorgio Cao[1], Paola De Rango[1], Simona Zannetti[2], Giuseppe Giordano[1], Stefano Ricci[3], Maria Grazia Celani[3]

[1]Unita' Operativa di Chirurgia Vascolare, Perugia, Italy. [2]Peripheral Vascular Division, Medtronic-Europe, Perugia, Italy. [3]Servizio di Neurologia e Ictus, USL 2, Perugia, Italy

Contact address: Piergiorgio Cao, Unita' Operativa di Chirurgia Vascolare, Via Brunamonti, Perugia, 06122, Italy. pcao@unipg.it.

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ABSTRACT

Background

Carotid endarterectomy (CEA) is conventionally undertaken by a longitudinal arteriotomy. Eversion CEA, which employs a transverse arteriotomy and reimplantation of the carotid artery, is reported to be associated with low perioperative stroke and restenosis rates but an increased risk of complications associated with a distal intimal flap.

Objectives

To determine whether eversion CEA was safe and more effective than conventional CEA. The null-hypothesis was that there was no difference between the eversion and the conventional CEA techniques (performed either with primary closure or patch angioplasty).

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched July 2002), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2002, Issue 4), MEDLINE (1966 to December 2002) and EMBASE (1980 to December 2002). In addition, eight surgical journals were handsearched and researchers were contacted to identify additional published and unpublished studies.

Selection criteria

All randomised trials comparing eversion to conventional techniques in patients undergoing carotid endarterectomy were examined in this review. Outcomes were stroke and death, carotid restenosis/occlusion, and local complications.

Data collection and analysis

Data were extracted independently by two reviewers to assess eligibility and describe trial characteristics, and by one reviewer for meta-analyses. When possible, unpublished data were obtained from investigators.

Main results

Five trials were included for a total of 2465 patients and 2589 arteries. Three trials included bilateral carotid endarterectomies. In one trial, arteries rather than patients were randomised so that it was not clear how many patients had been randomised in each group, therefore, information on the risk of stroke and death from this study were considered in a separate analysis. There were no significant differences in the rate of perioperative stroke and/or death (1.7% versus 2.6%, odds ratio (OR) 0.44, 95% confidence interval (CI) 0.10 to 1.82) and stroke during follow up (1.4% versus 1.7%, Peto OR 0.84, 95% CI 0.43 to 1.64) between eversion and conventional CEA techniques. Eversion CEA was associated with a significantly lower rate of restenosis > 50% during follow up (2.5% versus 5.2%, Peto OR 0.48, 95% CI 0.32 to 0.72). However, there was no evidence that the eversion technique for CEA was associated with a lower rate of neurological events

when compared to conventional CEA. There were no statistically significant differences in local complications between the eversion and conventional group. No data were available to define the cost-benefit of eversion CEA technique.

Authors' conclusions

Eversion CEA may be associated with low risk of arterial occlusion and restenosis. However, numbers are too small to definitively assess benefits or harms. Reduced restenosis rates did not appear to be associated with clinical benefit in terms of reduced stroke risk, either perioperatively or later. Until further evidence is available, the choice of the CEA technique should depend on the experience and familiarity of the individual surgeon.

PLAIN LANGUAGE SUMMARY

Eversion versus conventional carotid endarterectomy for preventing stroke

There is not enough evidence to decide the best way to do the operation of carotid endarterectomy (CEA) to prevent stroke. The carotid artery is one of the main arteries in the neck supplying blood to the brain. A blockage in the artery can cause a stroke (a sudden catastrophe in the brain either because an artery to the brain blocks, or because an artery in or on the brain ruptures and bleeds). CEA involves two different methods to clear the artery. This is done by either eversion (oblique division of the internal carotid artery at its origin, removing the blockage through this access and reimplantation (re-joining) of the vessel at the same original level) or conventional CEA (longitudinal opening of the artery followed by removal of the blockage and suture with or without an enlargement patch). The review found that there was not enough evidence to show either the benefits or adverse effects of these two methods. Eversion CEA may lower the risk of restenosis (renarrowing) of the artery but more research is needed.

BACKGROUND

In the last few decades carotid endarterectomy (CEA) has undergone intensive evaluation, criticism, and subsequent acceptance as an effective method for stroke prevention (ECST 1991; NASCET 1991; ACAS 1995; ECST 1998; NASCET 1998). Indications for CEA have been defined, outcomes have markedly improved, and technical aspects have evolved significantly. However, the ideal surgical technique to optimise early outcome and long-term durability of CEA has yet to be determined.

The most frequently employed technique for CEA is conventional CEA, performed through a longitudinal arteriotomy of the internal carotid artery. Eversion endarterectomy of the carotid artery was initially reported by DeBakey et al and later described by Etheredge (DeBakey 1959; Etheredge 1970). This technique is performed through a transverse rather than a longitudinal arteriotomy, thus the artery is less prone to restenosis, particularly when sutures are placed at the widest part of the artery (i.e. common carotid artery or the base of the carotid bulb). The reported perioperative major complication rate in patients undergoing eversion CEA, as part of non-randomised case series, ranges from 1% to 4% (Berguer 1993; Cao 1997; Darling III 1996; Entz 1996; Raithel 1993; Kieny 1993; Reigner 1995; Vanmaele 1990; Shah 1998; Peiper 1999; Economopoulos 1999; Raftopoulos 2000; Chang 2000; Green 2000; Radak 2000; Katras 2001; Mehta 2001). Long-term risk of recurrent stenosis is low, about 1% over five years (Koskas 1995). However, if not performed properly, there is the possibility that a distal intimal flap may remain, with potentially dangerous consequences.

Carotid restenosis after conventional CEA has been reported in 6% to 36% of patients; the reported risk of symptomatic restenosis ranges from 2% to 4%. The majority of carotid restenosis occur between three and 18 months after surgery (Frericks 1998; Moore 1998). Although the relationship between carotid restenosis and risk of stroke is still unclear, reduction in restenosis rates may decrease the need for restenosis-related procedures (diagnostic and therapeutic), patients' management, and costs.

There is still much controversy about the relative benefits of the different surgical techniques for CEA. To date there are no systematic reviews on this topic.

OBJECTIVES

To determine efficacy and safety of eversion CEA technique with respect to conventional technique for CEA. The null-hypothesis was that there was no difference between the eversion and the conventional CEA technique (performed either with primary closure or patch angioplasty) with respect to:

- stroke and death;
- carotid restenosis and carotid occlusion;
- risk of local complications;
- procedure-related costs (if available).

METHODS

Criteria for considering studies for this review

Types of studies

The aim was to identify and analyse randomised controlled trials (RCTs), i.e. trials comparing eversion to conventional CEA, employing true randomisation or quasi-randomisation methods (in quasi-randomised trials, the criteria for allocating type of treatment were not strictly random but based on factors such as patient's date of birth, hospital record number, alternation, etc), published or unpublished.

To prevent sampling bias and biased planned treatment, uncontrolled studies or trials in which the criteria for allocation of treatment was not clear were excluded.

True randomised and quasi-randomised controlled trials were combined in the analysis.

Studies were included when:

- patient follow up was included;
- the surgical operation performed was conventional (longitudinal arteriotomy closed by patch or primary closure) or eversion (carotid transection and reimplantation through transverse suture line) CEA;
- follow up was systematic and not performed only in the case of symptoms;
- patients (and carotid arteries) were followed up with clinical and/or imaging techniques (i.e. duplex scan).

Studies were excluded when:

- focused on combined carotid surgery only (i.e. CEA and coronary artery bypass grafting (CABG) or CEA plus peripheral vascular surgical repair);
- the carotid bifurcation was completely resected and replaced by a graft;
- only external carotid artery endarterectomies were performed;
- epiaortic vessels different from the internal carotid artery were involved (i.e. the subclavian or common carotid arteries).

The following variables were considered essential in determining the risk of outcomes and were extracted from each trial:

- number of patients and arteries at risk;
- number of patients and arteries with restenosis;
- number of patients with stroke and death after CEA;
- average follow-up time;
- definition of restenosis.

Types of participants

Patients of all ages and either gender with carotid stenosis undergoing CEA were considered eligible for inclusion. Patients were included regardless of the degree of carotid stenosis and whether the initial indication for endarterectomy was symptomatic or asymptomatic carotid stenosis.

Types of interventions

Eversion carotid technique for CEA versus standard technique for CEA performed with primary closure or patch carotid angioplasty.

Types of outcome measures

Outcome measures had been defined by the trial authors.

Primary outcomes

(1) All strokes and/or deaths occurred perioperatively (within 30 days of operation)
(2) Carotid restenosis or occlusion, early or during follow up

Strokes were classified as disabling or non-disabling (as defined by trial authors), fatal or non-fatal, contralateral, ipsilateral, brainstem, haemorrhage, or infarct.

Secondary outcomes

(1) Any perioperative stroke (within 30 days of operation)
(2) Perioperative disabling strokes (within 30 days of operation)
(3) Perioperative ipsilateral strokes (within 30 days of operation)
(4) Perioperative cardiac events (within 30 days of operation)
(5) All strokes during the follow-up period and perioperative deaths
(6) Local complications, perioperative (within 30 days) or later (e.g. cranial nerve injuries, rupture of the artery, infection, pseudoaneurysm formation)
(7) Duration of operation, length of hospital stay, and procedure-related costs (if data were available)

Search methods for identification of studies

Relevant trials were identified in the Cochrane Stroke Group Trials Register. The Register was last searched by the Trials Register Administrator on 29 July 2002.

(1) We also searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, 2002 Issue 4) and MEDLINE (1966 to December 2002) (Appendix 1), and EMBASE (1980 to December 2002) (Appendix 2).

(2) We carried out systematic handsearching of available volumes of the following journals:

- *American Journal of Surgery* (1990 to December 2002);
- *Annals of Surgery* (1990 to December 2002);
- *Annals of Vascular Surgery* (1992 to December 2002);
- *British Journal of Surgery* (1990 to December 2002);
- *European Journal of Vascular and Endovascular Surgery* (1995 to December 2002);
- *Giornale Italiano di Chirurgia Vascolare* (1990 to December 2002);
- *Journal of Vascular Surgery* (1989 to December 2002);
- *Surgery* (1990 to December 2002).

(3) Specialists currently involved in research were contacted and asked to review the list of identified trials and provide details of additional trials they knew of.

Data collection and analysis

Trial selection for inclusion in this review was carried out independently by two reviewers (PDR, SZ). One reviewer identified all trials of possible relevance and forwarded them to the second reviewer. Selected studies underwent independent assessment by both reviewers. The reviewers decided which trials were suitable and evaluated the methodological quality. Discrepancies were resolved by discussion. The two reviewers independently extracted and analysed data from the trials included. No score system was used to assess quality. The following items were evaluated:

- method of randomisation (i.e. generation of the randomised sequence and concealment of the random sequence from physicians participating in the trial);
- blinding of the assessment (duplex and clinical);
- number of patients lost to follow up;
- number of patients initially randomised but subsequently not included in the analysis (i.e. cross-over and withdrawn) were recorded for estimation of quality adequacy.

When any of the above details were not available from the published report, the authors were contacted directly either by mail or telephone to obtain further information.

Journal articles that reported patient data used in previous studies from the same Institution were excluded, except when in the methods section it was absolutely clear that patients did not overlap, or when methodology and outcomes were different among studies.

In patients with outcome events allocated according to type of treatment (eversion or conventional CEA), an intention-to-treat analysis, regardless of compliance with the planned treatment, was attempted.

Data analysis

For each specified outcome, a pooled estimate of treatment effects (odds ratio for binary outcomes) through the studies was calculated. The statistical package, RevMan, provided by the Cochrane Collaboration was used. We tested heterogeneity between trials using a standard Chi-squared test. A significance level less than 0.05 was interpreted as evidence of heterogeneity. Depending on the presence or absence of RCT variability, a random-effects model or a fixed model (Peto) was used. Odds ratios (OR) and 95% confidence intervals (CI) of homogeneous dichotomous data were calculated by the Peto method and the results were pooled using a fixed-effect model. A random-effects model was used for heterogeneous dichotomous data.

In the presence of significant heterogeneity, sensitivity analysis was planned based on the quality of the trials (allocation concealment, blinding, or sample size calculation).

Truly randomised and quasi-randomised controlled trials were combined in the analysis.

RESULTS

Description of studies

Six trials that achieved eligibility criteria for inclusion in the review were identified. One of these had been published as an abstract (Darling 1995) and was excluded. After clarification with the principal investigator, it became clear that this trial was planned with a randomised design; however, randomisation was discontinued and the study proceeded in a prospective non-randomised fashion. The randomised phase of this study could provide information on primary and secondary end-points considered in our review. Yet, a significant amount of data was missing. The author was contacted but data are no longer available for inclusion.

Five trials comparing conventional carotid endarterectomy to eversion carotid endarterectomy (Balzer 1998; Vanmaele 1994;

Ballotta 1999; Ballotta 2000; EVEREST 1998) were included in this review. Two reports were from the same trial referring to early and late results (EVEREST 1998). Two separate randomised trials by Ballotta were included: one (Ballotta 2000) included only patients requiring bilateral carotid endarterectomies. Patients were randomised to be treated with staged different techniques for CEA on each side: eversion followed by contralateral patch or patch followed by contralateral eversion CEA. Some patients in this study had been recruited also in the larger randomised trial by the same author included in this review (Ballotta 1999). To avoid that overlapping of patients which could influence the results of the review, we contacted the principal investigator of these trials. Correspondence with the author provided us with the exact number of patients (eighteen) and related outcome events already included in the previous study, and these were excluded, leading 68 patients in the analysis. Therefore, the results displayed in this review differ from those shown in the published report by the author.

For the purposes of this review, we considered only events occurring ipsilateral to the operated carotid artery.

All trials included in the review had two arms of randomisation: eversion and conventional CEA techniques. In the EVEREST trial (EVEREST 1998) the eversion technique was compared to both primary closure and patch angioplasty techniques for conventional carotid endarterectomy. In the study by Vanmaele et al (Vanmaele 1994) the eversion technique was compared to saphenous vein patch angioplasty. In three studies only synthetic patch, dacron (Balzer 1998) or polytetrafluoroethylene (Ballotta 1999; Ballotta 2000), was considered for comparison with the eversion technique.

In the study by Vanmaele two different types of eversion technique (retrograde endarterectomy and eversion division endarterectomy anastomosis) were employed (Vanmaele 1994).

Risk of bias in included studies

There were some methodological flaws in the included trials. Four studies used a list of random-generated numbers (Vanmaele 1994; Ballotta 1999; EVEREST 1998; Ballotta 2000). In three of these, sealed envelopes were employed for randomisation (Ballotta 1999; EVEREST 1998; Ballotta 2000). However, only in one study (EVEREST 1998) was it clear from the published report that patient allocation was performed with the use of sequentially numbered sealed envelopes. Correspondence with the investigators of the other studies confirmed that sequentially numbered opaque envelopes were used in two studies (Ballotta 1999; Ballotta 2000) but not in the other (Balzer 1998). The method of concealment of allocation was unknown in one trial (Vanmaele 1994).

In the EVEREST (EVEREST 1998) and Balzer (Balzer 1998) trials sample size calculations were used to manage the conduct of the study.

With respect to blinding in the assessment of outcome events, duplex evaluation in follow up was performed only in three trials by operators blinded to the initial treatment allocation (Ballotta 1999; Ballotta 2000; EVEREST 1998). However, due to the different morphology of the operated arteries in each treatment group (eversion or synthetic patch), complete blinding was impossible.

With respect to blinding in the post-operative clinical assessment, in four trials (EVEREST 1998; Ballotta 1999; Ballotta 2000, Vanmaele 1994) an independent auditor, such as a neurologist or ophthalmologist, evaluated patients. Instead, in the Balzer trial, clinical assessment and follow up were performed by the operating surgeon (Balzer 1998).

One of the main flaws in three of the trials was that a patient undergoing bilateral CEA could be randomised twice and have the two carotid arteries randomised to different treatment groups (Vanmaele 1994; Ballotta 1999; Ballotta 2000), so that the same patient could be exposed twice to risk.

In the EVEREST trial (EVEREST 1998) patients were randomised once. In the study by Balzer (Balzer 1998), correspondence with the author clarified that, in case of bilateral CEA, only the first operation was considered for randomisation and the same CEA technique was performed on both sides. In three trials, patients undergoing bilateral CEA were included so that the same patients could be exposed twice to risk (Ballotta 1999; Ballotta 2000; Vanmaele 1994). Fortunately, the number of bilateral procedures was low (124/2589, 4.7% of the total). In the studies by Ballotta et al (Ballotta 1999; Ballotta 2000), the exact number of randomised patients for each arm was specified in the published report. In the other study (Vanmaele 1994), the number of arteries randomised to each arm was available, yet it was not clear how many patients (as opposed to arteries) were randomised to each treatment group because 30/170 patients had undergone bilateral procedures. In this trial there was little information on patient risk for any stroke and death. Therefore, the study was excluded from the main analyses of clinical events of our review. However, we believe it is reasonable to include the study in a separate analysis of clinical outcomes (stroke, death, ipsilateral stroke).

Some differences were found in the definition of stroke. In two studies (Vanmaele 1994; Balzer 1998) only permanent neurological deficits were considered, whereas in three other studies (EVEREST 1998; Ballotta 1999; Ballotta 2000) all neurological deficits lasting more than 24 hours were reported as 'any stroke'.

Although local complications such as cranial nerve lesions were reported in most studies, not all considered these as outcome events, therefore there was no systematic evaluation of these lesions.

Mean age of patients was 68 years (range 38 to 92 years) and male patients were two times more frequent than females. All trials included patients with symptomatic and asymptomatic carotid disease. The percentage of asymptomatic patients between the eversion and conventional groups in all studies were similar.

There was no imbalance in the rates of risk factors between the eversion and conventional groups in all the examined studies.

In one study, 'in hospital' rather than 'perioperative' events were reported (Balzer 1998). However, because late data were also reported separately, information regarding the whole perioperative period (within 30 days after surgery) was obtained.

Follow up ranged from one to 69 months. Overall, 33 patients were lost to follow up: 20 in the eversion group and 13 in the conventional group.

Two studies had patients who crossed over from one treatment arm to the other (EVEREST 1998; Vanmaele 1994). Twenty-two of 24

overall crossover patients were from the EVEREST study and data were available for intention-to-treat analysis.

Further details on the included studies are shown in the table on 'Characteristics of Included Studies'.

Effects of interventions

Outcomes included

Perioperative stroke and/or death (Figure 1)

Four trials were eligible for the analysis (Ballotta 1999; Ballotta 2000; Balzer 1998; EVEREST 1998). The cumulative unweighted risk of stroke and/or death within 30 days of surgery was low (2.1%): 51 events were recorded, 20 events were found in the eversion CEA group and 31 in the conventional CEA group (OR 0.44, 95% CI 0.10 to 1.82). No definite conclusions could be drawn.

Significant heterogeneity was found among the results of the trials in this outcome; sensitivity analyses were performed (see Figures 9 and 10). This variability could be due to the fact that in the smallest trials (Ballotta 1999; Ballotta 2000) all operations were performed by a single surgeon and sample size of the study population had not been calculated. In fact, significant heterogeneity disappeared when these small studies were not taken into account (Figure 9).

Perioperative death (Figure 2)

There were 15 perioperative deaths in the four trials eligible for this analysis (Balzer 1998; Ballotta 1999; Ballotta 2000; EVEREST 1998) - seven in the eversion CEA and eight in the conventional CEA group. No definite conclusions can be drawn on whether conventional CEA is associated with higher or lower perioperative death than eversion CEA (Peto OR 0.86, 95% CI 0.31 to 2.37). Five perioperative deaths, four in the eversion CEA and one in the conventional CEA group, were stroke-related.

Any perioperative stroke (Figures 3 to 6)

The number of perioperative strokes was available in four trials. Forty-one perioperative strokes (fatal, non-fatal, contralateral, ipsilateral brainstem, haemorrhage, or infarct) were recorded: 17 in the eversion group and 24 in the conventional group. The benefits or hazards of eversion CEA in perioperative stroke risk from these data remains unclear (Peto OR 0.70; 95% CI 0.38 to 1.29).

In all of the trials available the absolute risks of perioperative stroke were low irrespective of treatment: 41/2363 (1.7%). Furthermore, the risk of perioperative stroke was particularly low in the small trials (i.e. excluding the EVEREST trial), especially in the eversion group. A possible influence on these results could be the lack of blinding in one of the small studies (Balzer 1998) in which post-operative clinical assessment was performed by the surgeon and not by an independent audit. Furthermore, in two other small trials (Ballotta 1999; Ballotta 2000) all operations were performed by a single surgeon and sample size of the study population had not been calculated. These methodological flaws could have biased the results in small trials. Sensitivity analyses were performed (Figures 4 to 6).

Any perioperative disabling stroke (Figure 7)

Four trials (Balzer 1998; Ballotta 1999; Ballotta 2000; EVEREST 1998) provided data on perioperative disabling stroke risk: 25 perioperative major strokes were recorded: nine in the eversion group and 16 in the conventional group. Again, the benefits or hazards of eversion CEA were still not clear (Peto OR 0.56, 95% CI 0.25 to 1.23).

Any perioperative ipsilateral stroke (Figure 8)

The overall risk was low (1.6%). There were no significant differences in the risk of perioperative strokes ipsilateral to the operated carotid artery: Peto OR 0.92, 95% CI 0.44 to 1.93.

Perioperative arterial complications occurring within 30 days of surgery (analysed in relation to arteries and not to patients)

Early carotid occlusion (Figure 11)

Four trials reported the risk of early carotid occlusion (Ballotta 1999; Ballotta 2000; EVEREST 1998; Vanmaele 1994). Overall, 18 carotid occlusion occurred. There was a non-significant trend in favour of eversion CEA (Peto OR 0.62, 95% CI 0.24-1.58). Six early carotid occlusions were associated with fatal or disabling stroke.

Neck hematoma (Figure 12)

Four trials reported the number of neck hematomas requiring surgical re-exploration. No significant differences were observed between the eversion and conventional CEA groups: 4.2% versus 5.5% (Peto OR 0.76, 95% CI 0.52 to 1.11).

Cranial nerve injuries (Figure 13)

Based on the available data, risk of cranial nerve lesions after CEA was not negligible (4.7%) and showed a non-significant trend in favour of the eversion technique. Yet, no definite conclusions can be drawn (OR 0.52, 95% CI 0.22 to 1.23).

Perioperative myocardial infarction (within 30 days of surgery) (Figure 14)

Two studies reported data for this outcome (EVEREST 1998; Ballotta 1999). Only nine myocardial infarctions were reported in the perioperative period, so the overall risk was low (0.5%). Due to the small number of events, no definite conclusions can be drawn (Peto OR 0.79, 95% CI 0.21 to 2.92).

Clinical outcomes during late follow up

All the studies had a minimum follow up of one year; a total of 33 patients lost to follow up were recorded.

Stroke during follow up (excluding perioperative) (Figure 15)

The overall risk of late stroke based on the three studies (EVEREST 1998; Balzer 1998; Ballotta 1999) available for the analysis was low (1.6%). If all the patients lost to follow up were assumed to be alive and stroke free, significant uncertainty remains on the benefit in terms of any stroke risk for patients undergoing eversion CEA: 16 late strokes in patients allocated to eversion CEA versus 19 in the conventional CEA group (Peto OR 0.84, 95% CI 0.43 to 1.64).

Ipsilateral stroke during follow up (excluding perioperative) (Figure 16)

There were few late ipsilateral strokes in the two studies eligible for the analysis - nine in the eversion group and four in the conventional group. Due to the small number and wide confidence intervals, no firm conclusions were drawn on the benefit of eversion CEA on the risk of late ipsilateral stroke (Peto OR 2.16, 95% CI 0.73 to 6.45).

Arterial occlusion or restenosis > 50% during follow up (Figures 17 to 22)

Five studies were considered (EVEREST 1998; Balzer 1998; Vanmaele 1994; Ballotta 1999; Ballotta 2000). Perioperative carotid occlusions were excluded from this analysis. All five trials provided data on the number of arteries that became occluded or developed restenosis > 50% (as assessed by duplex ultrasound) by the end of follow up. All studies had a minimum follow up of one year. A total of 33 patients lost to follow up were recorded. As all these patients were randomised only once, 33 arteries were lost to follow up, 20 in the eversion CEA group and 13 in the conventional CEA group.

In the main analysis all arteries lost to follow up were assumed not to have been restenosed or occluded (best clinical scenario; Figure 17). Eversion CEA was associated with a lower risk of carotid occlusion or restenosis (32/1290 versus 66/1267; Peto OR 0.48, 95% CI 0.32 to 0.72). This was equivalent to preventing occlusion or restenosis in about 100 of 3660 operated arteries. However, if all the arteries that were lost to follow up in the eversion group were assumed to have become restenosed while none of those lost to follow up in the conventional group became restenosed (worst scenario; Figure 18), the results became non-significant (OR 0.53, 95% CI 0.17 to 1.69). The clinical significance of this reduction in risk of carotid restenosis/occlusion is unknown.

All strokes during follow-up period and perioperative deaths (Figure 23)

There were no significant differences between treatment groups: 23 events were found after eversion CEA and 27 after conventional CEA (Peto OR 0.84, 95% CI 0.48 to 1.47). Similarly, no significant differences were found only for strokes occurring ipsilateral to the operated carotid artery during follow up together with perioperative deaths (Figure 24): due to the small number and wide confidence intervals, no firm conclusions were drawn.

Periprocedural costs, duration of operation and of hospital stay

No data are available for the analyses.

Sensitivity analysis

Sensitivity analyses were performed and the treatment effect still remained when the poorer quality trials were excluded. In detail, it was investigated whether:

- trials using adequate concealment in randomisation differed from trials using inadequate concealment methods;
- trials using more rigorous blinding differed from those with poor blinding assessment;
- small trials differed from those with large sample size;
- trials in which sample size had been calculated differed from those without this estimation.

Results are shown in Figures 3, 4, 5, 9, 10, 19, 20, 21 and 22 of the analyses.

Separate subsidiary analyses

(1) Separate analysis of clinical outcomes was performed including also the study in which the number of deaths and strokes was not available on a patient (rather than artery) basis in each allocated treatment group (ie, Vanmaele 1994). This study had been excluded in calculating patient-related outcome events such as death and any stroke in the main analysis of this review. However, given that relatively few patients had bilateral procedures, we felt it reasonable to include this study in a separate analysis. These results should be interpreted with caution.

No substantial differences were found with respect to the main analysis (see Figures 25 to 30); no definite conclusion can be drawn from these additional data in the benefits (or hazards) of eversion CEA for each of the outcomes analysed.

(2) An additional separate analysis of clinical outcomes was performed excluding the study in which all the patients had undergone bilateral procedures (Ballotta 2000). We specifically excluded this study from all the analyses of patient-level effect (death, stroke, etc). However, due to the small number of events reported in this study, no substantial differences were found with respect to the main results of our review. Risk of perioperative stroke and/or death based on this analysis is reported in Figure 31.

Other details of the main and separate analyses are shown.

DISCUSSION

Changes in surgical techniques may affect the outcome of CEA. Although encouraging results regarding restenosis rates have been described with eversion CEA, a relative reluctance to perform this technique remains. The results of the present review of five randomised trials suggest that eversion CEA appears to be associated with a similar rate of major clinical outcome events (i.e. perioperative or late stroke) when compared to conventional CEA; however, since these are few in number, significant uncertainty remains.

The unweighted absolute risk of stroke and/or death within 30 days of CEA found in our review was exceptionally low regardless of the type of treatment: 51/2363 (2.1%). This finding could be due to the high proportion, balanced between the treatment groups, of asymptomatic patients in the included studies.

Furthermore, we found that the risk of perioperative stroke was particularly low in the eversion group of small trials. The poor quality of blinding in assessment (and of allocation concealment) of some small trials could have biased the results of this analysis. Therefore, due to the low absolute risk of stroke, our results should be applied with caution to high-risk populations.

An insufficient number of local complications were reported to compare risks associated with eversion and conventional CEA. Similarly, with respect to risk of early carotid occlusion, the data of this review were inconclusive.

A statistically significant decrease in the risk of restenosis and arterial occlusion during follow up in patients undergoing eversion CEA when compared to conventional CEA was observed. This was equivalent to the prevention of about 100 carotid occlusion/restenosis per 3660 operated arteries with eversion technique. However, as yet these results are not statistically robust because of the limited number and the losses to follow up. Yet, if we consider the worst case scenario, i.e. assuming that all eversion CEA procedures lost to follow up were occluded or restenosed, while none were lost in the primary closure group, the difference between eversion and conventional CEA was not significant.

Carotid restenosis could be considered as a 'soft' outcome susceptible to poor reliability. Measurement of carotid restenosis was based on ultrasonography evaluations and criteria which differed in all the studies examined. Interobserver variability and potential inaccuracy may have biased the assessment of these outcomes. In this regard, differences in defining other outcomes in various studies should also be considered: i.e. not all trials used the same definition for stroke or the same criteria in evaluation of cranial nerve injuries. We accepted all outcome measures as defined by the trial author. Since we considered restenosis as a relevant measure of failure in CEA treatment, all restenoses as defined by the trial author were considered valid.

Furthermore, due to the different morphology of the operated arteries on duplex scan in each treatment group (eversion, synthetic patch, primary closure), complete blinding was impossible in detecting carotid restenosis. Due to these unavoidable flaws, the results of this review should be applied with caution.

It remains unclear whether restenosis or carotid occlusion increased the risk of clinical neurological events. Restenosis detected by routine duplex scanning may not be clinically important. In one study of our review (EVEREST 1998) there was no significant association between restenosis and risk of stroke, and only one patient with ipsilateral stroke subsequent to restenosis was found. However, no definite conclusions can be drawn on the impact of the eversion technique on the risk of restenosis-related stroke.

There is evidence that carotid patching is associated with reduced risk of arterial occlusion and restenosis (Counsell 1999), however, the costs of prosthetic material and procedural timing for patching have not been determined in the analysed trials. In four studies of our review, only CEA with patch (of different materials) was considered in comparison to the conventional CEA group: Dacron in Balzer study (Balzer 1998), polytetrafluorethylene in Ballotta studies (Ballotta 1999; Ballotta 2000) and saphenous vein in Vanmaele study (Vanmaele 1994). Data were insufficient to draw conclusions on whether carotid patching was associated with fewer outcome events in comparison to eversion CEA.

It should be noted that some flaws were present in the studies included in this review. Some of these trials were too small to achieve an adequate statistical power. Moreover, in the smallest trials (Ballotta 1999; Ballotta 2000), the sample size had not been calculated.

Finally, considering that three trials included patients undergoing bilateral endarterectomy, analysis of clinical outcome events for these patients may be inaccurate. In trials that had been randomised at the level of the artery, data analysis at the level of the patient was inevitably inaccurate because the same patient can be exposed twice to risk of death or stroke. In patients undergoing bilateral procedures, it is difficult to establish on which side stroke or perioperative complications were related. Fortunately, in most trials it was clear in the reports the exact number of randomised patients for each arm and whether strokes occurring after surgery were ipsilateral to the operated artery. Eversion CEA was not associated with increased risk of ipsilateral stroke.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence from randomised trials to reliably determine the relative risks and benefits of eversion and conventional CEA. It is possible that carotid eversion is associated with a lower risk of long-term carotid occlusion and restenosis but it is still unclear whether this is associated with a lower rate of subsequent neurological events. Procedural costs were not studied in RCTs, thereby no clear indication can be given on this matter. Until better evidence is available, the choice of the surgical technique for CEA should depend on the experience and preference of the operating surgeon.

Implications for research

Further randomised trials are needed to more precisely define the relative and absolute benefits and risks of eversion and conventional carotid endarterectomy, and establish the importance (or not) of restenosis of the carotid artery (that was previously operated on) as a cause of subsequent as far as we know, since our initial review two years ago. Studies analysing the costs of eversion and conventional carotid endarterectomy are also needed.

Further investigation is required to define the clinical significance of restenosis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ballotta 1999

Methods	Monocentric, single surgeon Randomisation: list of randomly generated binary digits No sample size calculation Patient assignment by sequentially numbered, sealed, opaque envelopes Recruitment period: 5 years Mean duration of follow up 34 months (range 1.69 months) No patients were lost to follow up
Participants	310 patients (31% female) Mean age 70 years (41 to 89 years)

Ballotta 1999 *(Continued)*

	336 CEA 26 bilateral CEA Asymptomatic = 46%: 45% in eversion group and 48% in control group
Interventions	Two groups. Control: PTFE patch CEA Treatment: 169 arteries by eversion CEA and 167 arteries by CEAP (carotid endarterectomy with PTFE patch) 158 patients by eversion and 152 patients by patch
Outcomes	Perioperative mortality Perioperative stroke Recurrent carotid stenosis/occlusion Local complications: neck hematoma, cranial nerve injuries Perioperative myocardial infarction
Notes	Exclusions: repeated CEA; CEA with combined CABG, or patients with associated supraaortic trunk lesions requiring contemporary surgery Patients randomised twice = 26 (bilateral procedures)

Risk of bias

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

Ballotta 2000

Methods	Monocentric, single surgeon Randomisation: list of randomly generated binary digits No sample size calculation Patient assignment by sequentially numbered, sealed, opaque envelopes Only patients undergoing bilateral CEA were randomised to sequential surgical treatment (staged eversion/patch or patch/eversion) Mean duration of follow up 40 months (range 6 to 69 months) No patients were lost to follow up
Participants	68 patients (25% female) Mean age 70 years (range 41 to 84 years) 68 CEA, all 68 bilateral Asymptomatic = 36%: 35% in eversion group and 38% in control group
Interventions	Two groups Control: PTFE patch CEA Treatment: 68 eversion CEA followed by contralateral PTFE patch CEA and 68 PTFE patch CEA followed by contralateral eversion CEA
Outcomes	Perioperative mortality Perioperative stroke Recurrent carotid stenosis/occlusion Local complications: neck hematoma, cranial nerve injuries
Notes	Some patients (18) were included in another study in the review. These patients and related outcome events were excluded from the analysis Exclusions: repeated CEA; CEA with combined CABG, or patients with associated supraaortic trunk lesions requiring combined surgery

Ballotta 2000 *(Continued)*

	All patients underwent CEA twice with a different technique on each side (= 68)

Risk of bias

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

Balzer 1998

Methods	Monocentric, different surgeons Randomisation: blocks of 50 changing the operative method on a monthly term Sample size: 300 for each group Recruitment period: 1 year Mean follow up: 24 months Lost to follow up: 22 (3.9%); 9 in Dacron patch group and 13 in eversion CEA
Participants	564 patients (34% female) Mean age 66 years No patients randomised twice
Interventions	Two groups Control: Dacron patch CEA Treatment: 286 eversion CEA and 278 Dacron patch CEA
Outcomes	Perioperative (in hospital) death Perioperative (in hospital) stroke Recurrent carotid stenosis Late stroke Late death Perioperative local complications: neck hematoma
Notes	Exclusions: repeated CEA, bilateral CEA

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

EVEREST 1998

Methods	Multicentric: 7 centers Randomisation: computer-generated list stratified for each site by the central co-ordinating center Sample size: 600 in each group Patient assignment by sequentially numbered, sealed envelopes Recruitment period: October 1994 to March 1997 Cross-over = 22 Mean follow up: 33 months (12 to 55 months) Lost to follow up: 11(0.8%): 4 in conventional CEA group and 7 in eversion CEA
Participants	1353 patients (27% female) Mean age 69 years (38 to 92 years) 1353 CEA

EVEREST 1998 *(Continued)*

	No patients randomised twice Asymptomatic = 56%: 55% in eversion group and 56% in control group
Interventions	Two groups Control: conventional CEA (primary closure or patch) Treatment: 678 eversion CEA and 675 conventional CEA (419 primary closure and 256 patch)
Outcomes	Perioperative death Perioperative and late stroke Early carotid occlusion Carotid restenosis/occlusion Perioperative local complications: neck hematoma, cranial nerve injuries Perioperative myocardial infarction
Notes	Exclusions: repeated CEA, CEA with concomitant CABG or requiring contemporary surgery; bilateral CEA; emergencies Bilateral CEA: all patients were randomised once

Risk of bias

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

Vanmaele 1994

Methods	Monocentric Randomisation: non-stratified; following a list of at random generated binary digits Cross-over = 2 Recruitment period: November 1988 to November 1991 Mean follow up = 338 days (375 + 276 days) No patients were lost to follow up
Participants	170 patients (23% female) Mean age 65 years (43 to 85 years) 200 CEA 30 patients randomised twice (bilateral procedures) Asymptomatic = 23%: 23% in eversion group and 23% in control group
Interventions	Two groups Control: sapheneous vein patch CEA Treatment: 102 eversion CEA and 98 saphenous vein patch CEA
Outcomes	Perioperative death Perioperative and late stroke Carotid restenosis/occlusion Local complications: cranial nerve injuries, false aneurysm
Notes	Exclusions: reinterventions, fibromuscolar dysplasia, kinking, carotid body tumor, aneurysm, dissection Two different techniques for eversion CEA Patients randomised twice = 30 (bilateral procedures)

Risk of bias

Bias	Authors' judgement	Support for judgement

Vanmaele 1994 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Darling 1995	This trial originally had a randomised design but randomisation was discontinued and the trial proceeded in a non-randomised fashion. The principal investigator has been contacted, but the data on the initial randomised patients are no longer available.

DATA AND ANALYSES

Comparison 1. Eversion vs conventional CEA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 perioperative stroke and/or death	4	2363	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.10, 1.82]
2 perioperative death	4	2363	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.31, 2.37]
3 perioperative stroke	4	2363	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.38, 1.29]
4 perioperative stroke large vs small trials	4	2363	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.38, 1.29]
4.1 large trials	1	1353	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.54, 2.43]
4.2 small trials	3	1010	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.24 [0.08, 0.71]
5 perioperative stroke; sample size calculated : yes vs no	4	2363	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.38, 1.29]
5.1 sample size yes	2	1917	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.46, 1.71]
5.2 sample size no	2	446	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.74]
6 perioperative stroke blinding vs no blinding	4	2363	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.38, 1.29]
6.1 blinding	3	1799	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.41, 1.64]

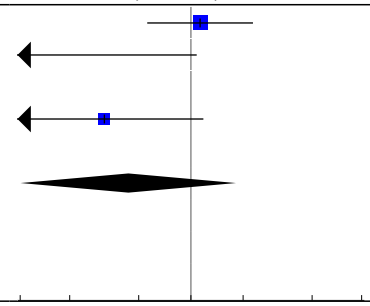
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 poor blinding	1	564	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.09, 1.42]
7 perioperative disabling stroke	4	2363	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.25, 1.23]
8 perioperative ipsilateral stroke	3	1799	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.44, 1.93]
9 perioperative stroke and/or death: sample size yes	4	2363	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.10, 1.82]
9.1 sample size: yes	2	1917	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.20, 2.32]
9.2 sample size: no	2	446	Odds Ratio (M-H, Random, 95% CI)	0.06 [0.00, 1.08]
10 perioperative stroke and/or death quality of randomisation	4	2363	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.10, 1.82]
10.1 class A studies (adequate concealment)	3	1799	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.02, 6.84]
10.2 class B studies (unadequate concealment)	1	564	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.08, 1.18]
11 early carotid occlusion	4	2025	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.24, 1.58]
12 neck hematoma	4	2389	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.52, 1.11]
13 cranial nerve injuries	4	2025	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.22, 1.23]
14 myocardial infarction	2	1663	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.21, 2.92]
15 stroke during follow-up (excluding perioperative)	3	2212	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.43, 1.64]
16 ipsilateral stroke during follow-up (excl. perioperative)	2	1652	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.73, 6.45]
17 restenosis/occlusion best	5	2557	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.32, 0.72]
18 restenosis/occlusion worst	5	2537	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.54, 1.13]
19 restenosis quality blinding	5	2557	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.32, 0.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 adequate blinding	4	1997	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.24, 0.61]
19.2 unadequate blinding	1	560	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.45, 2.54]
20 restenosis sample size	5	2557	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.32, 0.72]
20.1 large sample	2	1904	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.40, 0.99]
20.2 small sample size	3	653	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.07, 0.43]
21 restenosis large vs small trials	5	2557	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.19, 1.02]
21.1 large trials	1	1344	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.29, 0.88]
21.2 small trials	4	1213	Odds Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.44]
22 restenosis quality of randomisation	5	2557	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.32, 0.72]
22.1 class A studies (adequate concealment)	3	1810	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.24, 0.61]
22.2 class B studies (unadequate concealment)	2	747	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.42, 2.16]
23 all strokes during follow-up and perioperative deaths	3	2238	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.48, 1.47]
24 ipsilateral stroke during follow-up and perioperative deaths	2	1674	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.02, 22.08]
25 perioperative stroke and/or death (separate analysis)	5	2563	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.19, 1.29]
26 ipsilateral stroke during follow-up (separate analysis)	4	1983	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.73, 6.45]
27 stroke during follow-up (separate analysis)	4	2407	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.43, 1.64]
28 perioperative disabling stroke (separate analysis)	5	2563	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.28, 1.17]
29 perioperative stroke (separate analysis)	5	2563	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.35, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 perioperative death (separate analysis)	5	2563	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.33, 1.93]
31 perioperative stroke and/or death (separate analysis. 2)	3	2227	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.10, 1.82]

Analysis 1.1. Comparison 1 Eversion vs conventional CEA, Outcome 1 perioperative stroke and/or death.

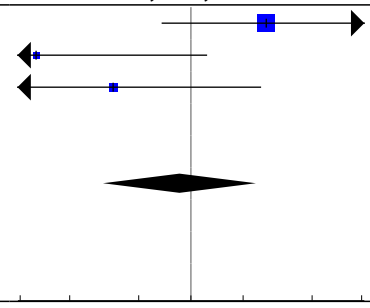
Study or subgroup	Eversion n/N	Conventional n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
EVEREST 1998	17/678	15/675		46.76%	1.13[0.56,2.28]
Ballotta 1999	0/158	7/152		16.83%	0.06[0,1.08]
Ballotta 2000	0/68	0/68			Not estimable
Balzer 1998	3/286	9/278		36.4%	0.32[0.08,1.18]
Total (95% CI)	**1190**	**1173**		**100%**	**0.44[0.1,1.82]**
Total events: 20 (Eversion), 31 (Conventional)					
Heterogeneity: Tau^2=1.01; Chi^2=6.21, df=2(P=0.04); I^2=67.8%					
Test for overall effect: Z=1.14(P=0.25)					



Favours eversion — Favours conventional

Analysis 1.2. Comparison 1 Eversion vs conventional CEA, Outcome 2 perioperative death.

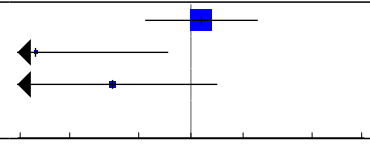
Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	6/678	2/675		53.36%	2.72[0.68,10.92]
Ballotta 1999	0/158	3/152		19.98%	0.13[0.01,1.24]
Balzer 1998	1/286	3/278		26.67%	0.36[0.05,2.54]
Ballotta 2000	0/68	0/68			Not estimable
Total (95% CI)	**1190**	**1173**		**100%**	**0.86[0.31,2.37]**
Total events: 7 (Eversion), 8 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=6.11, df=2(P=0.05); I^2=67.26%					
Test for overall effect: Z=0.29(P=0.77)					



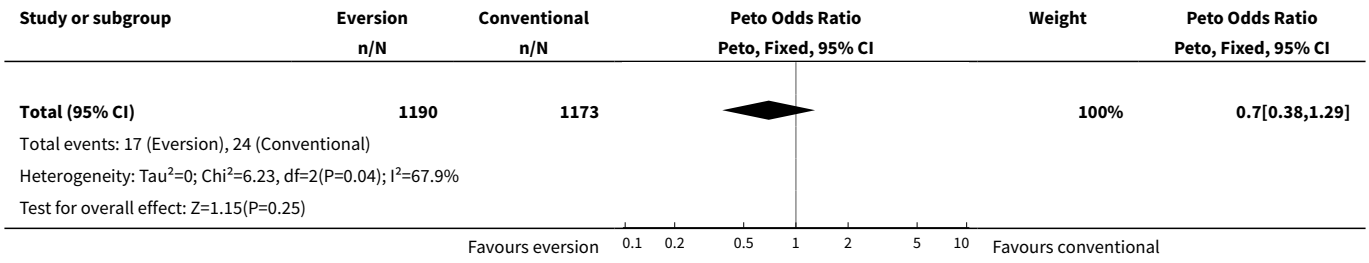
Favours eversion — Favours conventional

Analysis 1.3. Comparison 1 Eversion vs conventional CEA, Outcome 3 perioperative stroke.

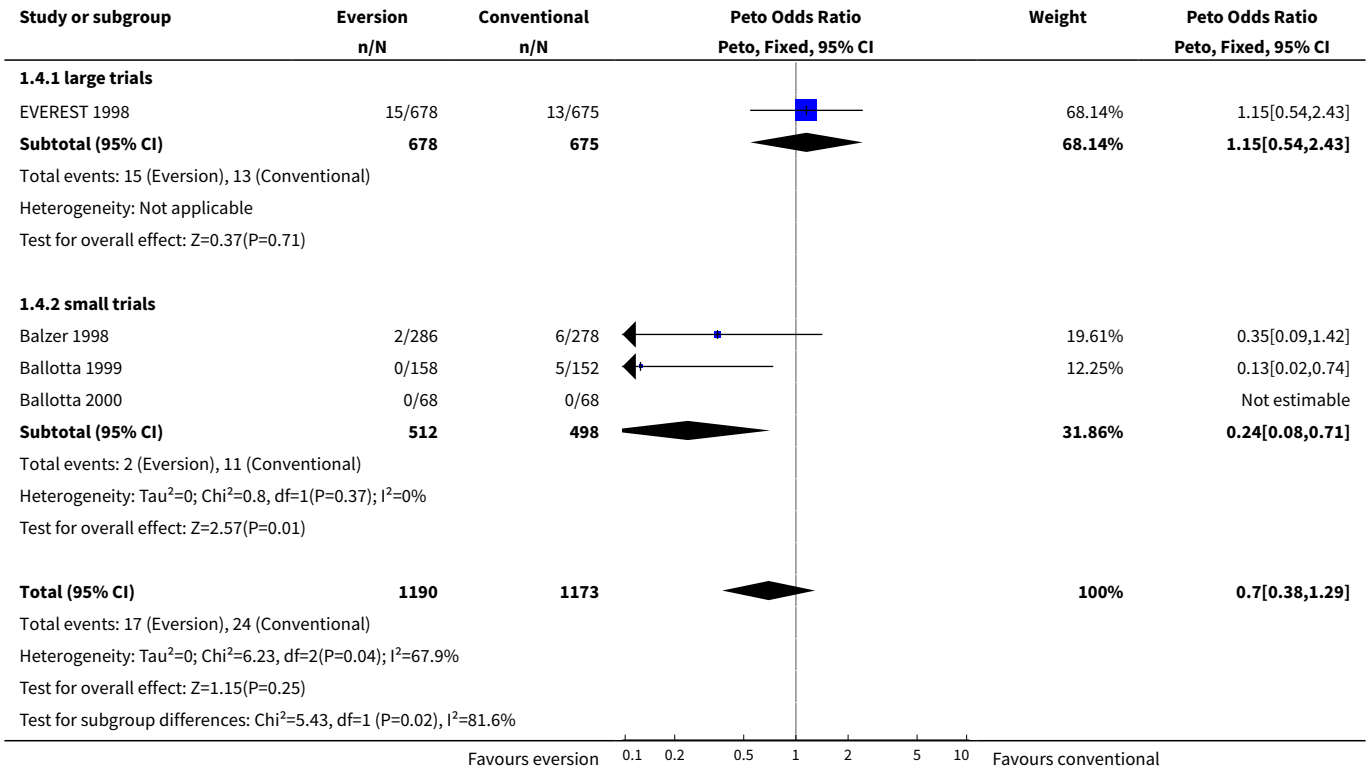
Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	15/678	13/675		68.14%	1.15[0.54,2.43]
Ballotta 1999	0/158	5/152		12.25%	0.13[0.02,0.74]
Balzer 1998	2/286	6/278		19.61%	0.35[0.09,1.42]
Ballotta 2000	0/68	0/68			Not estimable



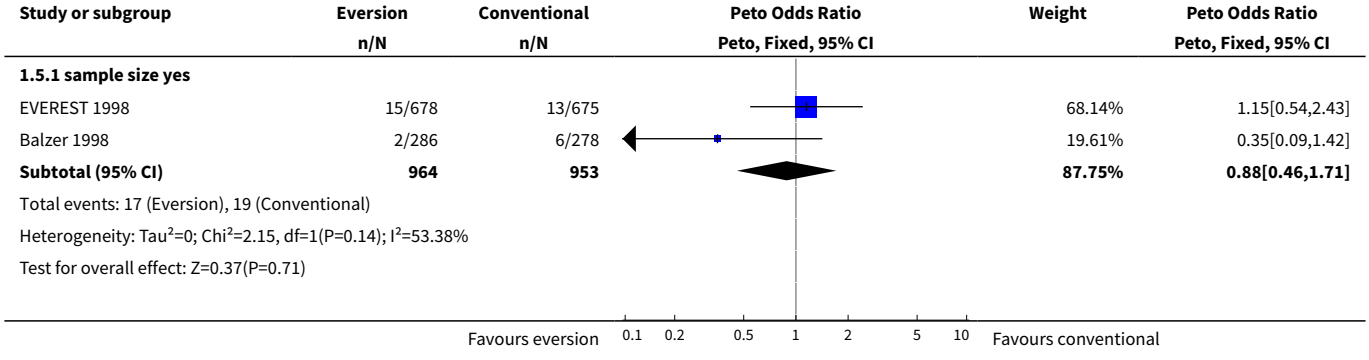
Favours eversion — Favours conventional

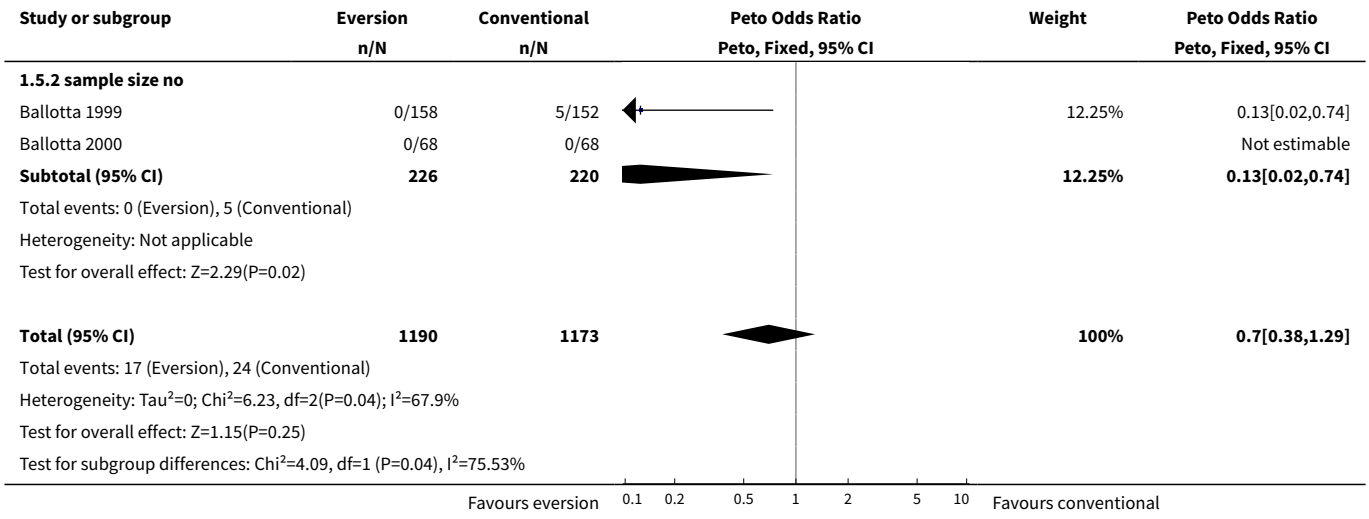


Analysis 1.4. Comparison 1 Eversion vs conventional CEA, Outcome 4 perioperative stroke large vs small trials.

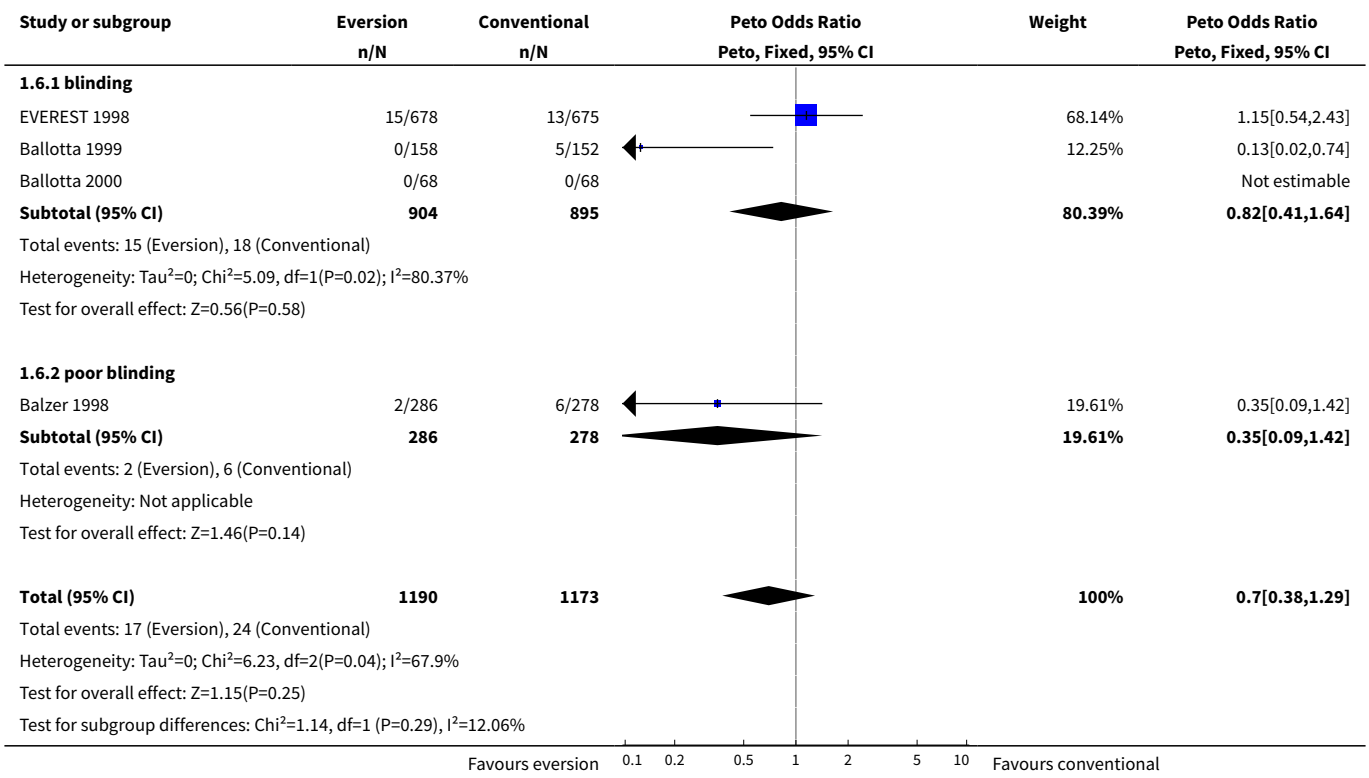


Analysis 1.5. Comparison 1 Eversion vs conventional CEA, Outcome 5 perioperative stroke; sample size calculated : yes vs no.

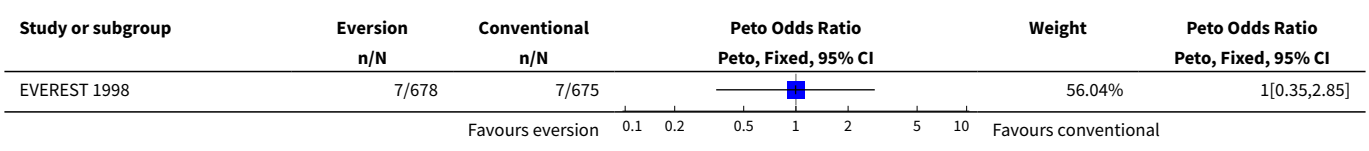


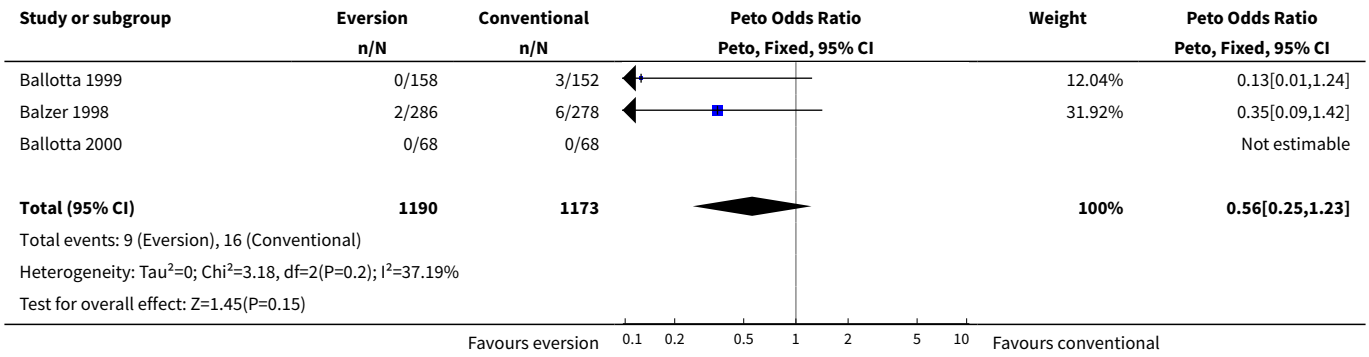


Analysis 1.6. Comparison 1 Eversion vs conventional CEA, Outcome 6 perioperative stroke blinding vs no blinding.

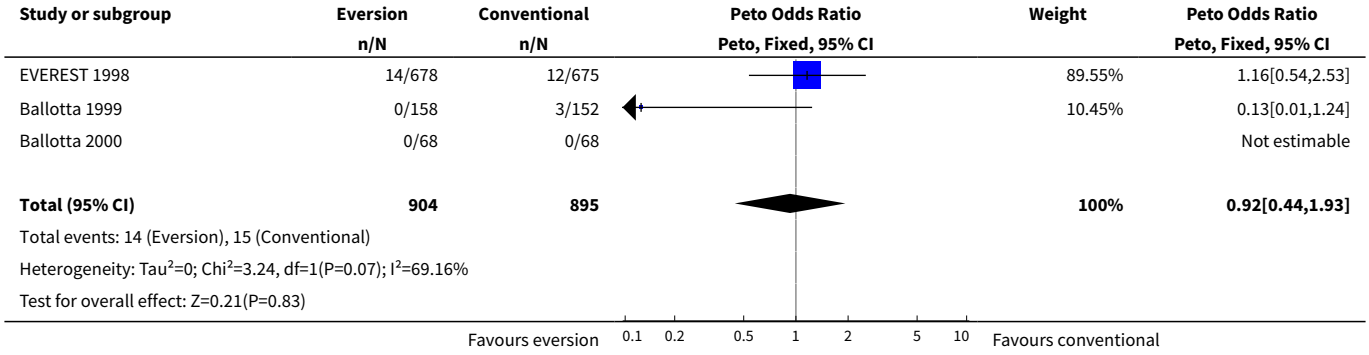


Analysis 1.7. Comparison 1 Eversion vs conventional CEA, Outcome 7 perioperative disabling stroke.

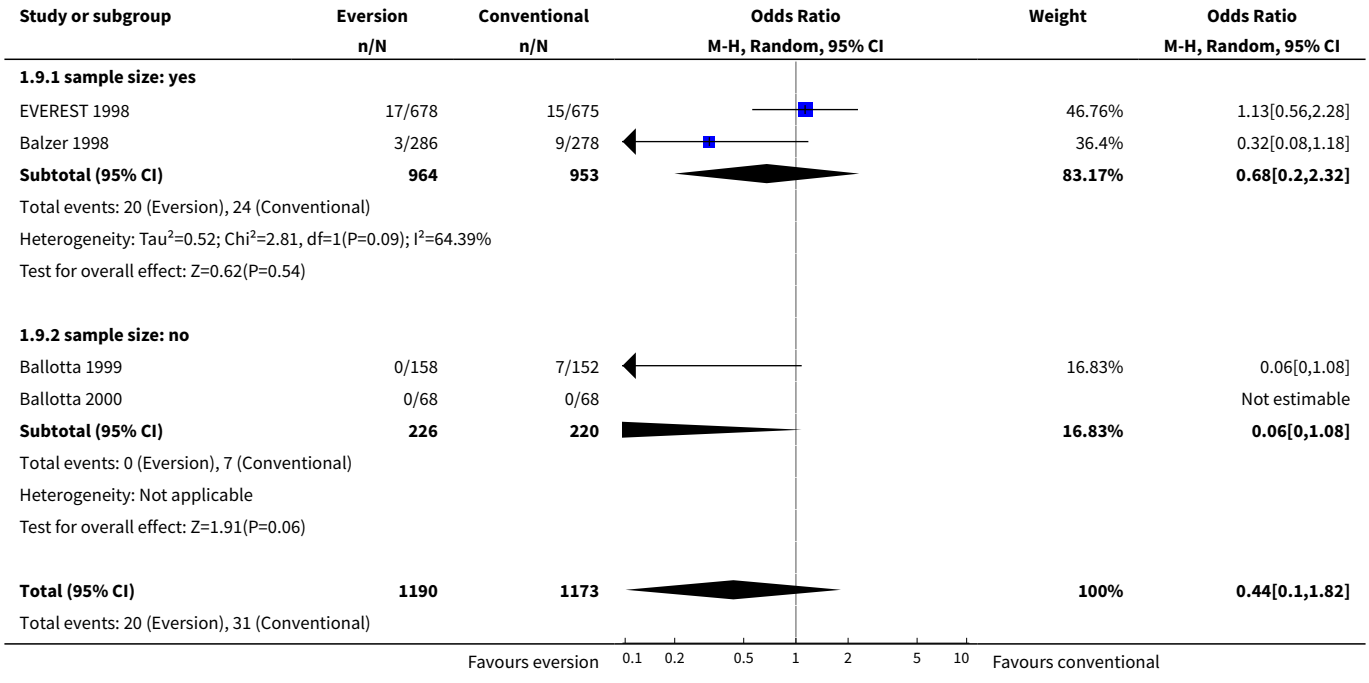




Analysis 1.8. Comparison 1 Eversion vs conventional CEA, Outcome 8 perioperative ipsilateral stroke.



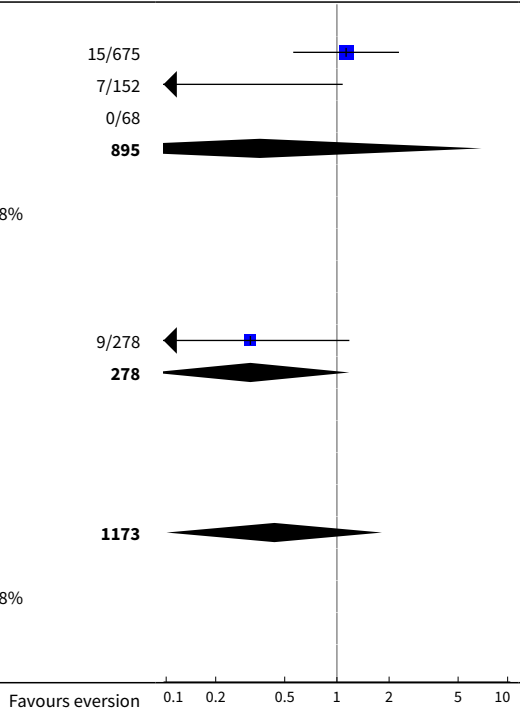
Analysis 1.9. Comparison 1 Eversion vs conventional CEA, Outcome 9 perioperative stroke and/or death: sample size yes.



Study or subgroup	Eversion n/N	Conventional n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=1.01; Chi²=6.21, df=2(P=0.04); I²=67.8%					
Test for overall effect: Z=1.14(P=0.25)					
Test for subgroup differences: Not applicable					

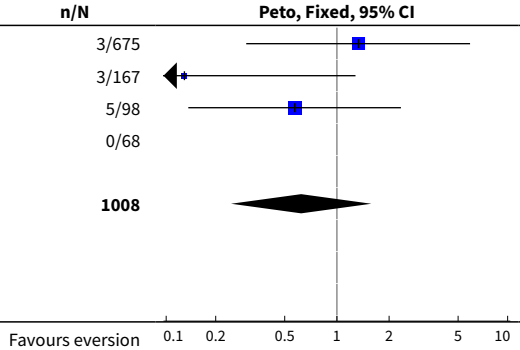
Analysis 1.10. Comparison 1 Eversion vs conventional CEA, Outcome 10 perioperative stroke and/or death quality of randomisation.

Study or subgroup	Eversion n/N	Conventional n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
1.10.1 class A studies (adequate concealment)					
EVEREST 1998	17/678	15/675		46.76%	1.13[0.56,2.28]
Ballotta 1999	0/158	7/152		16.83%	0.06[0,1.08]
Ballotta 2000	0/68	0/68			Not estimable
Subtotal (95% CI)	**904**	**895**		**63.6%**	**0.36[0.02,6.84]**
Total events: 17 (Eversion), 22 (Conventional)					
Heterogeneity: Tau²=3.6; Chi²=4.16, df=1(P=0.04); I²=75.98%					
Test for overall effect: Z=0.68(P=0.5)					
1.10.2 class B studies (unadequate concealment)					
Balzer 1998	3/286	9/278		36.4%	0.32[0.08,1.18]
Subtotal (95% CI)	**286**	**278**		**36.4%**	**0.32[0.08,1.18]**
Total events: 3 (Eversion), 9 (Conventional)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
Total (95% CI)	**1190**	**1173**		**100%**	**0.44[0.1,1.82]**
Total events: 20 (Eversion), 31 (Conventional)					
Heterogeneity: Tau²=1.01; Chi²=6.21, df=2(P=0.04); I²=67.8%					
Test for overall effect: Z=1.14(P=0.25)					
Test for subgroup differences: Not applicable					

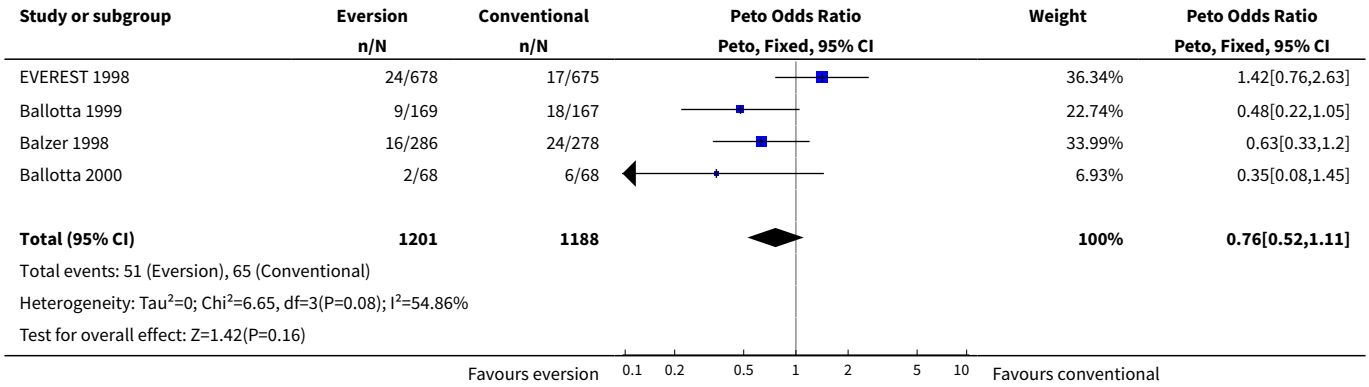


Analysis 1.11. Comparison 1 Eversion vs conventional CEA, Outcome 11 early carotid occlusion.

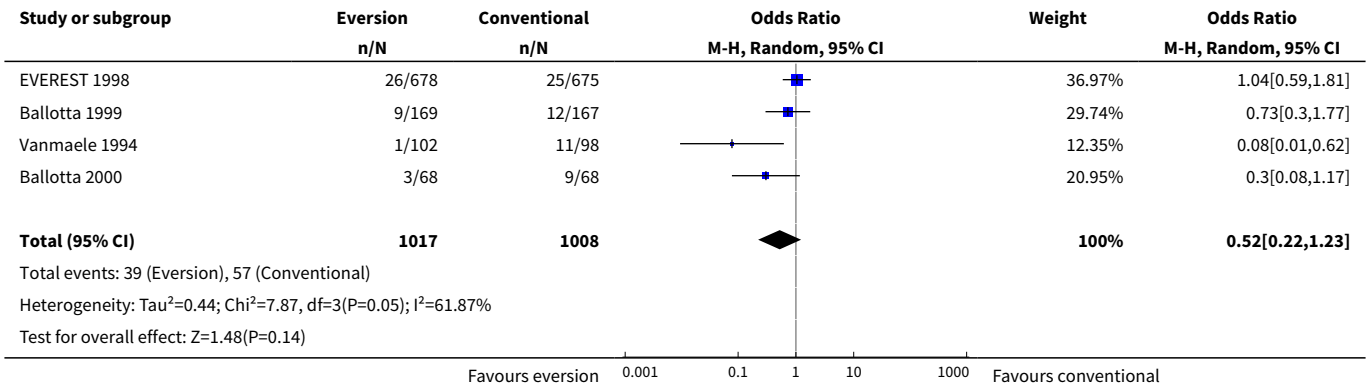
Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	4/678	3/675		39.45%	1.33[0.3,5.86]
Ballotta 1999	0/169	3/167		16.88%	0.13[0.01,1.28]
Vanmaele 1994	3/102	5/98		43.67%	0.57[0.14,2.34]
Ballotta 2000	0/68	0/68			Not estimable
Total (95% CI)	**1017**	**1008**		**100%**	**0.62[0.24,1.58]**
Total events: 7 (Eversion), 11 (Conventional)					
Heterogeneity: Tau²=0; Chi²=2.8, df=2(P=0.25); I²=28.64%					
Test for overall effect: Z=1(P=0.32)					



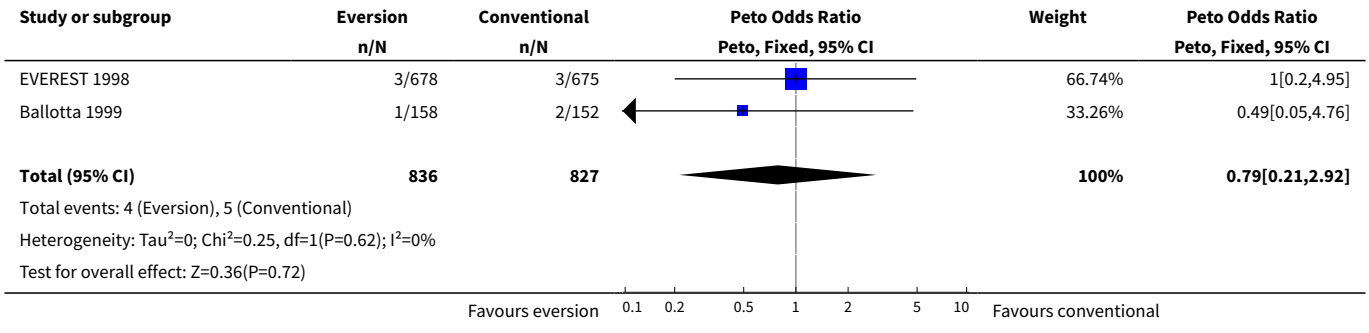
Analysis 1.12. Comparison 1 Eversion vs conventional CEA, Outcome 12 neck hematoma.



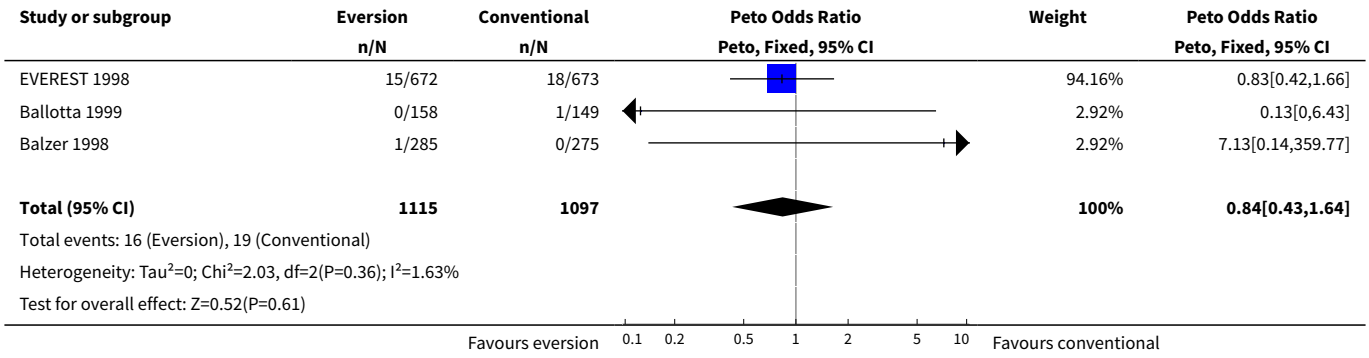
Analysis 1.13. Comparison 1 Eversion vs conventional CEA, Outcome 13 cranial nerve injuries.



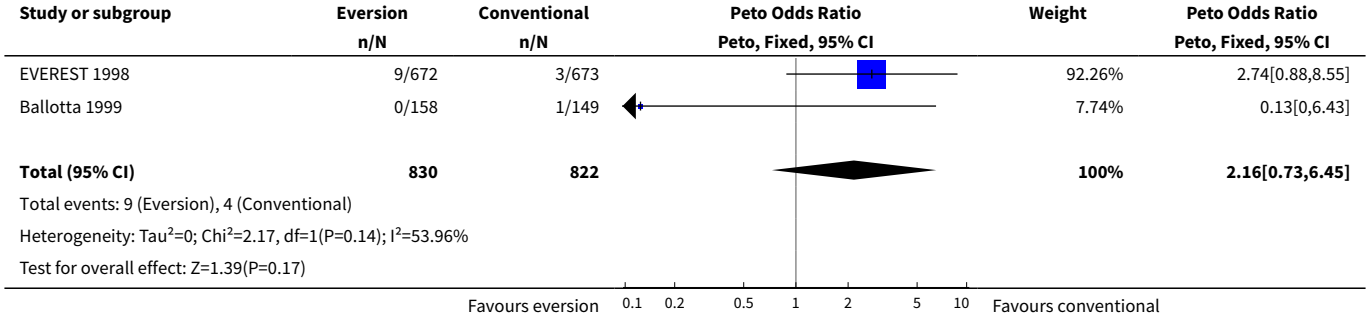
Analysis 1.14. Comparison 1 Eversion vs conventional CEA, Outcome 14 myocardial infarction.



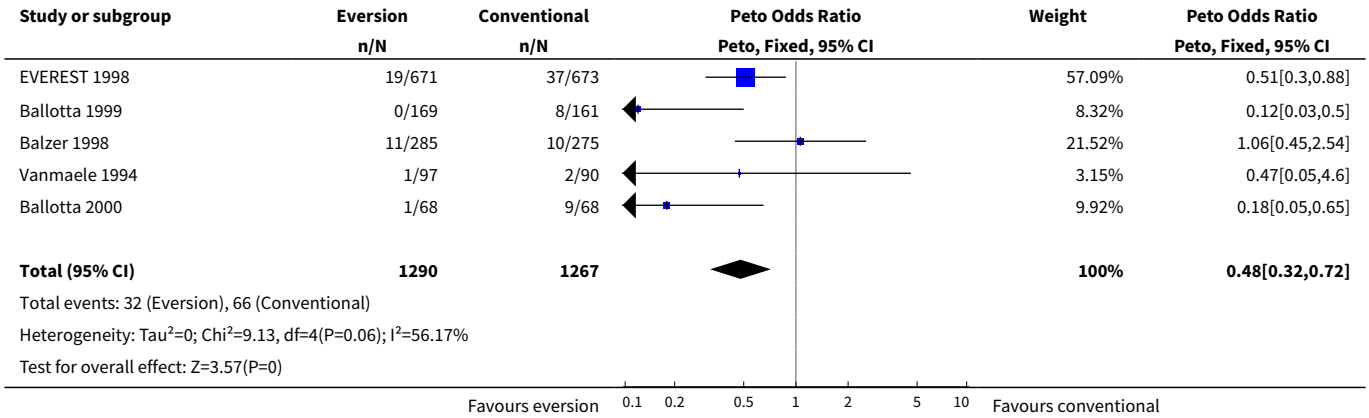
Analysis 1.15. Comparison 1 Eversion vs conventional CEA, Outcome 15 stroke during follow-up (excluding perioperative).



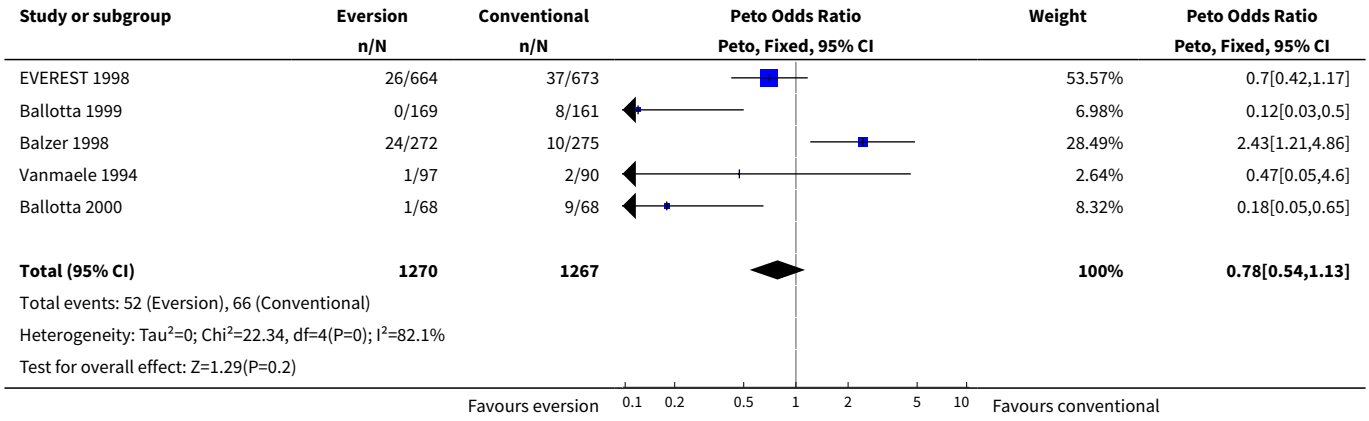
Analysis 1.16. Comparison 1 Eversion vs conventional CEA, Outcome 16 ipsilateral stroke during follow-up (excl. perioperative).



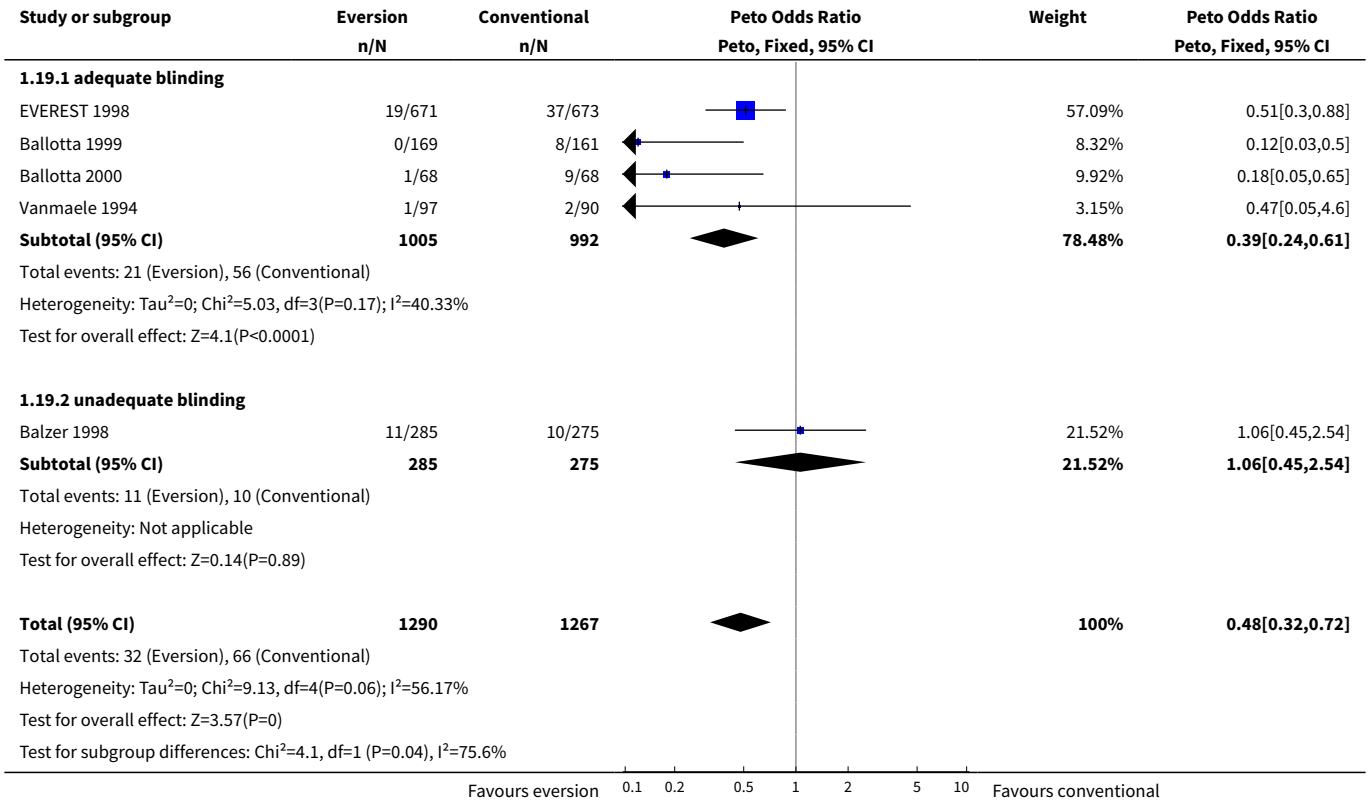
Analysis 1.17. Comparison 1 Eversion vs conventional CEA, Outcome 17 restenosis/occlusion best.



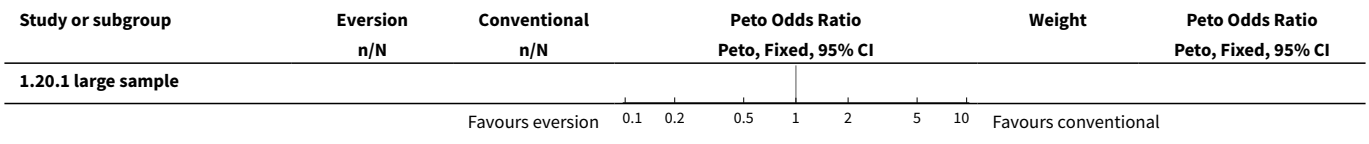
Analysis 1.18. Comparison 1 Eversion vs conventional CEA, Outcome 18 restenosis/occlusion worst.

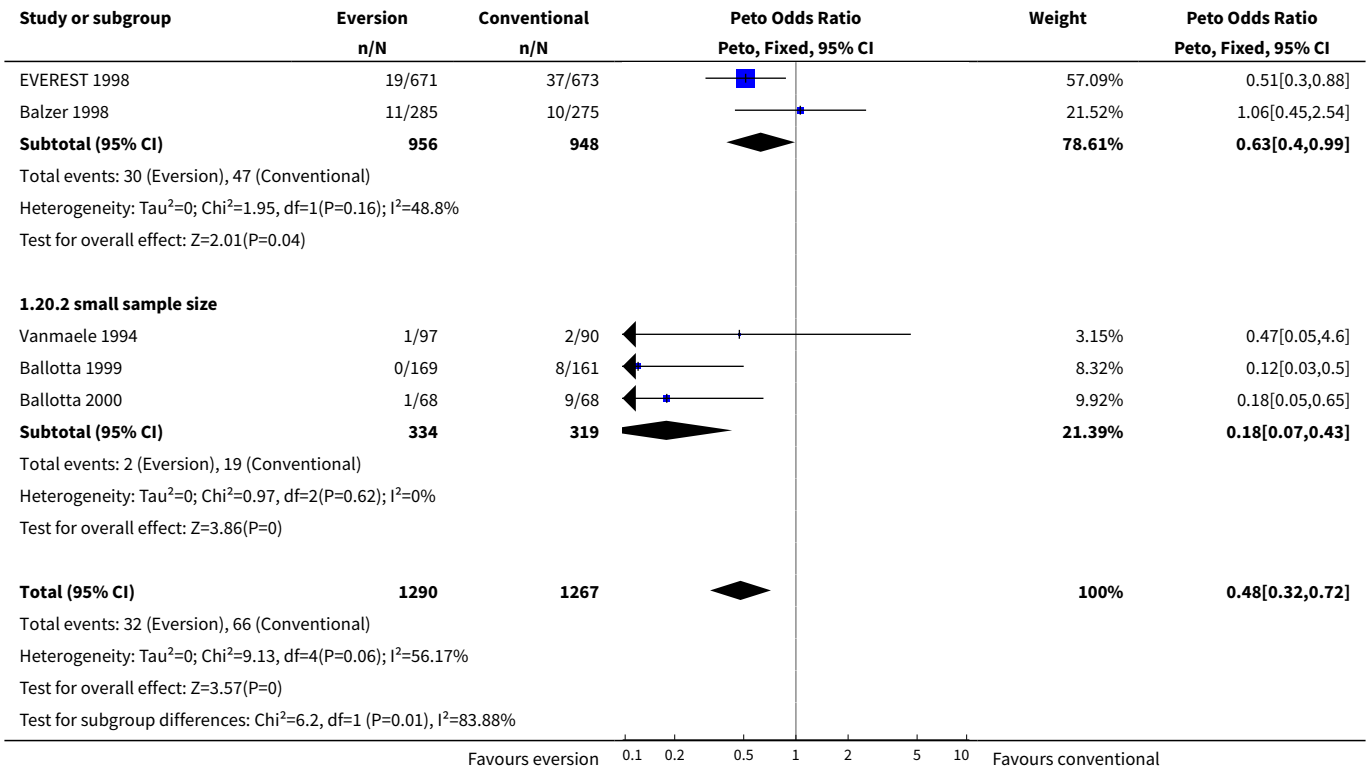


Analysis 1.19. Comparison 1 Eversion vs conventional CEA, Outcome 19 restenosis quality blinding.

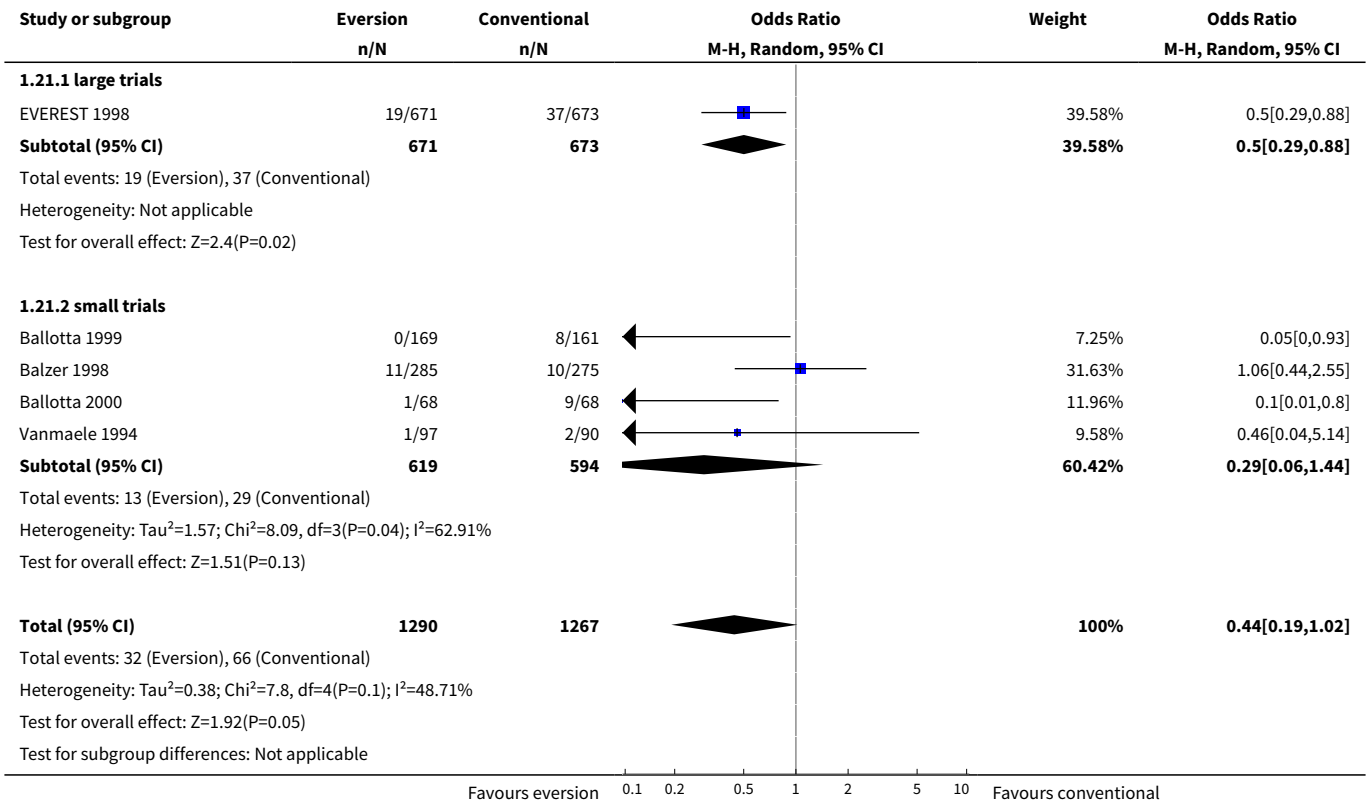


Analysis 1.20. Comparison 1 Eversion vs conventional CEA, Outcome 20 restenosis sample size.



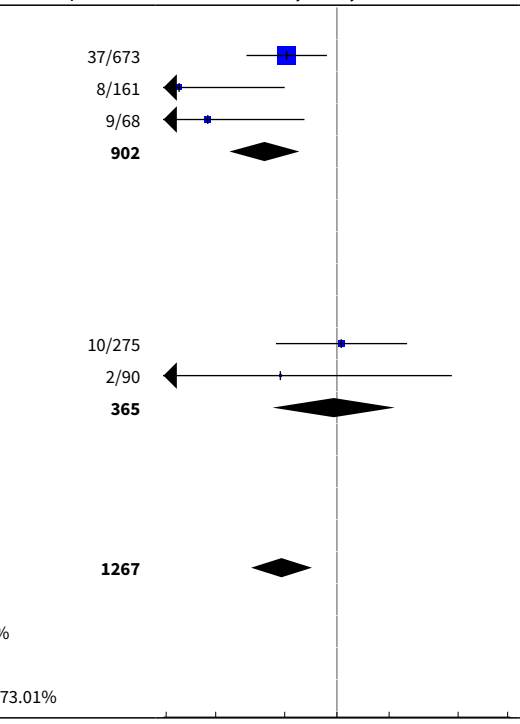


Analysis 1.21. Comparison 1 Eversion vs conventional CEA, Outcome 21 restenosis large vs small trials.



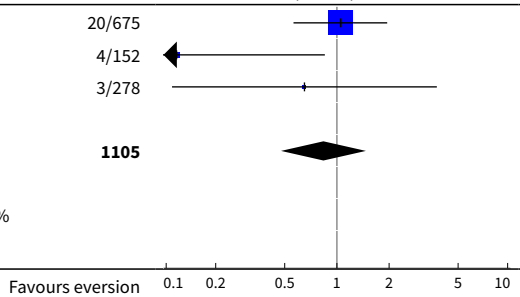
Analysis 1.22. Comparison 1 Eversion vs conventional CEA, Outcome 22 restenosis quality of randomisation.

Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.22.1 class A studies (adequate concealment)					
EVEREST 1998	19/671	37/673		57.09%	0.51[0.3,0.88]
Ballotta 1999	0/169	8/161		8.32%	0.12[0.03,0.5]
Ballotta 2000	1/68	9/68		9.92%	0.18[0.05,0.65]
Subtotal (95% CI)	**908**	**902**		**75.33%**	**0.38[0.24,0.61]**
Total events: 20 (Eversion), 54 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=5, df=2(P=0.08); I^2=59.96%					
Test for overall effect: Z=4.05(P<0.0001)					
1.22.2 class B studies (unadequate concealment)					
Balzer 1998	11/285	10/275		21.52%	1.06[0.45,2.54]
Vanmaele 1994	1/97	2/90		3.15%	0.47[0.05,4.6]
Subtotal (95% CI)	**382**	**365**		**24.67%**	**0.96[0.42,2.16]**
Total events: 12 (Eversion), 12 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=0.43, df=1(P=0.51); I^2=0%					
Test for overall effect: Z=0.1(P=0.92)					
Total (95% CI)	**1290**	**1267**		**100%**	**0.48[0.32,0.72]**
Total events: 32 (Eversion), 66 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=9.13, df=4(P=0.06); I^2=56.17%					
Test for overall effect: Z=3.57(P=0)					
Test for subgroup differences: Chi^2=3.7, df=1 (P=0.05), I^2=73.01%					



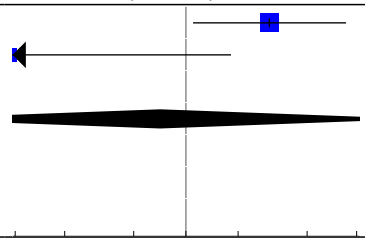
Analysis 1.23. Comparison 1 Eversion vs conventional CEA, Outcome 23 all strokes during follow-up and perioperative deaths.

Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	21/678	20/675		81.69%	1.05[0.56,1.95]
Ballotta 1999	0/169	4/152		8.11%	0.12[0.02,0.85]
Balzer 1998	2/286	3/278		10.19%	0.65[0.11,3.77]
Total (95% CI)	**1133**	**1105**		**100%**	**0.84[0.48,1.47]**
Total events: 23 (Eversion), 27 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=4.35, df=2(P=0.11); I^2=54.01%					
Test for overall effect: Z=0.63(P=0.53)					



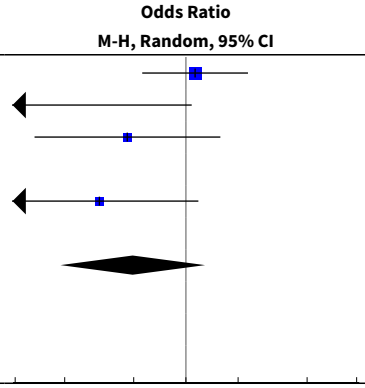
Analysis 1.24. Comparison 1 Eversion vs conventional CEA, Outcome 24 ipsilateral stroke during follow-up and perioperative deaths.

Study or subgroup	Eversion n/N	Conventional n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
EVEREST 1998	15/678	5/675		57.79%	3.03[1.1,8.39]
Ballotta 1999	0/169	4/152		42.21%	0.1[0.01,1.82]
Total (95% CI)	**847**	**827**		**100%**	**0.71[0.02,22.08]**
Total events: 15 (Eversion), 9 (Conventional)					
Heterogeneity: Tau^2=5.05; Chi^2=5.03, df=1(P=0.02); I^2=80.13%					
Test for overall effect: Z=0.2(P=0.85)					



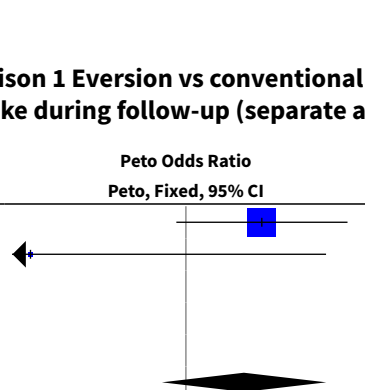
Analysis 1.25. Comparison 1 Eversion vs conventional CEA, Outcome 25 perioperative stroke and/or death (separate analysis).

Study or subgroup	Eversion n/N	Conventional n/N	Odds Ratio M-H, Random, 95% CI	Weight	Odds Ratio M-H, Random, 95% CI
EVEREST 1998	17/678	15/675		38.63%	1.13[0.56,2.28]
Ballotta 1999	0/158	7/152		9.06%	0.06[0,1.08]
Vanmaele 1994	4/102	8/98		26.95%	0.46[0.13,1.58]
Ballotta 2000	0/68	0/68			Not estimable
Balzer 1998	3/286	9/278		25.36%	0.32[0.08,1.18]
Total (95% CI)	**1292**	**1271**		**100%**	**0.49[0.19,1.29]**
Total events: 24 (Eversion), 39 (Conventional)					
Heterogeneity: Tau^2=0.49; Chi^2=6.64, df=3(P=0.08); I^2=54.82%					
Test for overall effect: Z=1.45(P=0.15)					



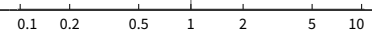
Analysis 1.26. Comparison 1 Eversion vs conventional CEA, Outcome 26 ipsilateral stroke during follow-up (separate analysis).

Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	9/672	3/673		92.26%	2.74[0.88,8.55]
Ballotta 1999	0/158	1/149		7.74%	0.13[0,6.43]
Vanmaele 1994	0/100	0/95			Not estimable
Ballotta 2000	0/68	0/68			Not estimable
Total (95% CI)	**998**	**985**		**100%**	**2.16[0.73,6.45]**
Total events: 9 (Eversion), 4 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=2.17, df=1(P=0.14); I^2=53.96%					
Test for overall effect: Z=1.39(P=0.17)					



Analysis 1.27. Comparison 1 Eversion vs conventional CEA, Outcome 27 stroke during follow-up (separate analysis).

Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	15/672	18/673		94.16%	0.83[0.42,1.66]
Ballotta 1999	0/158	1/149		2.92%	0.13[0,6.43]
Balzer 1998	1/285	0/275		2.92%	7.13[0.14,359.77]
Vanmaele 1994	0/100	0/95			Not estimable
Total (95% CI)	**1215**	**1192**		**100%**	**0.84[0.43,1.64]**
Total events: 16 (Eversion), 19 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=2.03, df=2(P=0.36); I^2=1.63%					
Test for overall effect: Z=0.52(P=0.61)					



Favours eversion — Favours conventional

Analysis 1.28. Comparison 1 Eversion vs conventional CEA, Outcome 28 perioperative disabling stroke (separate analysis).

Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	7/678	7/675		46.78%	1[0.35,2.85]
Ballotta 1999	0/158	3/152		10.05%	0.13[0.01,1.24]
Balzer 1998	2/286	6/278		26.65%	0.35[0.09,1.42]
Vanmaele 1994	2/102	3/98		16.52%	0.64[0.11,3.75]
Ballotta 2000	0/68	0/68			Not estimable
Total (95% CI)	**1292**	**1271**		**100%**	**0.57[0.28,1.17]**
Total events: 11 (Eversion), 19 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=3.2, df=3(P=0.36); I^2=6.32%					
Test for overall effect: Z=1.52(P=0.13)					

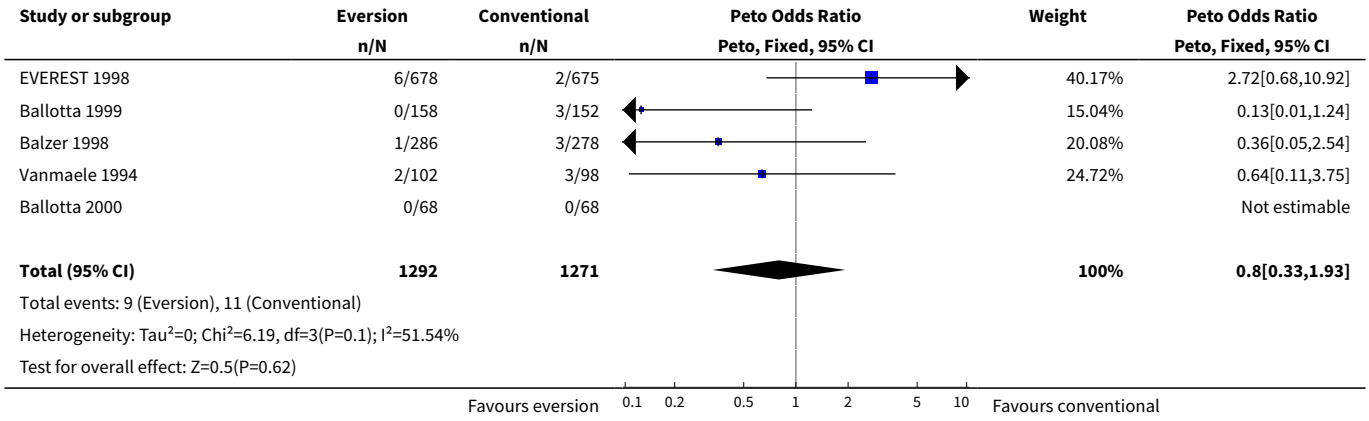
Favours eversion — Favours conventional

Analysis 1.29. Comparison 1 Eversion vs conventional CEA, Outcome 29 perioperative stroke (separate analysis).

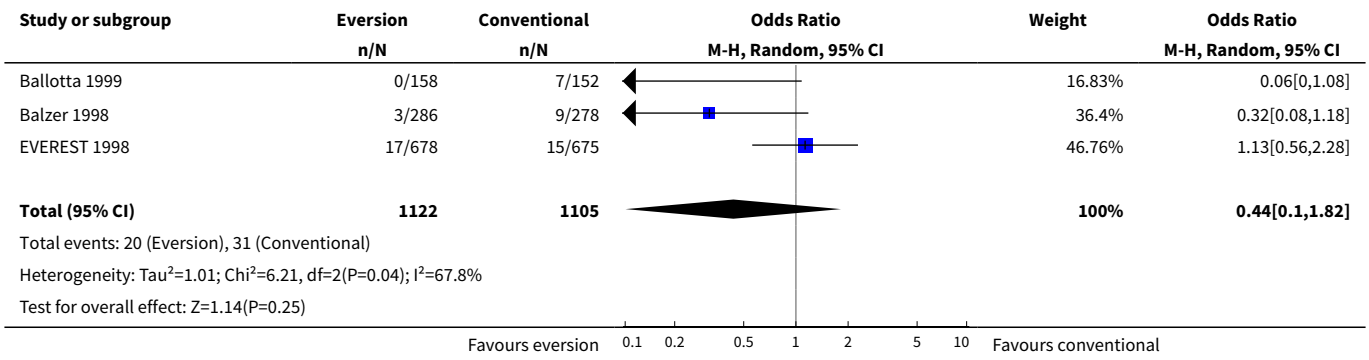
Study or subgroup	Eversion n/N	Conventional n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
EVEREST 1998	15/678	13/675		57.18%	1.15[0.54,2.43]
Ballotta 1999	0/158	5/152		10.28%	0.13[0.02,0.74]
Balzer 1998	2/286	6/278		16.46%	0.35[0.09,1.42]
Vanmaele 1994	2/102	6/98		16.08%	0.34[0.08,1.39]
Ballotta 2000	0/68	0/68			Not estimable
Total (95% CI)	**1292**	**1271**		**100%**	**0.62[0.35,1.09]**
Total events: 19 (Eversion), 30 (Conventional)					
Heterogeneity: Tau^2=0; Chi^2=7.06, df=3(P=0.07); I^2=57.53%					
Test for overall effect: Z=1.65(P=0.1)					

Favours eversion — Favours conventional

Analysis 1.30. Comparison 1 Eversion vs conventional CEA, Outcome 30 perioperative death (separate analysis).



Analysis 1.31. Comparison 1 Eversion vs conventional CEA, Outcome 31 perioperative stroke and/or death (separate analysis. 2).



APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (Ovid) and the Cochrane Central Register of Controlled Trials

1 exp carotid arteries/
2 exp carotid artery diseases/
3 endarterectomy, carotid/
4 carotid.tw
5 endarterectomy/ or endarterectomy.tw or surgery.tw
6 4 and 5
7 1 or 2 or 3 or 6
8 eversion.tw
9 7 and 8

Appendix 2. EMBASE search strategy

EMBASE (Ovid)

1 exp carotid artery/
2 exp carotid artery disease/

3 carotid artery surgery/
4 carotid endarterectomy/
5 carotid.tw
6 endarterectomy/ or endarterectomy.tw or surgery.tw or su.fs
7 5 and 6
8 1 or 2 or 3 or 4 or 7
9 eversion.tw
10 8 and 9

WHAT'S NEW

Date	Event	Description
19 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 1, 2001

Date	Event	Description
26 May 2003	New search has been performed	No substantive amendment was possible because no new recent randomised studies have been published. Because a number of non-randomised studies have been recently performed on this topic, new references have been added in the Additional references section and in the Background of the review.

CONTRIBUTIONS OF AUTHORS

Piergiorgio Cao: conception and design of study, analysis and interpretation of data, final approval of the version to be published.
Paola De Rango: conception and design of study, analysis and interpretation of data.
Simona Zannetti: drafting the review, writing the review.
Giuseppe Giordano: entering data into RevMan.
Stefano Ricci: data management for the review.
Maria Grazia Celani: data management for the review.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Confidence Intervals; Endarterectomy, Carotid [adverse effects] [*methods]; Odds Ratio; Randomized Controlled Trials as Topic; Recurrence; Stroke [etiology] [*prevention & control]

MeSH check words

Humans