Cochrane Library

Cochrane Database of Systematic Reviews

Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease (Review)

Fluri F, Engelter S, Lyrer P

Fluri F, Engelter S, Lyrer P.
Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease.
Cochrane Database of Systematic Reviews 2010, Issue 2. Art. No.: CD005953.
DOI: 10.1002/14651858.CD005953.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease

Felix Fluri[1], Stefan Engelter[1], Philippe Lyrer[1]

[1]Department of Neurology, University Hospital Basel, Basel, Switzerland

Contact address: Philippe Lyrer, Department of Neurology, University Hospital Basel, Petersgraben 4, Basel, 4031, Switzerland. plyrer@uhbs.ch.

Editorial group: Cochrane Stroke Group.
Publication status and date: New, published in Issue 2, 2010.

Citation: Fluri F, Engelter S, Lyrer P. Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD005953. DOI: 10.1002/14651858.CD005953.pub2.

ABSTRACT

Background

The EC/IC Bypass Study Group found no benefit of extracranial to intracranial (EC/IC) bypass surgery over medical therapy in patients with symptomatic carotid artery occlusion (sCAO). However, the study was criticised for many reasons and the real effect of this treatment is still not known conclusively.

Objectives

To determine whether bypass surgery plus medical care is superior to medical care alone in patients with sCAO.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched June 2009). In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2006), MEDLINE (1966 to June 2009) and EMBASE (1980 to June 2009). We also searched ongoing trials and research registers, checked reference lists of relevant articles, and contacted colleagues, trial authors and researchers.

Selection criteria

Randomised controlled trials (RCT) and non-random studies of EC/IC bypass surgery plus best medical treatment compared with best medical treatment alone to prevent subsequent stroke, improve cerebral haemodynamics and reduce dependency after stroke.

Data collection and analysis

Two review authors independently selected studies for inclusion, and extracted data items on the number of outcome events onto a data extraction form. We only analysed secondary outcomes if the study provided information on at least one primary outcome. We also used intention-to-treat analysis where possible.

Main results

We included 21 trials, including two RCTs, involving 2591 patients. For all endpoints, no benefit of EC/IC bypass surgery was shown either in the RCTs (any death: odds ratio (OR) 0.81, 95% confidence interval (CI) 0.62 to 1.05, P = 0.11; stroke: OR 0.99, 95% CI 0.79 to 1.23, P = 0.91; death and dependency: OR 0.94, 95% CI 0.74 to 1.21, P = 0.64), or in the non-RCTs (any death: OR 1.00, 95% CI 0.62 to 1.62, P = 0.99; stroke: OR 0.80, 95% CI 0.54 to 1.18, P = 0.25; death and dependency: OR 0.80, 95% CI 0.50 to 1.29, P = 0.37).

Authors' conclusions

EC/IC bypass surgery in patients with sCAO disease was neither superior nor inferior to medical care alone. However, most studies included patients irrespective of their cerebral haemodynamics. Participation in an ongoing RCT, which is restricted to patients with impaired haemodynamics, is recommended as these patients might benefit from bypass surgery.

PLAIN LANGUAGE SUMMARY

Extracranial-intracranial arterial bypass surgery for occlusive carotid artery disease

Patients with symptomatic occlusion (obstruction) of the carotid artery have a high risk of subsequent stroke. Anticoagulant treatment and antiplatelet agents are not very effective in these patients and a surgical procedure known as extracranial-intracranial (EC/IC) arterial bypass surgery has been a treatment option. In this review, we included 21 trials (two randomised controlled trials and 19 non-random studies, with a total of 2591 patients). We found that EC/IC bypass surgery in patients with symptomatic carotid artery occlusive disease was no better or worse than medical care alone. A multi-centre trial comparing EC/IC bypass surgery with best medical treatment in patients with both a high risk of stroke and haemodynamic compromise (impaired blood flow) is underway, and aims to discover whether EC/IC bypass surgery is beneficial in this specific group of patients.

BACKGROUND

Up to 15% of patients presenting with anterior circulation ischaemia have complete occlusion of the ipsilateral carotid artery (Bozzao 1989; Pessin 1977; Thiele 1980). Their annual risk for subsequent stroke is 5% to 7% (Grubb 1986; Klijn 1997), and the risk of stroke ipsilateral to the occluded carotid artery is 2% to 6% per year (Hankey 1991; Klijn 1997). The efficacy of anticoagulant treatment or antiplatelet agents in patients with symptomatic occlusion of the carotid artery is small (Klijn 1997). Cerebral revascularisation of the anterior or posterior circulation by extracranial to intracranial (EC/IC) anastomosis is thought to be a therapeutic option for preventing subsequent transient ischaemic attack or stroke in patients with occlusive carotid disease.

EC/IC bypass surgery is an operative procedure which most commonly involves the anastomosis of the superficial temporal artery to the middle cerebral artery. Results of the first EC/IC bypass were published in 1967 (Donaghy 1967; Yasargil 1969) and it became a widespread method in the next decade. In 1985, the EC/IC Bypass Study Group showed no benefit of EC/IC bypass surgery over medical therapy in patients with symptomatic carotid occlusion (EC/IC Bypass Study 1985). However, the study was criticised for including all patients with occlusion of the carotid artery irrespective of their cerebral haemodynamics. No stratification was done to separate patients with embolic stroke but sufficient intracranial haemodynamics from those with ongoing haemodynamic compromise. Thus, the negative result of the EC/IC bypass study does not necessarily mean that EC/IC bypass is not beneficial for some patients with substantial haemodynamic compromise due to occlusion of the carotid artery (Ausman 1986; Day 1986; Sundt 1987; Vorstrup 1992).

Haemodynamic compromise of ipsilateral artery occlusion is divided into three stages (Derdeyn 2002; Powers 1987; Powers 1991):

- Stage 0: normal cerebral haemodynamics;
- Stage 1: autoregulatory vasodilation;
- Stage 2: autoregulatory failure (increased oxygen extraction fraction (OEF)), also termed 'misery perfusion' (Baron 1981).

Several studies have been carried out to evaluate whether the subgroup of patients with haemodynamic compromise due to occlusion of the carotid artery might benefit from bypass surgery. In addition, more recently there have been two other randomised controlled trials (RCTs) of EC/IC bypass (COSS; JET 2006). With these considerations in mind, we tried to evaluate whether EC/IC bypass surgery plus best medical treatment compared with best medical treatment alone prevents subsequent stroke, improves cerebral haemodynamics and reduces dependency after stroke in all eligible patients for EC/IC bypass or only in patients with impaired haemodynamics.

OBJECTIVES

The objective was to determine whether bypass surgery and medical care in patients with a symptomatic carotid artery occlusion was superior to medical care alone, both in all patients and in the subgroup of patients with haemodynamic compromise.

A further purpose of this review was to determine to what degree the intervention resulted in the correction of haemodynamic compromise in the affected hemisphere.

Finally we aimed to assess safety: death (all causes, vascular, non-vascular) and stroke (all); intracranial haemorrhage; major extracranial haemorrhage; myocardial infarction; non-vascular complication of surgery; and infection.

METHODS

Criteria for considering studies for this review

Types of studies

The review has two parts, Part 1 and Part 2, each with two divisions, labelled (a) and (b). Division (a) included all patients undergoing EC/IC bypass surgery without measurement of cerebral haemodynamics, while division (b) assessed only those patients with impaired haemodynamics measured by positron emission tomography (PET), single photon emission computed tomography (SPECT), perfusion magnetic resonance (PMR) imaging, and ultrasound.

Part 1

Only randomised controlled trials (RCTs) of EC/IC bypass surgery plus best medical treatment compared with best medical treatment alone to prevent subsequent stroke, improve cerebral haemodynamics and reduce dependency after stroke, including:

- (a) all patients without measurement of haemodynamic status before the intervention;
- (b) only patients with impaired haemodynamics before the intervention measured using a method mentioned above.

Part 2

All studies (except RCTs) of EC/IC bypass surgery plus best medical treatment compared with best medical treatment alone to prevent subsequent stroke, improve cerebral haemodynamics and reduce dependency after stroke, including:

- (a) all patients without measurement of haemodynamic status before the intervention;
- (b) only patients with impaired haemodynamics before the intervention measured using a method mentioned above.

Types of participants

Patients with symptomatic (transient ischaemic attack or stroke) occlusion of internal carotid arteries demonstrated by angiography and less than 50% stenosis of the contralateral internal carotid artery and, where available, measured haemodynamic compromise identified by PET, SPECT, PMR imaging and ultrasound. Patients with transient ischaemic monocular blindness were not eligible unless hemispheric symptoms also were present. Patients with asymptomatic occlusion of the internal carotid artery were not eligible because of the low risk of subsequent ischaemic stroke (Powers 2000).

Patients who had undergone thrombendarterectomy of the contralateral internal carotid artery prior to EC/IC bypass were eligible. We excluded all studies including patients with non-atherosclerotic conditions causing or likely to cause cerebral

ischaemia (including carotid dissection, fibromuscular dysplasia, Moyamoya disease, arteritis and other vasculopathy likely to cause cerebral events) from the analysis. If this information was not available, we only used the published data.

Types of interventions

We included any surgical bypass procedure for the treatment of patients with radiologically demonstrated unilateral occluded internal carotid artery, irrespective of the approach and type of graft employed. The bypass patients as well as the control patients should have received best medical treatment for preventing stroke.

Types of outcome measures

Primary outcomes

1. Death from all causes.
2. Any stroke during the follow-up period. This combined outcome included ischaemic strokes, intracranial haemorrhage, or stroke of unknown aetiology.
3. Death or dependency at the end of follow up. This composite outcome included all patients who qualified either for death or dependency (handicap) which was defined according to the modified Rankin Scale (mRS): independency (mRS 0 to 2) was distinguished from dependency (3 to 5). If the Glasgow Outcome Scale (GOS) was used, we considered good recovery and moderate disability as surrogates for independence, and considered severe disability and persistent vegetative state as dependence. When mRS values were not available, we defined independence as recovery (that is, patients are able to look after their own affairs without assistance) or return to work. In cases of 'deterioration', 'worsened', 'fair' or 'poor' outcome, we assumed dependency as 'partial improvement', 'no improvement', 'no recovery', 'inability to walk without assistance', or 'requiring some help for bodily activities of daily living'. This algorithm was also used for the Cochrane Review of carotid artery dissection (Lyrer 2003).

Secondary outcomes

1. Vascular death, which we defined as death caused by:
   - stroke or a complication of stroke (e.g. brain herniation, status epilepticus);
   - coronary artery disease or a complication of it (e.g. myocardial infarction, congestive heart failure, arrhythmia);
   - sudden death;
   - pulmonary embolism;
   - peripheral vascular disease;
   - haemorrhage (intracranial or extracranial); or
   - other vascular causes (for example, rupture of aneurysm, dissection) including 'vascular death' mentioned without specification in the publications.
2. Serious vascular events (during follow-up period) or vascular death. This composite outcome included all patients who qualified for outcome events 1, 3, 4 or 5.
3. Myocardial infarction. All patients with fatal or non-fatal myocardial infarction. Patients who died of occlusive coronary artery disease as reported by autopsy, are classified as 'fatal myocardial infarction'.
4. Ischaemic stroke (during follow-up period). We defined ischaemic stroke as any neurological deficit due to cerebral ischaemia lasting longer than 24 hours, and showing no evidence of any other underlying pathology (e.g. haemorrhage, tumour).
5. Intracranial haemorrhage. Intracranial haemorrhage included any subarachnoid haemorrhage, subdural haemorrhage, epidural haematoma, or parenchymatous intracerebral haemorrhage, as confirmed by neuroradiological investigations or by autopsy. We did not consider haemorrhagic transformation of an ischaemic infarction as intracranial haemorrhage.
6. Major extracranial haemorrhage. We took the definition of a major extracranial haemorrhage from the original publication. If no definition was given, we defined major as a fatal bleeding, or one requiring surgery, transfusion or (prolonged) hospitalisation. If a haemorrhage was declared 'serious' or 'severe' in the publication, we considered it a major haemorrhage for the purpose of this review.
7. Local haemorrhage requiring surgery. All patients with local haematoma requiring surgical exploration, haematoma evacuation, or the application of a suture, a patch, or a bypass met the criteria for this outcome event.
8. Transient ischaemic attack or amaurosis fugax.
9. Normalisation of cerebral haemodynamics, using PET, computerised tomography (CT), SPECT or ultrasound criteria, which we defined as a normalisation of hemispheric oxygen extraction fraction (OEF) ratios or decreased OEF ratio after EC/IC-bypass surgery.
10. Non-vascular complications of surgery (for example, wound infection, limited function of the EC/IC bypass).

For all outcome events, we only included patients once. If one patient experienced more than one non-fatal event, we only recorded the first one.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in June 2009. In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2006), MEDLINE (1966 to June 2009) (Appendix 1) and EMBASE (1980 to June 2009) (Appendix 2). In an effort to identify further published, unpublished and ongoing studies we searched reference lists of relevant papers, contacted colleagues, trial authors and researchers, and searched the following clinical trials and research registers:

- Current Controlled Trials (http://www.controlled-trials.com/);
- National Institutes of Health ClinicalTrials.gov (http://clinicaltrials.gov/);
- Stroke Trials Registry (http://www.strokecenter.org/trials/).

Data collection and analysis

Two review authors (FF, SE) independently selected studies for inclusion. The same two review authors independently extracted data items on the number of outcome events onto a data extraction form. In cases of disagreement, the review authors reached consensus by discussion.

The data that we analysed are listed in the 'Types of outcome measures' section. We only analysed secondary outcomes if the study provided information on at least one primary outcome. We used intention-to-treat analysis. For the EC/IC bypass study, we also included the 118 patients who did not meet the inclusion criteria and, thus, were excluded from the analysis published in 1985 (EC/IC Bypass Study 1985).

Statistical methods

We calculated a weighted estimate of the odds for each outcome event across studies using the Peto odds ratio (OR) method.

RESULTS

Description of studies

See the 'Characteristics of included studies' and the' Characteristics of excluded studies' sections.

We have identified a total of two randomised controlled trials (RCTs) comparing EC/IC bypass and best medical treatment with medical care alone and fulfilling the inclusion criteria (EC/IC Bypass Study 1985; JET 2006). One RCT is still in progress (COSS). For Part 1a, we found a total of 1691 patients, whereas for Part 1b we only included data for 195 patients from the JET study (JET 2006). Length of follow up in the EC/IC bypass study was 55.8 months, and in the JET study was 25 months. We identified 118 drop-outs in the EC/IC bypass study, whereas in the JET study 10 patients dropped out. Furthermore, detailed patient data were only given as percentages in the EC/IC bypass study, thus we had to translate these percentages into patient numbers, a procedure which is only approximate (our efforts to get absolute numbers for all necessary outcome variables by contacting the investigators were unsuccessful). In the EC/IC bypass study, only 78% of all randomised patients had a brain CT. In Part 1b, haemodynamic compromise was determined by measuring quantitatively cerebral blood flow using PET, SPECT and the Xenon inhalation method in the JET study.

For Part 2a, we identified 19 non-randomised trials (900 patients), which reported at least one primary outcome variable. Part 2b included three studies, involving 65 patients. The methods of measuring haemodynamic compromise as a selection criteria for EC/IC bypass varied widely: PET study (Ishikawa 1992), acetazolamide test (Karnik 1992) and Xenon/CT cerebral blood flow measurements (Yonas 1996).

Risk of bias in included studies

See 'Characteristics of included studies' section.

Quality assessment of trials

We obtained details regarding blinding, randomisation (generation and concealment of randomisation sequence) and number of randomised patients, as well as the number of drop-outs, withdrawals, cross-over treatments and those lost to follow up. If information was missing, we tried to contact the corresponding authors. All three review authors independently performed quality assessment and, if there was disagreement, reached consensus by discussion.

Effects of interventions

Part 1a

Primary outcomes

Death from all causes

We obtained data from two included trials for 1691 participants. The EC/IC bypass study had a trend towards fewer fatal outcome events in the group who had EC/IC bypass surgery than in the control group (EC/IC Bypass Study 1985). In the JET study, death from all causes as an outcome event was uncommon and similar in the EC/IC bypass group (two events) to the group with best medical treatment only (one event) (JET 2006). Across both studies we observed no significant difference between treatment and control groups regarding death from all causes (OR 0.81, 95% CI 0.62 to 1.05, P = 0.11) (Analysis 1.1).

Any stroke during follow up

Analysis of 'any stroke during follow up' was based on two trials of 1691 participants. The OR of 0.99 (95% CI 0.79 to 1.23, P = 0.91) indicated neither harm nor benefit of EC/IC bypass for any stroke during follow up (Analysis 1.2).

Death or dependency

Only the EC/IC bypass study reported on death or dependency (1377 participants). We observed no significant difference between treatment and control groups for 'death or dependency' (OR 0.94, 95% CI 0.74 to 1.21) (Analysis 1.3).

Secondary outcomes

Vascular death

One trial (EC/IC Bypass Study 1985) reported data enabling us to analyse vascular death at the end of the follow-up period (1377 participants). Data analysis revealed no significant difference between patients who underwent EC/IC bypass surgery and the control group regarding vascular death (OR 0.96, 95% CI 0.71 to 1.29, P = 0.77) (Analysis 1.4).

Stroke, serious vascular events or vascular death

Both RCTs provided data enabling the analysis of this composite endpoint at the end of the follow-up period (1573 participants). Across both studies, the OR of 0.68 (95% CI 0.51 to 0.91) indicated a statistically significant beneficial effect in favour of surgery in reducing events at the end of the follow-up period (P = 0.009) (Analysis 1.5).

Myocardial infarction

Both RCTs reported myocardial infarction (1522 patients). No significant difference between the treatment groups was shown (OR 0.78, 95% CI 0.46 to 1.32, P = 0.35) (Analysis 1.6).

Ischaemic stroke

Both RCTs reported ischaemic stroke at the end of the follow-up period (1573 participants). No statistically significant difference between the surgical group and the group with best medical treatment was shown (OR 0.69, 95% CI 0.44 to 1.08) (Analysis 1.7).

Intracranial haemorrhage

Neither RCT reported on the occurrence of intracranial haemorrhage after EC/IC bypass surgery.

Major extracranial haemorrhage

Neither RCT collected data about major extracranial haemorrhage.

Local haemorrhage requiring surgery

Neither trial reported any data for this outcome event.

Transient ischaemic attack or amaurosis fugax

Neither trial reported on the occurrence of transient ischaemic attack or amaurosis fugax after EC/IC bypass surgery or best medical treatment alone.

Normalisation of cerebral haemodynamics

Normalisation of cerebral haemodynamics was not measured in either trial.

Non-stroke complication of surgery

No data about non-stroke complication of surgery are available.

Part 1b

Only the JET study randomised patients exclusively with haemodynamic compromise for EC/IC bypass surgery (JET 2006), thus it was not possible for us to conduct a meaningful meta-analysis.

Part 2a

Primary outcomes

Death from all causes

We obtained data from 19 trials (900 participants). Only 11 studies reported on such events. Data analysis indicated neither benefit nor harm of EC/IC bypass surgery (OR 1.00, 95% CI 0.62 to 1.62) (Analysis 2.1).

Any stroke during follow up

Analysis of 'any stroke during follow up' was based on 18 trials (881 participants). We did not observe any significant difference between the treatment and control groups regarding stroke (OR 0.80, 95% CI 0.54 to 1.18) (Analysis 2.2).

Death or dependency

Eight trials reported on death or dependency (346 participants). We did not observe any significant difference between the treatment and control groups regarding death or dependency (OR 0.80, 95% CI 0.50 to 1.29) (Analysis 2.3).

Secondary outcomes

Vascular death

Analysis of 'vascular death' was based on 19 trials (900 participants) and indicated no significant benefit of EC/IC bypass surgery compared with the group undergoing best medical treatment only (OR 0.95, 95% CI 0.56 to 1.63) (Analysis 2.4).

Stroke, serious vascular events or vascular death

Thirteen trials provided data enabling the analysis of this composite endpoint at the end of the follow-up period (673 participants). Across all studies a trend was indicated in favour of EC/IC bypass surgery (OR 0.69, 95% CI 0.45 to 1.04) (Analysis 2.5).

Myocardial infarction

Two studies reported on myocardial infarction (79 participants). No statistically significant difference between both treatment groups was shown (OR 2.67, 95% CI 0.41 to 17.60). Furthermore, due to the small number of events (N = 3), meaningful interpretation was not possible (Analysis 2.6).

Ischaemic stroke

Thirteen trials reported ischaemic stroke at the end of the follow-up period (640 participants). The OR was 0.72 in favour of EC/IC bypass surgery, but the 95% CI of 0.44 to 1.18 indicated no statistical significance (Analysis 2.7).

Intracranial haemorrhage

Data on this outcome event were sparse; only four trials provided data (361 participants). There was no statistically significant difference between the treated and the control group (OR 1.14, 95% CI 0.44 to 2.93) (Analysis 2.8).

Major extracranial haemorrhage

No trials reported data for this outcome.

Local haemorrhage requiring surgery

No trials contained data for this outcome event.

Transient ischaemic attack or amaurosis fugax

For the outcome 'transient ischaemic attack or amaurosis fugax' at the end of the follow-up period, we obtained data from 11 trials (524 participants). Across trials a statistically significant beneficial effect in favour of EC/IC bypass surgery in reducing transient ischaemic attack or amaurosis fugax was indicated (OR 0.34, 95% CI 0.16 to 0.69, P = 0.003) (Analysis 2.9).

Normalisation of cerebral haemodynamics

Analysis was based on three trials (56 participants) showing a lack of normalisation of cerebral haemodynamics after EC/IC bypass surgery (OR 6.63, 95% CI 1.85 to 23.78) (Analysis 2.10).

Non-stroke complication of surgery

No data were available for this outcome.

Part 2b

Three studies formed a subgroup of patients with haemodynamic compromise as a selection criterion for EC/IC bypass surgery. We only found data for the endpoints 'death from all causes' and 'any stroke during follow up' (Analysis 3.1; Analysis 3.2). No statistically significant difference between treatment groups was shown for these endpoints.

DISCUSSION

We identified 21 trials (including two RCTs) involving 2591 patients. For all primary endpoints, neither benefit nor harm from EC/IC bypass surgery could be shown either in the RCTs ('any death': OR 0.81, 95% CI 0.62 to 1.05, P = 0.11; 'stroke': OR 0.99, 95% CI 0.79 to 1.23, P = 0.91; 'death and dependency': OR 0.94, 95% CI 0.74 to 1.21, P = 0.64), or in the non-RCTs ('any death': OR 1.00, 95% CI 0.62 to 1.62, P = 0.99; 'stroke': OR 0.80, 95% CI 0.54 to 1.18, P = 0.25; 'death and dependency': OR 0.80, 95% CI 0.50 to 1.29, P = 0.37). One possible explanation for these neutral results

was the inclusion in most studies of patients with occlusion of the carotid artery irrespective of their cerebral haemodynamics. No stratification was done to separate patients with embolic stroke but sufficient intracranial haemodynamics from those with ongoing haemodynamic compromise. After the data analysis of studies selecting patients for EC/IC bypass without measurement of haemodynamic compromise, it still remained unclear whether EC/IC bypass was beneficial or not for some patients with substantial haemodynamic compromise due to occlusion of the carotid artery (Ausman 1986; Day 1986; Sundt 1987; Vorstrup 1992). In order to address this question, we carried out a sub-analysis of the randomised controlled trials (RCTs) (Part 1b) and of the non-RCTs (Part 2b). For the RCTs, only the JET study had randomised patients with haemodynamic compromise for EC/IC bypass surgery (JET 2006). However, this study did not compare surgically treated patients showing haemodynamic compromise with those with normal or almost normal haemodynamics. Of the non-RCTs, only three studies qualified for Part 2b. However, there were very few endpoints, preventing meaningful analysis. In summary, neither the RCTs nor the non-RCTs showed a benefit of EC/IC bypass, probably because haemodynamic compromise was not taken into account in most cases.

The findings about normalisation of impaired haemodynamics across the non-RCTs confirms that EC/IC bypass is effective in restoring normal haemodynamics (Yonas 1996). However, whether this surrogate marker translates into a clinical benefit is unproven. The fact that the JET trial (JET 2006) failed to show a clinical benefit for the primary outcomes ('death from all causes' or 'any stroke') prompts scepticism as to whether the criteria 'impaired haemodynamics' is clinically important enough to predict a potentially beneficial effect of EC/IC bypass surgery. In addition, the best method of determining the presence or absence of impaired haemodynamics remains to be established and the variability between methods used to determine haemodynamic compromise has yet to be defined. The ongoing COSS trial, which uses a more sophisticated measure of impaired haemodynamics, may give clearer answers (COSS).

As a limitation, only two RCTs (EC/IC Bypass Study 1985; JET 2006) have been identified for this meta-analysis. Furthermore, the inclusion criteria of both RCTs differ, thus a meta-analysis across both studies could produce misleading conclusions. Potential benefit or harm cannot be excluded definitively. For the non-RCTs, the most important limitation is the non-randomised treatment allocation, which involves a high risk of bias. In addition, the majority of studies available for this meta-analysis were single group reports of small numbers of participants without sub-stratification by haemodynamic compromise. In the studies reported, only 255 of 2591 patients (9.8%) had pre-operative assessments of cerebral haemodynamics, while 2336 of 2591 patients (90.2%) did not. Even fewer data were available comparing pre and post-operative measurements with clinical outcome parameters. Overall the quality of most studies was poor.

AUTHORS' CONCLUSIONS

Implications for practice

EC/IC-bypass surgery in patients with a symptomatic carotid artery occlusive disease was neither superior nor inferior to medical care alone. Thus, the role of EC/IC bypass surgery in symptomatic carotid disease remains undetermined. However, most studies included patients irrespective of their cerebral haemodynamics. Patients currently being submitted for EC/IC bypass procedures need protocol-driven assessment delivered by multi-disciplinary teams. Participation in an ongoing randomised controlled trial (RCT), which is restricted to patients with impaired haemodynamics, is recommended as these patients might benefit from bypass surgery.

Implications for research

The optimum bypass has yet to be determined and whether a branch of the superficial temporal artery is sufficient in all cases to reverse the degree of measured haemodynamic compromise and provide a measurable clinical benefit is unknown. In addition, establishing a reliable, widely accessible and cost-effective method of assessing impaired cerebral haemodynamics is of paramount importance.

The data suggest the necessity of a multicentre, prospective RCT comparing EC/IC bypass with the best medical treatment in a selected subgroup of patients at high risk of stroke and with identified haemodynamic compromise. One such study is still ongoing; it remains to be seen whether measuring haemodynamic compromise will help to determine whether patients with symptomatic carotid artery occlusive disease benefit from EC/IC bypass surgery. Establishing the safety, efficacy and benefit of surgical bypass can only be established by the future use of multicentre RCTs.

ACKNOWLEDGEMENTS

We wish to thank Hazel Fraser and Brenda Thomas for searching and providing us with lists of the relevant trials from the Cochrane Stroke Group Trials Register. We thank Graeme Hankey, Kameshwar Prasad, Brenda Thomas and David Porter for their helpful comments on an earlier version of this manuscript.

REFERENCES

References to studies included in this review

Auer 1980 *{published data only}*

Auer L, Gallhofer B, Ladurner G, Ott E, Heppner F, Lechner H. Medical versus surgical treatment of patients with cerebrovascular insufficiency. *European Neurology* 1980;**19**:152-62.

Benvenuti 1984 *{published data only}*

Benvenuti l, Gagliardi R, Giombini SM, Andreoli A, Limoni P, Piazza I, et al. Long-term follow up in 257 ICA occlusion: comparison between EIAB-treated and untreated patients. *Neurological Research* 1984;**6**:181-3.

de Weerd 1989 *{published data only}*

de Weerd AW, Veldhuizen RJ, Veering MM, Poortvliet DCJ, Jonkman EJ. Long-term clinical and neurophysiological effects of reconstructive vascular surgery for cerebral ischemia. *Acta Neurologica Scandinavica* 1989;**79**:311-5.

EC/IC Bypass Study 1985 *{published data only}*

EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *New England Journal of Medicine* 1985;**313**:1191-200.

Hartmann 1987 *{published data only}*

Hartmann A, Rommel T, Winter R, Tsuda Y, Menzel J. Measurements of regional cerebral blood flow in patients following superficial temporal artery-middle cerebral artery anastomosis. *Acta Neurochirurgica* 1987;**89**:106-11.

Heilbrun 1982 *{published data only}*

Heilbrun MP. Overall management of vascular lesions considered treatable with extracranial-intracranial bypass: part 1. *Neurosurgery* 1982;**11**:239-46.

Ishikawa 1992 *{published data only}*

Ishikawa T, Yasui N, Suzuki A, Hadeishi H, Shishido F, Uemura K. STA-MCA bypass surgery for internal carotid artery occlusion - comparative follow-up study. *Neurologia Medico Chirurfica (Tokyo)* 1992;**32**:5-9.

Jeffree 2009 *{published data only}*

Jeffree RL, Stoodley MA. STA–MCA bypass for symptomatic carotid occlusion and haemodynamic impairment. *Journal of Clinical Neurosciences* 2009;**16**:226-35.

JET 2006 *{published data only}*

Ogasawara K, Okawa A. JET-Study (Japanese EC-IC Bypass Trial). *Nippon Rinsho* 2006;**64 Suppl 7**:524-7.

Jordan 1984 *{published data only}*

Jordan BP, Mayschak DT, Flye MW. Treatment of the totally occluded carotid artery. *Archives of Surgery* 1984;**119**:952-5.

Karnik 1992 *{published data only}*

Karnik R, Valentin A, Ammerer HP, Donath P, Slany J. Evaluation of vasomotor reactivity by transcranial Doppler and acetazolamide test before and after extracranial-intracranial bypass in patients with internal carotid artery occlusion. *Stroke* 1992;**23**:812-7.

Kobayashi 1991 *{published data only}*

Kobayashi H, Hayashi M, Kawano H, Handa Y, Kabuto M, Maeda H, et al. Evaluation of extracranial-to-intracranial bypass surgery using iodine 123 iodoamphetamine single-photon emission computed tomography. *Surgical Neurology* 1991;**35**:436-40.

Ma 2007 *{published data only}*

Ma J, Mehrkens JH, Holtmannspoetter M, Linke R, Schmid-Elsaesser R, Steiger HJ, et al. Perfusion MRI before and after acetazolamide administration for assessment of cerebrovascular reserve capacity in patients with symptomatic internal carotid artery (ICA) occlusion: comparison with 99mTc-ECD SPECT. *Neuroradiology* 2007;**49**:317-26.

Powers 1989 *{published data only}*

Powers WJ, Grubb RL Jr, Raichle ME. Clinical results of extracranial-intracranial bypass surgery in patients with hemodynamic cerebrovascular disease. *Journal of Neurosurgery* 1989;**70**:61-7.

Satiani 1985 *{published data only}*

Satiani B, Burns J, Vasko JS. Surgical and nonsurgical treatment of total carotid artery occlusion. *American Journal of Surgery* 1985;**149**:362-7.

Tanahashi 1985 *{published data only}*

Tanahashi N, Meyer JS, Rogers RL, Kitagawa Y, Mortel KF, Kandula P, et al. Long-term assessment of cerebral perfusion following STA-MCA by-pass in patients. *Stroke* 1985;**16**:85-91.

Thomas 1984 *{published data only}*

Thomas M, Hennerici M, Marshall J. Cerebral blood flow after carotid occlusion and extracranial-intracranial bypass. *Journal of Neurology, Neurosurgery & Psychiatry* 1984;**47**:148-52.

Yasui 1991 *{published data only}*

Yasui N, Suzuki A, Sayama I, Kawamura S, Shishido F, Uemura K. Comparison of the clinical results of STA-MCA anastomosis and the medical treatment in the cerebral low perfusion patients with viable brain tissue. *Neurology Research* 1991;**13**:84-8.

Yonas 1996 *{published data only}*

Yonas H, Przybylski GJ, Webster MW, Smith HA, Johnson DW. Diagnosis and treatment of high-risk patients from symptomatic carotid occlusive disease with STA-MCA bypass. *Acta Neurologica Scandinavica Supplementum* 1996;**166**:114.

Yoshimoto 1995 *{published data only}*

Yoshimoto Y, Kwak S. Superficial temporal artery - middle cerebral artery anastomosis for acute cerebral ischemia: the effect of small augmentation of blood flow. *Acta Neurochirurgica* 1995;**137**:128-37.

Yoshinaga 1996 *{published data only}*

Yoshinaga S, Tanaka A, Kumate S, Nakayama Y, Tomonaga M. A comparison of hemodynamic effect on an STA/MCA bypass with that of anti-platelet therapy. *Acta Neurologica Scandinavica Supplementum* 1996;**166**:113.

References to studies excluded from this review

Binder 1982 *{published data only}*

Binder LM, Tanabe CT, Waller FT, Wooster NE. Behavioral effects of superficial temporal artery to middle cerebral artery bypass surgery: preliminary report. *Neurology* 1982;**32**:422-4.

Danaila 1984 *{published data only}*

Danaila L, Olarescu A, Gheorghitescu L, Lungu A, Bratu S. Extra-intracranial anastomosis between the superficial temporal artery and a cortical branch of the middle cerebral artery. *Neurologie et Psychiatrie* 1984;**22**:251-61.

Fields 1976 *{published data only}*

Fields WS, Lemak NA. Joint study of extracranial arterial occlusion. X. Internal carotid artery occlusion. *JAMA* 1976;**235**:2734-8.

Lenzi 1988 *{published data only}*

Lenzi B, Fiori L, Marconi F, Parenti G. Cerebral ischemia in young adults. *Minerva Medica* 1988;**79**:707-10.

McCormick 1991 *{published data only}*

McCormick PW, Tomecek FJ, McKinney J, Ausman JI. Disabling cerebral transient ischemic attacks. *Journal of Neurosurgery* 1991;**75**:891-901.

Meyer 1982 *{published data only}*

Meyer JS, Nakajima S, Okabe T, Amano T, Centeno R, Len YY, et al. Redistribution of cerebral blood flow following STA-MCA by-pass in patients with hemispheric ischemia. *Stroke* 1982;**13**:774-84.

Sunada 1989 *{published data only}*

Sunada I. Measurement of cerebral blood flow by single photon emission computed tomography in cases of internal carotid artery occlusion. *Neurologia Medico Chirurfica (Tokyo)* 1989;**29**:496-502.

Wu 1986 *{published data only}*

Wu RQ, Zhu JK, Zhang C, Zhang YJ, Zhang SM, Zhao MX. Follow-up study on 250 patients with extra-intracranial arterial bypass operation for ischemic stroke. *Chinese Medical Journal* 1986;**99**:703-7.

References to ongoing studies

COSS *{published data only}*

Grubb RL Jr, Powers WJ, Derdeyn CP, Adams HP Jr, Clarke WR. The Carotid Occlusion Surgery Study. *Neurosurgical Focus* 2003;**14**(3):e9.

Additional references

Ausman 1986

Ausman JI, Diaz FG. Critique of the extracranial-intracranial bypass study. *Surgical Neurology* 1986;**26**(3):218-21.

Baron 1981

Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia. A case study with 15O positron emission tomography. *Stroke* 1981;**12**(4):454-9.

Bozzao 1989

Bozzao L, Fantozzi LM, Bastianello S, Bozzao A, Fieschi C. Early collateral blood supply and late parenchymal brain damage in patients with middle cerebral artery occlusion. *Stroke* 1989;**20**(6):735-40.

Day 1986

Day AL, Rhoton AL Jr, Little JR. The extracranial-intracranial bypass study. *Surgical Neurology* 1986;**26**(3):222-6.

Derdeyn 2002

Derdeyn CP, Videen TO, Yundt KD, Fritsch SM, Carpenter DA, Grubb RL, et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. *Brain* 2002;**125**(3):595-607.

Donaghy 1967

Donaghy RMP. Patch and bypass in microangional surgery. In: Donaghy RMP, Yasargil MG editor(s). Microvascular Surgery. St. Louis: CV Mosby, 1967:75-86.

Grubb 1986

Grubb RL Jr. Management of the patient with carotid occlusion and a single ischemic event. *Clinical Neurosurgery* 1986;**33**:251-80.

Hankey 1991

Hankey GJ, Warlow CP. Prognosis of symptomatic carotid occlusion: an overview. *Cerebrovascular Disease* 1991;**1**:245-56.

Klijn 1997

Klijn CJ, Kappelle LJ, Tulleken CA, van Gijn J. Symptomatic carotid artery occlusion. A reappraisal of hemodynamic factors. *Stroke* 1997;**28**(10):2084-93.

Lyrer 2003

Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [Art. No.: CD000255. DOI: 10.1002/14651858.CD000255]

Pessin 1977

Pessin MS, Duncan GW, Mohr JP, Poskanzer DC. Clinical and angiographic features of carotid transient ischemic attacks. *New England Journal of Medicine* 1977;**296**(7):358-62.

Powers 1987

Powers WJ, Press GA, Grubb RL Jr, Gado M, Raichle ME. The effect of hemodynamically significant carotid artery disease on

the hemodynamic status of the cerebral circulation. *Annals of Internal Medicine* 1987;**106**(1):27-34.

Powers 1991

Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Annals of Neurology* 1991;**29**(3):231-40.

Powers 2000

Powers WJ, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, et al. Benign prognosis of never-symptomatic carotid occlusion. *Neurology* 2000;**54**(4):878-82.

Sundt 1987

Sundt TM Jr. Was the international randomized trial of extracranial-intracranial arterial bypass representative of the population at risk?. *New England Journal of Medicine* 1987;**316**(13):814-6.

Thiele 1980

Thiele BL, Young JV, Chikos PM, Hirsch JH, Strandness DE Jr. Correlation of arteriographic findings and symptoms in cerebrovascular disease. *Neurology* 1980;**30**(10):1041-6.

Vorstrup 1992

Vorstrup S, Paulson OB. Extracranial-intracranial bypass revisited. *Cerebrovascular Diseases* 1992;**2**:261-2.

Yasargil 1969

Yasargil MG. Anastomosis between the superficial temporal artery and a branch of the middle cerebral artery. Microsurgery Applied to Neurosurgery. Stuttgart: Georg Thieme, 1969:105-15.

CHARACTERISTICS OF STUDIES

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

Auer 1980

Methods	Non-random
Participants	38
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	—

Risk of bias

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

Benvenuti 1984

Methods	Non-random, retrospective
Participants	257
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	

Risk of bias

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

de Weerd 1989

Methods	Non-random
Participants	34
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

EC/IC Bypass Study 1985

Methods	RCT
Participants	1377
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	—

Risk of bias

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

Hartmann 1987

Methods	Non-random, retrospective
Participants	41
Interventions	EC/IC bypass
Outcomes	Increased mean rCBF after EC/IC bypass
Notes	Main focus: CBF measurement

Risk of bias

Bias	Authors' judgement	Support for judgement

Hartmann 1987 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Heilbrun 1982

Methods	Non-random
Participants	49
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

Ishikawa 1992

Methods	Non-random
Participants	63
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

Jeffree 2009

Methods	Non-random
Participants	23
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	—

Jeffree 2009 *(Continued)*

Risk of bias

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

JET 2006

Methods	RCT
Participants	206, report on 196, 1 excluded due to protocol violation
Interventions	EC/IC bypass
Outcomes	Death from all causes, re-stroke with disability
Notes	Randomisation procedure not described in detail

Risk of bias

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

Jordan 1984

Methods	Non-random
Participants	34
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

Karnik 1992

Methods	Non-random
Participants	104: 14 underwent EC/IC bypass, 14 received best medical treatment Blood flow velocity measurement was assessed in 6 patients with EC/IC bypass surgery and in 4 controls

Karnik 1992 *(Continued)*

Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, improvement of vasomotor reactivity in patients with EC/IC bypass after acetazolamide application
Notes	Randomisation procedure not described in detail

Risk of bias

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

Kobayashi 1991

Methods	Non-random
Participants	11
Interventions	EC/IC bypass
Outcomes	Any stroke during follow up, death or dependency
Notes	—

Risk of bias

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

Ma 2007

Methods	Non-random
Participants	11
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	—

Risk of bias

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

Powers 1989

Methods	Non-random
Participants	52
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

Satiani 1985

Methods	Non-random
Participants	42
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

Tanahashi 1985

Methods	Non-random
Participants	60
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	—

Risk of bias

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

Thomas 1984

Methods	Non-random
Participants	11
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, improvement of CBF after EC/IC bypass
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Yasui 1991

Methods	Non-random, retrospective
Participants	55
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	Only patients with viable brain tissue

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Yonas 1996

Methods	Non-random, retrospective
Participants	46
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Yonas 1996 *(Continued)*

Allocation concealment?	Unclear risk	D - Not used

Yoshimoto 1995

Methods	Non-random, retrospective
Participants	70
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up, death or dependency
Notes	—

Risk of bias

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

Yoshinaga 1996

Methods	Non-random
Participants	19
Interventions	EC/IC bypass
Outcomes	Death from all causes, any stroke during follow up
Notes	—

Risk of bias

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

CBF: cerebral blood flow
EC/IC bypass: extracranial to intracranial bypass
rCBF: regional cerebral blood flow
RCT: randomised controlled trial

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

Study	Reason for exclusion
Binder 1982	The study compared neuropsychological function between patients with EC/IC bypass and patients with aspirin and dipyridamole treatment, while data about primary and secondary outcome events defined for this review were not given

Study	Reason for exclusion
Danaila 1984	In this study, the authors present a mixture of Moyamoya disease, fibromuscular and atherosclerotic steno-occlusive ICA and MCA disease
Fields 1976	The surgical group had only thrombendarterectomy of occluded carotid artery rather than EC/IC bypass, and were compared with patients receiving only best medical treatment
Lenzi 1988	Patients who underwent EC/IC bypass procedure were not compared with a control group receiving best medical treatment
McCormick 1991	No comparison of surgically-treated patients with a medically-treated group
Meyer 1982	Patients with Moyamoya disease are mixed with atherosclerotic ICA occlusion
Sunada 1989	EC/IC bypass patients were compared with normal volunteers
Wu 1986	Patients with Moyamoya disease are mixed with atherosclerotic ICA occlusion

EC/IC bypass: extracranial to intracranial bypass
ICA: internal carotid artery
MCA: middle cerebral artery

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

COSS

Trial name or title	Carotid Occlusion Surgery Study
Methods	—
Participants	Patients with atherosclerotic occlusion of one or both carotid arteries, with hemispheric TIA or mild-to-moderate stroke (Barthel Index > 60) in the territory of an occluded carotid artery within 120 days and with increased OEF measured by PET ipsilateral to the symptomatic carotid artery occlusion
Interventions	EC/IC bypass
Outcomes	All strokes in patients with symptomatic carotid occlusion and high OEF
Starting date	February 2000
Contact information	http://www.cosstrial.org/coss/contact.asp
Notes	—

EC/IC bypass: extracranial to intracranial bypass
OEF: oxygen extraction fraction
PET: positron emission tomography
TIA: transient ischaemic attack

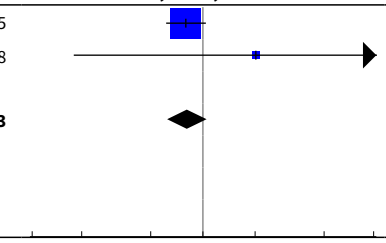
DATA AND ANALYSES

Comparison 1. EC/IC bypass versus best medical treatment: RCTs only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	2	1691	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.05]
2 Any stroke during follow up	2	1691	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.79, 1.23]
3 Death or dependency	1	1377	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.74, 1.21]
4 Vascular death	1	1377	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.29]
5 Stroke, serious vascular events or vascular death	2	1573	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.91]
6 Myocardial infarction	2	1522	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.46, 1.32]
7 Ischaemic stroke	2	1573	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.44, 1.08]

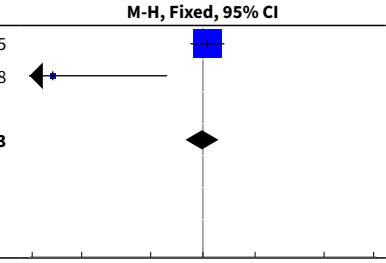
Analysis 1.1. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 1 Death from all causes.

Study or subgroup	EC/IC bypass n/N	medical treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
EC/IC Bypass Study 1985	123/730	155/765		99.23%	0.8[0.61,1.04]
JET 2006	2/98	1/98		0.77%	2.02[0.18,22.66]
Total (95% CI)	**828**	**863**		**100%**	**0.81[0.62,1.05]**
Total events: 125 (EC/IC bypass), 156 (medical treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=1.62(P=0.11)					

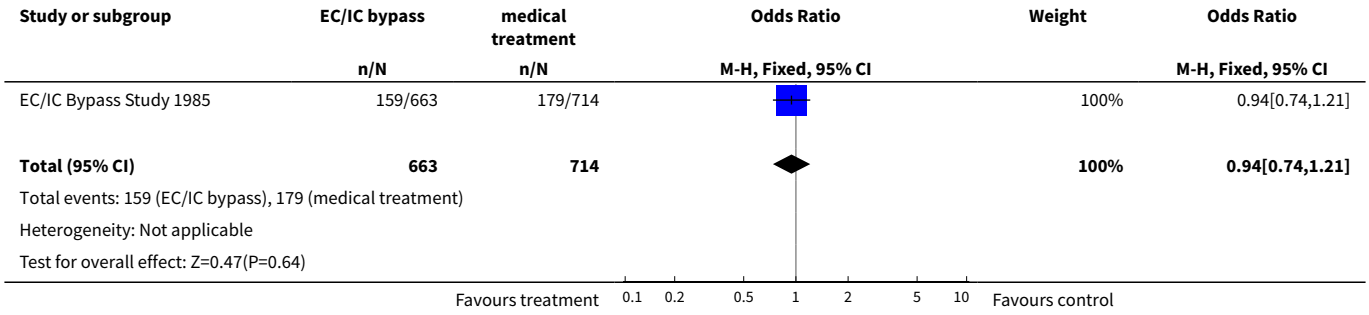


Analysis 1.2. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 2 Any stroke during follow up.

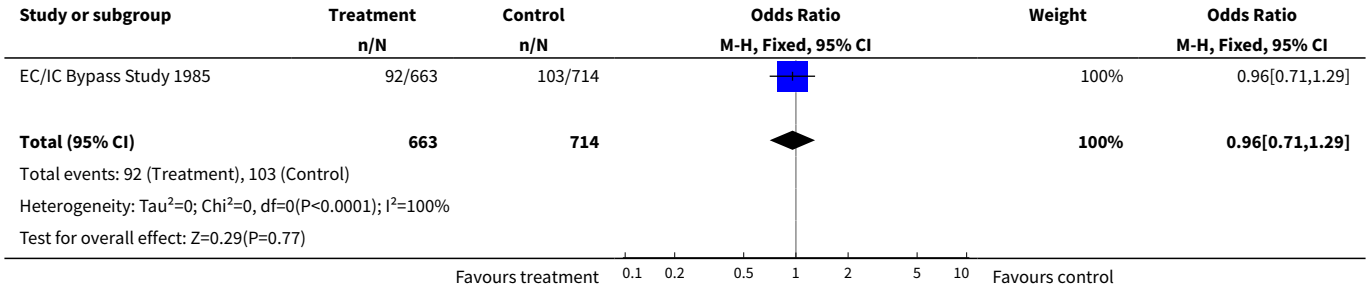
Study or subgroup	EC/IC bypass n/N	medical treatment n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
EC/IC Bypass Study 1985	213/730	214/765		92.08%	1.06[0.85,1.33]
JET 2006	2/98	13/98		7.92%	0.14[0.03,0.62]
Total (95% CI)	**828**	**863**		**100%**	**0.99[0.79,1.23]**
Total events: 215 (EC/IC bypass), 227 (medical treatment)					
Heterogeneity: Tau^2=0; Chi^2=6.94, df=1(P=0.01); I^2=85.59%					
Test for overall effect: Z=0.11(P=0.91)					



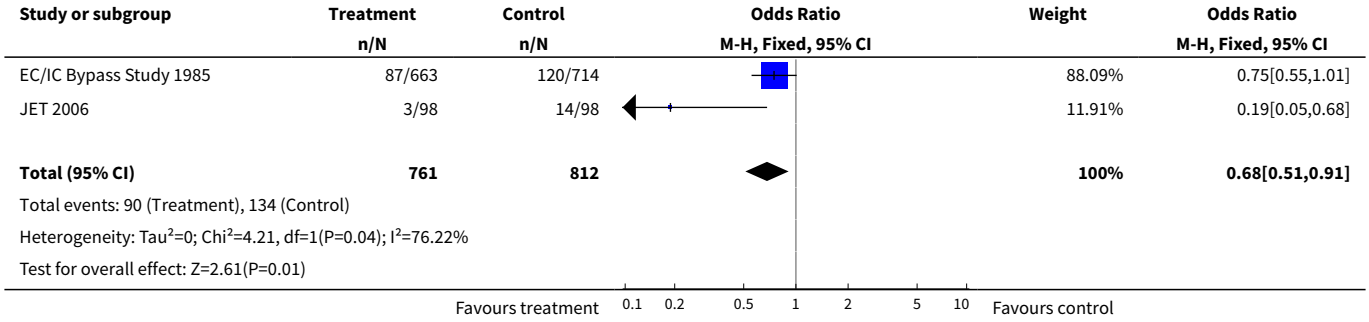
Analysis 1.3. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 3 Death or dependency.



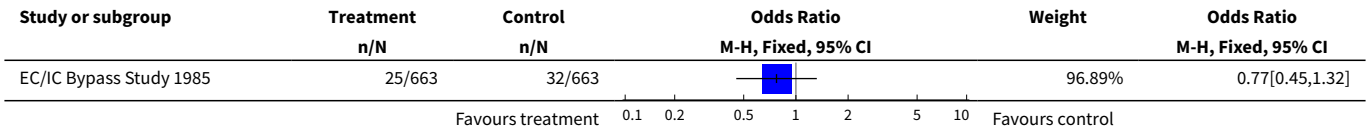
Analysis 1.4. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 4 Vascular death.

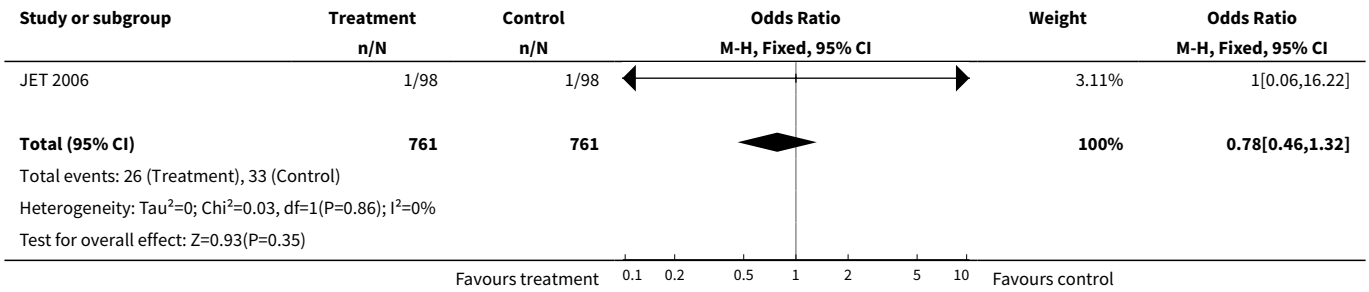


Analysis 1.5. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 5 Stroke, serious vascular events or vascular death.

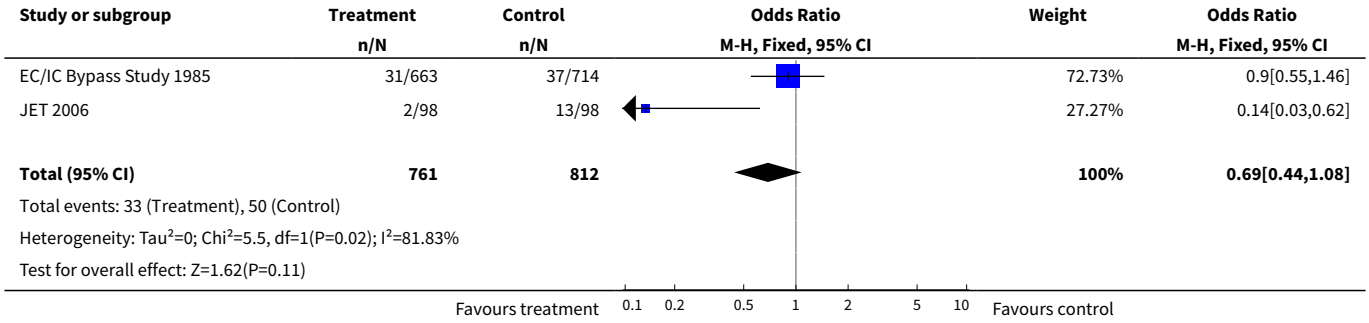


Analysis 1.6. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 6 Myocardial infarction.





Analysis 1.7. Comparison 1 EC/IC bypass versus best medical treatment: RCTs only, Outcome 7 Ischaemic stroke.



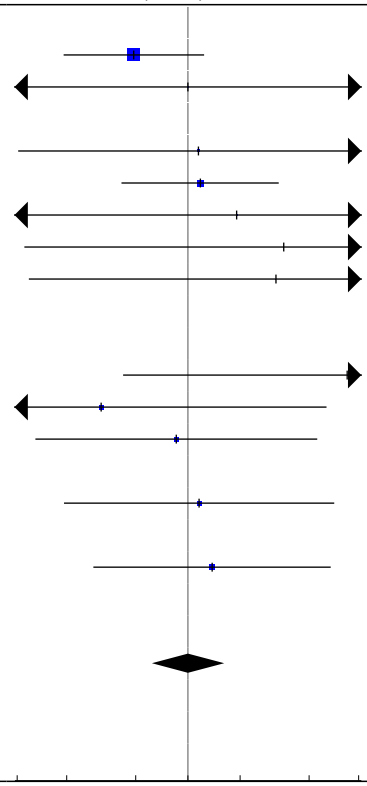
Comparison 2. EC/IC bypass versus best medical treatment: all studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	19	900	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.62, 1.62]
2 Any stroke during follow up	18	881	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.54, 1.18]
3 Death or dependency	8	346	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.50, 1.29]
4 Vascular death	19	900	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.56, 1.63]
5 Stroke, serious vascular events or vascular death	13	673	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.45, 1.04]
6 Myocardial infarction	2	79	Odds Ratio (M-H, Fixed, 95% CI)	2.67 [0.41, 17.60]
7 Ischaemic stroke	13	640	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.44, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Intracranial haemorrhage	4	361	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.44, 2.93]
9 Transient ischaemic attack or amaurosis fugax	11	524	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.16, 0.69]
10 Normalisation of cerebral haemodynamics	3	56	Odds Ratio (M-H, Fixed, 95% CI)	6.63 [1.85, 23.78]

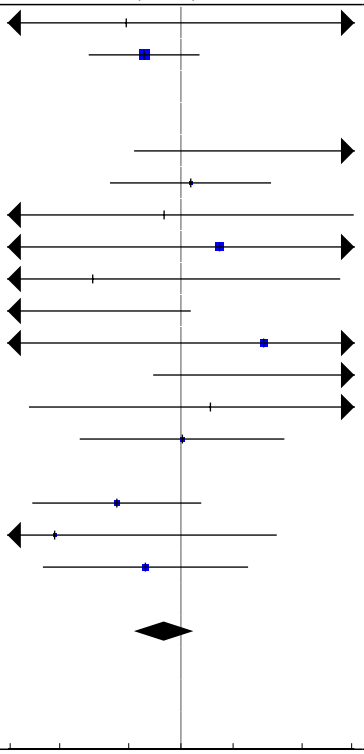
Analysis 2.1. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 1 Death from all causes.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	0/15	0/23			Not estimable
Benvenuti 1984	7/122	15/135		40.2%	0.49[0.19,1.24]
de Weerd 1989	1/17	1/17		2.82%	1[0.06,17.41]
Hartmann 1987	0/25	0/16			Not estimable
Heilbrun 1982	1/6	4/27		3.63%	1.15[0.1,12.62]
Ishikawa 1992	10/27	12/36		19.39%	1.18[0.41,3.34]
Jeffree 2009	3/19	0/4		1.98%	1.91[0.08,44.16]
Jordan 1984	2/2	3/5		1.16%	3.57[0.11,111.71]
Karnik 1992	1/14	0/14		1.35%	3.22[0.12,86.09]
Kobayashi 1991	0/10	0/1			Not estimable
Ma 2007	0/6	0/5			Not estimable
Powers 1989	4/29	0/23		1.41%	8.29[0.42,162.48]
Satiani 1985	0/8	5/34		6.36%	0.32[0.02,6.3]
Tanahashi 1985	3/38	2/22		6.99%	0.86[0.13,5.57]
Thomas 1984	0/5	0/5			Not estimable
Yasui 1991	4/35	2/20		6.75%	1.16[0.19,6.98]
Yonas 1996	0/10	0/36			Not estimable
Yoshimoto 1995	4/35	3/35		7.96%	1.38[0.28,6.66]
Yoshinaga 1996	0/4	0/15			Not estimable
Total (95% CI)	**427**	**473**		**100%**	**1[0.62,1.62]**
Total events: 40 (Treatment), 47 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.29, df=11(P=0.85); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					



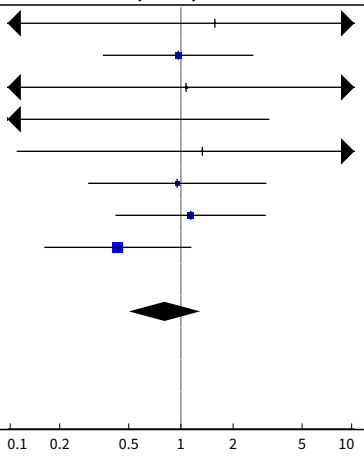
Analysis 2.2. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 2 Any stroke during follow up.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	0/15	1/23		2.09%	0.48[0.02,12.67]
Benvenuti 1984	13/122	22/135		33.48%	0.61[0.29,1.28]
de Weerd 1989	0/17	0/17			Not estimable
Hartmann 1987	0/25	0/16			Not estimable
Heilbrun 1982	1/6	0/27		0.28%	15[0.54,418.64]
Ishikawa 1992	9/27	11/36		11.28%	1.14[0.39,3.31]
Jeffree 2009	4/19	1/4		2.34%	0.8[0.06,9.92]
Jordan 1984	2/2	4/5		0.9%	1.67[0.05,58.28]
Karnik 1992	0/14	1/14		2.6%	0.31[0.01,8.29]
Kobayashi 1991	0/10	1/1		4.35%	0.02[0,1.14]
Ma 2007	1/6	0/5		0.76%	3[0.1,90.96]
Powers 1989	6/29	0/23		0.78%	13[0.69,244.12]
Satiani 1985	1/8	3/34		1.79%	1.48[0.13,16.39]
Tanahashi 1985	7/38	4/22		7.42%	1.02[0.26,3.95]
Thomas 1984	0/5	0/5			Not estimable
Yasui 1991	12/35	11/20		16.51%	0.43[0.14,1.31]
Yonas 1996	0/10	7/36		5.89%	0.19[0.01,3.57]
Yoshimoto 1995	4/35	6/35		9.54%	0.62[0.16,2.44]
Total (95% CI)	**423**	**458**		**100%**	**0.8[0.54,1.18]**
Total events: 60 (Treatment), 72 (Control)					
Heterogeneity: Tau²=0; Chi²=14.36, df=14(P=0.42); I²=2.52%					
Test for overall effect: Z=1.14(P=0.25)					



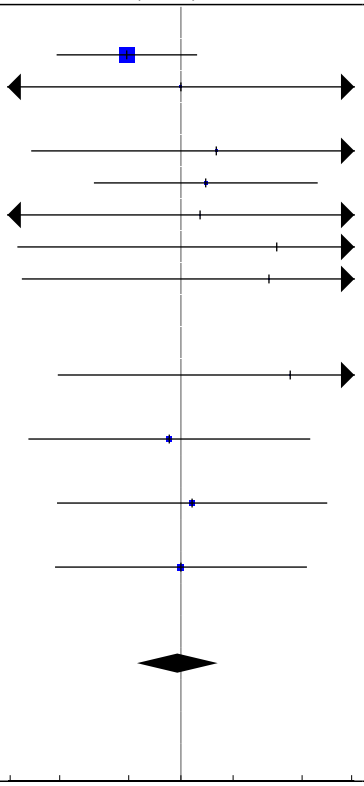
Analysis 2.3. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 3 Death or dependency.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	1/15	1/23		1.94%	1.57[0.09,27.21]
Ishikawa 1992	14/27	19/36		20.62%	0.96[0.35,2.62]
Jeffree 2009	5/19	1/4		3.2%	1.07[0.09,12.83]
Kobayashi 1991	2/10	1/1		5.16%	0.1[0,3.24]
Ma 2007	4/6	3/5		2.87%	1.33[0.11,15.7]
Tanahashi 1985	10/38	6/22		14.73%	0.95[0.29,3.11]
Yasui 1991	12/35	11/35		19.01%	1.14[0.42,3.09]
Yoshimoto 1995	17/35	24/35		32.46%	0.43[0.16,1.15]
Total (95% CI)	**185**	**161**		**100%**	**0.8[0.5,1.29]**
Total events: 65 (Treatment), 66 (Control)					
Heterogeneity: Tau²=0; Chi²=4.04, df=7(P=0.78); I²=0%					
Test for overall effect: Z=0.9(P=0.37)					



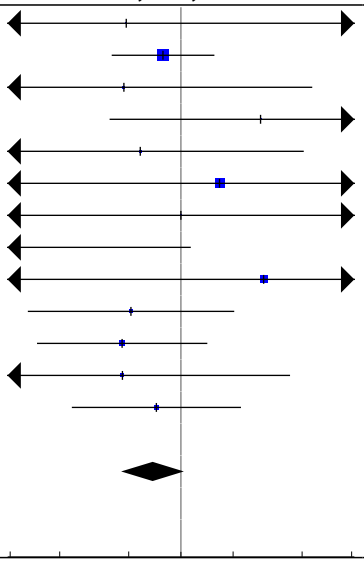
Analysis 2.4. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 4 Vascular death.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	0/15	0/23			Not estimable
Benvenuti 1984	7/122	15/135		48.68%	0.49[0.19,1.24]
de Weerd 1989	1/17	1/17		3.41%	1[0.06,17.41]
Hartmann 1987	0/25	0/16			Not estimable
Heilbrun 1982	1/6	3/27		3.3%	1.6[0.14,18.72]
Ishikawa 1992	4/27	4/36		10.59%	1.39[0.31,6.15]
Jeffree 2009	2/19	0/4		2.54%	1.29[0.05,31.8]
Jordan 1984	2/2	3/5		1.41%	3.57[0.11,111.71]
Karnik 1992	1/14	0/14		1.63%	3.22[0.12,86.09]
Kobayashi 1991	0/10	0/1			Not estimable
Ma 2007	0/6	0/5			Not estimable
Powers 1989	2/29	0/23		1.85%	4.27[0.2,93.52]
Satiani 1985	0/8	0/34			Not estimable
Tanahashi 1985	3/38	2/22		8.46%	0.86[0.13,5.57]
Thomas 1984	0/5	0/5			Not estimable
Yasui 1991	4/35	2/20		8.18%	1.16[0.19,6.98]
Yonas 1996	0/10	0/36			Not estimable
Yoshimoto 1995	3/35	3/35		9.95%	1[0.19,5.33]
Yoshinaga 1996	0/4	0/15			Not estimable
Total (95% CI)	**427**	**473**		**100%**	**0.95[0.56,1.63]**
Total events: 30 (Treatment), 33 (Control)					
Heterogeneity: Tau²=0; Chi²=4.51, df=10(P=0.92); I²=0%					
Test for overall effect: Z=0.18(P=0.86)					

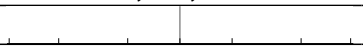


Analysis 2.5. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 5 Stroke, serious vascular events or vascular death.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	0/15	1/23		2.18%	0.48[0.02,12.67]
Benvenuti 1984	17/122	23/135		35.24%	0.79[0.4,1.56]
de Weerd 1989	1/17	2/17		3.53%	0.47[0.04,5.72]
Heilbrun 1982	2/6	4/27		1.82%	2.88[0.39,21.29]
Jeffree 2009	7/19	2/4		3.91%	0.58[0.07,5.11]
Jordan 1984	2/2	4/5		0.94%	1.67[0.05,58.28]
Karnik 1992	1/14	1/14		1.74%	1[0.06,17.75]
Kobayashi 1991	0/10	1/1		4.54%	0.02[0,1.14]
Ma 2007	1/6	0/5		0.79%	3[0.1,90.96]
Tanahashi 1985	5/38	5/22		10.31%	0.52[0.13,2.03]
Yasui 1991	11/35	10/20		16.36%	0.46[0.15,1.42]
Yonas 1996	1/10	7/36		5.14%	0.46[0.05,4.26]
Yoshimoto 1995	7/35	9/35		13.5%	0.72[0.24,2.22]
Total (95% CI)	**329**	**344**		**100%**	**0.69[0.45,1.04]**
Total events: 55 (Treatment), 69 (Control)					
Heterogeneity: Tau²=0; Chi²=7.07, df=12(P=0.85); I²=0%					



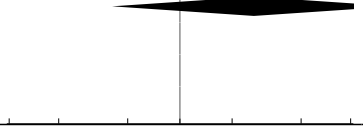
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.76(P=0.08)					



Favours treatment Favours control

Analysis 2.6. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 6 Myocardial infarction.

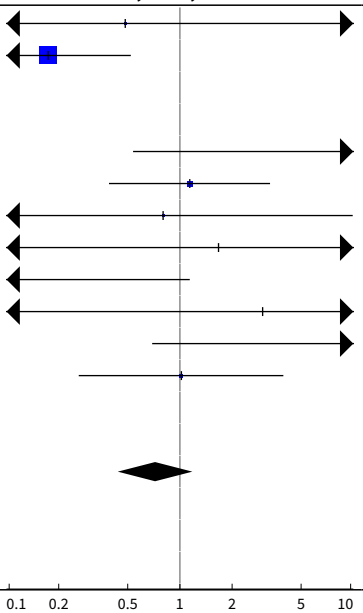
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heilbrun 1982	0/6	2/27		82.43%	0.78[0.03,18.42]
Yonas 1996	1/10	0/36		17.57%	11.53[0.43,306.09]
Total (95% CI)	**16**	**63**		**100%**	**2.67[0.41,17.6]**
Total events: 1 (Treatment), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.34, df=1(P=0.25); I^2=25.51%					
Test for overall effect: Z=1.02(P=0.31)					



Favours treatment Favours control

Analysis 2.7. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 7 Ischaemic stroke.

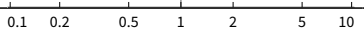
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	0/15	1/23		3.14%	0.48[0.02,12.67]
Benvenuti 1984	4/122	22/135		54.56%	0.17[0.06,0.52]
de Weerd 1989	0/17	0/17			Not estimable
Hartmann 1987	0/25	0/16			Not estimable
Heilbrun 1982	1/6	0/27		0.42%	15[0.54,418.64]
Ishikawa 1992	9/27	11/36		16.98%	1.14[0.39,3.31]
Jeffree 2009	4/19	1/4		3.52%	0.8[0.06,9.92]
Jordan 1984	2/2	4/5		1.35%	1.67[0.05,58.28]
Kobayashi 1991	0/10	1/1		6.54%	0.02[0,1.14]
Ma 2007	1/6	0/5		1.14%	3[0.1,90.96]
Powers 1989	6/29	0/23		1.18%	13[0.69,244.12]
Tanahashi 1985	7/38	4/22		11.16%	1.02[0.26,3.95]
Thomas 1984	0/5	0/5			Not estimable
Total (95% CI)	**321**	**319**		**100%**	**0.72[0.44,1.18]**
Total events: 34 (Treatment), 44 (Control)					
Heterogeneity: Tau^2=0; Chi^2=18.33, df=9(P=0.03); I^2=50.9%					
Test for overall effect: Z=1.3(P=0.19)					



Favours treatment Favours control

Analysis 2.8. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 8 Intracranial haemorrhage.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Benvenuti 1984	5/122	0/135		5.6%	12.69[0.69,231.83]
Jeffree 2009	0/19	1/4		28.86%	0.06[0,1.79]
Ma 2007	0/6	0/5			Not estimable
Yoshimoto 1995	4/35	6/35		65.54%	0.62[0.16,2.44]
Total (95% CI)	**182**	**179**		**100%**	**1.14[0.44,2.93]**
Total events: 9 (Treatment), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.28, df=2(P=0.04); I^2=68.14%					
Test for overall effect: Z=0.26(P=0.79)					



Favours treatment — Favours control

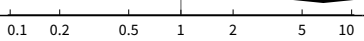
Analysis 2.9. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 9 Transient ischaemic attack or amaurosis fugax.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Auer 1980	1/15	2/23		4.91%	0.75[0.06,9.08]
Benvenuti 1984	2/122	24/135		74.69%	0.08[0.02,0.33]
de Weerd 1989	0/17	1/17		4.86%	0.31[0.01,8.27]
Hartmann 1987	0/25	0/16			Not estimable
Heilbrun 1982	1/6	1/27		1.01%	5.2[0.28,97.62]
Jeffree 2009	2/19	0/4		2.33%	1.29[0.05,31.8]
Jordan 1984	0/2	1/5		2.78%	0.6[0.02,20.98]
Karnik 1992	1/14	0/14		1.5%	3.22[0.12,86.09]
Ma 2007	1/6	0/5		1.41%	3[0.1,90.96]
Satiani 1985	0/8	1/34		1.93%	1.31[0.05,35.19]
Thomas 1984	0/5	1/5		4.58%	0.27[0.01,8.46]
Total (95% CI)	**239**	**285**		**100%**	**0.34[0.16,0.69]**
Total events: 8 (Treatment), 31 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.47, df=9(P=0.19); I^2=27.8%					
Test for overall effect: Z=2.98(P=0)					

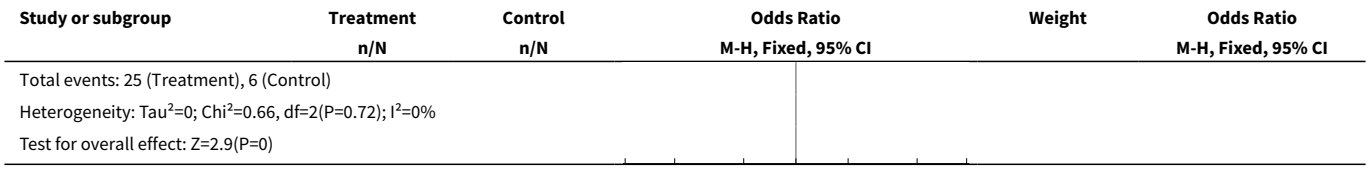
Favours treatment — Favours control

Analysis 2.10. Comparison 2 EC/IC bypass versus best medical treatment: all studies, Outcome 10 Normalisation of cerebral haemodynamics.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Jeffree 2009	14/16	2/4		22.76%	7[0.6,81.68]
Karnik 1992	10/14	3/14		48.78%	9.17[1.63,51.43]
Thomas 1984	1/3	1/5		28.46%	2[0.08,51.59]
Total (95% CI)	**33**	**23**		**100%**	**6.63[1.85,23.78]**



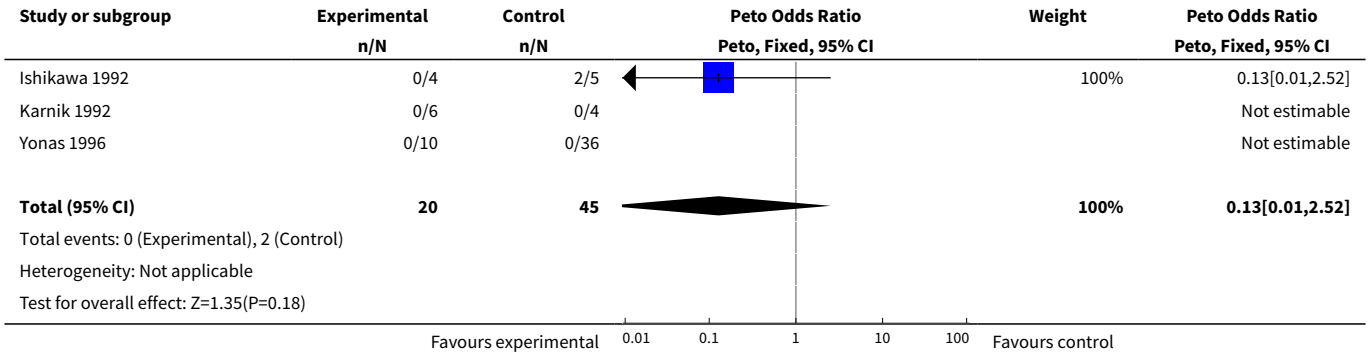
Favours treatment — Favours control



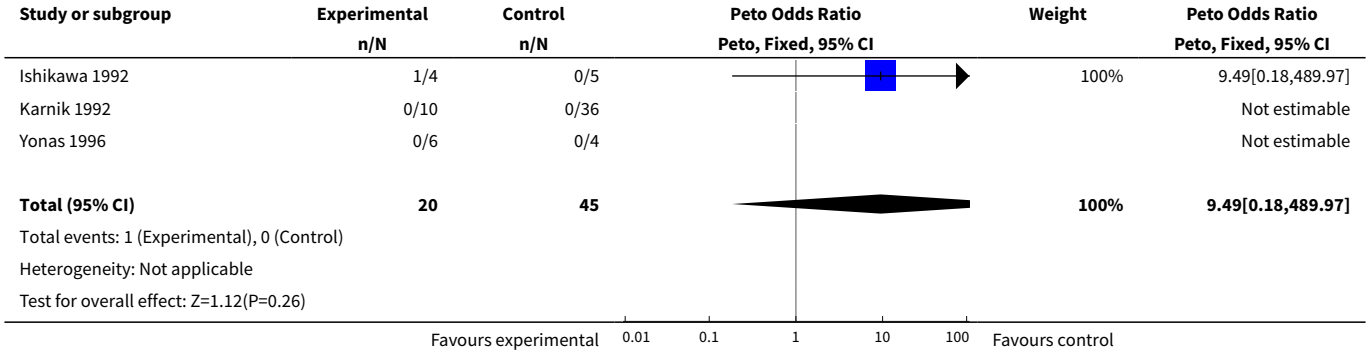
Comparison 3. Haemodynamic compromise as selection criterion for EC/IC bypass

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any stroke during follow up	3	65	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.52]
2 Death from all causes	3	65	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.49 [0.18, 489.97]

Analysis 3.1. Comparison 3 Haemodynamic compromise as selection criterion for EC/IC bypass, Outcome 1 Any stroke during follow up.



Analysis 3.2. Comparison 3 Haemodynamic compromise as selection criterion for EC/IC bypass, Outcome 2 Death from all causes.



APPENDICES

Appendix 1. MEDLINE search strategy

The following search strategy was used for MEDLINE (Ovid) and was modified for the other databases.

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/ or cerebrovascular accident/ or exp brain infarction/ or exp hypoxia-ischemia, brain/ or exp intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or vasospasm, intracranial/
2. (stroke$ or cva).tw.
3. ((cerebr$ or brain$ or carotid or cerebellar or intracranial or vertebrobasilar or MCA) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli $ or occlus$ or occlud$ or arteriosclero$ or stenosis or steno-occlus$ or obstruct$)).tw.
4. transient isch$.tw.
5. 1 or 2 or 3 or 4
6. cerebral revascularization/
7. exp cerebral arteries/su
8. arterial occlusive diseases/su
9. *vascular surgical procedures/
10. *anastomosis, surgical/
11. (extra?cranial adj5 intra?cranial).tw.
12. ((cerebral or brain or arterial or surgical or microsurgical) adj5 (anastomosis or revascular$ or bypass or graft)).tw.
13. (temporal artery adj5 middle cerebral artery).tw.
14. ((temporal or occipital) adj5 intracranial).tw.
15. (EC-IC or ECIC or EC#IC or extra-intracranial or STA-MCA).tw.
16. or/6-15
17. 5 and 16
18. limit 17 to human

Appendix 2. EMBASE search strategy

The following search strategy was used for EMBASE (Ovid).

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/
2. (stroke$ or cva).tw.
3. ((cerebr$ or brain$ or carotid or cerebellar or intracranial or vertebrobasilar or MCA) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli $ or occlus$ or occlud$ or arteriosclero$ or stenosis or steno-occlus$ or obstruct$)).tw.
4. transient isch$.tw.
5. brain atherosclerosis/
6. exp carotid artery/ or exp brain artery/
7. artery occlusion/ or exp thromboembolism/
8. 6 and 7
9. 1 or 2 or 3 or 4 or 5 or 8
10. cerebrovascular surgery/ or brain artery bypass/ or extraintracranial anastomosis/
11. artery anastomosis/ or artery bypass/
12. *bypass surgery/ or *artery graft/ or *revascularization/
13. *superficial temporal artery/
14. (extra?cranial adj5 intra?cranial).tw.
15. ((cerebral or brain or arterial or surgical or microsurgical) adj5 (anastomosis or revascular$ or bypass or graft)).tw.
16. (temporal artery adj5 middle cerebral artery).tw.
17. ((temporal or occipital) adj5 intracranial).tw.
18. (EC-IC or ECIC or EC#IC or extra-intracranial or STA-MCA).tw.
19. or/10-18
20. 9 and 19
21. limit 20 to human

HISTORY

Protocol first published: Issue 2, 2006
Review first published: Issue 2, 2010

Date	Event	Description
22 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Felix Fluri: developing the protocol, writing the protocol, extracting data, drafting the review.
Stefan Engelter: developing the protocol, extracting data, revising the review draft.
Philippe Lyrer: developing the protocol, writing the protocol, fundraising, revising the review draft.

DECLARATIONS OF INTEREST

The authors received an in-house grant from the Department of Neurology, University Hospital Basel, to perform the review.

SOURCES OF SUPPORT

Internal sources

- Scientific Fund of the Stroke Programme, Neurology Department, University Hospital, Basel, Switzerland.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Arterial Occlusive Diseases [*surgery]; Carotid Artery Diseases [*surgery]; Cerebral Revascularization [adverse effects] [*methods]; Combined Modality Therapy [methods]

MeSH check words

Humans