Antithrombotic drugs for carotid artery dissection (Review)

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[Intervention Review]

Antithrombotic drugs for carotid artery dissection

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ABSTRACT

Background

Extracranial internal carotid artery dissection (eICAD) is a leading cause of stroke in younger patients.

Objectives

1. To determine whether, in patients with eICAD, treatment with anticoagulants, antiplatelet agents or control was associated with a better functional outcome.

2. To compare, among patients treated with either anticoagulants or antiplatelet agents, the risk of ischaemic strokes and major bleeding episodes.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched 3 October 2009). In addition, we performed comprehensive searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 2, 2009), MEDLINE (January 1966 to November 2009) and EMBASE (January 1980 to November 2009), checked all relevant papers for additional eligible studies and contacted authors and researchers in the field.

Selection criteria

Randomised controlled trials, controlled clinical trials and non-randomised studies (if they reported on outcome stratified by antithrombotic treatment and included at least four patients) of anticoagulants or antiplatelet agents for the treatment of extracranial internal carotid artery dissection. Two review authors independently extracted data.

Data collection and analysis

Primary outcomes were death (all causes) and death or disability. Secondary outcomes were ischaemic stroke, symptomatic intracranial haemorrhage, and major extracranial haemorrhage during the reported follow-up period. The first choice treatment was taken for analyses.

Main results

We did not find any completed randomised trials. Comparing antiplatelets with anticoagulants across 36 observational studies (1285 patients), there were no significant differences in the odds of death (Peto odds ratio (Peto OR) 2.02, 95% CI 0.62 to 6.60), or the occurrence of ischaemic stroke (OR 0.63, 95% CI 0.21 to 1.86) (34 studies, 1262 patients). For the outcome of death or disability,

there was a non-significant trend in favour of anticoagulants (OR 1.77, 95% CI 0.98 to 3.22; P = 0.06) (26 studies, 463 patients). Symptomatic intracranial haemorrhages (5/627; 0.8%) and major extracranial haemorrhages (7/425; 1.6%) occurred only in the anticoagulation group; however, for both these outcomes, the estimates were imprecise and indicated no significant difference between the two treatment modalities.

Authors' conclusions

There were no randomised trials comparing either anticoagulants or antiplatelet drugs with control, thus there is no evidence to support their routine use for the treatment of extracranial internal carotid artery dissection. There were also no randomised trials that directly compared anticoagulants with antiplatelet drugs and the reported non-randomised studies did not show any evidence of a significant difference between the two.

PLAIN LANGUAGE SUMMARY

Antithrombotic drugs for carotid artery dissection

Carotid artery dissection means a tear in the lining in one of the main blood vessels carrying blood to the brain. Dissection can be caused by injury to the neck, but can sometimes develop for no obvious reason. Blood clots can form where the artery is torn. These blood clots can then block the artery and cause a stroke. Blood thinning drugs such as aspirin and anticoagulants might prevent clots forming and so prevent stroke in people with carotid artery dissection. We did not find any completed randomised trials testing these drugs in people with carotid artery dissection. However, there is one ongoing trial. We found only poor quality non-randomised studies that compared anticoagulants with aspirin. There was no evidence that anticoagulants were better than aspirin. Aspirin is likely to be similarly effective and safe as anticoagulants in such patients. More research is needed.

BACKGROUND

Extracranial internal carotid artery dissection (eICAD) can lead to the occlusion of the artery. It is the underlying stroke mechanism in approximately 2.5% of all strokes (Bogousslavsky 1987b), compared with between 5% and 22% in young stroke patients, hence being among the leading causes of stroke in patients younger than 45 years (Bogousslavsky 1987a; Gautier 1989; Leys 2002 Lisovoski 1991; Rouhart 1993). It was first recognised as a cause of ischaemic stroke in the mid-1950s (Anderson 1959; Jentzer 1954), although there are pathological reports on the condition dating from 1872 (Richaud 1980). The incidence is about 1.7 to 3/100,000 per year (Giroud 1994; Lee 2006; Schievink 1993). The recurrence rate of CAD is less than 1% per year (Beletsky 2003; Giroud 1994; Lee 2006; Schievink 1993; Touze 2003) except for familial cases. It is still debated whether, in eICAD patients, anticoagulation or antiplatelet agents are superior, balancing risk and benefits of either approach (New Reference; Lyrer 2004; Lyrer 2005; Norris 2005). Anticoagulation is widely advocated (Cimini 2004; Hart 1983; Sturzenegger 1995) and often used (Menon 2008b). However, there is no reliable evidence from randomised trials for the efficacy of this therapy (Leys 1997; Schievink 2001). The beneficial effect of anticoagulants over antiplatelets may be offset by an increase in the number of bleedings (IST 1997).

Case observations of worsening of carotid stenosis suggested the occurrence of anticoagulation-mediated perpetuation of intramural bleeding in some patients with eICAD (Dreier 2004; Fluri 2007; Mokri 1986). As a consequence, haemodynamic worsening might occur, which implies the risk of low-flow infarcts (Arauz 2006; Dreier 2004).

OBJECTIVES

The objective of this systematic review was to evaluate the efficacy and safety of anticoagulants (AC) versus antiplatelet drugs (AP) in patients with eICAD. Our primary objective was to determine whether patients with eICAD receiving AC were more likely to have a better functional outcome such as not being dead or not being disabled, compared with those receiving AP.

Our secondary objectives were to evaluate:

- whether patients had fewer ischaemic strokes, defined as the occurrence or recurrence of cerebral or retinal ischaemic events

lasting more than 24 hours, when treated with AC compared with AP;

- whether patients had more haemorrhages (symptomatic intracranial or major extracranial bleedings) when treated with AC compared with those treated with AP.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs), controlled clinical trials (CCTs), non-randomised studies or case series including at least four patients with eICAD that allowed comparisons between antithrombotic treatments for eICAD were eligible.
We sought information on the description of the diagnostic methods, the clinical presentation and the diagnostic findings. We searched for all information concerning treatment and all outcomes stratified to the used antithrombotic option (i.e. AP and AC). We included all studies that reported at least one primary outcome comparing patients treated with AC versus those treated with AP. We excluded studies reporting on a single treatment modality.
We excluded studies from any analysis when:

- there were three or fewer cases;
- they consisted of reviews summarising case reports;
- they were series with data repetition from former citations (we included only the most recent series);
- we could not make the distinction between dissections of internal carotid artery, common carotid artery, vertebral artery, or intracranial carotid artery dissection.

Types of participants

Studies and series reporting patients who had experienced eICAD were eligible. Patients with stroke, transient ischaemic attacks or local neurological deficits as an initial event were taken together. Studies with patients whose diagnosis of eICAD was made by arterial angiography, duplex scanning, computed tomography or magnetic resonance imaging demonstrating the specific features of dissection were eligible. We accepted the following angiographic signs consistent with eICAD: mural haematoma, pseudoaneurysm, long tapering stenosis, intimal flap, double lumen, or occlusion more than 2 cm above the carotid bifurcation revealing a pseudoaneurysm or a long tapering stenosis after recanalisation.

Types of interventions

We sought to identify all trials and studies where antithrombotic treatment (AP or AC) was given for eICAD. Antithrombotic treatment was defined as administration of any AP drug (i.e. acetylsalicylic acid (ASA), ticlopidine, clopidogrel, sulfinpyrazone, dipyridamole) or administration of full dose AC (such as intravenous or subcutaneous fractionated or unfractionated heparin or oral coumarin).
We only analysed the initially-used antithrombotic treatment. For example, if a patient had AC and later AP, the patient was analysed in the AC treatment group. If surgical intervention was mentioned as a treatment modality, we excluded the patient from the comparative analysis of AC versus AP treatment.
In patients receiving thrombolysis, the first antithrombotic agent used thereafter was deemed the 'initially-used antithrombotic treatment'. In cases of bleeding complications, we sought information on whether the bleed was associated with the thrombolytic treatment (rather than with the antithrombotic treatment).

Types of outcome measures

Primary outcomes

The primary outcomes were:

- death from all causes;
- death or disability (defined according to the modified Rankin Scale (mRS), see below) at the end of the follow-up period.

In the studies where the outcomes no disability and disability was not defined, we assessed the outcome based on the clinical information mentioned in the publications as follows.

- Where the mRS (UK-TIA Study 1988) is reported, mRS 0, 1 and 2 are judged as no or minor disability and mRS 3, 4 and 5 as major disability. We classified patients who are reported to be able to return to their original or similar job (part time or full time) as having no disability.
- We classified patients described as mild/slight or no deficits, asymptomatic or those who markedly improved as minor disability.
- We classified patients described as improved (without further detailed information) as major disability, as were patients with persisting neurological deficits such as hemiparesis. We also classified patients with some neurological deficits, requiring some assistance of activities in daily living but can still be in the home setting in the major disability group, and also patients who had to be transferred to a nursing home or who needed permanent help for daily living.

We intended to specify the length of the follow up after which outcome assessment should take place, i.e. three months or one

year. However, we had to use the latest outcome evaluations extractable from each study because of the lack of such information in the vast majority of studies.

Secondary outcomes

- Ischaemic stroke - according to the WHO definition (Hatano 1976) - occurring in patients under antithrombotic therapy, such as confirmed recurrent strokes during follow up, as well as the occurrence of ischaemic stroke in patients initially without stroke. We also included patients with retinal infarctions.
- The occurrence of symptomatic intracranial haemorrhage according to the definition used in the individual study/series. If no definition was given, we considered any neurological worsening associated with intracranial blood visible on neuroimages as a symptomatic intracranial haemorrhage.
- The occurrence of major extracranial haemorrhage as defined in the individual study/series. If no definition was given, we considered any clinically apparent extracranial bleeding resulting in a surgical or endoscopic intervention or a transfusion a major extracranial haemorrhage.

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 on 3 October 2009. In addition, we performed comprehensive searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library Issue* 2, 2009), MEDLINE (January 1966 to November 2009) and EMBASE (January 1980 to November 2009), checked all relevant papers for additional eligible studies including recent review papers (Debette 2009; Engelter 2007; Kim 2009; Menon 2008a) and contacted authors and researchers in the field. We searched for relevant studies in all languages and arranged translation of reports published in languages other than English, German, French or Italian.

We used the following strategies for MEDLINE (Appendix 1) and EMBASE (Appendix 2) and adapted them for the Cochrane Central Register of Controlled Trials (CENTRAL).

Data collection and analysis

In order to estimate treatment effects, we sought to analyse data from non-randomised studies. One of the review authors (SE) selected which trials met the inclusion criteria and another author (PL) independently reviewed the decisions. We extracted all outcome measures from the eligible studies. We resolved disagreements on inclusion (one study) and outcomes by discussion. We contacted study authors for additional information on the outcome stratified to the type of antithrombotic treatment, in any cases of uncertainty. We excluded studies without concise information on treatment or lacking follow-up information from further analysis.

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

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We did not identify any completed RCTs or CCTs. There is one ongoing RCT comparing AC with AP in cervical artery dissection - Cervical Artery Dissection in stroke (CADISS). The trial started in August 2006. The randomisation goal is 250 patients (CADISS 2009). As at 21 November 2009, 51 randomised and 66 non-randomised participants have participated in the trial and three endpoints have occurred (personal communication) (CADISS 2009).

We contacted the authors of an abstract about a planned trial (ECAD 1993); the trial never started because of lack of funding (personal communication).

Among the non-randomised studies for the primary outcome death from all causes, data from 36 studies were eligible. In some studies, patients with malignant infarction who died early (e.g. within seven days: Georgiadis 2009) were excluded. For the outcome death or disability, 26 studies fulfilled the eligibility criteria. We collected and analysed data on secondary outcomes if data on primary outcomes were available. Six studies included only trauma patients (Colella 1996; Eachempati 1998; Li 1994; Richaud 1980; Wahl 2002; Zelenock 1982). This might be a confounding factor. Studies were heterogenous in respect to their main issue. They included observational case reports or case series on the disease (Ast 1993; Biousse 1998; Campos 2007; Chen 1984; Dziewas 2003; Engelter 2000; Friedman 1980; Gonzales-Portillo 2002; Kaps 1990; Landre 1987; Lepojärvi 1988; Luken 1979; Marx 1987; Metso 2009; Miller-Fisher 1978; Mokri 1986; Pieri 2007; Schievink 1990; Sellier 1983; Treiman 1996; Vanneste 1984) or after blunt trauma (Colella 1996; Eachempati 1998; Li 1994; Richaud 1980; Wahl 2002; Zelenock 1982), communications on surgical interventions (Luken 1979), angiographic case reports (Biller 1986), ultrasound diagnostic studies (De Bray 1989; Eljamel 1990; Kaps 1990; Müller-Forell 1989), or clinical overviews drawn from databases or registries (Arauz 2006; Biller 1986; Bogousslavsky 1987b; Caso 2004; Georgiadis 2009; Touze 2003).

We excluded some studies from further analysis because of overlapping with other published case series (Arnold 2006; Baumgartner

2001; Bui 1993; Sturzenegger 1995; Watridge 1989), lack of information concerning treatment or outcome stratified to treatment (Barbour 1994; Bassetti 1996; Baumgartner 2001; Biousse 1995; ; Desfontaines 1995; Gelbert 1991; Kirsch 1998; Lisovoski 1991; Lucas 1998; Mokri 1990; O'Dwyer 1980; Pozzati 1990; Provenzale 1995; Schievink 1994; Thie 1993), and in part of the analysis about primary outcomes because of lack of information concerning disability (Ast 1993; Biller 1986; Bogousslavsky 1987b; Dziewas 2003; Georgiadis 2009; Gonzales-Portillo 2002; Müller-Forell 1989; Sellier 1983; Touze 2003; Treiman 1996). We excluded other studies because patients with eICAD were not reported separately from patients with other localisations of dissecting arteries, such as the vertebral artery, the common carotid artery or the intracranial carotid artery (Bassi 2003; Biffl 2002; Carrillo 1999; Chabrier 2003; Cimini 2004; Hughes 2000; Kerwin 2001; Lee 2006; Leys 1995; Miller 2001; Molina 2000; Nishino 2008; Pelkonen 2003).

Five studies were written in French, two in Italian, two in German, one in Dutch, and one in Portuguese. We obtained additional information for six studies from the authors (Campos 2007; Caso 2004; Dziewas 2003; Metso 2009; Pieri 2007; Touze 2003).

Risk of bias in included studies

None of the identified and completed studies were RCTs or CCTs. All studies were observational case series and none reported results from a pre-defined treatment protocol. In general, treatment was decided by the treating physician. The length of follow up was heterogeneous among studies and also varied within studies. Only one large study assessed outcome after three months in all patients (Georgiadis 2009). Among the identified studies there was limited consistency in reporting outcome measures and in six studies it was not reported for all patients which treatment they received (see Characteristics of included studies) (Ast 1993; De Bray 1989; Miller-Fisher 1978; Mokri 1986; Müller-Forell 1989; Richaud 1980).

Effects of interventions

Randomised studies

No results of RCTs are currently available.

Non-randomised studies

Primary outcomes

Death from all causes

For the outcome death from all causes, we analysed data from 36 studies with 1285 patients. In total, 20 of 1285 (1.56%) patients were reported dead at the end of follow up. The Peto odds ratio of 2.02 with a 95% CI ranging from 0.62 to 6.60 (P = 0.25) indicated neither harm nor benefit of anticoagulation with respect to death during the follow-up period. There was no significant heterogeneity between the included series (I^2 = 0%) (Analysis 1.1).

Death or disability

For the outcome death or disability, based on 26 studies (463 patients) there was a non-significant trend in favour of anticoagulants (OR 1.77, 95% CI 0.98 to 3.22; P = 0.06). There was no significant heterogeneity between the included series (I^2 = 0%) (Analysis 1.2).

Secondary outcomes

Ischaemic stroke

Thirty-four studies with 1262 patients reported on ischaemic strokes at the end of the follow-up period. In 24 patients (1.9%) ischaemic strokes, including two retinal infarcts, were recorded. Among the 16 patients in whom details about the timing were provided, strokes occurred or recurred in 10/16 patients within eight days after treatment with antithrombotic agents had been started; i.e. on day one (two patients), at day three (three patients), at day four (two patients), at day seven (two patients) and at day eight (one patient). In one patient, a stroke occurred at day 12. In another five patients, strokes happened "within two weeks". In four patients, strokes recurred or occurred at 80 days (one patient) and in between 30 to 39 months (three patients). In three patients no information about the time to recurrent ischaemic strokes was provided. The stroke rate in the anticoagulation group was 1.87% (18/962) and 2.0% (6/300) in the AP group. The Peto odds ratio of 0.63 (95% CI 0.21 to 1.86, P = 0.41) indicated no significant difference between treatment options. There was some, but no significant heterogeneity between the included series (I^2 = 19%) (Analysis 1.3).

Symptomatic intracranial haemorrhage

Twenty-five studies with 885 patients provided data about symptomatic intracranial haemorrhage stratified on the type of antithrombotic treatment. Symptomatic intracranial haemorrhages occurred only in the AC group and were present in five of 627 patients (0.8%). The Peto odds ratio of 0.25 with a 95% CI of 0.02 to 3.36 indicated no significant difference between the treatment options (P = 0.3). There was no significant heterogeneity between the included series (I^2 = 0%) (Analysis 1.4).

Major extracranial haemorrhage

Analysis in respect of major extracranial haemorrhage was based on 12 studies with 622 patients. Major extracranial haemorrhages occurred only in the AC group and were present in seven of 425 patients (1.6%). The Peto odds ratio of 0.19 with a 95% CI of 0.02 to 1.48 indicated no significant difference between the treatment options (P = 0.11). There was no significant heterogeneity between the included series (I^2 = 0%) (Analysis 1.5).

DISCUSSION

Extracranial internal carotid artery dissection (eICAD) is a major cause of ischaemic stroke in young individuals (Biller 1986; Bogousslavsky 1987b; Leys 2002) but currently there are no data based on randomised trials available to assess the effects of anticoagulation versus antiplatelets. Thus, it is impossible to draw any definite conclusions. Nevertheless, this systematic review of all relevant observational case studies provides findings important for the design and promotion of antithrombotic RCTs in eICAD. In addition, the findings about the frequency of outcome events and complications stratified to the type of antithrombotic treatment may also be useful for management decisions and counselling of individual eICAD patients.

There was no significant difference in the odds of death comparing antiplatelet drugs with anticoagulants among 1285 patients. Interestingly, the frequency of death (i.e. 1.6%, 95% CI 1.0 to 2.4%) was low, and certainly lower than originally suggested (Richaud 1980; Saver 1992). However, some patients with severe infarctions from several studies were excluded because they had received neither anticoagulants nor antiplatelet agents (Ast 1993; Bogousslavsky 1987b; Colella 1996; Wahl 2002) or had malignant infarctions (Georgiadis 2009) without information about antithrombotic treatment. Therefore, the estimated death rate of this review reflects not that of eICAD patients in general but that of patients who are well enough to receive any kind of antithrombotic treatment. The assumption that the risk of dying due to eICAD is probably higher than 2.4% (i.e. the upper end of the 95% CI) is supported by the three-month death rate of 5.5% in a recent series of 55 dissection patients treated with intravenous thrombolysis (Engelter 2009).

For the outcome death or disability, this systematic review showed a trend towards superiority of anticoagulants over antiplatelets across all relevant observation case series. The point estimate indicates that patients treated with anticoagulants might have a more than 70% higher chance of avoiding death or disability compared with patients treated with antiplatelets. However, the wide confidence interval (0.98 to 3.22) indicates that this effect could be either much smaller or larger.

For the outcome ischaemic strokes during follow up, there was no significant difference between patients treated with anticoagulants versus those who were treated with antiplatelets. Interestingly, the point estimate of 0.63 might suggest rather a superiority of antiplatelets over anticoagulants than vice versa. This is perhaps surprising as it might be assumed that emboli arising from the distal part of the dissected artery may be of clinical importance and may cause fatal or disabling strokes (Anson 1991; Droste 2001; Koennecke 1997; Oliveira 2001; Steinke 1996). Approximately, two out of three strokes occurred (or recurred in those with an initial stroke) within a week and three out of four (16 of 21 patients) within two weeks. These findings support the main results of a smaller previous series (Biousse 1995). Interestingly, while stroke recurrence/occurrence within one day was most common in the series reported by Biousse 1995, such a very early stroke occurrence was rare (2/16) in this review. These observations may have important implications. Firstly, there might be a chance to prevent strokes in eICAD patients, but preventive means have to start early. Secondly, randomising patients more than two weeks after the first symptom bears a remarkable risk of missing the most important treatment period in a randomised controlled trial.

For bleeding complications (i.e. symptomatic intracranial haemorrhages or major extracranial haemorrhages) there were no significant differences between the AC and the AP group. Such bleeding complications were rare (0.8% for symptomatic intracranial haemorrhages, 1.6% for major extracranial haemorrhages). Interestingly, they occurred exclusively in patients with anticoagulation. Likewise, the point estimates may suggest the possibility of a higher risk of relevant bleeding complications associated with anticoagulation - similar to the results from the International Stroke Trial (IST 1997). The lack of a statistically significant difference might be a matter of the sample size in combination with the infrequency of bleeding events.

Although there was an apparent trend in favour of anticoagulants (non-significant) for the outcome death or disability, this may have arisen from methodological biases. Antiplatelets could have been primarily applied in patients who were considered to have a poor prognosis, for example due to large infarcts (Bogousslavsky 1987b; Chen 1984) or who were in a poor condition. Anticoagulation might be preferred in patients with a transient ischaemic attack (TIA). The lack of information on baseline characteristics including stroke severity prevented us from studying whether imbalances in baseline variables might have influenced the seemingly better result for the anticoagulation group in avoiding death or disability.

We are aware of other limitations. Outcome measurement was not applied uniformly in the included studies and the studies differed in their focus. It is therefore likely that there are important biases. Non-randomised studies are known to be highly susceptible to bias and outcome events may be under-represented (Chalmers 1983). Such biases encountered in the reported studies may be: reporting favourable cases; reports on selected cases as well as editorial

biases, such as not allowing reports on already published issues by different authors; the choice of treatments may have been biased by the preference and experience of the treating physicians, and the habits and infrastructure of the institutions (Sackett 1979). In addition, the sample size of the only outcome with a result close to significance (i.e. death or disability P = 0.06) was much smaller than that of the other outcomes, as several studies did not provide data about disability. Thus, the trend towards superiority of anticoagulation with regard to death or disability among less than 500 patients might also be a chance finding.

As another limitation, we did not further study the impact of surgery in eICAD. As already shown in the 2003 update of this review, surgery appeared to have a higher rate of death (6% in excluded studies, 11% in included studies) compared with those who received antithrombotic drugs (i.e. 1.6%) (New Reference). We also did not study the effect of hyperacute treatment options such as thrombolysis or intra-arterial interventions including stenting, which was beyond the scope of this review. Furthermore, we focused on eICAD rather than on craniocervical artery dissections as it remains unclear whether carotid artery dissection and vertebral artery dissection as well as extracranial and intracranial dissections can be regarded as one entity.

This review attempted to systematically assess the evidence on antithrombotic eICAD treatment. Further steps could be to establish an international systematic registry for eICAD with standardised recording of diagnosis, therapeutic modalities and outcome. This would allow the gathering of more uniform information on the disease and its prognosis. The Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) Group (CADISP 2009a; CADISP 2009b) has initiated such a registry. Results are expected in early 2011.

A large RCT comparing anticoagulants with antiplatelets in eICAD is important and could solve the decades-long debate whether to use immediate anticoagulation or not. Indeed, a UK-based feasibility study is ongoing (CADISS 2009). If possible, randomisation of eICAD patients in such a RCT is encouraged. Other groups intend to initiate RCTs too (CADISP 2009a). All current and planned RCTs should consider predefining an individual patient data meta-analysis - as done in the carotid stenting versus endarterectomy trials - in order to gather the best evidence for antithrombotic treatment in eICAD. Taking into account our findings, protocols for RCTs should include a stringent definition of carotid dissection, a standardised diagnostic protocol, strictly random allocation to antiplatelet agents versus anticoagulants, as well as accurate unbiased assessment of outcome. In addition, imbalances in important prognostic variables must be avoided.

Our findings allow some estimation about the sample sizes. On the basis of our results, we recommended using death or disability as the outcome measure. We estimate a sample size of at least 1600 patients in each treatment arm in order to detect (power 90%) a 5% difference in the proportion of patients dead or disabled from 30% to 25% (a 25% relative odds reduction). For ischaemic stroke, the sample size to detect a 1% absolute odds reduction (from 2.5% to 1.5 %) is estimated to be at least 8000 patients (4000 in each arm) (power 90%, significance level 5%). Interestingly, if we had based a sample size calculation on the figures observed for either antithrombotic modality in this review, a sample size greater than 300,000 patients would have been required to detect a significant difference for ischaemic stroke (power 80%, significance level 5%). Fewer than 300 patients would have been necessary to detect a significant difference for the outcome death or disability (power 90%, significance level 5%).

Until more evidence-based information is available, our data showed that patients with eICAD are unlikely to be harmed by antiplatelet drugs and there seems little justification for giving anticoagulants as a first line therapy in all patients.

AUTHORS' CONCLUSIONS

Implications for practice

There is no randomised evidence to determine whether, for patients with carotid artery dissection, either antiplatelet or anticoagulant therapy is superior to control, or whether anticoagulant is superior to antiplatelet therapy. Participation in randomised controlled trials is strongly encouraged. If this is not possible, individually tailored treatment decisions should be made.

Implications for research

(1) Randomised trials comparing antiplatelet with anticoagulant therapy in carotid artery dissection are justified, and at least one randomised trial is ongoing. (2) Death or disability is an appropriate measure of outcome for such trials

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arauz 2006

Methods	Observational study, single-centre, stroke registry based, traumatic and spontaneous dissections
Participants	58 eICAD stroke patients (among 130 patients with cervical artery dissection)
Interventions	13 anticoagulation, 45 antiplatelets
Outcomes	Death, stroke during follow up, modified Rankin scale at 6 months, recanalisation, intracranial or systemic bleeding
Notes	Mexico

Ast 1993

Methods	Observational study, multicentre, retrospective from medical records
Participants	68 patients with eICAD 21 with stroke, 15 with TIA or AF
Interventions	30 anticoagulants, 21 antiplatelet drugs, 9 'no treatment', 2 surgery, 6 not mentioned
Outcomes	Death, stroke (ischaemic, haemorrhagic), TIA
Notes	France

Biller 1986

Methods	Observational study, retrospective from angiographical database
Participants	11 patients with eICAD, 10 with stroke, 1 with Horner's syndrome
Interventions	2 anticoagulants, 5 antiplatelet drugs, 4 surgery
Outcomes	Death, complications including stroke (ischaemic, haemorrhagic)
Notes	USA

Biousse 1998

Methods	Observational study, selection from large series of eICAD
Participants	4 patients with eICAD, 4 with ocular ischaemia
Interventions	3 anticoagulants, 1 antiplatelet drugs
Outcomes	Death, disability, stroke, symptomatic intracranial haemorrhage
Notes	France

Bogousslavsky 1987b

Methods	Observational study, data from Lausanne Stroke Registry, consecutive patients with first-ever stroke
Participants	30 patients with eICAD, 12 with stroke, 5 TIA or AF, 2 monocular blindness, 11 headache
Interventions	21 anticoagulants, 2 antiplatelet drugs, 7 'no treatment' (these patients died)
Outcomes	Death, stroke Reopening at 6 months
Notes	Switzerland

Campos 2007

Methods	Observational study
Participants	60 patient with cervical artery dissection, among those 36 with eICAD; all but 2 patients had ischaemic events before diagnosis of dissection
Interventions	6 eICAD patients had anticoagulation, 30 had antiplatelets
Outcomes	Death, disability, stroke, bleeding complications
Notes	Sao Paulo, Brazil Additional information obtained by personal communication

Caso 2004

Methods	Observational study, single centre, consecutive patients
Participants	19 eICAD with stroke or TIA (all had visible infarcts), only spontaneous eICAD
Interventions	9 anticoagulants, 10 antiplatelets
Outcomes	Death, disability, stroke, recanalisation, symptomatic intracranial haemorrhage, major extracranial haemorrhage

Caso 2004 (*Continued*)

Notes	Italy, additional information obtained by personal communication 1 patient with anticoagulation suffered a retinal infarction

Chen 1984

Methods	Observational study, selection not reported
Participants	7 patients with eICAD
Interventions	1 anticoagulants, 5 antiplatelet drugs, 1 surgery (EC/IC bypass)
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic)
Notes	Taiwan

Colella 1996

Methods	Observational study, case series from motor vehicle accidents or other trauma (2 falls)
Participants	18 patients with eICAD
Interventions	12 anticoagulants, 2 antiplatelet drugs, 2 no treatment, 2 surgery (type of intervention not stated)
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic)
Notes	USA Confounding with primary trauma possible

De Bray 1989

Methods	Observational study for ultrasound diagnosis
Participants	20 patients with eICAD, 12 with stroke, 6 with TIA, referred for ultrasound
Interventions	12 anticoagulants, 4 antiplatelet drugs, 2 no treatment, 2 not mentioned
Outcomes	Death, disability, stroke, bleeding complications
Notes	France

Dziewas 2003

Methods	Observational study of cervical artery dissection
Participants	78 patients with eICAD, 55 with stroke, 10 with TIA, 13 with only local signs
Interventions	7 antiplatelets, 71 anticoagulation
Outcomes	Death, stroke, symptomatic intracranial haemorrhage, major extracranial haemorrhage Follow up 6 months
Notes	Munster, Germany Additional information obtained by personal communication

Eachempati 1998

Methods	Observational study, case series of trauma registry
Participants	11 patients with traumatic eICAD
Interventions	2 no treatment, 3 antiplatelet drugs, 5 anticoagulants, 1 surgery
Outcomes	Death, disability, bleeding complication
Notes	USA Confounding with primary trauma injuries possible

Eljamel 1990

Methods	Observational study for ultrasound diagnosis
Participants	8 patients with eICAD, 5 stroke, 3 TIA
Interventions	4 anticoagulants, 4 antiplatelet drugs
Outcomes	Death, disability
Notes	UK

Engelter 2000

Methods	Observational, retrospective study on long-term outcome
Participants	33 patients with eICAD: 20 stroke, 6 TIA, 7 non-ischaemic
Interventions	25 anticoagulants, 8 antiplatelets
Outcomes	Death, disability, stroke, TIA, any haemorrhage, seizures

Engelter 2000 (*Continued*)

Notes	Basel, Switzerland

Friedman 1980

Methods	Observational study, consecutive patients
Participants	12 patients with eICAD, symptoms not mentioned
Interventions	4 anticoagulants, 1 antiplatelet drugs, 5 no treatment, 2 surgery (1 trapping, 1 EC/IC bypass)
Outcomes	Death, disability, stroke, symptomatic intracranial haemorrhage
Notes	USA

Georgiadis 2009

Methods	Observational study, databank-based, consecutive patients
Participants	298 patients with eICAD Presenting symptoms: ischaemic stroke 118/202 with anticoagulants and 47/96 with antiplatelets; TIA 25/202 with anticoagulants and 12/96 with antiplatelets; AF 7/202 with anticoagulants and 1/96 with antiplatelets; pure local signs 45/202 with anticoagulants and 35/96 with antiplatelets; asymptomatic 7/202 with anticoagulants and 1/96 with antiplatelets
Interventions	202 anticoagulants, 96 antiplatelet agents alone Those with surgical/endovascular treatment were excluded (17) as were those on aspirin followed by warfarin (30), those with no antithrombotic treatment and those who died within 7 days due to malignant MCA infarction (8, no treatment modalities mentioned)
Outcomes	Death, ischaemic stroke, TIA, symptomatic intracranial haemorrhage, major extracranial haemorrhage (assessment at 3 months)
Notes	Swizerland (Zurich, Bern)

Gonzales-Portillo 2002

Methods	Observational study, databank-based, consecutive patients
Participants	27 patients with cervical artery dissection (22 spontaneous, 5 traumatic): 21 strokes, 3 TIA, 3 non-ischaemic symptoms) 19 patients had eICAD (2 bilateral), 8 had eVAD
Interventions	5 eICAD patients had antiplatelets, 14 had anticoagulants
Outcomes	Death (strokes mentioned, but not stratified to treatment), mean follow up 58 months

Gonzales-Portillo 2002 (*Continued*)

Notes	Indiana, USA

Kaps 1990

Methods	Observational study for ultrasound diagnosis
Participants	11 patients with eICAD, 2 with stroke, 3 with TIA
Interventions	4 anticoagulants, 2 antiplatelet drugs, 2 no treatment
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic)
Notes	Germany

Landre 1987

Methods	Observational study, consecutive cases
Participants	5 patients with eICAD, 5 with stroke
Interventions	2 anticoagulants, 3 antiplatelet drugs
Outcomes	Death, disability
Notes	France

Lepojärvi 1988

Methods	Observational study, selection not reported
Participants	13 patients with eICAD, 8 with stroke, 3 with TIA
Interventions	7 anticoagulants, 4 antiplatelet drugs, 1 no treatment, 1 surgery (ligation)
Outcomes	Death, disability, stroke
Notes	Finland

Li 1994

Methods	Observational study, case series from trauma patients
Participants	7 patients with eICAD, 7 with stroke
Interventions	4 anticoagulants, 1 antiplatelet drugs, 2 surgery (1 embolectomy, 1 endarterectomy)

Li 1994 (*Continued*)

Outcomes	Death, disability, stroke, TIA
Notes	Canada 2 deaths due to suicide, confounding with trauma and premorbid status possible

Luken 1979

Methods	Observational study, consecutive case series
Participants	10 patients with eICAD, 4 with TIA or AF, 9 with pain
Interventions	1 anticoagulants, 2 antiplatelet drugs, 3 no treatment, 4 surgery (2 ligations, 1 silverstone clamp, 1 embolectomy)
Outcomes	Death, disability, stroke, symptomatic intracranial haemorrhage
Notes	USA

Marx 1987

Methods	Observational study on spontaneous dissections of cervical arteries
Participants	8 patients with eICAD, 4 with stroke, 2 with Horner's syndrome, 2 TIA
Interventions	6 anticoagulants, 1 antiplatelet drugs, 1 no treatment
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic)
Notes	Germany

Metso 2009

Methods	Observational study, single centre, consecutive patients with cervico-cerebral artery dissection
Participants	301 patients with either extra or intracranial internal carotid or vertebral artery dissection Data about outcome stratified to the type of antithrombotic treatment were obtained by personal communication
Interventions	For the 144 eICAD patients: 140 anticoagulants, 4 antiplatelets
Outcomes	Death, dependency, stroke, TIA, symptomatic intracranial haemorrhage
Notes	Finland Additional information obtained by personal communication In 1 of the 140 patients treated with anticoagulation there was no information on disability available

Miller-Fisher 1978

Methods	Observational study on spontaneous dissections of cervical arteries
Participants	16 patients with eICAD, 10 with TIA, 0 with stroke, 10 with pain
Interventions	2 anticoagulants, 1 antiplatelet drugs, 5 surgery (3 explorations, 2 embolectomies) 8 not mentioned
Outcomes	Death, disability, stroke, symptomatic intracranial haemorrhage
Notes	USA Information on treatment for 8 patients not given

Mokri 1986

Methods	Observational study, retrospective assessment
Participants	36 patients with eICAD, 30 with headache, 2 with stroke, 2 with TIA or AF, 1 syncope, 1 neck pain
Interventions	10 anticoagulants, 9 antiplatelet drugs, 14 no treatment, 1 surgery (EC/IC bypass), 3 not mentioned
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic), TIA
Notes	USA Information on initial therapy not reported in 2; 6 patients had EC/IC bypass surgery later

Müller-Forell 1989

Methods	Observational study, angiographical and ultrasound diagnosis
Participants	4 patients with eICAD, 2 with stroke, 2 with pain
Interventions	1 anticoagulants, 1 antiplatelet drugs, 1 no treatment, 1 not mentioned
Outcomes	Death, stroke
Notes	Germany Initial therapy not reported in 1 patient

Pieri 2007

Methods	Observational study, case series
Participants	66 patients with cervical artery dissection, 24/66 had eICAD
Interventions	10/24 had antiplatelets, 14/24 had anticoagulation
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic), symptomatic intracranial bleedings, TIA

Pieri 2007 (*Continued*)

Notes	Sao Paulo, Brazil Additional information obtained by personal communication

Richaud 1980

Methods	Observational study, case series from trauma patients
Participants	17 patients with eICAD, 9 with stroke, 2 with TIA (information or other patients not conclusive)
Interventions	5 anticoagulants, 1 antiplatelet drugs, 4 no treatment, 3 surgery (non-arterial operations), 4 not mentioned
Outcomes	Death, disability, stroke
Notes	France Confounding from trauma possible No report on initial therapy in 4 patients

Schievink 1990

Methods	Observational study, consecutive case series
Participants	7 patients with eICAD, 3 with stroke, 4 with local symptoms
Interventions	2 anticoagulants, 5 antiplatelet drugs
Outcomes	Death, disability, stroke
Notes	The Netherlands

Sellier 1983

Methods	Observational study, case series on spontaneous eICAD, traumatic cases excluded
Participants	46 patients with eICAD, 18 with stroke, 24 with TIA
Interventions	16 anticoagulants, 13 antiplatelet drugs, 10 no treatment, 7 surgery (intervention not specified)
Outcomes	Death, stroke (ischaemic, haemorrhagic)
Notes	France

Touze 2003

Methods	Multicentre observational study, databank-based, 24 neurology departments
Participants	Consecutive patients with cervical artery dissection (eICAD or eVAD or both) The data for the subgroup of patients with eICAD alone were obtained by personal communication
Interventions	For the 311 'eICAD alone' patients: 279 anticoagulants; 18 antiplatelets, 12 no antithrombotics, 2 tPA
Outcomes	Stroke, TIA, death, recurrent dissection
Notes	France Additional information obtained by personal communication

Treiman 1996

Methods	Observational case series
Participants	24 patients with eICAD, diagnosis made by angiography
Interventions	3 no antithrombotic treatment (died), 21 patients who survived the initial hospitalisation, 12 anticoagulation, 6 antiplatelets, 3 with combined antiplatelets plus anticoagulation
Outcomes	Vascular death, stroke, recurrent dissection, bleeding complication
Notes	USA No information about type of initial antithrombotic treatment available in 2 patients with non-vascular death years after the eICAD

Vanneste 1984

Methods	Observational study, selection not reported
Participants	5 patients with eICAD, 2 with stroke, 3 with pain
Interventions	4 anticoagulants, 1 antiplatelet drugs
Outcomes	Death, disability, stroke, symptomatic intracranial bleeds
Notes	The Netherlands

Wahl 2002

Methods	Observational study, traumatic carotid dissections (i.e. dissection of common carotid artery, eICAD, and intracranial dissections, trauma centre registry)
Participants	11 patients with traumatic eICAD (among 22 patients with carotid dissections of any kind)
Interventions	In subgroup of 11 patients with eICAD: 7 anticoagulants, 1 antiplatelets only, 1 no antithrombotic agents, 2 stents

Wahl 2002 (*Continued*)

Outcomes	Death, disability, stroke, major extracranial haemorrhage
Notes	USA Confounding of outcome assessment with trauma possible

Zelenock 1982

Methods	Observational study, case series of trauma patients
Participants	6 patients with eICAD
Interventions	1 anticoagulants, 1 antiplatelet drugs, 3 no treatment, 1 surgery (ligation)
Outcomes	Death, disability, stroke (ischaemic, haemorrhagic)
Notes	USA Confounding with trauma possible

AF: amaurosis fugax
EC/IC bypass: extracranial-intracranial bypass
eICAD: extracranial internal carotid artery dissection
eVAD: extracranial vertebral artery dissection
MCA: middle cerebral artery
TIA: transient ischaemic attack
tPA: tissue plasminogen activator

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

Study	Reason for exclusion
Alimi 1996	No treatment with antithrombotic drugs Observational study
Andre-Sereys 1996	No treatment with antiplatelet drugs Observational study
Arnold 2006	No information on outcome stratified by type of antithrombotic treatment Outcome not stratified by type of affected cervical artery dissection (i.e. eICAD and vertebral artery dissection reported together) Gender differences was primary objective Overlap with included study Georgiadis 2009; the latter focused on treatment and outcome

(*Continued*)

Bakke 1996	No treatment with anticoagulants Observational study
Barbour 1994	No information on management and outcome
Bassetti 1996	No information on treatment No separation between dissection of ICAD and VA
Bassi 2003	Outcome information not stratified to treatment Observational study
Baumgartner 2001	No information on treatment
Berne 2004	None of the eICAD patients was treated with antiplatelet agents alone
Biffl 2002	No separation between dissection of ICAD and VA No separation of traumatic eICAD from patients with carotid injury other than dissection All trauma patients Observational study
Biousse 1995	Information on outcomes not available in respect to treatment
Bradac 1981	No treatment with antithrombotic drugs Observational study
Bui 1993	Diagnostic study, no outcome information
Carrillo 1999	No separation between dissections of ICA and those of the CCA
Chabrier 2003	Outcome not stratified by type of involved artery
Chan 2001	No treatment with antiplatelets drugs All patients treated with anticoagulants
Cimini 2004	Outcome not stratified to type of treatment
Cusmano 1988	Treatment only with antiplatelet drugs Observational study
Davis 1990	Treatment only with anticoagulants Observational study
Desfontaines 1995	Outcome information not stratified to treatment Observational study

(*Continued*)

Djouhri 2000	No information on treatment Diagnostic study (MRA) Overlapping with included study Biousse 1998 and excluded studies Biousse 1995 and Guillon 1999
Dreier 2004	Treatment only with anticoagulants
Droste 2001	Diagnostic study (transcranial doppler sonography) 'Recurrent ischemic events' not specified
Early 1991	Treatment only with anticoagulants Observational study
Ehrenfeld 1976	No treatment with antithrombotic drugs Observational study
Fabian 1990	No treatment with antiplatelet drugs Observational study
Fabian 1996	No separation of ICA dissection from ICA thrombosis or carotid cavernous fistulas
Gelbert 1991	No information on therapy
Guillon 1999	No antiplatelet therapy Overlapping with included study Biousse 1998and excluded studies Biousse 1995 and Djouhri 2000 All patients included had aneurysms (observational study)
Hughes 2000	No separation between extra and intracranial ICA dissection Observational study Only trauma patients
Kerwin 2001	No outcome and therapy-related separation between A: eICAD and vertebral artery dissection B: eICAD and other non-dissection ICA injuries (e.g. carotid-cavernous sinus fistula) All patients had trauma
Kirsch 1998	No information on treatment Diagnostic study (MRA)
Koennecke 1997	No treatment with antiplatelet drugs No follow-up information
Landini 1996	No treatment with anticoagulants Observational study
Leclerc 1998	Diagnostic study (CT follow up) No treatment with antiplatelet drugs Overlapping with excluded study Leys 1995

(*Continued*)

Lee 2006	Information on outcomes not available in respect to treatment and affected artery Epidemiological, population-based study
Leys 1995	No separation between ICAD and VA dissection
Lisovoski 1991	No information on management
Lucas 1998	No information on therapy
Miller 2001	No outcome and therapy-related separation between A: eICAD, CCA and VA dissection B: eICAD and other non-dissection ICA injuries (e.g. carotid-cavernous sinus fistula) All patients had trauma
Mokri 1990	Information on outcomes not available in respect to treatment Confounding with included study Mokri 1986 possible
Molina 2000	No separation between extra and intracranial ICA dissection All patients had anticoagulation Diagnostic study (emboli detection by transcranial doppler sonography)
Morgan 1994	No treatment with antiplatelets Observational study
Mueller 2000	Study on surgery for eICAD (all patients had surgery)
Müllges 1992	No treatment with anticoagulants Observational study
Nishino 2008	Outcome not stratified to involved artery and treatment Observational study
O'Dwyer 1980	No separation between ICAD and CCA dissection Observational study
Oliveira 2001	Outcome not stratified to treatment Diagnostic study (transcranial doppler emboli monitoring) Observational study
Parenti 1989	No treatment with anticoagulants Observational study
Pelkonen 2003	Outcome information not stratified to treatment Observational study
Perry 1980	No treatment with antithrombotic drugs Observational study

(*Continued*)

Petro 1987	No treatment with antiplatelet drugs Observational study
Power 1991	No treatment with antiplatelet drugs Observational study
Pozzati 1990	No treatment with antithrombotics Observational study
Pretre 1994	No treatment with antiplatelet drugs Observational study
Provenzale 1995	No information on management Observational study
Schievink 1994	No information on management Observational study
Sperling 1996	No treatment with antiplatelet drugs Observational study
Steiger 1988	No treatment with antiplatelet drugs Observational study
Steinke 1994	No treatment with antiplatelet drugs Observational study
Stringer 1980	No treatment with antiplatelet drugs Observational study
Sturzenegger 1995	Data included in Georgiadis 2009
Sue 1992	No treatment with antiplatelet drugs Observational study
Thie 1993	Missing information on treatment and outcomes
Touze 2001	No information on treatment No separation between dissections of ICA and those of VA
Van Damme 1990	No treatment with anticoagulants
Verdalle 2001	No treatment with antiplatelets
Vishteh 1998	No separation between extracranial ICAD and intracranial ICA pathologies (e.g. cavernous ICAD, carotid cavernous fistula)

(*Continued*)

Watridge 1989	Confounding with data from excluded study Fabian 1990 possible
Welling 1989	No treatment with antiplatelet drugs Observational study

CCA: common carotid artery
CT: computerised tomography
eICAD: extracranial internal carotid artery dissection
ICA: internal carotid artery
ICAD: internal carotid dissection
MRA: magnetic resonance angiography
VA: vertebral artery

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

CADISS

Trial name or title	Cervical Artery Dissection In Stroke Study
Methods	Randomised prospective multicentre study comparing antiplatelet therapy with anticoagulation
Participants	Patients with carotid and vertebral dissection Recruitment must be within 7 days of onset of symptoms
Interventions	Either antiplatelet or anticoagulation therapy initially for at least 3 months, and thereafter at the discretion of the attending physician (1) Antiplatelet therapy: aspirin, dipyridamole or clopidogrel alone or in dual combination (2) Anticoagulation with heparin (either unfractionated heparin or a therapeutic dose of low-molecular-weight heparin) followed by warfarin aiming for an INR in the range 2 to 3
Outcomes	Primary endpoint: ipsilateral stroke or death (any cause) within 3 months from randomisation Secondary endpoints: ipsilateral TIA, stroke or death (any cause) within 3 months from randomisation; any TIA and stroke; any stroke, major bleeding; presence of residual stenosis at 3 months (> 50%); mortality
Starting date	August 2006
Contact information	http://www.dissection.co.uk/
Notes	Recrutiment status 51 patients (update November 2009)

INR: International normalisation ratio
TIA:transient ischaemic attack

DATA AND ANALYSES

Comparison 1. Antiplatelet drugs versus anticoagulants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death from all causes	36	1285	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.62, 6.60]
1.1 Non-randomised studies	36	1285	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.62, 6.60]
2 Death or disability	26	463	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.98, 3.22]
2.1 Non-randomised studies	26	463	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [0.98, 3.22]
3 Ischaemic stroke (during follow-up)	34	1262	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.21, 1.86]
3.1 Non-randomised studies	34	1262	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.21, 1.86]
4 Symptomatic intracranial haemorrhage	25	885	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.02, 3.36]
4.1 Non-randomised studies	25	885	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.02, 3.36]
5 Major extracranial haemorrhage	12	622	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.02, 1.48]
5.1 Non-randomised studies	12	622	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.02, 1.48]

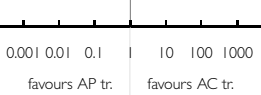
Analysis 1.1. Comparison 1 Antiplatelet drugs versus anticoagulants, Outcome 1 Death from all causes.

Review: Antithrombotic drugs for carotid artery dissection

Comparison: 1 Antiplatelet drugs versus anticoagulants

Outcome: 1 Death from all causes

Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Non-randomised studies					
Arauz 2006	4/44	0/14		25.4 %	4.02 [0.38, 42.28]
Ast 1993	0/21	0/30			Not estimable
Biller 1986	0/5	0/1			Not estimable
Biousse 1998	0/1	0/3			Not estimable
Bogousslavsky 1987b	0/2	0/21			Not estimable
Campos 2007	1/6	3/30		18.6 %	1.93 [0.12, 30.15]
Caso 2004	1/10	0/9		9.1 %	6.69 [0.13, 338.79]



(*Continued* . . .)

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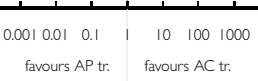
Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Chen 1984	0/5	0/1			Not estimable
Colella 1996	0/2	2/12		8.3 %	0.28 [0.00, 17.43]
De Bray 1989	0/4	0/14			Not estimable
Dziewas 2003	0/7	1/71		3.0 %	0.33 [0.00, 317.00]
Eachempati 1998	0/3	0/5			Not estimable
Eljamel 1990	0/4	0/4			Not estimable
Engelter 2000	0/8	1/25		6.7 %	0.27 [0.00, 25.88]
Friedman 1980	0/1	0/4			Not estimable
Georgiadis 2009	0/96	0/202			Not estimable
Gonzales-Portillo 2002	0/5	0/14			Not estimable
Kaps 1990	0/2	0/4			Not estimable
Landre 1987	1/3	0/2		8.8 %	5.29 [0.10, 289.29]
Lepojärvi 1988	0/4	0/7			Not estimable
Li 1994	0/1	1/4		5.9 %	0.29 [0.00, 38.47]
Luken 1979	0/2	0/1			Not estimable
Marx 1987	0/1	0/6			Not estimable
Metso 2009	0/4	1/140		1.0 %	0.36 [0.00, 54069.54]
Miller-Fisher 1978	0/1	0/2			Not estimable
Mokri 1986	0/9	0/10			Not estimable
Müller-Forell 1989	0/1	0/1			Not estimable
Pieri 2007	0/10	0/14			Not estimable
Richaud 1980	1/1	0/5		5.1 %	403.43 [2.10, 77585.45]
Schievink 1990	0/5	0/2			Not estimable
Sellier 1983	0/13	0/16			Not estimable
Touze 2003	0/18	2/279		4.2 %	0.34 [0.00, 115.59]
Treiman 1996	0/6	0/12			Not estimable
Vanneste 1984	0/1	0/4			Not estimable
Wahl 2002	0/1	1/7		4.0 %	0.32 [0.00, 119.52]
Zelenock 1982	0/1	0/1			Not estimable
Total (95% CI)	**308**	**977**		**100.0 %**	**2.02 [0.62, 6.60]**
Total events: 8 (antiplatelets), 12 (anticoagulation)					
Heterogeneity: Chi^2 = 8.12, df = 11 (P = 0.70); I^2 =0.0%					



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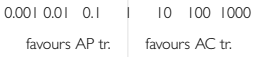
Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Not applicable					



Analysis 1.2. Comparison 1 Antiplatelet drugs versus anticoagulants, Outcome 2 Death or disability.

Review: Antithrombotic drugs for carotid artery dissection

Comparison: 1 Antiplatelet drugs versus anticoagulants

Outcome: 2 Death or disability

Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Non-randomised studies					
Arauz 2006	34/44	8/14		20.0 %	2.69 [0.71, 10.22]
Biousse 1998	0/1	0/3			Not estimable
Campos 2007	3/6	11/30		11.3 %	1.73 [0.29, 10.16]
Caso 2004	4/10	3/9		10.8 %	1.31 [0.21, 8.07]
Chen 1984	2/5	0/1		2.1 %	4.48 [0.07, 286.49]
Colella 1996	0/2	2/12		2.1 %	0.28 [0.00, 17.43]
De Bray 1989	0/4	0/14			Not estimable
Eachempati 1998	1/3	1/5		3.7 %	1.86 [0.08, 41.03]
Eljamel 1990	2/4	0/4		4.0 %	10.31 [0.52, 205.87]
Engelter 2000	2/8	5/25		9.7 %	1.34 [0.20, 9.10]
Friedman 1980	0/1	0/4			Not estimable
Kaps 1990	1/2	1/4		3.3 %	2.55 [0.10, 68.34]
Landre 1987	1/3	1/2		3.3 %	0.57 [0.02, 15.05]

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Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Lepojärvi 1988	1/4	1/7		3.9 %	1.92 [0.09, 40.11]
Li 1994	0/1	3/4		2.2 %	0.08 [0.00, 4.49]
Luken 1979	0/2	0/1			Not estimable
Marx 1987	0/1	0/6			Not estimable
Metso 2009	0/4	36/139		6.8 %	0.26 [0.03, 2.50]
Miller-Fisher 1978	0/1	0/2			Not estimable
Mokri 1986	0/9	0/10			Not estimable
Pieri 2007	5/10	1/14		10.6 %	8.94 [1.43, 55.99]
Richaud 1980	1/1	2/5		2.3 %	7.39 [0.15, 372.38]
Schievink 1990	0/5	1/2		1.9 %	0.03 [0.00, 2.31]
Vanneste 1984	0/1	0/4			Not estimable
Wahl 2002	1/1	4/7		2.2 %	4.95 [0.09, 283.86]
Zelenock 1982	0/1	0/1			Not estimable
Total (95% CI)	**134**	**329**		**100.0 %**	**1.77 [0.98, 3.22]**

Total events: 58 (antiplatelets), 80 (anticoagulation)

Heterogeneity: Chi^2 = 15.52, df = 16 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 1.88 (P = 0.060)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Antiplatelet drugs versus anticoagulants, Outcome 3 Ischaemic stroke (during follow-up).

Review: Antithrombotic drugs for carotid artery dissection

Comparison: 1 Antiplatelet drugs versus anticoagulants

Outcome: 3 Ischaemic stroke (during follow-up)

Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Non-randomised studies					
Arauz 2006	3/44	2/14		25.8 %	0.39 [0.05, 3.30]
Ast 1993	0/21	1/30		7.3 %	0.18 [0.00, 9.80]
Biller 1986	0/5	0/2			Not estimable
Biousse 1998	0/1	1/3		5.7 %	0.26 [0.00, 24.36]
Bogousslavsky 1987b	0/2	1/21		2.4 %	0.33 [0.00, 350.94]
Campos 2007	0/6	1/30		4.2 %	0.30 [0.00, 57.92]
Caso 2004	1/10	1/9		14.3 %	0.89 [0.05, 15.55]
Chen 1984	0/5	0/1			Not estimable
Colella 1996	0/2	1/12		3.7 %	0.31 [0.00, 84.30]
De Bray 1989	0/4	0/14			Not estimable
Dziewas 2003	0/7	0/71			Not estimable
Eachempati 1998	0/3	0/5			Not estimable
Eljamel 1990	0/4	0/4			Not estimable
Engelter 2000	0/8	2/25		10.8 %	0.26 [0.01, 6.84]
Friedman 1980	0/1	0/4			Not estimable
Georgiadis 2009	0/96	1/202		6.6 %	0.23 [0.00, 15.17]
Kaps 1990	0/2	0/4			Not estimable
Lepojärvi 1988	0/4	1/7		7.0 %	0.21 [0.00, 12.22]
Li 1994	0/1	0/4			Not estimable
Luken 1979	0/2	0/1			Not estimable
Marx 1987	0/1	1/6		3.7 %	0.31 [0.00, 84.30]
Metso 2009	1/4	3/140		3.2 %	4468.90 [10.78, 1851951.72]
Miller-Fisher 1978	0/1	0/2			Not estimable
Mokri 1986	0/9	0/10			Not estimable

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Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Müller-Forell 1989	0/1	0/1			Not estimable
Pieri 2007	0/10	0/14			Not estimable
Richaud 1980	0/1	0/5			Not estimable
Schievink 1990	0/5	0/2			Not estimable
Sellier 1983	0/13	0/16			Not estimable
Touze 2003	1/18	2/279		5.1 %	124.33 [1.07, 14494.06]
Treiman 1996	0/6	0/12			Not estimable
Vanneste 1984	0/1	0/4			Not estimable
Wahl 2002	0/1	0/7			Not estimable
Zelenock 1982	0/1	0/1			Not estimable
Total (95% CI)	**300**	**962**		**100.0 %**	**0.63 [0.21, 1.86]**

Total events: 6 (antiplatelets), 18 (anticoagulation)

Heterogeneity: Chi^2 = 14.84, df = 12 (P = 0.25); I^2 =19%

Test for overall effect: Z = 0.83 (P = 0.41)

Test for subgroup differences: Not applicable

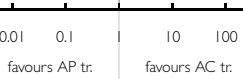
Analysis 1.4. Comparison 1 Antiplatelet drugs versus anticoagulants, Outcome 4 Symptomatic intracranial haemorrhage.

Review: Antithrombotic drugs for carotid artery dissection

Comparison: 1 Antiplatelet drugs versus anticoagulants

Outcome: 4 Symptomatic intracranial haemorrhage

Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Non-randomised studies					
Arauz 2006	0/44	0/14			Not estimable
Ast 1993	0/21	0/30			Not estimable
Biller 1986	0/5	0/2			Not estimable
Biousse 1998	0/1	0/3			Not estimable
Campos 2007	0/6	0/30			Not estimable
Caso 2004	0/10	0/9			Not estimable
Chen 1984	0/5	0/1			Not estimable
Colella 1996	0/2	0/12			Not estimable
De Bray 1989	0/4	0/14			Not estimable
Dziewas 2003	0/7	1/71		14.3 %	0.33 [0.00, 317.00]
Eachempati 1998	0/3	0/5			Not estimable
Eljamel 1990	0/4	0/4			Not estimable
Engelter 2000	0/8	0/25			Not estimable
Friedman 1980	0/1	0/4			Not estimable
Georgiadis 2009	0/96	2/202		76.3 %	0.23 [0.01, 4.44]
Kaps 1990	0/2	0/5			Not estimable
Luken 1979	0/2	0/1			Not estimable
Marx 1987	0/1	0/6			Not estimable
Metso 2009	0/4	2/140		9.4 %	0.35 [0.00, 1681.10]
Miller-Fisher 1978	0/1	0/2			Not estimable
Pieri 2007	0/10	0/14			Not estimable
Sellier 1983	0/13	0/16			Not estimable
Treiman 1996	0/6	0/12			Not estimable
Vanneste 1984	0/1	0/4			Not estimable



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Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Zelenock 1982	0/1	0/1			Not estimable
Total (95% CI)	**258**	**627**		**100.0 %**	**0.25 [0.02, 3.36]**
Total events: 0 (antiplatelets), 5 (anticoagulation)					
Heterogeneity: Chi^2 = 0.02, df = 2 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.05 (P = 0.30)					
Test for subgroup differences: Not applicable					

Analysis 1.5. Comparison 1 Antiplatelet drugs versus anticoagulants, Outcome 5 Major extracranial haemorrhage.

Review: Antithrombotic drugs for carotid artery dissection

Comparison: 1 Antiplatelet drugs versus anticoagulants

Outcome: 5 Major extracranial haemorrhage

Study or subgroup	antiplatelets n/N	anticoagulation n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Non-randomised studies					
Arauz 2006	0/44	0/14			Not estimable
Campos 2007	0/6	0/30			Not estimable
Caso 2004	0/10	0/9			Not estimable
Colella 1996	0/2	0/12			Not estimable
De Bray 1989	0/4	0/14			Not estimable
Dziewas 2003	0/7	0/71			Not estimable
Eachempati 1998	0/3	1/5		25.5 %	0.20 [0.00, 11.57]
Engelter 2000	0/8	0/25			Not estimable
Georgiadis 2009	0/96	2/202		47.3 %	0.23 [0.01, 4.44]

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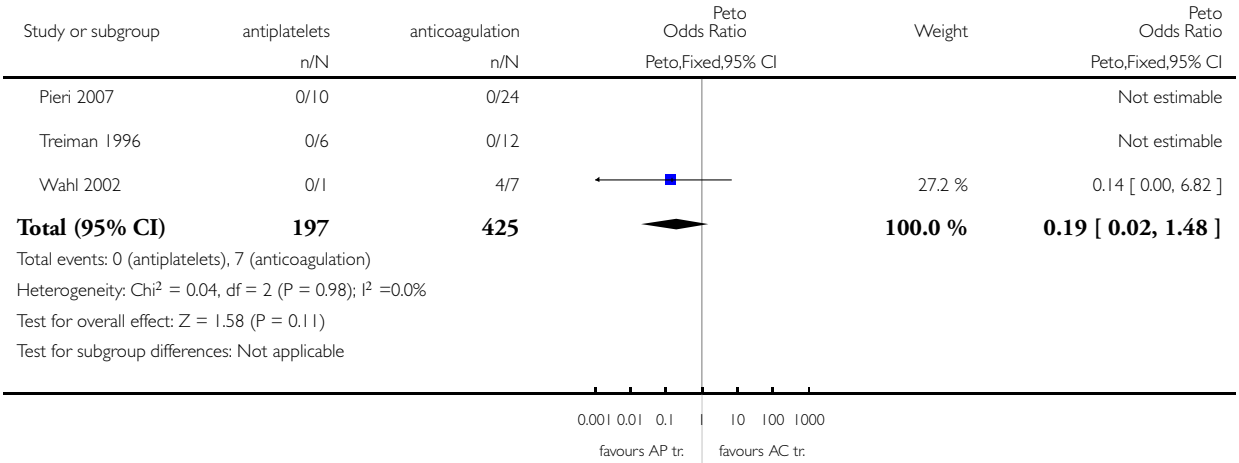

APPENDICES

Appendix 1. MEDLINE search strategy

We used the following search strategy, using a combination of controlled vocabulary and text word terms, for MEDLINE (Ovid) and modified it to search the Cochrane Central Register of Controlled Trials.

MEDLINE (Ovid) 1966-November 2009

1 exp carotid artery injuries/ or carotid artery, internal, dissection/
2 (carotid adj5 (injur$ or dissection or trauma$)).tw.
3 exp carotid arteries/
4 carotid artery diseases/
5 carotid artery thrombosis/
6 carotid$.tw.
7 3 or 4 or 5 or 6
8 exp aneurysm, dissecting/ or aneurysm, false/ or exp aneurysm, ruptured/
9 exp wounds, nonpenetrating/
10 (traumatic adj5 (dissection or aneurysm or pseudoaneurysm)).tw.
11 (blunt adj5 (injur$ or trauma)).tw.
12 dissecting aneurysm.tw.
13 rupture, spontaneous/ or rupture/
14 spontaneous dissection.tw.
15 8 or 9 or 10 or 11 or 12 or 13 or 14
16 7 and 15
17 1 or 2 or 16
18 exp platelet aggregation inhibitors/
19 blood platelets/de
20 platelet aggregation/de

21 exp fibrinolytic agents/
22 exp anticoagulants/
23 Thrombolytic therapy/
24 exp thromboembolism/dt
25 thrombosis/dt
26 (antiplatelet$ or antithromb$ or anticoag$).tw.
27 (aspirin or acetylsalicylic acid or indobufen).tw.
28 (dipyridamole or ticlopidine or clopidogrel or sulfinpyrazone or sulphinpyrazone).tw.
29 (heparin$ or coumarin$ or coumadin$ or warfarin).tw.
30 or/18-29
31 17 and 30
32 limit 31 to human

Appendix 2. EMBASE search strategy

We used the following search strategy, using a combination of controlled vocabulary and text word terms, for EMBASE (Ovid)
EMBASE (Ovid) 1980-November 2009
1 carotid artery thrombosis/dt
2 carotid artery obstruction/dt
3 carotid artery aneurysm/dt
4 internal carotid artery occlusion/dt
5 internal carotid artery aneurysm/dt
6 1 or 2 or 3 or 4 or 5
7 exp carotid artery/
8 exp carotid artery disease/
9 carotid.tw.
10 Artery dissection/ or Artery injury/ or Artery rupture/ or Artery thrombosis/
11 artery wall dissection/
12 blood vessel injury/
13 False aneurysm/
14 blunt trauma/
15 rupture/
16 (traumatic adj5 (dissection or aneurysm or pseudoaneurysm)).tw.
17 (blunt adj5 (injur$ or trauma)).tw.
18 dissecting aneurysm.tw.
19 spontaneous dissection.tw.
20 7 or 8 or 9
21 or/10-19
22 20 and 21
23. carotid artery injury/ or (carotid adj5 (injur$ or dissection or trauma$)).tw
24 6 or 22 or 23
25 exp Anticoagulant agent/
26 exp Antithrombocytic agent/
27 Thrombocyte aggregation/
28 Thrombocyte/
29 Fibrinolytic therapy/
30 thromboembolism/dt
31 (antiplatelet$ or anticoagulant$ or antithromb$).tw.
32 (aspirin or acetylsalicylic acid or indobufen).tw.
33 (dipyridamole or ticlopidine or clopidogrel or sulfinpyrazone or sulphinpyrazone).tw.
34 (heparin$ or coumarin$ or coumadin$ or warfarin).tw.
35 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36 24 and 35
37 Limit 36 to human

FEEDBACK

Feedback

Summary

Feedback received for the previous version of this review, and other reviews and protocols of anticoagulants, is available on the Cochrane Editorial Unit website at http://www.editorial-unit.cochrane.org/anticoagulants-feedback

WHAT'S NEW

Last assessed as up-to-date: 2 May 2010.

Date	Event	Description
7 March 2011	Feedback has been incorporated	Link to feedback added.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 2000

Date	Event	Description
23 August 2010	New citation required but conclusions have not changed	After the updated review was published in Issue 7 2010 of *The Cochrane Library*, it was subsequently agreed that the review merits a new citation because a significant number of new studies had been added and new secondary outcomes were included in the update. This re-published version only amends the citation date of the review; there have been no changes to the content of the review since it was last updated on 3 May 2010 (see History)
3 May 2010	New search has been performed	The Cochrane Stroke Group Trials Register was last searched for randomised trials on 3 October 2009. No results from randomised trials are currently available (one feasibility RCT is ongoing) Since the second publication of the review, searches of

(*Continued*)

		MEDLINE (November 2009), EMBASE (November 2009), and the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 2, 2009) have identified 10 additional non-randomised trials and case series eligible for the update. In addition, the following secondary outcomes were studied: ischaemic stroke, symptomatic intracranial haemorrhage, and major extracranial haemorrhage The conclusions of the review are unchanged.
23 June 2008	New search has been performed	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Philippe Lyrer developed the protocol, undertook fund raising, analysed the data, wrote the (first) review, and made critical revisions to the current update.

Stefan Engelter did the literature search, extracted outcome measures, prepared the figures, undertook fund raising, contacted authors of studies for additional data, and drafted the updated review.

DECLARATIONS OF INTEREST

Both authors were investigators in the Engelter 2000 study.

SOURCES OF SUPPORT

Internal sources

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

(Support for the current update)

External sources

- Freiwillige Akademische Gesellschaft (FAG), Basel (supported the first review), Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticoagulants [*therapeutic use]; Carotid Artery, Internal, Dissection [*drug therapy]; Controlled Clinical Trials as Topic; Fibrinolytic Agents [*therapeutic use]; Platelet Aggregation Inhibitors [*therapeutic use]

MeSH check words

Humans