

# Treatment of Carotid Artery Dissection

## EBEM Commentator Contact

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection (Cochrane Review). In: Cochrane Stroke Group. *The Cochrane Library, Issue 1*. Chichester, United Kingdom: John Wiley & Sons, Ltd; 2005.

The *Annals'* EBEM editors assisted in the preparation of the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

To determine whether antithrombotic drugs (antiplatelet drugs, anticoagulation) are effective and safe in the treatment of patients with extracranial internal carotid artery dissection and which is the better treatment.

## DATA SOURCES

The authors searched the Cochrane Stroke Group Trials Register (last searched October 3, 2002). In addition, they performed searches of the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 2, 2002), MEDLINE (January 1966 to May 2002), and EMBASE (January 1980 to June 2002) and checked all relevant articles for additional eligible studies.

## STUDY SELECTION

Because of the rarity of extracranial internal carotid artery dissection, the authors intended to include not only randomized controlled trials (RCTs) but also other controlled clinical trials (CCTs), nonrandomized studies, and case series of at least 4 patients, all of which enabled comparisons between antithrombotic treatments.

## DATA EXTRACTION AND ANALYSIS

One of the reviewers (SE) selected which trials met the inclusion criteria, and another reviewer (PL) independently

reviewed the decisions. All outcome measures (mortality, ischemic stroke, disability, hemorrhage) were extracted from the eligible studies. Disagreements on inclusion (1 study) and outcomes were resolved by discussion. Peto odds ratio (OR) and 95% confidence intervals (CIs) are reported.

## MAIN RESULTS

No RCTs or CCTs were identified. Twenty-six studies with 327 patients reported comparisons between antiplatelet and anticoagulation with respect to the outcome of death. Two of 109 patients (1.8%) treated with antiplatelet drugs died compared with 4 of 218 (1.8%) treated with anticoagulants (OR 1.59; 95% CI 0.22 to 11.59). Twenty studies involving 178 patients reported on the composite endpoint of death or disability. Overall, 14 of 59 patients (23.7%) treated with antiplatelets compared with 17 of 119 (14.3%) patients treated with anticoagulants died or were disabled; this difference was not significant (OR 1.94; 95% CI 0.76 to 4.91). There was no significant heterogeneity between the included series. Of the 157 patients treated with antiplatelets, 6 (3.8%) patients experienced a first or recurrent stroke, whereas none had an intracranial hemorrhage. Of 414 patients receiving anticoagulation, 5 (1.2%) patients were reported to have had a first or recurrent stroke on treatment, and a further 2 patients (0.5%) had intracranial hemorrhages.

## CONCLUSIONS

There is no evidence to support the routine use of antithrombotic agents in extracranial internal carotid artery dissection. The available evidence does not reliably establish whether anticoagulants are better than antiplatelet drugs in patients with extracranial internal carotid artery dissection.

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## COMMENTARY: CLINICAL IMPLICATION

A dissection of the internal carotid artery is a rare but potentially devastating neurologic emergency. Although likely

underreported, the annual incidence of extracranial internal carotid artery dissection is believed to be approximately 2 to 3 per 100,000 and an important cause of stroke in patients younger than 50 years.<sup>1</sup> Suspected etiologies for extracranial internal carotid artery dissection include chiropractic neck manipulations and arteriopathies such as fibromuscular dysplasia and cystic medial necrosis. Furthermore, the reported incidence may be on the rise because imaging modalities such as magnetic resonance imaging continue to improve detection. An expanding hematoma in the vessel wall is the root lesion in extracranial internal carotid artery dissection. This intramural hematoma can arise spontaneously or as a result of minor trauma through hemorrhage of the vasa vasorum within the media of the vessel. It can also be introduced through an intimal flap that develops at the level of the inner lumen of the vessel. Thrombosis of major and branch vessels, as well as distal embolization of thrombus created by the impaired blood flow at the site of the dissection, is believed to mediate the morbidity associated with extracranial internal carotid artery dissection.<sup>1</sup>

The evidence base informing decisionmaking with regard to the management of extracranial internal carotid artery dissection is limited by its size and quality. As a result, this Cochrane review appropriately points out that there is insufficient evidence to recommend antiplatelet over anticoagulation therapy for patients with suspected extracranial internal carotid artery dissection. Moreover, Lyrer and other authors<sup>2</sup> have suggested the need for a head-to-head RCT that would enroll 2,800 patients with either the rarer version of cervical artery dissection involving the vertebral artery or extracranial internal carotid artery dissection. To date, this RCT has not been initiated.

How are emergency physicians to proceed in what might be an extremely long interim? The Cochrane review does support the conclusion that treating extracranial internal carotid artery dissection with either an antiplatelet or an anticoagulant results in low rates of mortality, intracranial hemorrhage, and recurrent stroke. In light of the favorable risk profile associated with antiplatelet regimens, this approach is certainly warranted; however, the decision to initiate or change to anticoagulation can be guided by considerations of symptom severity and stability, as well as response to empiric therapy and bleeding risk.

### TAKE HOME MESSAGE

For patients who present with suspected or confirmed carotid artery dissection and who lack contraindications, antiplatelet therapy is associated with a good prognosis. However, although evidence is limited, some patients (severe or ongoing symptoms, low bleeding risk) may derive benefit from anticoagulation.

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### EBEM TEACHING POINT

*The biases associated with non-RCT evidence.* RCTs are considered to be the criterion standard for determining effectiveness, efficacy, or both between therapeutic interventions and clinical outcomes. The arguments advanced mainly focus on the overestimation of treatment effect when nonobservational studies are compared with similar RCTs. More recently, some authors have argued that high-quality observational (non-RCT) evidence can provide generally accurate measures of association.<sup>3,4</sup> However, in comparisons drawn from non-RCT research designs, treatment assignments are influenced by physician preference and severity of illness, to name only a few of the biases that can confound measures of efficacy. In other words, the effects of therapies reported in observational studies may be inextricably tied to factors other than the intervention itself, despite well-meaning efforts and statistical adjustment.<sup>5</sup>

Only truly randomized treatment allocation can achieve a balanced distribution of known and unknown prognostic factors between intervention and control arms, thus enabling an unhindered assessment of the therapeutic intervention. Not only are known prognostic factors generally balanced in the arms of an RCT but also characteristics that are either unmeasurable or unrecognized can be controlled for only through randomization. Whenever possible, RCT evidence should be sought in therapeutic areas; however, as in the case of carotid artery dissection, the best evidence may arise from nonobservational studies.

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