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## Use of Anticoagulants in Acute Ischemic Stroke

**EBEM Commentator**  
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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: Gubitza G, Counsell C, Sandercock P, Signorini D. Anticoagulants for acute ischaemic stroke (Cochrane Review). In: *The Cochrane Library*. Issue 3. Oxford, United Kingdom: Update Software; 2004.

The *Annals'* EBEM editors helped prepare the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

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### OBJECTIVE

To assess the effect of anticoagulant therapy in the early treatment of patients with acute ischemic stroke.

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### DATA SOURCES

The Cochrane Stroke Group Trials Register was searched up to October 2003, and Medstrategy was searched to 1995. A search of the trials register held by the Antithrombotic Therapy Trialists' Collaboration was searched up to August 1998. Additionally, pharmaceutical companies and researchers in the field were contacted in an effort to identify unpublished and ongoing trials. This review was updated in January 2004.

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### STUDY SELECTION

Studies were included if they were randomized, unconfounded, blinded, controlled clinical trials. Patients had to receive an anticoagulant agent or placebo within 2 weeks of their acute stroke, whether ischemic or hemorrhagic. The agents included in this review are standard unfractionated heparin (subcutaneous and intravenous routes), low-molecular-weight heparins (dalteparin, nadroparin, tinzaparin, CY 222), heparinoids (danaparoid administered subcutaneously and intravenously, mesoglycan), oral anticoagulants (dicumerol, phenindione), and thrombin inhibitors (MD 805). The majority of the data for this review come from the International Stroke Trial, which studied subcutaneous heparin as the anticoagulant agent (83% of total patients).

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### DATA EXTRACTION

Two authors independently selected trials, extracted data, and assessed the quality of the trials. The drugs' effects on death and disability, intracranial hemorrhage, pulmonary emboli, and deep venous thromboses were evaluated.

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### MAIN RESULTS

A total of 22 trials involving 23,547 patients were identified. Overall, there was no evidence that anticoagulant therapy reduced the odds of death from all causes (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.98 to 1.12). On the benefits side, there were 9/1,000 fewer recurrent ischemic strokes (OR 0.76, 95% CI 0.65 to 0.88) and 4/1,000 fewer pulmonary emboli (OR 0.60, 95% CI 0.44 to 0.81). These benefits are negated by the results of 9/1,000 more symptomatic intracranial hemorrhages (OR 2.52, 95% CI 1.92 to 3.30) and 9/1,000 more extracranial hemorrhages (OR 2.99, 95% CI 2.24 to 3.99). In a sensitivity analysis, no particular regimen was associated with any net benefit.

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### CONCLUSION

Immediate anticoagulation for acute ischemic stroke is not associated with net short-term or long-term benefit. There is no support for routine use of any type of anticoagulant in this setting.

**Cochrane Systematic Review Author Contact***Gordon Gubitz, MD**Division of Neurology**Halifax Infirmary**Halifax, Nova Scotia, Canada**E-mail [ggubitz@dal.ca](mailto:ggubitz@dal.ca)***COMMENTARY: CLINICAL IMPLICATION**

Acute ischemic stroke is a common emergency department (ED) presentation, with high stakes. Approximately 7.6% of ischemic strokes and 37.5% of hemorrhagic strokes result in death within 30 days, and 22% of men and 25% of women who have an initial stroke die within a year.<sup>1</sup> It is the third and fourth leading cause of death in the United States and Canada, respectively, and the number one cause of disability in North America, with around 50% of survivors left with some permanent deficit.

The rationale behind the use of anticoagulants for acute ischemic stroke is that the majority of ischemic strokes are caused by a thrombus obstructing an artery supplying a region of the brain. Therefore, one could postulate that prevention of further clot formation or propagation could affect survival and recurrence. The history of anticoagulant use for acute ischemic stroke has changed drastically over time. In 1994, the American Heart Association's (AHA) recommendation for use of anticoagulants was a "matter of physician preference." They noted that anticoagulants were often prescribed to patients with recent stroke in an effort to prevent early recurrent stroke and to improve neurologic outcomes. Specific groups for whom anticoagulants were thought to be of benefit included patients with ischemic stroke of unknown origin who have a combination of a patent foramen ovale and atrial septal aneurysm (because these patients have an increased risk of recurrent stroke despite treatment with aspirin); patients with fluctuating basilar artery thrombosis; patients with impending carotid artery occlusion from thrombosis or dissection; and patients with cardioembolic cerebral infarction. From the emergency physician's standpoint, none of the above clinical entities would be apparent in the ED.

This Cochrane Review evaluated 22 trials involving 23,547 patients and concludes that the use of anticoagulants is not beneficial in acute ischemic stroke. Over time and in keeping with this review evidence, the AHA has changed their position on anticoagulation therapy in the setting of acute ischemic stroke. They

clearly state that early administration of anticoagulants does not lower the risk of early recurrent stroke, including among patients with cardioembolic stroke, and does not lessen the risk of neurologic worsening (level I evidence). Furthermore, they clarify that there are no adequate data to demonstrate efficacy of anticoagulants in potentially high-risk groups such as those patients with intracardiac or intra-arterial thrombi. As for potentially high-risk groups, they agree that more studies are required to determine whether certain subgroups (large-vessel atherothrombosis or patients perceived to be at high risk of recurrent embolism) may benefit from urgent anticoagulation. The clinical "bottom line" from the AHA report<sup>1</sup> is that anticoagulation for acute ischemic stroke is not recommended as treatment for patients with moderate-to-severe stroke because of a high risk of serious intracranial bleeding complications (grade A). Anticoagulation is also not recommended within 24 hours of treatment of intravenous thrombolytics (grade A evidence). Despite the Cochrane evidence and AHA position, emergency physicians may observe instances in which an anticoagulant (especially heparin) is administered for acute ischemic stroke. Moreover, emergency physicians may still be requested to administer heparin by neurologists in certain situations, such as progressive stroke, stuttering transient ischemic attacks, posterior circulation strokes, and patients having their event on aspirin (especially when presenting from an outside facility). The data to support anticoagulation even in these groups are sparse; however, the prognosis tends to be poorer for these patients, which is given as the rationale for anticoagulation. If one is considering anticoagulation for acute ischemic stroke, one must ensure that there is no hemorrhage evident on the computed tomography scan, and that the patient is ineligible for thrombolytics. Overall, given the evidence provided here, routine anticoagulation for acute ischemic stroke should be abandoned.

**TAKE HOME MESSAGE**

On average, every 45 seconds in the United States<sup>2</sup> and every 10 minutes in Canada<sup>3</sup> someone suffers an acute stroke. To date, few interventions have been unequivocally proven to be beneficial, despite a multitude of stroke trials. Evidence to date dictates that routine anticoagulation for acute ischemic stroke should be abandoned. However, in an era in which options for acute stroke treatment are still limited, many still use heparin as a last resort for high-risk groups.

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**EBEM TEACHING POINT**

**Forrest plot.** The Forrest plot is used for displaying results of individual and pooled studies in a systematic review and can be used to visually investigate the presence of heterogeneity in a meta-analysis. The Forrest plot is also colloquially referred to as a “blob-o-gram,” a “meta table,” or a “meta view” (after the software program in the Cochrane Database by the same name). Compared with other systematic review

graphic presentations, the Forrest plot displays the name of the study, the summary estimate with 95% CIs for each individual study, and the “weighting” of the study (usually based on an inverse variance technique). Where pooling is appropriate, the graph also displays the pooled estimate (and 95% CIs), the heterogeneity statistics, and the  $I^2$  statistic. The Forrest plot is the most common graphical display used in Cochrane Reviews.

**REFERENCES**

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