Review: Anticoagulants increase intracerebral bleeding and do not reduce death or disability in acute cardioembolic stroke

Paciaroni M, Agnelli G, Micheli S, Caso V. **Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials.** Stroke. 2007;38:423-30.

Clinical impact ratings: Referred Care ★★★★★☆ Emerg Med ★★★★★☆ Cardiology ★★★★☆☆ Hematology ★★★★★☆ Neurology ★★★★★☆

QUESTION

In patients with acute cardioembolic stroke, are anticoagulants effective and safe as initial treatment?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (1980 to February 2006), the Cochrane Library (2006, issue 1), bibliographies of relevant studies, and abstracts of major international meetings.

Study selection and assessment: Randomized controlled trials (RCTs) that compared anticoagulants (unfractionated heparin, low-molecular-weight heparin, or heparinoids) with other treatments or placebo in patients (randomized within 48 h of stroke onset) who received an objective diagnosis of stroke of presumed cardioembolic origin and were assessed using objective methods. 7 RCTs (n = 4624) were included. 3797 patients had atrial fibrillation, and 827 had other mixed cardioembolic sources. The anticoagulants were intravenous dalteparin (1 RCT), intravenous heparin (2 RCTs), subcutaneous heparin (1 RCT), intravenous danaparoid (1 RCT), subcutaneous nadroparin (1 RCT), and tinzaparin (1 RCT). Studies were assessed for allocation methods, allocation concealment, blinding, and completeness of follow-up.

Outcomes: A composite outcome of death or disability at ≥ 3 months, all strokes or early recurrent stroke within 14 d, and symptomatic intracranial bleeding.

MAIN RESULTS

Anticoagulants did not differ significantly from placebo or aspirin for death or disability, all strokes, or recurrent stroke, but they increased the risk for symptomatic intracranial bleeding (Table).

CONCLUSIONS

In patients with acute cardioembolic stroke, anticoagulants do not differ significantly from placebo or aspirin for the composite outcome of death or disability or for stroke, including recurrent early stroke. However, they increase the risk for intracranial bleeding.

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Anticoagulants vs aspirin or placebo for acute cardioembolic stroke*

Outcomes	Number of RCTs (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Anticoagulants	Aspirin or placebo		
Death or disability at ≥ 3 mo	6 (4568)	73.8%	73.5%	0 (−5.4 to 5.3)	Not significant
All strokes	4 (4031)	4.3%	3.7%	17% (−25 to 82)	Not significant
Intracranial bleeding	{5}†	2.5%	0.7%	185% (19 to 572)	78 (25 to 759)
				RRR (CI)	**NNT**
Recurrent stroke at 14 d	{5}†	3.0%	4.9%	31% (−5.7 to 55)	Not significant

*RCT = randomized controlled trial; other abbreviations defined in Glossary. RRR, RRI, NNH, and CI calculated from odds ratio in article using a random-effects model.
†Information provided by author.

COMMENTARY

Ischemic stroke was commonly treated with short-term anticoagulation 10 years ago, most frequently with heparin. A series of randomized trials, many included in this meta-analysis by Paciaroni and colleagues, showed that there was no benefit to anticoagulation when given within hours of an ischemic stroke and that it increased the risk for major hemorrhagic complications. However, cardioembolic strokes were not well-represented in most of these trials.

The benefit of long-term anticoagulation with warfarin in patients with cardioembolic stroke is well-established. Some experts have argued that short-term anticoagulation in patients with recent cardioembolic stroke should reduce the risk for early recurrence and that this benefit is likely to outweigh the risk for hemorrhagic complications. This meta-analysis argues that they are wrong, and in doing so, it eliminates one of the last widely accepted indications for full-dose heparin after ischemic stroke.

This meta-analysis extracted data from subgroups in larger trials (including data not previously reported) and thus adds to the literature rather than just summarizing it. With the data clearly presented, the conclusions are obvious: Any benefit from short-term anticoagulation in reducing risk for recurrent ischemic stroke is outweighed by the risk for hemorrhagic stroke, with no net benefit in mortality and disability.

Prophylaxis of deep venous thrombosis remains an uncertain indication for heparins in nonambulatory patients with stroke and is currently being studied in randomized trials. The lower doses required for prophylaxis are more effective than compression devices, but this benefit may be balanced by a greater risk for brain hemorrhage (1). Patients with cardioembolic transient ischemic attack may also benefit from short-term anticoagulation since the risk for recurrence is particularly high in these patients, and the risk for brain hemorrhage should be substantially lower in the absence of major brain infarction. However, this indication needs to be evaluated in trials (2). Short-term aspirin does improve outcomes after ischemic stroke and should be given to all patients.

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