Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that the use of early anticoagulation in patients with acute ischaemic cardioembolic stroke to prevent early recurrence or to improve functional outcome is not supported by the evidence. This was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To evaluate the efficacy and safety of anticoagulants for the initial treatment of patients with acute cardioembolic stroke.

Searching
MEDLINE, EMBASE (both from 1980 to February 2006) and the Cochrane Library (Issue 1, 2006) were searched using the reported search terms. The reference lists of journal articles were screened for additional studies and abstracts from major international meetings were screened for unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared initial treatment (within 48 hours) with anticoagulants (subcutaneous and intravenous unfractionated heparin, subcutaneous low molecular weight heparin, subcutaneous and intravenous heparinoids) with other treatments (placebo or aspirin) were eligible for inclusion. The included studies evaluated unfractionated heparin, low molecular weight heparin (tinzaparin, dalteparin and nadroparin) and a heparinoid (danaparoid). The control treatments were aspirin, placebo and no heparin. Treatment duration ranged from 5 to 14 days. The time interval to treatment ranged from less than 3 hours to less than 48 hours.

Participants included in the review
Studies of patients randomised within 48 hours of an objectively diagnosed stroke of presumed cardioembolic aetiology were eligible for inclusion. Most of the participants in the included studies had atrial fibrillation; there was a variety of cardioembolic sources in the other participants.

Outcomes assessed in the review
Studies that used objective methods to assess death, disability, all strokes, recurrent ischaemic stroke and cerebral symptomatic bleeding were eligible for inclusion. The review assessed a composite outcome of death or disability at final follow-up (at least 3 months), all strokes (ischaemic and haemorrhagic) within 14 days, early recurrent stroke (within 14 days), pulmonary embolism and symptomatic intracranial bleeding.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies.

Assessment of study quality
Two reviewers independently assessed validity using the criteria described by Schultz et al.: methods used to generate randomisation sequence; allocation concealment; blinding of the patient and outcome assessor; and completeness of follow-up.
Data extraction
Two reviewers independently extracted the outcome data of interest. A third reviewer confirmed the data extracted and any differences were resolved by consensus. Odds ratios (ORs) were calculated for each study. In studies where it was not possible to extrapolate data regarding patients with cardioembolism from patients with acute stroke resulting from other etiologies, data were sought through correspondence with the authors.

Methods of synthesis
How were the studies combined?
Pooled ORs with 95% confidence intervals (CIs) were calculated for each outcome of interest using the Mantel-Haenszel random-effects method. The number-needed-to-treat with anticoagulants to prevent one recurrent stroke and the number-needed-to-harm (NNH) to cause one symptomatic intracranial bleeding were calculated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test and the I-squared statistic.

Separate analyses were conducted to compare anticoagulants with placebo and anticoagulants with aspirin. Sensitivity analysis was conducted by repeating the analysis after omitting each study in turn.

Results of the review
Seven RCTs (n=4,624) were included.

All studies reported the method of randomisation. In 5 studies both patients and outcome assessors were blinded. Six studies reported the number of patients lost to follow-up.

There was no statistically significant difference between anticoagulant and other treatment in death or disability at final follow-up (73.5% versus 73.8%; OR 1.01, 95% CI: 0.82, 1.24, p=0.9) or all strokes (OR 1.18, 95% CI: 0.74, 1.88, p=0.09). No significant heterogeneity was found for either analysis. Anticoagulants were associated with a non significant reduction in recurrent stroke within 7 to 14 days compared with other treatments (3.0% versus 4.9%; OR 0.68, 95% CI: 0.44, 1.06, p=0.09), but were associated with a significant increase in symptomatic intracranial bleeding (2.5% versus 0.7%; OR 2.89, 95% CI: 1.19, 7.01, p=0.02; NNH =55).

Compared with placebo, anticoagulants were associated with a non significant reduction in death or disability at final follow-up (OR 0.90, 95% CI: 0.67, 1.22). Compared with aspirin, anticoagulants were associated with a non significant increase in death or disability at final follow-up (OR 1.14, 95% CI: 0.95, 1.38). There was no significant difference between anticoagulants and aspirin in pulmonary embolism (OR 0.94, 95% CI: 0.44, 2.00, p=0.87).

Authors' conclusions
The meta-analysis does not support the use of early anticoagulation in patients with acute ischaemic cardioembolic stroke.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and attempts were made to minimise publication bias; no attempts to minimise language bias were reported. Methods were used to minimise reviewer error and bias in the study selection, validity assessment and data extraction processes. Validity was assessed using specified criteria and the results of this assessment reported. Statistical heterogeneity was assessed and appropriate methods used to combine the studies. Subgroup analysis was used to examine the effect of control treatments. This was a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that it is reasonable to administer early aspirin followed by vitamin K antagonists for long-term secondary prevention in patients with acute ischaemic cardioembolic stroke.

Research: The authors stated the need for further research to evaluate the very early (within 3 hours of stroke onset) administration of heparin in patients with acute cardioembolic stroke. Such research should take account of known risk factors for haemorrhagic adverse events.

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