Low-molecular-weight heparins and heparinoids in acute ischemic stroke: a meta-analysis of randomized controlled trials

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Authors' objectives
To assess the safety and efficacy of low molecular weight heparins and heparinoids (LMWH) in acute ischaemic stroke.

Searching
The studies were identified through searches of the Cochrane Stroke Group's Specialised Register, the Cochrane Library (Issue 2, 1999), published reviews and systematic reviews of anticoagulant treatment in acute stroke, and a recent study of publication quality of acute stroke randomised controlled trials. The reference lists of retrieved articles were also examined for additional trials. Publication in a language other than English was not an exclusion criteria.

Study selection
Study designs of evaluations included in the review
The included trials had to be randomised, placebo- or open-controlled, and be completed by the end of 1998. Trials were excluded if they were pseudo-randomised or confounded, i.e. LMWH was tested against another active treatment.

Specific interventions included in the review
LMWH (CY222, dalteparin, danaparoid, mesoglycan, nadroparin, tinzaparin) were compared with placebo or no treatment. The dosages and routes used varied between included trials. Treatment was started within 24 to 72 hours in all but one included trial, and was given for between 7 and 30 days (median and mode: 14 days). Follow-up ranged from 2 weeks to 6 months.

Participants included in the review
Adult patients with acute ischaemic stroke. Only trials that recruited patients within 7 days of having a stroke, and used computed tomography for the exclusion of primary intracerebral haemorrhage, were included in the review. Four trials explicitly excluded patients with presumed cardioembolic stroke, whilst the remaining trials recruited between 14.0 and 29.8% (median: 20.9%) of patient with presumed cardioembolic stroke. The mean age of participants within individual studies, where given, ranged from 57 to 75 years. The proportion of males included in the trials ranged from 45 to 61%.

Outcomes assessed in the review
For inclusion, studies had to report one or more outcome measures relevant to stroke patients. These included case fatality, combined death and disability, venous thromboembolism and symptomatic bleeding.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors independently extracted the following trial information and data, according to treatment group: protocol, including type and dose of LMWH, treatment window, duration of treatment and follow-up period; the number of patients; the number of events on treatment for each group with respect to case fatality, intracranial haemorrhage, extracranial haemorrhage, pulmonary embolism (PE), deep vein thrombosis (DVT) and fatal myocardial infarction; and end-of-trial case fatality, death and disability. Information on method used to diagnose symptomatic intracranial
haemorrhage, PE and DVT was also recorded, as was information regarding whether patients with presumed cardioembolic stroke could be enrolled in the study.

Where more than one active treatment group was compared with a single control group, the event rate and group size for the control group were divided between the active groups equally.

**Methods of synthesis**

**How were the studies combined?**

Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using a random-effects model because heterogeneity was expected among the trials.

**How were differences between studies investigated?**

Heterogeneity was assessed with respect to protocol differences, by grouping studies according to their aim (phase II or III, or DVT prophylaxis), time to treatment (within 24 hours, or longer), route of drug administration (intravenous, intramuscular or subcutaneous), inclusion or exclusion of patients with presumed cardioembolic stroke, and type of drug used (heparin or heparinoid). Statistical heterogeneity among trials was also assessed using a chi-squared test, and the results of individual studies were presented in forest plots. Sensitivity analyses were performed by excluding trials on the grounds of quality, e.g. the effect of LMWH on the incidence of DVT was studied for all trials, and then separately for those trials that prospectively assessed DVT by imaging at the end of treatment. Lack of identification and inclusion of trials through publication or location bias was assessed by quantitative analysis of the asymmetry of funnel plots, as described by Egger et al. (see Other Publications of Related Interest).

**Results of the review**

Ten randomised controlled trials involving 2,855 patients were included.

Treatment with LMWH was associated with significant reductions in prospectively identified DVT (OR 0.27, 95% CI: 0.08, 0.96) and symptomatic PE (OR 0.34, 95% CI: 0.17, 0.69), and with increased major extracranial haemorrhage (OR 2.17, 95% CI: 1.10, 4.28). Non significant increases in end-of-treatment (OR 1.20, 95% CI: 0.86, 1.69) and end-of-trial (OR 1.05, 95% CI: 0.83, 1.32) case fatality, and symptomatic intracranial haemorrhage (OR 1.77, 95% CI: 0.95, 3.31) were observed. There was a non significant reduction in end-of-trial death and disability (OR 0.87, 95% CI: 0.72, 1.06).

The trials did not show significant heterogeneity for outcomes other than DVT. In addition, a funnel plot analysis did not suggest that trials had not been identified, although data on one small trial of danaparoid involving 180 patients were unavailable for analysis. Statistical heterogeneity was present for DVT, and was largely due to one trial that found nadroparin had no effect in prevention of DVT, although it did reduce PE events.

**Authors' conclusions**

LMWHs reduce venous thromboembolic events in patients with acute ischaemic stroke, and increase risk of extracranial bleeding. A non significant reduction in combined death and disability, and non significant increases in case fatality and symptomatic intracranial haemorrhage, were also observed. On the basis of the current evidence, LMWH should not be used in the routine management of patients with ischaemic stroke.

**CRD commentary**

This was a fairly well-conducted review that used a clearly stated objective with predefined inclusion and exclusion criteria. A relatively comprehensive search of the literature was undertaken, although no attempt was made to look for unpublished studies. The authors did, however, statistically investigate the potential presence of publication bias. The authors did not report assessing the validity of included trials, although they did perform a sensitivity analysis by excluding trials on quality grounds. Studies were combined using a random-effects model as the authors believed that there would be heterogeneity between studies. However, this was not found to be the case. Significant heterogeneity was only present for the outcome DVT. The use of a fixed-effect model may, therefore, have been preferable for
homogeneous trials. The authors state in their discussion that, despite the absence of statistical heterogeneity in most of the results, considerable differences existed in the trial aims and protocols, and that their 'mixing' of apparently very different studies was questionable. The conclusions of the review appear to follow on from the results.

**Implications of the review for practice and research**

**Practice:** The authors state that it can be argued, on the basis of this meta-analysis, that LMWHs should be used routinely in acute ischaemic stroke even though they do not significantly reduce the rate of combined death and disability. After all, LMWHs do appear to reduce disability, especially if started later than 24 hours after stroke onset, and they do reduce PE, an often fatal condition. These advantages could be construed to outweigh the hazards of a definite increase in extracranial bleeding, a situation that can normally be treated with a blood transfusion, and probably symptomatic intracranial haemorrhage. However, the authors go on to recommend that LMWH should not be used routinely in acute ischaemic stroke until additional trial data become available and substantiate or refute their findings.

**Research:** The authors state that sufficient questions remain about the use of LMWH in acute ischaemic stroke that warrant additional larger trials. Further systematic analysis of individual patient data from the existing LMWH trials is also warranted, to facilitate more detailed investigation of some questions that the current report cannot adequately address; particular attention should be paid to the effects of LMWH by timing of administration, stroke subtype (cardioembolic or large-vessel stroke) and stroke severity. The authors go on to state that they are initiating a collaboration of the trialists with these aims in mind.

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