Differences between low-molecular-weight and unfractionated heparin for venous thromboembolism prevention following ischemic stroke: a metaanalysis

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CRD summary
This review found that low molecular weight heparins are associated with reduced risk of venous thromboembolism following ischaemic stroke, and no increased risk of bleeding compared with unfractionated heparin use. Overall this was a well-conducted review and the results appear to be reliable.

Authors’ objectives
To compare low molecular weight heparin (LMWH) with unfractionated heparin (UFH) for the prevention of venous thromboembolism (VTE) following ischaemic cerebrovascular accidents (CVA).

Searching
The databases MEDLINE (1966 - April 2006), EMBASE (Jan 1990 - April 2006), Cochrane library and clinicaltrials.gov were searched in duplicate. Search terms were reported. Abstracts from the annual meetings of the American Academy of Neurology, the American College of Chest Physicians, the American Heart Association, the American Society of Hematology, the American Thoracic Society and the International Society of Thrombosis and Haemostasis were also handsearched from 2001 to 2006. Reference lists were reviewed and experts were contacted to identify any additional studies. No language restrictions were applied.

Study selection
Studies were eligible for this review if they used a prospective randomised design, comparing LMWH and UFH in the prevention of VTE in ischemic stroke patients. Studies comparing either LMWH or UFH with placebo were excluded, as were studies where heparin was not administered expressly for the prevention of VTE. Trials were required to report VTE occurrence as a primary endpoint.

Included studies were all randomised controlled trials (RCTs) which conformed to all of the stated inclusion criteria. The majority of included participants had experienced severe, debilitating, ischaemic CVAs based on National Institutes of Health stroke severity scores (mean NIH stroke score ranged from 8.5 to 11.3 where reported). Two different LMWHs were used in these trials (enoxaparin and certoparin), and time from CVA to drug administration ranged from 24 to 48 hours. Frequency of VTE, bleeding and safety outcomes were reported in all trials.

Studies were assessed for inclusion by two independent reviewers.

Assessment of study quality
Two reviewers independently rated the quality of the included studies using the Jadad scale, which contains items on blinding, randomisation and withdrawals giving a score between 0-5.

Data extraction
The odds ratios (ORs) and associated 95% confidence intervals (CIs) describing rates of VTE, mortality and bleeding were extracted for each study, and used to calculate risk differences.

Two reviewers extracted all data in duplicate.

Methods of synthesis
A random-effects model was used to calculate a pooled OR and 95% CI for the relationship between pharmacological prophylaxis type and VTE prevention. Safety outcomes (bleeding and mortality) were explored using both fixed and random effects meta-analysis. Sensitivity analysis was carried out according to intervention type. Heterogeneity was assessed using Galbraith plots and the Q statistic. Publication bias was evaluated using funnel plots and the Begg
Results of the review
A total of three RCTs were included in this review (n=2,028, range 148 to 1,335) and there was no indication of publication bias. The median Jadad quality score was reported as 6 and no significant heterogeneity was noted.

VTE: The pooled OR favoured a significant reduction in risk of VTE with LMWH, OR 0.54 (95% CI: 0.41, 0.70; p=0.001) and similar results were found when the analysis was restricted to proximal VTE only.

Bleeding and safety: There were no significant differences between LMWH and UHF for intracerebral bleeding, OR 0.70 (95% CI: 0.26, 1.84; p=0.466), or for nonintracerebral major haemorrhage, OR 1.31 (95% CI: 0.63, 2.71; p=0.467). Mortality was reported both at the end of treatment (early) and after 90 days (late) but there was no difference in either measure between different heparin groups.

Sensitivity analysis was carried out comparing enoxaparin versus UFH, but the results did not differ significantly from those reported above.

Using a random or fixed effects analysis model did not substantially alter the results for safety and bleeding outcomes.

Authors' conclusions
Although relatively few studies have been carried out comparing LMWH with UFH in the prevention of VTE, LMWHs are associated with reduced risk of VTE following ischaemic stroke, with no increased risk of bleeding when compared with UFH use.

CRD commentary
This review addressed a clear clinical question with detailed inclusion criteria and searches which were likely to have detected relevant studies and reduce the likelihood of publication and language biases. Overall the review methodology was well reported and reduced the potential for reviewer bias or error to impact on the results. Although quality was mentioned, the assessment process was not reported, and a median score of 6 was given, despite the maximum Jadad score being 5. The meta-analysis appears to be appropriate and heterogeneity was explored. The authors mention the limitations placed on conclusions drawn from only three RCTs including lack of generalisability to certain patient groups. Overall this was a well-conducted review and the results appear to be reliable, despite the limited number of included studies.

Implications of the review for practice and research
Practice: The authors stated that broader use of LMWHs for VTE prevention following ischaemic stroke may enhance patient outcomes.

Research: The authors did not state any implications for research.

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