Authors' objectives
To compare the efficacy and safety of fixed-dose subcutaneous low-molecular-weight heparin (LMWH) with adjusted-dose unfractionated heparin for the initial treatment of acute venous thrombosis.

Searching
MEDLINE was searched from 1984 to 1994 for English language articles using the keywords 'heparin', 'low-molecular-weight heparin' or 'venous thrombo*'. Current Contents (Clinical Medicine) and bibliographies of appropriate articles were examined, and colleagues in the field were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) in which dosages of LMWHs were similar to those in current use, doses of standard heparin in control groups were adjusted, objective tests were used to confirm deep venous thrombosis, and double-blinding or blinded outcome assessors were used.

Specific interventions included in the review
LMWH (fraxiparine, logiparin, fragmin, clexane) given subcutaneously once or twice daily; unfractionated heparin given subcutaneously or intravenously, with doses adjusted to maintain the anticoagulant effect within a defined therapeutic range.

Participants included in the review
Patients with symptomatic venous thrombosis of the leg, as documented by venography, were included.

Outcomes assessed in the review
Incidence of symptomatic recurrent venous thromboembolic disease, incidence of clinically-important bleeding, mortality, and change in thrombus size after initial treatment, were assessed.

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 authors performed the selection.

Assessment of study quality
The validity of studies was assessed on whether patients were actively followed-up prospectively at study centres, and whether venography was repeated 5 to 10 days after treatment. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
A predefined set of data were extracted. No further details of the data extraction procedures were given.

Methods of synthesis
How were the studies combined?
For clinical outcomes, a fixed-effect model (Mantel-Haenszel procedure) was used to calculate an overall odds ratio (OR), which took into account the number of events in each group in each study. Common ORs were converted to relative risk (RR) reductions. A random-effects model (der Simonian and Laird, see Other Publications of Related Interest no 1) was also used, but since comparable estimates resulted, only the fixed-effect results are presented.
Overall estimates of changes in thrombus size were calculated using the Mantel-Haenszel test for trend.

How were differences between studies investigated?
Statistical tests for heterogeneity of outcome were applied, and were negative for all outcomes.

Results of the review
Ten RCTs (753 patients treated with LMWH and 759 with adjusted-dose standard heparin) were included.

RR reductions with LMWH compared to adjusted-dose standard heparin:

Symptomatic venous thromboembolic complications (17 events in 540 patients in LMWH groups, compared with 36 events in 546 patients in control groups): 53% (95% confidence interval, CI: 18, 73, p<0.01).

Haemorrhagic complications during treatment (6 events in 753 patients in LMWH groups, compared with 21 events in 759 patients in control groups): 68% (95% CI: 31, 85, p<0.005).

Mortality during initial treatment and long-term follow-up (21 events in 540 patients in LMWH groups, compared with 39 events in 546 patients in control groups): 47% (95% CI: 10, 69, p<0.04).

Venograms showed a reduction in thrombus size in 63% of patients in LMWH groups, and in 52% of patients in control groups.

Authors' conclusions
LMWH preparations are more effective and safer than adjusted doses of unfractionated heparin for treatment of deep venous thrombosis. The administration of LMWH by subcutaneous injection once or twice daily, without laboratory monitoring of the anticoagulant effect, represents an important advance in the treatment of venous thrombosis.

CRD commentary
This review applied stringent criteria for the inclusion of studies. The methods by which studies were identified and combined were appropriate, rigorous and well documented (although it is not clear to what extent study selection and data abstraction decisions were checked by a second reviewer). Some studies published in languages other than English may have been missed, as may unpublished studies. The results of all the individual studies included in this review tended to favour LMWH, and the pooling of their results in this meta-analysis allowed a statistically significant result to be obtained.

Implications of the review for practice and research
LMWH preparations are more effective and safer than adjusted doses of standard heparin for the treatment of deep venous thrombosis.

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Other publications of related interest

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