Low molecular weight heparin versus unfractionated heparin in the initial treatment of venous thromboembolism
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Authors' objectives
To analyse data from randomised trials in which low molecular weight heparin was compared with unfractionated heparin, to estimate the treatment effect of low molecular weight heparin in the initial treatment of venous thromboembolism, with regard to recurrent venous thromboembolism, mortality and major bleeding complications. In addition, the authors wished to evaluate the effect of the varied proportion of included cancer patients on the incidence of these outcome events and on the estimated treatment effect.

Searching
MEDLINE, Current Contents and EMBASE were searched (search dates not provided) using the following keywords and terms: 'deep vein (venous) thrombosis', 'pulmonary embolism', 'low molecular weight heparin', 'unfractionated heparin', 'venous thromboembolic disease', and 'thromboembolism'. The reference lists of the identified articles were then manually checked for any additional publications. Enquiries about any relevant studies that were not yet published, or pending publication were made through personal contact.

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

Specific interventions included in the review
Low molecular weight heparin (LMWH) (CY 222, nadroparin, tinzaparinn, enoxaparin, dalteparin, and reviparin) compared with unfractionated heparin. The initial treatment lasted for a period of 5-10 days and was followed by oral anticoagulants for at least 3 months. Studies were excluded if the low molecular weight heparin dose was adjusted or administered intravenously, or if the unfractionated heparin dose was not adjusted.

Participants included in the review
Patients with a confirmed venous thromboembolism and/or pulmonary embolism. Studies of patients where venous thromboembolism was not confirmed were excluded from the review.

Outcomes assessed in the review
Three-month incidence of recurrent thromboembolism, mortality, and 14-day incidence of major bleeding complications. Studies were excluded when outcome event assessment was incomplete or unclear.

How were decisions on the relevance of primary studies made?
Potential studies were evaluated by two investigators, using a structured evaluation form.

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

Data extraction
Two investigators extracted the data. Data were extracted on: method of randomisation, patient eligibility and diagnosis of index venous thromboembolism (clinical or confirmed), medication regimes, outcome events criteria and assessment procedures, and availability of complete data.
Methods of synthesis

How were the studies combined?
The odds ratio (OR) and 95% confidence intervals (95% CI) were calculated separately for each study and then pooled across studies to estimate a summary OR and 95% CI using the Mantel-Haenszel method. To evaluate the effect of the proportion of patients with cancer on the incidence of outcome events and on estimated treatment effect, linear regression was used.

How were differences between studies investigated?
Meta-regression was used to investigate possible sources of heterogeneity.

Results of the review

Thirteen trials with a total of 4509 participants (3333 with DVT and 1176 with DVT and/or pulmonary embolism). The outcome of 3-month recurrent venous thromboembolism was evaluated in 4019 participants, the outcome of major bleeding during initial treatment was evaluated in 4506 participants, and the outcome of 3 month mortality was evaluated in 3815 participants.

Low molecular weight heparin has been extensively investigated in patients with deep vein thrombosis, but few trials have included patients with pulmonary embolism. The risk of recurrence of venous thromboembolism (odds ratio, 0.77; 95% CI, 0.56-1.04), major bleeding (odds ratio, 0.60; 95% CI, 0.38-0.95), and mortality (odds ratio, 0.72; 95% CI, 0.55-0.96) was less with low molecular weight heparins compared with unfractionated heparin. The proportion of cancer patients in these studies had a statistically significant effect on the incidence of recurrent venous thromboembolism (P = 0.03) and mortality (P = 0.002), but no influence on the estimated treatment effects of low molecular weight heparins.

Authors’ conclusions

Low molecular weight heparin is effective and safe in the initial treatment of venous thromboembolism. The results of trials involving more than 400 patients justify the use of fixed-dose subcutaneous low molecular heparins in the initial treatment of venous thromboembolism. However, caution should be taken in patients with pulmonary embolism, because it is as yet not possible to arrive at a definitive conclusion with the available evidence.

CRD commentary

This was a clear and well-written review that addressed an important clinical question. The search strategy was adequate, but no systematic attempt was made to identify unpublished studies although authors were contacted for 'not yet published studies'; the possibility of publication bias cannot, therefore, be ruled out. Furthermore, the authors did not state if there were any language restrictions. The validity of the trials was not assessed but only randomised trials were included; lesser quality trials were excluded. The authors’ conclusions on the effectiveness of the treatments appear to follow on from the results of the included studies. However, they make a judgement about safety of the treatment, which was not assessed in the review.

Implications of the review for practice and research

Practice: The authors state that the results of trials involving more than 400 patients justify the use of fixed-dose subcutaneous low molecular heparins in the initial treatment of venous thromboembolism. However, caution should be taken in patients with pulmonary embolism, because it is as yet not possible to arrive at a definitive conclusion with the available evidence.

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

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.