The treatment of venous thromboembolism with low-molecular-weight heparins: a meta-analysis

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CRD summary
The review found that low molecular weight heparins were safer and as effective as vitamin K antagonists, for venous thromboembolism, for the general population and for cancer patients. The authors' conclusions reflected the evidence presented, but limitations in the review process and reporting, and the low quality of the included trials, mean that their reliability is unclear.

Authors' objectives
To compare the efficacy and safety of low molecular weight heparins with vitamin K antagonists, for venous thromboembolism, in the general population, in pregnant women, and in patients with cancer.

Searching
Searches were made in January 2008, in MEDLINE, EMBASE, BioMed Central, The Cochrane Library, and databases of health technology assessments, clinical guidelines, and government reviews. No search terms were reported. Contact was made with experts in the field, consultant angiologists, and pharmaceutical companies. Grey literature was sought, but no further details were given. The reference lists of included studies and relevant systematic reviews were searched. Language restrictions were not reported.

Study selection
Clinical studies that compared low molecular weight heparins with vitamin K antagonists were eligible for inclusion if they included patients who had experienced at least one episode of venous thromboembolism. No outcome inclusion criteria were stipulated. It seems that only randomised controlled trials (RCTs) were eligible.

The included trials were of six low molecular weight heparins: enoxaparin, dalteparin, tinzaparin, bemiparin, nadroparin, and reviparin; dosages were reported. The vitamin K antagonists were: warfarin, acenocoumarol or coumarin. Treatment duration was usually three or six months. Initial treatment was one of unfractionated heparin or the low molecular weight heparin studied. The percentage time in therapeutic range, where stated, ranged from 41 to 67.2. Few trials reported the percentage of patients on target. The outcomes were deep vein thrombosis, pulmonary embolism, symptomatic recurrent venous thromboembolism, vein re-canalisation, thrombocytopaenia with or without heparin cause, complications from thrombocytopaenia, bleeding (major or minor), bone fractures, other osteoporotic complications, all osteoporotic complications, and deaths. The definitions of these appear to have been those used in the individual trials.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The Jadad scale (score range zero to five) was used to assess trial quality. Only trials with a score of two or more were included in the analyses. The authors did not state how many reviewers assessed quality.

Data extraction
Data were extracted to calculate odds ratios and 95% confidence intervals, for the reported outcomes, for the duration of treatment and for the duration of treatment and follow-up. Where reported, intention-to-treat results were used. If a trial compared different doses, the results were pooled. Where two publications of one trial were identified, the one with the larger number of patients was included. Where two publications referred to different time periods, the one with the longer follow-up was included, if it was clearly defined, if not, the publication for the treatment period only was included.

Trials were separated into preventative or therapeutic, based on the dose of the low molecular weight heparin; the cut-off was not stated. Where major and minor bleeding were reported separately and it was certain that the patients did not
overlap, total bleeding was calculated, and similarly for deep vein thrombosis and pulmonary embolism, recurrent venous thromboembolism was calculated.

The authors did not state how many reviewers extracted the data.

**Methods of synthesis**

Pooled odds ratios with 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effect meta-analysis. Heterogeneity was assessed using $X^2$ and $I^2$, and investigated in subgroup analyses for cancer or non-cancer patients. Meta-regression was used to analyse the effect of the dose of the low molecular weight heparin on the results.

**Results of the review**

The review included 17 trials, with 3,983 participants (range 40 to 737). All scored either two or three on the Jadad scale. Follow-up ranged from zero to nine months.

The risk of deep vein thrombosis was significantly lower with low molecular weight heparin compared with vitamin K antagonists, both during the treatment period (OR 0.51, 95% CI 0.36 to 0.73) and during treatment and follow-up (OR 0.67, 95% CI 0.50 to 0.89; 14 trials). There was little evidence of statistical heterogeneity. The risk of venous thromboembolism was significantly lower with low molecular weight heparin during treatment (OR 0.62, 95% CI 0.46 to 0.83) and during treatment and follow-up (OR 0.75, 95% CI 0.59 to 0.97; 13 trials), with minor to moderate statistical heterogeneity.

The risk of bleeding was significantly lower with low molecular weight heparin during treatment (OR 0.56, 95% CI 0.43 to 0.71; 11 trials) and during treatment and follow-up (OR 0.59, 95% CI 0.47 to 0.74; 13 trials). There was moderate statistical heterogeneity for the latter analysis. The risk of minor bleeding was significantly lower with low molecular weight heparin during treatment (OR 0.56, 95% CI 0.43 to 0.73; 12 trials) and during treatment and follow-up (OR 0.61, 95% CI 0.48 to 0.79; 14 trials), with moderate statistical heterogeneity.

Subgroup analyses showed similar patterns of effect for cancer and non-cancer patients for most outcomes. For recurrent venous thromboembolism, the effect of low molecular weight heparin was stronger in patients with cancer than in those without, whereas the reverse was found for minor and total bleeding. Meta-regression showed few differences in outcomes between the different low molecular weight heparin doses, other than for bleeding within the treatment period, where a higher risk of bleeding was seen for patients receiving a higher dose.

**Authors’ conclusions**

Low molecular weight heparins were safer and as effective as vitamin K antagonists, for the general population and for cancer patients, but their costs should be considered.

**CRD commentary**

The review addressed a clear question. The search covered many published and unpublished sources. Publication bias was not assessed and search terms were not reported, making it impossible to assess the efficacy of the search. It was unclear whether the results could have been affected by language bias and it was unclear whether sufficient attempts were made to reduce error and bias in the review process. The authors did not discuss the effects of trial quality on the results; one study was excluded due to low quality.

The meta-analysis was appropriate, but it was not clear why a random-effects model was not used where there was heterogeneity. The decision to combine different doses was unusual, and seems to have been unnecessary, as no trials separated them. The authors noted that low molecular weight heparin use was more common in pregnant women, but in the meta-regression the proportion of the non-cancer patients who were pregnant was unclear. The authors noted that there were 56 comparisons in their primary meta-analysis, and these were repeated for the subgroup analyses and meta-regression. The likelihood that some results arose by chance, due to multiple testing, was not discussed.

The authors’ conclusions reflected the evidence presented, but limitations in the review process and reporting, and the low quality of the included trials, mean that their reliability is unclear.

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

**Practice:** The authors did not state any implications for practice.
Research: The authors stated that a cost-effectiveness analysis was needed to decide whether guidelines for the treatment of venous thromboembolism should be modified.

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