Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials

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CRD summary
This review reported that fixed-dose low molecular weight heparin appeared to be as effective and safe as dose-adjusted intravenous unfractionated heparin for the initial treatment of nonmassive pulmonary embolism. The authors also found no differences between the treatments in major and minor bleeding, and all-cause mortality. The review was well conducted and the findings are likely to be reliable.

Authors' objectives
To compare the efficacy and safety of fixed-dose subcutaneous low molecular weight heparin (LMWH) with that of dose-adjusted intravenous unfractionated heparin (UFH) to treat acute pulmonary embolism (PE).

Searching
MEDLINE, EMBASE and the Cochrane Library were searched (up to August 2003) using the search terms listed in the review. The reference lists of studies were checked for additional studies. Abstracts from major international meetings were reviewed and manufacturers of LMWHs were contacted for unpublished studies.

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

Specific interventions included in the review
Studies comparing fixed-dose LMWH with dose-adjusted intravenous UFH were eligible for inclusion. The LMWH preparations included were certoparin, dalteparin, enoxaparin, nadroparin, reviparin and tinzaparin.

Participants included in the review
Studies of patients objectively diagnosed with symptomatic PE or asymptomatic PE in the context of symptomatic deep venous thrombosis were eligible for inclusion. The mean age of the included patients ranged from 56 to 72 years.

Outcomes assessed in the review
Studies that used objective methods to assess one or more clinical outcomes were eligible for inclusion. Studies assessing a primary outcome of recurrent symptomatic venous thromboembolism (VTE), including deep venous thrombosis and PE, at the end of treatment were eligible. Secondary outcomes eligible for inclusion were recurrent symptomatic VTE at 3 months, all-cause mortality, and major and minor bleeding.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion, and any disagreements were resolved by discussion.

Assessment of study quality
The studies were assessed for quality using the criteria of Schultz et al. (see Other Publications of Related Interest). The criteria considered the following: proper generation of treatment allocation sequence; proper concealment of the allocation sequence; blinding of the patient and the investigator (who assessed the clinical outcomes) to treatment allocation; and the completeness of follow-up. Two reviewers independently assessed the studies for quality.

Data extraction
Two reviewers independently extracted details of the studies. Data on the occurrence of each outcome at the end of treatment and at 3 months were extracted from the individual studies and used to calculate odds ratios (ORs). The data extracted for each trial were confirmed by reviewer consensus, then sent to the study author for verification and to request any missing data.

Methods of synthesis

How were the studies combined?
The studies were combined in a meta-analysis, using a Mantel-Haenszel fixed-effect model to derive a pooled OR and 95% confidence interval (CI). The studies were also discussed in a narrative synthesis.

Publication bias was assessed using an inverted funnel plot of treatment effect versus study precision in studies investigating the primary outcome.

How were differences between studies investigated?
The Mantel-Haenszel method was used to assess heterogeneity. Sensitivity analyses were conducted to examine the effect of removing lower quality studies from the analysis, and a comparison was made between the results obtained when using fixed-effect and random-effects models.

Results of the review

Twelve RCTs (n=1,951) were included.

All of the studies used proper methods to generate the randomised treatment allocation, and appeared to adequately conceal treatment allocation. One of the 12 studies blinded both the patients and investigators to treatment allocation. Five studies had 100% clinical follow-up, while 7 studies had 90% or greater follow-up. Further information on the quality of the included studies is available on the Annals of Internal Medicine website (accessed 07/07/2005). See Web Address at end of abstract.

Symptomatic VTE at the end of heparin treatment.

There was no significant difference between symptomatic events with LMWH compared with UFH (1.4% versus 2.4%; OR 0.63, 95% CI: 0.33, 1.18); there was no evidence of statistical heterogeneity. There was no significant difference between LMWH and UFH in patients presenting with symptomatic PE (1.7% versus 2.3%; OR 0.72, 95% CI: 0.35, 1.48) and patients presenting with asymptomatic PE in the context of symptomatic deep venous thrombosis (1.2% versus 3.2%; OR 0.53, 95% CI: 0.15, 1.88).

Symptomatic VTE at 3 months.

There was no significant difference in symptomatic events with LMWH compared with UFH (3.0% versus 4.4%; OR 0.68, 95% CI: 0.42, 1.09); there was no evidence of statistical heterogeneity. There was no significant difference between LMWH and UFH in patients presenting with symptomatic PE (3.3% versus 4.3%; OR 0.72, 95% CI: 0.4, 1.28) and patients presenting with asymptomatic PE in the context of symptomatic deep venous thrombosis (3.5% versus 3.8%; OR 1.07, 95% CI: 0.4, 2.91).

All-cause mortality.

There was no significant difference in the rate of all-cause mortality between patients receiving LMWH and those receiving UFH, either at the end of treatment (1.4% versus 1.2%; OR 1.20, 95% CI: 0.59, 2.45) or at 3 months (4.7% versus 6.1%; OR 0.77, 95% CI: 0.52, 1.15).

Bleeding.

There was no significant difference between patients receiving LMWH and those receiving UFH in the incidence of major bleeding (1.4% versus 2.3%; OR 0.67, 95% CI: 0.36, 1.27) or minor bleeding (6.8% versus 5.5%; OR 1.08, 95% CI: 0.73, 1.59). There was no evidence of statistical heterogeneity in either analysis.
Different LMWH preparations.

There was no evidence of differences in the efficacy or safety outcomes between different LMWH preparations (data not shown).

The primary outcome did not differ with the removal of individual studies, nor with the removal of low-quality studies (studies with incomplete follow-up). There were no important differences in the results of the fixed-effect analysis compared with the random-effects analysis.

The funnel plot was reported to show no evidence of publication bias (plot not shown).

**Authors’ conclusions**

Fixed-dose LMWH treatment appeared to be as effective and safe as dose-adjusted intravenous UFH for the initial treatment of nonmassive PE.

**CRD commentary**

The review question was well-defined with specific inclusion criteria for the intervention, participants, outcomes and study design. Several databases were searched and the authors attempted to identify unpublished studies. No evidence of publication bias was reported. It was unclear whether the authors included non-English language papers, therefore it was not possible to assess language bias. The study selection, data extraction and quality assessment processes were carried out in duplicate, thus minimising the possibility of selection bias and reviewer error. The studies appear to have been sensibly combined in meta-analyses, and the sensitivity analyses seemed appropriate. The authors’ findings are likely to be reliable.

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

The authors did not state any implications for practice or further research.

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**Other publications of related interest**


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Record Status
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.