For the initial treatment of venous thromboembolism: are all low-molecular-weight heparin compounds the same?

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Authors' objectives
To compare the efficacy and safety of different low molecular weight heparin (LMWH) compounds in the initial treatment of patients with venous thromboembolism (VTE).

Searching
EMBASE, MEDLINE, and Current Contents were searched. Authors of studies published only in abstract form were contacted, and references in recently published meta-analyses were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Dose-finding studies, duplicate publications, and publications from which it was not possible to extract clinical data were excluded.

Specific interventions included in the review
Comparisons of dose-adjusted unfractionated heparin (UFH; either subcutaneous or intravenous) and fixed-dose subcutaneous LMWH were eligible. Non-therapeutic doses of either UFH or LMWH were excluded. The initial treatment lasted 5 to 10 days and the treatment was continued for at least 3 months with vitamin K antagonists. The following types of LMWH were included: CY 222 (one study), nadroparin (4 studies), tinzaparin (2 studies), enoxaparin (3 studies), dalteparin (3 studies), reviparin (2 studies), and certoparin (1 study). The molecular weight of the heparins ranged from 3,800 to 5,000. The anti-factor Xa (a-Xa) activity ranged from 87.5 to 200 units/kg, and the a-Xa to a-IIa ratio ranged from 1.9 to 5.0.

Participants included in the review
VTE. Studies including patients with objectively confirmed VTE, i.e. deep venous thrombosis and/or pulmonary embolism, were eligible.

Outcomes assessed in the review
Studies that assessed at least one of the following major outcomes were eligible: rate of symptomatic and objectively confirmed recurrent VTE during 3 months of follow-up; rate of major haemorrhage during the initial treatment period; and mortality rate in the first 3 months after the initial episode of VTE.

How were decisions on the relevance of primary studies made?
Two independent reviewers assessed the identified studies according to the inclusion criteria. Any discrepancies were resolved by consensus.

Assessment of study quality
No formal assessment of validity was undertaken. The included studies were restricted to RCTs.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The following information were tabulated in the review: the author and year of publication; the number of patients; a-Xa dose; frequency of administration; type of LMWH; molecular weight; and a-XA to a-IIa ratio. The odds ratio (OR) and 95% confidence interval (CI) were calculated for each study for the efficacy and safety outcomes.
Methods of synthesis

How were the studies combined?
The Peto method was used to calculate a pooled OR and 95% CI for those outcomes that were reported in a sufficient number of studies with adequate methodology and similar design.

How were differences between studies investigated?
A meta-regression was used to find differences in the results between different LMWH compounds. Linear regression, with weighting by the inverse of the variance, was used to explore the influence of the following variables on the observed treatment effect: the incidence of the outcome; the percentage of patients with cancer; the type of LMWH; and year of publication (using 1996 as a cut-off). The relationship between the efficacy and safety of the various LMWH preparations was examined by plotting the log OR of bleeding and recurrent VTE.

Results of the review

Sixteen RCTs (6,055 patients) were included.

Efficacy (13 RCTs, 5,568 patients).

Recurrent VTE was significantly less common in patients treated with LMWH, compared with UFH; the OR was 0.66 (95% CI: 0.51, 0.86). A high absolute VTE recurrence rate in the UFH group (range: 0.0 to 8.2%) was associated with a higher relative efficacy of the LMWH compound (p=0.007). The relationship was stronger after adjusting for the proportion of patients with cancer (p=0.001). The year of publication and a diagnosis of deep venous thrombosis or pulmonary embolism did not influence this relationship.

Safety (16 RCTs, 6,055 patients).

Major haemorrhage was significantly less common in patients treated with LMWH, compared with UFH; the pooled OR was 0.56 (95% CI: 0.38, 0.83). No relationship was found between the absolute percentage in UFH groups (range: 0.0 to 8.65%) and the safety of the LMWH groups (plot of log OR against absolute percentage of major bleeding in the UFH group: beta = -0.015, p=0.845). Corrections for the frequency of cancer or the year of publication did not change this finding.

Mortality (12 RCTs, 5,364 patients).

Mortality was significantly less common in patients treated with LMWH, compared with UFH; the pooled OR was 0.68 (95% CI: 0.53, 0.88). There was a non-statistically significant trend towards a smaller treatment effect with higher mortality in the UFH group (range: 1.4 to 10.6%; plot of log OR against absolute mortality in the UFH group: beta=0.06, p=0.132). Corrections for the proportion of patients with cancer in the various studies, or the year of publication, did not change this association.

Comparison of different LMWH compounds.

The studies involved 7 different LMWH preparations with most compounds being studied in only one trial. No studies directly compared different LMWH compounds. In view of this, the authors stated that the interpretation of analyses comparing compounds was difficult.

Dalteparin (3 RCTs) appeared to be significantly less effective than other LMWH compounds (plot of log OR against absolute percentage of recurrent VTE in the UFH group: beta=0.730, p=0.30).

Dalteparin (3 RCTs) appeared to be significantly less likely to be associated with major haemorrhage than other LMWH compounds (plot of log OR against absolute percentage of recurrent VTE in the UFH group: beta = -0.592, p=0.008.

Authors' conclusions
There appeared to be some variation in efficacy and safety among the currently available LMWH heparin preparations.

**CRD commentary**

The aims were stated and the inclusion criteria were defined in terms of the study design, participants, intervention and outcome. Several relevant sources of literature were searched and the methods used to select the studies were described. The lack of an attempt to locate unpublished material raises the possibility of publication bias. In addition, keywords used in the search were not reported, and it was not stated whether any language restrictions were applied. The included studies were restricted to RCTs but no formal validity assessment was undertaken. Some relevant data were extracted but the methods used to extract the data were not described. The data were pooled in a meta-analysis, and the influence of several variables on the results was examined using a variety of statistical techniques. The influence of study validity, or the definition of outcomes used in the individual studies, on the results was not investigated.

The evidence presented appears to support the authors’ conclusions, though it must be remembered that these conclusions were based on indirect comparisons.

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

Practice: The authors state that findings suggest that both the safety and efficacy for LMWH compounds appears to be better than standard treatment with UFH, but the limited number of studies does not allow firm conclusions to be drawn about clinically relevant differences between LMWH.

Research: The authors suggest that LMWH compounds could be compared by using statistical techniques similar to those used in the review on the larger database of prophylactic studies, or studies conducted in the setting of acute coronary syndrome.

**Bibliographic details**

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