Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis: meta-analysis based on original patient data

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Authors' objectives
To compare the efficacy and safety of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) for thrombosis prophylaxis after general and orthopaedic surgery.

Searching
A collaborative trialists group (Heparin Meta-analysis Trialist Group), which contained representatives of study groups and pharmaceutical companies, was formed to undertake the review. Eligible studies were those included in a previous meta-analysis of summary data (see Other Publications of Related Interest). The original studies were located by searching MEDLINE (from January 1988 to March 1996) and EMBASE (from January 1990 to March 1996). The search was restricted to studies published in English, French, German, Italian or Spanish. The search terms were reported. The reference lists of retrieved articles were also searched, and pharmaceutical companies were contacted in an attempt to locate unpublished clinical trials.

Study selection
Study designs of evaluations included in the review
Individual patient data (IPD) from randomised double-blind trials were included in the review.

Specific interventions included in the review
Studies of LMWH compared with UFH in the prevention of post-operative thrombosis were eligible for inclusion. The heparins included in the review were fragmin (dose range: 2,500 to 7,500 anti-Xa international units, IU), embolex (3,100 anti-Xa IU), mono-embolex (3,000 or 3,100 anti-Xa IU), clivarin (1,750 or 2,500 anti-Xa IU), logiparin (2,500 or 3,500 anti-Xa IU), fraxiparin (4,700 anti-Xa IU) and enoxaparin (2,000 anti-Xa IU). Studies where dihydroergotamine was used were included if dihydroergotamine was given to both treatment groups. Studies investigating the heperinoid Organon were excluded.

Participants included in the review
Studies in patients undergoing orthopaedic and general surgery were eligible for inclusion. General surgery included gynaecological, urological and cancer operations.

Outcomes assessed in the review
The primary outcomes were the occurrence of deep vein thrombosis (DVT) and wound haematoma. The secondary outcomes included the occurrence of distal and proximal DVTs, pulmonary embolism, and intra- and post-operative bleeding and death.

How were decisions on the relevance of primary studies made?
The studies were those used in a previous meta-analysis of summary data for which IPD could be obtained.

Assessment of study quality
The authors stated that the consistency of information provided with the original trial protocol, case record forms, the publication and, where available, the original analysis report, was checked. No further details were given. The authors did not state explicitly how judgments of validity were made.

Data extraction
The authors contacted the principal investigators of the studies and requested the full, original datasets. The data
collected included: type of surgery; LMWH product and dose; age; gender; number of smokers; presence of malignancy, cardiac or respiratory disease; previous thromboembolic event; varicose veins or ulcer; previous anticoagulant treatment; and previous leg fracture. If the results of more than one diagnostic test for DVT were available, the results of the method regarded as most reliable were used. Studies undertaken on general surgical patients were divided into those using low-dose (3,400 anti-Xa IU or less) and high-dose (more than 3,400 anti-Xa IU) LMWH.

**Methods of synthesis**

**How were the studies combined?**

The authors undertook a meta-analysis (Mantel-Haenszel estimates of odds ratios, ORs, and 95% confidence intervals, CIs) using intention-to-treat analysis. A fixed-effect analysis was undertaken with all studies combined and for three subgroups: orthopaedic surgery, and high-dose and low-dose LMWH in general surgery. A random-effects analysis (a more conservative analysis giving wider CIs than the fixed-effect approach) was also carried out for the primary outcomes; the results were compared with those of the fixed-effect analysis.

**How were differences between studies investigated?**

The authors investigated statistical heterogeneity using the Breslow-Day test. Further subgroup analyses of the low-dose LMWH studies in general surgery were conducted to investigate the effect of age, gender, smoking, malignancy, cardiac or respiratory disease, previous thrombosis, varicose veins/ulcer, previous anticoagulant treatment, and previous leg fracture. This was restricted to LMWH, as the number of studies was sufficient and heterogeneity was greater than the other subgroups.

**Results of the review**

IPD from 23 of the 36 eligible studies were obtained and included (n=12,919): 18 involved general surgery (n=12,058) and 5 orthopaedic surgery (n=861).

There were no statistically-significant differences in the proportion of DVTs between LMWH and UFH when all studies were pooled, or in any of the surgical subgroups: OR 0.86 (95% CI: 0.62, 1.19) for orthopaedic surgery, 1.01 (95% CI: 0.83, 1.24) for general surgery (all doses), 1.12 (95% CI: 0.89, 1.41) for general surgery (low-dose LMWH), and 0.81 (95% CI 0.56, 1.18) for general surgery (high-dose LMWH).

There were no statistically-significant differences in the proportion of wound haematoma between LMWH and UFH in orthopaedic surgery (OR 0.86, 95% CI: 0.59, 1.25) or general surgery (all doses, OR 0.89, 95% CI: 0.75, 1.05). When the high- and low-dose LMWH studies in general surgery were analysed separately, compared with UFH, a statistically-significant reduction in wound haematoma was shown among patients given the low-dose LMWH (OR 0.74, 95% CI: 0.61, 0.90, P=0.002); among those given the high- dose LMWH, the rate of wound haematoma was significantly greater (OR 1.82, 95% CI 1.26, 2.63, P=0.001). Thirteen studies were included in the low-dose LMWH analysis (n=9,842), and six in the high-dose LMWH analysis (n=2,645). When a random-effects analysis was used, the superiority of low-dose LMWH was no longer statistically significant (OR 0.81, 95% CI: 0.60, 1.09).

Among the secondary outcomes, across all studies, there were fewer proximal DVTs (OR 0.71, 95% CI: 0.50,1.00) in patients receiving the LMWH, with this just reaching statistical significance (P=0.05). Pulmonary embolism was also statistically significantly reduced with LMWH (OR 0.66, 95% CI: 0.45, 0.97, P=0.03). No statistically-significant difference was demonstrated between LMWH and UFH for death or bleeding.

Of the eleven factors investigated in the subgroup of low-dose LMWH in general surgery studies, only previous varicose veins or ulcers was shown to influence the efficacy of LMWH. Patients who had prior varicose veins or ulcers had a statistically significantly higher incidence of DVT with LMWH than UFH (OR 1.44, 95% CI: 1.03, 2.03, P=0.05).

**Authors' conclusions**

The authors concluded that there is no general superiority of LMWH over UFH. The efficacy of LMWH is significantly better in orthopaedic surgery when proximal DVT is used as the end point, whereas there is a trend for increased efficacy of LMWH when pulmonary embolism is used as the end point. LMWHs may increase bleeding.
complications without increased efficacy in general surgery.

CRD commentary
This study was an analysis of IPD from studies included in a previous meta-analysis of summary data (see Other Publications of Related Interest). The authors were only able to obtain IPD for 23 of the original 36 trials, and although the most recent study included in the previous meta-analysis was published in 1996, the search for relevant trials was not updated for the IPD analysis. As a meta-analysis of IPD, this review lacked methodological rigor. The reliability of the conclusions is therefore uncertain.

Implications of the review for practice and research
Practice: The authors did not specifically state any implications for practice. However, they highlighted the greater efficacy of LMWHs in orthopaedic surgery.

Research: The authors stated that proximal DVT and pulmonary embolism may be more appropriate end points than distal DVT when investigating the efficacy of heparin compounds. They also recommended that new studies should be designed with a population defined by an appropriate risk profile, instead of division according to general and orthopaedic surgery.

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