Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery

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Authors' objectives
The authors' objectives were three-fold.

1. To verify the clinical effect of low molecular weight heparin (LMWH) in comparison with placebo, no treatment or unfractionated heparin (UFH), in patients undergoing general surgery.

2. To evaluate the clinical effect in cancer surgery patients.

3. To assess the efficacy and safety of low and high prophylactic doses of LMWH in patients undergoing general surgery.

Searching
MEDLINE and Current Contents were searched using the following search terms: 'general surgery', 'abdominal surgery', 'cancer surgery', 'heparin', 'low molecular weight heparin', 'postoperative complications', 'prophylaxis', 'controlled trial', 'randomized trial', 'venous thromboembolism', 'deep vein thrombosis', 'pulmonary embolism' and 'mortality'. Abstracts of meetings were searched and the reference lists of reviews, studies and previous meta-analyses were also examined. The methods for dealing with duplicate reports were detailed in the review. Studies published in any language were considered.

Study selection
Study designs of evaluations included in the review
Open-label, single- or double-blind randomised controlled studies evaluating a LMWH in terms of efficacy and/or safety were included. The studies had to use one of the outcomes listed to be included. Studies were excluded if they were not randomised or clearly stated as such, or they were conducted according to a 'play-the-winner' design. Dose-ranging studies without a control group were also excluded.

Specific interventions included in the review
The review included trials that compared LMWH with any other prophylactic treatment in patients undergoing general surgery. Only studies with a control group, (untreated, placebo, or UFH) were included. Studies that included dihydroergotamine or elastic stockings were eligible, whereas those involving heparinoids were excluded.

The following interventions were used.

LMWH compared with placebo or no treatment. The LMWH included the following drugs (doses specified in anti-Xa units): enoxaparin (4,000 and 6,000), parnaparin (3,200), dalteparin (2,500), nadroparin (2,850), and tinzaparin (3,500).

LMWH compared with UFH. The LMWH included the following drugs (doses in anti-Xa units unless stated otherwise): certoparin (2,500 with dihydroergotamine), certoparin (3,000 with or without dihydroergotamine, twice daily), semi-synthetic heparin analogue (37.5 and 50 mg), nadroparin (2,850), dalteparin (2,500, 5,000 and 7,500), enoxaparin (2,000, 4,000, 5,000 and 6,000), parnaparin (3,200 and 6,400), reviparin (1,750), ardiparin (50 and 90 units/kg, twice daily), antixarin (2,500), bemiparin (2,500), and tinzaparin (2,500 and 3,500). UFH was administered in doses of 5,000, 10,000 or 15,000 units, with or without dihydroergotamine.

Participants included in the review
The included patients were those undergoing general surgery or cancer surgery. General surgery was defined as abdomino-thoracic (excluding vascular surgery), urological and gynaecological surgery. Studies were excluded if they were conducted in patients undergoing orthopaedic surgery, non-cancer thoracic surgery, extra-corporeal circulation...
surgery or non-cancer laparoscopic surgery.

Outcomes assessed in the review
The primary end point was the incidence of deep vein thrombosis (DVT). This was detected systematically by ultrasonography, the fibrinogen uptake test, impedance plethysmography, thermography or venography at the end of the treatment period, or earlier in cases of clinical suspicion. Positive results from impedance plethysmography or thermography had to be confirmed by venography.

The secondary end points were:
- the incidence of pulmonary embolism (PE), both fatal and non-fatal;
- symptomatic venous thromboembolism (VTE), including DVT and/or PE;
- death;
- major haemorrhage, wound haematoma and other haemorrhage, but excluding haematoma at the injection site; and
- the percentage of patients requiring post-operative transfusion, or if unavailable, the percentage of patients requiring transfusion irrespective of when it was used.

The definitions of each of these end points were clearly given in the review. These were used if there was no clear definition in the primary study. If possible, the authors’ definitions from the primary studies were used.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection. However, they did state that any discrepancies were resolved by three reviewers at a concordance meeting, thus suggesting that three reviewers selected the studies.

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

Data extraction
Data from the primary studies were extracted independently by three reviewers. Any discrepancies were resolved by three reviewers at a concordance meeting.

The following data were extracted: name of the author or study acronym; year of publication; the number of patients randomised; indication for surgery, (general, abdominal, gynaecological or cancer); the percentage of patients undergoing surgery for cancer, and if there was any stratification of cancer patients; the type, dose and duration of the treatment regimen; whether the treatment was administered before or after the operation; the study design (open-label, single- or double-blind); the type of anaesthesia (general or regional); the method used to detect DVT; the outcomes assessed and at which time point; and the duration of follow-up.

Methods of synthesis
How were the studies combined?
The results were summarised on an intention to treat basis for each end point. The studies were combined for each end point and comparison (i.e. LMWH versus placebo or no treatment and LMWH versus UFH) using a variety of methods. These included the logarithm of the relative risk (RR), the logarithm of the odds ratio, and the methods of Mantel-Haenszel, Cochran and Peto (see Other Publications of Related Interest). The authors stated that since all the methods gave similar results, only the logarithms of the RR results were presented.

How were differences between studies investigated?
Heterogeneity tests were conducted for each meta-analysis, using a P-value of less than or equal to 0.10 to indicate...
statistical significance. The authors stated that in the absence of a clear explanation for heterogeneity, a random-effects model was planned. This implies that in all other cases, a fixed-effect model was used. Two sensitivity analyses were performed: one according to whether or not dihydroergotamine was used in combination with LMWH, the other according to the UFH dose (5,000 units, two versus three times daily).

Subgroup analyses were performed for the following: studies that were identified as double-blind trials; studies of cancer surgery (greater than 90% of the patients undergoing such surgery); studies of non-cancer surgery; and LMWH dose regimens of less than or equal to 3,400 anti-Xa units, and greater than 3,400 anti-Xa units.

Results of the review
LMWH versus placebo or no treatment: 8 studies including 5,520 patients. Of these, 6 were double-blind and 2 were open; the latter were conducted in cancer patients.

LMWH versus UFH: 51 studies including 48,624 patients, of which 33 studies were double-blind. Eight studies were conducted in cancer patients.

The authors also documented the number of studies according to the type of LMWH used and the dose of UFH.

LMWH versus placebo or no treatment: a reduction in the risk of DVT was seen in the LMWH group; the RR was 0.28 (95% confidence interval, CI: 0.14, 0.54, P<0.001). Similar reductions were seen for the clinical end points: the RR was 0.25 (95% CI: 0.08, 0.79, P=0.018) for PE and 0.29 (95% CI: 0.11, 0.73, P=0.009) for clinical VTE. There was a non significant reduction in the overall mortality rate (RR 0.54, 95% CI: 0.27, 1.10, P=0.09).

All side-effects were more common in the LMWH group. The RR was 2.03 (95% CI: 1.37, 3.01, P<0.001) for major haemorrhage, 2.06 (95% CI: 1.77, 2.39, P<0.001) for total haemorrhage, 1.88 (95% CI: 1.54, 2.28, P<0.001) for wound haematoma, and 1.53 (95% CI: 1.28, 1.82, P<0.001) for transfusion.

None of the tests for heterogeneity in this group reached statistical significance.

LMWH versus UFH: a non significant reduction in risk was seen in the LMWH group for asymptomatic DVT (RR 0.90, 95% CI: 0.79, 1.02, P=0.10). The RR was 0.88 (95% CI: 0.64, 1.20, P=0.41) for PE, 0.71 (95% CI: 0.51, 0.99, P=0.049) for clinical VTE, and 1.04 (95% CI: 0.89, 1.20, P=0.63) for overall mortality rate.

There were no differences between the two groups in terms of the side-effects studied. The RR was 0.89 (95% CI: 0.75, 1.05, P=0.16) for major haemorrhage, 0.92 (95% CI: 0.79, 1.07, P=0.27) for total haemorrhage, 0.89 (95% CI: 0.74, 1.07, P=0.21) for wound haematoma, and 1.03 (95% CI: 0.94, 1.12, P=0.54) for transfusion. The last three results were obtained from a random-effects model because there was heterogeneity between the studies, yet no clear explanation of why this heterogeneity was present.

The authors stated that the results were not modified when either the dihydroergotamine treatment or the UFH dose regimen were taken into account (results were not shown in the paper). When only double-blind studies were considered, the trends in favour of the efficacy and safety of LMWH over UFH disappeared. The efficacy and safety of LMWH relative to UFH were similar in patients with and without cancer, although the incidence of the efficacy and safety criteria were higher in patients undergoing cancer surgery than in other patients. Compared with UFH, low-dose LMWH achieved similar efficacy and was associated with a lower risk of haemorrhage. Conversely, high-dose LMWH was more effective than UFH, but the people treated with this were at a higher risk of haemorrhage.

Authors' conclusions
The prophylactic treatment of general surgery patients with LMWH, compared with placebo or no treatment, was associated with a reduction in the risk of DVT, clinical PE and clinical VTE. Despite an increase in major haemorrhage, treatment was also associated with a non significant reduction in mortality. Compared with UFH, the authors concluded that LMWH was at least as safe and effective. However, the superiority of LMWH over UFH is doubtful, since the efficacy and safety profiles of the two treatments were similar when only double-blind studies were considered. The authors also concluded that asymptomatic DVT may be regarded as a reliable surrogate end point for
clinical outcomes in studies investigating thrombo-prophylaxis in general surgery.

**CRD commentary**
This was a well-conducted review, which was reported clearly. The review question was clearly stated, and the inclusion criteria for the studies appeared valid. The search was fairly comprehensive, with no language restrictions. However, the search could have been improved by searching other sources, such as the Cochrane Library and EMBASE, as well as grey literature. Consequently, some relevant trials might have been missed. It appears from the paper that the validity of the papers was not assessed. However, the authors did examine differences between blinded and non-blinded studies. The generalisability may be restricted by the authors' definition of general surgery.

Details from the primary studies were tabulated, although these could have been improved by including the patients' age and gender. The methods used to pool the data were valid. A suitable investigation of heterogeneity between the studies, and the possible modifying effect of various attributes of the studies, was presented. The authors reported the RRs for each drug separately, and noted the limitations of pooling data from studies that used different treatment regimes. The results from the quantitative synthesis were clear and accessible, providing a useful answer to the posed research question.

Funding for the study came from Sanofi-Synthelabo. It was not indicated whether this company are involved in the manufacture of one or more of the drugs under study; if so, this represents a possible conflict of interest.

The conclusions reached by the authors, regarding the equivalence of LMWH and UFH in terms of the efficacy and safety, are supported by the data presented. The conclusions in terms of research (suitability of asymptomatic DVT as a surrogate outcome, and dosage of LMWH) are also appropriate.

**Implications of the review for practice and research**
Practice: The authors state that LMWH is at least as safe and effective as UFH.

Research: The authors state that asymptomatic DVT may be regarded as a reliable surrogate end point for clinical outcomes in studies investigating thrombo-prophylaxis in general surgery. Further research is required to determine the optimal dose regimen of LMWH in general surgery.

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