Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials
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Authors' objectives
To carry out a meta-analysis of randomised trials studying prophylactic unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for the prevention of venous thromboembolism in internal medicine (excluding myocardial infarction or ischaemic stroke).

Searching
MEDLINE and Current Contents were searched, although the dates and search terms were not reported. All the manufacturers of LMWH in France were contacted for published or unpublished trial data. The reference lists of retrieved material were also handsearched.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials were included in the review.

Specific interventions included in the review
Studies of prophylactic LMWH or UFH, compared with either each other or with a control, were eligible for inclusion. The eligible doses of UFH were 10,000 to 15,000 IU daily, given as two or three subcutaneous injections. For LMWH, the eligible dose was the stated prophylactic dose for each product.

The interventions reported in the review included nadroparin (3,075 to 6,150 IU/day), enoxaparin (2100 to 6,300 IU/day) and dalteparin (2,500 IU). The duration of the treatments ranged from 5 days to discharge of the patient. The maximum duration was 90 days. Studies of danaparoid sodium were excluded.

Participants included in the review
Studies of internal medicine patients confined to bed for at least 72 hours, but excluding those with myocardial infarction or stroke, were eligible for inclusion. The patients included in the review were categorised as having pulmonary infections and heart failure; infectious disease; chronic obstructive pulmonary disease; cardiopulmonary disease; or various illnesses including critical illness and elderly.

Outcomes assessed in the review
The primary outcome was the incidence of deep-vein thrombosis systematically detected at the end of treatment by an isotopic fibrinogen uptake test, venous ultrasonography, venography of the lower limbs or impedance phlethysmography. The incidence of early mortality (10 days to 3 months), clinical pulmonary embolism confirmed by lung-scan or necropsy, and major haemorrhage were also reported.

How were decisions on the relevance of primary studies made?
Two reviewers independently judged the studies for inclusion in the review, and any discrepancies were resolved by a third reviewer.

Assessment of study quality
Validity was not formally assessed.

Double-blind studies with a 'good' randomisation method were selected as a best-study group for the sensitivity analysis.
Data extraction
Two reviewers independently extracted data from the included studies, and any discrepancies were resolved by a third reviewer.

The method used to extract the data was not described. The extracted data included: drug and dose; treatment duration; basic diagnosis; the number of patients; if the study was double-blind; how deep-vein thrombosis was assessed; the number of events; the time point at which the risk of mortality was assessed; and if the study was included in the 'best-study subgroup'. The data were examined on an intention to treat basis.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to combine the studies. Separate analyses were performed for those comparing heparin with a control, and for those comparing either type of heparin with each other. The meta-analysis was performed using the relative risk (RR). The meta-analysis was performed separately for each of the different outcomes examined, and was presented graphically and in the narrative.

How were differences between studies investigated?
A sensitivity analysis, which was restricted to the 'best-study group', was performed. Differences between the studies were examined with a heterogeneity test, and a random-effects model was planned for the RR when there was evidence of heterogeneity.

Results of the review
A total of 17 studies were included. Sixteen studies were included in the main meta-analysis: 7 examining heparin versus control, and 9 comparing LMWH with UFH. A further study was considered as part of a separate analysis of heparin compared with control. Four studies examining heparin versus control and 6 comparing LMWH and UFH were included in an analysis restricted to 'best-study subgroup'. The 16 trials in the meta-analysis incorporated 19,764 patients: 15,095 patients in trials comparing heparin with control, and 4,669 patients in trials comparing LMWH and UFH.

Heparin (LMWH or UFH) versus control (n=7).

The pooled RR for deep-vein thrombosis was 0.44 (95% confidence interval, CI: 0.29, 0.64, p<0.001; heterogeneity p=0.31).

The pooled RR for clinical pulmonary embolism was 0.48 (95% CI: 0.34, 0.68, p<0.01; heterogeneity p=0.63).

The pooled RR for major bleeding was 1.87 (95% CI: 0.94, 3.75, p=0.08; heterogeneity p=0.53).

The pooled RR for death was 0.95 (95% CI: 0.84, 1.07, p=0.40; heterogeneity p=0.39).

The pooled risk estimates were reduced when the analysis was restricted to 4 studies in the 'best-study subgroup': the RR was 0.50 (95% CI: 0.33, 0.76) for deep-vein thrombosis, 0.57 (95% CI: 0.27, 1.20) for clinical pulmonary embolism, 1.20 (95% CI: 0.41, 3.56) for major bleeding, and 0.98 (95% CI: 0.79, 1.21) for death.

LMWH versus UFH (n=9).

The pooled RR for deep-vein thrombosis was 0.83 (95% CI: 0.56, 1.24, p=0.37; heterogeneity p=0.93).

The pooled RR for clinical pulmonary embolism was 0.74 (95% CI: 0.29, 1.88, p=0.52; heterogeneity p=0.84).

The pooled RR for major bleeding was 0.48 (95% CI: 0.23, 1.00, p=0.049; heterogeneity p=0.65).

The pooled RR for death was 1.07 (95% CI: 0.79, 1.45, p=0.66; heterogeneity p=0.47).
After restricting the analysis to 6 trials in the 'best-study subgroup', the pooled risk estimates were 0.87 (95% CI: 0.49, 1.59) for deep-vein thrombosis, 0.76 (95% CI: 0.27, 2.19) for clinical pulmonary embolism, 0.51 (95% CI: 0.23, 1.12) for major bleeding, and 1.26 (95% CI: 0.82, 1.93) for death.

**Authors’ conclusions**

Heparins are beneficial in the prevention of venous thromboembolism in internal medicine.

**CRD commentary**

The search for potential studies for the review was basic, and it is therefore possible that relevant studies were missed. The only attempt to identify unpublished data was through contact with manufacturers of heparin who were based in France. Thus, the results may be subject to publication bias. No information was provided about the search terms used and whether any date or language restrictions were applied. Two reviewers independently selected the studies for the review and abstracted the data.

Standard techniques were used to perform the meta-analysis. Validity was not formally assessed. However, all of the studies included in the review were randomised controlled trials, and the authors performed a sensitivity analysis which was restricted to those studies that were double-blind and appropriately randomised. Limited study details were reported; these would have benefited from further details of the patients, such as age and gender.

The authors’ conclusions are appropriate given the strength of the presented evidence, but should be interpreted with some degree of caution due to the limitations highlighted.

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

Practice: The authors state that prophylactic heparin treatment for internal medicine patients confined to bed for at least 72 hours may be effective in preventing venous thromboembolism. However, this cannot be generalised without taking into account the level of thrombotic risk to which the patient is exposed, as the number of major bleeding episodes is higher with heparin than in the absence of treatment.

Research: The authors state that prophylactic heparin treatment needs to be assessed to estimate the risk-benefit for different sub-populations of internal medicine patients, stratified according to their risk of deep-vein thrombosis.

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