Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that both unfractionated heparin and low-molecular weight heparin/heparinoid reduce the risk of venous thromboembolism in hospitalised medical patients; neither drug affects mortality. There were limitations to this review but, overall, the main conclusions appear to be supported by the results presented and are likely to be reliable.

Authors’ objectives
To compare the efficacy and safety of pharmacologic agents used for thromboprophylaxis in hospitalised medical patients.

Searching
MEDLINE (1950 to June 2006), EMBASE (1966 to June 2006) and the Cochrane CENTRAL Register (1800 to June 2006) were searched for papers published in English that were about humans; the search terms were reported. The reference lists of retrieved and relevant trials were handsearched.

Study selection
Study designs of evaluations included in the review
Prospective randomised controlled trials (RCTs) with at least 30 patients were eligible for inclusion. The included control groups were labelled as no heparin, placebo, or no prophylaxis.

Specific interventions included in the review
Studies were eligible for inclusion if they compared unfractionated heparin (UFH) or low molecular weight heparin/heparinoid (LMWH) with a control; LMWH with UFH; or a selective factor Xa inhibitor (SFI) with a placebo. The included drugs were heparin, heparin sodium and heparin calcium; enoxaparin, danaparoid sodium, dalteparin and nadroparin; fondaparinux. Drugs were administered one to three times daily at various doses, either intravenously or subcutaneously. The duration of treatment ranged from 2 to 28 days, or until the patient was mobile or discharged or a contraindication had occurred.

Participants included in the review
Studies of hospitalised medical patients were eligible for inclusion. Studies of surgical, trauma or critical care patients were excluded, as were studies of medical patients not analysed separately, studies of cancer patients with central venous catheters, and studies of patients admitted to intensive care units. The populations in the included studies were patients with myocardial infarction, stroke, heart failure and/or chest infection, severe respiratory disease or heart failure, infectious diseases, chronic obstructive pulmonary disease, and unspecified medical patients. The age of the included patients ranged from 18 to 85 years.

Outcomes assessed in the review
Studies that assessed deep venous thrombosis (DVT), pulmonary embolism (PE), mortality and total bleeding were eligible for inclusion. Additional outcomes in the included studies were major bleeding, minor bleeding, thrombocytopenia and injection site haematoma. Study definitions of outcomes were used, with the exception of those for total and major bleeding. For the review, total and major bleeding included intracerebral and intracranial haemorrhages, and haemorrhagic transformations. Total bleeding included major, minor and fatal bleeding episodes, but excluded subcutaneous injection site haematomas. The methods used to diagnose DVT and PE were reported. Mortality was defined mostly as the number of patients who died during a trial; otherwise, mortality included deaths during and after a trial, or was ill defined.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected studies in a standardised, unblinded manner. Questions regarding eligibility were resolved by conferring with two other reviewers.
Assessment of study quality
Two independent reviewers assessed the validity of the studies in a standardised, unblinded manner. Apart from double-blinding, it was not clear which validity criteria were used.

Data extraction
Two independent reviewers extracted the data in a standardised, unblinded manner. Questions regarding trial results were resolved by conferring with two other reviewers. With the exception of analyses involving DVT, totals were based on the number of participants who started treatment. For DVT, totals were based on the number who completed a trial. Bleeding outcomes were measured by tallying the number of patients who experienced bleeding or the number of episodes. At times, totals were computed by adding patients or episodes reported by subcategory. The number of events or participants who experienced an outcome was extracted per treatment group to estimate relative risks (RRs) and corresponding 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The review compared the following treatments: UFH versus control; LMWH versus control; LMWH versus UFH; prophylaxis (UFH, LMWH or fondaparinux) versus no prophylaxis; and SFI versus placebo. For all but the last subgroup (which comprised 1 study), pooled RR estimates and corresponding 95% CIs per outcome were obtained using Mantel-Haenszel fixed-effect models, and DerSimonian and Laird random-effects models. The studies were weighted according to treatment group size and number of observed events. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Statistical heterogeneity was investigated using chi-squared test statistics. Sensitivity analyses were conducted to assess the influence of each trial on pooled estimates of risk. Each trial was omitted in turn for analyses using fixed-effect and random-effects models. Studies comparing 5,000 units of UFH twice and three times daily were analysed separately. Study features were tabulated and discussed.

Results of the review
Thirty-six RCTs (approximate n=49,031) were included in the review.

Twenty-one RCTs were double blind. Asymmetric funnel plots of various risk estimates for prophylaxis versus no prophylaxis suggested publication bias.

The following results pertain to pooled estimates based on fixed-effect models.

UFH versus control (14 RCTs).
When compared with a control group, UFH significantly reduced the risk of DVT and PE: RR 0.33 (95% CI: 0.26, 0.42, p=0.001; 12 RCTs) and RR 0.64 (95% CI: 0.50, 0.82, p=0.001; 10 RCTs), respectively. UFH significantly increased the risk of total bleeding: RR 3.11 (95% CI: 2.44, 3.96, p=0.001; 5 RCTs). The difference in mortality was statistically non significant. A dose of 5,000 units of UFH given three times daily reduced the risk of DVT compared with 5,000 units of UFH given twice daily: RR 0.27 (95% CI: 0.20, 0.36, p=0.001; 4 RCTs) and RR 0.52 (95% CI: 0.28, 0.96, p=0.04; 3 RCTs), respectively. The heterogeneity of DVT risk estimates was statistically significant for UFH versus control (p=0.02) and for 5,000 units of UFH given twice daily versus control (p=0.02), but non significant for the other outcomes mentioned here.

LMWH versus control (11 RCTs).
When compared with a control group, LMWH significantly reduced the risk of DVT and PE: RR 0.56 (95% CI: 0.45, 0.70, p=0.001; 9 RCTs) and RR 0.37 (95% CI: 0.21, 0.64, p=0.001; 8 RCTs), respectively. LMWH significantly increased the risk of total bleeding: RR 1.51 (95% CI: 1.31, 1.74, p=0.001; 10 RCTs). The difference in mortality was statistically non significant. Heterogeneity was statistically non significant for DVT, PE, total bleeding and mortality.
LMWH versus UFH (10 RCTs).

When compared with UFH, LMWH significantly reduced the risk of DVT: RR 0.68 (95% CI: 0.52, 0.88, p=0.004; 9 RCTs). Differences in risk of PE, total bleeding and mortality were statistically non significant. Heterogeneity was statistically non significant for DVT, PE, total bleeding and mortality.

Prophylaxis versus no prophylaxis (22 RCTs).

Prophylaxis significantly reduced the risk of DVT and PE: RR 0.45 (95% CI: 0.39, 0.53, p=0.001; 22 RCTs) and RR 0.57 (95% CI: 0.45, 0.72, p=0.001; 19 RCTs), respectively. Prophylaxis significantly increased the risk of total bleeding: RR 1.90 (95% CI: 1.69, 2.14, p=0.001; 16 RCTs). The difference in mortality was statistically non significant. Heterogeneity was statistically significant for DVT (p=0.002) and total bleeding (p<0.001), but non significant for PE and mortality.

Further analyses were reported.

**Authors’ conclusions**

For hospitalised medical patients, both UFH and LMWH reduce the risk of venous thromboembolism; neither agent affects mortality. LMWH more effectively prevents DVT than UFH.

**CRD commentary**

The review question and inclusion criteria were clearly specified with respect to the participants, interventions, outcomes and study design. Some relevant databases were searched for articles published in English, which might have introduced language bias. No specific attempts were made to minimise publication bias; funnel plots suggested that publication bias might have been present for analyses comparing prophylaxis with no prophylaxis. Efforts were made to control reviewer error and bias during the study selection and data extraction processes. The authors stated that they assessed the validity of the included studies, but results of this assessment, other than for double-blinding, were not reported. If the quality of some of the studies was poor, the estimates of study-level treatment effects and subsequent meta-analyses may not be reliable.

The authors grouped the meta-analyses by treatment comparisons, possibly controlling for a source of heterogeneity. Statistical heterogeneity was observed in two of the subgroups. However, based on forest plots, the direction of treatment effects appeared to be generally consistent among studies. Influential trials were identified from the sensitivity analyses, but their features were not investigated. The conclusions regarding UFH dose (5,000 units given two or three times daily) may not be reliable because the comparisons were indirect, the number of trials was small, and statistical heterogeneity was present. There were limitations to this review but, overall, the main conclusions appear to be supported by the results presented and are likely to be reliable.

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

Practice: The authors stated that routine prophylactic anticoagulation is important in medical settings because it will reduce the occurrence of DVT and PE. In addition, if UFH is given, a dose of 5,000 units three times daily is preferable to twice daily. However, these doses were not directly compared in the review.

Research: The authors did not state any implications for further research.

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**Bibliographic details**

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.