Individual patient data meta-analysis of enoxaparin vs unfractionated heparin for venous thromboembolism prevention in medical patients

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CRD summary
This individual patient data review concluded that subcutaneous enoxaparin 4000IU reduced the risk of venous thromboembolism in hospitalised medical patients compared with unfractionated heparin without a significant increase in major bleeding. The conclusion about reduced risk is likely to be reliable (but may not be generalisable). The conclusion about major bleeding does not fully reflect the uncertainty in the evidence.

Authors' objectives
To evaluate the relative efficacy of unfractionated heparin and low-molecular-weight heparin for prevention of venous thromboembolism in hospitalised patients.

Searching
MEDLINE, EMBASE, Medscape, The Cochrane Library, Google Scholar and clinicaltrials.org were searched with specified search terms (no restrictions on language). Relevant conference abstracts and bibliographies were searched for additional studies. Search dates were not reported.

Study selection
Randomised controlled trials that compared low-molecular-weight heparin (subcutaneous enoxaparin, 4000IU once-daily) with unfractionated heparin (5000IU two or three times daily) in patients hospitalised for medical conditions were eligible for inclusion. Specified outcomes were thromboembolic events (deep venous thrombosis or pulmonary embolism), major haemorrhages and all-cause mortality.

Trial populations were primarily Caucasian elderly patients (mean age 71 years), 49% were female. Acute stroke was the most prevalent diagnosis (two trials recruited stroke patients exclusively), but patients with cancer, diabetes, respiratory diseases and cardiac insufficiency were also included. Some patients had multiple diagnoses.

Two reviewers independently assessed trial eligibility with reference to a third reviewer to resolve discrepancies.

Assessment of study quality
Trial validity was assessed using the Jadad scale and trials required a minimum score of 3 out of 5 to be considered eligible. Checks on the integrity of randomisation were performed using individual patient data along with checks of consistency and plausibility.

Data extraction
Individual patient data were obtained from the study sponsors and used to develop a common database.

Methods of synthesis
A two stage approach was utilised to analyse the individual patient data. Both fixed-effect and random-effects models were used to pool relative risks (RR) and odds ratios based on intention to treat data. Heterogeneity between trials was quantified using $I^2$ and tested with $X^2$. Funnel plots were used to examine discrepancies between large and small trials. Subgroup analyses were performed on stroke versus cancer, age (under 75 versus 75 years or over), obesity (less than 30 versus 30kgm$^{-2}$ or above body mass index), cardiac versus respiratory impairment, diabetes (present or absent) and renal insufficiency (less than 50 versus 50mL or above min$^{-1}$ creatinine clearance).

Results of the review
Four trials comprising 3,600 patients were eligible and individual patient data was available for all. Results of trial quality assessment were not reported although two of the four trials were double-blind and two were open-label.

Low-molecular-weight heparin significantly reduced total venous thromboembolism by 36% at day 15 compared with
unfractionated heparin (RR 0.64, 95% CI 0.50 to 0.81). This result was driven by a significant reduction in deep venous thrombosis. There was no significant difference between treatments for pulmonary embolism. There was no evidence of variation in treatment effectiveness with covariates except age where treatment was more effective in younger (under 75 years) patients. There was no evidence of a difference between low-molecular-weight heparin and unfractionated heparin in relative risk of all cause mortality or major bleeding. Confidence intervals for these effects were large and the point estimate of the latter favoured unfractionated heparin. There was no evidence of interaction for any of the subgroups. Heterogeneity was low in all analyses and analysis at one month was consistent with analysis at day 15. There was no evidence of publication bias.

Authors’ conclusions
Subcutaneous enoxaparin 4000IU once-daily reduced the risk of venous thromboembolism in hospitalised medical patients compared with unfractionated heparin without a significant increase in major bleeding.

CRD commentary
Methods of searching, study selection, validity assessment and data extraction were all appropriate and minimised potential for bias. There was some uncertainty regarding the quality of the trials which were not fully reported. Methods of pooling were appropriate and interaction tests were used appropriately. The conclusion that there was no significant increase in major bleeding relies on the assumption that statistical and clinical significance were synonymous. Event rates for bleeding were low and confidence intervals were large, suggesting that the findings could represent absence of evidence rather than evidence of no difference between treatments. Generalisability remains problematic given the small number of trials, variation in the comparator and focus on a single dose. Additional uncertainty surrounds the conclusion regarding major bleeding.

The author’s primary conclusion that enoxaparin reduced the risk of venous thromboembolism reflected the evidence and was likely to be reliable but the extent of generalisability from four studies was unclear.

Implications of the review for practice and research
Practice: The authors state that there was a strong rationale for the use of enoxaparin 4000IU rather than unfractionated heparin for venous thromboembolism prophylaxis in a broad spectrum of medical patients.

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

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