Meta-analysis of venous thromboembolism prophylaxis in medically ill patients
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CRD summary
This review concluded that low molecular weight heparin prophylaxis in medically ill patients can reduce rates of deep vein thrombosis, but does not offer enhanced protection against pulmonary embolism. The conduct of this review was generally good, but the reliability of the conclusions cannot be assessed given that details of individual study results and between-study differences were lacking.

Authors' objectives
To review randomised controlled trials (RCTs) of venous thromboembolism (VTE) prophylaxis in medically ill patients in order to evaluate treatment efficacy and safety.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched from January 1981 to September 2007; the search terms were reported. Additional searches of reference lists and other key review papers were also performed. Only English language papers were included in the review.

Study selection
RCTs of medically ill patients with risk factors for VTE who had been followed up for between 7 and 21 days were eligible for inclusion. The patients had a mean age of 72.8 years and 27.7% were elderly. The reason for hospital admission was heart failure in 29.4% of patients, acute respiratory disease in 22.4% and acute infection or inflammation in 24.7%. Most of the studies excluded patients who were mechanically ventilated, had activated bleeding, renal failure or conditions requiring anticoagulation, or who were pregnant.

Eligible interventions were unfractionated heparin (UFH) or low molecular weight heparin (LMWH). The included studies of LMWH assessed dalteparin, enoxaparin, nadroparin and fondaparinux (which was included in this group as it has similar properties) in comparison with placebo or heparin (5,000 U). Doses varied between the studies and treatment duration ranged from 6 to 21 days.

Eligible outcomes were VTE, deep vein thrombosis (DVT), fatal or nonfatal pulmonary embolism (PE), major or minor bleeding, fatal bleeding and VTE-related death. Studies not reporting drug dose, or outcomes of VTE, PE or bleeding, were excluded from the review.

Three reviewers independently selected studies for inclusion, with any disagreements resolved by discussion and consensus.

Assessment of study quality
Study validity was assessed using the Jadad scale. Only studies scoring 3 out of a possible maximum of 5 were included in the review.

Three reviewers independently assessed validity, with any disagreements resolved by discussion and consensus.

Data extraction
Data on patient characteristics, VTE risk factors, drug administration and outcomes were extracted. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated for each outcome, as well as the absolute risk reduction and the number-needed-to-treat (NNT) or to-harm (NNH).

The authors did not state how many reviewers performed the data extraction.
Methods of synthesis
The studies were pooled in a meta-analysis using the DerSimonian and Laird random-effects model. Heterogeneity was assessed using the I² statistic. Meta-regression analyses were also used to explore the relationship between baseline risk factors and efficacy and safety outcomes. Subgroup analyses were performed depending on the control treatment used (UFH or placebo), while sensitivity analyses assessed the influence of individual studies.

Results of the review
Nine RCTs (n=12,391, ranging from 223 to 3,706 across trials) were included in the review.

All of the trials scored 3 on the Jadad scale, but further quality details were not reported.

Thrombotic events.
LMWH/fondaparinux was associated with a statistically significant reduction in DVT compared with placebo (OR 0.60, 95% CI: 0.47, 0.75, p<0.001), with a corresponding NNT of 74. A similar reduction in VTE was also observed (OR 0.59, 95% CI: 0.47, 0.74, p<0.001). When compared with UFH or placebo, there was also a statistically significant reduction in both DVT (OR 0.64, 95% CI: 0.51, 0.79, p<0.001) and VTE (OR 0.64, 95% CI: 0.52, 0.79, p<0.001). However, there was no evidence of a difference between LMWH/fondaparinux and UFH alone. For PE, there was no evidence of any difference between any of the treatment comparisons.

Safety (bleeding and VTE-related deaths).
LMWH/fondaparinux was associated with a statistically significant increase in minor bleeds compared with placebo (OR 1.64, 95% CI: 1.18, 2.29, p=0.003), with a corresponding NNH of 45. There was no evidence of a difference in minor bleeding for comparisons with UFH, or UFH or placebo. There was also no evidence of any differences for major bleeding. For all bleeding events (major and minor), LMWH/fondaparinux was associated with a statistically significant increase compared with placebo (OR 1.68, 95% CI: 1.24, 2.27, p<0.001). These results were influenced by one large trial.

Bleeding or VTE death.
The composite end point of any bleeding or death from VTE showed a statistically significant increase for LMWH/fondaparinux compared with placebo (OR 1.35, 95% CI: 1.07, 1.70, p=0.01), with a corresponding NNH of 58. There was no evidence of any difference between LMWH/fondaparinux and either UFH, or UFH or placebo.

Authors’ conclusions
Rates of DVT appear to be reduced in medically ill patients when given prophylaxis with an LMWH (including fondaparinux), but no protection was seen against PE. Rates of bleeding with LMWH and UFH were similar.

CRD commentary
This review had clearly specified inclusion and exclusion criteria. Relevant databases were searched, as were reference lists and other reviews. However, a limitation was the fact that only studies published in English were included, a fact which the authors acknowledged in their discussion. The studies were screened and quality assessed by more than one reviewer, which reduces the risk of error and bias, but it was not reported whether the data extraction was performed similarly. The methods used for meta-analysis and the assessment of heterogeneity appear appropriate. The conduct of this review was generally good, but the reliability of the conclusions cannot be assessed as the authors have not presented the results of the individual studies or details of any heterogeneity.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: RCTs comparing LMWH agents and fondaparinux are needed to determine whether specific drugs can reduce thrombotic events in medically ill patients.
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