Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials

Eikelboom J W, Quinlan D J, Douketis J D

Authors' objectives
To assess the efficacy and safety of extended-duration prophylaxis on symptomatic thromboembolic events after total hip or knee replacement.

Searching
MEDLINE and EMBASE were searched from January 1980 to July 2000 using the following terms: 'thrombosis', 'thromboembolism', 'pulmonary embolism', 'randomised controlled trials', 'controlled clinical trials', 'random', 'placebo', 'hip arthroplasty' and 'knee arthroplasty', in combination with generic and trade terms of individual LMWH preparations. In addition, the biographies of journals were handsearched, and the manufacturers of LMWH preparations were contacted for details of unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible.

Specific interventions included in the review
Comparisons of extended-duration prophylaxis with low molecular weight heparin (LMWH), unfractionated heparin (UFH), or warfarin with placebo or untreated control were eligible. Prophylaxis was with fixed-dose UFH (5,000 IU three times daily) and the following LMWH: ardeparin (50 IU kg twice daily while in hospital and 100 IU /kg/day out-of-hospital); dalteparin (5,000 IU once daily); enoxaparin (40 mg once daily, or 30 mg twice daily while in hospital and 40 mg once daily when out-of-hospital); and nadroparin (weight adjusted). Prophylaxis was started pre-operatively and post-operatively. The duration of in-hospital prophylaxis ranged from 4 to 10 days in more recent studies, and from 10 to 15 days in older studies. The total duration of prophylaxis was 4 to 6 weeks in all studies.

Participants included in the review
Patients undergoing elective total hip or knee arthroplasty were eligible.

Outcomes assessed in the review
Studies that used objective methods to confirm the diagnosis of thromboembolism were eligible. Studies that assessed symptomless deep vein thrombosis were only included if screening was conducted with ascending lower-limb contrast venography. Other outcomes that were assessed included major bleeding, minor bleeding, and all-cause mortality. The definition provided by the primary study investigators for deep vein thrombosis, pulmonary embolism, and major and minor bleeding was accepted. Three studies screened patients before hospital discharge using bilateral venography, duplex ultrasound, or impedance plethysmography.

How were decisions on the relevance of primary studies made?
Two investigators independently assessed the studies for inclusion, and any disagreements were resolved by discussion. The agreement on selecting the studies was assessed using a weighted kappa-statistic.

Assessment of study quality
Study quality was assessed using the criteria described by Schultz et al. (see Other Publications of Related Interest no.1): proper generation of treatment allocation sequence; proper concealment of allocation sequence; masking of the patients and the investigator assessing the outcome; and completeness of follow-up. Two reviewers independently extracted data on the quality criteria.
Data extraction
Two reviewers independently extracted data on the following: author and date of publication; study design; type of surgery; sample size; regimen used for in-hospital and out-of-hospital prophylaxis; the presence and type of screening for venous thrombosis; and the total duration of prophylaxis. The data extracted were agreed by consensus and then sent to the primary investigator for verification, together with a request for missing data.

Methods of synthesis
How were the studies combined?
The fixed-effect Mantel-Haenszel model was used to calculate the pooled odds ratios (ORs) and 95% confidence intervals (CIs). The number-needed-to-treat (NNT) and the number-needed-to-harm (NNH) were also calculated. An inverted funnel plot of treatment effect against study precision was created for the primary outcome, in order to look for possible publication bias.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Mantel-Haenszel method. The following subgroup analyses were determined a priori for the primary outcome: hip replacement versus knee replacement; specific agent (LMWH, UFH, warfarin); duration of in-hospital prophylaxis (up to 10 days, 10 to 14 days, 15 days or more); and in trials with mandatory discharge, venography versus trials in which mandatory discharge venography was not performed.

Sensitivity analyses were also conducted: the influence of each individual study on the results was explored by excluding each study in turn; study quality was explored by repeating the analysis after excluding lower-quality studies (open-label studies and studies with incomplete follow-up); and the results from fixed-effect and random-effects models were compared.

Results of the review
Nine RCTs (3,999 patients) were included.

All studies used proper methods to generate the randomised treatment allocation and all trials appeared to use adequate concealment. In 7 of the 9 studies, neither the patient nor investigator was aware of the treatment allocation.

The follow-up was 100% in 6 RCTs and greater than 90% in the other 3 RCTs.

Out-of hospital symptomatic venous thromboembolism. Extended-duration prophylaxis significantly reduced the risk of symptomatic venous thromboembolism, compared with placebo or untreated control; the OR was 0.38 (95% CI: 0.24, 0.61) and the NNT was 50. There was no evidence of statistical heterogeneity (chi-squared 5.65, d.f.=8, p=0.69). There was a significant reduction in deep vein thrombosis (OR 0.41, 95% CI: 0.24, 0.68; NNT = 62), but a low event rate for pulmonary embolism with a non statistically-significant reduction (OR 0.43, 95% CI: 0.17, 1.06; NNT = 250).

There was a greater risk reduction in patients undergoing hip replacement (OR 0.33, 95% CI: 0.19, 0.56; NNT = 34), compared with knee replacement (the OR from 2 RCTs was 0.74, 95% CI: 0.26, 2.15; NNT = 250).

Out-of hospital symptomatic venous thromboembolism (1,901 patients).

Extended-duration prophylaxis significantly reduced deep vein thrombosis; the OR was 0.48 (95% CI: 0.36, 0.63) and the NNT was 10. There was no evidence of statistical heterogeneity (chi-squared 5.89, d.f.=6, p=0.43).

There was no evidence of heterogeneity between: UFH and LMWH (p=0.96); different durations of in-hospital prophylaxis; or studies that used mandatory bilateral venography at hospital discharge, compared with trials not undertaking this investigation.

The results were similar after excluding each individual study in turn and after excluding lower-quality studies. There were no important differences between the results from fixed- and random-effects models.

A funnel plot was consistent with no evidence for publication bias.
Adverse reactions.

Extended-duration prophylaxis did not increase major bleeding (0.1% versus 0.3%) or all-cause mortality (0.1% versus 0.3%). However, it was associated with an increased risk of minor bleeding (3.7% versus 2.5%); the OR was 1.56 (95% CI: 1.08, 2.26; NNH = 83).

Cost information
The cost of preventing venous thromboembolism using the most widely used agents was estimated at US$4 to US$7 in the UK and US$24 to US$28 per day in the USA (see Other Publications of Related Interest no.2).

Authors' conclusions
Extended-duration prophylaxis significantly reduced the frequency of symptomatic venous thromboembolism among patients undergoing total hip or knee replacement. The reduction in risk was equivalent to about 20 symptomatic events per 1,000 patients treated.

CRD commentary
This was a well-conducted and well-presented review. The aims were stated, and the inclusion criteria were defined in terms of the study design, participants, intervention, and outcome. Several relevant sources of trials were searched, key terms were stated, attempts were made to locate unpublished material, and publication bias was assessed. The methods used to select the studies were also described. Studies eligible for inclusion were restricted to RCTs, and their quality was formally assessed using validated criteria. Relevant data were extracted and tabulated, and details of the methods used were given. The characteristics of studies were described in the text of the review, while the data were appropriately combined in a meta-analysis. Statistical heterogeneity was assessed and the influence of various factors (defined a priori) was explored.

The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that extended prophylaxis with LMWH or UFH significantly reduces the risk of symptomatic venous thromboembolism in patients undergoing major hip or knee replacement surgery, with no excess of major bleeding but an increased risk of minor bleeding.

Research: The authors state there is a need to reliably predict the risk of venous embolism through adequately powered studies. They also state that several anti-thrombotic agents were not addressed in the review (including warfarin and aspirin).

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