Short-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of prospective studies investigating symptomatic outcomes

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Authors' objectives
To provide reliable estimates of the risk of symptomatic venous thromboembolism (VTE), occurring within 3 months of hip or knee replacement in patients who received short-duration (7 to 10 days) anticoagulant prophylaxis.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched for studies of anticoagulant prophylaxis after hip or knee replacement that were published between January 1993 and March 2001. Only studies in the two most recent MEDLINE database fields (i.e. 1993 to 1996, and January 1997 to March 2001) were searched, in order to increase the generalisability of any findings to current practice. The keywords used were 'hip prosthesis', 'knee prosthesis', 'arthroplasty', 'thromboembolism', 'thrombophlebitis', 'randomized controlled trials', 'cohort study' and 'anticoagulants'. The database search was supplemented by a manual search of relevant bibliographies and conference abstracts from January 1993 to March 2001.

Study selection

Study designs of evaluations included in the review
Prospective cohort studies or randomised controlled trials (RCTs). The studies were required to include at least 100 patients or 50 in each treatment arm.

Specific interventions included in the review
Studies were included if the patients received, on average, 7 to 10 days of fixed-dose low molecular weight heparin, administered once or twice a day, starting within 12 hours before surgery or within 24 hours after surgery, or adjusted-dose warfarin administered to achieve a target international normalised ratio (INR) of 2.0 to 3.0, starting the evening before or the day of surgery. The specific antithrombotic agents and doses included in the review were: warfarin, INR 2 to 3; warfarin, INR 1.8 to 2.8; enoxaparin, 30 mg twice daily; enoxaparin, 40 mg once daily; ardeparin, 50 IU/kg twice daily; tinzaparin, 75 IU/kg twice daily; nadroparin 60 IU/kg once daily; and dalteparin 5,000 IU once daily. Studies were excluded if the patients received an anticoagulant dose that is ineffective, an additional anticoagulant, or active mechanical prophylaxis.

Participants included in the review
Patients undergoing hip or knee replacement, who received short-duration prophylaxis against VTE, were included.

Outcomes assessed in the review
Studies were included: (1) if the patients did not undergo venography, but underwent follow-up for 3 months (7 days), and episodes of symptomatic VTE were confirmed by objective diagnostic testing; or (2) if bilateral lower limb venography was performed after anticoagulant prophylaxis was completed.

How were decisions on the relevance of primary studies made?
Two authors reviewed the eligible studies independently to assess their suitability for inclusion. Agreement was assessed using the weighted kappa statistic, and any disagreements were resolved by consensus.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The data were extracted independently by two reviewers. Agreement was assessed using the weighted kappa statistic, and any disagreements were resolved by consensus.

For the clinical outcome studies, data were extracted on: reference details; the number of participants; antithrombotic agent and dose; when treatment was initiated (pre- or post-operatively); mean treatment duration; follow-up duration; and the number and percentage of patients with fatal or nonfatal VTEs during prophylaxis and postprophylaxis. For the venographic outcome studies, data were extracted on: reference details; the number of evaluable venograms; type of surgery; antithrombotic agent and dose; when treatment was initiated (pre- or post-operatively); mean treatment duration; the total number and percentage of deep vein thromboses (DVTs); and the number and percentage of proximal DVTs.

**Methods of synthesis**

How were the studies combined?
The authors followed guidelines for the meta-analysis of observational studies in which patients from cohort studies are combined, and an analysis of the pooled results is undertaken (see Other Publications of Related Interest no.1). For the meta-analysis, the patients from a treatment arm of a randomised trial were considered as a separate patient cohort, and were combined with patient cohorts from other randomised trials and prospective cohort studies provided they satisfied the study inclusion criteria.

The crude risk of an outcome was calculated for each cohort, as the number of thromboembolic events divided by the number of patients at risk. To determine the pooled thromboembolic event rates for the combined patient cohorts, the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2) and Laird and Mosteller (see Other Publications of Related Interest no.3) was used.

How were differences between studies investigated?
Heterogeneity between the included studies was not assessed explicitly. The statistical methods used accounted for potential heterogeneity in thromboembolic event rates between patient cohorts, and provided a summary point estimate by combining the weighted average of event rates from the individual patient cohorts. The weighting was based on the reciprocal of the variance of thromboembolic event rates from each patient cohort, and the between-cohort variance.

**Results of the review**

Seventeen studies satisfied the inclusion criteria: 4 clinical outcome studies (n=6,089) with 5 separate patient cohorts, and 13 venographic outcome studies (7,080 evaluable venograms) with 19 separate patient cohorts.

In clinical outcome studies, the 3-month (combined during-prophylaxis and postprophylaxis period) incidence of nonfatal VTE was 3.2% (95% confidence interval, CI: 2.0, 4.4), and the 3-month incidence of fatal pulmonary embolism was 0.10% (95% CI: 0.02, 0.20). The postprophylaxis incidence of nonfatal VTE was 2.2% (95% CI: 1.4, 3.0), and the incidence of fatal pulmonary embolism was 0.06% (95% CI: 0, 0.12). The postprophylaxis incidence of symptomatic VTE was higher after hip than after knee replacement: 2.5% versus 1.4% (P= 0.02).

In venographic outcome studies, the prevalence of DVT (total and proximal) was higher after knee than after hip replacement: the prevalence was 38.8% versus 16.4% for total DVT (P<0.001) and 7.6% versus 3.8% for proximal DVT (P<0.001).

**Authors' conclusions**

In patients who undergo hip or knee replacement and receive short-duration anticoagulant prophylaxis, symptomatic nonfatal VTE will occur in about 1 in 32 patients and fatal pulmonary embolism in about 1 in 1,000 patients, within 3 months of the surgery. While the prevalence of asymptomatic DVT is more than 2-fold higher after knee replacement than after hip replacement 7 to 10 days after surgery, in the subsequent 3 months, symptomatic VTE is more likely to occur after hip replacement.
CRD commentary
This was a reasonably well-conducted review with some limitations. The review question was fairly well defined, with inclusion criteria relating to the interventions, participants, study designs and outcomes. The studies were identified through searches of electronic databases, supplemented by manual searches of bibliographies and conference abstracts. It is unclear whether relevant non-English language studies were eligible for inclusion. Identification of such studies would be necessary to limit bias. Quality was assured in the selection and data extraction processes through the use of two independent reviewers.

While the authors attempted to minimise between-study heterogeneity with the use of pre-specified inclusion criteria, further details of the included studies would have been desirable. For example, the composition of patient cohorts extracted from each study would give the reader an indication of any possible clinical heterogeneity between these groups. Data on the validity of the individual studies included in the review were also lacking. No formal validity assessment was carried out, nor were methodological details relating to the validity of the individual studies given.

The authors' conclusions seem to follow from the evidence presented, though the above comments should be considered with regard to the generalisability of the observed results.

Implications of the review for practice and research
Practice: The authors state 'The decision regarding extended-duration prophylaxis should be based on the potential benefits and risks of this approach, and individual patient risks'. They also state 'as the incidence of symptomatic venous thromboembolism is at least as high after hip replacement as after knee replacement, the aggressiveness and duration of prophylaxis should not be influenced by the type of joint replacement surgery a patient is having'.

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

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Other publications of related interest

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Record Status
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.