Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review

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CRD summary
This generally well-conducted review concluded that symptomatic venous thromboembolism developed prior to hospital discharge in approximately one in 100 patients undergoing knee arthroplasty and one in 200 patients undergoing hip arthroplasty who received venous thromboembolism prophylaxis. The conclusions reflect the results presented but given the substantial variation between studies, the applicability of the overall pooled results is questionable.

Authors' objectives
To estimate symptomatic venous thromboembolism (venous thromboembolism) event rates prior to hospital discharge in patients undergoing total or partial hip arthroplasty and total or partial knee arthroplasty.

Searching
MEDLINE, EMBASE, and the Cochrane Library were searched with no language restrictions up to September 2011; search terms were reported. The search strategy was available in an online appendix. Bibliographies of relevant articles were searched. Authors working in the field contacted for additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated venous thromboembolism prophylaxis regimens, and observational studies of patients receiving venous thromboembolism prophylaxis, that reported confirmed postoperative symptomatic venous thromboembolism that occurred before hospital discharge following total or partial arthroplasty of the knee or hip, were eligible for inclusion. Eligible inpatients had to be over 18 years of age. Eligible venous thromboembolism prophylactic regimens were low-molecular weight heparin or direct and indirect Xa and IIa factor inhibitors. Deep vein thrombosis had to be confirmed by venography or ultrasonography (with or without impedance plethysmography). Clinical diagnosis of pulmonary embolism had to be confirmed by perfusion/ventilation scintigraphy, pulmonary angiography, spiral computed tomography, or autopsy.

Across the included studies, the proportion of women ranged from 12 to 85%, mean age ranged from 58 to 74 years, and mean duration of post-surgical follow-up ranged from eight to 35 days. The prophylactic regimens varied considerably across studies, although enoxaparin was the most commonly evaluated drug.

Two reviewers selected studies for the review.

Assessment of study quality
Two reviewers evaluated study quality using GRADE (Grading of Recommendations Assessment, Development and Evaluation). Allocation concealment, blinding, sparse data, attrition bias, indirectness, potential measurement bias, and potential conflict of interest were assessed at the study level. Risk of bias, imprecision, inconsistency, and indirectness was assessed at the group level.

Data extraction
The number of events were extracted by two independent reviewers. Events rates and 95% confidence intervals (CIs) were calculated.

Methods of synthesis
Pooled event rates and 95% confidence intervals were calculated using a fixed-effect Mantel-Haenszel method weighted by standard error for the overall analyses, and the random-effects DerSimonian and Laird model for stratified analyses when substantial heterogeneity was observed. Heterogeneity was assessed using $I^2$; 50% was considered substantial heterogeneity.
Stratified analyses were used to investigate a range of potential sources of heterogeneity, including gender, age, length of hospital stay, venous thromboembolism prophylactic regimen, study design, trial location and publication date, and internal and external validity.

Publication bias was assessed using funnel plots and the Begg and Egger tests.

**Results of the review**

Forty-seven studies met the inclusion criteria (n=44,844 patients); 41 were RCTs and 6 were observational studies. Of the 47 included studies, 21 had total or partial hip arthroplasty procedures, 20 total or partial knee arthroplasty procedures, and six included both procedures. Subgroup and pooled estimates showed consistency, but large confidence intervals indicated lack of precision. A potential measurement bias was present in less than 13% of RCTs, but in 67 to 75% of observational studies. Indirectness of evidence varied between subgroups (zero to 93%).

The pooled rates of postoperative symptomatic venous thromboembolism before hospital discharge were 1.09% (95% CI 0.85 to 1.33) after total or partial knee arthroplasty and 0.53% (95% CI 0.35 to 0.70) after total or partial hip arthroplasty.

The pooled rates of symptomatic deep vein thrombosis were 0.63% (95% CI 0.47 to 0.78) after total or partial knee arthroplasty and 0.26% (95% CI 0.1% to 0.37) after total or partial hip arthroplasty.

The pooled rates for pulmonary embolism were 0.27% (95% CI 0.16 to 0.38) after knee arthroplasty and 0.14% (95% CI 0.07 to 0.21) after hip arthroplasty.

Significant heterogeneity was observed for the analysis of venous thromboembolism after total or partial knee arthroplasty; less heterogeneity was observed for deep vein thrombosis and pulmonary embolism after total or partial knee arthroplasty and venous thromboembolism, deep vein thrombosis, and pulmonary embolism after total or partial hip arthroplasty.

Further results of a wide range of stratified analyses were presented.

Publication bias was observed for the analyses of RCTs that evaluated oral direct factor Xa/IIa inhibitor in patients undergoing total or partial knee arthroplasty, and RCTs that evaluated low-molecular weight heparin in patients undergoing total or partial hip arthroplasty.

**Authors’ conclusions**

Using available venous thromboembolism prophylaxis, approximately one in 100 patients that underwent total or partial knee arthroplasty and approximately one in 200 patients that underwent total or partial hip arthroplasty developed symptomatic venous thromboembolism prior to hospital discharge.

**CRD commentary**

The review addressed a clear question supported by appropriate inclusion criteria. Several relevant sources were searched. Publication bias was investigated. Each stage of the review process was conducted in duplicate, which reduced the risk of error and bias.

Study quality was assessed and the results were considered in the analysis. Appropriate methods of analysis were used. Potential sources of heterogeneity that had been identified a priori were investigated. This was a generally well-conducted review and the conclusions reflect the results presented. However, given the substantial heterogeneity across the studies, the generalisability of the overall pooled results is questionable.

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

**Practice**: The authors stated that the event rates reported could be used as a benchmark to evaluate patient safety indicators derived from routinely collected data.
Research: The authors did not state any implications for research.

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