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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Background: The prevalence of asymptomatic deep vein thrombosis (DVT) diagnosed by venography after hip or knee replacement remains high despite 7 to 10 days of anticoagulant prophylaxis. However, the risk of symptomatic events in such patients is unclear. We performed a meta-analysis to provide reliable estimates of the risk of symptomatic venous thromboembolism occurring within 3 months of hip or knee replacement in patients who received short-duration (7-10 days) anticoagulant prophylaxis.

Methods: The MEDLINE, EMBASE, and Cochrane databases were searched from January 1993 to March 2001, supplemented by a manual search of bibliographies and conference abstracts, to identify prospective studies of patients undergoing hip or knee replacement who received short-duration prophylaxis (ie, 7-10 days of fixed-dose low-molecular-weight heparin or adjusted-dose warfarin, with a target international normalized ratio of 2.0-3.0). Studies were classified as clinical outcome studies if the outcome was symptomatic venous thromboembolism or as venographic outcome studies if the outcome was asymptomatic deep vein thrombosis diagnosed after bilateral venography.

Results: There were 4 clinical outcome studies with 6089 patients who had 3 months of follow-up, and 13 venographic outcome studies with 7080 patients who had venography 7 to 10 days after surgery. In clinical outcome studies, the 3-month incidence of nonfatal venous thromboembolism 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 venous thromboembolism was 2.2% (95% CI, 1.4%-3.0%), and the incidence of fatal pulmonary embolism was 0.05% (95% CI, 0.0%-0.12%). The postprophylaxis incidence of symptomatic venous thromboembolism was higher after hip than after knee replacement (2.5% vs 1.4%; P = .02). In venographic outcome studies, the prevalence of deep vein thrombosis (total and proximal) was higher after knee than after hip replacement (total: 38.8% vs 16.4%; P < .001; proximal: 7.6% vs 3.8%; P < .001).

Conclusions: In patients who undergo hip or knee replacement and receive short-duration anticoagulant prophylaxis, symptomatic nonfatal venous thromboembolism will occur in about 1 of 100 patients and fatal pulmonary embolism will occur in about 1 of 1000 patients within 3 months of the surgery. Although the prevalence of asymptomatic deep vein thrombosis 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 venous thromboembolism is more likely to occur after hip replacement.

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PARTICIPANTS AND METHODS

STUDY IDENTIFICATION AND CLASSIFICATION

The MEDLINE, EMBASE, and Cochrane Controlled Trials Register databases were searched for studies of anticoagulant prophylaxis after hip or knee replacement that were published between January 1993 and March 2001. A priori, we decided to limit the search to studies in the 2 most recent MEDLINE database fields (ie, 1993-1996, January 1997-March 2001) to increase the generalizability of our findings to current practice. In recent years, changes in the management of patients undergoing hip or knee replacement have occurred, including earlier postoperative mobilization, improved operative techniques, and increased use of regional anesthesia, which might decrease the incidence of venous thromboembolism independent of anticoagulant therapy.10-22 The key words used for the database search 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. Studies were classified as clinical outcome studies if the main outcome was symptomatic venous thromboembolism or as venographic outcome studies if the main outcome was asymptomatic deep vein thrombosis diagnosed by venography.

STUDY SELECTION

Studies were included if they satisfied 4 criteria: (1) the design was a prospective cohort study or randomized controlled trial; (2) patients received, on average, 7 to 10 days of fixed-dose LMWH, 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 INR of 2.0 to 3.0, starting the evening before or the day of surgery; (3) the study included at least 100 patients, or 50 in each treatment arm; (4) in clinical outcome studies, patients did not undergo venography, underwent follow-up for 3 months (±7 days), and episodes of symptomatic venous thromboembolism were confirmed by objective diagnostic testing; and (5) in venographic outcome studies, bilateral lower limb venography was performed after anticoagulant prophylaxis was completed. Studies were excluded if patients received an anticoagulant dose that is ineffective (eg, enoxaparin, 10 mg, once a day), an additional anticoagulant (eg, dextran), or active mechanical prophylaxis (eg, intermittent pneumatic compression device). Eligible studies were reviewed independently by 2 authors (J.D.D. and M.A.C.) to assess suitability for inclusion, and to assess the accuracy of outcome data extraction. Agreement was assessed using the weighted κ statistic, and disagreements were resolved by consensus. If relevant outcome data were not reported or were unclear, the study investigators were contacted to clarify the data.

DATA EXTRACTION

From clinical outcomes studies, we extracted data on symptomatic nonfatal venous thromboembolism defined as deep vein thrombosis or pulmonary embolism that was confirmed by objective diagnostic tests, and fatal pulmonary embolism that was defined as definite based on autopsy findings or highly suggestive clinical findings, or possible in cases of sudden death of undetermined cause. From venographic outcome studies, we extracted data on total deep venous thromboembolic event rates after hip or knee replacement, and in determining the duration of anticoagulant prophylaxis.

RESULTS

STUDIES

Our search identified 502 articles, of which 41 were considered for inclusion after screening the abstracts. Seventeen of 41 studies satisfied the inclusion criteria. There were 4 clinical outcome studies with 5 separate patient cohorts involving a total of 6089 patients.9-12 There were 13 venographic outcome studies with 19 separate patient cohorts involving a total of 7080 patients.26-38 There was moderate to high interrater agreement in study selection (κ, 0.76), and data extraction (κ, 0.64). The patient cohorts in the clinical outcome studies, and venographic outcome studies are summarized in Table 1 and Table 2, respectively.

VENOUS THROMBOEMBOLIC EVENT RATES

Clinical Outcome Studies

Data for incidence and case-fatality rate of venous thromboembolism and incidence of fatal pulmonary embolism...
vein thrombosis defined as thrombosis of proximal or distal veins, and data on proximal deep vein thrombosis defined as thrombosis of the popliteal or more proximal veins.

**APPROPRIATENESS OF COMBINING PATIENTS FROM INDIVIDUAL STUDIES**

We used the guidelines of Stroup and associates for meta-analysis of observational studies in which patients from cohort studies are combined, and an analysis of the pooled results is undertaken. For meta-analysis, patients from a treatment arm of a randomized trial were considered as a separate patient cohort and were combined with patient cohorts from other randomized trials and prospective cohort studies as long as they satisfied the study inclusion criteria. For example, in randomized controlled trials of short-duration (7-10 days) vs extended-duration (4-5 weeks) anticoagulant prophylaxis, only the short-duration treatment arm was included in the analysis. The combining of patient cohorts from individual studies was justified because the patient populations from these studies were similar (ie, patients undergoing elective hip or knee replacement), all patients received a standardized intervention (ie, prespecified anticoagulant regimen), and all patients underwent a standardized duration of follow-up (ie, 3 months for clinical outcome studies and 7-10 days for venographic outcome studies).

**STATISTICAL ANALYSIS**

For each patient cohort, we determined the crude risk of an outcome, defined as the number of thromboembolic events divided by the number of patients at risk. To determine pooled thromboembolic event rates for the combined patient cohorts, we used the random effects model calculated after excluding patients who had symptomatic venous thromboembolism before venography (n=55).

**Comparison of Thromboembolic Event Rates After Hip or Knee Replacement**

In clinical outcome studies, the 3-month incidence of symptomatic nonfatal venous thromboembolism was not significantly different after hip or knee replacement (3.4% vs 2.4%; P=.37). However, as shown in Table 4, the incidence of symptomatic nonfatal venous thromboembolism in the postprophylaxis period was significantly higher after hip replacement than after knee replacement (2.5% vs 1.4%; P=.02). In venographic outcome studies, there was a greater than 2-fold higher rate of asymptomatic deep vein thrombosis (total and proximal) after knee replacement than hip replacement (total: 38.8% vs 16.4%; P < .001; proximal: 7.6% vs 3.8%; P < .001). A significantly higher rate of asymptomatic deep vein thrombosis (total and proximal) was also found after knee replacement than after hip replacement when the analysis was performed in patient subgroups who received LMWH initiated after surgery, and those who received warfarin. In patients who received LMWH initiated before surgery, there was a trend toward a higher rate of total deep vein thrombosis after knee replacement than after hip replacement (ie, 23.5% vs 14.9%; P = .06).
Table 1. Clinical Outcome Studies: Patient Characteristics, Antithrombotic Treatment, and Thromboembolic Events

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Surgery Type</th>
<th>Antithrombotic Treatment</th>
<th>Treatment Initiation</th>
<th>Mean Treatment Duration, d</th>
<th>Follow-up Duration, d</th>
<th>During-Prophylaxis VTE, No. (%)</th>
<th>Postprophylaxis VTE, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson et al,1997</td>
<td>506</td>
<td>THR or TKR</td>
<td>Warfarin, INR, 2-3</td>
<td>Postoperative</td>
<td>9.8</td>
<td>90</td>
<td>0</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Leclerc et al,1998</td>
<td>1984</td>
<td>THR or TKR</td>
<td>Enoxaparin, 30 mg BID</td>
<td>Postoperative</td>
<td>9.0</td>
<td>84</td>
<td>37 (1.9)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Colwell et al,1999</td>
<td>1516</td>
<td>THR</td>
<td>Warfarin, INR, 2-3</td>
<td>Preoperative/</td>
<td>7.5</td>
<td>90</td>
<td>17 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Heit et al,2000</td>
<td>588</td>
<td>THR or TKR</td>
<td>Ardeparin, 50 IU/kg BID</td>
<td>Postoperative</td>
<td>7.3</td>
<td>90</td>
<td>13 (2.2)</td>
<td>0 [1]†</td>
</tr>
</tbody>
</table>

*VTE indicates venous thromboembolism; during-prophylaxis, initial 7 to 10 days after surgery while patients are receiving antithrombotic treatment; postprophylaxis, period from completion of antithrombotic treatment until 3 months after surgery; THR, total hip replacement; TKR, total knee replacement; INR, international normalized ratio; and BID, twice daily.
†Number in brackets indicates number of events if episodes of possible fatal pulmonary embolism are included.
‡Number in parentheses refers to number of evaluable venograms used to determine prevalence of total DVT.

Table 2. Venographic Outcome Studies: Patient Characteristics, Antithrombotic Treatment, and Thrombotic Events

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Evaluable Venograms</th>
<th>Surgery Type</th>
<th>Antithrombotic Treatment</th>
<th>Treatment Initiation</th>
<th>Mean±SD Treatment Duration, d</th>
<th>Total DVT: Proximal and Distal DVT</th>
<th>Proximal DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al,1993</td>
<td>590</td>
<td>THR or TKR</td>
<td>Tinzaparin, 75 IU/kg BID</td>
<td>Postoperative</td>
<td>9 ± 3</td>
<td>185 (31)</td>
<td>36 (6)</td>
</tr>
<tr>
<td></td>
<td>617</td>
<td>THR or TKR</td>
<td>Warfarin, INR, 2-3</td>
<td>Postoperative</td>
<td>9 ± 3</td>
<td>231 (37)</td>
<td>47 (8)</td>
</tr>
<tr>
<td>Spiro et al,1994</td>
<td>143</td>
<td>THR</td>
<td>Enoxaparin, 30 mg BID</td>
<td>Postoperative</td>
<td>7</td>
<td>16 (11)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Colwell et al,1994</td>
<td>136</td>
<td>THR</td>
<td>Enoxaparin, 30 mg BID</td>
<td>Postoperative</td>
<td>7</td>
<td>8 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Fauno et al,1995</td>
<td>260</td>
<td>THR or TKR</td>
<td>Nadroparin, 60 IU/kg OD</td>
<td>Preoperative</td>
<td>7 ± 2</td>
<td>43 (17)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>Hamulyak et al,1995</td>
<td>257</td>
<td>THR or TKR</td>
<td>Warfarin, INR, 2-3</td>
<td>Postoperative</td>
<td>10 ± 2</td>
<td>50 (19)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Leclerc et al,1996</td>
<td>206</td>
<td>TKR</td>
<td>Enoxaparin, 30 mg BID</td>
<td>Postoperative</td>
<td>9 ± 3</td>
<td>76 (37)</td>
<td>24 (12)</td>
</tr>
<tr>
<td></td>
<td>211</td>
<td>TKR</td>
<td>Warfarin, INR, 2-3</td>
<td>Postoperative</td>
<td>9 ± 3</td>
<td>109 (52)</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Eriksson et al,1997</td>
<td>785</td>
<td>THR</td>
<td>Enoxaparin, 40 mg OD</td>
<td>Preoperative</td>
<td>10 ± 2</td>
<td>196 (25)</td>
<td>59 (8)</td>
</tr>
<tr>
<td>Francis et al,1997</td>
<td>192</td>
<td>THR</td>
<td>Dalteparin, 5000 IU OD†</td>
<td>Preoperative</td>
<td>7 ± 2</td>
<td>28 (15)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Comp et al,1998</td>
<td>190</td>
<td>THR</td>
<td>Warfarin, INR, 1.8-2.8</td>
<td>Preoperative</td>
<td>7 ± 2</td>
<td>42 (26)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Hull et al,2000</td>
<td>337 (354)†</td>
<td>THR</td>
<td>Dalteparin, 5000 IU OD†</td>
<td>Preoperative</td>
<td>6 ± 2</td>
<td>53 (27)</td>
<td>8 (4)</td>
</tr>
<tr>
<td></td>
<td>336 (358)†</td>
<td>THR</td>
<td>Dalteparin, 5000 IU OD†</td>
<td>Preoperative</td>
<td>6 ± 2</td>
<td>36 (9)</td>
<td>3 (1)</td>
</tr>
<tr>
<td></td>
<td>338 (363)†</td>
<td>THR</td>
<td>Warfarin, INR, 2-3</td>
<td>Postoperative</td>
<td>6 ± 2</td>
<td>44 (11)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Lassen,2000</td>
<td>918 (927)†</td>
<td>THR</td>
<td>Enoxaparin, 40 mg OD</td>
<td>Preoperative</td>
<td>6 ± 2</td>
<td>83 (9)</td>
<td>23 (2)</td>
</tr>
<tr>
<td>Turpie,2000</td>
<td>796 (830)†</td>
<td>THR</td>
<td>Enoxaparin, 30 mg BID</td>
<td>Postoperative</td>
<td>6 ± 2</td>
<td>65 (8)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Bauer,2000</td>
<td>361 (372)†</td>
<td>TKR</td>
<td>Enoxaparin, 30 mg BID</td>
<td>Postoperative</td>
<td>6 ± 2</td>
<td>98 (27)</td>
<td>20 (5)</td>
</tr>
</tbody>
</table>

*DVT indicates deep vein thrombosis; THR, total hip replacement; TKR, total knee replacement; BID, twice daily; INR, international normalized ratio; and OD, once daily.
†Units of dalteparin administered before surgery, 2500 IU.
‡Number in parentheses refers to number of evaluable venograms used to determine prevalence of total DVT.

P = .07). In this patient subgroup, the rate of proximal deep vein thrombosis was not significantly different after knee or hip replacement (ie, 4.3% vs 4.3%; P = .92).

This meta-analysis provides reliable estimates of the risks of symptomatic nonfatal venous thromboembolism and fatal pulmonary embolism occurring within 3 months of hip or knee replacement in patients who have received short-duration (7-10 days) anticoagulant prophylaxis. There are 2 conclusions that can be derived from this study. First, although the prevalence of asymptomatic deep vein thrombosis is high after hip or knee replacement (about 1 in 5 patients), symptomatic nonfatal venous thromboembolism is much less frequent within 3 months, occurring in 3.2% of patients, and fatal pulmonary embolism is rare, occurring in 0.10% of patients. Second, although the prevalence of asymptomatic deep vein thrombosis is more than 2-fold higher following knee replacement than following hip replacement after 7 to 10 days of antiocoagulant prophylaxis, symptomatic venous thromboembolism is more likely to occur after hip replacement in the subsequent 3 months.

Our estimates of the rates of symptomatic nonfatal venous thromboembolism and fatal pulmonary embolism...
eral weeks after hip or knee replacement.  

...period of increased risk persists for sev-

After discontinuing anticoagulant prophylaxis was stopped also supports the concept that a period of increased risk persists for several weeks after hip or knee replacement.

During-prophylaxis defined as initial 7 to 10 days after surgery when patients are receiving antithrombotic treatment; postprophylaxis, period from completion of antithrombotic treatment until 3 months after surgery.

In terms of the incidence of fatal pulmonary embolism, all patients who died during the 3-month follow-up period did not undergo an autopsy and, therefore, the true incidence may be higher than reported. However, even if we include episodes of possible fatal embolism, reported as sudden death of undetermined cause, the incidence of fatal pulmonary embolism in the during-prophylaxis and postprophylaxis periods remains low at 0.07% and 0.12%, respectively. These rates are lower than those reported in hip or knee replacement patient registries, in which the incidence of fatal pulmonary embolism is consistent with the rate of 4.1% reported in a retrospective cohort study of patients who underwent hip or knee replacement and received some type of anticoagulant or mechanical prophylaxis.14

When patients who underwent hip or knee replacement were analyzed separately, the prevalence of asymptomatic deep vein thrombosis 7 to 10 days after surgery...
was more than 2-fold higher after knee replacement. However, there was no difference in the 3-month incidences of symptomatic venous thromboembolism in patients who underwent hip or knee replacement. Furthermore, if the analysis was limited to the postprophylaxis period, patients who underwent hip replacement had a higher incidence of symptomatic thromboembolism. This finding suggests that asymptomatic venous thrombi are more likely to be clinically unimportant in patients who undergo knee replacement compared with those who undergo hip replacement. The reason for this is not clear. One possible explanation might be related to differences in the size and occlusiveness of thrombi occurring after hip or knee replacement. There is evidence that hip replacement–associated thrombi may be larger, as they tend to originate in the femoral vein due to intraoperative hip rotation and femoral vein torsion and injury. On the other hand, knee replacement–associated thrombi may be smaller, as they tend to originate in the calf or popliteal veins, due to intraoperative knee flexion and vein injury, and below knee tourniquet use. An alternative explanation might be related to differences in postoperative mobility, as some patients who undergo uncemented hip replacement are not fully weightbearing, whereas after knee replacement, patients are required to be fully weightbearing. Overall, this finding is in agreement with a large retrospective cohort study that found that hip replacement was associated with a 25% higher rate of symptomatic venous thromboembolism than knee replacement (odds ratio [OR], 1.4; 95% CI, 1.2-1.6).46

Our study has potential limitations. First, we acknowledge that pooling of results across studies in which patients received different anticoagulant regimens may be problematic, as it differs from the traditional metaanalytic approach. However, we attempted to have consistency of patients, treatments, and outcomes across studies: all patients who underwent hip or knee replacement received a standardized anticoagulant regimen, and had the same duration of follow-up. All thromboembolic outcomes were confirmed with objective tests. Furthermore, the use of a random effects model accounted for potential heterogeneity in outcome rates across studies. Thus, we believe our results provide valid estimates of the risks of symptomatic venous thromboembolism in patients who received short-duration prophylaxis after hip or knee replacement. Second, we could not determine outcome rates in high-risk patients with previous thromboembolism, cancer, or poor mobility. Based on available data, such patients represented a small proportion of the combined patient population. In studies that provided such data, patients with previous thromboembolism were excluded or represented less than 10% of study patients. In clinical outcome studies that documented patients’ postoperative mobility status, about 90% of patients were fully weightbearing at the time of discharge from the hospital. Third, because meta-analysis is retrospective research based on patients who are enrolled in clinical trials, there is the potential that our results are not generalizable to patients outside of clinical trials who may have greater comorbidity. Although we cannot refute this possibility, as information about patients’ clinical characteristics was generally not provided, our findings are consistent with results from patient registries and databases involving unselected patients who have undergone hip or knee replacement.

Our results provide clinicians with a framework to decide about the adequacy of short-duration anticoagulant prophylaxis in patients who are undergoing hip or knee replacement. Based on our findings, patients who receive 7 to 10 days of prophylaxis and do not develop symptomatic thromboembolism during this period have a 2.2% risk of nonfatal venous thromboembolism, and a 0.05% risk of fatal pulmonary embolism in the subsequent 3 months. The decision regarding extended-duration prophylaxis should be based on the potential benefits and risks of this approach, and individual patient risks. In a meta-analysis of patients who underwent hip or knee replacement, extended-duration prophylaxis decreased the risk of symptomatic venous thromboembolism by 60%, from 3.3% to 1.3% (OR, 0.38; 95% CI, 0.24-0.61). Extended-duration prophylaxis did not confer an increased risk of major bleeding, but was associated with an excess in minor bleeding from 2.5% to 3.7% (OR, 1.56; 95% CI, 1.08-2.26). Individual patients at increased risk for venous thromboembolism include those who are not fully weightbearing after surgery, and those with previous thromboembolism or obesity. The use of pneumatic compression devices in nonobese patients and extended-duration warfarin therapy appears to confer a decreased risk of thromboembolism. Another clinical consideration relates to our comparison of thromboembolic outcome rates after hip or knee replacement. Our findings challenge the traditional perception that total knee replacement is the highest-risk orthopedic procedure. 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.

To summarize, in patients who undergo hip or knee replacement and receive short-duration anticoagulant prophylaxis, symptomatic nonfatal venous thromboembolism will occur in about 1 of 32 patients and fatal pulmonary embolism will occur in about 1 of 1000 patients within 3 months of surgery.

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