Reduction of Out-of-Hospital Symptomatic Venous Thromboembolism by Extended Thromboprophylaxis With Low-Molecular-Weight Heparin Following Elective Hip Arthroplasty

A Systematic Review

Martin O’Donnell, MB, MRCPI; Lori-Ann Linkins, MD, FRCPC; Clive Kearon, MB, MRCPI, FRCPC, PhD; Jim Julian, MMath; Jack Hirsh, MD, FRCPC, FRCPA

Background: Numerous trials and meta-analyses have shown that extended out-of-hospital prophylaxis with low-molecular-weight heparin reduces asymptomatic and symptomatic venous thromboembolism after total hip arthroplasty. We hypothesized that knowledge of the results of screening tests may have resulted in overdiagnosis of symptomatic venous thromboembolism in many of these studies. The purpose of this analysis was to obtain an accurate estimate of the absolute risk reduction (ARR) of symptomatic venous thromboembolism after discharge from hospital in controlled studies that avoided this potential bias for overdiagnosis.

Methods: Articles were identified using MEDLINE, EMBASE, and the Cochrane Library databases (January 1980–April 2002). Studies were eligible if the assessment of symptomatic venous thromboembolism was standardized and performed independently of mandatory objective testing.

Results: Two studies (907 patients) were eligible for assessment of symptomatic venous thromboembolism, 5 studies (1917 patients) for symptomatic pulmonary embolism, and 7 studies (2425 patients) for fatal pulmonary embolism. In controls vs extended treatment groups, after hospital discharge, the frequency of symptomatic venous thromboembolism was 2.7% vs 1.1% (ARR, 1.56%; 95% confidence interval [CI], −0.21% to 3.3%; number needed to treat, 64); symptomatic pulmonary embolism was 0.36% vs 0% (ARR, 0.36%; 95% CI, −0.3% to 1.36%; number needed to treat, 278); and fatal pulmonary embolism was 0.09% vs 0% (ARR, 0.09%; 95% CI, −0.08% to 0.27%; number needed to treat, 1093).

Conclusions: The absolute reduction in symptomatic venous thromboembolism attributed to extended prophylaxis in some studies and meta-analyses seems to have been overestimated.
studies. Unless precautions are taken to ensure that results of screening studies do not influence clinical assessment, it is possible that knowledge that patients had deep vein thrombosis detected by routine screening could prompt questioning for symptoms of deep vein thrombosis. Leg discomfort and swelling, which is common following total hip arthroplasty, may be incorrectly attributed to deep vein thromboses that were detected by screening venography. As a result, the incidence of symptomatic deep vein thrombosis in both the control and low-molecular-weight heparin arms could be inflated, leading to an exaggerated estimate of the absolute reduction in symptomatic venous thromboembolism due to extended prophylaxis.

We hypothesized that detection of asymptomatic venous thromboembolism by routine screening may have led to an overestimation of the frequency of symptomatic venous thromboembolism in some studies of extended prophylaxis following total hip arthroplasty. To obtain an accurate estimate of the absolute reduction in symptomatic venous thromboembolism attributable to extended low-molecular-weight heparin prophylaxis, we reanalyzed the randomized controlled studies, including only those in which assurance was provided that assessment for symptomatic venous thromboembolism was made independently of the result of mandatory venography and/or ventilation perfusion scanning. Because out-of-hospital prophylaxis with low-molecular-weight heparin is inconvenient and expensive, it is important to have an accurate estimate of this benefit.

METHODS

DATA IDENTIFICATION

Relevant articles were identified through searches of the National Library of Medicine's MEDLINE database, Excerpta Medica online (EMBASE), and the Cochrane Library database (January 1980–April 2002) using the following terms and keywords: venous thrombosis, thromboprophylaxis, hip arthroplasty, hip replacement, extended duration low-molecular-weight heparin, randomized trials, and extended thromboprophylaxis. Bibliographies of retrieved articles and previous meta-analyses on this topic were searched to find further reports. Abstracts from the International Society on Thrombosis and Haemostasis 2001 and American Society of Hematology 2001 conferences were included. A cited reference search was conducted for the first 2 authors of each eligible article. Two investigators (M.O. and L.-A.L.) conducted literature searches, assessed reports for eligibility, and extracted data from eligible reports independently. Disagreements were resolved by consensus with a third investigator (J.H.).

STUDY ELIGIBILITY

Inclusion Criteria

Randomized placebo-controlled studies that evaluated extended low-molecular-weight heparin therapy after completion of an initial 7 to 12 days of prophylaxis following hip arthroplasty were potentially eligible. Trials were required to have reported the number of patients studied and the number of symptomatic episodes of venous thromboembolism that occurred in the placebo and low-molecular-weight heparin groups. At least 90% of enrolled patients needed to have been included in the analysis of symptomatic venous thromboembolism.

Exclusion Criteria

Studies were excluded if (1) it was not clear that mandatory objective testing was performed independently of assessment for symptomatic venous thromboembolism or (2) if a standardized a priori approach to diagnosing symptomatic venous thromboembolism was not used (we required that there was at least one scheduled clinical follow-up review and that objective testing, with predefined criteria, was used to diagnose symptomatic or fatal venous thromboembolism). These eligibility criteria were considered separately for (1) symptomatic venous thromboembolism, (2) symptomatic pulmonary embolism, and (3) fatal pulmonary embolism. We assumed that the results of mandatory venography would not interfere with the diagnosis of symptomatic pulmonary embolism and that results of mandatory venography and/or ventilation perfusion scanning and/or clinical review would not interfere with the diagnosis of fatal pulmonary embolism.

DATA EXTRACTION AND OUTCOMES

The following data were collected from studies that satisfied the inclusion criteria: (1) temporal relationship between detection of asymptomatic venous thromboembolism by routine screening and clinical assessment for venous thromboembolism during the study period (ie, Were they performed separately?), (2) timing of mandatory objective testing (ie, before randomization, at the end of the study period, or both), (3) whether objective testing was used when clinical signs and symptoms developed, and (4) duration of clinical follow-up (Table 1). In addition, the following frequencies were extracted from studies that satisfied the inclusion criteria (ie, eligible studies): (1) symptomatic venous thromboembolism, (2) symptomatic pulmonary embolism, and (3) fatal pulmonary embolism that occurred after randomization and within 3 months of surgery.

STATISTICAL ANALYSIS

The absolute risk reduction was considered the primary measure of effect. We calculated numbers needed to treat using the reciprocal of the absolute risk reduction. The outcomes of symptomatic venous thromboembolism, symptomatic pulmonary embolism, and fatal pulmonary embolism were considered separately. For symptomatic venous thromboembolism, outcome values were combined in a fixed-effects model with a 95% confidence interval (CI) calculated. For symptomatic and fatal pulmonary embolism, we were unable to combine rates in a fixed-effects model because of the lack of events. We therefore summed events and compared the frequency of symptomatic pulmonary embolism by calculating the difference of 2 binomial proportions with 95% CIs. We considered a CI that crossed 0 as nonsignificant and a P value of less than .05 to be statistically significant for all tests. Validity of combining results from different studies was assessed using the Zelen exact test for statistical heterogeneity.16 The computer programs StatXact-4.0 (Cytel, Cambridge, Mass) and MINITAB-13.32 (Mini-tab Inc, State College, Pa) were used to calculate all summary absolute risk reductions, numbers needed to treat, and odds ratios.

RESULTS

SYMPTOMATIC VENOUS THROMBOEMBOLISM

Seven studies2-8 met our inclusion criteria for evaluation of symptomatic venous thromboembolism, of which 5...
were excluded because (1) the assessment of symptomatic venous thromboembolism may not have occurred independently of knowledge of the mandatory objective testing and (2) a standardized a priori approach to diagnosing symptomatic venous thromboembolism was not used. Therefore, 2 studies, including a total of 907 patients, were eligible for this portion of the meta-analysis (Table 2).

Overall, the frequency of symptomatic venous thromboembolism was 2.7% in the control group and 1.1% in the treatment group. The absolute risk reduction was 1.56% (95% CI, 0.21% to 3.30%). Therefore, the number needed to treat to prevent 1 episode of symptomatic venous thromboembolism was 64. Extended prophylaxis was associated with an overall odds ratio of 0.39 (95% CI, 0.14-1.11) (Table 2). There was no statistically significant evidence of heterogeneity between the 2 studies with respect to absolute risk reduction.

### SYMPTOMATIC PULMONARY EMBOLISM

Seven studies met our inclusion criteria for evaluation of symptomatic pulmonary embolism, of which 2 studies were excluded because (1) the assessment of symptomatic venous thromboembolism may not have occurred independently of knowledge of the mandatory objective testing and (2) a standardized a priori approach to diagnosing symptomatic pulmonary embolism was not used. Therefore, 5 studies, including a total of 1917 patients, were eligible for inclusion in this portion of the meta-analysis (Table 2). Overall, the frequency of symptomatic pulmonary embolism was 0.36% in the control group and 0% in the treatment group. The absolute risk reduction was 0.36% (95% CI, 0.3% to 1.36%). Therefore, the number needed to treat to prevent 1 episode of symptomatic pulmonary embolism was 278. There was no statistically significant evidence of heterogeneity between studies with respect to absolute risk reduction.
Seven studies\(^2-8\) met our inclusion criteria for evaluation of fatal pulmonary embolism, of which none were excluded. Therefore, 7 studies,\(^2-8\) including a total of 2425 patients, were eligible for this portion of the meta-analysis (Table 3). Overall, the frequency of objectively documented fatal pulmonary embolism was 0.09% in the control group and 0% in the low-molecular-weight heparin group. The absolute risk reduction was 0.09% (95% CI, −0.08% to 0.27%). Therefore, the number needed to treat to prevent 1 episode of fatal pulmonary embolism was 1093. There was no statistically significant evidence of heterogeneity between studies with respect to absolute risk reduction.

### Table 3. Fatal Pulmonary Embolism at 3 Months Following Total Hip Arthroplasty

<table>
<thead>
<tr>
<th>Source</th>
<th>No./Total No. (%) of Patients</th>
<th>ARR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planes et al,(^2) 1996</td>
<td>0/90 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bergqvist et al,(^2) 1996</td>
<td>0/131 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dahl et al,(^1) 1997*</td>
<td>0/117 (0)</td>
<td>1/110 (0.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Lassen et al,(^4) 1998*</td>
<td>0/140 (0)</td>
<td>0/141 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Heit et al,(^7) 2000†</td>
<td>0/241 (0)</td>
<td>0/231 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Hull et al,(^6) 2000*</td>
<td>0/389 (0)</td>
<td>0/180 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Comp et al,(^8) 2001</td>
<td>0/224 (0)</td>
<td>0/211 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>0/1332 (0)</td>
<td>1/1093 (0.09)</td>
<td>0.09% (−0.08% to 0.27%)</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; NA, not applicable; NNT, number needed to treat.
*Follow-up was for 35 days only.
†Heit et al\(^7\) reported 2 deaths, 1 in the control (sudden death and pulmonary embolism could not be ruled out but was not objectively confirmed) and 1 in the treatment group (not believed to be due to pulmonary embolism).

### Table 4. Symptomatic Venous Thromboembolism at 3 Months Following Total Hip Arthroplasty

<table>
<thead>
<tr>
<th>Source</th>
<th>No. (%) of Patients</th>
<th>OR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eikelboom et al,(^9) 2001*</td>
<td>NA (1.4)</td>
<td>NA (4.3)</td>
<td>0.33 (0.19-0.56)</td>
</tr>
<tr>
<td>Hull et al,(^10) 2001</td>
<td>15/1091 (1.4)</td>
<td>36/862 (4.2)</td>
<td>0.35 (0.19-0.66)†</td>
</tr>
<tr>
<td>Current analysis</td>
<td>5/465 (1.1)</td>
<td>12/442 (2.7)</td>
<td>0.39 (0.14-1.11)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not available; NNT, number needed to treat; OR, odds ratio.
*Data include 1 study with unfractionated heparin and 1 study with oral anticoagulation as intervention.
†Calculated from risk ratio and percentage of control.

### FATAL PULMONARY EMBOLISM

Routine detection of asymptomatic venous thromboembolism may have led to overdiagnosis of symptomatic venous thromboembolism in most studies\(^2-6\) that have evaluated extended prophylaxis with low-molecular-weight heparin after total hip arthroplasty. This risk was avoided in only 2 studies\(^7,8\); in one study,\(^7\) mandatory testing for asymptomatic venous thromboembolism was not performed, whereas in the other,\(^8\) precautions were taken to ensure that assessment for symptomatic venous thromboembolism was made independently of the results of mandatory venography. Results from these 2 studies suggest that extending prophylaxis with low-molecular-weight heparin for an additional 3 weeks reduces the frequency of symptomatic venous thromboembolism by 1.56%. Hence, 64 patients need to be treated to prevent 1 late episode of symptomatic venous thromboembolism.

This number is larger than the values of 34\(^9\) and 45\(^10\) that previous meta-analyses have estimated needed to be treated to prevent an episode of symptomatic venous thromboembolism in this setting (Table 4). Unlike our analysis, those meta-analyses included studies in which knowledge of asymptomatic thrombosis had the potential to cause overdiagnosis of symptomatic venous thromboembolism; this may account for the greater absolute reduction in symptomatic venous thromboembolism that was attributed to use of extended prophylaxis in those analyses. We estimated that hip arthroplasty patients who do not receive extended prophylaxis (ie, control patients) have a 2.7% risk of developing symptomatic venous thromboembolism after discharge from hospital. This value is consistent with previous prospective studies\(^12-14\) that reported this risk to be 1.4%\(^12\) to 3.0%.\(^14\) Similarly, this value is consistent with the risk of 1.7% found in a large, retrospective, epidemiologic study\(^15\) from California in which fewer than one third of patients received extended prophylaxis. We estimated that 278 patients needed to be treated with extended prophylaxis to prevent 1 episode of symptomatic pulmonary embolism. This number is twice as large as the value of 143 that was reported by Eikelboom and colleagues\(^9\) in the only previous meta-analysis, to our knowledge, that assessed symptomatic pulmonary embolism in this setting. This difference was due to the findings of a single study that was included by Eikelboom et al\(^9\) but excluded from our analysis. That particu-

©2003 American Medical Association. All rights reserved.
lar study, which performed mandatory ventilation perfusion lung scanning 35 days after surgery, reported a frequency of symptomatic pulmonary embolism of 2.8% (3/106, 1 fatal) in patients who did not receive extended prophylaxis. These 3 symptomatic pulmonary emboli accounted for 50% (3/6) of the total number of symptomatic pulmonary embolisms from all 7 low-molecular-weight heparin studies included by Eikelboom et al. We estimated that hip arthroplasty patients who do not receive extended prophylaxis have a 0.36% risk of developing symptomatic pulmonary embolism after discharge from hospital. This frequency is consistent with previous prospective studies that reported this value to be 0.2% to 0.8%.\(^{14}\)

Consistent with the findings of previous meta-analyses, extended prophylaxis with low-molecular-weight heparin reduced the risk of symptomatic venous thromboembolism by approximately two thirds.\(^{9,11}\) Therefore, although knowledge of the results of mandatory testing may lead to over-diagnosis of symptomatic venous thromboembolism, since this effect will occur in both control and low-molecular-weight heparin arms of trials, it does not seem to result in a biased estimate of the relative risk reduction for symptomatic venous thromboembolism achieved by extended prophylaxis.

The main limitation of our analysis is that the number of eligible patients who were included and the number of symptomatic episodes of venous thromboembolism that occurred were small; there were fewer than 1000 patients in the 2 studies\(^8,9\) that were used to evaluate the frequency of symptomatic venous thromboembolism, and there were only 3 episodes of objectively confirmed symptomatic pulmonary embolism in the 5 studies\(^3,6-8\) that were used to evaluate this outcome.

When calculating the numbers needed to treat to prevent different presentations of venous thromboembolism, we assumed that patients who do not receive extended prophylaxis with low-molecular-weight heparin would not receive any prophylaxis after discharge from the hospital. There is evidence that a month of aspirin therapy reduces the risk of symptomatic venous thromboembolism by approximately one third after orthopedic surgery.\(^{17,18}\) This finding suggests that, compared with aspirin rather than no prophylaxis, the numbers needed to treat with extended low-molecular-weight heparin to prevent an episode of symptomatic venous thromboembolism will be twice as large as the values that we calculated.

Our analysis highlights one problem that may occur when studies evaluating venous thromboembolism prophylaxis assess both asymptomatic and symptomatic outcomes. Another concern that we did not address but that applies to all but 1 of the studies\(^3\) that have evaluated extended prophylaxis with low-molecular-weight heparin is that detection and treatment of asymptomatic venous thromboembolism 1 month after surgery are expected to reduce the subsequent frequency of symptomatic venous thromboembolism. For these 2 reasons, we suggest that an accurate estimate of the frequency of symptomatic venous thromboembolism with and without prophylaxis is best obtained from studies that do not include screening for asymptomatic thrombi. Because the number of symptomatic episodes of venous thromboembolism that are prevented is central to determining the cost-effectiveness of extended prophylaxis, it is important that this estimate be as accurate as possible.\(^{19}\)

Accepted for publication September 13, 2002.

Dr O’Donnell is a recipient of the Fraser Foundation Research Fellowship, Hamilton Health Sciences Foundation, Hamilton, Ontario; Dr Linkins is a recipient of the Thrombosis Interest Group Research Fellowship, Ontario; Dr Kearon is a Research Scholar of the Heart and Stroke Foundation of Canada, Ottawa, Ontario.

Corresponding author and reprints: Martin O’Donnell, MB, MRCPI, Henderson General Hospital, 711 Concession St, Hamilton, Ontario, Canada L8V 1C3 (e-mail: odonnell@mcmaster.ca).

### References