Timing of Initial Administration of Low-Molecular-Weight Heparin Prophylaxis Against Deep Vein Thrombosis in Patients Following Elective Hip Arthroplasty

A Systematic Review

Russell D. Hull, MBBS; Graham F. Pineo, MD; Paul D. Stein, MD; Andrew F. Mah, BSc; Susan M. MacIsaac, MSc; Ola E. Dahl, MD, PhD; William A. Ghali, MD, MPH; Matthew S. Butcher, BSc; Rollin F. Brant, PhD; David Bergqvist, MD, PhD; Karly Hamulyak, MD; Charles W. Francis, MD; Victor J. Marder, MD; Gary E. Raskob, PhD

Background: Perioperative and postoperative venous thrombosis are common in patients undergoing elective hip surgery. Prophylactic regimens include subcutaneous low-molecular-weight heparin 12 hours or more before or after surgery and oral anticoagulants. Recent clinical trials suggest that low-molecular-weight heparin initiated in closer proximity to surgery is more effective than the present clinical practice. We performed a systematic review of the literature to assess the efficacy and safety of low-molecular-weight heparin administered at different times in relation to surgery vs oral anticoagulant prophylaxis.

Methods: Reviewers (A.F.M. and S.M.M.) identified studies by searching MEDLINE, reviewing references from retrieved articles, scanning abstracts from conference proceedings, and contacting investigators and pharmaceutical companies. Randomized trials comparing low-molecular-weight heparin administered at different times relative to surgery with oral anticoagulants in patients undergoing elective hip arthroplasty, evaluated using contrast phlebography, were selected. Two reviewers (A.F.M. and S.M.M.) extracted data independently.

Results: The literature review identified 4 randomized trials meeting predefined inclusion criteria. The results indicate that low-molecular-weight heparin initiated in close proximity to surgery resulted in absolute risk reductions of 11% to 13% for deep vein thrombosis, corresponding to relative risk reductions of 43% to 55% compared with oral anticoagulants. Low-molecular-weight heparin initiated 12 hours before surgery or 12 to 24 hours postoperatively was not more effective than oral anticoagulants. Low-molecular-weight heparin initiated postoperatively in close proximity to surgery at half the usual dose was not associated with a clinically or statistically significant increase in major bleeding rates (P=.16).


Epidemiologic data demonstrate that perioperative and postoperative venous thrombosis are common in high-risk surgical patients. In the absence of thromboprophylaxis, this disorder occurs in 40% to 60% of patients undergoing hip arthroplasty. Prophylactic regimens include warfarin and subcutaneous low-molecular-weight heparin.

Oral anticoagulant prophylaxis is a common practice in the United States and Canada for patients undergoing elective total hip replacement. The requirement for laboratory monitoring to maintain a therapeutic international normalized ratio has led investigators to search for alternative therapies. Low-molecular-weight heparin prophylaxis is a standard regimen in Europe and is widely accepted in the United States and Canada. Clinical practice differs in North America and Europe regarding the initiation time of antithrombotic prophylaxis in surgical patients. In Europe, low-molecular-weight heparin is usually initiated 12 hours preoperatively. The European approach recognizes that deep vein thrombosis typically originates perioperatively and that preoperative prophylaxis may optimize antithrombotic effectiveness. Delayed initiation (12-24 hours postoperatively) of low-molecular-weight heparin prophylaxis is standard practice in North America to minimize bleeding risk. This difference in clinical practice has led to the expressed need (by the International Consensus Statement) for...
a level 1 randomized trial evaluating the time of initiation of low-molecular-weight heparin thromboprophylaxis.8

Low-molecular-weight heparin prophylaxis has been administered once daily in patients undergoing elective hip surgery, except in the United States, where the most common regimen has been twice daily. Clinical practice in the United States reflects initial regulatory agencies approval of a twice-daily low-molecular-weight heparin regimen.7,12,28 Subsequently, once-daily administration of low-molecular-weight heparin was approved because similar outcomes were observed by direct comparison with the twice-daily regimen in a double-blind randomized trial.19

It is possible that low-molecular-weight heparin administered in closer proximity to surgery, either immediately preoperatively or early postoperatively once daily, may be more effective than the present clinical practice. This just-in-time concept harmonizes with the understanding that the risk of thrombosis starts perioperatively.30-32 Recently, 2 published studies evaluated low-molecular-weight heparin prophylaxis administered either immediately preoperatively or early postoperatively vs oral anticoagulant prophylaxis.

In light of these studies, we performed a systematic review of the literature to assess the efficacy and safety of low-molecular-weight heparin administered at different times in relation to surgery vs the classic reference standard, oral anticoagulant prophylaxis.

MATERIALS AND METHODS

To ensure high methodologic quality, we adhered to the 15 criteria outlined by McAlister et al.35 The first 10 criteria assess methodologic rigor, and the last 5 assess the scientific basis of treatment recommendations.35 We systematically identified articles for inclusion in this analysis, described variations in study design and execution, evaluated study quality,36 and quantified the relative benefits of prophylaxis with low-molecular-weight heparin vs oral anticoagulants with respect to preoperative and postoperative initiation time in proximity to surgery.37

STUDY IDENTIFICATION

All published and unpublished randomized trials comparing prophylaxis using low-molecular-weight heparin vs oral anticoagulants in patients undergoing hip arthroplasty were included. A strategy was developed for locating all published studies in the MEDLINE database:

1. S1 keyword (LMWH or “low-molecular-weight heparin” or cleixane or clivar or CY 216 or CY 222 or dalteparin or enoxaparin or fraxiparine or logoiparin ceroxiparin or nadroparin or peparin or reviparin or tinzaparin) and kw (OAC or warfarin or coumadin).
2. S2 (S1 and kw prophylaxis).
3. S3 (S2 and kw hip).
4. S4 (S3 and kw (“deep-vein thrombosis” or “deep-venous thrombosis” or “venous thromboembolism” or “proximal vein thrombosis”)).
5. S5 (S4 and kw (randomized or randomised or randomly)).
6. S6 (S5 and kw (venograms or venography or phlebography)).

We augmented our MEDLINE search by manually reviewing the reference lists of original articles and review articles. We also reviewed abstracts from conference proceedings and contacted investigators and pharmaceutical companies. Abstracts reporting full methods and results were eligible for inclusion.

STUDY ELIGIBILITY

Two investigators (A.F.M. and S.M.M.) independently evaluated studies for inclusion; disagreements were resolved by discussion. Investigators were not blinded to journal, author, or institution. Studies were included if they (1) enrolled patients undergoing elective hip arthroplasty, (2) randomly assigned patients to treatment groups, (3) investigated the efficacy and safety of once-daily subcutaneous low-molecular-weight heparin compared with oral anticoagulants in the prevention of deep vein thrombosis, (4) objectively documented the presence or absence of deep vein thrombosis and proximal vein thrombosis by bilateral ascending contrast phlebography, and (5) used objective methods for assessing major bleeding complications. Deep vein thrombosis was defined as the presence of constant intraluminal filling defects in the deep veins; and proximal vein thrombosis, as constant intraluminal filling defects in the popliteal or more proximal deep veins. Safety was evaluated by documenting the frequency of bleeding complications.

VARIATION IN STUDY DESIGN AND EXECUTION

Two investigators (A.F.M. and S.M.M.) collected data on the following study-level factors: (1) type of low-molecular-weight heparin used, (2) timing of administration of low-molecular-weight heparin before or after surgery, (3) timing and adequacy of warfarin, (4) whether low-molecular-weight heparin dosing was fixed or weight adjusted, (5) whether a high-risk dose approved by regulatory agencies was used, and (6) the interval after surgery when phlebography was performed.

OTHER SOURCES OF POTENTIAL VARIABILITY

Two investigators (A.F.M. and S.M.M.) collected data on other variables potentially affecting study outcomes. These included patient characteristics on enrollment into the study, primary or revision hip replacement, anesthesia type (general and/or regional), and type of graduated pressure stockings.

ASSESSMENT OF STUDY QUALITY

Four key issues were reviewed to assess the quality and strength of the studies. They include (1) proper randomization derived from the use of a randomized numbers table or a computer program; (2) masking of the allocation sequences from the investigators, staff, and patients involved in the study; (3) use of double blinding; and (4) determining the proportion of patients who under-
went successful phlebography. Two investigators (A.F.M. and S.M.M.) extracted these data from the primary studies. When details were not reported in the articles, additional information was requested from the authors.

DATA EXTRACTION

Two investigators (A.F.M. and S.M.M.) independently extracted data on the frequency of the major outcomes: (1) all deep vein thrombosis, (2) proximal vein thrombosis, and (3) major bleeding complications as defined by the investigators. Data for other complications as defined by the international scientific committee, and (3) major bleeding complications as defined by the investigators.

Data for other variables, such as minor bleeding, wound hematomas, and thrombocytopenia, were also recorded. The selections of studies for inclusion in the analysis by the 2 investigators were compared, and the percentage agreement and k coefficient were between the 2 investigators were calculated. Investigator disagreements were resolved by discussion.

DATA ANALYSIS AND STATISTICAL ANALYSIS

For each of the major outcomes in the individual studies, we calculated absolute risk reduction, relative risk reduction, odds ratio, number needed to treat to prevent one thromboembolic event, and number needed to harm to cause one major bleeding event. We considered P<.05 to be statistically significant for all statistical tests. P values, number needed to treat, and number needed to harm are reported when the comparison is significant. Analyses were performed using the Meta procedure of Stata, release 6.0. To assess the validity of combining results from individual studies, we used the Mantel-Haenszel test for statistical heterogeneity. We did not perform statistical analyses to pool results across studies because of heterogeneity (see the “Interstudy Analysis” subsection of the “Results” section).

Funnel plots were examined to evaluate interstudy variation in odds ratios for the 3 major outcomes in relation to sample size to assess the possibility that publication bias might be a contributing factor. Logistic regression methods were used in conjunction with analysis of deviance to assess other potential sources of heterogeneity. Linear mixed-effects models were applied to the variance-stabilized (arc sine-transformed) event rates to test the effect of close proximity administration of prophylaxis on these rates, and to the odds ratios to obtain the quadratic fit. By incorporating oral anticoagulant group event rates as controls in this analysis, it was possible to take into account the contribution of nonsystematic between-study variation.

A secondary analysis was performed including the one study that used a unilateral phlebogram; the effects of including the once-daily low-molecular-weight heparin group from this study on heterogeneity, funnel plots, and logistic regression analysis were evaluated.

RESULTS

STUDY IDENTIFICATION AND SELECTION

Our MEDLINE and manual search strategies identified 149 potentially relevant studies. One hundred forty-two of these articles were excluded after reviewing their titles and abstracts: 62 were unrelated to thromboprophylaxis in patients undergoing hip arthroplasty, 60 were reviews or letters to the editor, 4 were surveys of physician practice, 9 were cost-effectiveness analyses, 4 were meta-analyses, and 3 were not randomized controlled trials. The remaining 7 articles were original studies of low-molecular-weight heparin used for prophylaxis against deep vein thrombosis in patients undergoing hip arthroplasty and were retained for further evaluation.

Of these 7 articles, 3 were subsequently excluded from our analysis because they did not meet the a priori eligibility criteria outlined in the “Study Eligibility” subsection of the “Materials and Methods” section: one did not use phlebographic evidence of deep vein thrombosis as the end point, one used unilateral rather than bilateral phlebography and included a twice-daily administered low-molecular-weight heparin group, and one addressed the postphlebographic outcome of patients for a trial already included in our analysis. Interrater agreement for study eligibility was 100% (κ=1.0). These articles were published between 1994 and 2000.

DESCRIPTION OF VARIATION IN STUDY METHODS

Table 1 displays study design characteristics and methodologic quality among the 4 included studies. The low-molecular-weight heparins evaluated were tinzaparin sodium,17 nadroparin calcium,21 and dalteparin sodium.25,34 Initiation of low-molecular-weight heparin prophylaxis was 18 to 24 hours postoperatively in one study,17 the evening of the preoperative day in one study,21 and 2 hours preoperatively in another study.22 The remaining study41 evaluated separate randomized groups for preoperative (within 2 hours of surgery) and postoperative (4–6 hours after surgery) low-molecular-weight heparin initiation.

The specific doses used for each low-molecular-weight heparin evaluated were the high-risk doses with demonstrated effectiveness in patients undergoing elective hip arthroplasty and approved by regulatory agencies (Table 1). For the 2 studies that initiated prophylaxis in close proximity to surgery, the preoperative regimens initiated prophylaxis using a split dose (half the usual high-risk dose given just before surgery and half given shortly after surgery)25,34 and the postoperative regimen initiated prophylaxis using half the usual high-risk dose shortly after surgery.41 Full high-risk doses were resumed the day after surgery. Two studies7,21 used weight-adjusted doses of low-molecular-weight heparin, and 25,34 used fixed doses.

Initiation of oral anticoagulant prophylaxis in the control group occurred the day before surgery in 2 studies21,25 and on the evening of the day of surgery in 2 studies7,34 (Table 1). In all studies, the oral anticoagulant dose was adjusted daily to maintain equivalence with an international normalized ratio between 2.0 and 3.0. Each study is a contributing factor. Logistic regression methods were used in conjunction with analysis of deviance to assess other potential sources of heterogeneity. Linear mixed-effects models were applied to the variance-stabilized (arc sine-transformed) event rates to test the effect of close proximity administration of prophylaxis on these rates, and to the odds ratios to obtain the quadratic fit. By incorporating oral anticoagulant group event rates as controls in this analysis, it was possible to take into account the contribution of nonsystematic between-study variation.

A secondary analysis was performed including the one study that used a unilateral phlebogram; the effects of including the once-daily low-molecular-weight heparin group from this study on heterogeneity, funnel plots, and logistic regression analysis were evaluated.

RESULTS

STUDY IDENTIFICATION AND SELECTION

Our MEDLINE and manual search strategies identified 149 potentially relevant studies. One hundred forty-two of these articles were excluded after reviewing their titles and abstracts: 62 were unrelated to thromboprophylaxis in patients undergoing hip arthroplasty, 60 were reviews or letters to the editor, 4 were surveys of physician practice, 9 were cost-effectiveness analyses, 4 were meta-analyses, and 3 were not randomized controlled trials. The remaining 7 articles were original studies of low-molecular-weight heparin used for prophylaxis against deep vein thrombosis in patients undergoing hip arthroplasty and were retained for further evaluation.

Of these 7 articles, 3 were subsequently excluded from our analysis because they did not meet the a priori eligibility criteria outlined in the “Study Eligibility” subsection of the “Materials and Methods” section: one did not use phlebographic evidence of deep vein thrombosis as the end point, one used unilateral rather than bilateral phlebography and included a twice-daily administered low-molecular-weight heparin group, and one addressed the postphlebographic outcome of patients for a trial already included in our analysis. Interrater agreement for study eligibility was 100% (κ=1.0). These articles were published between 1994 and 2000.

DESCRIPTION OF VARIATION IN STUDY METHODS

Table 1 displays study design characteristics and methodologic quality among the 4 included studies. The low-molecular-weight heparins evaluated were tinzaparin sodium,17 nadroparin calcium,21 and dalteparin sodium.25,34 Initiation of low-molecular-weight heparin prophylaxis was 18 to 24 hours postoperatively in one study,17 the evening of the preoperative day in one study,21 and 2 hours preoperatively in another study.22 The remaining study41 evaluated separate randomized groups for preoperative (within 2 hours of surgery) and postoperative (4–6 hours after surgery) low-molecular-weight heparin initiation.

The specific doses used for each low-molecular-weight heparin evaluated were the high-risk doses with demonstrated effectiveness in patients undergoing elective hip arthroplasty and approved by regulatory agencies (Table 1). For the 2 studies that initiated prophylaxis in close proximity to surgery, the preoperative regimens initiated prophylaxis using a split dose (half the usual high-risk dose given just before surgery and half given shortly after surgery)25,34 and the postoperative regimen initiated prophylaxis using half the usual high-risk dose shortly after surgery.41 Full high-risk doses were resumed the day after surgery. Two studies7,21 used weight-adjusted doses of low-molecular-weight heparin, and 25,34 used fixed doses.

Initiation of oral anticoagulant prophylaxis in the control group occurred the day before surgery in 2 studies21,25 and on the evening of the day of surgery in 2 studies7,34 (Table 1). In all studies, the oral anticoagulant dose was adjusted daily to maintain equivalence with an international normalized ratio between 2.0 and 3.0. Each study
achieved therapeutic international normalized ratios in many patients: 76% by day 3 in one study, 17 70% by day 4 in another, 21 66% by day 2 in a third, 25 and 86% by day 6 in the remaining study. 34 The day phlebography was performed after surgery varied among the studies, ranging from 5.7 34 to 10 days 21 (Table 1).

ASSESSMENT OF STUDY QUALITY

All studies used proper randomization techniques and objective methods for the detection of deep vein thrombosis (Table 1). Two studies, 17,34 were double blinded, and 21,25 were single blinded. One single-blinded study 25 reviewed efficacy and safety outcomes by a central adjudication committee that was unaware of treatment allocation, the patients’ clinical findings, or the results of other diagnostic tests. The other single-blinded study 25 reviewed all lung scans and pulmonary angiograms by an independent third-party evaluator who did not have knowledge of the treatment group assignment. The proportion of patients undergoing successful phlebography is reported in Table 1. A summary of clinical characteristics of the patient populations is reported in Table 2.

DATA ANALYSIS

Individual study findings for all and proximal deep vein thrombosis are shown in Table 3 and in Figure 1 and Figure 2. The effect of the time from surgery when prophylaxis was initiated on the rate of deep vein thrombosis for the low-molecular-weight heparin groups from each study is shown in Figure 3. A large absolute risk reduction was observed in the 2 trials 23,34 initiating low-molecular-weight heparin at half the usual high-risk dose in close proximity to surgery. These close-proximity regimens administered prophylaxis less than 2 hours before surgery, 23,34 or 4 to 6 hours after surgery. 34 This large absolute risk reduction was not observed in patients receiving low-molecular-weight heparin administered using the conventional timing of 12 to 24 hours before surgery 23 or 18 to 24 hours after surgery. 17

Individual study findings for major bleeding are shown in Table 3 and Figure 4. Major bleeding was significantly more frequent in only one study 34; this occurred in the group administered low-molecular-weight heparin preoperatively in close proximity to surgery. The frequencies of minor bleeding, thrombocytopenia, and wound hematomas were similar and low for each

Table 1. Characteristics and Methodologic Quality of Studies Included in the Systematic Review*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>No. of Patients</th>
<th>Prophylaxis Type</th>
<th>Time of Initiation of Prophylaxis</th>
<th>Frequency of Administration</th>
<th>Dose</th>
<th>Time toVenography, Mean ± SD, d</th>
<th>Double Blinding</th>
<th>Patients Undergoing Successful Venography‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al, 17 1993</td>
<td>398</td>
<td>Tinzaparin</td>
<td>Postop: 18-24 h</td>
<td>Once daily</td>
<td>NA</td>
<td>75 IU/kg</td>
<td>9.4 ± 3.5</td>
<td>Yes</td>
</tr>
<tr>
<td>397</td>
<td>Warfarin</td>
<td>Postop: evening before the day of surgery</td>
<td>Adjusted daily</td>
<td>NA</td>
<td>INR 2-3</td>
<td>INR 2-3</td>
<td>9.4 ± 3.5</td>
<td></td>
</tr>
<tr>
<td>Hamulyák et al, 1995</td>
<td>330</td>
<td>Nadroparin</td>
<td>Preop: evening before the day of surgery</td>
<td>Once daily</td>
<td>3075 IU</td>
<td>10 ± 2</td>
<td>No</td>
<td>517/672 (76.9)</td>
</tr>
<tr>
<td>334</td>
<td>Acenocoumarol</td>
<td>Preop: day before surgery</td>
<td>Adjusted daily</td>
<td>4 mg</td>
<td>2 mg</td>
<td>INR 2-3</td>
<td>10 ± 2</td>
<td></td>
</tr>
<tr>
<td>Francis et al, 1997</td>
<td>288</td>
<td>Dalteparin</td>
<td>Preop: ~2 h</td>
<td>Once daily</td>
<td>2500 IU</td>
<td>8 ± 2</td>
<td>No</td>
<td>382/580 (65.9)</td>
</tr>
<tr>
<td>292</td>
<td>Warfarin</td>
<td>Preop: evening before the day of surgery</td>
<td>Adjusted daily</td>
<td>5.0-7.5 mg</td>
<td>5.0-7.5 mg</td>
<td>INR 2.5</td>
<td>7 ± 2</td>
<td></td>
</tr>
<tr>
<td>Hull et al, 2000</td>
<td>496</td>
<td>Dalteparin</td>
<td>Preop: ~2 h</td>
<td>Once daily</td>
<td>2500 IU</td>
<td>5.7 ± 1.2</td>
<td>Yes</td>
<td>110/5/1472 (75.1)</td>
</tr>
<tr>
<td>487</td>
<td>Dalteparin</td>
<td>Postop: 4-6 h</td>
<td>Once daily</td>
<td>NA</td>
<td>5-10 mg</td>
<td>INR 2-3</td>
<td>5.7 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>489</td>
<td>Dalteparin</td>
<td>Postop: evening of day of surgery</td>
<td>Adjusted daily</td>
<td>NA</td>
<td>5000 IU</td>
<td>5.7 ± 1.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Preop indicates preoperatively; Postop, postoperatively; INR, international normalized ratio; and NA, data not applicable. Tinzaparin was given as tinzaparin sodium; warfarin, warfarin sodium; nadroparin, nadroparin calcium; and dalteparin, dalteparin sodium.
†In all studies, there was proper randomization, ie, there was generation and masking of the allocation sequence.
‡Data are given as the number of patients/total number of patients in that group (percentage).
§Oral anticoagulants were adjusted daily by a prescriptive protocol according to the prothrombin INR findings using a predefined nomogram.
¶Includes patients undergoing hip and knee arthroplasty.
‡Data are given as the number of patients/total number of patients in that group (percentage).
* Patients weighing 57 kg or less received 5.0 mg; and those weighing more than 57 kg, 7.5 mg.
©2001 American Medical Association. All rights reserved.
Table 2. Clinical Characteristics of Patients in Studies Included in the Systematic Review*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Male-Female Ratio</th>
<th>Age, y†</th>
<th>Cemented‡</th>
<th>Duration of Anesthesia, min†</th>
<th>General/Regional/Combined Anesthesia§</th>
<th>Primary/Revision Surgery§</th>
<th>Graduated Pressure Stockings</th>
<th>Previous VTE</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hull et al,17 1993</td>
<td>181:217</td>
<td>66 ± 12</td>
<td>123</td>
<td>128 ± 52</td>
<td>235/18/145</td>
<td>309/89</td>
<td>NR</td>
<td>0</td>
<td>30/368</td>
</tr>
<tr>
<td>Warfarin sodium</td>
<td>162:235</td>
<td>66 ± 12</td>
<td>154</td>
<td>127 ± 48</td>
<td>230/23/144</td>
<td>305/92</td>
<td>NR</td>
<td>0</td>
<td>35/362</td>
</tr>
<tr>
<td>Hamulyák et al,21 1995¶</td>
<td>92:238</td>
<td>67 ± 10</td>
<td>NR</td>
<td>NR</td>
<td>151/179#</td>
<td>238/0</td>
<td>330/330</td>
<td>0</td>
<td>8/330</td>
</tr>
<tr>
<td>Acenocoumarol</td>
<td>98:244</td>
<td>67 ± 11</td>
<td>NR</td>
<td>NR</td>
<td>179/163#</td>
<td>244/0</td>
<td>342/342</td>
<td>0</td>
<td>10/342</td>
</tr>
<tr>
<td>Francis et al,25 1997</td>
<td>127:147</td>
<td>63 ± 13</td>
<td>NR</td>
<td>NR</td>
<td>80/271</td>
<td>221 ± 75</td>
<td>183/88#</td>
<td>207/64</td>
<td>NR</td>
</tr>
<tr>
<td>Warfarin sodium</td>
<td>132:147</td>
<td>63 ± 14</td>
<td>83/279</td>
<td>225 ± 67</td>
<td>177/102#</td>
<td>194/85</td>
<td>NR</td>
<td>25/279</td>
<td>36/292</td>
</tr>
<tr>
<td>Hull et al,34 2000</td>
<td>248:248</td>
<td>64 ± 12</td>
<td>112/496</td>
<td>NR</td>
<td>327/122/47</td>
<td>406/88</td>
<td>140/496</td>
<td>27/496</td>
<td>59/496</td>
</tr>
<tr>
<td>Preoperatively</td>
<td>219:268</td>
<td>63 ± 13</td>
<td>122/487</td>
<td>NR</td>
<td>341/100/46</td>
<td>397/87</td>
<td>139/487</td>
<td>23/487</td>
<td>46/292</td>
</tr>
<tr>
<td>Warfarin sodium</td>
<td>242:247</td>
<td>63 ± 13</td>
<td>110/489</td>
<td>NR</td>
<td>314/105/70</td>
<td>420/69</td>
<td>135/489</td>
<td>23/489</td>
<td>37/489</td>
</tr>
</tbody>
</table>

*Data are given as the number of patients/total number of patients who responded in that group unless otherwise indicated. VTE indicates venous thromboembolism; LMWH, low-molecular-weight heparin; and NR, not reported.
†Data are given as the mean ± SD.
‡Indicates patients who underwent cemented hip replacement surgery.
§Data are given as the number of patients in each group.
| One patient in the LMWH group and 2 in the warfarin sodium group had an unknown prosthesis.
¶Includes patients who underwent hip and knee surgery.
#Anesthesia reported as general/regional; combined anesthesia not reported.

Table 3. Individual Study Findings*

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Oral Anticoagulant Group</th>
<th>Absolute Risk Reduction, % (95% CI)</th>
<th>P Value</th>
<th>NNT or NNH†</th>
<th>Relative Risk Reduction, %</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source, y</td>
<td>LMWH Group</td>
<td>Oral Anticoagulant Group</td>
<td>Absolute Risk Reduction, % (95% CI)</td>
<td>P Value</td>
<td>NNT or NNH†</td>
<td>Relative Risk Reduction, %</td>
</tr>
<tr>
<td>Studies Using Remote From Surgery LMWH Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hull et al,17 1993</td>
<td>All DVTs</td>
<td>69/332 (20.8)</td>
<td>79/340 (23.2)</td>
<td>. . . . . . . . . . . . 0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>16/332 (4.8)</td>
<td>13/340 (3.8)</td>
<td>. . . . . . . . . . . . 1.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding‡</td>
<td>11/398 (2.8)</td>
<td>6/397 (1.5)</td>
<td>. . . . . . . . . . . . 1.85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamulyák et al,21 1995¶</td>
<td>All DVTs</td>
<td>27/195 (13.8)</td>
<td>27/196 (13.8)</td>
<td>. . . . . . . . . . . . 1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>12/195 (6.2)</td>
<td>9/196 (4.6)</td>
<td>. . . . . . . . . . . . 1.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding‡</td>
<td>3/250 (1.2)</td>
<td>7/269 (2.6)</td>
<td>. . . . . . . . . . . . 0.45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies Using Close Proximity to Surgery LMWH Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Francis et al,25 1997</td>
<td>All DVTs</td>
<td>28/192 (14.6)</td>
<td>49/190 (25.8)</td>
<td>11.2 (3.2-19.2)</td>
<td>.006</td>
<td>9</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>10/192 (5.2)</td>
<td>16/190 (8.4)</td>
<td>. . . . . . . . . . . . 0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding‡</td>
<td>6/271 (2.2)</td>
<td>4/279 (1.4)</td>
<td>. . . . . . . . . . . . 1.56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hull et al,34 2000</td>
<td>Preoperative group</td>
<td>All DVTs</td>
<td>36/337 (10.7)</td>
<td>81/338 (24.0)</td>
<td>13.3 (7.6-18.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>3/354 (0.8)</td>
<td>11/363 (3.0)</td>
<td>2.2 (0.2-4.2)</td>
<td>.04</td>
<td>46</td>
<td>72.0</td>
</tr>
<tr>
<td>Major bleeding‡</td>
<td>18/496 (3.6)</td>
<td>15/489 (3.1)</td>
<td>. . . . . . . . . . . . 1.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site investigator classified</td>
<td>44/496 (8.9)</td>
<td>22/489 (4.5)</td>
<td>4.4 (1.3-7.5)</td>
<td>.006</td>
<td>23</td>
<td>−97.2</td>
</tr>
<tr>
<td>Centrally adjudicated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative group</td>
<td>All DVTs</td>
<td>44/336 (13.1)</td>
<td>81/338 (24.0)</td>
<td>10.9 (5.1-16.7)</td>
<td>&lt;.001</td>
<td>10</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>3/358 (0.8)</td>
<td>11/363 (3.0)</td>
<td>2.2 (0.2-4.2)</td>
<td>.03</td>
<td>46</td>
<td>72.2</td>
</tr>
<tr>
<td>Major bleeding‡</td>
<td>12/487 (2.5)</td>
<td>15/489 (3.1)</td>
<td>. . . . . . . . . . . . 0.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site investigator classified</td>
<td>32/487 (6.6)</td>
<td>22/489 (4.5)</td>
<td>. . . . . . . . . . . . 1.49</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as the number of patients/total number of patients in that group (percentage) unless otherwise indicated. CI indicates confidence interval; NNT, number needed to treat; NNH, number needed to harm; LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; and ellipses, data not provided because difference was not significant.
†Data are given as the number of patients.
‡As defined by the investigators.
study across randomized groups (data not shown).

**INTERSTUDY ANALYSIS**

Statistical tests detected heterogeneity between studies for total and proximal deep vein thrombosis (P < .02 for each outcome). Consequently, the results for these studies were not pooled. Indeed, a pooled analysis would have masked the impact of the time of administration of low-molecular-weight heparin prophylaxis.

A separate examination of the low-molecular-weight heparin and oral anticoagulant arms revealed significant interstudy variability (low-molecular-weight heparin, P = .004; and oral anticoagulants, P = .01). Among the oral anticoagulant arms, heterogeneity was attributable to the low event rate in one study. A mixed-effects analysis indicated that a significant (P = .008) decrease in deep vein thrombosis rates in the studies using close proximity to surgery prophylaxis protocols accounted for the heterogeneity between low-molecular-weight heparin arms.

For proximal deep vein thrombosis, results were heterogeneous, with the timing of initiation of prophylaxis accounting for a statistically significant (P = .004) component of variability. There was no strong indication of heterogeneity in the results for major bleeding events.

One hip arthroplasty prophylaxis study was not included in our primary review because it did not meet the inclusion criteria of having performed bilateral phlebography (unilateral phlebography was performed). The study included a once- and a twice-daily low-molecular-weight heparin group. The results of including both study groups and the once-daily group alone were consistent with the results arising from the main data set.

Inverted funnel plots of study odds ratios vs study sample size were uninformative because of the similarity of the sample sizes among the studies and are, therefore, not presented.

**INTRASTUDY ANALYSIS AND THE QUADRATIC FUNCTION**

An analysis using the $\chi^2$ test, the Fisher exact test, and the t test found that the clinical characteristics of patients were comparable across treatment groups within each study.

An intrastudy analysis of the comparative frequencies of deep vein thrombosis expressed as relative odds is shown in Table 3. The relationship between the odds ratios for deep vein thrombosis occurrence for each trial and the time of administration based on a quadratic function is shown in Figure 3. A visual understanding of the findings derived from within each clinical trial is provided by the quadratic figure; the peak efficacy for low-molecular-weight heparin ranges between 2 hours preoperatively and 6 to 8 hours postoperatively.

**COMMENT**

Our analysis identifies that the interval between surgery and the first administration of low-molecular-weight heparin is a critical variable that significantly influences the occurrence of deep vein thrombosis in patients undergoing elective hip arthroplasty. Low-
molecular-weight heparin begun in close proximity to hip arthroplasty either preoperatively or postoperatively.17,21 Initiated at half the usual high-risk dose was more effective than low-molecular-weight heparin regimens that were administered 12 hours preoperatively or 12 to 18 hours postoperatively.17,21 The just-in-time postoperative regimen (low-molecular-weight heparin administered 4-6 hours after surgery) provided superior efficacy vs oral anticoagulant treatment without significantly increased overt bleeding34 (Table 3). In contrast, the close-proximity preoperative regimen (<2 hours before surgery), although highly effective, resulted in increased major bleeding.34

Traditionally in North America, low-molecular-weight heparin prophylaxis for patients undergoing hip arthroplasty has been delayed postoperatively for at least 12 to 24 hours to minimize bleeding.7,12,17,19,20 European practice has largely used low-molecular-weight heparin 12 hours preoperatively,8,11,13-15,18,21,24,26-29 recognizing that deep vein thrombosis typically commences perioperatively.30-32,44 The findings of the randomized trials25,34 that administered low-molecular-weight heparin in a modified regimen (the initial dose was half the usual high-risk dose) in close proximity to surgery indicate the need to administer prophylaxis close to the time of surgery. The aggregate data suggest that either 12 hours preoperatively or 18 to 24 hours postoperatively is temporally too distant from the time of perioperative initiation of venous thrombosis. The just-in-time postoperative low-molecular-weight heparin regimen administered in close proximity to surgery, unlike the immediate preoperative regimen, did not sacrifice safety.

Our findings are unlikely to be due to differences in the patient characteristics (Table 1); these were comparable within each study for the randomized groups. The interval to phlebography and the duration of prophylaxis were also comparable within each study.

The time of initiation of oral anticoagulant prophylaxis did not influence our findings. Indeed, independent clinical trial data45-47 show similar efficacy for this delayed onset of action prophylactic regimen, whether given preoperatively or postoperatively.

The low-molecular-weight heparin regimens evaluated in this review for in-hospital prophylaxis have been shown to be effective in multiple randomized trials. The dose of low-molecular-weight heparin administered is unlikely to be a significant variable, as high-risk doses based on documented effectiveness and approved by the regulatory agencies were used. The particular low-molecular-weight heparin used varied, but recent randomized trials18,29 suggest that specific high-risk low-molecular-weight heparin regimens in patients undergoing elective hip arthroplasty have similar effectiveness and safety profiles.

Our findings are consistent with emerging results of clinical trials evaluating newer antithrombotic regimens using the close proximity to surgery prophylaxis approach. Regimens using either bithridin administered immediately before or a pentasaccharide administered early after hip arthroplasty were compared with low-molecular-weight heparin initiated 12 hours preoperatively or postoperatively48-50; these close-proximity regimens were more effective. Furthermore, studies51-55 demonstrated that low-dose unfractionated heparin was effective in at-risk patients; low-dose heparin prophylaxis was administered 2 hours preoperatively. Our data suggest that the best efficacy with heparin-derived compounds is obtained between 2 hours preoperatively and 6 to 8 hours postoperatively.

Recently in the United States, there has been concern about the associated use of neuraxial anesthesia and low-molecular-weight heparin prophylaxis because of a cluster of spinal hematomas.56,57 In Europe, there has not been a reported cluster of spinal hematomas. This intriguing difference between Europe and the United States in bleeding complications may arise from local practice patterns,56,57 with a predominant tendency toward once-daily low-molecular-weight heparin prophylaxis in Europe and twice-daily prophylaxis using a higher total daily dose in the United States. Since half the usual high-risk dose of low-molecular-weight heparin is administered using the close-proximity postoperative regimen and the average time of initiation after spinal anesthesia was 9 hours, the close-proximity postoperative regimen may be a safe approach in conjunction with a spinal anesthesia.39

In conclusion, our findings strongly suggest that the present practice in the United States and Canada of delayed initiation of
low-molecular-weight heparin prophylaxis 12 to 24 hours postoperatively results in suboptimal antithrombotic effectiveness without evidence of a substantive safety advantage.

Accepted for publication April 27, 2001.

From the Thrombosis Research Unit (Dr Hull), University of Calgary, Calgary, Alberta; St Joseph Mercy Oakland, Pontiac, Mich; the Research Forum, Department of Orthopaedics, Uppsala University Hospital, Oslo, Norway (Dr Dahl); Uppsala University, Uppsala, Sweden (Dr Bergqvist); the Department of Haematology, University Hospital Maastricht, Maastricht, the Netherlands (Dr Hamulyak); the Vascular Medicine Unit, University of Rochester Medical Center, Rochester, NY; Vascular Medicine Program, Los Angeles Orthopaedic Hospital/University of California, Los Angeles (Dr Marder); and the University of Oklahoma Health Sciences Center, Oklahoma City (Dr Raskob). We thank Adrian Jorgenson, BSc, Jeanne Sheldon, BA, Rita Bie, BSc, Vicki Stagg, and Jennifer Ringrose, MSc, for their assistance.

Corresponding author and reprint: Russell D. Hull, MBBS, Thrombosis Research Unit, Foothills Hospital, Room 601 South Tower, 1403 29th St NW, Calgary, Alberta, Canada T2N 2T9 (e-mail: Jeanne.Sheldon@chra-health.ca).

REFERENCES


©2001 American Medical Association. All rights reserved.