Low-Molecular-Weight Heparin Prophylaxis Using Dalteparin Extended Out-of-Hospital vs In-Hospital Warfarin/Out-of-Hospital Placebo in Hip Arthroplasty Patients

A Double-blind, Randomized Comparison

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Background: No randomized trials have directly evaluated the need for extended out-of-hospital thromboprophylaxis for patients who have hip arthroplasty in the United States or Canada. The uncertainty as to the need for extended prophylaxis in North American patients is complicated by early hospital discharge, resulting in a short thromboprophylaxis interval.

Methods: To resolve this uncertainty, we performed a randomized double-blind trial in 569 patients who underwent hip arthroplasty comparing the use of dalteparin sodium started immediately before surgery or early after surgery and extended out-of-hospital to an overall interval of 35 days with the use of warfarin sodium in-hospital and placebo out-of-hospital.

Results: For patients with interpretable venograms in the preoperative, postoperative, and combined dalteparin groups, new proximal vein thrombosis out-of-hospital was observed in 1.3%, 0.7% (P=.04), and 1.0% (P=.02) of patients, respectively, compared with 4.8% in the in-hospital warfarin/out-of-hospital placebo group. The respective overall cumulative frequencies of all deep vein thrombosis were 30 (17.2%) of 174 patients (P<.001), 38 (22.2%) of 171 (P=.003), and 68 (19.7%) of 345 (P<.001) in the dalteparin groups compared with 69 (36.7%) of 188 for the in-hospital warfarin/out-of-hospital placebo group. For proximal deep vein thrombosis, the respective frequencies were 3 (3.1%) of 162 (P=.02), 3 (2.0%) of 151 (P=.007), and 8 (2.6%) of 313 (P=.002) compared with 14 (9.2%) of 153. No major bleeding occurred during the extended prophylaxis interval.

Conclusions: Extended dalteparin prophylaxis resulted in significantly lower frequencies of deep vein thrombosis compared with in-hospital warfarin therapy. Despite in-hospital thromboprophylaxis, patients having hip arthroplasty in the United States and Canada remain at moderate risk out-of-hospital. The number needed to treat provides a public health focus; only 24 to 28 patients require extended prophylaxis to prevent 1 new out-of-hospital proximal vein thrombosis. Recent studies demonstrate that asymptomatic deep vein thrombi cause the postphlebitic syndrome; thus, extended out-of-hospital prophylaxis will lessen the burden to both the patient and society.

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The use of accurate objective testing by ascending contrast venography to detect deep vein thrombosis in patients who undergo hip arthroplasty has led to randomized trials of various prophylactic regimens against venous thromboembolism. The need for in-hospital prophylaxis has been firmly established. Indeed, evidence-based medicine guidelines recommend low-molecular-weight heparin or warfarin prophylaxis in patients having elective hip surgery (grade A1 level of certainty). The results of randomized trials performed in Europe suggest a need for extended out-of-hospital prophylaxis in hip arthroplasty patients. In contrast, investigators of limited outcome descriptive studies performed in North America have inferred from the relatively low rates of clinically evident venous thromboembolism observed on long-term follow-up that out-of-hospital prophylaxis is not required. For these reasons, the Fifth American College of Chest Physicians Consensus Conference stated, “Emerging level 1 data suggest that a 29- to 35-day duration of low-molecular-weight heparin prophylaxis may offer additional protection. This is an A2 recommendation because of uncertainty regarding the risk-benefit ratio.”

See also page 2199
PATIENTS AND METHODS

STUDY DESIGN

Our study was a multicenter, randomized, double-blind clinical trial comparing 3 prophylactic regimens in patients who had undergone hip arthroplasty. Patients were allocated to receive subcutaneous dalteparin sodium (Fragmin; Pharmacia & Upjohn, Stockholm, Sweden) once daily, initiated either preoperatively or postoperatively and continued for 35 ± 2 days, or warfarin sodium (Coumadin; Dupont Pharmaceuticals, Wilmington, Del) in-hospital (6 ± 2 days) followed by placebo injection out-of-hospital to 35 ± 2 days. Eighteen centers in the United States and Canada participated in this extended prophylaxis trial.

The protocol was approved by each center’s institutional review board. Twenty-nine centers in the United States and Canada participated in our overall clinical trial program. Patients from all centers participated in an in-hospital study, which is described in detail elsewhere. The primary outcome end points were venogram-confirmed deep vein and proximal deep vein thrombosis.

A priori, 18 centers were selected to participate in a concurrent study to investigate extended out-of-hospital prophylaxis. Fewer centers were required because of the smaller sample size required for this study. Patients from these 18 centers consented at study entry to participate in the combined in-hospital and out-of-hospital protocol.

PATIENTS

Consecutive eligible patients aged 18 years and older scheduled for elective unilateral total hip arthroplasty (primary or revision) who gave informed consent were enrolled. Patients were ineligible for in-hospital and out-of-hospital prophylaxis if they had any of the following (the rationale for not including patients with these characteristics was largely based on safety or the avoidance of contamination): documented bleeding within 3 months before surgery; known hypersensitivity to heparin, low-molecular-weight heparin, warfarin, or contrast media; defective hemostasis (eg, thrombocytopenia <100 × 10^9/L), ongoing anticoagulant therapy; pregnancy or breastfeeding; clinically significant hepatic dysfunction; renal insufficiency (serum creatinine >1.7 mg/dL); severe hypertension (diastolic blood pressure >120 mm Hg); septic endocarditis; weight less than 40 kg; eye, ear, or central nervous system surgery within 1 month before hip surgery; diseases with unfavorable prognosis (eg, malignancy) or concurrent disease making study participation impractical or medically complicated; simultaneous participation in another pharmacological study or participation impractical or medically complicated; simultaneous participation in another pharmacological study or participation impractical or medically complicated; simultaneous participation in another pharmacological study or participation impractical or medically complicated; simultaneous participation in another pharmacological study.

TREATMENT REGIMENS

Patients randomized to preoperative dalteparin received their initial 2500-IU subcutaneous dalteparin sodium injection within 2 hours before surgery (mean ± SD, 34.4 ± 47.1 minutes) only if the surgical procedure was uncomplicated. The patients initiated preoperative dalteparin received a second dose of dalteparin sodium, 2500 IU subcutaneously 4 or more hours postoperatively (mean ± SD, 7.1 ± 2.4 hours). Patients randomized to receive postoperative dalteparin received a placebo injection immediately before surgery as described above. Their first active dalteparin injection was administered 4 or more hours postoperatively (mean ± SD, 7.2 ± 2.7 hours). On subsequent days, all patients receiving dalteparin sodium were given 3000 IU subcutaneously once daily each morning.

During the acute in-hospital interval, patients randomized to receive warfarin (both warfarin and placebo for warfarin were administered in capsules to maintain blinding) also received a subcutaneous placebo injection once daily, and patients assigned to dalteparin received placebo capsules until hospital discharge. During the extended out-of-hospital prophylaxis interval, patients randomized to the placebo regimen discontinued warfarin and received placebo injections until day 35 ± 2; patients continued the dalteparin regimen using 5000 IU once daily until day 35 ± 2. The description of the double-dummy technique used during the in-hospital phase to maintain blinding of each patient’s treatment assignment is described elsewhere.

Anticoagulant use (other than study treatment), acetylsalicylic acid, dipyridamole, ticlopidine, and pneumatic compression devices were prohibited during the study. The use of nonsteroidal anti-inflammatory drugs was strongly discouraged.

SURVEILLANCE AND FOLLOW-UP

Patients were examined daily during the acute hospital stay; a follow-up visit was performed on day 35 ± 2. Bleeding episodes, perioperative and postoperative blood loss, blood replacement requirements, and platelet levels were documented. Patients in whom overt symptoms and/or signs of deep vein thrombosis or pulmonary embolism developed underwent objective testing. Noninvasive screening for deep vein thrombosis was not performed in patients without clinically suspected deep vein thrombosis because such screening is relatively insensitive in this context.

All patients consented to undergo bilateral ascending radiopaque venography. This was performed on day 6 ± 2 or at the time of hospital discharge if this occurred earlier. A second venogram was obtained at the end of the extended prophylaxis interval (day 35 ± 2) except when the patient had a positive venographic finding on day 6 ± 2. Venography was performed and the results interpreted according to a method described elsewhere.

Constant intraluminal filling defects in the popliteal, superficial femoral, common femoral, external iliac, or common iliac veins (with or without constant intraluminal filling defects in the deep veins of the calf) were classified as proximal vein thrombosis; those confined to the deep veins of the calf were classified as calf vein thrombosis. The venographic findings were classified as normal if the deep veins of the calf and the proximal deep veins (including the popliteal, superficial femoral, common femoral, and...
A recent epidemiological study using a linked hospital discharge database provided by the State of California reports the outcome in 19,586 patients undergoing a primary hip arthroplasty. Ninety-five percent of patients received in-hospital prophylaxis. Of the patients with symptomatic venous thrombembolism, 76% experienced these events after discharge from the hospital (median time, 17 days after surgery). The overall frequency of documented venous thromboembolism within 3 months of surgery was 2.8%. This symptomatic rate is lower than incidence rates reported in studies using screening venography, reflecting the fact that in most cases the venous thrombi do not cause symptoms that patients or physicians perceive as significant. However, these thrombi, and in particular proximal vein thrombi, are the source for fatal pulmonary embolism. Thus, a randomized clinical trial using all thrombosis and proximal deep vein thrombosis events as end points should provide clinically useful information.

The diagnosis of fatal pulmonary embolism is problematic. Proximal vein thrombosis is readily detected by contrast venography. Epidemiological data have identified that proximal deep vein thrombosis is a striking prognostic marker for a poor outcome due to subsequent pulmonary embolism. Thus, a randomized clinical trial using all thrombosis and proximal deep vein thrombosis events as end points should provide clinically useful information.

Overall patient recruitment and flow through the study protocol are shown in the Figure. Of the 569 patients in the study, 199 received preoperative dalteparin (commenced immediately before surgery), 190 received postoperative dalteparin (commenced early after surgery), and 180 received warfarin in-hospital (commenced the evening of the day of surgery) and placebo out-of-hospital (Figure).

The characteristics of the patients were similar among the out-of-hospital treatment groups (Table 1). Venography was successful in a high proportion of patients (Figure); unsuccessful or inadequate venography was equally distributed among the 3 treatment groups. The primary end points were deep vein and proximal deep vein thrombosis as determined by venography. Since thrombosis rates of both dalteparin arms were adequate visualization of both legs.

Venograms were interpreted by the local radiologist and an independent, blinded central reader. Disagreements between the local radiologist and the central reader were resolved by a second blinded central independent interpretation; this second reading was decisive. The same process occurred in occasional patients with suspected pulmonary embolism who underwent lung scanning or pulmonary angiography.

Bleeding was documented according to a widely used international classification. Bleeding was classified as major if it was clinically overt and associated with a decrease in hemoglobin level of 20 g/L or more, if it required the transfusion of 2 or more units of blood, if it was intracranial, intraocular, intraspinal, or retroperitoneal, or if it occurred into a prosthetic joint. Bleeding was defined as minor if it was clinically overt without meeting the major bleeding criteria, and defined as trivial if it was clearly of no consequence. Wound hematomas that occurred in the absence of clinically overt blood loss were documented, as were associated complications (infection, persistent drainage, wound dehiscence, and prolongation of the hospital stay). Two central committee members not involved in the patient’s care independently adjudicated the bleeding data using the international classification; disagreements were resolved by the independent safety monitor.

If patients had clinically evident venous thrombosis, objective testing with duplex ultrasonography or ascending contrast venography was required. For patients with suspected pulmonary embolism, objective documentation was required by a high-probability lung scan, a pulmonary angiogram, or autopsy. The methods of performing and interpreting the objective tests are reported in detail elsewhere.

**STATISTICAL ANALYSIS**

It was estimated that 900 patients (300 per treatment group) would be required. This estimate was based on cumulative deep vein thrombosis rates on day 0 to 35±2 of 21% and 40% for patients receiving preoperative dalteparin vs in-hospital warfarin/out-of-hospital placebo. The sample size required for a detectable treatment difference with a power of 0.80 (2-tailed test) at the .05 significance level requires at least 102 patients per group. If an ineligible frequency of approximately 60% from start of phase 1 is considered, about 253 patients are required for each group.

The uncorrected $\chi^2$ test and Fisher exact test (depending on event frequency) were used to compare the frequencies of death, venous thrombosis events, and bleeding events among the treatment groups during the out-of-hospital period. Unless otherwise noted, reported $P$ values reflect the uncorrected $\chi^2$. Cochran-Mantel-Haenszel tests and Mantel-Haenszel estimates were applied to assess relative risks for all and proximal deep vein thrombosis rates after stratification by study period (ie, acute in-hospital and extended out-of-hospital). Analysis of deviance based on logistic regression was used to evaluate center variability. All $P$ values were 2-tailed. Ninety-five percent confidence intervals for the difference between 2 treatment groups in the incidence of venous thrombosis and bleeding complications were calculated with the normal approximation to the binomial distribution.
consistent during the out-of-hospital interval and during the entire study interval, we included pooled results for these 2 arms (Table 2).

OUT-OF-HOSPITAL PROPHYLAXIS

Deep Vein Thrombosis by Venography

The incidences of new deep vein thrombosis by venography during the out-of-hospital interval (day 6 to 35 ± 2) are shown in Table 2. Among patients with interpretable venograms during the extended out-of-hospital interval, the frequencies for all deep vein thrombosis for the preoperative, postoperative, and combined dalteparin groups, respectively, compared with placebo were 8 (5.3%) of 152, 6 (4.3%) of 139 (P = .05), and 14 (10.5%) of 133. For patients with proximal vein thrombosis, the respective frequencies were 2 (1.3%) of 159, 1 (0.7%) of 149 (P = .04 by Fisher exact test), and 3 (1.0%) of 308 (P = .02 by Fisher exact) vs 7 (4.8%) of 146 (Table 2).

Bleeding Complications and Thrombocytopenia

There were no major bleeding events during the extended out-of-hospital prophylaxis interval (Table 3). An excess of trivial bleeding was observed for the patients receiving preoperative dalteparin compared with placebo (17.6% vs 8.9%; P = .02) and for patients receiving postoperative dalteparin compared with placebo (20.0% vs 8.9%; P = .002). The majority of trivial bleeding events consisted of bruising at the injection site. The rates of minor bleeding complications and wound hematomas were low and similar among the groups; complicated wound hematomas were rare (Table 3). There were no decreases in platelet counts to less than

Table 1. Clinical Characteristics of Patients Who Received Out-of-Hospital Prophylaxis or Placebo*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Preoperative Dalteparin (n = 199)</th>
<th>Postoperative Dalteparin (n = 190)</th>
<th>Warfarin In-Hospital/Placebo (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62 ± 12</td>
<td>63 ± 12</td>
<td>63 ± 12</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82 ± 17</td>
<td>80 ± 17</td>
<td>81 ± 18</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168 ± 11</td>
<td>167 ± 10</td>
<td>169 ± 11</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29 ± 6</td>
<td>29 ± 6</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135 ± 19</td>
<td>136 ± 21</td>
<td>136 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80 ± 11</td>
<td>81 ± 11</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>106/93</td>
<td>87/103</td>
<td>94/86</td>
</tr>
<tr>
<td>Previous venous thromboembolism</td>
<td>8</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Previous pulmonary embolism</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>History of varicose veins</td>
<td>44</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>History of malignancy</td>
<td>28</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>History of chronic heart failure</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>146</td>
<td>144</td>
<td>145</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Arterial necrosis</td>
<td>7</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hip replacement</td>
<td>170</td>
<td>158</td>
<td>159</td>
</tr>
<tr>
<td>Revision hip replacement</td>
<td>29</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Cemented</td>
<td>30</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>Noncemented</td>
<td>114</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>Other†</td>
<td>55</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>Type of anesthesia‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidural</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Spinal</td>
<td>81</td>
<td>72</td>
<td>84</td>
</tr>
<tr>
<td>General</td>
<td>142</td>
<td>150</td>
<td>133</td>
</tr>
<tr>
<td>Combined general and epidural or spinal</td>
<td>27</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Graduated pressure stocking use</td>
<td>15</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD or number of patients. Dalteparin was given as dalteparin sodium and warfarin as warfarin sodium.
†Other types of fixation include hybrid, noncemented acetabular plus cemented femur, cancellous bone screw, cement plus screws, and bone graft.
‡Patients may be included in more than 1 category.

Clinically Evident Thromboembolic Events

Twenty-eight patients had objectively documented deep vein thrombosis during the out-of-hospital interval, of which 7 were symptomatic; thus, the majority had asymptomatic deep vein thrombosis (75%). These symptomatic thrombi occurred in 3 (2.0%) of 152, 1 (0.7%) of 139, and 3 (2.3%) of 133 of the patients receiving preoperative dalteparin, postoperative dalteparin, or warfarin, respectively.

No patients had symptomatic, objectively documented pulmonary embolism. One patient in the warfarin arm died of myocardial infarction.
Table 2. Deep Vein Thrombosis by Venography in the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Immediately Preoperative Dalteparin</th>
<th>Early Postoperative Dalteparin</th>
<th>Combined Preoperative and Postoperative Dalteparin</th>
<th>Warfarin In-Hospital/Placebo Out-of-Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of All Deep Vein Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-hospital study interval, proportion (%) of patients</td>
<td>8/152 (5.3)</td>
<td>6/139 (4.3)</td>
<td>14/291 (4.8)</td>
<td>14/133 (10.5)</td>
</tr>
<tr>
<td>Absolute risk reduction, % (95% CI)</td>
<td>5.3 (~1.1 to 11.6)</td>
<td>6.2 (0.0 to 12.4)</td>
<td>5.7 (~0.1 to 11.5)</td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction vs placebo, %</td>
<td>...</td>
<td>59 (P = .05)</td>
<td>54 (P = .03)</td>
<td></td>
</tr>
<tr>
<td>Overall interval (cumulative frequencies),† proportion (%) of patients</td>
<td>30/174 (17.2)</td>
<td>38/171 (22.2)</td>
<td>68/345 (19.7)</td>
<td>69/188 (36.7)</td>
</tr>
<tr>
<td>Absolute risk reduction, % (95% CI)</td>
<td>19.5 (10.6 to 28.3)</td>
<td>14.5 (5.2 to 23.8)</td>
<td>17.0 (8.9 to 25.1)</td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction vs in-hospital warfarin/out-of-hospital placebo, %</td>
<td>55 (P&lt;.001)</td>
<td>41 (P = .003)</td>
<td>48 (&lt;.001)</td>
<td></td>
</tr>
<tr>
<td>Frequency of Proximal Deep Vein Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Out-of-hospital study interval, proportion (%) of patients</td>
<td>2/159 (1.3)</td>
<td>1/149 (0.7)</td>
<td>3/308 (1.0)</td>
<td>7/146 (4.8)</td>
</tr>
<tr>
<td>Absolute risk reduction, % (95% CI)</td>
<td>3.5 (~0.3 to 7.4)</td>
<td>4.1 (0.4 to 7.8)</td>
<td>3.8 (0.2 to 7.5)</td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction vs placebo, %</td>
<td>...</td>
<td>85 (P = .04)</td>
<td>79 (P = .02)</td>
<td></td>
</tr>
<tr>
<td>Overall interval (cumulative frequencies),‡ proportion (%) of patients</td>
<td>5/162 (3.1)</td>
<td>3/151 (2.0)</td>
<td>8/313 (2.6)</td>
<td>14/153 (9.2)</td>
</tr>
<tr>
<td>Absolute risk reduction, % (95% CI)</td>
<td>6.1 (0.8 to 11.4)</td>
<td>7.2 (2.1 to 12.1)</td>
<td>6.6 (1.7 to 11.5)</td>
<td></td>
</tr>
<tr>
<td>Relative risk reduction vs in-hospital warfarin/out-of-hospital placebo, %</td>
<td>67 (P = .02)</td>
<td>79 (P = .007)</td>
<td>73 (P = .002)</td>
<td></td>
</tr>
</tbody>
</table>

*C.I indicates confidence interval; ellipses, data not applicable.
†Patients with proximal or distal deep vein thrombosis by central adjudication during the overall study interval.
‡Patients with distal deep vein thrombosis by central adjudication during the in-hospital interval without an adequate out-of-hospital venogram because it was not known whether the patient developed proximal deep vein thrombosis out-of-hospital and (2) including patients whose out-of-hospital venogram showed adequately visualized for the proximal segments.
§One patient with symptomatic clinically suspected deep vein thrombosis was confirmed by duplex ultrasonography (during the interval).
**By Fisher exact test.

CUMULATIVE FREQUENCIES OF DEEP VEIN THROMBOSIS

Since clinical practice includes in-hospital prophylaxis, we have provided the cumulative results that reflect the entire in-hospital and out-of-hospital study prophylaxis interval (up to day 35±2). Deep vein thrombosis venographic results during the entire study interval (day 0 to 35±2) are shown in Table 2. Cumulative frequencies for all deep vein thrombosis of patients in the preoperative, postoperative, and combined dalteparin groups compared with the in-hospital warfarin/out-of-hospital placebo group were 30 (17.2%) of 174 (P<.001), 38 (22.2%) of 171 (P = .003), and 68 (19.7%) of 345 (P<.001) vs 69 (36.7%) of 188. For proximal deep vein thrombosis, the respective frequencies were 5 (3.1%) of 162 (P = .02), 3 (2.0%) of 151 (P = .007), and 8 (2.6%) of 313 (P = .002) vs 14 (9.2%) of 153 (Table 2).

COMMENT

Out-of-hospital thromboprophylaxis using dalteparin resulted in lower frequencies of all and proximal deep vein thrombosis compared with a regimen of in-hospital warfarin followed by placebo out-of-hospital. For the cumulative in-hospital and out-of-hospital period, both preoperative and postoperative dalteparin use was significantly superior to in-hospital warfarin followed by placebo in reducing the rates of all and proximal deep vein thrombosis.

Our study protocol enabled assessment of new deep vein thrombosis rates out-of-hospital (Table 2). Proximal deep vein thrombosis occurred not infrequently in patients receiving placebo out-of-hospital (7 [4.8%] of 146 patients); this represented 50% of all proximal deep vein thrombosis observed during the entire study interval. Out-of-hospital dalteparin use was associated with substantive risk reductions; the observed rates for proximal deep vein thrombosis were 1.3%, 0.7% (P = .04 by Fisher exact test), and 1.0% (P = .02 by Fisher exact test) for preoperative, postoperative, and combined dalteparin groups, respectively.

European trials of extended low-molecular-weight heparin prophylaxis vs in-hospital low-molecular-weight heparin/out-of-hospital placebo have shown the need for and the effectiveness26-31 of prolonged thromboprophylaxis in the European context.

Our findings demonstrate that patients who undergo hip arthroplasty in the United States and Canada, despite in-hospital thromboprophylaxis, remain at moderate risk after discharge from the hospital. For moderate-risk patients, the Fifth American College of Chest Physicians Consensus Conference (1998) has recommended the use of thromboprophylaxis at an A1 level of certainty. Our findings for patients undergoing elective hip arthroplasty in the United States and Canada demonstrate that for patients receiving only in-hospital warfarin followed by placebo out-of-hospital, frequencies of deep vein and proximal vein thrombosis for the cumulative study interval and for the extended out-of-hospital interval are more frequent or similar to those observed in unprotected moderate-risk patients. It is illogical to infer that out-of-hospital prophylaxis is not warranted, given the fact that placebo rates are similar to those
Table 3. Bleeding Complications During the Extended Out-of-Hospital Interval in the Study Groups

<table>
<thead>
<tr>
<th>Event</th>
<th>Preoperative Dalteparin (n = 199)</th>
<th>Postoperative Dalteparin (n = 190)</th>
<th>Placebo (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3 (1.5)</td>
<td>4 (2.1)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Melena</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hemitrhea</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bruising at injection site</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous*</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Trivial bleeding</td>
<td>35 (17.6)‡</td>
<td>38 (20.0)§</td>
<td>16 (8.9)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bruising at injection site</td>
<td>31</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Miscellaneous†</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Wound hematoma</td>
<td>Complicated</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>5 (2.5)</td>
<td>4 (2.1)</td>
<td>5 (2.8)</td>
</tr>
</tbody>
</table>

* Miscellaneous minor bleeding included hematochezia, hematoma at intravenous access, bleeding due to dental extraction, and bleeding from urethra around catheter.
† Miscellaneous trivial bleeding included hemorrhoids, hematoma at intravenous access, subconjunctival bleeding, and bruising at noninjection site.
‡ Preoperative dalteparin sodium (17.6%) vs warfarin sodium (8.9%), P = .02.
§ Postoperative dalteparin (20.0%) vs warfarin (8.9%), P = .002.

observed in moderate-risk patients. Our findings demonstrate that patients undergoing elective hip surgery in the United States and Canada are at continued moderate risk of out-of-hospital if unprotected. It would be reasonable, provided that extended out-of-hospital low-molecular-weight heparin is a safe treatment (a favorable benefit to risk ratio), to consider an A1 recommendation23,25 for out-of-hospital prophylaxis.

There were no major bleeding complications in the 3 treatment groups. Similar low rates of minor bleeding were observed among the groups. Trivial bleeding occurred more frequently in patients receiving dalteparin during extended prophylaxis (Table 3); this was largely due to bruising at the injection site. These aggregate findings indicate that the benefit of out-of-hospital prophylaxis is not outweighed by the risk for bleeding.

Patients undergoing elective hip arthroplasty are now being discharged earlier from the hospital. The mean time of discharge from the hospital for patients participating in our study was approximately 5 days. Based on an abundance of level 1 trials, the 1998 American College of Chest Physicians Consensus Report has recommended a minimum prophylactic interval of 7 to 10 days.24 Irrespective of the debate for the need for prolonged extended out-of-hospital prophylaxis, this recommendation obliges clinicians in Canada and the United States to consider prophylaxis out-of-hospital because the in-hospital stay is too short to provide adequate thromboprophylaxis.

The rates of proximal deep vein thrombosis in the in-hospital warfarin/out-of-hospital placebo group (5%-9%) predict that a cohort or descriptive study would have to include many thousands of patients to rule out a significant frequency of clinically evident pulmonary embolism. To date, none of the cohort studies32-36 arguing against the need for out-of-hospital prophylaxis has sufficient power to do so. The rates of proximal deep vein thrombosis observed here would be expected to be associated with a frequency of fatal pulmonary embolism of between 0.3% and 0.5% provided autopsies were done in all patients who died.24,60,61 Unfortunately, autopsy rates are low in studies reported to date. Recent autopsy data continue to demonstrate that in the majority of patients who die of pulmonary embolism, fatal pulmonary embolism was not considered to be the cause of death prior to autopsy.62-65 Data from a National Confidential Enquiry Into Perioperative Deaths in the United Kingdom provide evidence that pulmonary embolism constitutes a significant cause of mortality following total hip replacement.66,67

Recent data demonstrate the important clinical observation that asymptomatic deep vein thrombosis is associated with an increased risk of postphlebitic syndrome.66 The postphlebitic syndrome is well documented to be a significant cause of morbidity and an economic burden to both the patient and society. Thus, reducing the frequency of asymptomatic deep vein thrombosis will lessen this burden.

During the in-hospital stay, warfarin was ineffective by comparison with dalteparin administered in close proximity to surgery.19,43 We chose to follow in-hospital warfarin prophylaxis with an out-of-hospital placebo group to settle the debate about the risks and benefits of extended prophylaxis using low-molecular-weight heparin regimens shown to be superior in-hospital. In-hospital administration of warfarin was adequate; 86% of patients achieved adequate anticoagulation by day 6.

Our findings cannot be attributed to bias; randomization was successful because the baseline characteristics of the patients were comparable among groups, and the study was conducted in a double-blind fashion to avoid bias in searching for or interpreting events. The proportion of patients evaluated of those eligible are comparable to other rigorous randomized trials evaluating pharmacological interventions.3-22,26-29 Adequate venography was successful in a high proportion of patients. The frequencies of symptomatic venous thromboembolism were inevitably low due to case finding by venography leading to early treatment of deep vein thrombosis.

The concept of number needed to treat provides a useful public health overview69,70; only 24 to 28 patients require out-of-hospital dalteparin treatment to prevent 1 new episode of out-of-hospital proximal vein thrombosis compared with placebo. From a population perspective, extended prophylaxis will prevent 41 cases of proximal deep vein thrombosis for every 1000 patients having elective hip surgery. Even if the death rate is as low as 8% of these 41 cases, extended prophylaxis will allow the saving of about 3.5 lives per 1000 patients undergoing elective hip surgery to early treatment of deep vein thrombosis.

The concept of number needed to treat provides a useful public health overview69,70; only 24 to 28 patients require out-of-hospital dalteparin treatment to prevent 1 new episode of out-of-hospital proximal vein thrombosis compared with placebo. From a population perspective, extended prophylaxis will prevent 41 cases of proximal deep vein thrombosis for every 1000 patients having elective hip surgery. Even if the death rate is as low as 8% of these 41 cases, extended prophylaxis will allow the saving of about 3.5 lives per 1000 patients undergoing elective hip surgery to be preventable; for every 500000 patients undergoing elective hip surgery in North America, extended prophylaxis would save 1750 lives. Even if the death rate is as low as 0.1%,71 this still reflects 500 lives saved.
Our findings in patients discharged from the hospital early, together with the data from Europe strongly indicate the need for out-of-hospital prophylaxis. The effectiveness and safety of out-of-hospital low-molecular-weight heparin prophylaxis is evident. Determining the cost-effectiveness of extended prophylaxis for 1 month is beyond the scope of this article and should be addressed separately. Preliminary data from other studies suggest that extended prophylaxis is cost-effective.22,23 Patient compliance did not detract from the study; the majority of patients self-administered the once-daily subcutaneous dalteparin injection.

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A list of additional participants of North American Fragmin Trial appears in the box above. We would like to thank Gary Raskob, PhD, of the Clinical Epidemiology Unit, University of Oklahoma Health Sciences Center, Oklahoma City.

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