Low-Molecular-Weight Heparin Prophylaxis Using Dalteparin in Close Proximity to Surgery vs Warfarin in Hip Arthroplasty Patients

A Double-blind, Randomized Comparison

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Background: Based on the current understanding that venous thrombosis starts perioperatively, administration of just-in-time low-molecular-weight heparin immediately before or in close proximity after hip arthroplasty may be more effective than usual clinical practice.

Methods: We performed a randomized, double-blind trial comparing subcutaneous dalteparin sodium given once daily immediately before or early after surgery with the use of postoperative warfarin sodium in 1472 patients undergoing elective hip arthroplasties. The primary end point was deep vein thrombosis detected using contrast venography performed after surgery (mean, 5.7 days) in each group.

Results: The frequencies of deep vein thrombosis for patients with interpretable venograms receiving preoperative and postoperative dalteparin for all deep vein thrombosis were 36 (10.7%) of 337 (P < .001) and 44 (13.1%) of 336 (P < .001), respectively, vs 81 (24.0%) of 338 for warfarin; for proximal deep vein thrombosis, 3 (0.8%) of 354 (P = .03) and 3 (0.8%) of 358 (P = .03), respectively, vs 11 (3.0%) of 363. Relative risk reductions for the dalteparin groups ranged from 45% to 72%. Symptomatic thrombi were less frequent in the preoperative dalteparin group (5/337 patients [1.5%]) vs the warfarin group (15/338 patients [4.4%]) (P = .02). Serious bleeding was similar among groups. Increased major bleeding at the surgical site was observed for patients receiving preoperative dalteparin vs warfarin (P = .01).

Conclusions: A modified dalteparin regimen in close proximity to surgery resulted in substantive risk reductions for all and proximal deep vein thrombosis, compared with warfarin therapy. Such findings have not been observed with low-molecular-weight heparin therapy commenced 12 hours preoperatively or 12 to 24 hours postoperatively vs oral anticoagulants. Increased major but not serious bleeding occurred in patients receiving preoperative dalteparin. Dalteparin therapy initiated postoperatively provided superior efficacy vs warfarin without significantly increased overt bleeding.

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*References 8-11, 13-16, 18, 21-24, 26-29.

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PATIENTS AND METHODS

STUDY DESIGN

This study was a multicenter, randomized, double-blind clinical trial comparing 3 prophylactic regimens in patients undergoing hip arthroplasty. Regimens consisted of dalteparin sodium (Fragmin; Pharmacia & Upjohn, Stockholm, Sweden) and warfarin sodium (Coumadin; Dupont Pharmaceuticals, Wilmington, Del). Twenty-nine centers in the United States and Canada participated in the trial. The efficacy and safety of these approaches were evaluated during the acute hospital stay (day 0-6 ± 2). A second concurrent study investigated extended out-of-hospital prophylaxis; this is beyond the scope of this article and will be reported separately. The protocol was approved by each center’s institutional review board.

PATIENTS

We enrolled consecutive eligible patients aged at least 18 years and scheduled for elective unilateral total hip arthroplasty (primary or revision) who gave informed consent. Patients were eligible if they had none of the following: 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 anticoagulants; pregnancy or breastfeeding; clinically significant hepatic dysfunction; renal insufficiency (serum creatinine level, > 150 μmol/L [> 1.7 mg/dL]); severe hypertension (diastolic blood pressure, > 120 mm Hg); septic endocarditis; weight of less than 40 kg; eye, ear, or central nervous system surgery within 1 month before surgery; diseases with unfavorable prognosis (eg, malignant neoplasms or other intercurrent disease making study participation impractical or medically complicated); inability to follow instructions or perform procedures, including self-injections required during the home prophylaxis study; simultaneous participation in another pharmacological study or use of any investigational drug within 30 days before surgery; previous randomization into this study; or use of placebo capsules and injections and the assignment of an independent anticoagulant monitor to adjust INR values maintained double-blinding throughout the study. Of the 3114 patients undergoing screening, 1585 consented to participate. The remaining did not participate because of ongoing anticoagulant use or defective hemostasis (258 patients); diseases with unfavorable prognosis or intercurrent diseases making participation impractical (264 patients); inability to perform procedures (eg, self-injections) required by the study (337 patients); participation declined (1990 patients); previous randomization into the trial (98 patients); or miscellaneous reasons (382 patients).

TREATMENT REGIMENS

Patients randomized to preoperative dalteparin sodium received their initial 2500-IU subcutaneous injection within 2 hours before surgery (mean ± SD, 49 ± 49 minutes) and only if the spinal procedure was uncomplicated. These patients received a second dose of dalteparin sodium, 2500 IU, subcutaneously at least 4 hours postoperatively (mean ± SD, 6.6 ± 2.3 hours). Patients randomized to postoperative dalteparin received a placebo injection immediately before surgery as described above. Their first active dalteparin injection was administered at least 4 hours postoperatively (mean ± SD, 6.6 ± 2.4 hours). On subsequent days, all patients receiving dalteparin sodium were given 5000 IU subcutaneously once daily each morning.

Patients randomized to warfarin received an initial dose postoperatively on the evening of surgery day. The initial dose was 10 mg, except for patients aged 70 years or older or weighing less than 57 kg, who received a 5-mg dose. Thereafter, warfarin doses were adjusted daily using a prescriptive protocol according to the prothrombin international normalized ratio (INR) findings with a predefined warfarin nomogram. Patients randomized to receive warfarin also received subcutaneous placebo injections. Patients randomized to receive dalteparin also received placebo capsules (warfarin and its placebo were encapsulated to maintain blinding). To maintain blinding of each patient’s treatment assignment, the prothrombin time results were not recorded in the patient’s chart or reported to the health care team. The INR results were reported only to an unblinded anticoagulant monitor not involved in assessing outcomes. Daily warfarin dose adjustments or dummy orders (for patients receiving placebo capsules for warfarin) were made by the unblinded anticoagulant monitor according to a prescribed dosage schedule. Thus, the use of placebo capsules and injections and the assignment of an independent anticoagulant monitor to adjust INR values maintained double-blinding throughout the study.

Use of anticoagulants (other than study treatment), aspirin, dipyridamole, ticlopidine hydrochloride, and pneumatic compression devices was prohibited during the study. The use of nonsteroidal anti-inflammatory drugs was strongly discouraged.
SURVEILLANCE AND FOLLOW-UP

All patients were examined daily. 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 surveillance for deep vein thrombosis was not performed in patients without clinically suspected deep vein thrombosis, because results of such screening are relatively insensitive in this context.\(^{36-41}\)

Bilateral ascending radiocontrast venography was mandated by the protocol and was performed on day 6±2 or at the time of discharge from hospital if this occurred earlier. Venography was performed and the results were interpreted as described elsewhere.\(^{42,43}\) 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. 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, external iliac, and common iliac veins) were visualized adequately in both legs.

Venograms were interpreted by the local radiologist and an independent, blinded central reader (R.D.H.). Disagreements between the local radiologist and the central reader were resolved by a second blinded independent central 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.\(^{44,45}\) Bleeding was classified as major if it was clinically overt and associated with a decrease in hemoglobin level of 20 g/L or more or required transfusion of 2 U of blood or more; 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 as trivial if it was clearly of no consequence. Wound hematomas that occurred in the absence of clinically overt blood 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\(^{44,45}\); disagreements were resolved by the independent safety monitor (D.B.).

The frequency of major bleeding was also reported by the site investigator. This differed from the centrally adjudicated bleeding rates as the site investigator decided whether the bleeding was clinically important based on clinical judgment. In contrast, the centrally adjudicated bleeding rates were determined only by the information reported in the case report forms using the criteria described above, which were applied to all reports of bleeding independent of the site investigators’ clinical judgment.

In a previous study\(^{25}\) where low-molecular-weight heparin was given within 2 hours before surgery and where safety events were reported based on clinical judgment, there was an increased number of transfusions given in the low-molecular-weight heparin group compared with the warfarin group. The reason, however, for the increased transfusions could not be identified by the recorded blood loss or incidence of major bleeding. For this reason, central adjudication of safety events in our trial included all events from the commencement of surgery up to postoperative day 8.

Serious bleeding as defined by Eriksson et al\(^{26}\) is also provided in the results. Serious bleeding is defined to include patients receiving transfusion of more than 5 U of whole blood or concentrates of red blood cells perioperatively, patients receiving transfusion of more than 7 U of whole blood or concentrates of red blood cells anytime after surgery, or patients with total blood loss of more than 3500 mL.\(^{26}\)

If patients had clinically suspected venous thrombosis, objective testing with duplex ultrasonography or ascending contrast venography was required. For patients with suspected pulmonary embolism, objective documentation was required using high-probability lung scan, pulmonary angiogram, or autopsy findings. The methods of performing and interpreting the objective tests are reported in detail elsewhere.\(^{44,46-48}\)

STATISTICAL ANALYSIS

We estimated that 1500 patients (500 per treatment group) would be required. This was based on deep vein thrombosis rates on day 6±2 of 12% vs 20% for patients receiving preoperative dalteparin vs warfarin, respectively. The sample size required for a detectable treatment difference with a power of 80% at the 5% significance level (2-tailed test) requires at least 354 patients per group. If an unequivocal frequency of 20% is considered, about 442 patients are required for each group.

The uncorrected χ² was used to compare frequencies of venous thrombosis, bleeding, and death among treatment groups. The Fisher exact test was not used, as expected event frequencies exceeded 5 in all cases. Analysis of deviance based on logistic regression was used to evaluate center variability.\(^{49}\) 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.\(^{49}\)

RESULTS

Of 1501 consecutive randomized patients, 496, 487, and 489 patients receiving preoperative and postoperative dalteparin and warfarin, respectively, characteristics of the treatment groups were similar on entry (Table 1). Twenty-nine patients were randomized but did not receive study medication; this occurred because of traumatic spinal tap (1, 3, and 3 patients per group, respectively), cancelled operation, (0, 2, and 1 patients, respectively), presence of exclusion criteria (1, 1, and 1 patient, respectively), withdrawn...
Since thrombosis rates in both dalteparin arms were consistent, we pooled results for both arms (Table 2).

Among centers with 30 or more patients (9 centers), rates of deep vein thrombosis in the 3 treatment arms ranged from 0% to 7.1% for proximal deep vein thrombosis, and 4.4% to 44.8% for deep vein thrombosis overall. Analysis of all centers using logistic regression showed no evidence of interaction between treatment and center.

**BLEEDING COMPLICATIONS**

Bleeding complications are shown in **Table 3** and **Table 4**. Increased major bleeding was observed for the preoperative dalteparin group compared with the warfarin group (Table 3) (*P*= .01).

Major bleeding events documented by the local site investigators were infrequent and similar among groups. Serious bleeding episodes were also infrequent and similar among groups (Table 3).

Minor and trivial bleeding occurred infrequently (Table 3). Wound hematoma rates were similar among groups, and complicated wound hematomas were rare (Table 3).

Mean hemoglobin levels and blood loss were similar among groups (Table 5). The proportion of patients receiving transfusions was significantly higher (Table 5) for the dalteparin groups compared with the warfarin group (*P*= .001 and *P*= .002, respectively). Transfusion volumes were similar among groups (Table 5).

The frequency and distribution of thrombocytopenia (platelet count, <100 x 10^9/L) is shown in Table 5. Most had concomitant blood loss and decreased hemoglobin levels.

No patient had spinal or epidural hematomas or bleeding associated with neurologic defects.

**CLINICALLY EVIDENT THROMBOEMBOLIC EVENTS**

Objectively documented deep vein thrombosis was observed in 161 patients; only 30 (18.6%) of these patients were symptomatic (Table 2). Thrombosis in 27 of these 30 patients was documented using venography; in 3, using duplex ultrasound. Symptomatic thrombi occurred significantly less frequently in the preoperative dalteparin vs warfarin groups (*P*= .02) (Table 2).

No patient had objectively documented pulmonary embolism.

**PROTHROMBIN TIME (INR)**

Warfarin therapy was adjusted to achieve an INR of 2.0 to 3.0; INR results exceeded 2.0 in 86.0% of patients by day 6.

Our findings demonstrate that dalteparin in the immediate preoperative or early postoperative period was more effective than warfarin for preventing deep vein thrombosis in patients undergoing hip arthroplasty. Frequen-
thrombosis associated with preoperative dalteparin vs warfarin decreased substantially in patients receiving dalteparin; the relative risk reductions for all and proximal deep vein thrombosis were 55% (P = .001) vs 72% (P < .001) for deep vein thrombosis and 72% (P = .009) vs 72% (P = .00) for symptomatic deep vein thrombosis. Symptomatic thrombi occurred less frequently in the preoperative dalteparin group (5/337 patients [1.5%]) vs the warfarin group (15/338 patients [4.4%]) (P = .02).

Venography was performed early in our trial (mean, 5.7 days), but the rates of all and proximal deep vein thrombosis were due to myocardial infarction.

Table 2. Deep Vein Thrombosis by Venography, Objectively Documented Symptomatic Venous Thromboembolism, and Death*

<table>
<thead>
<tr>
<th>Event</th>
<th>Preoperative Dalteparin (n = 496)</th>
<th>Postoperative Dalteparin (n = 487)</th>
<th>Combined Dalteparin (n = 983)</th>
<th>Warfarin (n = 489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venogram unsuccessful or not performed†</td>
<td>83/496 (16.7)</td>
<td>73/487 (15.0)</td>
<td>156/983 (15.9)</td>
<td>75/489 (15.3)</td>
</tr>
<tr>
<td>Venography adequate</td>
<td>337/413 (81.6)</td>
<td>336/414 (81.2)</td>
<td>673/827 (81.4)</td>
<td>338/414 (81.6)</td>
</tr>
<tr>
<td>Visualization of all segments</td>
<td>354/413 (85.7)</td>
<td>358/414 (86.5)</td>
<td>712/827 (86.1)</td>
<td>363/414 (87.7)</td>
</tr>
<tr>
<td>Visualization of proximal segments only</td>
<td>5.7 ± 1.2</td>
<td>5.7 ± 1.3</td>
<td>...</td>
<td>5.7 ± 1.2</td>
</tr>
<tr>
<td>Frequency of all deep vein thrombosis</td>
<td>36/337 (10.7)</td>
<td>44/338 (13.1)</td>
<td>80/673 (11.9)</td>
<td>81/338 (24.0)</td>
</tr>
<tr>
<td>Absolute risk reduction, % (95% CI)</td>
<td>13.3 (7.6-18.9)</td>
<td>10.9 (5.1-16.7)</td>
<td>12.1 (6.9-17.2)</td>
<td>...</td>
</tr>
<tr>
<td>Symptomatic objectively documented deep vein thrombosis§</td>
<td>3/354 (0.8)</td>
<td>3/358 (0.8)</td>
<td>6/712 (0.8)</td>
<td>11/363 (3.0)</td>
</tr>
<tr>
<td>Absolute risk reduction, % (95% CI)</td>
<td>2.2 (0.2-4.2)</td>
<td>2.2 (0.2-4.2)</td>
<td>2.2 (0.2-4.2)</td>
<td>...</td>
</tr>
<tr>
<td>Relative risk reduction vs warfarin, % (P)</td>
<td>72 (.04)</td>
<td>72 (.03)</td>
<td>72 (.009)</td>
<td>...</td>
</tr>
<tr>
<td>Death¶</td>
<td>2/496 (0.4)</td>
<td>0/487</td>
<td>2/983 (0.2)</td>
<td>1/489 (0.2)</td>
</tr>
</tbody>
</table>

*Data are given as proportion (percentage) of patients, unless otherwise indicated. Dalteparin was given as dalteparin sodium; warfarin, as warfarin sodium.
†Two patients in the postoperative dalteparin arm and 1 patient in the warfarin arm received a diagnosis using positive ultrasound findings subsequent to reoperation.
‡P = .03 vs warfarin.
§Includes patients with adequate venograms for proximal segments (popliteal, superficial femoral, external, and common iliacs); calf may be inadequate.
¶One patient in the preoperative dalteparin group died abruptly while in hospital (no autopsy was performed); the other 3 deaths occurred during follow-up and were due to myocardial infarction.

Table 3. Frequency of Bleeding*

<table>
<thead>
<tr>
<th>Event</th>
<th>Preoperative Dalteparin (n = 496)</th>
<th>Postoperative Dalteparin (n = 487)</th>
<th>Warfarin (n = 489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>33 (6.7)</td>
<td>28 (5.7)</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>11 (2.2)</td>
<td>4 (0.8)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>6 (1.2)</td>
<td>8 (1.6)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Trivial bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>6 (1.2)</td>
<td>6 (1.2)</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>19 (3.8)</td>
<td>16 (3.3)</td>
<td>13 (2.7)</td>
</tr>
<tr>
<td>Wound hematoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated, day 0-8</td>
<td>2 (0.4)</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Uncomplicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>10 (2.0)</td>
<td>8 (1.6)</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>51 (10.3)</td>
<td>46 (9.4)</td>
<td>45 (9.2)</td>
</tr>
<tr>
<td>Site investigator-classified major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>14 (2.8)</td>
<td>9 (1.8)</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>4 (0.8)</td>
<td>3 (0.6)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Serious bleeding episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-8</td>
<td>10 (2.0)</td>
<td>5 (1.0)</td>
<td>8 (1.6)</td>
</tr>
</tbody>
</table>

*Data are given as proportion (percentage) of patients, unless otherwise indicated. Major bleeding includes surgical site bleeding, surgical site bleeding requiring transfusion, major bleeding requiring transfusion, and other major bleeding. Minor bleeding includes surgical site bleeding not requiring transfusion, minor bleeding requiring transfusion, and other minor bleeding.
†Prolonged hospitalization was associated with bleeding in 2, 0, and 4 patients in the preoperative and postoperative dalteparin, and warfarin arms, respectively. Dalteparin was given as dalteparin sodium; warfarin, as warfarin sodium.
‡Reasons included refusal, inability to perform for technical reasons, and contradiction for medical reasons, equally distributed among the treatment groups.
§Includes hematemesis (n = 3), hematuria (n = 2), melena (n = 1), or other (n = 6), similarly distributed among the treatment groups.
¶P = .02 vs warfarin.
†‡P = .04 vs warfarin.

Table 4. Description of Centrally Adjudicated Bleeding*

<table>
<thead>
<tr>
<th>Event</th>
<th>Preoperative Dalteparin (n = 496)</th>
<th>Postoperative Dalteparin (n = 487)</th>
<th>Warfarin (n = 489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical site bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>32 (6.5)</td>
<td>27 (5.5)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>9 (1.8)</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Other†</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical site bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0-1</td>
<td>...</td>
<td>1 (0.2)</td>
<td>...</td>
</tr>
<tr>
<td>Day 2-8</td>
<td>...</td>
<td>2 (0.4)</td>
<td>...</td>
</tr>
<tr>
<td>Other§</td>
<td>9 (1.8)</td>
<td>8 (1.6)</td>
<td>10 (2.0)</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not applicable.
†Includes hematemesis (n = 3), hematuria (n = 2), and epistaxis (n = 1).
‡P = .03 vs warfarin.
§Includes hematemesis (n = 3), hematuria (n = 15), melena (n = 1), epistaxis (n = 2), and miscellaneous (n = 6), similarly distributed among the treatment groups.
¶P = .04 vs warfarin.

Dalteparin were 55% (P < .001) vs 72% (P = .04), respectively; with postoperative dalteparin vs warfarin, 45% (P < .001) vs 72% (P = .03), respectively. The relative risk reduction for the combined dalteparin group vs warfarin was 50% (P < .001) for deep vein thrombosis and 72% (P = .009) for proximal vein thrombosis. Symptomatic thrombi occurred less frequently in the preoperative dalteparin group (5/337 patients [1.5%]) vs the warfarin group (15/338 patients [4.4%]) (P = .02).
thrombosis observed in the warfarin group were similar to those observed by means of venography performed in patients undergoing hip arthroplasty on days 7 through 14.17,21,25,50

The all and proximal deep vein thrombosis rates for the dalteparin groups were reduced markedly compared with the warfarin group and likely reflect the initiation of dalteparin therapy in close proximity to surgery. Warfarin and low-molecular-weight heparin thromboprophylaxis are recommended by the 1998 American College of Chest Physicians Consensus Conference for patients undergoing elective hip surgery.5 Warfarin traditionally has been used; however low-molecular-weight heparin regimens are assuming increasing predominance. At the time of our clinical trial program implementation, warfarin was the dominant prophylactic approach used in North America. The use of a delayed prophylaxis regimen of low-molecular-weight heparin was not standard clinical practice.

In North America, low-molecular-weight heparin prophylaxis in patients undergoing hip arthroplasty is usually delayed postoperatively for at least 12 to 24 hours to minimize bleeding.7,12,17,19,20 Despite high-risk doses or a twice-daily regimen, these regimens have not shown significant reductions in all or proximal deep vein thrombosis rates compared with warfarin or unfractionated heparin prophylaxis in patients undergoing hip arthroplasty.7,12,17,19,20

We administered low-molecular-weight heparin postoperatively in close proximity to surgery (mean±SD, 6.6±2.4 hours). To minimize bleeding, the initial postoperative dalteparin sodium dose was only half the high-risk dose (2500 IU); the usual high-risk dose (5000 IU) subcutaneously was resumed the next day. We found that postoperative dalteparin administered early in close proximity to surgery was more effective than warfarin, without a significant increase in major bleeding. This finding is in contrast to studies using 12- to 24-hour postoperative low-molecular-weight heparin regimens that have failed to demonstrate significant risk reductions against oral anticoagulants,17,21 while providing supportive evidence of the superiority of the close proximity strategy.

Dalteparin administered in close proximity to surgery also resulted in unusually low proximal deep vein thrombosis rates compared with those found in European randomized trials that initiated low-molecular-weight heparin therapy 12 hours preoperatively in patients undergoing hip arthroplasty.9 Low-molecular-weight heparin therapy commenced the evening before hip implant surgery was compared with acenocoumarol therapy commenced the day before surgery in an open-label randomized trial in Europe; results of venographic evaluation showed similar proximal and all deep vein thrombosis rates (6.5% vs 5.8%, respectively, and 16.5% vs 19.5%, respectively). Dalteparin therapy commenced 2 hours preoperatively in an open-label hip implant study was significantly more effective than warfarin therapy commenced the evening before surgery.25 These findings suggest that our thromboprophylaxis approach in close proximity to surgery is more effective.4

Recently, hirudin administered immediately before hip arthroplasty surgery was compared with low-molecular-weight heparin therapy commenced 12 hours preoperatively.20 The just-in-time thrombin-inhibitor regimen was more effective, and serious bleeding episodes were infrequent; these observations are also consistent with our findings.

Major bleeding at the operative site was significantly more frequent in patients receiving preoperative dalteparin vs warfarin using central adjudication (Tables 3 and 4). The centrally adjudicated major bleeding rate

### Table 5. Blood Loss, Blood Replacement, Transfusion Frequency, Hemoglobin Levels, and Incidence of Thrombocytopenia

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Preoperative Dalteparin (n = 496)</th>
<th>Postoperative Dalteparin (n = 487)</th>
<th>Warfarin (n = 489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean perioperative blood loss, mL, day 0</td>
<td>869 ± 937</td>
<td>811 ± 676</td>
<td>799 ± 773</td>
</tr>
<tr>
<td>Mean postoperative blood loss, mL</td>
<td>461 ± 427</td>
<td>493 ± 367</td>
<td>476 ± 297</td>
</tr>
<tr>
<td>Day 1-8</td>
<td>182 ± 178</td>
<td>199 ± 193</td>
<td>196 ± 158</td>
</tr>
<tr>
<td>Transfusion frequency, proportion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>209/496 (42.1)</td>
<td>199/487 (40.9)</td>
<td>185/489 (37.8)</td>
</tr>
<tr>
<td>Day 1-8</td>
<td>212/496 (42.7) †</td>
<td>183/487 (37.6) †</td>
<td>138/489 (28.2)</td>
</tr>
<tr>
<td>Mean volume of blood replacement in patients receiving transfusion, mL</td>
<td>827 ± 574</td>
<td>785 ± 449</td>
<td>740 ± 456</td>
</tr>
<tr>
<td>Day 0</td>
<td>729 ± 314</td>
<td>689 ± 270</td>
<td>690 ± 323</td>
</tr>
<tr>
<td>Mean hemoglobin levels, g/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>134 ± 16</td>
<td>133 ± 16</td>
<td>133 ± 16</td>
</tr>
<tr>
<td>Day 1</td>
<td>98 ± 15</td>
<td>100 ± 15</td>
<td>102 ± 14</td>
</tr>
<tr>
<td>Day 6</td>
<td>100 ± 13</td>
<td>100 ± 14</td>
<td>103 ± 13</td>
</tr>
<tr>
<td>Thrombocytopenia§</td>
<td>6/496 (1.2)</td>
<td>4/487 (0.8)</td>
<td>10/489 (2.0)</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD, unless otherwise indicated. Dalteparin was given as dalteparin sodium; warfarin, as warfarin sodium.

†P = 0.001 vs warfarin.

‡P = 0.002 vs warfarin.

§Indicates decrease in platelet count to below 100×10⁹/L.
in the warfarin group on days 0 through 1 was 4.1%. Since the first warfarin dose was not administered until the night before surgery, this bleeding rate largely reflected usual bleeding associated with surgery. The central adjudicators lacked the clinical perspective at the bedside and may have overestimated major bleeding from the case report forms because of the difficulty of discriminating between usual operative bleeding and increased bleeding for the perioperative and immediate postoperative interval. Major bleeding reported by site investigators based on clinical judgment using the same criteria as the central adjudicators was low and similar among groups. Serious bleeding episodes as defined by Eriksson et al\textsuperscript{26} were infrequent and similar among groups. No deaths occurred among patients with major blood loss.

The frequency of major bleeding postoperatively is similar to that reported in the cited literature for patients receiving postoperative low-molecular-weight heparin or warfarin prophylaxis after hip-arthroplasty surgery in North America.\textsuperscript{12,17,19} The frequency of minor and trivial bleeding was low and similar among groups. Uncomplicated wound hematoma rates were similar among the groups. Complicated wound hematomas occurred infrequently. Blood transfusions were significantly more frequent in the dalteparin groups (Table 5).

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 double-blind fashion to avoid bias in searching for or interpreting outcome events. Our findings cannot be attributed to inadequate administration of warfarin, as most patients (86.0%) underwent adequate anticoagulation by day 6. The proportion of patients undergoing evaluation, of those eligible, is comparable to that of other rigorous randomized trials evaluating pharmacological interventions. The frequencies of symptomatic venous thromboembolism were inevitably low as a result of case finding by means of venography, leading to early treatment of deep vein thrombosis.

The proportion of patients with adequate venograms was high (86.6% for proximal visualization of those who underwent venography) and can be attributed to education and feedback provided to participating radiologists throughout the course of the study. Another high-quality double-blind trial reported venogram adequacy rates similar to ours.\textsuperscript{26}

Recently in the United States, concern has arisen about the associated use of neuraxial anesthesia and low-molecular-weight heparin prophylaxis because of a reported cluster of spinal hematomas.\textsuperscript{31-33} A twice-daily low-molecular-weight heparin regimen has prevailed in the United States, whereas a once-daily regimen has prevailed in Europe; the latter has not been associated with a reported cluster of spinal hematomas. This intercontinental difference may reflect the dominant regimes used.

Our findings indicate that a once-daily low-molecular-weight heparin regimen is sufficient. The once-a-day postoperative regimen has the advantages that accumulation is less likely, that it is effective, and that the postoperative bleeding rates are low. Since half of the usual high-risk dose of dalteparin is given the day of surgery, and the average time of initiation of therapy after spinal anesthesia was 9 hours, the modified postoperative regimen of once-daily dalteparin reported herein may be a safe approach in avoiding spinal hematoma. The cost-effectiveness of in-hospital prophylaxis is beyond the scope of this article and should be addressed separately.
Low-molecular-weight heparin prophylaxis administered preoperatively or postoperatively using a modified dalteparin regimen in close proximity to hip arthroplasty resulted in substantive risk reductions for all and proximal deep vein thrombosis compared with warfarin. Such findings have not been observed with low-molecular-weight heparin therapy commenced 12 hours preoperatively or 12 to 24 hours postoperatively. Major but not serious bleeding occurred more frequently in patients receiving dalteparin in the immediate preoperative period. Dalteparin therapy initiated postoperatively provided superior efficacy vs warfarin, without significantly increased overt bleeding.

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A list of additional participants of the North American Fragmin Trial appear in a box on page 2205.

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