Preoperative or Postoperative Start of Prophylaxis for Venous Thromboembolism With Low-Molecular-Weight Heparin in Elective Hip Surgery?

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Background: Prophylaxis of venous thromboembolism with low-molecular-weight heparins in patients undergoing major orthopedic surgery is currently initiated according to at least 3 different regimens. In Europe, traditionally, prophylaxis is started 12 hours before surgery, whereas in North America it is initiated 12 to 48 hours postoperatively. The third regimen (perioperative) begins prophylaxis either earlier than 12 hours before or 12 hours after surgery. Unfortunately, the optimal regimen is uncertain because direct comparisons among these regimens with sufficiently large sample sizes are not available.

Objective: To assess, in a systematic review, the relative efficacy and safety of the 3 low-molecular-weight heparin regimens used to prevent thrombosis after total hip replacement. The incidence of postoperative thrombosis detected by contrast venography was used as the measure of efficacy and the rate of major bleeding was used as the measure of safety.

Methods: We pooled the results of all published studies, which met the following criteria: (1) inclusion of at least 1 arm of the study of a dose of low-molecular-weight heparin that is approved for both preoperative and postoperative initiation of prophylaxis; (2) the use of mandatory bilateral contrast venography, performed between days 6 and 15 postoperatively; (3) thromboprophylaxis continued until venography; (4) independent reading of venograms; and (5) assessment of clinically overt major bleeding by predefined criteria. Articles were excluded if no separate data could be obtained for patients undergoing elective hip surgery (in case of patient mix), or if they were reported more than once.

Results: In the 1926 patients who used a preoperative regimen, the incidence of postoperative deep vein thrombosis was 19.2% (95% confidence interval [CI], 17%-21%). In the cohort of 925 patients who received a perioperative regimen, the rate of deep vein thrombosis was 12.4% (95% CI, 10%-14%), whereas in the group of 694 patients who received a postoperative regimen, it was 14.4% (95% CI, 12%-17%). The rate of major bleeding was 1.4% (95% CI, 1%-2%) in the preoperative group, 6.3% (95% CI, 5%-7%) in the perioperative group, and 2.5% (95% CI, 1%-3%) in the postoperative group.

Conclusions: We find no convincing evidence that starting prophylaxis preoperatively is associated with a lower incidence of venous thromboembolism than starting postoperatively. Perioperative regimens may lower the risk of postoperative thrombosis, but if so, this positive effect is offset by an increase in postoperative major bleeding.

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preoperatively or postoperatively. In the absence of clinical trials with adequate sample sizes comparing the 3 regimens directly, we conducted a systematic review to assess the rate of venous thrombosis (as assessed by mandatory venography) and the occurrence of major hemorrhage with each of these LMWH regimens in patients undergoing elective hip surgery. Our aim was to determine whether starting prophylaxis prior to surgery is advantageous. To allow a fair comparison, we limited the analysis to studies using the same dose of LMWH preoperatively or postoperatively.

**METHODS**

**SEARCH STRATEGY**

We searched for randomized controlled trials reporting on the incidence of venous thrombosis and bleeding in patients undergoing elective hip surgery with LMWH prophylaxis. Studies were identified through MEDLINE (Medical Subject Headings of the National Library of Medicine keywords: hip prosthesis, venous thrombosis, and low molecular weight heparins). The reference lists of the identified articles were then manually checked for additional publications.

**ELIGIBILITY CRITERIA FOR STUDIES**

Included in the systematic review were all trials that met the following criteria: (1) at least 1 arm of the study should have included a currently recommended dose of LMWH that is approved for both preoperative and postoperative initiation; (2) mandatory bilateral contrast venography, performed between days 6 and 15 postoperatively; (3) continuation of thromboprophylaxis until venography; (4) independent reading of venogram; and (5) assessment of clinically overt major bleeding by predefined criteria. Articles were excluded if separate data could not be obtained for patients undergoing elective hip surgery (in case of patient mix), or if they were reported more than once.

**CLASSIFICATION OF THE PROPHYLACTIC REGIMENS**

Studies were divided into 3 groups according to the time of the initiation of prophylaxis. Preoperative regimens had to start prophylaxis at least 12 hours before the operation, usually defined as the evening before surgery. The perioperative group included all trials that began prophylaxis 2 hours before or up to 4 hours after surgery. In the group using postoperative regimens, prophylaxis was started 12 to 48 hours after the surgical procedure.

**OUTCOMES**

Efficacy was assessed by the incidence of venographically documented DVT between 6 and 15 days postoperatively, or documented symptomatic DVT that occurred earlier. Safety was assessed by documenting the number of major bleeding episodes. No attempt was made to compare the frequency of minor bleeding because of the large variation in definitions used.

**STATISTICAL ANALYSIS**

The incidences of DVT and major bleeding were pooled for trials in each of the 3 regimens. Pooling was weighted based on sample size, and 95% confidence intervals (CIs) were calculated.

**RESULTS**

**LITERATURE SEARCH AND TRIAL SELECTION**

Of the 49 identified trials, 14 were not eligible (4 trials used doses of LMWH that are currently not recommended for preoperative and postoperative use;14-17) venography was not mandatory in 5 trials;18-22 in 3 other studies, the time of venography was outside the 6- to 15-day postoperative window;23-25 in 1 trial, venography was only unilateral;26 and in 1 study, bleeding was not systematically documented.27 Of the 35 potentially eligible studies, another 21 had to be excluded. Of these, 13 were published more than once.18-27 Six studies investigated patients with hip and/or knee arthroplasty where the data could not be analyzed separately.28-33 and 2 studies included patients with hip fractures.34,35 Thus, a total of 14 trials that reported on 19 cohorts of patients were included.36-49

**INCIDENCE OF POSTOPERATIVE DVT**

Eleven trials were included for analysis of efficacy of the preoperative regimens; 9 with enoxaparin sodium, 1 with dalteparin sodium, and 1 with tinzaparin sodium (Table 1). Three studies were included for the perioperative regimen, 1 with enoxaparin and 2 with dalteparin, whereas 4 studies used a postoperative regimen, all using enoxaparin.

The overall incidence of DVT, as well as that for proximal and distal DVT separately, for the study cohorts is presented in Table 2. In the preoperative group of trials, a total of 1926 patients (Table 3) were available with an incidence of thrombosis of 19.2% (95% CI, 17%-21%). The perioperative group included 925 patients (Table 3) and showed an incidence of postoperative DVT of 12.4% (95% CI, 10%-14%). In the postoperative group, a total of 694 patients were studied. The incidence of postoperative DVT was 14.4% (95% CI, 12%-17%). The incidence of proximal DVT was 7.6% for the preoperative group, 2% for the perioperative group, and 5% for the postoperative group. The majority of patients in both the preoperative and postoperative groups were treated with enoxaparin. If we limit the analysis to this LMWH only, the incidence of thrombosis for the preoperative group is 18% (95% CI, 16%-20%) and 14.4% (95% CI, 12%-17%) for the postoperative group (Table 2).

**INCIDENCE OF MAJOR BLEEDING**

The incidence of major bleeding in each of the cohorts is summarized in Table 2. In the preoperative group (2785 patients), the incidence of ma-

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The main conclusion of our pooled analysis across different studies with a preoperative, perioperative, or postoperative initiation of thromboprophylaxis with LMWH is that there is no convincing evidence that starting prophylaxis approximately 12 hours before surgery is more effective in preventing venography-detected DVT than starting 12 to 48 hours postoperatively (total DVT rate preoperatively and postoperatively; 19.2% [95% CI, 17%-21%] and 14.4% [95% CI, 12%-17%], respectively). Similarly, there is no evidence that the postoperative regimen is safer than the preoperative regimen. In contrast, when thromboprophylaxis is started either soon before (2 hours) or after (4 hours) surgery, even with reduced doses, there is a trend for a lower risk of venous thrombosis, but this benefit appears to be counterbalanced by a marked increase in the risk of major bleeding in comparison with the other 2 regimens (major bleeding rate was 6.3% [95% CI, 5%-7%] in the perioperative group compared with 1.4% [95% CI, 1%-2%] and 2.5% [95% CI, 1%-3%] in the preoperative and postoperative groups, respectively).

Since the across-study comparisons used in our analysis has obvious limitations, it is important to compare our findings with those of the few studies that have compared several regimens directly, as well as with an earlier overview on this topic. The only published study that compared a 12-hour preoperative regimen with a perioperative regimen (1 hour after induction of anesthesia) and a postoperative regimen (12 hours) was performed by Planes et al—and it found no statistical difference in efficacy. This study was performed to evaluate the safety of combining LMWH with various types of anesthesia and only about 60 patients were included in each of the 3 groups.

Recently, Hull and colleagues compared an early preoperative regimen (2 hours preoperatively) with an early postoperative regimen (4 hours postoperatively) with reduced doses of an LMWH (dalteparin, 2500 IU, 2 hours preoperatively, 4 hours postoperatively, respectively, followed by 5000 IU/d). There were about 300 patients in each group. The incidence of postoperative thrombosis was 11% in the group that started prophylaxis 2 hours preoperatively and 13% in the early postoperative group. This relatively low incidence of thrombosis is offset by a relatively high rate of major bleeding of 8.8% in the early preoperative group and 6.8% in the early postoperative group. The rates of bleeding in both of these perioperative groups are higher than those observed in our pooled postoperative and preoperative groups as well as in the 2 other perioperative groups reported by Planes et al and Frances et al.---
cis et al. Comparisons of major bleeding in our analysis with the study reported by Hull et al are limited both because they are indirect and because they did not use identical definitions of major bleeding. Our conclusions also differ from those reported in a meta-analysis published in 1999 in which the efficacy and safety of preoperative and postoperative initiation of a single LMWH was compared. This ear-

<table>
<thead>
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<th>Drugs and Source</th>
<th>Preoperative Regimens</th>
<th>Perioperative Regimens</th>
<th>Postoperative Regimens</th>
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<tr>
<td><strong>Enoxaparin</strong></td>
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<td>Borris et al, 1991</td>
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<td>Kaloliki et al, 1996</td>
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<td>Planes et al, 1988</td>
<td>15/120 (13)</td>
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<td>Planes, 1993</td>
<td>18/209 (9)</td>
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<td>Planes et al, 1999</td>
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<td>23 (11)</td>
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<td><strong>Total</strong></td>
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<td>7 (11)</td>
<td>12 (19)</td>
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<td>Tinzaparin</td>
<td>48/221 (22)</td>
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<td><strong>Total</strong></td>
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*DVT indicates deep vein thrombosis.
†2500 IU, first dose 2 hours preoperatively and 2500 IU evening after surgery, afterwards daily 5000 IU.
‡2500 IU, 4 hours postoperatively followed by 5000 IU/d.

<table>
<thead>
<tr>
<th>All DVT</th>
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<th>Perioperatively‡</th>
<th>Postoperatively§</th>
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<td>95% CI</td>
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<td>20/925 (2)</td>
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<td>95% CI</td>
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<td>4-7</td>
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<td>Distal DVT</td>
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<td>95/925 (10)</td>
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<tr>
<td>95% CI</td>
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<td>Major bleeding episodes</td>
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<td>83/1315 (6)</td>
<td>19/751 (3)</td>
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<tr>
<td>95% CI</td>
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<td>5-7</td>
<td>1-3</td>
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</table>

*DVT indicates deep vein thrombosis; CI, confidence interval.
†Twelve hours preoperatively.
‡Two hours preoperatively until 4 hours postoperatively.
§Twelve to 48 hours postoperatively.
lier meta-analysis concluded that the preoperative regimen was more effective and as safe as the postoperative regimen. The major differences between the 2 meta-analyses are that we included more studies, allowed the inclusion of different LMWHs, and did not exclude the large study by Eriksson et al.⁵⁹ We limited our analysis to one and the same dose regimen used preoperatively and postoperatively so as not to introduce bias due to larger doses used postoperatively. If, however, we limit the analysis to the same LMWH that was studied in the other meta-analysis, our overall conclusions do not change.

The optimal timing for initiating postoperative thromboprophylaxis remains controversial. For example, the recent pentasaccharide study⁴ initiated prophylaxis subcutaneously 6 hours after surgery with a major reduction in the rate of venous thrombosis without an apparent increase in clinically important bleeding. In another dose-finding study with a compound directed against the tissue factor VIIa complex, prophylaxis using the subcutaneous route was started within 1 hour after surgery, without an apparent increase in major bleeding.

It is likely that with the increasing use of regional anesthesia, the preoperative initiation of thromboprophylaxis will gradually disappear and that future research will be directed toward the optimal timing of postoperative prophylaxis. It is also possible that the optimal timing might differ depending on the mechanism of action of the agent in question.

We conclude that for the currently used LMWHs, there is no convincing evidence that starting prophylaxis 12 hours preoperatively is associated with a lower risk of venous thrombosis than when prophylaxis is started 12 to 24 hours postoperatively. Perioperative thromboprophylactic regimens require further investigation before their role can be defined.

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REFERENCES
