A COMPARISON OF LOW-DOSE HEPARIN WITH LOW-MOLECULAR-WEIGHT HEPARIN AS PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER MAJOR TRAUMA


ABSTRACT

Background Patients who have had major trauma are at very high risk for venous thromboembolism if they do not receive thromboprophylaxis. We compared low-dose heparin and a low-molecular-weight heparin with regard to efficacy and safety in a randomized clinical trial in patients with trauma.

Methods Consecutive adult patients admitted to a trauma center who had Injury Severity Scores of at least 9 and no intracranial bleeding were randomly assigned to heparin (5000 units) or enoxaparin (30 mg), each given subcutaneously every 12 hours in a double-blind manner, beginning within 36 hours after the injury. The primary outcome was deep-vein thrombosis as assessed by contrast venography performed on or before day 14 after randomization.

Results Among 344 randomized patients, 136 who received low-dose heparin and 129 who received enoxaparin had venograms adequate for analysis. Sixty patients given heparin (44 percent) and 40 patients given enoxaparin (31 percent) had deep-vein thrombosis (P = 0.014). The rates of proximal-vein thrombosis were 15 percent and 6 percent, respectively (P = 0.012). The reductions in risk with enoxaparin as compared with heparin were 15 percent (95 percent confidence interval, 4 to 50 percent) for all deep-vein thrombosis and 58 percent (95 percent confidence interval, 12 to 87 percent) for proximal-vein thrombosis. Only six patients (1.7 percent) had major bleeding (one in the heparin group and five in the enoxaparin group, P = 0.12).

Conclusions Low-molecular-weight heparin was more effective than low-dose heparin in preventing venous thromboembolism after major trauma. Both interventions were safe. (N Engl J Med 1996;335:701-7.)

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VENOUS thromboembolism is a common, life-threatening complication of major trauma.1-5 Pulmonary embolism has been observed in 2 to 22 percent of patients with trauma,4,6 and fatal pulmonary embolism is the third most common cause of death in patients who survive the first 24 hours.1,3,5,7 We recently reported the results of a prospective study of thromboembolism in 349 patients with trauma.1 Deep-vein thrombosis was found by contrast venography in 58 percent of the patients, and proximal-vein thrombosis was detected in 18 percent. The factors associated with an increased risk of thrombosis included increasing age, surgery, blood transfusion, fracture of the femur or tibia, and spinal cord injury.1

The effectiveness and safety of thromboprophylaxis are largely unknown in patients with major trauma.2,8,9 Although numerous clinical trials have assessed the options for prophylaxis in other patients at high risk, such as those undergoing hip or knee surgery8,10,11 and those with spinal cord injuries,8,12,13 there are few such studies of patients with trauma.2,8 Most of the available studies have limitations that reduce their potential to guide recommendations for prophylaxis in this group of patients.6,9,14-16 Noninvasive methods of diagnosis have low sensitivity as screening tests in trials of prophylaxis in high-risk, asymptomatic patients.17-19 We therefore designed this study as a randomized, double-blind trial and used contrast venography as the means of assessing efficacy.

Among the potential options for the prophylaxis of patients with trauma, graduated-compression stockings and intermittent pneumatic compression have limited efficacy6,8,9,20 and cannot be used by many patients with leg fractures (who constitute a large proportion of patients with trauma).1 Oral anticoagulants have several disadvantages: they have a delayed onset of action, require regular laboratory monitoring, have effects difficult to reverse in the event of a surgical procedure, create concern about the risk of bleeding, and cannot be used in patients with impaired gastrointestinal function. Inferior vena caval filters have been studied only in uncontrolled series of patients, have uncertain long-term safety in these patients, and cost an estimated $5,000 each.21,22 We selected low-dose heparin as one of our study interventions because it has been assessed extensively in other groups of patients, has been shown to be effective in reducing thromboembolism and mortality after gen-

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eral surgery, is not associated with an increased risk of major bleeding, and is both inexpensive and simple to use.\textsuperscript{8,23} Low-dose heparin is also used widely for thromboprophylaxis in patients with trauma.\textsuperscript{5,9,14,15,24} We chose a low-molecular-weight heparin as the alternative intervention because of its proved efficacy after orthopedic surgery, its low risk of bleeding, and the vast experience with low-molecular-weight heparins in large trials.\textsuperscript{8,10,11,25,26}

We sought to compare the efficacy of low-dose heparin with that of low-molecular-weight heparin in patients with major trauma, using deep-vein thrombosis demonstrated by contrast venography as the principal outcome measure. There is widespread concern among trauma surgeons that the use of anticoagulants is associated with a high risk of bleeding in patients with trauma,\textsuperscript{8,27,28} and therefore our second objective was to assess the safety of beginning prophylaxis with anticoagulants early after an injury.

\section*{METHODS}

\subsection*{Study Patients}

From November 1992 through November 1994, consecutive adult patients admitted for trauma to Sunnybrook Health Science Centre, the largest level 1 trauma facility in Canada, were assessed to determine their eligibility for the study. Patients were excluded if they had an estimated Injury Severity Score\textsuperscript{1} below 9, were likely to survive for less than seven days or remain in the hospital for less than seven days; had frank intracranial bleeding on computed tomographic scanning (patients with a cerebral contusion, localized petechial hemorrhages, or diffuse axonal damage were not excluded); had bleeding that remained uncontrolled 36 hours after the injury; had systemic coagulopathy, as defined by a prothrombin time more than 3 seconds above the control value or a platelet count of less than 50,000 per cubic millimeter; needed therapeutic anticoagulation; could not undergo venography because of an allergy to contrast material; had renal failure (defined as a serum creatinine level higher than 3.4 mg per deciliter [300 \(\mu\)mol per liter]); or were pregnant; or if venous access could not be achieved because of amputation or a major foot injury. These criteria were very similar to those used in our previous study, except that the earlier study included patients with intracranial bleeding.\textsuperscript{1} The protocol was approved by the research ethics board of the hospital.

\subsection*{Study Design and Interventions}

This was a randomized, double-blind trial in which the patients were stratified according to the presence or absence of lower-extremity fracture.\textsuperscript{1} Eligible, consenting patients were randomly assigned by a computer-derived protocol to receive either 5000 units of heparin calcium (Organon Teknika, Toronto) or 30 mg of enoxaparin (100 anti–factor Xa units per milligram; Rhône–Poulenc Rorer, Montreal), both given as 0.3-ml subcutaneous injections every 12 hours in a blinded fashion with preloaded syringes. The protocol mandated that the first dose of the study medication be given within 36 hours of the injury and that the treatment be continued for up to 14 days. No mechanical or other pharmacologic methods of antithrombotic prophylaxis were allowed. The study drug was generally not withheld in the event of a surgical procedure, although in exceptional circumstances such as spinal fixation, a single preoperative dose was permitted to be withheld. Treatment with the study medication was then resumed at the first dosing time after the operation.

\subsection*{Surveillance for Thromboembolism}

The participating patients were assessed daily to ensure compliance with the protocol and to review their clinical status. Between day 10 and day 14, or just before discharge if that occurred earlier, each patient underwent venography of both legs with iovera and a nonionic contrast agent.\textsuperscript{3} Deep-vein thrombosis was defined as a constant intraluminal filling defect in a deep leg vein that was seen on two or more views. Proximal-vein thrombosis was defined as thrombosis involving the popliteal or more proximal veins.

Patients in whom deep-vein thrombosis was clinically suspected underwent duplex ultrasonography, followed by venography if the results were positive.\textsuperscript{29} If the ultrasound examination was normal, the patient continued in the trial until the time of the scheduled venography at the end of the study. Patients with clinical features suggestive of pulmonary embolism underwent ventilation–perfusion lung scanning.\textsuperscript{30} A normal perfusion scan was considered to rule out pulmonary embolism, whereas a scan indicating a high probability of embolism, defined as a scan that showed one or more segmental or larger perfusion defects, with relatively preserved ventilation, was considered to confirm the diagnosis. Patients with nondiagnostic lung scans underwent pulmonary angiography, venous ultrasonography, contrast venography, or a combination of these, if necessary, within 24 hours after the scanning.

\subsection*{Outcome Measures}

The primary outcome measure was proved venous thromboembolism (deep-vein thrombosis or pulmonary embolism).\textsuperscript{1} Venous thrombi were subclassified into four groups: small (<5 cm) calf thrombi, extensive calf thrombi, small proximal thrombi (<5 cm and nonocclusive), and extensive proximal thrombi. The venograms were also scored quantitatively with the validated Marder index.\textsuperscript{21} Major bleeding was defined as overt bleeding that was associated with a decrease in the hematocrit level of at least 2 g per deciliter, the transfusion of two or more units of packed red cells, an intracranial or retroperitoneal site of bleeding, or the need for surgical intervention. The requirements for transfusion and an index of bleeding, determined by adding the number of units of blood transfused to the change in the hematocrit (the value obtained on the day of randomization minus that obtained on the day of venography) divided by 0.03, were quantitated for each patient.\textsuperscript{32} The results of the imaging studies and the data on episodes of bleeding were adjudicated by a panel of experts who were unaware of the clinical data, the results of other tests, and the patients’ treatment assignments.

\subsection*{Statistical Analysis}

The base-line comparability of the treatment groups was assessed by the chi-square test or Fisher’s exact test in the case of proportions and by the t-test in the case of continuous variables. The most important factor in determining comparability was the predicted risk of venous thromboembolism without prophylaxis (see the Appendix). The primary analysis compared the rates of deep-vein thrombosis and pulmonary embolism in the patients receiving low-dose heparin with the rates in the patients receiving enoxaparin. Rates of thromboembolism were also assessed for several specific injuries, including spinal cord injuries and fractures of the pelvis, femur, and tibia.

Before initiating this study, we estimated the event rates on the basis of an anticipated reduction in risk of approximately 45 percent with low-dose heparin as compared with no prophylaxis and an anticipated further reduction in risk of 50 percent with enoxaparin. We calculated that a study sample containing 250 patients would be needed in order to achieve 80 percent power with a one-tailed test at a significance level of 0.05. Because the efficacy of both interventions in this group of patients was uncertain, an independent review of the data was performed by a statistician who was not involved in the conduct of the study after adjudicat-
ed outcomes were available for 244 patients. The recruitment of patients was discontinued after this formal review.

RESULTS

During the study period, there were 1076 admissions to our trauma unit. A total of 698 patients were excluded for the following reasons: intracranial bleeding (220 patients); discharge likely within seven days (202); an estimated Injury Severity Score below 9 (145); uncontrolled bleeding at the time of potential randomization (47); survival likely to be less than seven days (29); a need for therapeutic anticoagulation (13); inability to undergo venography because of leg amputation (12), severe foot injury (9), allergy to contrast material (7), or pregnancy (4); and a delayed transfer to our center (10). Eighteen patients or their surrogate family members refused to participate in the trial, and consent could not be obtained from 16.

One hundred seventy-three patients were randomly assigned to receive low-dose heparin, and 171 were assigned to receive enoxaparin. Thirteen randomized patients did not complete the study. Three patients assigned to heparin withdrew their consent; two more were given full doses of anticoagulants (one to preserve an arterial graft and the other, whose condition was too unstable for the patient to be studied, to treat a suspected pulmonary embolism); and an additional two were too ill to undergo venography. One patient assigned to enoxaparin withdrew her consent; two others died (one of multisystem organ failure and the other of cardiac arrest), neither of whom had pulmonary embolism at autopsy; another patient underwent craniotomy because of a tumor; and two patients were withdrawn from the study because of bleeding. Venography was nondiagnostic (either venous access in both legs could not be achieved or the venogram was inadequate at the time of adjudication) in 30 patients assigned to heparin and 36 patients assigned to enoxaparin. A total of 265 patients completed the study and had adequate assessments of outcome. There were no significant differences between the treatment groups with regard to any demographic variables or injury characteristics (Table 1). In particular, the predicted risks of deep-vein thrombosis if the patients had received no prophylaxis were 55 percent in the heparin group and 54 percent in the enoxaparin group (P = 0.69). Venography was performed in both groups a mean (±SD) of 11.9 ± 2.3 days after randomization.

Deep-Vein Thrombosis

The overall rates of deep-vein thrombosis, as shown in Table 2, were 44.1 percent (60 of 136 patients) in the heparin group and 31.0 percent (40 of 129 patients) in the enoxaparin group (relative risk reduction with enoxaparin, 30 percent; 95 percent confi-
The frequencies of the subclasses of deep-vein thrombi were as follows: extensive proximal thrombi, 13 in the heparin group and 4 in the enoxaparin group; small proximal thrombi, 7 and 3; extensive calf thrombi, 29 and 22; and small calf thrombi, 11 and 10. The Marder scores for limbs with adequate venography were 2.3 ± 5.0 in the heparin group and 1.0 ± 2.8 in the enoxaparin group (P = 0.012 by the Wilcoxon rank-sum test).

Among both strata of patients, those with lower-extremity fractures and those without such fractures, rates of thrombosis were lower in the enoxaparin group than in the heparin group. In the patients with lower-extremity fractures, the reductions in the risk of all deep-vein thrombosis and proximal-vein thrombosis were 21 percent and 73 percent, respectively, in favor of enoxaparin. In the patients without lower-extremity fractures, the risk reduction for all deep-vein thrombosis was 48 percent in favor of enoxaparin, with no difference between treatment groups in the small numbers of proximal thrombi. When we compared the observed rates of thrombosis with the predicted risks if these patients had not received prophylaxis, the reduction in the relative risk of all deep-vein thrombosis was 19 percent with low-dose heparin and 43 percent with enoxaparin, and the reductions in the risk of proximal-vein thrombosis were 12 percent for heparin and 65 percent for enoxaparin (Table 3).

**Bleeding**

Only 6 of the 344 patients (1.7 percent; 95 percent confidence interval, 0.6 to 3.8 percent) had major bleeding, with one such episode in the heparin group (0.6 percent) and five episodes in the enoxaparin group (2.9 percent, P = 0.12) (Table 4). One patient had excessive drainage from a chest tube three days after the injury; she was withdrawn from the study and subsequently received three units of blood. A second patient with severe facial fractures had a 1000-ml epistaxis on day 3. He continued in the study after one dose of medication was withheld. During the repair of an acetabular fracture, a third patient had considerable intraoperative blood loss and was given 11 units of red cells in transfusion. The patient’s hemoglobin level did not drop, the surgeon did not believe that the bleeding was related to the anticoagulation, and no dose of study medication was withheld. A fourth patient had a subdural hematoma with hemiparesis four days after craniotomy for a severe skull fracture. The hematoma was evacuated with complete neurologic recovery. In a fifth patient, bleeding into the soft tissues of the face occurred eight days after an internal fixation of facial fractures. The superficial temporal artery required endovascular embolization, and one dose of medication was withheld. On day 13, pain developed in the flank of a sixth patient, who had a pelvic fracture. A retroperitoneal hematoma that had been documented on admission was found to be enlarged. There was no associated blood transfusion or decrease in hemoglobin.

Therefore, no patient had a measured drop in hemoglobin of more than 2 g per deciliter, and only two patients had any active intervention. Four patients received blood transfusions within 48 hours after their episodes of bleeding. In two patients, one dose of the study medication was withheld, and in a third patient none were withheld.

The two groups did not differ significantly with regard to other measures of bleeding. From the day of randomization to the day of venography, 99 patients in the heparin group (57.2 percent) and 101 patients in the enoxaparin group (59.1 percent) received transfusions (P = 0.50). They received a mean of 3.8 ± 2.6 and 4.2 ± 3.1 units of blood, respectively (P = 0.30), and their indexes of bleeding were 2.2 ± 3.3 and 2.7 ± 3.2 (P = 0.18).

**Other Outcomes**

There were no fatal pulmonary emboli. One patient in the enoxaparin group had symptoms of pulmonary embolism and a lung scan showing a high probability of pulmonary embolism three days after entering the study. This patient is counted among the patients with proximal-vein thrombosis in the comparisons here and in Table 2. Two patients, both receiving low-dose heparin, had symptomatic proximal thrombi that were associated with heparin-induced thrombocytopenia, as proved by the finding of heparin-dependent IgG antibodies.

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**Table 3. Predicted and Observed Risks of Venous Thrombosis.**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>RISK OF DEEP-VEIN THROMBOSIS</th>
<th>PREDICTED</th>
<th>OBSERVED WITH</th>
<th>OBSERVED WITH</th>
<th>REDUCTION†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IF NO</td>
<td>LOW DOSE HEPARIN</td>
<td>ENOXAPARIN</td>
<td>percent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PHYLAXIS*</td>
<td>REASON</td>
<td>REASON</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>All deep-vein thrombosis</td>
<td></td>
<td>54 (51–57)</td>
<td>44 (36–52)</td>
<td>31 (23–59)</td>
<td>30 (4–50)</td>
</tr>
<tr>
<td>Proximal-vein thrombosis</td>
<td></td>
<td>17 (13–21)</td>
<td>15 (9–21)</td>
<td>6 (2–10)</td>
<td>58 (12–87)</td>
</tr>
</tbody>
</table>

*The predictions shown were made by the method described by Geerts et al.1 and summarized in the Appendix.

†The reductions in risk in the patients given enoxaparin as compared with the patients given low-dose heparin are shown.
DISCUSSION

This study confirms that patients with major trauma are at very high risk for venous thromboembolism and demonstrates that enoxaparin, a low-molecular-weight heparin, is efficacious in preventing such thromboembolic events. In comparison, low-dose heparin is relatively ineffective as prophylaxis in this population of patients. The risk of major bleeding is low in both groups, even when anticoagulant therapy is initiated within 36 hours of the injury.

When we compared our observed data with the predicted risks of thrombosis in these patients, low-dose heparin was found to decrease the rates of deep-vein thrombosis and proximal-vein thrombosis by only 19 percent and 12 percent, respectively, whereas the risk reductions with enoxaparin were 43 percent and 65 percent. The efficacy of enoxaparin was therefore greater for proximal thrombi than for calf-vein thrombi.

Other investigators using less rigorous methods have also suggested that low-dose heparin fails to protect patients with trauma from venous thrombosis.9,16,24 The greater efficacy of low-molecular-weight heparin in such patients is consistent with the results of studies of hip and knee arthroplasty8,10,11 and spinal cord injury12,13 but is at variance with most studies of patients undergoing general surgery, in which the reported differences have been small.8,25,26 This implies that from the perspective of the risks of thromboembolism and its prevention, major trauma should be considered analogous to orthopedic surgery of the lower extremity rather than to general surgery.

The relatively high rate of residual thrombosis in calf veins despite prophylaxis with low-molecular-weight heparin is probably due to the combination of a very high thrombogenic stimulus in patients with trauma and the delay between the injury and the start of prophylaxis (in this study, a delay of approximately 30 hours). The clinical significance of calf thrombi in this population of patients is unknown, but such thrombi cannot be ignored. Since many patients with trauma do not become fully mobile for weeks or months, these thrombi have the potential to extend and cause delayed proximal-vein thrombosis and pulmonary embolism.34-36 Although starting prophylaxis earlier or combining low-molecular-weight–heparin therapy with a mechanical method of prophylaxis may further reduce the incidence of thrombosis, the nature of the patient’s injuries often limits the feasibility of these options.

Perhaps our most important finding is that, despite the protocol-mandated early commencement of prophylaxis, the risk of major bleeding with both standard heparin and enoxaparin remained low. There were more episodes of major bleeding in the enoxaparin group than in the heparin group, but the difference was not statistically significant. Although the bleeding rates in patients with major trauma who do not receive anticoagulant prophylaxis are unknown, controlled trials in patients undergoing elective orthopedic surgery that have used a definition of bleeding similar to ours have found similar rates of major bleeding (mean rate, 3 percent) in patients receiving either low-molecular-weight heparin or placebo.25,26,37,39 In placebo-controlled trials after hip and knee arthroplasty, rates of major bleeding were not higher in the patients treated with low-molecular-weight heparin.37,39

In summary, our study demonstrates that enoxaparin is more efficacious than low-dose heparin in preventing deep-vein thrombosis in patients recovering from major trauma. Major hemorrhage, the most feared complication of anticoagulant prophylaxis in such patients, was very uncommon in this trial. We recommend that thromboprophylaxis be considered for all patients with major trauma. Our findings suggest that low-molecular-weight heparin should be considered the method of choice for the prophylaxis of such patients, provided they do not

### Table 4. Episodes of Major Bleeding in the Study Patients.*

<table>
<thead>
<tr>
<th>PATIENT No.</th>
<th>STUDY GROUP</th>
<th>DAY OF TREATMENT</th>
<th>SITE OR TYPE OF BLEEDING</th>
<th>EFFECT ON STUDY TREATMENT</th>
<th>UNITS OF BLOOD TRANSFUSED WITHIN 48 HR</th>
<th>SURGERY OR INVASIVE PROCEDURE NEEDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enoxaparin 3</td>
<td>Chest-tube drainage</td>
<td>Discontinued</td>
<td>3</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Heparin 3</td>
<td>Epistaxis</td>
<td>1 Dose withheld</td>
<td>4</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Enoxaparin 5</td>
<td>Intraoperative</td>
<td>No effect</td>
<td>11</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Enoxaparin 7</td>
<td>Subdural hematoma</td>
<td>Discontinued</td>
<td>0</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Enoxaparin 11</td>
<td>Facial soft tissues</td>
<td>1 Dose withheld</td>
<td>1</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Enoxaparin 13</td>
<td>Retroperitoneum</td>
<td>None (end of study)</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*None of the bleeding events were associated with a decrease in the hemoglobin level by more than 2 g per deciliter.
have frank intracranial bleeding. In most patients prophylaxis can safely be started within 36 hours of the injury, and there is generally no need to withhold it in the event of a subsequent surgical procedure. The optimal duration of prophylaxis in these patients with trauma is not known, but our data suggest that it should continue at least until their discharge from the hospital.

APPENDIX

Predicting the Risk of Thromboembolism in Patients with Trauma Who Do Not Receive Prophylaxis

In our previous study, data on 249 consecutive patients with trauma who were not receiving thromboprophylaxis and who had adequate venography were used to construct a multiple logistic regression model that could predict the development of deep-vein thrombosis. We found five risk factors to be independent predictors: increasing age, the need for blood transfusion, the need for surgery, the presence of a fracture of the femur or tibia, and spinal cord injury. On the basis of this model, we can estimate the probability of thrombosis in patients with trauma who do not receive prophylaxis with the following equation:

\[
\text{Probability of deep-vein thrombosis} = \frac{e^x}{1 + e^x},
\]

where \( x = -3.16 + (0.05 \times \text{the patient’s age in years}) + 0.55 \) (if a transfusion was needed) + 0.83 (if surgery was needed) + 1.57 (if the femur or tibia was fractured) + 2.15 (if the spinal cord was injured).

For example, a 40-year-old victim of a motor vehicle accident with a ruptured spleen and no other major injuries who requires laparotomy has a predicted risk of deep-vein thrombosis of 38 percent, whereas a 40-year-old patient with trauma who has a femoral fracture requiring internal fixation and who also needs a transfusion has a predicted risk of thrombosis of 84 percent. The goodness-of-fit test of Hosmer and Lemeshow confirmed the adequacy of the model (\( P = 0.63 \)).

When the patients in the present trial were compared with those in our previous study with regard to the clinical characteristics listed in Table 1, there were few differences (data not shown). The most obvious difference was that 26 percent of the patients in the earlier study had major head injuries, as compared with 5 percent in this study. In addition, a greater proportion of the patients in the earlier study received transfusions (58 percent, vs. 39 percent in this study). None of the other factors predictive of thromboembolic risk, including increasing age, surgical interventions, and orthopedic or spinal cord injuries, differed. We have therefore used this model to estimate the risk of thrombosis among the patients in the present trial that would be expected if they had not received prophylaxis. The observed incidence of deep-vein thrombosis in our earlier study (58 percent) is similar to the predicted risk of 54 percent in the randomized patients described here.

REFERENCES