

## LOW-MOLECULAR-WEIGHT HEPARIN (ENOXAPARIN) AS PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER TOTAL HIP REPLACEMENT

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### ABSTRACT

**Background** The risk of venous thromboembolism in patients undergoing total hip replacement is known to be high. However, the optimal duration of prophylaxis with anticoagulant agents after this procedure is unknown. We sought to determine whether one month of anticoagulant therapy with the low-molecular-weight heparin enoxaparin is more effective than enoxaparin therapy given only during the hospitalization for surgery.

**Methods** Two hundred sixty-two patients undergoing total hip replacement received enoxaparin during their hospitalizations (average stay, 10 to 11 days). They were then randomly assigned to receive enoxaparin or placebo (131 patients each). Blinded outpatient therapy (or placebo) was continued long enough that the total treatment period, inpatient plus outpatient, was one month for each patient. Bilateral ascending phlebography was performed 19 to 23 days after discharge, with deep-vein thrombosis as the primary end point. Distal and proximal thrombosis, pulmonary embolism, and hemorrhage were also recorded, as were deaths.

**Results** Venography was adequate in 116 patients in the placebo group and 117 in the enoxaparin group. We observed 43 episodes of deep-vein thrombosis and 2 episodes of pulmonary embolism in the placebo group, but only 21 episodes of deep-vein thrombosis and no episodes of pulmonary embolism in the enoxaparin group (incidence of thromboembolism, 39 percent and 18 percent, respectively;  $P < 0.001$ ). The difference in the incidence of proximal deep-vein thrombosis was also significant (24 percent and 7 percent in the placebo and enoxaparin groups, respectively;  $P < 0.001$ ). Six patients in the enoxaparin group and one patient in the placebo group had hematomas at their injection sites. No patients died or had major complications.

**Conclusions** There were significantly fewer venous thromboembolic complications in patients undergoing elective hip replacement when prophylaxis with enoxaparin was given for a total of one month, rather than only during the hospitalization. (N Engl J Med 1996;335:696-700.)

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WITHOUT prophylactic anticoagulation, the frequency of deep-vein thrombosis after total hip replacement is high, in the range of 50 to 60 percent.<sup>1,2</sup> With various methods of anticoagulant therapy, this frequency can be substantially reduced,<sup>3,4</sup> the best option at present being low-molecular-weight heparin,<sup>1,2,4-6</sup> which is also cost effective.<sup>7-9</sup>

In addition to the high risk of deep-vein thrombosis, hip surgery has certain special characteristics. The risk of deep-vein thrombosis is more protracted after hip surgery than after general surgery, when it usually develops during the first few postoperative days.<sup>10,11</sup> The surgical technique, which kinks the femoral vein, seems to stimulate proximal deep-vein thrombosis in the leg that is operated on,<sup>12,13</sup> whereas calf-vein thrombosis is more likely to develop in either leg. Another result of surgery can be the impairment of venous hemodynamics, which may last several weeks, in the leg that is operated on.<sup>14</sup> In a study of patients undergoing general abdominal surgery, Scurr et al.<sup>15</sup> found that deep-vein thrombosis continued to be a problem after the patients had left the hospital. During the first month, the condition developed in about 25 percent of those without thrombosis at discharge.

A recent study of patients undergoing total hip arthroplasty showed a 10.5 percent incidence of deep-vein thrombosis during the first six weeks after surgery.<sup>16</sup> Thus, the thrombogenic period may be prolonged in some patients, and the risk of fatal pulmonary embolism continues for at least one month after surgery.<sup>17,18</sup> In patients with trauma, the risk may last even longer.<sup>19-21</sup> For these reasons, the question of providing extended prophylactic anticoagulant therapy has been raised and was said to be of key importance in the European Consensus Statement.<sup>22</sup>

We therefore attempted to determine whether enoxaparin, a low-molecular-weight heparin, prevented thrombosis better if it was given only during

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the hospitalization for surgery (according to the usual practice) or if it was continued for a full month postoperatively.

## METHODS

### Study Design

This was a prospective, randomized, double-blind study conducted at a single center. Patients undergoing primary elective hip arthroplasty were included in the study if they were more than 39 years old and weighed more than 60 kg. They were excluded from the study if they had renal insufficiency; hypersensitivity to contrast medium, heparin, or low-molecular-weight heparin; a past or present risk of hemorrhage; endocarditis, severe liver disease, or untreated hypertension; or venous thromboembolism within the preceding three months; if they had received treatment with heparin, low-molecular-weight heparin, oral anticoagulants, or nonsteroidal antiinflammatory drugs within the five days before surgery; or if they had undergone ipsilateral hip surgery within the preceding six months; if they were pregnant or lactating; or if they did not give informed consent.

During the hospitalization (which was scheduled to last 9 days; anticipated range, 7 to 11 days), all the patients received prophylaxis against thrombosis with 40 mg (0.4 ml) of enoxaparin (Klexane, Rhône-Poulenc Rorer) injected subcutaneously into the abdominal wall once daily, with the first dose given the evening before surgery (according to the schedule, 12 hours beforehand; range, 10 to 14). At the end of the hospitalization, the patients were randomly assigned to continue receiving enoxaparin (40 mg once daily) or to receive placebo (0.4 ml of saline) once daily.

The first injection after the hospitalization was given the day after discharge. The post-discharge prophylaxis was given by study nurses who visited the patients daily in their homes. The outpatient prophylaxis was scheduled to last 21 days (range, 19 to 23), or until the time of phlebography. To enter the double-blind phase of the trial, patients could not have undergone a reoperation or have had clinical venous thromboembolism or major hemorrhage. They also had to have received prophylaxis with enoxaparin starting the evening before their surgery, as stated in the protocol.

Hip surgery was performed through a lateral incision, with or without osteotomy, with the patient supine.

### Assessment of Outcome

On day 21 (range, 19 to 23) after hospital discharge, the protocol called for bilateral ascending phlebography of the legs to screen for deep-vein thrombosis. During this procedure, the patient was seated with the lower leg in a vertical position. Fifty milliliters of contrast medium (Hexabrix [with 160 mg of iodine per milliliter] or Omnipaque [180 mg of iodine per milliliter]) was injected into a dorsal foot vein. Frontal and lateral films of the lower leg were obtained. The patient was then placed in a supine position, and a tourniquet was applied to the uppermost part of the thigh to occlude the great saphenous vein. An additional 50 ml of contrast medium was injected into the same vein that had been used in the lower leg, and frontal films of the popliteal, femoral, iliac, and inferior caval veins were obtained. With this technique, even bedridden patients who had just undergone surgery could be examined adequately.

When thrombosis was suspected for clinical reasons before the time of the scheduled phlebography, the procedure was performed on an emergency basis. If deep-vein thrombosis was found, no further phlebography was performed. If the study was negative, the planned bilateral phlebography was performed according to protocol.

Each phlebogram was examined by a committee of three radiologists unaware of the patients' group assignments. All the interpretations and classifications were made before the randomization code was broken. Each film was interpreted independently by each radiologist. If there were discrepancies in diagnoses, the

committee members discussed the case further and reached a consensus.

A thrombus was considered to be present when there was a filling defect surrounded by contrast medium, or the consistent nonvisualization of a deep vein, caused by increased subfascial pressure or total obliteration. Collateral flow through the superficial leg veins was seen when there was increased subfascial pressure or total obliteration. In the latter case, the tip of the thrombus was often visible. Only thrombi in venous segments located within the deep fascia were considered to be deep-vein thrombi.

The results of phlebography were considered inadequate if the amount of contrast medium injected was too small and the resulting phlebograms were uninterpretable. The thrombi were classified according to whether they occurred in the leg that was operated on or the contralateral leg and according to whether the thrombosis was proximal, distal, or both proximal and distal (involving the whole leg). The border between proximal and distal thromboses was the knee joint. In the case of clinically suspected pulmonary embolism, ventilation-perfusion lung scanning or pulmonary angiography was performed.

Follow-up was performed three months postoperatively to determine the patients' vital status.

### Hemorrhagic Complications

The anesthetist estimated the amount of blood lost intraoperatively by examining swabs and suction bottles. The volume of blood drained postoperatively was recorded, as were the transfusion requirements and all instances of postoperative hemorrhage, wound hematoma, and reoperation. Hemorrhages were classified as minor or major. Major hemorrhage was defined as clinically overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more, requiring the transfusion of two or more units of blood products; bleeding that was retroperitoneal or intracranial in location; or bleeding that necessitated reoperation. Hemorrhage that did not meet any of these criteria was classified as minor.

### Statistical Analysis

The analysis of thromboembolic events (both deep-vein thrombosis and pulmonary embolism) included 233 patients who had adequate venography (116 in the placebo group and 117 in the enoxaparin group). The analysis of hemorrhagic complications included only the patients who were actually treated. Most of the data were expressed in terms of descriptive statistics or 95 percent confidence intervals. In the analysis of efficacy, two-tailed chi-square tests and odds ratios derived from a logistic-regression analysis were used. In the analysis of safety, two-tailed Fisher's exact tests were used. The study was approved by the ethics committee of the University of Lund, Sweden. All the patients provided witnessed informed consent.

## RESULTS

Two hundred eighty-eight patients were enrolled in the study, 262 of whom underwent randomization for outpatient prophylaxis. The results for the hospital period (before randomization) and the period from discharge to the time of phlebography (the double-blind period) are presented separately here.

### Hospital Period

During the hospital period, all the patients received prophylaxis with enoxaparin. The patients later assigned to enoxaparin and those later assigned to placebo were well matched with regard to demographic variables, surgical procedures, and variables pertaining to the hospital course after surgery (Table 1). The

**TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND RISK FACTORS IN 262 PATIENTS WHO UNDERWENT TOTAL HIP REPLACEMENT, ACCORDING TO STUDY GROUP.**

CHARACTERISTIC	PLACEBO (N = 131)	ENOXAPARIN (N = 131)
Sex — M/F	57/74	56/75
Age — yr		
Median	70	70
Range	44–87	44–87
Body-mass index*		
Median	26.8	25.8
Range	19.2–49.1	18.6–37.9
Previous venous thromboembolism — no. of patients (%)	12 (9)	8 (6)
Varicose veins — no. of patients (%)	31 (24)	27 (21)
Leg ulcer — no. of patients (%)	3 (2)	2 (2)

\*Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

**TABLE 2. INCIDENCE OF THROMBOEMBOLIC EVENTS IN THE PATIENTS WITH ADEQUATE VENOGRAPHY, WITH ODDS RATIOS AND 95 PERCENT CONFIDENCE INTERVALS (CI).**

EVENT	PLACEBO (N = 116)	ENOXAPARIN (N = 117)	ESTIMATED ODDS RATIO (95% CI)	P VALUE
	no. of patients (%)			
All thromboembolism	45 (39)	21 (18)	2.9 (1.6–5.3)	<0.001
Deep-vein thrombosis				
Proximal	28 (24)	8 (7)	4.3 (1.9–10.0)	<0.001
Indeterminate	2 (2)*	0	—	—
Distal	15 (13)	13 (11)	—	—

\*These patients had pulmonary embolism before phlebography was performed. The origin of the thrombi was undetermined.

median time from the preoperative dose of enoxaparin to the start of surgery was 12.3 hours (range, 9.6 to 33.5) in the placebo group and 12.2 hours (range, 9.0 to 15.9) in the enoxaparin group. There was no difference between the groups in the side of the body on which the surgery was performed, the surgical approach (Hardinge or Charnley), the type of prosthesis used (cemented or uncemented), or intraoperative blood loss (median in both groups, 700 ml). In the majority of operations (95 percent), epidural anesthesia was used. The median duration of surgery was 1.9 hours (range, 1.0 to 5.0) in the placebo group and 1.7 hours (range, 1.1 to 5.2) in the enoxaparin group. The amount of blood lost through drainage, the amount given in transfusion, and the decrease in hemoglobin did not differ between the groups. The open-label period lasted 11 days (range, 7 to 12) in the placebo group and 10 days (range, 6 to 11) in the enoxaparin group. Five patients had

hemorrhagic complications: three in the enoxaparin group and two in the placebo group. All were due to bleeding from the surgical wound. There were no clinical episodes of thromboembolism during hospitalization.

**Post-Discharge Period**

Of the 288 patients initially enrolled, 262 were randomized, 131 to each study group. Twenty-six patients were not randomized: eight withdrew their consent, the condition of five was deteriorating, four had violations of the study protocol, two had intercurrent events, one died (acute myocardial infarction was suspected, but no autopsy was performed), one was excluded for administrative reasons, and five were not randomized for various other reasons. After randomization, no patients were excluded from the analysis of patients who were actually treated.

Phlebography could not be performed at all in four patients and was performed in only one leg in an additional five. In 20 cases, the phlebography was considered inadequate. The median time from discharge to phlebography was 18 days (range, 1 to 23) in the placebo group and 19 days (range, 1 to 23) in the enoxaparin group.

**Thromboembolic Complications**

Of the 233 patients who could be evaluated, 66 had deep-vein thrombosis or pulmonary embolism (28 percent). Table 2 shows the frequencies of these conditions. The reduction in the frequency of venous thromboembolic disease with enoxaparin treatment was significant, especially in the case of proximal deep-vein thrombosis. There were two pulmonary emboli in the placebo group, one diagnosed by pulmonary angiography and the other by scintigraphy.

Table 3 shows the location of thrombi in the patients undergoing unilateral hip replacement who could be evaluated, according to whether the thrombi occurred in the leg that was operated on, the contralateral leg, or both legs. In 34 patients (18 percent) the thrombi occurred exclusively in the leg that was operated on, in 4 (2 percent) only in the contralateral leg, and in the remaining 12 (6 percent) in both legs.

Rehospitalization because of deep-vein thrombosis was judged necessary for 32 patients in the placebo group and 11 patients in the enoxaparin group, for totals of 269 and 99 days, respectively (median duration of rehospitalization in the placebo group, 8.4 days [range, 4 to 29]; in the enoxaparin group, 9.0 days [range, 1 to 21]). The majority of patients (80 percent) were treated with low-molecular-weight heparin and warfarin. The remaining patients, who had small thrombi in muscular veins, were treated with elastic compression stockings, antiphlogistic agents, or both, without rehospitalization.

Clinical symptoms or signs of venous thromboembolism developed in 12 patients (included in Ta-

**TABLE 3.** DEEP-VEIN THROMBOSIS IN THE STUDY PATIENTS UNDERGOING UNILATERAL HIP REPLACEMENT WHO COULD BE EVALUATED, ACCORDING TO THE LOCATION OF THE THROMBOSIS.

LOCATION OF THROMBOSIS	PLACEBO GROUP (N=98)			ENOXAPARIN GROUP (N=96)		
	ALL SITES	PROXIMAL	DISTAL	ALL SITES	PROXIMAL	DISTAL
	no. of patients (%)					
Leg with hip replacement	22 (22)	17 (17)	5 (5)	12 (12)	4 (4)	8 (8)
Contralateral leg	3 (3)	1 (1)	2 (2)	1 (1)	0	1 (1)
Both legs	9 (9)	5 (5)	4 (4)	3 (3)	2 (2)	1 (1)

ble 2) during the outpatient phase. Ten of these patients (eight with deep-vein thrombosis and two with pulmonary embolism) were in the placebo group, and two (both with deep-vein thrombosis) were in the enoxaparin group. The thrombi were all verified objectively. No further episodes of symptomatic thromboembolism occurred. No patients died during the post-discharge period.

**Hemorrhagic Complications**

Hematomas were seen at the injection site in one patient in the placebo group (1 percent) and six patients in the enoxaparin group (5 percent). Four patients in the placebo group and two patients in the enoxaparin group had decreases in hemoglobin of at least 2 g per deciliter; no patient had an absolute hemoglobin level below 8 g per deciliter. An increase in alanine aminotransferase to more than three times the upper limit of normal was found in one patient in the enoxaparin group. One patient in the enoxaparin group and none in the placebo group had mild thrombocytopenia (defined as a platelet count of 100,000 to 125,000 cells per cubic millimeter). This patient, a man 78 years old, had a preoperative platelet count of 263,000 per cubic millimeter. The count was lowest on postoperative day 23, at 121,000, and was 161,000 three days later. The patient’s treatment was continued.

**Other Adverse Events**

There were no rehospitalizations for nonthrombotic, nonhemorrhagic causes. The incidence of adverse events leading to a discontinuation of the study medication, except for those related to venous thromboembolism, was similar in the two study groups. No patients died during the three months after randomization.

**DISCUSSION**

In several studies, a beneficial effect of low-molecular-weight heparin in the prevention of postoperative thrombosis has been found.<sup>1,23-25</sup> In our study, enoxaparin was used for routine prophylaxis during hospi-

talization in all patients. This prophylaxis was well tolerated, and there were no problems that could have been attributed to the administration of enoxaparin. It should be noted that the first dose was given about 12 hours before surgery, that the majority of patients (95 percent) received epidural or spinal anesthesia, and that in keeping with previous observations, no complications were observed in patients receiving enoxaparin and epidural anesthesia.<sup>26,27</sup>

The design of our study could be criticized in that patients in whom deep-vein thrombosis developed during the period of open-label therapy with enoxaparin were not identified and excluded before randomization. There were several reasons for the design we used. Ultrasonography is not optimal for the detection of thrombi in asymptomatic patients, especially distal and small proximal thrombi.<sup>28-30</sup> Moreover, ultrasonography was not available at the time the study started. At least theoretically, phlebography performed at the time of discharge could have induced deep-vein thrombosis in some patients, although such a result is uncommon with the technique used in our hospital.<sup>31</sup> Diagnostic surveillance is not routinely performed at hospital discharge in this population of patients. The frequency of deep-vein thrombosis at discharge is therefore unknown, but it was 11 percent at the same point in the study by Turpie et al.<sup>1</sup> In our study, the 18 percent incidence of deep-vein thrombosis in the group given enoxaparin for one month may mean that there is a period of continued risk after hospital discharge even with extended prophylaxis, but that without such prophylaxis the risk is significantly higher.

In studies of patients undergoing hip-replacement surgery, bilateral phlebography must be used to diagnose deep-vein thrombosis. Ultrasonography lacks sensitivity as a screening instrument in asymptomatic patients.<sup>30</sup> In our study, the use of a strict study protocol implemented by a few investigators made it possible to obtain adequate phlebograms in the vast majority of patients. Moreover, there was high compliance with the treatment protocol.

The main outcome was that prolonged prophylax-

is with enoxaparin significantly reduced the incidence of venous thromboembolism; in addition, the frequency of proximal thrombi was significantly reduced. An important question is whether these findings have economic implications, but answering that question requires a formal economic analysis.<sup>9</sup> The prophylactic effect at one month was in keeping with recently abstracted data<sup>32</sup> and study findings.<sup>33</sup> The frequency of clinical thromboembolism in the placebo group was equivalent to that recently reported in a study of total hip replacement in which there was no routine pharmacologic prophylaxis.<sup>34</sup>

Another important question is whether the beneficial results seen in this study can be reproduced in a routine clinical setting. Compliance was guaranteed in this trial because the study nurses administered the injections of the study drug. However, our clinical impression is that most patients, when motivated, are able to give themselves injections of the medication without difficulty.

In conclusion, patients receiving prophylaxis with enoxaparin for a full month after surgery had significantly less venous thromboembolic disease (most of which was asymptomatic), including proximal deep-vein thrombosis, than patients receiving enoxaparin prophylaxis only during their hospitalizations. In addition, there was a significant reduction in the incidence of symptomatic thromboembolic events.

Supported by a grant (00759) from the Swedish Medical Research Council, by the Swedish Heart and Lung Foundation, and by Rhône-Poulenc Rorer.

*We are indebted to the project nurses, Christine Persson and Lill Borgström, for their efforts and contributions; to the following members of the research staff at Rhône-Poulenc Rorer for important contributions: Alistair Bone, Jean Bouthier, Sophie Combe, Jarl Molin, Ghislaine Pisapia, Björn Rubin, and Theodore Spiro; and to the following members of the research team for their dedication: Anne Guerriero, Mary Keiser, Ann Maher, Jennifer Rohr, Mary Jane Seipp, Susan Snyder, and Mary J. Sparks.*

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