

PROLONGED ENOXAPARIN THERAPY TO PREVENT VENOUS THROMBOEMBOLISM AFTER PRIMARY HIP OR KNEE REPLACEMENT

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Background: Patients undergoing hip or knee joint replacement are at risk for venous thromboembolic complications for up to twelve weeks postoperatively. We evaluated the efficacy and safety of a prolonged post-hospital regimen of enoxaparin, a low-molecular-weight heparin, in this patient population.

Methods: Following elective total hip or knee replacement, 968 patients received subcutaneous enoxaparin (30 mg twice daily) for seven to ten days, and 873 were then randomized to receive three weeks of double-blind outpatient treatment with either enoxaparin (40 mg once daily) or a placebo. The primary efficacy end point was the prevalence of objectively confirmed venous thromboembolism or symptomatic pulmonary embolism during the double-blind phase of treatment.

Results: Of the 873 randomized patients, 435 underwent elective total hip replacement and 438 underwent elective total knee replacement. Enoxaparin was superior to the placebo in reducing the prevalence of venous thromboembolism in patients treated with hip replacement: 8.0% (eighteen) of the 224 patients treated with enoxaparin had venous thromboembolism compared with 23.2% (forty-nine) of the 211 patients treated with the placebo ($p < 0.001$; odds ratio, 3.62; 95% confidence interval, 2.00 to 6.55; relative risk reduction, 65.5%). Enoxaparin had no significant benefit in the patients treated with knee replacement: thirty-eight (17.5%) of the 217 patients treated with enoxaparin had venous thromboembolism compared with forty-six (20.8%) of the 221 patients treated with the placebo ($p = 0.380$; odds ratio, 1.24; 95% confidence interval, 0.76 to 2.02; relative risk reduction, 15.9%). Symptomatic pulmonary embolism developed in three patients, one with a hip replacement and two with a knee replacement; all had received the placebo. There was no significant difference in the prevalence of hemorrhagic episodes or other types of toxicity between the enoxaparin and placebo-treated groups.

Conclusions: Prolonging enoxaparin thromboprophylaxis following hip replacement for a total of four weeks provided therapeutic benefit, by reducing the prevalence of venous thromboembolism, without compromising safety. A similar benefit was not observed in patients treated with knee replacement.

Venous thromboembolic complications occur in 40% to 70% of patients who undergo hip or knee replacement without postoperative thromboprophylaxis¹². The low-molecular-weight heparin enoxaparin has proved to be superior to a placebo and to be as effective as, or more effective than, other prophylactic anticoagulants (for example, unfractionated heparin, dextran, and warfarin) for reducing the prevalence of these complications³⁻¹². Patients may be at risk for pulmonary embolism for at least one month postoperatively¹³⁻¹⁵ and at risk for deep-vein thrombosis for at least six weeks postoperatively¹⁶.

In response to this observation, recent consensus conference statements have suggested that thromboprophylactic therapy should be extended beyond the first seven to ten postoperative days and continued until the risk of thrombosis returns to a low or normal level¹⁶⁻¹⁸. Two studies demonstrated that the extension of treatment for up to five weeks after total hip replacement reduced the prevalence of deep-vein thrombosis as observed venographically at the time that the extended treatment was discontinued^{19,20}. Patients who have undergone total knee arthroplasty might be expected to have a similar long-term risk for development of venous thromboembolic complications and to likewise benefit from extension of thromboprophylaxis.

In the current study, we evaluated the efficacy and safety of a prolonged post-hospital regimen of subcutaneous enox-



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TABLE I Summary of Patient Accountability

Population	Placebo*			Enoxaparin*		
	Hip	Knee	Combined (Hip and Knee)	Hip	Knee	Combined (Hip and Knee)
Randomized	211	221	432	224	217	441
Treated	211	221	432	224	217	441
Evaluable†	138 (65.4%)	144 (65.2%)	282 (65.3%)	152 (67.9%)	155 (71.4%)	307 (69.6%)
Nonevaluable	73 (34.6%)	77 (34.8%)	150 (34.7%)	72 (32.1%)	62 (28.6%)	134 (30.4%)
Inadequate or absent final end point	63 (86.3%)	71 (92.2%)	134 (89.3%)	69 (95.8%)	56 (90.3%)	125 (93.3%)
Insufficient study therapy	8 (11.0%)	6 (7.8%)	14 (9.3%)	1 (1.4%)	5 (8.1%)	6 (4.5%)
Inappropriate open-label period	2 (2.7%)	0 (0.0%)	2 (1.3%)	1 (1.4%)	1 (1.6%)	2 (1.5%)
Inappropriate surgical procedure	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.7%)
Discontinued‡	65 (30.8%)	57 (25.8%)	122 (28.2%)	52 (23.2%)	58 (26.7%)	110 (24.9%)
Evaluable	30	30	60	27	33	60
Nonevaluable	35	27	62	25	25	50

*The values are given as the number of patients, with the percentage in parentheses. †Evaluable patients were required to have undergone bilateral venography (or a lung scan in the case of suspected pulmonary embolism), received at least 75% of the required study treatment, and undergone a primary total hip or knee replacement. ‡The investigator defined the patient's status. Patients were independently classified as evaluable or nonevaluable on the basis of criteria specified in the statistical analysis plan.

aparin (40 mg once daily) compared with a placebo in patients who underwent elective primary total hip or knee replacement. All patients were treated initially with enoxaparin (30 mg twice daily) prior to randomization to the prolonged post-hospital treatment.

Materials and Methods

Study Design and

Patient Characteristics

This was a prospective, parallel-group, multicenter study with an open-label phase of treatment with 30 mg of subcutaneous enoxaparin twice daily followed by a randomized, double-blind outpatient phase comparing treatment with 40 mg of subcutaneous enoxaparin once daily with a placebo. Institutional review boards approved the study protocol before the study commenced. Fifty-seven investigators enrolled one or more patients in the study between December 1994 and February 1996. Patients undergoing elective primary total hip or knee replacement who gave written informed consent were eligible for enrollment in the open-label phase.

Enoxaparin treatment was initiated twelve to twenty-four hours postoperatively and was continued for seven to ten days. Patients who received adequate medication during the open-label phase of the study (the prescribed enoxaparin dose for at least seven days), did not require a reoperation or have venous thrombosis or major hemorrhage during hospitalization, and did not receive excluded concomitant medications were eligible for inclusion in the outpatient double-blind phase of the study. During the open-label period, use of nonsteroidal anti-inflammatory agents, antiplatelet agents, and corticosteroids was permitted whereas use of oral anticoagulants was prohibited.

Qualified health-care personnel administered all open-label inpatient or outpatient treatments. Patients were then randomized to receive double-blind therapy with either subcutaneous enoxaparin (40 mg once daily) or matching injections of saline solution for three weeks (eighteen to twenty-one days). The computer-generated randomization scheme was stratified by surgical procedure. The double-blind therapy was self-administered by the patients, with the administration of the first dose witnessed by health-care personnel.

Patients undergoing multiple joint replacement or in whom hemostasis was not achieved within twelve to twenty-four hours after the surgery were excluded from the open-label phase of the study. Patients treated with hip replacement who had undergone surgery on the ipsilateral hip within the preceding six months or on the ipsilateral knee, the contralateral knee, or the contralateral hip within the preceding three months were excluded. Patients treated with knee replacement who had undergone surgery on the ipsilateral knee within the preceding six months or on the ipsilateral hip, the contralateral hip, or the contralateral knee within the preceding three months were also excluded. Other exclusion criteria were clinical evidence of chronic or acute deep-vein thrombosis; a history of venous thromboembolic disease within twelve months before the surgery; generalized hemorrhagic diathesis or hypercoagulable syndrome; a documented allergy to unfractionated heparin or a history of heparin-associated thrombocytopenia; a skin rash or necrosis; allergy to fish or swine products, iodine, or radiopaque contrast medium; current drug or alcohol abuse; surgery on the eye, spinal cord, or central nervous system; documented stroke or myocardial infarction within one month before entry into the

study; active ulcerative disease or angiodysplasia of the gastrointestinal tract; active gastrointestinal bleeding within the last six months; uncontrolled hypertension; use of aspirin-containing products or nonsteroidal anti-inflammatory agents daily within the four days preceding hospitalization; receipt of another investigational drug within the preceding four weeks; and clinically relevant diseases or treatments that could interfere with the study medications or their evaluation (including severe hepatic disease or renal insufficiency). Patients could enter the trial only once.

Assessment of Deep-Vein Thrombosis and Pulmonary Embolism

The prevalence of objectively confirmed deep-vein thrombosis or symptomatic pulmonary embolism during the double-blind phase was the primary efficacy end point. Venous segment-filling defects on lower-extremity ascending contrast venograms (on at least two venograms for calf thrombi and on one for proximal thrombi) were required to confirm the diagnosis of deep-vein thrombosis. A high-probability ventilation-perfusion lung scan or pulmonary vein-filling defects on a pulmonary angiogram were required to document the diagnosis of pulmonary embolism. Throughout and at the end of the open-label phase (on the seventh to tenth day), patients were examined for clinical evidence of deep-vein thrombosis or pulmonary embolism. These assessments were repeated at the beginning of the double-blind phase (on the eighth to eleventh day) and during that phase (on the fifteenth to twentieth day). Patients presenting with clinical evidence of deep-vein thrombosis during either phase of the study underwent lower-extremity ultrasonography to exclude or confirm the diagnosis of acute deep-vein thrombosis. During the double-blind phase, confirmation of the diagnosis of deep-vein thrombosis by venography was required. A ventilation-perfusion lung scan or pulmonary angiography was performed on patients with clinical evidence of pulmonary embolism. At the end of double-blind treatment (on the twenty-seventh, twenty-eighth, or twenty-ninth day), the protocol required bilateral venography and ultrasonography to be performed on all patients. A central independent expert panel composed of at least three vascular radiologists blinded to the treatment assignment and outcome interpreted all venograms, ventilation-perfusion lung scans, and pulmonary angiograms made during the double-blind phase. The final diagnosis was assigned by a consensus method. The expert panel did not assess ultrasonograms. During a follow-up evaluation (on the ninetieth day, plus or minus one week), patients were assessed to determine whether there had been a recent hospitalization and whether venous thromboembolic disease had developed.

Safety Assessment

The patients were assessed for hemorrhage daily during the hospitalization and at outpatient visits. Hemorrhage was defined as major if it was clinically overt and resulted in death, transfusion of two or more units of blood products, a decrease in the hemoglobin level of ≥ 2.0 g/dL (≥ 20 g/L) compared with

the most recent preceding postoperative value, or a serious or life-threatening clinical event or one requiring surgical intervention or if it was retroperitoneal, intracranial, or intraocular in location. The hemorrhage was classified as minor if it was overt, did not meet the criteria for major hemorrhage, and was associated with at least one of the following features: epistaxis lasting more than five minutes or requiring intervention, ecchymosis or hematoma larger than 5 cm at its greatest dimension, hematuria not associated with urinary catheter-related trauma, gastrointestinal hemorrhage not related to intubation or placement of a nasogastric tube, wound hematoma or complications, or subconjunctival hemorrhage necessitating cessation of medication.

Standard biochemistry and hematology tests were performed during and at the end of each of the study phases. Details of all adverse events, together with the investigator's assessment of their relationship to the study medication, were recorded.

Statistical Analysis

The estimation of the total sample size in each of the surgical strata was based on a prevalence of venous thromboembolic disease of 30% in placebo-treated patients and 15% in enoxaparin-treated patients, a type-I error rate of 5%, and a power of 80%. The sample size necessary for each surgical stratum and treatment group was 268 patients. If it was assumed that 35% of the randomized patients would not be evaluable, then 824 patients had to be randomized to ensure 536 evaluable patients. The primary efficacy analysis was performed on all randomized patients who received at least one dose of study medication (the all-treated-patients population). All patients, including those who did not have venography performed at the end of the study, were included in this analysis. Such patients were assigned an efficacy outcome on the basis of the results of ultrasonography, if it had been performed, or on the basis of the occurrence of clinically symptomatic venous thromboembolism that was documented by means other than venography or ultrasonography. An analysis of patients who completed the study according to the protocol (evaluable patients) was likewise performed. Evaluable patients were defined as patients treated with primary total hip or knee replacement who had received at least 75% of the prescribed enoxaparin or placebo and had undergone bilateral venography, had undergone unilateral venography that was positive for deep-vein thrombosis, or had a confirmed diagnosis of deep-vein thrombosis or pulmonary embolism during treatment. The prevalences of venous thromboembolism and proximal deep-vein thrombosis in the two treatment groups (both within the hip and knee replacement groups and within a combined surgical group) were compared with use of the chi-squared test. Odds ratios, 95% confidence intervals, and relative risk reductions were calculated. The prevalences of hemorrhagic episodes and adverse events in the groups were compared within each surgical stratum with use of the Fisher exact test and in the combined group with use of the chi-squared test. All comparisons were two-tailed at the 5% significance level.

TABLE II Demographic, Clinical, and Surgical Characteristics of the All-Treated-Patients Population

Characteristic	Placebo			Enoxaparin		
	Hip (N = 211)	Knee (N = 221)	Combined (Hip and Knee) (N = 432)	Hip (N = 224)	Knee (N = 217)	Combined (Hip and Knee) (N = 441)
Gender (M/F)*	106/105	98/123	204/228	111/113	89/128	200/241
Age† (yr)	63.4 (26.0-88.0)	66.3 (34.0-88.0)	64.9 (26.0-88.0)	64.4 (28.0-90.0)	66.2 (39.0-87.0)	65.3 (28.0-90.0)
Weight† (kg)	82.7 (40.8-139.3)	89.2 (45.5-147.4)	86.0 (40.8-147.4)	81.4 (40.4-149.7)	88.7 (52.2-147.4)	85.0 (40.4-149.7)
Body-mass index†† (kg/m ²)	28.5 (16.6-45.0)	31.1 (17.2-55.7)	29.9 (16.6-55.7)	28.4 (16.1-53.7)	31.4 (19.8-51.8)	29.9 (16.1-53.7)
Obesity*§	118 (55.9%)	163 (73.8%)	281 (65.0%)	115 (51.3%)	163 (75.1%)	278 (63.0%)
Surgical diagnosis*						
Osteoarthritis	162 (76.8%)	197 (89.1%)	359 (83.1%)	177 (79.0%)	199 (91.7%)	376 (85.3%)
Avascular necrosis	27 (12.8%)	1 (0.5%)	28 (6.5%)	27 (12.1%)	0 (0.0%)	27 (6.1%)
Rheumatoid arthritis	6 (2.8%)	12 (5.4%)	18 (4.2%)	9 (4.0%)	8 (3.7%)	17 (3.9%)
Traumatic arthritis	9 (4.3%)	9 (4.1%)	18 (4.2%)	2 (0.9%)	7 (3.2%)	9 (2.0%)
Other	7 (3.3%)	2 (0.9%)	9 (2.1%)	9 (4.0%)	3 (1.4%)	12 (2.7%)
Surgical procedure*						
Unilateral primary replacement	165 (78.2%)	168 (76.0%)	333 (77.1%)	176 (78.6%)	157 (72.4%)	333 (75.5%)
Revision	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.2%)
Previous joint replacement	46 (21.8%)	53 (24.0%)	99 (22.9%)	47 (21.0%)	60 (27.6%)	107 (24.3%)
Anesthetic technique*						
At least regional (epidural or spinal)	64 (30.3%)	71 (32.1%)	135 (31.3%)	56 (25.0%)	70 (32.3%)	126 (28.6%)
Only inhalation or intravenous	147 (69.7%)	150 (67.9%)	297 (68.8%)	168 (75.0%)	147 (67.7%)	315 (71.4%)

*The values are given as the number of patients, with the percentage in parentheses. †The values are given as the mean, with the range in parentheses. ††Body-mass index = weight (kg)/height (m²). §Obesity = body-mass index of more than 27.2 for males and more than 26.9 for females.

Results

Patient Characteristics

In total, 968 patients were enrolled in the open-label phase of the study. Ninety-five patients were not randomly assigned to a study treatment: thirty-nine (41.1%), because of an adverse event; twenty-four (25.3%), because they withdrew consent; twenty-one (22.1%), because of a violation of the protocol; three (3.2%), because of an abnormal laboratory test; two (2.1%), because of an inability to administer the study medication; and six (6.3%), because of other reasons. The remaining 873 patients were randomly assigned and received at least one dose of a double-blind treatment (432 received the placebo and 441, enoxaparin); they were included in the all-treated-patients population (Table I). Of these 873 patients, 589 (67.5%) (282 who received the placebo and 307 who received the enoxaparin) were in the evaluable population. Two hundred and eighty-four patients (150 who received the

placebo and 134 who received the enoxaparin) were not evaluable: 259 (134 who received the placebo and 125 who received the enoxaparin) either did not have the required final examination (venography, ultrasonography, or ventilation-perfusion lung-scanning) or had an assessment that was inadequate; twenty (fourteen who received the placebo and six who received the enoxaparin) had received the therapy for an insufficient duration; four (two who received the placebo and two who received the enoxaparin) had an inappropriate open-label period; and one who received the enoxaparin had an inappropriate surgical procedure (Table I).

In all, 122 placebo-treated patients and 110 enoxaparin-treated patients were considered by the investigators to have not completed the study and were classified accordingly as having discontinued the study. The reasons for discontinuing included deviation from the protocol (ninety-six placebo and eighty-seven enoxaparin-treated patients), a clinical adverse

TABLE III Prevalence of Venous Thromboembolic Disease in the All-Treated-Patients and Evaluable Populations

Outcome	Placebo*		Enoxaparin*	
	Hip	Knee	Hip	Knee
All treated patients	211	221	224	217
Venous thromboembolic disease	49 (23.2%)†	46 (20.8%)†	18 (8.0%)	38 (17.5%)
Deep-vein thrombosis	49 (23.2%)	46 (20.8%)	18 (8.0%)	38 (17.5%)
Proximal	27 (12.8%)§	17 (7.7%)#	6 (2.7%)	9 (4.1%)
Distal only	22 (10.4%)	27 (12.2%)	12 (5.4%)	29 (13.4%)
Indeterminate	0 (0.0%)	2 (0.9%)	0 (0.0%)	0 (0.0%)
Pulmonary embolism	1 (0.5%)	2 (0.9%)	0 (0.0%)	0 (0.0%)
Evaluable patients	138	144	152	155
Venous thromboembolic disease	39 (28.3%)**	38 (26.4%)††	15 (9.9%)	33 (21.3%)
Deep-vein thrombosis	39 (28.3%)	37 (25.7%)	15 (9.9%)	33 (21.3%)
Proximal	20 (14.5%)‡‡	11 (7.6%)§§	5 (3.3%)	8 (5.2%)
Distal only	19 (13.8%)	26 (18.1%)	10 (6.6%)	25 (16.1%)
Pulmonary embolism	0 (0.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)
All treated patients' subgroups##				
Male	25/106 (23.6%)	15/98 (15.3%)	7/111 (6.3%)	21/89 (23.6%)
Female	24/105 (22.9%)	31/123 (25.2%)	11/113 (9.7%)	17/128 (13.3%)
Regional anesthesia	20/64 (31.3%)	16/71 (22.5%)	5/56 (8.9%)	13/70 (18.6%)
General anesthesia	29/147 (19.7%)	30/150 (20.0%)	13/168 (7.7%)	25/147 (17.0%)
Obesity (based on body-mass index)	34/118 (28.8%)	35/163 (21.5%)	10/115 (8.7%)	25/163 (15.3%)

*The values are given as the number of patients, with the percentage in parentheses. †p < 0.001 compared with enoxaparin (chi-squared test); odds ratio, 3.62; 95% confidence interval, 2.00 to 6.55. ‡p = 0.380 compared with enoxaparin (chi-squared test); odds ratio, 1.24; 95% confidence interval, 0.76 to 2.02. §p < 0.001 compared with enoxaparin (chi-squared test); odds ratio, 5.33; 95% confidence interval, 2.15 to 13.19. #p = 0.116 compared with enoxaparin (chi-squared test); odds ratio, 1.93; 95% confidence interval, 0.84 to 4.42. **p < 0.001 compared with enoxaparin (chi-squared test); odds ratio, 3.83; 95% confidence interval, 1.97 to 7.44. ††p = 0.282 compared with enoxaparin (chi-squared test); odds ratio, 1.35; 95% confidence interval, 0.78 to 2.32. ‡‡p = 0.001 compared with enoxaparin (chi-squared test); odds ratio, 4.98; 95% confidence interval, 1.82 to 13.67. §§p = 0.380 compared with enoxaparin (chi-squared test); odds ratio, 1.52; 95% confidence interval, 0.59 to 3.89. ##The values are given as the number of patients with venous thromboembolic disease/the number of patients in the subgroup.

event (nine placebo and nine enoxaparin-treated patients), withdrawal of consent (ten placebo and six enoxaparin-treated patients), inability or unwillingness to self-administer the study medication (four placebo and two enoxaparin-treated patients), abnormal results on laboratory testing (zero placebo and two enoxaparin-treated patients), and other reasons (three placebo and four enoxaparin-treated patients). The most common protocol deviation was an incorrect dosage of the study medication—that is, a too long or too short duration of treatment or missed doses. Of the patients who discontinued the study, sixty in each treatment group were still considered to be evaluable (Table I) and were included in the evaluable-patients analysis. All patients who discontinued were included in the all-treated-patients analysis.

The treatment groups were similar with respect to demographic characteristics, including gender and age, and in terms of physical characteristics, including weight, body-mass index, and obesity (Table II). Similarly, there were no major differences between the treatment groups with regard to surgical diagnosis, surgical procedure, or type of anesthesia. The treatment groups were also similar with respect to medical history and use of concomitant medications, although

estrogen-containing medications were used by slightly more patients in the enoxaparin group (20.2%) than in the placebo group (12.3%). The primary surgical diagnosis for the majority of the patients was osteoarthritis resulting in unilateral total joint replacement (Table II). Of the 873 patients, 616 (70.6%) reportedly used graduated compression stockings. A tourniquet reportedly had been used for 432 (98.6%) of the 438 patients treated with knee replacement, and continuous passive motion reportedly had been used for 354 (80.8%). The mean time from the surgery to the administration of the first postoperative dose of enoxaparin was 19.3 hours (range, -1.3 to 42.0 hours). The mean duration of enoxaparin treatment was 8.1 days (range, five to twelve days) during the open-label phase and 19.0 days (range, one to twenty-eight days) during the double-blind phase. These variables were comparable across the treatment groups and surgical procedures.

Prevention of Venous Thromboembolic Disease

In the combined surgical group (total hip and knee replacement), the overall prevalence of venous thromboembolism after one month of treatment in the enoxaparin-treated patients

TABLE IV Treatment and Rehospitalization for Venous Thromboembolic Disease in the All-Treated-Patients Population

Outcome	Placebo		Enoxaparin	
	Hip (N = 211)	Knee (N = 221)	Hip (N = 224)	Knee (N = 217)
Patients with venous thromboembolic disease*	49 (23.2%)	46 (20.8%)	18 (8.0%)	38 (17.5%)
Patients treated for venous thromboembolic disease*	21 (10.0%)	13 (5.9%)	3 (1.3%)	7 (3.2%)
Deep-vein thrombosis*	20 (95.2%)	12 (92.3%)	3 (100.0%)	7 (100.0%)
Pulmonary embolism*	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
Deep-vein thrombosis and pulmonary embolism*	1 (4.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asymptomatic*	14 (66.7%)	10 (76.9%)	3 (100.0%)	5 (71.4%)
Symptomatic*	7 (33.3%)	3 (23.1%)	0 (0.0%)	2 (28.6%)
Treatment				
Medication* (e.g., aspirin)	3 (14.3%)	3 (23.1%)	1 (33.3%)	2 (28.6%)
Anticoagulant* (e.g., warfarin, heparin)	16 (76.2%)	9 (69.2%)	2 (66.7%)	6 (85.7%)
Unknown*	2 (9.5%)	1 (7.7%)		
Patients rehospitalized*	22 (10.4%)	12 (5.4%)	3 (1.3%)	7 (3.2%)
Total duration (days)	137.0	77.0	16.0	52.0
Mean duration (range) (days)	6.2 (1.0-12.0)	6.4 (2.0-10.0)	5.3 (3.0-7.0)	7.4 (6.0-9.0)

*The values are given as the number of patients, with the percentage in parentheses.

was significantly lower ($p < 0.001$) than the prevalence in the placebo-treated patients (12.7% [fifty-six] of 441 compared with 22.0% [ninety-five] of 432; odds ratio, 1.96; 95% confidence interval, 1.36 to 2.82; relative risk reduction, 42.3%). In the hip replacement group, the prevalence of venous thromboembolism in the enoxaparin-treated patients was significantly lower ($p < 0.001$) than the prevalence in the placebo-treated patients (8.0% [eighteen] of 224 compared with 23.2% [forty-nine] of 211; odds ratio, 3.62; 95% confidence interval, 2.00 to 6.55; relative risk reduction 65.5%) (Table III). In the knee replacement group, there was no significant difference ($p = 0.380$) between the prevalences in the enoxaparin and placebo-treated patients (17.5% [thirty-eight] of 217 compared with 20.8% [forty-six] of 221; odds ratio, 1.24; 95% confidence interval, 0.76 to 2.02; relative risk reduction, 15.9%). Analysis of the evaluable population revealed similar results, with enoxaparin producing a significantly lower prevalence of venous thromboembolism than the placebo in the hip replacement group (9.9% compared with 28.3%; $p < 0.001$; odds ratio, 3.83; 95% confidence interval, 1.97 to 7.44; relative risk reduction, 65.0%) but not in the knee replacement group (21.3% compared with 26.4%; $p = 0.282$; odds ratio, 1.35; 95% confidence interval, 0.78 to 2.32; relative risk reduction, 21.3%).

Enoxaparin treatment decreased the prevalence of venous thromboembolism in men in the hip replacement group, but it did not lead to a meaningful reduction in the prevalence of venous thromboembolic disease in men in the knee replacement group (Table III). Enoxaparin reduced the prevalence of venous thromboembolic disease in women in both the hip and the knee replacement group. Patients with regional anesthesia had no difference in the prevalence of venous thromboembolism when compared with patients with

general anesthesia. Obese patients were not at increased risk for the development of venous thromboembolism when compared with nonobese patients.

Enoxaparin was significantly superior ($p < 0.001$) to the placebo in reducing the prevalence of proximal deep-vein thrombosis in the hip replacement group (2.7% compared with 12.8%; odds ratio, 5.33; 95% confidence interval, 2.15 to 13.19; relative risk reduction, 78.9%) but showed no significant benefit ($p = 0.116$) in the knee replacement group (4.1% compared with 7.7%; odds ratio, 1.93; 95% confidence interval, 0.84 to 4.42; relative risk reduction, 46.8%). While the percentage of patients with proximal deep-vein thrombosis was not influenced by the type of joint replacement in the placebo group, the prevalence of only distal deep-vein thrombosis in the enoxaparin group was higher in the patients with a knee replacement (13.4%) than in those with a hip replacement (5.4%). The proximal and/or distal distribution of the thrombi in the evaluable patients was similar to that in the all-treated-patients population.

Symptomatic pulmonary embolism occurred in three placebo-treated patients (one patient with a hip replacement who also had deep-vein thrombosis and two patients with a knee replacement) but in no enoxaparin-treated patients.

During the study period, three (1.3%) of the 224 patients with a hip replacement and seven (3.2%) of the 217 with a knee replacement in the enoxaparin group were rehospitalized for venous thromboembolic disease compared with twenty-two (10.4%) of the 211 patients with a hip replacement and twelve (5.4%) of the 221 with a knee replacement in the placebo group (Table IV). In both surgical groups, the placebo-treated patients were rehospitalized for a larger total number of days than were the enoxaparin-treated patients. No statistical analysis of these results was performed.

TABLE V Prevalence of Hemorrhagic Events, Abnormal Laboratory Tests, and Adverse Events in the All-Treated-Patients Population During the Double-Blind Phase

Outcome	Placebo*			Enoxaparin*		
	Hip (N = 211)	Knee (N = 221)	Combined (Hip and Knee) (N = 432)	Hip (N = 224)	Knee (N = 217)	Combined (Hip and Knee) (N = 441)
Hemorrhage	5 (2.4%)†	6 (2.7%)†	11 (2.5%)§	2 (0.9%)	8 (3.7%)	10 (2.3%)
Major hemorrhage	0 (0.0%)	1 (0.5%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abnormal laboratory test						
Mild thrombocytopenia#	2 (0.9%)	2 (0.9%)	4 (0.9%)	3 (1.3%)	2 (0.9%)	5 (1.1%)
Alanine aminotransferase elevation**	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	2 (0.9%)	3 (0.7%)
Adverse events††						
Injection-site hemorrhage	3 (1.4%)	2 (0.9%)	5 (1.2%)	4 (1.8%)	1 (0.5%)	5 (1.1%)
Injection-site pain	1 (0.5%)	3 (1.4%)	4 (0.9%)	3 (1.3%)	2 (0.9%)	5 (1.1%)
Ecchymosis	2 (0.9%)	1 (0.5%)	3 (0.7%)	6 (2.7%)	1 (0.5%)	7 (1.6%)

*The values are given as the number of patients, with the percentage in parentheses. †p = 0.272 compared with enoxaparin (Fisher exact test). †p = 0.598 compared with enoxaparin (Fisher exact test). §p = 0.811 compared with enoxaparin (chi-squared test). #Mild thrombocytopenia, >100 to 125 × 10⁹ platelets per liter; moderate, 50 to 100 × 10⁹ platelets per liter; and severe, ≤ 50 × 10⁹ platelets per liter. **A level three times the upper limit of normal. ††Adverse events include those related to the study drug that had a frequency of more than 1.0% in either treatment group. In all, adverse events were reported in twenty-nine (6.7%) of the placebo-treated patients and in thirty-four (7.7%) of the enoxaparin-treated patients.

Of the 151 patients in whom venous thromboembolic disease developed, 105 (69.5%) had thrombosis in only the extremity that had been operated on; twenty-six (17.2%), in only the extremity that had not been operated on; and eighteen (11.9%), in both extremities (bilateral). The location of the thrombosis in two patients, who had pulmonary embolism, was classified as unknown. Bilateral thrombi were more common after hip replacement (16.4%) than after knee replacement (8.3%), whereas thrombi in only the operatively treated extremity were more common after knee replacement than after hip replacement (64.2% compared with 73.8%).

Safety Results

Hemorrhagic Episodes

During the double-blind phase of the study, twenty-one hemorrhagic episodes were reported in twenty-one (2.4%) of the 873 patients in the all-treated-patients population: eleven (2.5%) of the patients in the placebo group and ten (2.3%) in the enoxaparin group had such an episode (Table V). The differences between the placebo and enoxaparin-treated patients in this respect were not significant in either the combined surgical group (p = 0.811), the hip replacement group (p = 0.272), or the knee replacement group (p = 0.598). Hemorrhage occurred at a nonoperative site in thirteen patients (1.5%) and at the operative site in eight (0.9%). Only one major hemorrhagic episode (intraarticular hemorrhage in a placebo-treated patient with a knee replacement) was reported.

Abnormal Laboratory Tests

Abnormal laboratory tests were rare during the double-blind

phase (Table V). Mild, transient thrombocytopenia occurred in four (0.9%) of the placebo-treated patients and five (1.1%) of those treated with enoxaparin. Increased alanine aminotransferase levels were detected in three patients treated with enoxaparin but not in any treated with the placebo. No differences with regard to the occurrence of hyperkalemia were observed between the two treatment groups.

Adverse Events and Death

During the double-blind phase of the study, twenty-nine (6.7%) of the placebo-treated patients and thirty-four (7.7%) of the enoxaparin-treated patients reported at least one adverse event that was considered to be related to the study medication (Table V). All of these events were mild or moderate in severity, and none had a prevalence of more than 2%, with the exception of ecchymosis in the enoxaparin-treated patients with a hip replacement (prevalence, 2.7%). Injection-site hemorrhage and pain and ecchymosis were observed in approximately 1% of the patients in each treatment group, with no apparent intergroup difference.

Only one death occurred in the randomized population: a patient died from a suspected pulmonary embolism after receiving a single dose of the placebo. No autopsy was performed. Pulmonary embolism was stated to be the cause of death on the death certificate.

Follow-up Assessment

Follow-up assessment for clinical events occurring between one month and three months was possible for 819 (93.8%) of the 873 randomized patients: 406 placebo-treated patients and 413 enoxaparin-treated patients. Only two patients, both in

the group treated with enoxaparin and hip replacement (a prevalence of 0.9% of 224 in that group) were rehospitalized for treatment of clinically symptomatic deep-vein thrombosis occurring after the end of the treatment evaluation.

Discussion

In this study, patients who received conventional short-term enoxaparin therapy (30 mg twice daily) were approximately twice as likely to have venous thromboembolic disease after elective hip or knee joint replacement compared with those for whom the short-term enoxaparin therapy was followed by a prolonged (three-week) course of enoxaparin therapy (40 mg once daily). However, different patterns of response were observed after the two types of surgery. While the prolonged regimen reduced the likelihood of venous thromboembolism developing in patients who had undergone hip replacement, it provided no significant benefit following knee replacement. These conclusions are based primarily on the occurrence of asymptomatic deep-vein thrombosis detected by venography. No socioeconomic analysis was performed in this study. No statistical analysis of symptomatic venous thromboembolic disease was performed, and the follow-up duration was not long enough to allow assessment of chronic venous insufficiency.

The difference observed between the two types of joint replacement may have been influenced by differences in body weight or obesity. The patients treated with knee replacement weighed more, had a higher body-mass index, and were more often obese compared with those treated with hip replacement. Additional differences in the patterns of response emerged in the analysis of the subpopulations. The prolonged enoxaparin treatment regimen was superior to the short-term regimen in both male and female patients who underwent hip replacement. However, in the knee replacement group, a benefit was observed only in female patients. Enoxaparin did not reduce the prevalence of venous thrombosis, compared with the placebo, in male patients treated with knee replacement. It is possible that the dose of enoxaparin was insufficient or the dosing interval was too long for the male patients because of their greater weight, height, and body-surface area relative to the female patients. The average weight of the men undergoing knee arthroplasty was 96.8 kg compared with 83.1 kg for the women. The prolonged regimen demonstrated a protective effect in obese patients after both surgical procedures, although this effect was more marked in the hip replacement group than in the knee replacement group. No proven explanations for the differences observed between women and men after total knee arthroplasty are available. However, pharmacokinetic studies²¹ of volunteers have revealed that body weight is associated with peak anti-factor-Xa activity, with peak levels being decreased as body weight increases. In our study, no tests of significance were performed in any analysis of patient subgroups as they were not prespecified in the protocol or in the plan for statistical analysis.

A survey of medical records in the state of California was performed in order to estimate the frequency of venous thromboembolism within three months after hip and knee

replacements²². The authors observed a significant difference between hip and knee replacements with regard to both the number of clinical venous thromboembolic events and the median time to diagnosis of the event (seventeen and seven days, respectively). Seventy-six percent of the patients in whom a clinical venous thromboembolic event developed following hip arthroplasty were diagnosed after hospital discharge compared with 47% of the patients in whom an event developed following knee arthroplasty. A study comparing venographic findings at one and six days after knee replacement in a cohort of fifty-nine patients (seventy-six knees) showed that 86% of the limbs in which venous thrombosis developed had it at the early time-period (at one day)²². The earlier appearance of clinical venous thromboembolic events after knee replacement suggests that there may be a lower prevalence of late-occurring venous thromboembolism after this procedure, and this may have affected the overall benefit of extended-duration enoxaparin thromboprophylaxis in the present study.

Two studies of low-molecular-weight heparin demonstrated that both fixed and weight-adjusted once-daily postoperative dosing regimens may be less efficacious overall than twice-daily postoperative dosing regimens after either hip or knee replacement^{7,24}. Studies of twice-daily dosing regimens with enoxaparin and ardeparin demonstrated that fixed-dose (enoxaparin) and weight-adjusted (ardeparin) regimens provided effective and safe thromboprophylaxis after knee replacement when compared with heparin, warfarin, and placebo controls^{9,12,24,25}. Enoxaparin and other low-molecular-weight heparins have consistently been shown to be more effective for thromboprophylaxis following hip replacement than for thromboprophylaxis following knee replacement^{3,12,24,26}.

The results of the present study support previous evidence of the beneficial effect of extending the duration of thromboprophylaxis after total hip replacement. In a recent double-blind study, patients without deep-vein thromboembolism after total hip replacement were randomized (after thirteen, fourteen, or fifteen days of hospitalization) to receive twenty-one days of treatment with a placebo or subcutaneous enoxaparin (40 mg once daily)¹⁹. The enoxaparin-treated patients had a significantly lower prevalence of deep-vein thrombosis (7.1% compared with 19.3% in the placebo-treated patients; $p = 0.018$). In a study with a design similar to that of the present study²⁰, patients were treated with enoxaparin from the evening before the surgery until discharge (at a mean of ten or eleven days), at which point the patients were randomly assigned to receive enoxaparin therapy or a placebo for an additional twenty-one days. Again, the prevalence of venous thromboembolic disease in the patients treated with enoxaparin (18%) was significantly lower ($p < 0.001$) than the prevalence in the patients treated with the placebo (39%). These data are supported by those from studies of dalteparin, another low-molecular-weight heparin, after hip replacement surgery^{27,28}.

Clearly, the benefit of outpatient thromboprophylaxis must be balanced against any potential increase in the risk of hemorrhagic episodes. However, in this study such episodes

were similarly infrequent in the two treatment groups, and only one case, in a placebo recipient, was considered major. Moreover, the prevalences of adverse events and abnormal clinical laboratory tests associated with the long-term enoxaparin therapy were comparable with those associated with the placebo. Thrombocytopenia is a recognized complication of heparin therapy²⁹, with a prevalence of about 1.7% in patients treated with intravenous porcine heparin when the thrombocytopenia was defined as a platelet count of $<100 \times 10^9/L$. During the extended-therapy phase of the present study, there were no platelet counts of $<100 \times 10^9/L$, and only nine patients (four treated with a placebo and five treated with enoxaparin) had mild thrombocytopenia (a platelet count of >100 to $125 \times 10^9/L$). Increased aminotransferase levels, which may occur with both conventional and low-molecular-weight heparins^{30,31}, occurred only rarely with the enoxaparin regimen used during the double-blind phase of this study.

In summary, these results, which are based primarily on venographic evidence, indicate that the recommended seven to ten-day postoperative thromboprophylactic regimen of 30 mg of enoxaparin twice daily for patients treated with total hip replacement is suboptimal and that a substantial therapeutic benefit is gained, without compromising safety, by prolonging the enoxaparin treatment (at a dose of 40 mg once daily) for an additional three weeks postoperatively (resulting in a total of four weeks of enoxaparin treatment). This benefit was not observed in patients who underwent knee replacement, and additional studies of this patient population are warranted. ■

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One or more of the authors has received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article. Funds were received in total or partial support of the research or clinical study presented in this article. The funding source was Aventis Pharmaceuticals, Incorporated, Bridgewater, New Jersey, and Aventis Pharma, S.A., Antony, France, formerly Rhône-Poulenc Rorer Pharma, S.A., Collegenille, Pennsylvania, and Antony, France.

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