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Ardeparin Sodium for Extended Out-of-Hospital Prophylaxis against Venous Thromboembolism after Total Hip or Knee Replacement

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: The optimal duration of prophylaxis against venous thromboembolism after total hip or knee replacement is uncertain.

Objective: To determine the efficacy and safety of extended out-of-hospital prophylaxis with low-molecular-weight heparin (ardeparin sodium).

Design: Randomized, double-blind, placebo-controlled trial.

Setting: 33 community, university, or university-affiliated hospitals.

Patients: 1195 adults who had elective total hip or knee replacement and completed 4 to 10 days of postoperative ardeparin prophylaxis.

Intervention: Daily subcutaneous ardeparin (100 anti-X_a IU/kg of body weight) or placebo from time of hospital discharge to 6 weeks after surgery.

Measurements: Symptomatic, objectively documented venous thromboembolism or death, along with major bleeding, from time of hospital discharge to 12 weeks after surgery.

Results: Patients who received ardeparin ($n = 607$) and those who received placebo ($n = 588$) did not differ significantly in the cumulative incidence of venous thromboembolism or death (9 cases [1.5%] compared with 12 cases [2.0%]; odds ratio, 0.7 [95% CI, 0.3 to 1.7]; $P > 0.2$; absolute difference, -0.56 percentage points [CI, -2.2 to 1.1 percentage points]) or major bleeding (2 cases [0.3%] compared with 3 cases [0.5%]).

Conclusions: Among patients who had total knee or total hip replacement and received 4 to 10 days of postoperative ardeparin prophylaxis, the cumulative incidence of symptomatic venous thromboembolism or death after hospital discharge was not significantly reduced by extended out-of-hospital ardeparin prophylaxis. Extended ardeparin use could provide a maximum 2.2-percentage point true reduction in such events. The benefit of extended ardeparin use is not clinically important for most

patients. Future research should identify high-risk patients who would benefit most from extended prophylaxis.

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The optimal duration of prophylaxis against venous thromboembolism after elective total hip or knee replacement is uncertain. In previous clinical trials, prophylaxis was given until hospital discharge and ranged from 7 to 14 days. However, the prevalence of asymptomatic deep venous thrombosis at hospital discharge was still approximately 15% for patients who had total hip replacement and 30% for those who had total knee replacement (1). Because most patients are now discharged by the third or fourth postoperative day, in-hospital prophylaxis may be inadequate.

Two clinical trials found that 19% to 26% of patients who had total hip replacement developed new asymptomatic deep venous thrombosis 3 to 4 weeks after hospital discharge (2, 3). Four trials reported that extended out-of-hospital prophylaxis with low-molecular-weight heparin substantially reduced the prevalence of asymptomatic deep venous thrombosis (2–5). The investigators of these trials concluded that prophylaxis with low-molecular-weight heparin should be extended beyond hospital discharge. However, in a large cohort study of patients who had total knee or total hip replacement

See editorial comment on pp 914-915.

and received solely in-hospital low-molecular-weight heparin prophylaxis, Leclerc and coworkers (6) found that the 90-day incidence of symptomatic venous thromboembolism and fatal pulmonary embolism was only 4.1% and 0.15%, respectively. They concluded that there was little to gain by extending prophylaxis beyond hospital discharge. However, the mean duration of prophylaxis in their study was 9 days, substantially longer than the current length of hospitalization.

Because of continuing uncertainty about the need for out-of-hospital prophylaxis after total hip or knee replacement, we performed a randomized clinical trial of extended out-of-hospital prophylaxis with low-molecular-weight heparin. Symptomatic venous thromboembolism or death was the primary outcome measure.

Methods

Study Design

The study consisted of two parts, part A and part B. In part A, all patients received open-label, in-hospital prophylaxis twice daily with ardeparin sodium (Normiflo, Wyeth-Ayerst, Philadelphia, Pennsylvania), 50 anti-X_a IU/kg of body weight subcutaneously. Prophylaxis was started within 24 hours after surgery. Part B was a randomized clinical trial involving patients who completed 4 to 10 days of open-label prophylaxis in part A without developing symptomatic, objectively documented venous thromboembolism.

After giving informed consent, all patients in part B were randomly assigned to receive double-blind, out-of-hospital prophylaxis with ardeparin sodium (100 anti-X_a IU/kg [maximum dose, 10 000 anti-X_a IU]) or placebo, administered subcutaneously once daily until 6 weeks after surgery. Randomization was done at the end of part A and included stratification by clinical center, type of surgery, and history of venous thromboembolism. Using block randomization derived from a randomization table, the study sponsor provided each clinical center with the part B treatment allocation in consecutively numbered sealed envelopes. Patients in part B received a double-blind package of identical-appearing Tubex cartridges (Wyeth-Ayerst) containing 0.5 mL of ardeparin sodium (anti-X_a activity, 20 000 IU/mL) or placebo (sodium chloride solution).

The first assigned dose in part B was administered within 12 hours of the last dose in part A. After appropriate instruction, the patient, a family member, or a friend administered the part B prophylaxis. Compliance was defined as receiving at least 50% of the scheduled doses for the first 2 weeks of part B and at least 50% of the assigned

part B prophylaxis overall. Patients recorded in a diary all concurrent medications and the date, time, and location of each daily injection. After part B was completed, we assessed compliance by diary review and syringe count. The study was conducted at 33 clinical centers in the United States. The institutional review board of each center approved the protocol.

Study Sample

Patients were eligible for enrollment in both parts of the study if they were 18 years of age or older and received elective primary or revision unilateral total hip replacement, primary unilateral or bilateral total knee replacement, or revision unilateral total knee replacement during the study period (November 1994 through November 1997). Pregnant or lactating women and women of childbearing age were excluded, as were patients with a clinical bleeding disorder, uncontrolled hypertension, severely impaired hepatic or renal function, or active alcohol or drug abuse. Patients who could not comply with home subcutaneous injections or complete a 10-week postoperative follow-up were also excluded. Similarly, patients who were receiving warfarin or thrombolytic therapy, had had major surgery in the previous 7 days, or had had major orthopedic surgery involving the lower extremities (including arthroscopy) in the previous 6 weeks were excluded, as were patients with a history of substantial internal bleeding, active peptic ulcer, myocardial infarction, or stroke. In addition, patients who had had intracranial or intraocular surgery in the previous 8 weeks were excluded.

We excluded patients who were planning to undergo staged bilateral total knee replacement with an anticipated interval of less than 10 weeks between surgeries. Other exclusion criteria were hypersensitivity to heparin, pork products, metabisulfite, methylparaben, or propylparaben; weight greater than 120 kg; a prolonged activated partial thromboplastin time or prothrombin time at baseline; or a baseline platelet count less than 100×10^9 cells/L. We did not exclude patients with a history of venous thromboembolism. The concurrent use of dextran sulfate, desmopressin acetate, other low-molecular-weight heparins, oral anticoagulants, thrombolytic agents, or external pneumatic compression was prohibited. However, concurrent use of aspirin, nonsteroidal anti-inflammatory drugs, elastic compression stockings, and passive range-of-motion devices was permitted, as was irrigation of intravenous catheters with unfractionated heparin.

Evaluation of Efficacy and Safety

The primary outcome was the incidence of symptomatic, objectively documented deep venous

thrombosis or pulmonary embolism or death during part B of the study, defined as the time interval from part B enrollment to the last follow-up contact (at least 12 weeks after surgery). Secondary outcomes were the incidence of major and minor bleeding and thrombocytopenia. During part A, all patients were examined daily for bleeding and for symptoms or signs of deep venous thrombosis or pulmonary embolism. Before hospital discharge, patients were educated about the symptoms of deep venous thrombosis, pulmonary embolism, and bleeding and were instructed to notify their physician promptly of any such symptoms. Patients were questioned about symptoms at 2 to 3 weeks, at 6 weeks, and at 10 to 12 weeks after surgery. Hemoglobin and platelet count were measured at 2 to 3 weeks and at 6 weeks. A clinic visit was required at 6 weeks or at 10 to 12 weeks. Routine screening for deep venous thrombosis was prohibited.

Patients with clinically suspected deep venous thrombosis had leg compression venous duplex ultrasonography or venography, and patients with suspected pulmonary embolism underwent ventilation-perfusion lung scanning or pulmonary angiography. Patients with suspected pulmonary embolism who had a nondiagnostic lung scan underwent pulmonary angiography, bilateral leg duplex ultrasonography, or venography. Patients with suspected pulmonary embolism and negative or indeterminate results on duplex ultrasonography or venography had pulmonary angiography. If anticoagulation was withheld, if no additional evidence of venous thromboembolism was seen, and if death did not occur during the subsequent 4 weeks, we categorized the following patients as negative for venous thromboembolism in part B: 1) those who had suspected

deep venous thrombosis and negative results on duplex ultrasonography but did not have venography or serial duplex ultrasonography and 2) those who had suspected pulmonary embolism and a nondiagnostic ventilation-perfusion lung scan but did not undergo pulmonary angiography, venography, or serial duplex ultrasonography. Experienced physicians who were blinded to prophylaxis assignment centrally interpreted all venography, lung scan, and pulmonary angiography films according to previously defined criteria (7). After all disagreements were resolved by consensus, films were scored as positive, negative, or indeterminate for venous thromboembolism.

We defined major bleeding as 1) overt bleeding associated with a hemoglobin decrement of at least 20 g/L or transfusion of at least 2 units of blood products or 2) any intracranial, retroperitoneal, intraocular, or mediastinal bleeding that occurred after at least one dose of the part B study drug or within 48 hours of the last dose of the part B study drug. Minor bleeding was defined as overt bleeding that did not meet the other criteria for major bleeding. We defined clinically significant thrombocytopenia as a persistent decrease in the platelet count to less than 100×10^9 cells/L during treatment or discontinuation of prophylaxis with the study drug because of thrombocytopenia.

By consensus, a central adjudication committee that was blinded to part B treatment assignment categorized all patients as having an efficacy outcome, having no efficacy outcome, or having an indeterminate outcome. The committee classified all bleeding episodes in each part of the study as major, minor, expected, or unrelated to the study medication. Patients who were believed to have deep

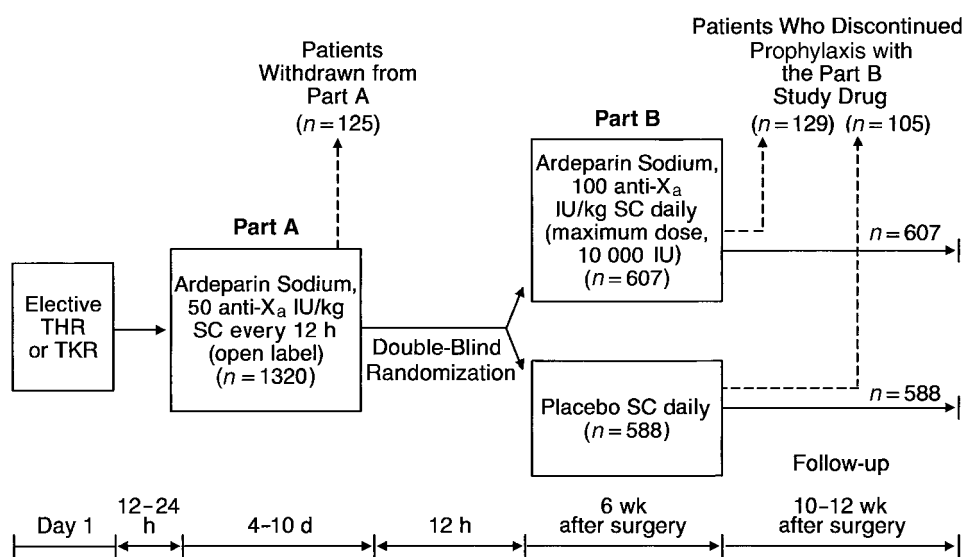


Figure 1. Flow diagram of study design, drug intervention, patient enrollment, patient withdrawal, discontinuation of prophylaxis with the study drug, and duration of follow-up. THR = total hip replacement; TKR = total knee replacement; SC = subcutaneously.

Table 1. Characteristics of Patients in Part B, according to Out-of-Hospital Prophylaxis Assignment

Characteristic	Ardeparin Sodium Group (n = 607)	Placebo Group (n = 588)
Mean age ± SD (range), y	65 ± 11 (26–89)	66 ± 11 (23–92)
Women/men, n/n	342/265	313/275
Mean weight ± SD (range), y	84 ± 16 (42–140)	86 ± 16 (38–136)
Mean duration of surgery ± SD (range), min	125 ± 51 (23–345)	127 ± 57 (25–560)
Mean estimated blood loss during surgery ± SD (range), mL	353 ± 353 (0–3000)	368 ± 393 (0–4000)
Type of total knee replacement, n (%)		
Primary unilateral	366 (60.3)	357 (60.7)
Simultaneous bilateral	288 (78.7)	299 (83.8)
Revision	38 (10.4)	30 (8.4)
Combination*	40 (10.9)	28 (7.8)
0 (0)	0 (0)	1 (0.3)
Type of total hip replacement, n (%)	241 (39.7)	231 (39.3)
Primary unilateral	192 (79.7)	175 (75.8)
Revision	48 (19.9)	56 (24.2)
Simultaneous bilateral	1 (0.4)	0 (0)
Type of anesthesia, n (%)		
Regional (spinal or epidural)	239 (39.4)	227 (38.6)
General	366 (60.3)	361 (61.4)
Other, unknown, or none	2 (0.3)	0 (0)
Mechanical device, n (%)		
Elastic compression stocking	517 (85.2)	501 (85.2)
Continuous passive range-of-motion device	307 (50.6)	294 (50.0)
Previous venous thromboembolism, n (%)	40 (6.6)	36 (6.1)
Compliance with protocol, n (%)	482 (79.4)	475 (80.8)
Concurrent aspirin therapy during part B, n (%)	85 (14.0)	87 (14.8)

* Combination of simultaneous primary and revision total knee replacements.

venous thrombosis or pulmonary embolism and patients who died were categorized as having efficacy outcome failure. Patients who completed the 12-week follow-up without symptoms of deep venous thrombosis or pulmonary embolism or were not believed to have either of these conditions were categorized as having no efficacy outcome. In addition, the committee categorized all deaths as due to venous thromboembolism, bleeding, heparin-induced thrombocytopenia, sudden death for which venous thromboembolism could not be excluded, or death due to unrelated causes.

Statistical Analysis

We believed that during part B, the incidence of symptomatic deep venous thrombosis or pulmonary embolism or death would be 4% in the placebo group and 1.5% in the ardeparin sodium group. Based on a 0.9 power to detect a significant difference ($P = 0.05$, two-sided), 976 patients were required for each study group. To compensate for nonevaluable patients, we planned to enroll 1000 patients per group. Baseline demographic and surgical characteristics, duration of part A prophylaxis, history of venous thromboembolism, compliance, and concurrent aspirin therapy during part B were compared by using *t*-tests for continuous variables and chi-square tests or the Fisher exact test for categorical variables. The primary analysis was intention-to-treat and involved all patients who were randomly assigned in part B.

After adjustment for type of surgery and history of venous thromboembolism, we tested for a signif-

icant difference in the primary efficacy outcome using the Cochran–Mantel–Haenszel procedure (8, 9). Secondary analyses were performed for deep venous thrombosis alone and for pulmonary embolism with or without deep venous thrombosis. Primary and secondary analyses were done for all patients and for type of surgery. Interactions between treatment and study center, history of venous thromboembolism, or type of surgery were determined by using the Breslow–Day test.

Interim Analysis

As prescribed by the protocol, an independent data safety monitoring board performed an interim analysis when approximately 50% of the projected sample size reached an evaluable efficacy outcome. The board noted that the primary efficacy outcome rates did not differ by group and were much lower than previously estimated. The board determined that a definitive conclusion in favor of extended out-of-hospital prophylaxis was highly unlikely if the study was continued to include the planned total sample size of 2000 patients. Although the major bleeding rates were low, the board concluded that any risk for bleeding was unjustified and recommended study closure.

Role of the Funding Source

All statistical analyses were performed at a central data coordinating center operated by the sponsor (Wyeth-Ayerst Research, Philadelphia, Pennsylvania). Data interpretation and manuscript preparation were done solely by the writing committee. The

sponsor did not have prior right of approval for final manuscript publication.

Results

Patient Sample

Of the 1320 patients enrolled in part A (**Figure 1**), 125 withdrew for the following reasons: adverse event ($n = 29$), patient request ($n = 37$), unsatisfactory efficacy response ($n = 7$), protocol violation ($n = 7$), other medical event ($n = 30$), or other non-medical event ($n = 15$). Of the remaining 1195 patients, 607 were randomly assigned to receive ardeparin sodium and 588 were randomly assigned to receive placebo in part B. The two groups were similar with regard to demographic and surgical characteristics, history of venous thromboembolism, compliance, and concurrent aspirin therapy during part B (**Table 1**). Patients withdrawn from part A ($n = 125$) and patients enrolled in part B ($n = 1195$) were also similar, but withdrawn patients had a slightly longer mean duration of surgery (136 minutes compared with 126 minutes; $P = 0.04$). In part B, the mean duration (\pm SD) of part A prophylaxis was 7.2 ± 2.1 days (median, 7 days) for patients assigned to ardeparin sodium and 7.3 ± 2.2 days (median, 7 days) for those assigned to placebo. The duration of part A prophylaxis according to part B treatment assignment is shown in **Figure 2**. The safety evaluation sample included 1161 patients who received at least one dose of the part B study drug; in 234 of these 1161 patients, prophylaxis with the part B study drug was discontinued. The two groups in part B did not differ significantly with regard to reasons for discontinuation of prophylaxis with the study drug (**Table 2**).

Table 2. Reasons for Discontinuing Prophylaxis with the Part B Study Drug

Reason	Ardeparin Sodium Group ($n = 607$)	Placebo Group ($n = 588$)
	<i>n</i> (%)	
Adverse event	33 (5.4)	19 (3.2)
Patient did not return	0 (0)	1 (0.2)
Patient request	32 (5.3)	25 (4.3)
Unsatisfactory efficacy response	4 (0.7)	7 (1.2)
Protocol violation	3 (0.5)	4 (0.7)
Other medical event	30 (4.9)	28 (4.8)
Other nonmedical event	27 (4.5)	21 (3.6)
Total	129 (21.3)	105 (17.9)

Incidence of Deep Venous Thrombosis, Pulmonary Embolism, or Death

One hundred forty-five patients in part A (11.0%) were tested for a clinical suspicion of deep venous thrombosis, pulmonary embolism, or both. During part A, 15 patients (1.1%) had objectively documented venous thromboembolism or died. Of these 15 patients, 7 (0.5%) had isolated deep venous thrombosis of the calf, 2 (0.15%) had proximal deep venous thrombosis, and 4 (0.3%) had nonfatal pulmonary embolism. Two patients died, 1 of heparin-induced thrombocytopenia and thrombosis (stroke). The other, who had a history of hypertension, died suddenly, and pulmonary embolism could not be excluded as a cause of death.

In part B, 37 patients in the ardeparin sodium group (6.1%) and 43 patients in the placebo group (7.3%) were tested for a clinical suspicion of deep venous thrombosis, pulmonary embolism, or both. Twenty-one patients (1.8%) had objectively documented venous thromboembolism or died during

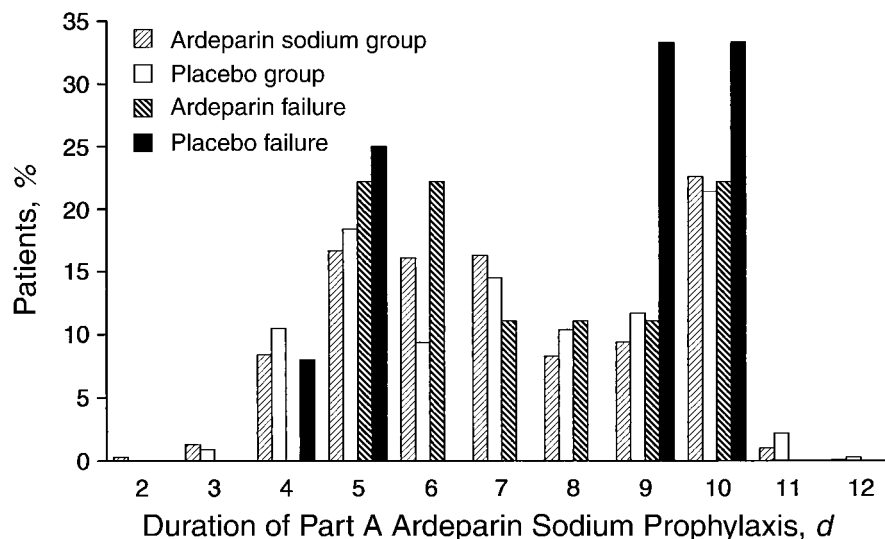


Figure 2. Duration of part A ardeparin sodium prophylaxis according to out-of-hospital prophylaxis assignment, overall and among patients who had efficacy failure.

Table 3. Cumulative Incidence of Symptomatic, Objectively Documented Deep Venous Thrombosis or Pulmonary Embolism or Death during Part B, according to Out-of-Hospital Prophylaxis Assignment*

Outcome	Ardeparin Sodium Group	Placebo Group	Odds Ratio (95% CI)	Absolute Difference (95% CI)
	<i>n</i> (%)			<i>percentage points</i>
Overall†				
Deep venous thrombosis, pulmonary embolism, or death	9 (1.5)	12 (2.0)	0.7 (0.3–1.7)	–0.56 (–2.2 to 1.1)
Deep venous thrombosis	4 (0.7)	8 (1.4)	0.5 (0.1–1.6)	
Pulmonary embolism with or without deep venous thrombosis	3 (0.5)	2 (0.3)	1.5 (0.2–8.7)	
Knee replacement‡				
Deep venous thrombosis, pulmonary embolism, or death	5 (1.4)	6 (1.7)	0.8 (0.2–2.7)	–0.31 (–2.2 to 1.8)
Deep venous thrombosis	1 (0.3)	3 (0.8)	0.3 (0.03–3.1)	
Pulmonary embolism with or without deep venous thrombosis	3 (0.8)	2 (0.6)	1.5 (0.2–8.8)	
Hip replacements§				
Deep venous thrombosis, pulmonary embolism, or death	4 (1.7)	6 (2.6)	0.6 (0.2–2.3)	–0.94 (–4.0 to 2.1)
Deep venous thrombosis	3 (1.2)	5 (2.2)	0.6 (0.1–2.4)	
Pulmonary embolism with or without deep venous thrombosis	0 (0)	0 (0)		

* $P > 0.2$ for all comparisons.

† 607 patients in the ardeparin sodium group and 588 in the placebo group.

‡ 366 patients in the ardeparin sodium group and 357 in the placebo group.

§ 241 patients in the ardeparin sodium group and 231 in the placebo group.

part B. The incidence of efficacy failure did not differ significantly between patients assigned to ardeparin sodium prophylaxis ($n = 9$ [1.5%]) and those assigned to placebo ($n = 12$ [2.0%]; odds ratio, 0.7 [95% CI, 0.3 to 1.7]; $P > 0.2$) (Table 3). The absolute difference in the incidence of efficacy failure during part B was -0.56% (CI, -2.2% to 1.1%) in favor of extended ardeparin sodium prophylaxis. The proportion of patients in part B who met our criteria for protocol compliance did not differ significantly between groups (482 of 607 [79.4%] in the ardeparin sodium group and 475 of 588 [80.8%] in the placebo group; $P > 0.2$).

Among part B patients who met our criteria for protocol compliance, 6 in the ardeparin sodium group (1.24%) and 6 in the placebo group (1.26%) had efficacy failure (absolute difference, -0.02 percentage point [CI, -1.6 to 1.6 percentage points]). When type of venous thromboembolism was analyzed according to type of surgery, the efficacy failure rate did not differ significantly between the two groups in part B (Table 3). No significant interaction was seen between treatment and study center,

history of venous thromboembolism, or type of surgery. Of the 2 deaths among patients assigned to ardeparin prophylaxis in part B, 1 was caused by acute myocardial infarction and the other was caused by chronic obstructive pulmonary disease with pneumonia. Both deaths among patients assigned to placebo were sudden, and pulmonary embolism could not be excluded; 1 of these 2 patients had a history of myocardial infarction and hypertension, and the other had a history of hypertension and cardiac arrhythmia.

In part B, the duration and number of doses (\pm SD) of part A prophylaxis among patients who had efficacy failure was 7.3 ± 2.1 days (13.2 ± 4.0 doses) in the ardeparin sodium group and 7.5 ± 2.4 days (14.0 ± 4.9 doses) in the placebo group. The duration of part A prophylaxis among patients who had efficacy failure is shown in Table 4. In the ardeparin sodium group, the 2 patients who died received part A prophylaxis for 5 and 6 days and the 3 patients who developed pulmonary embolism received part A prophylaxis for 5, 8, and 10 days. In the placebo group, the 2 patients who died received part A prophylaxis for 5 and 10 days and the 2 patients who developed pulmonary embolism received part A prophylaxis for 4 and 10 days.

Two of the 68 patients who had revision total knee replacement (2.9%) had efficacy failure: 1 in the ardeparin sodium group (2.5%) and 1 in the placebo group (3.6%). Three of the 104 patients who underwent revision total hip replacement (2.9%) had efficacy failure: 2 (4.2%) in the ardeparin sodium group and 1 (1.8%) in the placebo group. Of the 2 patients in the ardeparin sodium group who died, 1 underwent revision total knee replacement and 1 underwent total hip replacement. Of the patients who had efficacy failure, 1 in the ardeparin sodium group and 2 in the placebo group

Table 4. Duration of Part A Ardeparin Sodium Prophylaxis among Patients Who Had Efficacy Failure in Part B, according to Out-of-Hospital Prophylaxis Assignment

Duration	Ardeparin Sodium Group	Placebo Group
	<i>n</i>	
Patients with 4 days of part A prophylaxis	0	1
Patients with 5 days of part A prophylaxis	2	3
Patients with 6 days of part A prophylaxis	2	0
Patients with 7 days of part A prophylaxis	1	0
Patients with 8 days of part A prophylaxis	1	0
Patients with 9 days of part A prophylaxis	1	4
Patients with 10 days of part A prophylaxis	2	4
Total patients	9	12

had a history of venous thromboembolism; all 3 of these patients underwent primary total knee replacement.

Incidence of Bleeding and Thrombocytopenia

During part A, 34 patients (2.6%) developed major bleeding and 70 patients (5.3%) developed minor bleeding. Eight patients (0.6%) developed clinically significant thrombocytopenia. During part B, 5 patients (0.4%) developed major bleeding and 42 patients (3.5%) developed minor bleeding. The two groups in part B did not differ with regard to the incidence of major and minor bleeding, overall or according to surgery type (Table 5). Two patients, both of whom received ardeparin prophylaxis, developed clinically significant thrombocytopenia during part B. Although neither was tested for heparin-dependent platelet-activating antibodies, the clinical course of 1 patient was consistent with heparin-induced thrombocytopenia and thrombosis. The other patient remained asymptomatic, and thrombocytopenia persisted despite discontinuation of prophylaxis with vardeparin sodium.

Discussion

We used acute symptomatic, objectively documented venous thromboembolism or all-cause death (clinically important end points) rather than venography (a surrogate end point) to determine the effect of extended ardeparin prophylaxis. We found no significant difference in the overall incidence of symptomatic deep venous thrombosis, pulmonary embolism, or death when prophylaxis with ardeparin was not continued after hospital discharge. However, we cannot exclude the possibility that a small difference (as much as 2.2 percentage points) exists in favor of continued outpatient ardeparin prophylaxis.

In addition, because only a small percentage of patients (4% to 6%) develop the venous stasis syndrome after major hip or knee surgery (10, 11) and because the risk for this syndrome is no greater for patients with asymptomatic calf or proximal deep venous thrombosis than for those without (10), extended out-of-hospital ardeparin prophylaxis is unlikely to reduce its subsequent incidence.

We believe that our findings are valid. The randomization was successful, as seen by the between-group similarity in demographic and surgical characteristics, duration of part A prophylaxis, history of venous thromboembolism, and compliance. In addition, our findings are consistent with those of two recent large cohort studies (6, 12). Robinson and colleagues (12) found that the 90-day out-of-hospital incidence of venous thromboembolism was 1% among 506 patients who had total hip or knee replacement and received postoperative warfarin prophylaxis for 10 days. Similarly, Leclerc and coworkers (6) found that the 90-day out-of-hospital incidence of venous thromboembolism was 1.7% among 1984 patients who had total hip or knee replacement and received enoxaparin sodium prophylaxis for 9 days.

It is unlikely that our results were due to an excess number of events during part A. Only 1% of patients (13 of 1320) developed symptomatic venous thromboembolism during part A, and none of the four cases of pulmonary embolism were fatal. These results are similar to those of Leclerc and coworkers (6), who found a 1.5% incidence of symptomatic venous thromboembolism and a 0.1% incidence of death during in-hospital prophylaxis after knee or hip replacement.

On the basis of previous studies, we estimate that 7% of patients who underwent total hip replacement and 25% of those who underwent total knee replacement in our study had asymptomatic deep venous thrombosis at hospital discharge (13, 14).

Table 5. Cumulative Incidence of Bleeding during Part B, according to Out-of-Hospital Prophylaxis Assignment*

Outcome	Ardeparin Sodium Group	Placebo Group	Odds Ratio (95% CI)	Absolute Difference (95% CI)
	n (%)			
Overall†				
Major bleeding	2 (0.3)	3 (0.5)	0.6 (0.1–3.9)	
Minor bleeding	26 (4.4)	16 (2.8)	1.6 (0.9–3.0)	
Total bleeding	28 (4.8)	19 (3.3)	1.5 (0.8–2.6)	1.4 (–1.0 to 3.9)
Knee replacement‡				
Major bleeding	2 (0.6)	2 (0.6)	1.0 (0.1–7.1)	
Minor bleeding	16 (4.6)	13 (3.8)	1.2 (0.6–2.6)	
Total bleeding	18 (5.1)	15 (4.3)	1.2 (0.6–2.4)	0.8 (–2.6 to 4.3)
Hip replacement§				
Major bleeding	0 (0)	1 (0.4)	0.3 (0.01–7.7)	
Minor bleeding	10 (4.2)	3 (1.3)	3.2 (0.9–12.0)	
Total bleeding	10 (4.2)	4 (1.8)	2.4 (0.8–8.0)	2.4 (–1.1 to 5.9)

* $P \geq 0.2$ for all comparisons.

† 589 patients in the ardeparin sodium group and 572 in the placebo group.

‡ 350 patients in the ardeparin sodium group and 346 in the placebo group.

§ 239 patients in the ardeparin sodium group and 226 in the placebo group.

The low rate of symptomatic venous thromboembolism in the part B placebo group is consistent with the hypothesis that most cases of asymptomatic deep venous thrombosis that occur despite in-hospital low-molecular-weight heparin prophylaxis are not clinically important (6, 12). Our findings call into question the need for extended out-of-hospital prophylaxis in all patients undergoing elective hip replacement or major knee surgery. To prevent one of our composite outcome events, we estimate that 179 patients (although possibly as few as 45) must receive extended out-of-hospital ardeparin prophylaxis.

Of the more convenient antithrombotic agents that could be used for extended prophylaxis, warfarin sodium is less expensive than low-molecular-weight heparin and can be taken orally. However, any cost savings and convenience are offset by the need for laboratory monitoring and dose adjustment. Aspirin is even less expensive, does not require monitoring, and is safe. However, its efficacy after major orthopedic surgery is uncertain. Studies using mandatory venography at hospital discharge have shown no relative risk reduction in incidence of deep venous thrombosis with aspirin prophylaxis (1). In contrast, a recent large randomized study of patients with hip fracture reported a modest relative risk reduction in clinical venous thromboembolism in patients assigned to aspirin (15). It is possible, therefore, that aspirin therapy could provide some protection to high-risk patients if begun at hospital discharge.

We emphasize that primary prophylaxis is indicated for all patients receiving total hip or knee replacement. Four to 10 days of postoperative in-hospital ardeparin sodium prophylaxis seems adequate for most patients. However, this length may be inadequate for less effective prophylaxis regimens or for patients that were not fully represented in our study. Future studies should examine patient characteristics (for example, history of venous thromboembolism, obesity, and persistent immobilization), type of surgery (for example, revision arthroplasty), and familial or acquired thrombophilia (16) as potential predictors of postoperative venous thromboembolism after total hip or knee replacement. Such predictors may enable physicians to identify patients who are at high and low risk for symptomatic postoperative venous thromboembolism and thereby target extended prophylaxis to those who would benefit the most.

Appendix

The following investigators and institutions participated in this study: James Benjamin, MD, University of

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References

1. Clagett GP, Anderson FA Jr, Geerts W, Heit JA, Knudson M, Lieberman JR, et al. Prevention of venous thromboembolism. Fifth ACCP Consensus Conference on Antithrombotic Therapy. *Chest*. 1998;114(5 Suppl):531S-60S.
2. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet*. 1996;348:224-8.
3. Dahl OE, Andreassen G, Aspelin T, Müller C, Mathiesen P, Nyhus S, et al. Prolonged thromboprophylaxis following hip replacement surgery—results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin. *Thromb Haemost*. 1997;77:26-31.
4. Bergqvist D, Benoni G, Björgell O, Fredin H, Hedlundh U, Nicolas S, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med*. 1996;335:696-700.
5. Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejbro HP, Andersen G, et al. Efficacy and safety of prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) after total hip arthroplasty—the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res*. 1998;89:281-7.
6. Leclerc JR, Gent M, Hirsh J, Geerts WH, Ginsberg JS. The incidence of symptomatic venous thromboembolism during and after prophylaxis with enoxaparin: a multi-institutional cohort study of patients who underwent hip or knee arthroplasty. Canadian Collaborative Group. *Arch Intern Med*. 1998;158:873-8.
7. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA*. 1990;263:2753-9.
8. Cochran WG. Some methods for strengthening the common chi-square tests. *Biometrics*. 1954;10:417-51.
9. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719-48.
10. Ginsberg JS, Gent M, Turkstra F, Büller HR, MacKinnon B, Magier D, et al. Post thrombotic syndrome after hip or knee arthroplasty: a cross-sectional study. *Arch Intern Med*. 2000;160:669-72.
11. Francis CW, Ricotta JJ, Everts CM, Marder VJ. Long-term clinical observations and venous functional abnormalities after asymptomatic venous thrombosis following total hip or knee arthroplasty. *Clin Orthop*. 1986;232:271-8.
12. Robinson KS, Anderson DR, Gross M, Petrie D, Leighton R, Stanish W, et al. Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: the post-arthroplasty screening study. A randomized, controlled trial. *Ann Intern Med*. 1997;127:439-45.
13. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. RD Heparin Arthroplasty Group. *J Bone Joint Surg Am*. 1994;76:1174-85.
14. Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Ardeparin Arthroplasty Study Group. *Thromb Haemost*. 1997;77:32-8.
15. Prentice CRM, Collins R, Rodgers A, MacMahon. The Pulmonary Embolism Prevention (PEP) trial: efficacy of low-dose aspirin on major vascular events in patients with hip fracture [Abstract]. The PEP Trial investigators. *Thromb Haemost*. 1999;August (Suppl):193.
16. Lindahl TL, Lundahl TH, Nilsson L, Andersson CA. APC-resistance is a risk factor for postoperative thromboembolism in elective replacement of the hip or knee—a prospective study. *Thromb Haemost*. 1999;81:18-21.