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Prevention of Venous Thromboembolism after Knee Arthroplasty

A Randomized, Double-Blind Trial Comparing Enoxaparin with Warfarin

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Objective: To compare the effectiveness and safety of fixed-dose enoxaparin and adjusted-dose warfarin in preventing venous thromboembolism after knee arthroplasty.

Design: A randomized, double-blind controlled trial.

Setting: 8 university hospitals.

Patients: 670 consecutive patients who had knee arthroplasty.

Intervention: Patients were randomly assigned to receive enoxaparin (30 mg subcutaneously every 12 hours) or adjusted-dose warfarin (international normalized ratio, 2.0 to 3.0). Both regimens were started after surgery.

Measurements: The primary end point was the incidence of deep venous thrombosis in patients with adequate bilateral venograms; the secondary end point was hemorrhage.

Results: Among the 417 patients with adequate venograms, 109 of 211 warfarin recipients (51.7%) had deep venous thrombosis compared with 76 of 206 enoxaparin recipients (36.9%) ($P = 0.003$). The absolute risk difference was 14.8% in favor of enoxaparin (95% CI, 5.3% to 24.1%). Twenty-two warfarin recipients (10.4%) and 24 enoxaparin recipients (11.7%) had proximal venous thrombosis ($P > 0.2$). The absolute risk difference was 1.2% in favor of warfarin (CI, −7.2% to 4.8%). The incidence of major bleeding was 1.8% (6 of 334 patients) in the warfarin group and 2.1% (7 of 336 patients) in the enoxaparin group ($P > 0.2$). The absolute risk difference was 0.3% in favor of warfarin (CI, −2.4% to 1.8%).

Conclusions: A postoperative, fixed-dose enoxaparin regimen is more effective than adjusted-dose warfarin in preventing total deep venous thrombosis after knee arthroplasty. No differences were seen in the incidence of proximal venous thrombosis or clinically overt hemorrhage.

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Despite modern surgical techniques and early patient mobilization, venous thromboembolism remains a major complication of knee arthroplasty (1–3). Without prophylaxis, the reported incidences of venographically verified deep venous thrombosis and proximal venous thrombosis have ranged from 55% to 70% and from 10% to 30%, respectively (2, 4–8). Fatal pulmonary embolism, allegedly uncommon (incidence <1% [9]), remains an avoidable cause of perioperative death in these patients. The burden of postoperative venous thromboembolism must also be assessed in terms of the morbidity from the acute event, the risk for long-term postphlebitic complications (10, 11), and the effect of venous thromboembolism on the cost of health care delivery (12, 13).

Preventing venous thromboembolism after knee arthroplasty is difficult because of the relative resistance of this type of surgery to the effects of most thromboprophylaxis options (6, 14–18), the substantial hemorrhagic risk associated with the surgical procedure (19), and the lack of consensus on the safest and most effective method. The main hemorrhagic threat of thromboprophylaxis in knee surgery is hemarthrosis, which may require surgical drainage or may compromise the result of the reconstruction.

Less intense warfarin and low-molecular-weight heparins have been evaluated as prophylaxis after knee surgery (8, 20–24). Warfarin has the advantage of oral administration, and low-molecular-weight heparins do not require laboratory monitoring. In previous studies comparing warfarin with low-molecular-weight heparins, patients having either hip or knee surgery were evaluated together (20, 21), interventions were unblinded (21, 22), or unilateral venography was done (21–23). We thus conducted a double-blind, randomized trial with bilateral venographic assessment of the effectiveness and safety of postoperative, adjusted-dose warfarin compared

with those of postoperative, fixed-dose enoxaparin in patients having knee arthroplasty.

Methods

Patients

Eight hundred sixty-five consecutive adult patients having knee arthroplasty at eight hospitals were evaluated. Sixty-eight patients were excluded for the following reasons: allergy to contrast material (20 patients); need for oral anticoagulant or antiplatelet agents (18 patients); bleeding diathesis (9 patients); gastrointestinal hemorrhage within 3 months of surgery (7 patients); renal or hepatic insufficiency (4 patients); uncontrolled hypertension (3 patients); illicit drug use or alcohol abuse (3 patients); participation in the present study within the last 3 months (1 patient); hemorrhagic stroke within 3 months of surgery (1 patient); receipt of other investigational drugs in the past month (1 patient); and warfarin allergy (1 patient). Of the 797 patients eligible for the study, 670 (84%) gave informed consent.

Interventions

The 670 eligible and consenting patients were randomly allocated after surgery to receive either warfarin sodium (334 patients) or enoxaparin (336 patients) in a 1:1 ratio in blocks of four. A computer generated the randomization schedule. We stratified randomization by study center, history of venous thromboembolism, and use of a cemented or uncemented prosthesis. Patients in the warfarin group also received subcutaneous saline placebo every 12 hours. The treatment goal was to maintain the international normalized ratio between 2.0 and 3.0 using a prespecified nomogram. Patients in the enoxaparin group received 30 mg of enoxaparin subcutaneously every 12 hours and warfarin placebo once daily. Therapy with oral medications began on the evening of the day on which surgery was done (day 1), and therapy with subcutaneous medications began on the morning of the first day after surgery (day 2). Study medications were administered for 14 days or until hospital discharge, whichever occurred first. No other thromboprophylactic agents or antiembolic stockings were used.

Patient Surveillance and Outcome Measures

The primary end point was the incidence of deep venous thrombosis in patients with adequate bilateral venograms and symptomatic pulmonary embolism. Venography was done on day 14 or earlier if the patient was discharged or if patients developing clinically suspected deep venous thrombosis had abnormal noninvasive test results. The diagnostic criterion for thrombosis was a constant intraluminal filling defect seen on two or more views. Venograms were considered adequate if the entire deep venous system could be seen to at least the level of the common femoral vein. Bilateral compression ultrasonography of the tibioperoneal trunk, popliteal vein, superficial femoral vein in at least two sites, and common femoral vein was routinely done before venography. A positive venous ultrasound was defined as the noncompressibility of a vein segment.

Patients with clinically suspected venous thrombosis had either compression ultrasonography or impedance plethysmography when symptoms developed. Venography was done immediately if the noninvasive test result was abnormal. Symptomatic patients with a normal noninvasive test result had repeated testing every other day until predischarge venography was done. Patients with suspected pulmonary embolism had lung scanning. Pulmonary embolism was excluded on the basis of a normal perfusion scan and was confirmed by a high-probability scan; the latter was defined as showing one or more segmental perfusion defects with normal or near-normal ventilation. Patients with abnormal lung scans that did not show a high probability of embolism subsequently had pulmonary angiography. Patients with proven venous thromboembolism received heparin treatment followed by oral anticoagulant agents as per local practice. Patients who did not develop venous thromboembolism received no further thromboprophylaxis after hospital discharge.

Secondary end points were clinically overt hemorrhage and postoperative blood loss. Major hemorrhage was defined as overt bleeding that 1) decreased the hemoglobin level by 20 g/L or more or 2) necessitated transfusion of 2 or more units of packed red cells, hemarthrosis requiring evacuation, discontinuation of prophylaxis, or interruption of physiotherapy for at least 24 hours. Minor hemorrhage was defined as overt bleeding that did not meet the criteria for major hemorrhage.

All patients were followed for 6 months. During this interval, patients were instructed to contact the investigator if they developed symptoms suggestive of venous thromboembolism.

Blinding

Oral medications were monitored by an independent physician who was aware of the randomization schedule but was not otherwise involved in the study. Dosage adjustments were based on the measured international normalized ratios in patients receiving warfarin and on phantom international normalized ratios, generated a priori, in patients receiving warfarin placebo. Patients receiving warfarin placebo also had daily blood sampling for sham measure-

ments of the international normalized ratio. International normalized ratios were not recorded in the patients' charts. All diagnostic tests and bleeding episodes were adjudicated by a central committee that was unaware of treatment allocation or clinical findings.

Statistical Analysis

The rates of deep venous thrombosis in the two treatment groups were compared using the chi-square test with Yates correction. Blood loss was analyzed using one-way analysis of variance. The rates of pulmonary embolism and the proportion of patients receiving packed red cells were analyzed using the Fisher exact test. We used the statistical package S-PLUS version 3.1 (StatSci, Seattle, Washington).

Estimation of Sample Size

On the basis of the assumption that the incidence of deep venous thrombosis in enoxaparin recipients would be approximately 20% (8) and with an α value of 0.05 (two-tailed) and a β value of 0.20, we determined that 200 patients with adequate venograms per group would be required to show at least a 50% reduction in the rate of thrombosis in the enoxaparin group compared with the warfarin group.

Interim Analysis

We did a preplanned interim analysis after 200 patients with adequate venograms were enrolled. An independent committee reviewed the results without breaking the code. We formally used an O'Brien–Fleming stopping boundary (25) but also analyzed the overall rate of thrombosis and bleeding complications to arrive at a conclusion. We decided to continue the trial until 400 patients had adequate venograms.

Study Logistics

The investigators independently designed the study and interpreted the results. The research coordinators at each site collected the data, and the sponsoring pharmaceutical firm monitored the quality of the data at each study center. Biostatisticians from the Division of Clinical Epidemiology of the Montreal General Hospital designed the database, and the clinical research firm Biopharmaceutical Research Consultants (Ann Arbor, Michigan) independently analyzed the data.

Results

The two treatment groups had similar important baseline characteristics (Table 1). Adequate venographic outcomes were obtained in 417 of 670 patients (62%). Adequate venograms were not obtained in the remaining patients for the following reasons: technically inadequate venogram (129 patients), failed venous access (94 patients), refusal of the patient (24 patients), pulmonary embolism (3 patients), refusal of the treating physician (2 patients), and unavailable films (1 patient). These reasons were equally balanced between the two groups. All technically inadequate venograms resulted from incomplete opacification of the deep venous system. In many instances, radiologists were uncomfortable

Table 1. Patient Characteristics

Characteristic	Warfarin Group (n = 334)	Enoxaparin Group (n = 336)
Age, *y*		
Mean ±SD	69.2 ± 9.2	68.0 ± 9.4
Range	26–92	31–92
Female patients, *n (%)*	211 (63.2)	212 (63.1)
Male patients, *n (%)*	123 (36.8)	124 (36.9)
Mean weight ± SD, *kg*	78.2 ± 15.9	79.2 ± 16.0
Previous venous thromboembolism, *n (%)*	34 (10.2)	32 (9.5)
Reason for surgery, *n (%)*		
Osteoarthritis	276 (82.6)	277 (82.4)
Rheumatoid arthritis	33 (9.9)	30 (8.9)
Mechanical prosthesis failure	22 (6.6)	23 (6.8)
Avascular necrosis	1 (0.3)	3 (0.9)
Loosening of septic prosthesis	0	3 (0.9)
Psoriatic arthritis	2 (0.6)	0
Leg in which surgery was done, *n (%)*		
Left	164 (49.1)	166 (49.4)
Right	161 (48.2)	164 (48.8)
Both	9 (2.7)	6 (1.8)
Type of surgery, *n (%)*		
Primary	312 (93.4)	310 (92.3)
Revision	22 (6.6)	26 (7.7)
Type of prosthesis, *n (%)**		
Genesis (Richards)	181 (54.2)	173 (51.5)
Miller Gallante (Zimmer)	36 (10.8)	37 (11.0)
Self-aligning (Protek)	21 (6.3)	16 (4.8)
Insall Burnstein (Johnson & Johnson)	17 (5.1)	20 (6.0)
AMK Total Knee System (DePuy)	17 (5.1)	23 (6.8)
Modular Whiteside (Wright Medical)	17 (5.1)	14 (4.2)
PCA Modular System (Howmedica)	11 (3.3)	18 (5.4)
Hermes (Ceraver Osteal)	11 (3.3)	10 (3.0)
PFC (Johnson & Johnson)	6 (1.8)	10 (3.0)
Omnifit (Osteonics)	6 (1.8)	5 (1.5)
Modular II Cartier (Richards)	5 (1.5)	3 (0.9)
Duracon (Howmedica)	2 (0.6)	1 (0.3)
Guépar (Howmedica)	0	1 (0.3)
Tricon (Richards)	1 (0.3)	0
Landmarks (Link America)	0	1 (0.3)
Not recorded	3 (0.9)	4 (1.2)
Use of surgical cement, *n (%)*		
Yes	298 (89.2)	299 (89.0)
No	36 (10.8)	37 (11.0)
Type of anesthesia, *n (%)*		
General	287 (85.9)	293 (87.2)
Regional	47 (14.1)	43 (12.8)
Mean duration of surgery ± SD, *min*†	124.3 ± 38.5	126.2 ± 44.7
Use of tourniquet during surgery, *n (%)*	319 (95.5)	323 (96.1)
Mean duration of tourniquet ± SD, *min*	100.8 ± 25.1	102.3 ± 28.5
Tourniquet release, *n (%)*	180 (53.9)	172 (51.2)
Intake of nonsteroidal anti-inflammatory drugs during hospitalization, *n (%)*	37 (11.1)	45 (13.4)
Mean duration of prophylaxis ± SD, *d*	8.7 ± 2.8	8.8 ± 2.8

* The following are the locations of the manufacturers. Richards: Memphis, Tennessee; Zimmer and De Puy: Warsaw, Indiana; Protek: Berne, Switzerland; Johnson & Johnson: Raynham, Massachusetts; Wright Medical: Arlington, Tennessee; Howmedica: Rutherford, New Jersey; Ceraver Osteal: St-Laurent, Québec, Canada; Osteonics: Allendale, New Jersey.
† Defined as the "skin-to-skin" time.

Table 2. Main Outcome Events in the Two Treatment Groups

Outcome Event	Warfarin Group (n = 334)	Enoxaparin Group (n = 336)	P Value	Absolute Risk Difference (95% CI), %*
Adequate venography, *n (%)*	211 (63.2)	206 (61.3)	>0.2	–
Deep venous thrombosis, *n (%)*				
Total	109 (51.7)	76 (36.9)	0.003	14.8 (5.3 to 24.1)
Proximal	22 (10.4)	24 (11.7)	>0.2	−1.2 (−7.2 to 4.8)
Pulmonary embolism, *n (%)*	3 (0.9)	1 (0.3)	>0.2	0.6 (−2.0 to 1.0)
Bleeding, *n (%)*				
Major	6 (1.8)	7 (2.1)	>0.2	−0.3 (−2.4 to 1.8)
Minor	83 (24.9)	94 (28.0)	>0.2	−3.1 (−9.8 to 3.5)
Total	89 (26.6)	101 (30.1)	>0.2	−3.4 (−10.2 to 3.4)

* Calculated by subtracting the percentage for the enoxaparin group from the percentage for the warfarin group.

administering additional contrast material, particularly because the protocol required bilateral venography. An additional complicating factor was the overshadowing of the popliteal vein by the knee prosthesis, despite the protocol requirement to obtain lateral views of this area. The requirement for bilateral venography also affected our venography success rate, because approximately one third of failures occurred only in the leg in which surgery was not done.

Incidence of Deep Venous Thrombosis

Deep venous thrombosis was detected by venography in 109 of 211 patients in the warfarin group (51.7%; 95% CI, 44.7% to 58.5%) compared with 76 of 206 patients in the enoxaparin group (36.9%; CI, 30.4% to 43.9%) (Table 2). This represents a relative risk reduction of 28.6% (CI, 11.1% to 43.1%) for enoxaparin compared with warfarin (P = 0.003). The absolute risk difference was 14.8% in favor of enoxaparin (CI, 5.3% to 24.1%). Twenty-two patients in the warfarin group (10.4%; CI, 6.7% to 15.6%) developed proximal venous thrombosis compared with 24 patients in the enoxaparin group (11.7%; CI, 7.8% to 17.0%) ($P > 0.2$). The absolute risk difference was 1.2% in favor of warfarin (CI, −7.2% to 4.8%).

Among the 253 patients without adequate venograms, compression ultrasonography was done in 93 warfarin recipients and 100 enoxaparin recipients; impedance plethysmography alone was obtained in 4 patients in each treatment group. Fifty-two patients (7.8%) were not evaluable by either venography or noninvasive testing. Two warfarin recipients and five enoxaparin recipients evaluable by ultrasonography had proximal venous thrombosis. None of the eight patients evaluable by impedance plethysmography alone had proximal venous thrombosis.

An analysis of international normalized ratios in patients receiving warfarin showed that from day 4 onward, most ratios were between the prescribed interval of 2.0 to 3.0. No difference in the proportion of therapeutic values was seen between patients with and those without deep venous thrombosis.

We examined rates of deep venous thrombosis at each of the eight study centers. Six of the eight sites had results close to the overall study results for the warfarin and enoxaparin groups. One center had a higher incidence of deep venous thrombosis in both treatment groups (88.2% in the warfarin group and 53.8% in the enoxaparin group) but also had a significantly higher rate of inadequate venograms than did the other sites. Thus, the apparent rate of thrombosis was increased. In the remaining center, the number of patients was small (n = 13).

In the warfarin group, venous thrombosis occurred in the leg in which surgery was done in 79 patients (72.5%), in the leg in which surgery was not done in 15 patients (13.8%), and in both legs in 15 patients (13.8%). In the enoxaparin group, thrombosis occurred in the leg in which surgery was done in 59 patients (77.6%), in the leg in which surgery was not done in 11 patients (14.5%), and in both legs in 6 patients (7.9%).

Deaths and Pulmonary Embolism

No patients died during hospitalization. Four patients (0.6%) developed symptomatic pulmonary embolism; three of the four were in the warfarin group. The first warfarin recipient developed sudden dyspnea on day 5. Pulmonary embolism was confirmed by a high-probability lung scan; the ultrasonographic result was normal in the proximal veins, and venography was not done. The second patient had cardiopulmonary arrest on day 2. Pulmonary embolism was diagnosed by pulmonary angiography; neither venography nor ultrasonography was done. The patient eventually recovered and was discharged from the hospital. The third patient developed acute shortness of breath on day 3 and had a high-probability lung scan; neither venography nor ultrasonography was done. One enoxaparin recipient who had deep venous thrombosis in both calves was noted to be unusually short of breath at the

time of venography; subsequent lung scanning showed a high probability of pulmonary embolism.

Hemorrhage

Clinically overt bleeding occurred in 89 warfarin recipients (26.6%; CI, 22.2% to 31.7%) and 101 enoxaparin recipients (30.1%; CI, 25.4% to 35.2%) ($P > 0.2$) (Table 2). Six patients in the warfarin group (1.8%; CI, 0.8% to 3.8%) developed major hemorrhage compared with 7 patients in the enoxaparin group (2.1%; CI, 1.0% to 4.2%) ($P > 0.2$). The absolute risk difference was 0.3% in favor of warfarin (CI, −2.4% to 1.8%). Five warfarin recipients developed hemarthrosis that required discontinuation of therapy with study medication; the remaining patient had continuous oozing from the surgical site and received transfusion of 2 units of packed red cells. Six enoxaparin recipients developed hemarthrosis: Three required surgical drainage and transfusion of 2 units of packed red cells, and three discontinued or interrupted therapy with the study medication. A seventh enoxaparin recipient had a wound hematoma and received 2 units of packed red cells.

Eighty-three patients in the warfarin group (24.9%; CI, 20.6% to 29.8%) developed minor bleeding compared with 94 enoxaparin recipients (28.0%; CI, 23.5% to 33.1%) ($P > 0.2$). Ninety-five minor bleeding episodes occurred in the warfarin group, and 104 occurred in the enoxaparin group; the most common type of bleeding was ecchymosis.

The amount of blood lost during and after surgery and the number of red cell transfusions are shown in Table 3. No significant differences were noted between groups in the amount of blood loss or in the mean number of units of packed cells transfused per patient. However, more enoxaparin recipients received packed red cells after their stay in the recovery room. Of 334 warfarin recipients, 108 (32.3%) received red cell transfusions compared with 141 of 336 (42.0%) enoxaparin recipients ($P = 0.01$).

An analysis of bleeding rates among patients who received nonsteroidal anti-inflammatory agents showed that 25 of 82 patients (30.5%) who received these agents had hemorrhage compared with 165 of 588 (28.1%) who did not receive these drugs. This corresponds to an odds ratio of 1.09 (CI, 0.68 to 1.86).

Follow-up

No patient was lost to follow-up. Two patients died, one in each treatment group. The patient in the warfarin group had been discharged with a prescription for warfarin for distal venous thrombosis. On day 26, he developed a major upper gastrointestinal hemorrhage associated with a supratherapeutic international normalized ratio; he died on day 34 after cessation of life support measures. The patient in the enoxaparin group died of metastatic breast carcinoma on day 139.

Table 3. Types of Hemorrhagic Episodes, Postoperative Blood Loss, and Red Cell Transfusions

Variable	Warfarin Group (n = 334)	Enoxaparin Group (n = 336)
Major hemorrhagic episodes, *n*		
Hemarthrosis	5	6
Wound hematoma	1	1
Total	6	7
Minor hemorrhagic episodes, *n*		
Ecchymosis*	68	70
Wound hematoma	17	17
Hemarthrosis	3	8
Drain insertion site	2	1
Hematemesis	3	2
Rectal bleeding	1	3
Melena	1	0
Hematuria	0	2
Hemoptysis	0	1
Total	95	104
Mean blood loss ± SE, *mL*		
Intraoperative plus recovery room†	369.5 ± 18.1	380.2 ± 17.8‡
Day 1 to removal of surgical drain§	529.1 ± 20.2	545.3 ± 20.1‡
Total drainage‖	878.2 ± 30.7	907.3 ± 30.3‡
Red cell transfusions during surgery or in recovery room¶		
Units transfused, *n*	56	47
Patients transfused, *n*(%)	32 (9.6)	31 (9.2)**
Mean units per transfused patient ± SD, *n*	1.8 ± 0.6	1.5 ± 1.7‡
Transfusions after recovery room‖		
Units transfused, *n*	213	296
Patients transfused, *n*(%)	108 (32.3)	141 (42.0)††
Mean units per transfused patient ± SD, *n*	1.97 ± 0.66	2.10 ± 0.79‡

* ≥10 cm in greatest dimension at any site.
† Measurements based on the 320 warfarin recipients and 329 enoxaparin recipients for whom data were available.
‡ $P > 0.5$ (two-sided P value from the two-way analysis of variance model with treatment and investigator effects).
§ Measurements based on the 321 warfarin recipients and 320 enoxaparin recipients for whom data were available.
‖ Measurements based on the 333 warfarin recipients and 335 enoxaparin recipients for whom data were available.
¶ Including autologous transfusions.
** $P > 0.2$. Absolute risk difference (calculated by subtracting the percentage for the enoxaparin group from the percentage for the warfarin group), 0.4% in favor of enoxaparin (95% CI, −4.4% to 5.1%).
†† $P = 0.011$. Absolute risk difference, 9.7% in favor of warfarin (CI, −17.2% to −2.0%).

Four patients developed proven venous thromboembolism: one in the warfarin group and three in the enoxaparin group. The patient in the warfarin group had contralateral knee arthroplasty 4 months after the initial surgery. Six weeks after the second operation, he developed symptomatic, venographically proven thrombosis in the leg in which surgery was done.

In one patient in the enoxaparin group, the surgical prosthesis was drained because of septic arthritis on day 14. On day 18, the patient developed symptomatic, venographically proven venous thrombosis in the calf of the leg in which surgery was done. Another patient presented on day 25 with pleuritic pain and shortness of breath; a lung scan showed a high probability of pulmonary embolism. The third patient presented on day 52 with symp-

tomatic, venographically proven thrombosis in the right calf.

Other Complications

Patients were surveyed for the development of thrombocytopenia in which platelet counts were less than 100×10^9/L. Two warfarin recipients developed thrombocytopenia (platelet counts of 98×10^9/L and 93×10^9/L, respectively) on day 3. No case of thrombocytopenia occurred in the enoxaparin group, and no warfarin-related skin necrosis developed in the warfarin group.

Discussion

Our study shows that a postoperative, fixed-dose enoxaparin regimen without monitoring or adjustment for body weight is more effective than postoperative, adjusted-dose warfarin for preventing total deep venous thrombosis after knee arthroplasty. The observed relative and absolute risk reductions were approximately 29% and 15%, respectively, in favor of enoxaparin. No statistical difference was found in the incidence of proximal thrombosis between the two groups, but the absolute risk reduction was 1.2% in favor of warfarin. The CI, however, indicates that the true incidence of proximal thrombosis in enoxaparin recipients could be as much as 7.2% higher or 4.8% lower than the incidence in warfarin recipients. Knowing which value is correct within this range of absolute differences in proximal thrombosis rates may influence the choice of prophylactic agent. In terms of safety, no statistical difference was seen in the incidence of major hemorrhage between the two groups, although the absolute risk difference was 0.3% in favor of warfarin. The CI obtained does not rule out risk differences as high as 2.4% in favor of warfarin or a 1.8% difference in favor of enoxaparin. Because all rates are less than 5%, different values within this range are not likely to influence the choice of prophylactic agent. No statistical or clinically meaningful differences were seen between the two groups in measured blood loss from the surgical drain. The mean number of units of packed red cells transfused per patient did not differ, but more enoxaparin recipients received packed red cells after their stay in the recovery room, possibly reflecting a trend toward more blood loss.

Our randomized study used strong clinical trial methods. The two patient groups were similar at the time of randomization, and care was taken to avoid bias by blinding the interventions and outcome assessments. We obtained adequate venographic outcomes in 62% of our patients. No difference was seen between the two groups in the proportion of patients with adequate venograms; the reasons for failure to obtain adequate venograms were also equally balanced. An analysis of patients with adequate venograms showed that their baseline characteristics (data not shown) were no different than those of the entire study group. Approximately one third of venographic failures occurred in the leg in which surgery was not done, an outcome that underscores the difficulty of obtaining adequate venography in both legs. However, bilateral venography detects more thrombi than does venography only in the leg in which surgery is done; we found approximately 14% of the thrombi only in the limb in which surgery was not done. This observation emphasizes the importance of bilateral venography in prophylaxis trials after knee arthroplasty.

Proximal venous thrombosis occurred in 11% of the 417 patients with adequate venograms in both groups. Proximal thrombosis was detected by venous ultrasonography in only 3.6% (7 of 193) of patients in whom venography was not done. This difference in detection rates between the two diagnostic methods reinforces the need to use contrast venography in efficacy trials of prophylaxis in patients having knee arthroplasty. The difference also raises concerns about the reduced sensitivity of venous ultrasonography (26) as the possible outcome measure in these types of studies.

We have previously reported the results of a randomized trial comparing enoxaparin with placebo after major knee surgery (8). In our earlier study, distal venous thrombosis occurred in 45% of placebo recipients, and proximal venous thrombosis occurred in 20%. We also found a 19% incidence of distal deep venous thrombosis with no proximal venous thrombosis in enoxaparin recipients. The lower incidence of both distal and proximal venous thrombosis in enoxaparin recipients that we found in our earlier study may have been due to the smaller sample size and the smaller number of study centers. Moreover, a larger number of study centers allows the recruitment of a broader spectrum of patients with more varied disease severity, comorbid conditions, and type of surgical care and should therefore increase the external validity of the current findings.

The results of studies that have compared low-molecular-weight heparins with warfarin in knee arthroplasty are summarized in Table 4. Three of the trials, including ours, were double-blinded (20, 23); the remaining two were open-label (21, 22). Both we and Hull and colleagues (20) used bilateral venography as the effectiveness outcome; investigators in the remaining three trials relied on unilateral venography (21–23). In all five studies, low-molecular-weight heparin resulted in overall greater efficacy than warfarin in reducing the incidence of deep

Table 4. Comparative Studies of Warfarin and Low-Molecular-Weight Heparin after Knee Arthroplasty*

Study (Reference)	Intensity	Warfarin					Low-Molecular-Weight Heparin			
		DVT	Proximal DVT	Wound Hematoma	Major Bleeding	Regimen	DVT	Proximal DVT	Wound Hematoma	Major Bleeding
		← n/n(%)† →					← n/n(%)† →			
Hull et al. (20)	INR, 2.0–3.0	152/277 (55)	34/277 (12)	19/324 (6)	3/324 (1)	Tinzaparin, 75 U/kg per day	116/258 (45)	20/258 (8)	28/317 (9)	9/317 (3)
RD Heparin Group (21)	Prothrombin time ratio, 1.2–1.5	60/147 (41)	15/147 (10)	NA	NA	Ardeparin, 90 U/kg per day	41/149 (28)	7/149 (5)	NA	NA
				NA	NA	Ardeparin, 50 U/kg twice daily	37/150 (25)	9/150 (6)	NA	NA
Spiro et al. (22)	INR, 2.0–3.0	72/122 (59)	16/122 (13)	6/176 (3)	4/176 (2)	Enoxaparin, 30 mg twice daily	41/108 (38)	3/108 (3)	12/173 (7)	9/173 (5)
Heit et al. (23)	INR, 2.0–3.0	81/222 (36)	15/222 (7)	NA	NA	Ardeparin, 50 U twice daily	58/230 (25)	14/230 (6)	NA	NA
Present study	INR, 2.0–3.0	109/211 (52)	22/211 (10)	18/334 (5)	6/334 (2)	Enoxaparin, 30 mg twice daily	76/206 (37)	24/206 (12)	18/336 (5)	7/336 (2)

* DVT = Deep venous thrombosis; INR = international normalized ratio; NA = not available.
† Values are the number of patients with events/number of patients studied (%).

venous thrombosis. In two of these studies, the superior benefit of low-molecular-weight heparin also extended to proximal thrombosis. The lower rates of proximal thrombosis in the patients receiving low-molecular-weight heparin studied by Spiro and colleagues (22) and the RD Heparin Group (21) may be due to the initiation of low-molecular-heparin therapy on the day of surgery rather than the first day after surgery. The lower rate of proximal thrombosis reported by Spiro and coworkers is paralleled by a higher incidence of wound hematoma and major hemorrhage, possibly because prophylaxis with low-molecular-weight heparin was started within 8 hours after surgery. Hull and colleagues (20) also observed a higher wound hematoma rate in the low-molecular-weight heparin group than was seen in our study, perhaps because of the dosage regimen used or differences in the pharmacokinetics profile of tinzaparin.

All North American studies of prophylaxis with low-molecular-weight heparin in orthopedic patients (8, 20–23, 27–30) have used postoperative regimens. These regimens do not contribute to intraoperative bleeding and thus allow hemostasis to begin before the start of prophylaxis and alleviate the fear of anesthesiologists who are reluctant to administer regional anesthesia with preoperative prophylaxis. The relative efficacy and safety of preoperative and postoperative thromboprophylaxis in orthopedic patients remain uncertain.

Our finding of a residual proximal thrombosis rate of approximately 10% to 12% with either warfarin or enoxaparin is clinically important; this rate is higher than that seen in patients having hip arthroplasty and receiving similar interventions (20, 21). Additional methodologically rigorous studies are required to further improve the efficacy, safety, and cost-effectiveness of thromboprophylaxis after knee arthroplasty.

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References

1. **Lotke PA, Ecker ML, Alavi A, Berkowitz H.** Indications for the treatment of deep venous thrombosis following total knee replacement. J Bone Joint Surg [Am]. 1984;66:202-8.
2. **Stulberg BN, Insall JN, Williams GW, Ghelman B.** Deep-vein thrombosis following total knee replacement. An analysis of six hundred and thirty-eight arthroplasties. J Bone Joint Surg [Am]. 1984;66:194-201.
3. **Lieberman JR, Geerts WH.** Prevention of venous thromboembolism after total hip and knee arthroplasty. J Bone Joint Surg [Am]. 1994;76:1239-50.
4. **Cohen SH, Ehrlich GE, Kauffman MS, Cope C.** Thrombophlebitis following knee surgery. J Bone Joint Surg [Am]. 1973;55:106-12.
5. **McKenna R, Bachmann F, Kaushal SP, Galante JO.** Thromboembolic disease in patients undergoing knee replacement. J Bone Joint Surg [Am]. 1976;58:928-32.
6. **Hull R, Delmore TJ, Hirsh J, Gent M, Armstrong P, Lofthouse R, et al.** Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. Thromb Res. 1979;16:37-45.
7. **Stringer MD, Steadman CA, Hedges AR, Thomas EM, Morley TR, Kakkar VV.** Deep vein thrombosis after elective knee surgery. An incidence study in 312 patients. J Bone Joint Surg [Br]. 1989;71:492-7.
8. **Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, et al.** Prevention of deep vein thrombosis after major knee surgery—a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. Thromb Haemost. 1992;67:417-23.
9. **Khaw FM, Moran CG, Pinder IM, Smith SR.** The incidence of fatal pulmonary embolism after knee replacement with no prophylactic anticoagulation. J Bone Joint Surg [Br]. 1993;75:940-1.
10. **Strandness DE Jr, Langlois Y, Cramer M, Randlett A, Thiele BL.** Long-term sequelae of acute venous thrombosis. JAMA. 1983;250:1289-92.
11. **Francis CW, Ricotta JJ, Evarts CM, Marder VJ.** Long-term clinical observations and venous functional abnormalities after asymptomatic venous thrombosis following total hip or knee arthroplasty. Clin Orthop. 1988;232:271-8.
12. **Bergqvist D, Jendteg S, Lindgren B, Mätzsch T, Persson U.** The economics of general thromboembolic prophylaxis. World J Surg. 1988;12:349-55.
13. **Seagroatt V, Tan HS, Goldacre M, Bulstrode C, Nugent I, Gill L.** Elective total hip replacement: incidence, emergency readmission rate and postoperative mortality. BMJ. 1991;303:1431-5.
14. **McKenna R, Galante J, Bachmann F, Wallace DL, Kaushal SP, Meredith P.** Prevention of venous thromboembolism after total knee replacement by high-dose aspirin or intermittent calf and thigh compression. Br Med J. 1980;280:514-7.
15. **Francis CW, Marder VJ, Evarts CM, Yaukoolbodi S.** Two-step warfarin therapy. Prevention of postoperative venous thrombosis without excessive bleeding. JAMA. 1983;249:374-8.
16. **Francis CW, Pellegrini VD Jr, Stulberg BN, Miller ML, Totterman S, Marder VJ.** Prevention of venous thrombosis after total knee arthroplasty. Comparison of antithrombin III and low-dose heparin with dextran. J Bone Joint Surg [Am]. 1990;72:976-82.
17. **Haas SB, Insall JN, Scuderi GR, Windsor RE, Ghelman B.** Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg [Am]. 1990;72:27-31.
18. **Hodge WA.** Prevention of deep vein thrombosis after total knee arthroplasty. Coumadin versus pneumatic compression. Clin Orthop. 1991;271:101-5.
19. **Cushner FD, Friedman RJ.** Blood loss in total knee arthroplasty. Clin Orthop. 1991;269:98-101.
20. **Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, et al.** A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. N Engl J Med. 1993;329:1370-6.
21. 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.
22. **Spiro TE, Fitzgerald RH, Trowbridge AA, Overdyke WL, Gardiner GA, Young TR, et al.** Enoxaparin a low molecular weight heparin and warfarin for the prevention of venous thromboembolic disease after elective knee replacement surgery [Abstract]. Blood. 1994;84:246A.
23. **Heit J, Berkowitz S, Bona R, Comp P, Corson J, Cushner F, et al.** Efficacy and safety of normiflo (a LMWH) for prevention of venous thromboembolism following total knee replacement: a double-blind, dose-ranging study [Abstract]. Thromb Haemost. 1995;73:978A.
24. **Fauno P, Suomalainen O, Rehnberg V, Hansen TB, Kroner K, Soimakallio S, et al.** Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. J Bone Joint Surg Am. 1994;76:1814-8.
25. **O'Brien PC, Fleming TR.** A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-56.
26. **Wells PS, Lensing AW, Davidson BL, Prins MH, Hirsh J.** Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery. A meta-analysis. Ann Intern Med. 1995;122:47-53.
27. **Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, et al.** A randomized controlled trial of a low molecular weight heparin (enoxaparin) to prevent deep vein thrombosis in patients undergoing elective hip surgery. N Engl J Med. 1986;315:925-9.
28. **Levine MN, Hirsh J, Gent M, Turpie AG, Leclerc JR, Powers P, et al.** Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. Ann Intern Med. 1991;114:545-51.
29. **Spiro TE, Johnson GJ, Christie MJ, Lyons RM, MacFarlane DE, Blasier RB, et al.** Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. Enoxaparin Clinical Trial Group. Ann Intern Med. 1994;121:81-9.
30. **Colwell CW Jr, Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Blaha JD, et al.** Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am. 1994;76:3-14.