

Ximelagatran versus Warfarin for the Prevention of Venous Thromboembolism after Total Knee Arthroplasty

A Randomized, Double-Blind Trial

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Background: Warfarin is used for prophylaxis of venous thromboembolism in patients undergoing total knee arthroplasty. However, it is associated with rates of deep venous thrombosis (DVT) of approximately 38% to 55% and requires routine coagulation monitoring and frequent dose adjustment. Ximelagatran, an oral direct thrombin inhibitor, has shown promising efficacy and tolerability in patients undergoing total hip or knee arthroplasty.

Objective: To compare the efficacy and safety of ximelagatran and warfarin for prophylaxis of venous thromboembolism after total knee arthroplasty.

Design: Randomized, double-blind, parallel-group trial.

Setting: 74 North American hospitals.

Patients: 680 patients who had undergone total knee arthroplasty.

Intervention: 7 to 12 days of treatment with oral ximelagatran, 24 mg twice daily, starting on the morning after surgery, or warfarin (target international normalized ratio, 2.5 [range, 1.8 to 3.0]), starting on the evening of the day of surgery.

Measurements: Principal end points were asymptomatic DVT

on mandatory venography; symptomatic DVT confirmed by ultrasonography or venography; symptomatic, objectively proven pulmonary embolism; and bleeding. All were assessed by blinded adjudication locally and at a central study laboratory.

Results: On central adjudication, incidence of venous thromboembolism was 19.2% (53 of 276 patients) in the ximelagatran group and 25.7% (67 of 261 patients) in the warfarin group (difference, -6.5 percentage points [95% CI, -13.5 to 0.6 percentage points]; $P = 0.070$). On local assessment, incidence was 25.4% in the ximelagatran group and 33.5% in the warfarin group ($P = 0.043$). In the ximelagatran and warfarin groups, respectively, major bleeding occurred in 1.7% and 0.9% of patients and minor bleeding occurred in 7.8% and 6.4% of patients. No variables related to bleeding differed significantly between the two groups.

Conclusions: For prophylaxis of venous thromboembolism, fixed-dose ximelagatran started the morning after total knee arthroplasty is well tolerated and at least as effective as warfarin, but it does not require coagulation monitoring or dose adjustment.

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Venous thromboembolism is common after major orthopedic surgery. Meta-analysis has indicated that without prophylaxis, the incidence of deep venous thrombosis (DVT) is 50% to 60% (1). Prophylaxis with low-molecular-weight heparin (LMWH) or warfarin is recommended, but the incidence of venographically confirmed DVT at the time of hospital discharge remains approximately 31% with the former and 47% with the latter (1). In addition, proximal DVT is found in 7% to 12% of patients who receive prophylaxis with either regimen (1). Currently, the use of LMWH and warfarin is approximately evenly divided in North America (2, 3). Warfarin has a slow onset of action and is inconvenient because it requires frequent coagulation monitoring and dose adjustment (3, 4). Low-molecular-weight heparin does not require monitoring but must be administered parenterally, which can be difficult after hospital discharge.

Ximelagatran is a novel oral direct thrombin inhibitor. After administration, it is rapidly absorbed and transformed to its active form, melagatran (5), which provides competitive, direct inhibition of both free and clot-bound thrombin. Administration of ximelagatran results in predictable plasma concentrations of melagatran that increase linearly in relation to dose in healthy volunteers (5) and surgical patients (6, 7). Fixed doses of ximelagatran with-

out coagulation monitoring have been studied in phase II trials and have shown promising results in prophylaxis of venous thromboembolism after total hip or knee arthroplasty (8, 9). In this phase III trial, we compared the efficacy and safety of ximelagatran and warfarin for the prevention of venous thromboembolism after total knee arthroplasty.

METHODS

Study Design

We performed a randomized, double-blind study comparing ximelagatran with warfarin for the prevention of venous thromboembolism after total knee arthroplasty. Patients were recruited from 74 hospitals in the United States and Canada. The study was performed in accordance with the Declaration of Helsinki and was approved by the institutional review board at each hospital. Patients were evaluated for eligibility 1 to 30 days before surgery and were randomly assigned to treatment postoperatively on the day of surgery. Those that appeared to meet the inclusion criteria were approached before surgery to discuss the study and to sign consent forms if they were interested. Those who agreed to participate were reevaluated after surgery and before randomization to ensure that they still met

entry criteria. Randomization was stratified by unilateral or bilateral surgery at each center and was implemented through an interactive voice response system. Treatment was given for 7 to 12 days, and venography was performed within 12 hours of the final dose. Patients were followed clinically for 4 to 8 weeks after surgery.

Patients

Patients were eligible if they were scheduled for elective total knee arthroplasty, were at least 18 years of age, weighed 40 to 125 kg, and provided consent. Women had to be surgically sterile, postmenopausal for at least 2 years, or using reliable contraception. Criteria for exclusion were scheduled hemiarthroplasty, surface repair, or revisionary surgery; planned external pneumatic compression prophylaxis; immobilization for 3 or more days before surgery; major surgery, ischemic stroke, myocardial infarction, or administration of any investigational drug within 30 days before surgery; a history of intracranial, retroperitoneal, or intraocular bleeding or any other disorder associated with increased risk for bleeding; gastrointestinal bleeding within 90 days before surgery or endoscopically verified ulcer disease within 30 days before surgery; uncontrolled hypertension; cytotoxic treatment for active malignancy; clinically significant liver disease; thrombocytopenia; drug or alcohol abuse in the past 6 months; allergy to contrast media or iodine; contraindication to warfarin; severe renal impairment (defined as estimated creatinine clearance < 0.5 mL/s [< 30 mL/min]); or traumatic epidural or spinal puncture before surgery. Metformin was stopped before administration of contrast media for venography and was restarted after 48 hours if renal function was normal. If an epidural or spinal catheter was used, it had to be removed within 36 hours after surgery and at expected trough levels of melagatran. Treatment with thrombolytic drugs and the following anticoagulants or antiplatelet agents was not allowed within 7 days before surgery or during administration of the study drug: heparins, warfarin, dipyridamole, sulfinpyrazone, ticlopidine, clopidogrel, non-selective cyclooxygenase anti-inflammatory drugs with half-life exceeding 20 hours, at least 500 mg of aspirin per day, or dextran.

Treatment Regimens

Tablets containing 24 mg of ximelagatran (AstraZeneca, Wilmington, Delaware) or placebo were given in the morning and evening, with the first dose given on the morning after surgery and at least 12 hours after surgery. Capsules containing warfarin (Coumadin, DuPont Pharmaceuticals, Wilmington, Delaware) or placebo were given each evening, starting on the day of surgery after hemostasis was adequate. Warfarin was started at a minimum dose of 5 mg and was then titrated to achieve a target international normalized ratio (INR) of 2.5 (range, 1.8 to 3.0). Patients remained in the hospital according to local practice, usually for 3 to 4 days, after which they self-administered the medication.

Context

Warfarin is associated with rates of deep venous thrombosis of 38% to 55% when prescribed during total knee arthroplasty and requires frequent monitoring and dose adjustment. The oral thrombin inhibitor ximelagatran has shown promise in prophylaxis of venous thromboembolism in patients undergoing hip and knee arthroplasty. Ximelagatran does not require monitoring or dose adjustment.

Contribution

This randomized, controlled trial compared ximelagatran with warfarin in 680 patients undergoing total knee arthroplasty and found that ximelagatran was at least as effective as warfarin.

Implications

Ximelagatran is an option for prophylaxis of venous thromboembolism in patients undergoing total knee arthroplasty, but this study had limited power to compare adverse effects.

—The Editors

To guide dosing, INRs were measured locally by using a point-of-care device or a laboratory on postoperative days 1 to 3 and as needed in the interim and after discharge until the day of venography. The point-of-care devices were preprogrammed to encrypt INR values, which could be decrypted only by the central anticoagulation management center (Omnicare Clinical Research, Lake Bluff, Illinois). International normalized ratios from local laboratories were reported to the Center, which then faxed real or sham INR values to the investigator. The investigator used these values to determine the next dose of warfarin or placebo. Sham INR values were generated to mimic usual values in persons receiving warfarin. Treatment adherence was assessed by counting tablets and capsules used in the hospital, dispensed at discharge, and returned at the end of the study.

Efficacy Assessments

The primary efficacy variable was the incidence of DVT (proximal or distal) or pulmonary embolism. The secondary efficacy variable was the incidence of proximal DVT or pulmonary embolism. Both variables considered events that occurred during treatment. Deep venous thrombosis was evaluated by ascending venography on the leg or legs that had undergone surgery (10, 11). Standardized film documentation contained no more than nine images per leg. The Central Adjudication Committee assessed venograms for the primary efficacy end point. The criterion for DVT was a consistent intraluminal filling defect on at least two images. Evaluable venograms required visualization of all of the deep veins except the muscular veins and the anterior tibial veins, although DVT was counted if these veins were seen and thrombus was detected. Non-

Table 1. Overview of the Study Sample

Variable	Ximelagatran Group	Warfarin Group	Total
	← n (%) →		
Total patients randomly assigned	348 (100.0)	332 (100.0)	680 (100.0)
Patients who did not receive study medication	3 (0.9)	2 (0.6)	5 (0.7)
Safety sample	345 (99.1)	330 (99.4)	675 (99.3)
Nonevaluable venogram and no confirmed symptomatic venous thromboembolism	69 (19.8)	69 (20.8)	138 (20.3)
Venography not done	36 (10.3)	45 (13.6)	81 (11.9)
Indeterminate results on venography	33 (9.5)	24 (7.2)	57 (8.4)
Efficacy sample	276 (79.3)	261 (78.6)	537 (79.0)

evaluable venograms were defined as those that showed a lack of filling in a region of the deep system of the leg without the presence of an intraluminal filling defect elsewhere in the same region. Ultrasound diagnosis was sufficient for symptomatic proximal DVT, but venography was required for diagnosis of symptomatic distal DVT. Analysis of local interpretations of venograms was included in the statistical analysis plan before unblinding.

Pulmonary embolism was diagnosed when a lung scan showed high probability, defined as one or more segmental perfusion defects seen in at least two views with corresponding normal ventilation. Pulmonary embolism was also diagnosed by pulmonary angiography showing a persistent intraluminal defect or abrupt cutoff of a vessel greater than 2.5 mm in diameter. All cases of suspected pulmonary embolism were adjudicated centrally. Patients with thrombosis were treated according to local practice.

Safety Assessments

All bleeding events were recorded, including bleeding at the site of surgery, volumes of blood loss and transfusion, and wound appearance. Independent experts classified bleeding events as major if they were clinically overt and showed one or more of the following: critical site involvement (intracranial, retroperitoneal, intraocular, intraspinal, or pericardial), bleeding index of 2.0 or greater (calculated as the number of units of red blood cells transfused plus the difference between prebleeding hemoglobin level minus postbleeding event hemoglobin level [g/dL]), medical or surgical intervention at the operative site, or fatal bleeding. The bleeding index provides a measure of hemoglobin change as modified by transfusion and has been used in other studies of prophylaxis after orthopedic procedures (12, 13). Clinically overt bleeding with none of the other characteristics was classified as minor. The investigators also classified the overall appearance and characteristics of the surgical wound as being “as expected,” “worse than expected,” or “better than expected.” Clinical chemistry and hematology variables were assessed at screening, on the last day of study drug administration, and at the 6-week follow-up examination.

Statistical Analysis

Previous studies have shown that deep venous thrombosis occurs in approximately 49% of patients receiving

warfarin and in 20% of those receiving ximelagatran (1, 9). To be conservative, and because most venography in our study would be unilateral, we anticipated an incidence of 35% for DVT in the warfarin group. On the basis of these estimates, approximately 480 evaluable patients would be needed to provide 95% power at a 5% significance level to demonstrate superiority of ximelagatran. We selected a sample size of 600 patients, anticipating that 20% would have nonevaluable venograms.

The efficacy analyses included all patients with an evaluable venogram or symptomatic, objectively confirmed DVT or pulmonary embolism during the treatment period. The incidences of total venous thromboembolism and of proximal DVT or pulmonary embolism during treatment were calculated by using the observed rates and 95% CIs in each treatment group; the differences in incidence and 95% CIs were calculated. Group comparisons were tested by using the Cochran–Mantel–Haenszel chi-square test stratified by unilateral or bilateral surgery. Incidences of symptomatic venous thromboembolism and deaths during the follow-up period were also tabulated. Clinical events occurring no more than 2 days after the last dose of study drug were considered to have occurred during treatment; after 2 days, they were considered follow-up events.

The safety analysis included all patients who took at least one dose of study medication. The frequencies and 95% CIs of bleeding events and of individual bleeding complications associated with the surgical wound were analyzed by using methods similar to those used in the efficacy analysis. Appearance of the surgical wound was recorded as the worst appearance noted during the study, and differences were tested by using the Cochran–Mantel–Haenszel chi-square test stratified by unilateral or bilateral surgery. The descriptions of wound appearance were summarized by the percentage of patients for whom each characteristic was “worse than expected.” Volumes of operative blood loss, postoperative wound drainage and transfusion, and the bleeding index were estimated by using the means for both treatment groups, and between-treatment differences were tested by using an analysis of variance model blocked by unilateral or bilateral surgery.

Role of the Funding Source

AstraZeneca funded the study and performed all statistical analyses with guidance from the Executive Committee. The Executive Committee, which was composed of six physicians, was involved in study design and monitoring, had full access to the data, and made all decisions regarding publication. A list of the members of the Executive Committee, the Data Safety Monitoring Board, the Central Adjudication Committee, and the site investigators and coordinators can be found in the Appendix (available at www.annals.org).

RESULTS

Patients

Between March and September 2000, 758 patients consented to participate in the study and 680 were randomly assigned to treatment (Table 1). Five patients did not receive study medication for the following reasons: death from myocardial infarction (1 patient in the ximelagatran group), withdrawn consent (1 patient in each group), use of prohibited medication (1 patient in the ximelagatran group), and unfulfilled eligibility criteria (1 patient in the warfarin group). Thus, the safety sample consisted of 345 patients in the ximelagatran group and 330 patients in the warfarin group. Within this sample, 21 patients from the ximelagatran group and 30 from the warfarin group discontinued treatment prematurely be-

cause of adverse events (14 and 17 patients, respectively), withdrawn consent (2 and 4 patients, respectively), and "other reasons" (5 and 9 patients, respectively). "Other reasons" in the warfarin group included confirmed pulmonary embolism (3 patients) and confirmed DVT (2 patients). The duration of the treatment was 7 to 9 days for most patients; approximately 25% received treatment for 10 to 12 days. Fewer patients in the ximelagatran group (6%) than in the warfarin group (17%) received treatment for fewer than 6 days, mostly because warfarin therapy was sometimes held to keep INRs in the desired range.

The efficacy sample comprised 276 patients in the ximelagatran group and 261 patients in the warfarin group. One hundred thirty-eight patients (69 in each group) were excluded from the efficacy sample because they had non-evaluative venograms and no confirmed symptomatic DVT or pulmonary embolism. Within the efficacy sample, predefined protocol deviations occurred in 25 patients assigned to ximelagatran and 36 patients assigned to warfarin. Each type of protocol deviation occurred in a similar proportion of patients in either group. Patients with predefined protocol deviations were included in the efficacy analyses. Patient characteristics were well matched (Table 2), and adherence to treatment was approximately 90%.

Thromboembolic Events

When venograms were interpreted centrally, patients receiving ximelagatran had a lower incidence of total ve-

Table 2. Characteristics of the Safety Sample and the Efficacy Sample*

Characteristic	Ximelagatran Group	Warfarin Group
Safety sample		
Patients, <i>n</i>	345	330
Age, <i>y</i>	67.8 ± 10.1	67.7 ± 10.4
Women, %	63.2	64.2
Weight, <i>kg</i>	87.3 ± 17.7	86.8 ± 18.2
Body mass index, <i>kg/m</i> ²	31.4 ± 5.9	31.0 ± 6.1
Estimated creatinine clearance, <i>mL/s (mL/min)</i>	1.64 ± 0.67 (98.4 ± 40.0)	1.66 ± 0.68 (99.2 ± 40.5)
Ethnicity, <i>n (%)</i>		
White	319 (92.5)	302 (91.5)
African American	23 (6.7)	27 (8.2)
Asian	2 (0.6)	1 (0.3)
Other	1 (0.3)	0 (0.0)
Treatment duration, <i>d</i>	8.1 ± 2.1	7.7 ± 2.3
Efficacy sample		
Patients, <i>n</i>	276	261
History of deep venous thrombosis or pulmonary embolism, <i>n (%)</i>	8 (3.0)	9 (3.4)
History of varicose veins, <i>n (%)</i>	41 (14.9)	31 (11.9)
Anesthesia, <i>n (%)</i>		
General	200 (72.5)	170 (65.1)
Regional	64 (23.2)	75 (28.8)
Other	12 (4.3)	16 (6.1)
Type of surgery, <i>n (%)</i>		
Unilateral	257 (93.1)	248 (95.0)
Bilateral	19 (6.9)	13 (5.0)
Tourniquet duration, <i>min</i>	70.1 ± 23.9	71.2 ± 25.7
Duration of surgery, <i>min</i>	92.5 ± 39.8	87.8 ± 29.6
Time from surgery to first dose, <i>h</i>	20.9 ± 4.1	20.8 ± 3.0
Time to ambulation, <i>d</i>	1.3 ± 0.6	1.2 ± 0.6
Duration of hospital stay, <i>d</i>	5.0 ± 2.8	4.9 ± 2.4
Day of venography	8.6 ± 1.7	8.5 ± 1.6

* Values presented with plus/minus signs are means ± SD.

Table 3. Incidence of Venous Thrombosis during the Treatment Period*

Event†	Ximelagatran Group	Warfarin Group	Mean Risk Reduction for Ximelagatran vs. Warfarin	P Value‡
	% (n/n)			
Central interpretation				
Total thromboembolism	19.2 [14.7 to 24.4] (53/276)	25.7 [20.5 to 31.4] (67/261)	-6.5 [-13.5 to 0.6]	0.070
Proximal DVT or PE	3.3 [1.5 to 6.1] (9/274)	5.0 [2.7 to 8.5] (13/258)	-1.8 [-5.2 to 1.6]	>0.2
Local interpretation				
Total thromboembolism	25.4 [20.3 to 31.0] (68/268)	33.5 [27.8 to 39.5] (88/263)	-8.1 [-15.8 to -0.4]	0.043
Proximal DVT or PE	5.7 [3.2 to 9.3] (15/262)	9.2 [5.9 to 13.5] (23/249)	-3.5 [-8.1 to 1.1]	0.119

* Numbers in square brackets are 95% CIs. Values in parentheses are numbers of patients/total numbers of evaluable patients. DVT = deep venous thrombosis; PE = pulmonary embolism.

† Total thromboembolism refers to both distal and proximal DVT. Proximal DVT includes only patients with thrombi in the popliteal or more proximal veins.

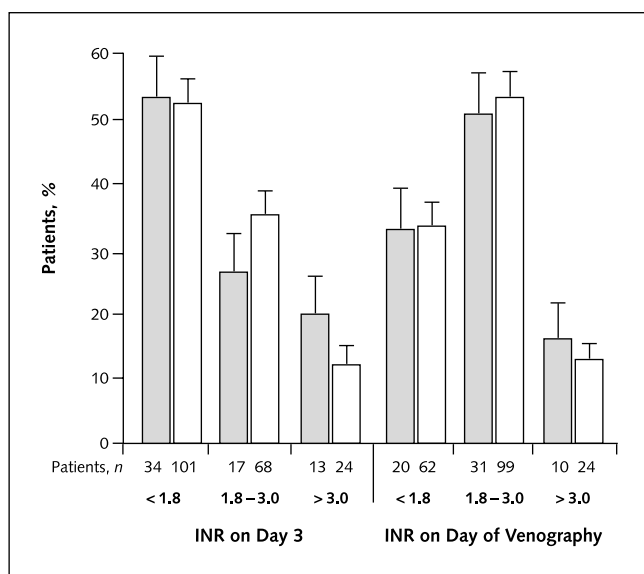
‡ Treatment differences were tested by using the Cochran-Mantel-Haenszel test, adjusted for type of surgery (unilateral or bilateral).

nous thromboembolism than those treated with warfarin (19.2% vs. 25.7%) (difference, -6.5 percentage points [95% CI, -13.5 to 0.6 percentage points]; $P = 0.070$) (Table 3). Both treatments were associated with low incidences of proximal DVT or pulmonary embolism (3.3% in the ximelagatran group vs. 5.0% in the warfarin group; $P > 0.2$). Bilateral surgery was performed in fewer than 10% of patients, and no significant differences were apparent between the overall results for unilateral or bilateral surgery. When venograms were interpreted locally, the incidence of total venous thromboembolism was significantly lower in the ximelagatran group (25.4%) than in the warfarin group (33.5%) ($P = 0.043$). The locally assessed incidences of proximal DVT or pulmonary embolism were

5.7% in the ximelagatran group and 9.2% in the warfarin group ($P = 0.12$). We performed a sensitivity analysis assuming several outcomes in patients without venograms, including 1) that the rate of thrombosis was the overall mean rate or 2) that the rates in ximelagatran- and warfarin-treated patients would be the observed rates in patients who had available venograms. We performed two additional analyses with these same two assumptions but used sex-adjusted rates because of the slightly higher percentage of women without venography in the warfarin group. The analysis was virtually unchanged by these modifications.

Confirmed symptomatic DVT occurred at similar frequencies in the ximelagatran group (6 of 345 patients [1.7%]) and the warfarin group (6 of 330 patients [1.8%]). During the treatment period, symptomatic pulmonary embolism was confirmed in one patient in the ximelagatran group and four patients in the warfarin group, including one fatal pulmonary embolism on day 3. One additional patient in the ximelagatran group developed symptomatic pulmonary embolism on day 14, 4 days after treatment was stopped. International normalized ratios on day 3 and at venography were not significantly different in patients with or without venous thromboembolism (Figure). Approximately one third of patients had INRs in the range of 1.8 to 3.0 at day 3, and one half had INRs in this range at venography. No trend was seen toward a higher rate of venous thromboembolism when INRs were subtherapeutic.

Figure. Presence (shaded bars) or absence (white bars) of venous thrombosis in patients receiving warfarin, according to international normalized ratio (INR) on postoperative day 3 and day of venography.



Data are means; error bars represent upper bounds of 95% CIs. On day 3, 64 patients had confirmed venous thrombosis and 193 patients did not; on the day of venography, 61 patients had confirmed venous thrombosis and 185 patients did not.

Bleeding

Major bleeding occurred in 6 of 345 patients (1.7%) in the ximelagatran group and 3 of 330 patients (0.9%) in the warfarin group; no statistically significant differences were seen in the rates of bleeding events (Table 4). Major bleeding events included gastrointestinal bleeding (3 patients in the ximelagatran group and 1 in the warfarin group) and wound hematomas (3 patients in the ximelagatran group and 2 in the warfarin group). Of the 6 major bleeding events in the ximelagatran group, 5 occurred in the first 3 days, whereas all 3 major bleeding events in the warfarin group occurred more than 7 days after surgery. Transfusion volumes, operative blood loss, postoperative wound drainage, and bleeding indices were similar for both

treatment groups. Minor bleeding occurred in 7.8% and 6.4% of patients in the ximelagatran and warfarin groups, respectively.

Wound appearance and bleeding complications were assessed on days 1 to 3, on the day of venography, and at follow-up visits. For all time points combined, overall wound appearance was rated "as expected" in 90% of patients in the ximelagatran group and 92% of patients in the warfarin group and "worse than expected" in 9.9% of patients in the ximelagatran group and 7.9% of patients in the warfarin group. There were no statistically significant differences between treatments at any time. For patients with a "worse than expected" rating at any time, wound appearance was further characterized as due to hematoma, bleeding, unusual bruising, intra-articular bleeding, swelling, drainage, or erythema, and there was no statistically significant difference in any characteristic between the groups. The most common complication was wound bleeding (7.0% of patients in the ximelagatran group and 5.5% of patients in the warfarin group; $P > 0.2$).

DISCUSSION

Our findings indicate that ximelagatran, an oral direct thrombin inhibitor, is at least as effective as adjusted-dose warfarin for prophylaxis of DVT after total knee arthroplasty. Symptomatic DVT was infrequent, and incidences were similar in the ximelagatran and warfarin groups (1.7% and 1.8%, respectively). Symptomatic pulmonary embolism occurred in 0.6% and 1.2%, respectively, of these groups. Efficacy was evaluated by venography between days 7 and 12, when most thrombi are present, and also by clinical evaluation between weeks 4 and 8. Any effect on later events cannot be evaluated. Bleeding complications were infrequent and did not differ significantly in the two groups when assessed by objective or subjective measures.

Venography is the gold standard for diagnosis of venous thromboembolism and was performed only on the operated leg to minimize patient discomfort and risk. In two recent trials, the rates of DVT occurring only in the contralateral leg after total knee arthroplasty were 5.2% (14) and 6.2% (15), indicating that unilateral venography would identify the vast majority of thrombi. Our study prospectively included two blinded interpretations of venography. The central reading was the primary end point and ensured uniformity of interpretation across centers while using strict criteria for interpretation. The local interpretation represented usual clinical practice, had the benefit of fluoroscopy, and may have yielded more readily generalizable results. The results of the two interpretations were generally consistent with each other, but the local interpretation indicated that ximelagatran was statistically significantly more effective than warfarin whereas the central reading showed a trend.

Current guidelines recommend prophylaxis with

Table 4. Rates of Bleeding Events*

Event	Ximelagatran Group (n = 345)	Warfarin Group (n = 330)
Major bleeding, %	1.7 (0.6–3.7)	0.9 (0.2–2.6)
Any bleeding, %	9.0 (6.2–12.5)	7.0 (4.5–10.3)
Transfusion, %	38	34
Mean transfusion volume, U	0.7 (0.6–0.9)	0.7 (0.6–0.8)
Mean operative blood loss, mL†	148 (129–167)	143 (124–163)
Mean postoperative wound drainage, mL‡	625 (574–675)	598 (546–651)
Bleeding index§	3.0 (2.9–3.2)	2.9 (2.8–3.1)

* Numbers in parentheses are 95% CIs. $P > 0.2$ for all comparisons. Treatment differences were tested by using the Cochran–Mantel–Haenszel test, adjusted for type of surgery (unilateral or bilateral) and for other variables (analysis of variance blocked by type of surgery).

† Data were available for 323 patients in the ximelagatran group and 311 patients in the warfarin group.

‡ Data were available for 283 patients in the ximelagatran group and 262 patients in the warfarin group.

§ Data were available for 318 patients in the ximelagatran group and 299 patients in the warfarin group. Bleeding index = number of units of blood transfused + (baseline – postvenography hemoglobin value [g/dL]).

LMWH or warfarin for patients undergoing total knee arthroplasty, and both treatments are widely used. In six studies directly comparing LMWH with warfarin, the rates of venographically confirmed DVT in patients receiving LMWH ranged from 25% to 45%, with a pooled mean of 31% (1, 14, 16–20). In the corresponding warfarin groups, the rates were 38% to 55%, with a pooled mean of 47% (14, 16–21). Proximal DVT, which is more likely to be symptomatic and associated with pulmonary embolism (22–26), was found in approximately 8% to 12% of patients (21). In our ximelagatran group, the rates of 19.2% and 25.4% for venous thromboembolism on central and local interpretation, respectively, compare favorably with previous results. In a dose-finding study, venous thromboembolism was detected in 16% of patients undergoing total knee arthroplasty in whom ximelagatran, 24 mg twice daily, was started 12 to 24 hours after surgery (9). In a European study, venous thromboembolism was seen in 22% of patients undergoing total knee arthroplasty who received melagatran, 3 mg subcutaneously, before surgery and for 1 to 3 days after surgery, followed by oral ximelagatran, 24 mg twice daily (8). The rates of proximal DVT or pulmonary embolism in the ximelagatran groups of these studies were 3.2% (8) and 2.0% (9), similar to our results.

In our study, the rate of DVT in patients receiving warfarin was lower than that in any other multicenter study and was also lower than the rate of 35% projected in the calculations of sample size. The reason for this is unclear but may be partly related to the use of unilateral rather than bilateral venography. Control of INRs was good, but no clear relation was seen between INR and the occurrence of thrombosis, a finding similar to previous reports (27). Results in our patients receiving ximelagatran were similar to those seen with parenterally administered direct thrombin inhibitors. Rates of DVT of 7% to 18%

have been reported after total hip arthroplasty in patients receiving the recombinant hirudin desirudin (28–30), and venous thromboembolism has been reported to occur in 17% of patients who received bivalirudin after orthopedic procedures (31).

The use of warfarin requires routine coagulation monitoring and dose adjustment because of issues such as drug interactions, diet, concomitant diseases, and varying metabolisms. Furthermore, warfarin has a delayed onset and does not achieve the target anticoagulant level until at least the third postoperative day; this is problematic after orthopedic surgery, when thrombosis may start during the first postoperative day (32). In contrast, ximelagatran is rapidly absorbed and converted to its active form, melagatran (5), which acts directly on thrombin and is eliminated unmetabolized through the kidneys (33). Given in fixed doses, ximelagatran produces predictable plasma melagatran concentrations (5, 7) and has no known food (34, 35) or drug (36–39) interactions. Animal studies indicate that ximelagatran has a wide therapeutic window and increases bleeding only slightly at therapeutic doses (40–42). Melagatran is excreted through the kidney, and plasma concentrations are influenced by renal function and weight in orthopedic patients (43, 44).

Bleeding is a major concern with postoperative anticoagulation, but no statistically significant differences were seen between groups in any measure of bleeding. Other published studies using warfarin in total knee arthroplasty have shown major bleeding in 0.9% (14) and 1.8% (17) of patients, similar to the rates observed in our study; slightly higher rates of 2.8% (14) and 2.1% (17) were seen in the comparator groups receiving LMWH. We performed a detailed analysis of complications at the surgical site, taking particular care to assess wound bleeding and appearance because surgeons are often concerned about wound healing in the presence of antithrombotic therapy. No differences in wound complications were observed.

In summary, in this randomized trial, postoperative ximelagatran was effective and well tolerated for prevention of venous thromboembolism. It was at least as effective as adjusted-dose warfarin, and no differences were seen in bleeding or wound complications between groups. Fixed oral doses of ximelagatran without routine coagulation monitoring or dose adjustment seem to be suitable for thromboprophylaxis after total knee arthroplasty.

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APPENDIX

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