Ximelagatran vs Low-Molecular-Weight Heparin and Warfarin for the Treatment of Deep Vein Thrombosis
A Randomized Trial

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Current therapy for patients with acute venous thromboembolism consists of 5 to 7 days of unfractionated heparin or low-molecular-weight heparin, overlapped with and followed by long-term oral anticoagulation with a vitamin K antagonist such as warfarin. Heparins must be given parenterally, and their administration requires considerable health care resources. Warfarin has an unpredictable dose response, interacts with many drugs, and can be affected by changes in diet; thus, continued coagulation monitoring and dose adjustment are necessary.1,2

Ximelagatran, an orally administered direct thrombin inhibitor, is rapidly absorbed and quickly converted to its active form, melagatran, which has a bioavailability of approximately 20%.3,4 Melagatran is a reversible, active-site inhibitor of both free and clot-bound thrombin5 and has predictable and reproducible pharmacokinetic and pharmacodynamic properties.6

See also pp 690, 699, and 736.
pharmacodynamic properties unaffected by obesity, ethnic origin, food, and alcohol. Melagatran also has a low binding affinity for plasma proteins and a low potential for drug interactions. These factors support the use of fixed dosing without the need for coagulation monitoring and subsequent dose adjustment.

In studies to date, ximelagatran has been shown to be effective and well tolerated for the prevention of venous thromboembolism after major elective hip or knee surgery, for the prevention of stroke and systemic embolism in patients with atrial fibrillation, and for the long-term secondary prevention of venous thromboembolism. In addition, ximelagatran showed promise for the effective treatment of acute deep vein thrombosis in a phase 2 study. In long-term studies, ximelagatran has been consistently associated with increased levels of liver enzymes in some patients. We conducted a large international, multicenter, double-blind, randomized trial (the Thrombin Inhibitor in Venous Thromboembolism [THRIVE] Treatment Study) in patients with acute deep vein thrombosis with or without pulmonary embolism, to compare the efficacy and safety of oral ximelagatran with that of standard enoxaparin/warfarin treatment.

**METHODS**

**Study Design**

The THRIVE Treatment Study was a randomized, double-blind trial that began as 2 separate and almost identical trials, each designed to demonstrate the noninferiority of ximelagatran relative to enoxaparin/warfarin for the prevention of recurrent venous thromboembolism. Originally, 1 of the trials was to have been conducted in North America and the other in countries outside North America. However, due to a low recruitment rate in North America and a low overall blinded event rate in countries outside North America, the executive committees agreed to merge the trials into a single large joint study approximately 1 year after the initial commencement to deliver conclusive results in a timely manner. A single executive committee was then formed, comprising all members of both committees, to supervise trial conduct. No examination or unblinded analysis of recurrence rates per treatment group was performed at any time before completion of the merged study.

The primary objective of the THRIVE Treatment Study was to compare the efficacy of ximelagatran (Exanta, AstraZeneca) with that of enoxaparin/warfarin for the prevention of recurrent venous thromboembolism. Secondary objectives were to compare safety, particularly with respect to bleeding, a combined end point of recurrent venous thromboembolism or major bleeding, and all-cause mortality. The study groups were ximelagatran in combination with enoxaparin placebo/warfarin placebo or enoxaparin/warfarin in combination with ximelagatran placebo. Oral ximelagatran, 30 mg, or placebo was given twice daily without coagulation monitoring or dose adjustment for 6 months. Enoxaparin, 1.0 mg/kg, or placebo was given subcutaneously twice daily for at least 5 days (maximum, 20 days) and, concomitantly, encapsulated warfarin (1.0 mg and 2.5 mg) or placebo tablets were administered once daily and adjusted to maintain an international normalized ratio (INR) between 2.0 and 3.0. Enoxaparin or enoxaparin placebo was stopped after 2 consecutive INR measurements reached the target range.

Blood samples were drawn per usual clinical practice for INR measurements to adjust warfarin (or warfarin placebo) dose, either at local laboratories or using a point-of-care device that provided encrypted values. In either case the results were sent to an independent study monitor who provided the attending physicians with the actual INR (enoxaparin/warfarin group) or a sham INR (ximelagatran group) to maintain blinding. The sham INR value was computer-generated according to an algorithm that took into account the previous warfarin placebo doses, sex, age, previous INR results, and phase of therapy. The attending physician adjusted the doses of warfarin or placebo according to the reported results (either real or sham).

**Patients**

Eligible patients were 18 years or older, with acute, objectively confirmed deep vein thrombosis, with or without pulmonary embolism, for whom anticoagulant therapy was planned for at least 6 months. The diagnosis of deep vein thrombosis was based on a clear-cut noncompressible proximal venous segment identified by venous ultrasonography or a persistent intraluminal filling defect in the calf or proximal veins identified by contrast venography.

The criteria for exclusion from the study included the presence of 1 or more of the following: symptoms of deep vein thrombosis for longer than 2 weeks; contraindications to anticoagulants; weight greater than 140 kg; clinically significant bleeding disorder; stroke within the previous 30 days; hemodynamically unstable pulmonary embolism; platelet count less than 90 × 10^9/L; calculated creatinine clearance less than 30 mL/min (0.501 mL/s); significantly liver disease or levels of aminotransferases persistently increased to greater than twice the upper limit of normal; thoracic or central nervous system surgery within the previous 2 weeks or planned major surgery during the study; expected survival of less than 6 months; or treatment with thrombolytic agents within 14 days before randomization. Women of childbearing potential had to be using reliable contraception or have a negative pregnancy test. Therapeutic doses of unfractionated or low-molecular-weight heparin were allowed for a maximum of 24 hours before randomization. Concomitant use of other anticoagulant or fibrinolytic agents was not allowed. Acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors were discouraged but permitted at the lowest effective dose. Other antiplatelet drugs were not allowed.

Randomization occurred after objective confirmation of deep vein thrombosis.
Bleeding and other clinical events were there was a clinically suspected event. All significant bleeding that did not meet the criteria for major bleeding. Each suspected bleeding event was reported and centrally adjudicated.

All deaths were adjudicated and classified as fatal pulmonary embolism, fatal bleeding, or death from other causes. Monthly liver function testing (levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin) was performed. The protocol was amended after approximately 1 year, requiring weekly testing if any test result was greater than twice the upper limit of normal; the protocol also required discontinuation of study drug if the test results increased to greater than 5 times the upper limit of normal or if an increase to more than 3 times the upper limit of normal persisted during 4 weeks. An independent data and safety monitoring board reviewed the outcome measures on a regular basis to ensure patient safety throughout the study. A stopping rule for a negative trend with respect to efficacy of ximelagatran vs standard therapy was to be applied, but no formal interim analyses were performed.

Outcome Measures
If a suspected recurrent thromboembolic event occurred, diagnostic testing was performed. Recurrent deep vein thrombosis was diagnosed by ultrasonography if there was a new noncompressible venous segment in the proximal veins, an increase of 4 mm or more in thrombus diameter with compression, or an increase of between 1 and 4 mm in diameter combined with an extension of at least 4 cm in length. When venography was performed, a new persistent intraluminal defect or extension of a previous defect by 4 cm or more was considered diagnostic of recurrence. Pulmonary angiography was required for confirmation of suspected distal (calf) deep vein thrombosis. In patients with suspected pulmonary embolism during follow-up, recurrence was diagnosed if repeat lung scanning showed a new segmental perfusion defect with normal ventilation, if computed tomography or pulmonary angiography showed a persistent intraluminal filling defect, or if new perfusion lung scan defects, not meeting the criteria for a high probability of pulmonary embolism, were seen together with new objectively confirmed deep vein thrombosis. All suspected recurrences were adjudicated by an independent central adjudication committee that reviewed the diagnostic testing.

Major bleeding was defined as fatal bleeding, bleeding in critical sites, or overt bleeding with a reduction in hemoglobin of at least 2 g/dL (20 g/L) or leading to transfusion of 2 or more units of blood or packed red cells. Minor bleeding was defined as clinically significant bleeding that did not meet the criteria for major bleeding. All suspected bleeding events were reported and centrally adjudicated.

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95% confidence interval (CI) around the absolute difference in cumulative risk of recurrence between treatments at 6 months should be less than 4%. Based on International Conference on Harmonisation guidelines, the noninferiority margin aimed to be less than the largest clinically acceptable difference against the comparator and to preserve the effect of the comparator against a putative placebo comparison. Similar noninferiority margins (3%-5%) have been used in other studies comparing different heparin regimes in acute venous thromboembolism. Kaplan-Meier estimates of the cumulative risk and the corresponding variance according to the Greenwood formula were used when calculating the CI and the corresponding P values. For bleeding, only on-treatment analyses were performed since no data on bleeding were collected beyond 2 days after discontinuation of study medication. Other outcomes were compared using both the intention-to-treat and on-treatment approaches. A Cox regression model was used to explore possible interactions between treatment and various baseline characteristics. The Fisher exact test was used for comparison of proportions. All reported P values are 2-sided; P<.05 was considered statistically significant. Analyses were conducted using SAS version 8.2 (SAS Institute Inc, Cary, NC) and Proc-StatXact version 5 (Cytel Software Corp, Cambridge, Mass).

For the North American study, which began recruiting in September 2000, the planned sample size was 1650, based on an expected recurrence rate of 4%15-19 and a noninferiority margin of 4%, accepting a 2-sided type I error of 5% and a type II error of less than 5%. For the study outside North America, which began recruiting in October 2000, the planned sample size was 1200, based on the same expected recurrence rate and noninferiority margin, accepting a 2-sided type I error of 5% and a type II error of 10%. After consultation with the study statistician, the Joint Executive Committee decided that a revised sample size, sufficient to show at least 50 recurrent events (approximately 2500 patients) would be the target of enrollment for the merged study.

**RESULTS**

**Study Patients**

Between September 2000 and May 2002, 2528 patients were randomized at 279 centers in 28 countries. Thirty-nine patients did not receive study drug (18 in the ximelagatran arm, 21 in the enoxaparin/warfarin arm) (FIGURE 1). Of the remaining 2489 patients, 1240 received ximelagatran and 1249 received ximelagatran and 1249 received enoxaparin/warfarin as assigned.

**Table 1. Baseline Characteristics of Study Patients**

<table>
<thead>
<tr>
<th>Characteristic/Medical History</th>
<th>Ximelagatran (n = 1240)</th>
<th>Enoxaparin/Warfarin (n = 1249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>56.7 (18-93)</td>
<td>57.1 (18-97)</td>
</tr>
<tr>
<td>Weight, mean (range), kg</td>
<td>81.5 (35-140)</td>
<td>80.9 (40-147)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>654 (53)</td>
<td>665 (53)</td>
</tr>
<tr>
<td>Calculated creatinine clearance, mean (range), mL/min*</td>
<td>105.3 (19-314)</td>
<td>104.5 (19-432)</td>
</tr>
<tr>
<td>Diagnosis at presentation, No. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal deep vein thrombosis</td>
<td>660 (53)</td>
<td>681 (55)</td>
</tr>
<tr>
<td>Distal deep vein thrombosis only</td>
<td>107 (9)</td>
<td>108 (9)</td>
</tr>
<tr>
<td>Deep vein thrombosis and pulmonary embolism</td>
<td>461 (37)</td>
<td>455 (36)</td>
</tr>
</tbody>
</table>

**Medical history, No. (%)**

<table>
<thead>
<tr>
<th></th>
<th>Ximelagatran (n = 1240)</th>
<th>Enoxaparin/Warfarin (n = 1249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous venous thromboembolism</td>
<td>274 (22)</td>
<td>266 (21)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>158 (13)</td>
<td>169 (14)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>125 (10)</td>
<td>131 (10)</td>
</tr>
<tr>
<td>Liver disorder</td>
<td>13 (1)</td>
<td>21 (2)</td>
</tr>
</tbody>
</table>

*SI conversion factor: To convert creatinine clearance from mL/min to mL/s, multiply values by 0.0167.
*Creatinine clearance (mL/min) = b × (140 – age ) × weight/serum creatinine, where b = 1.23 (males) or 1.04 (females) and age is in years, weight in kilograms, and serum creatinine level in µmol/L.
†One patient (randomized to receive ximelagatran) presented with pulmonary embolism only.
ceved enoxaparin/warfarin, representing the intention-to-treat population. The 2 groups were similar with respect to age, weight, sex, creatinine clearance, and risk factors for venous thromboembolism (Table 1). Pulmonary embolism was considered by local assessment to be present in 37% of the ximelagatran-treated and 36% of the enoxaparin/warfarin–treated patients.

**Treatment and Follow-up**

At least 24 weeks of study treatment was completed (December 2002) by 76% (947/1240) and 82% (1018/1249) of patients in the ximelagatran and enoxaparin/warfarin groups, resulting in an average exposure of 154 and 158 days, respectively (Figure 1). The average proportion of time within the target INR range of 2.0 to 3.0 after the initial 30 days was 75% of sham INRs in the ximelagatran group, compared with 61% in the enoxaparin/warfarin group. Adherence was estimated by the proportion of ximelagatran/ximelagatran placebo tablets taken (according to pill count) in relation to days from first dose to last dose. Ninety-three percent of patients in the ximelagatran and enoxaparin/warfarin groups took more than 80% of the ximelagatran placebo tablets.

During the follow-up period, 11 patients in the ximelagatran group withdrew consent, 10 were lost to follow-up, and 4 terminated the study follow-up for other reasons. In the enoxaparin/warfarin group, 11 withdrew consent, 14 were lost to follow-up, and 2 terminated the study follow-up for other reasons.

**Recurrent Venous Thromboembolism**

The primary efficacy end point of recurrent venous thromboembolism (intention-to-treat analysis) occurred in 26 and 24 patients in the ximelagatran and enoxaparin/warfarin groups, respectively, corresponding to estimated cumulative risks of 2.1% and 2.0% (Table 2 and Figure 2). The upper limit of the 2-sided 95% CI for the difference between the groups was 1.3%, establishing our prespecified noninferiority criterion for ximelagatran compared with enoxaparin/warfarin. The on-treatment analysis showed 6-month cumulative recurrence rates of 2.0% and 1.5% in the ximelagatran and enoxaparin/warfarin groups, respectively (Table 2).

**Table 2. Recurrent Venous Thromboembolism Events During 6 Months, by Treatment**

<table>
<thead>
<tr>
<th>Event</th>
<th>Ximelagatran (n = 1240)†</th>
<th>Enoxaparin/Warfarin (n = 1249)†</th>
<th>Difference (95% CI), %‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total recurrent venous thromboembolism</td>
<td>26 (2.1)$§</td>
<td>24 (2.0)$§</td>
<td>0.2 (−1.0 to 1.3)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>15</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>On-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total recurrent venous thromboembolism</td>
<td>23 (2.0)$§</td>
<td>17 (1.5)</td>
<td>0.5 (−0.6 to 1.6)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>14[1]</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

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Bleeding and Mortality
The cumulative risk of major bleeding (on-treatment analysis) at 6 months in the ximelagatran-treated patients was 1.3% compared with 2.2% for those receiving enoxaparin/warfarin (Table 3 and Figure 2). Major or minor bleeding was comparable in the 2 treatment groups. The locations of major bleeding in the ximelagatran group were gastrointestinal (5), urogenital (3), intraocular (2), nasal (1), and subarachnoidal (1); in the enoxaparin/warfarin group the locations were gastrointestinal (11), intramuscular (4), urogenital (3), intra-articular (2), gynecological (2), subdural (1), intracerebral (1), and unspecified location (1).

All-cause mortality was not significantly different between the 2 groups (intention-to-treat and on-treatment analyses) (Table 3).

Combined End Point of Recurrent Venous Thromboembolism or Major Bleeding
The time-to-event analysis suggested a greater rate of early recurrence of venous thromboembolism in the ximelagatran group, but the maximum difference of 0.7% at 30 days was not statistically significant (95% CI, –0.1% to 1.6%) (Figure 2). The same analysis of major bleeding shows an apparent increase in early events in the ximelagatran/warfarin group, with a nonsignificant difference of 0.6% at 30 days (95% CI, –1.3% to 0.1%) (Figure 2). The resulting cumulative risk for the combined end point of recurrent venous thromboembolism or major bleeding was similar over time for both groups.

Adverse Events
The incidences of alanine aminotransferase levels that increased to greater than 3 times the upper limit of normal in the ximelagatran and enoxaparin/warfarin groups were 9.6% (n = 119) and 2.0% (n = 25), respectively. In a post hoc analysis including local laboratory data collected outside protocol specifications or posttreatment, 8 and 2 additional patients with alanine aminotransferase levels increased to greater than 3 times the upper limit of normal were identified in the ximelagatran and enoxaparin/warfarin groups, for a total of 127 patients [10.2%] and 27 patients [2.2%], respectively. In the ximelagatran-treated patients, peak elevations of alanine aminotransferase levels were reached after a median of 84 days (second and third quartiles, 64-116 days). Treatment was discontinued in 76 patients and continued in 43 patients. Alanine aminotransferase values normalized during follow-up in 68 of the 76 patients discontinuing and in 36 of the 43 patients continuing ximelagatran, with a similar recovery pattern. Normalization occurred after a median of 74 days (second and third quartiles, 45-114 days). Of the remaining 15 patients, 1 died (see below), 1 had alcohol abuse as a probable explanation of enzyme elevation, the results of 10 had returned to below twice the upper limit of normal at the latest observation, and 3 were lost to follow-up. Of the 25 patients in the enoxaparin/warfarin group, normalization during follow-up was documented in 23 patients but not in the remaining 2. In the ximelagatran group, there was 1 patient with fatal outcome of hepatitis B not known at the time of inclusion and 1 patient with suspected study drug–induced hepatitis that resolved after discontinuation of treatment. Most of the elevations in enzyme levels occurred without any associated clinical symptoms.

In the ximelagatran group, 2 additional fatal outcomes occurred follow-
ing investigator-reported serious hepatobiliary adverse events. One patient had hepatorenal syndrome. The other patient had cholecystitis, which revealed cholecystic carcinoma at surgery. In the enoxaparin/warfarin group, 2 patients died following hepatobiliary serious adverse events: 1 with hepatitis C not known at inclusion, the other with pancreatic carcinoma. None of these 4 cases had alanine aminotransferase levels increased to greater than 3 times the upper limit of normal.

Locally reported serious coronary events, with symptomatic myocardial ischemia warranting hospitalization, were noted in 10 of 1240 ximelagatran-treated patients compared with 1 of 1249 enoxaparin/warfarin–treated patients (P = .006). Four of the 10 events in the ximelagatran group were diagnosed as myocardial infarctions (1 fatal), compared with none in the enoxaparin/warfarin group. One of the myocardial infarctions in the ximelagatran group occurred 6 weeks after discontinuation of ximelagatran and switching of study therapy to aspirin and open-label warfarin, during investigation of peripheral vascular disease.

COMMENT

This study, the largest to date of anticoagulant therapy in patients with acute deep vein thrombosis, shows that during 6 months of treatment, oral ximelagatran, 36 mg twice daily, administered without coagulation monitoring or dose adjustment, is as effective as enoxaparin followed by warfarin, with a similar bleeding risk.

The overall recurrence and major bleeding rates over 6 months in our study were somewhat lower than the rates reported over 3 months of follow-up for similar studies (4%-5%10-21 and 2%-3%, respectively).19,22 It is possible that the complexity of the study introduced a selection bias, leading to the enrollment of patients with lower risks of recurrent venous thromboembolism and bleeding. However, except for a somewhat lower proportion of patients with cancer, a group that has higher recurrence and bleeding rates,22,23 patient characteristics are consistent with those seen in other studies.19 and more than one fifth of patients had previous venous thromboembolism and one third had pulmonary embolism.

The choice of the prespecified non-inferiority efficacy margin (4%) was based on a higher expected primary event rate than what was actually observed. However, the upper limit of the CI for the observed absolute difference in event rate was 1.3% at 6 months, which is considered clinically acceptable and consistent with noninferiority of ximelagatran compared with standard treatment.

To ensure validity of results, patients and their physicians and nurses were blinded as to study group, and an independent adjudication committee confirmed all outcomes. Strict adjudication criteria may have contributed to the low recurrence rate. An increase in the sample size to achieve narrower CIs around the point estimates for recurrence and bleeding maintained internal validity. Treatment was given for at least 6 months, consistent with common clinical practice.

The 6-month treatment with ximelagatran was generally well tolerated except for the development of increased levels of alanine aminotransferase in about 10% of patients, leading to more frequent discontinuation of study drug in the ximelagatran group. Elevated levels of alanine aminotransferase have been observed in 6% to 13% of patients in previous studies of prolonged ximelagatran use.10,11,24 The mechanism is under investigation but currently is not known, and the clinical importance of the elevation of liver enzymes remains to be fully determined. Of 43 patients who experienced alanine aminotransferase levels increased to more than 3 times the upper limit of normal and who continued treatment with ximelagatran, 36 showed normalized levels during follow-up. Normalization while continuing therapy has also been reported in other studies.10,11 It is not yet certain on the basis of this study how frequently liver enzyme levels need to be tested.

The retrospective observation that there appeared to be significantly more acute coronary events in ximelagatran-treated patients is unexplained. This will be explored in further studies, with prospective evaluation and independent adjudication of suspected events.

The results of this study were achieved using a fixed oral dose of ximelagatran, 36 mg twice daily. During the early treatment period there was an apparent difference in recurrent venous thromboembolism favoring the enoxaparin/warfarin group, and of major bleeding favoring the ximelagatran group; however, in a post hoc analysis, neither of these differences was statistically significant.

In conclusion, for the initial and prolonged treatment of deep vein thrombosis, direct thrombin inhibition with oral ximelagatran, 36 mg twice daily, was as effective as enoxaparin/warfarin, without the need for coagulation monitoring or dose adjustment. The mechanism and clinical importance of the increased liver enzyme levels in ximelagatran-treated patients requires further evaluation. Prospective assessment of coronary events in future studies is warranted.

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Author Contributions: Drs Fiessinger, Huisman, and Ginsberg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: Fiessinger, Huisman, Ginsberg, Davidson, Bounaumeaux, Francis, Eriksson, Ginsberg.

Analysis and interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding; study supervision: Fiessinger, Huisman, Davidson, Bounaumeaux, Francis, Eriksson, Ginsberg.

Acquisition of data: Fiessinger, Huisman, Davidson, Bounaumeaux, Francis, Eriksson, Ginsberg.

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XIMELAGATRAN VS LMWH AND WARFARIN FOR DEEP VEIN THROMBOSIS

Davidson, Francis, Eriksson, Lundström, Berkowitz, Nyström, Dufour, Comp, Ginsberg. Statistical analysis: Nyström. Administrative, technical, or material support: Berkowitz, Thorsén.

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Role of the Sponsor: The Joint Executive Committee was entirely responsible for the design, conduct, and analyses of the study. The committee had no sponsor-appointed members. Four members of the committee were from the sponsor (Dr Lundström, Dr Berkowitz [medical input to trial design, conduct, and interpretation], Mr Nyström [medical input to trial design data analysis, and interpretation], and Ms Tedroff [collection, management, and analysis of study data]). The sponsor, AstraZeneca, held the data and performed the data analysis and made the decision to submit the manuscript. This committee had no free access to all primary data and had full independence in deciding what to publish. Dr Lundström, Dr Berkowitz, Mr Nyström, and Ms Thorsén were involved in the preparation, review, and approval of the manuscript.

Independent Statistical Analysis: Dr Hans Wedel (Professor of Epidemiology and Biostatistics, Nordic School of Public Health, Stockholm, Sweden) performed an independent statistical review of the study and validated methodology, primary and secondary analyses performed, and results obtained.


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XIMELAGATRAN VS LMWH AND WARFARIN FOR DEEP VEIN THROMBOSIS

Just don’t give up trying to do what you really want to do. Where there is love and inspiration, I don’t think you can go wrong.
—Ella Fitzgerald (1917-1996)