

ORIGINAL ARTICLE

Secondary Prevention of Venous Thromboembolism with the Oral Direct Thrombin Inhibitor Ximelagatran

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ABSTRACT

BACKGROUND

For many patients with venous thromboembolism, secondary prevention with vitamin K antagonists is not extended beyond six months, since the risk of recurrence may be outweighed by the risk of major bleeding.

METHODS

In a double-blind, multicenter trial, we randomly assigned 1233 patients with venous thromboembolism who had undergone six months of anticoagulant therapy to extended secondary prevention with the oral direct thrombin inhibitor ximelagatran (24 mg) or placebo, taken twice daily, for 18 months without monitoring of coagulation. At base line, bilateral ultrasonography of the legs and perfusion lung scanning were performed.

RESULTS

Data from 612 patients in the ximelagatran group and 611 in the placebo group were analyzed. The occurrence of the primary end point, symptomatic recurrent venous thromboembolism, was confirmed in 12 patients assigned to ximelagatran and 71 patients assigned to placebo (hazard ratio, 0.16; 95 percent confidence interval, 0.09 to 0.30; $P < 0.001$). Death from any cause occurred in 6 patients in the ximelagatran group and 7 patients in the placebo group, and bleeding occurred in 134 patients and 111 patients, respectively (hazard ratio, 1.19; 95 percent confidence interval, 0.93 to 1.53; $P = 0.17$). The incidence of major hemorrhage was low (six events in the ximelagatran group and five in the placebo group), and none of these hemorrhages were fatal. The cumulative risk of a transient elevation of the alanine aminotransferase level to more than three times the upper limit of normal was 6.4 percent in the ximelagatran group, as compared with 1.2 percent in the placebo group ($P < 0.001$).

CONCLUSIONS

Oral ximelagatran was superior to placebo for the extended prevention of venous thromboembolism. There was no significant increase in the frequency of bleeding complications, but there was an increase in the number of patients with a transient elevation in the alanine aminotransferase level.

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DESPITE PROGRESS IN DIAGNOSIS AND treatment, venous thromboembolism continues to be associated with high morbidity and mortality.¹ Previous studies have shown a risk of recurrence after six months of anticoagulant therapy of 5 to 7 percent per year.^{2,3} The rate of recurrence can be reduced with the use of vitamin K antagonists such as warfarin,⁴⁻⁷ but such therapy is associated with an annual risk of major hemorrhage of 3 to 4 percent.⁴⁻⁶ Treatment with lower-intensity anticoagulants for a longer period may reduce the risk of hemorrhage,⁷ although this hypothesis is controversial.⁸ Routine monitoring of coagulation and frequent adjustments of the dose are required during treatment with vitamin K antagonists. The optimal duration of secondary prevention remains a matter of debate. There is currently no general recommendation that therapy be continued beyond six months in patients who have had a first event but have no major risk factors for recurrent venous thromboembolism.⁹

Ximelagatran, a novel oral direct thrombin inhibitor, is rapidly absorbed and converted to its active form, melagatran, with bioavailability of approximately 20 percent.^{10,11} Melagatran has predictable and reproducible pharmacokinetic and pharmacodynamic properties, with a low binding affinity for plasma proteins and mainly renal clearance.¹⁰⁻¹² Animal models of thrombosis¹³ and clinical data¹⁴ have indicated that melagatran has a wider therapeutic window than warfarin. Oral ximelagatran administered at a fixed dose of 24 mg twice daily without monitoring of coagulation has been studied both for the postoperative prevention of venous thromboembolism¹⁵⁻¹⁷ and for the immediate treatment of deep venous thrombosis.¹⁴ We conducted a study to evaluate the long-term efficacy and safety of treatment with fixed-dose oral ximelagatran initiated after six months of standard anticoagulant therapy for venous thromboembolism.

METHODS

STUDY PATIENTS

Patients 18 years of age or older were eligible for inclusion if they had had symptomatic, objectively confirmed deep venous thrombosis of the leg or pulmonary embolism and had been treated with anticoagulant therapy for six months without subsequent recurrence. The main criteria for exclusion were an indication for continuous anticoagulant

treatment, a condition associated with an increased risk of bleeding, a hemoglobin concentration of less than 9.0 g per deciliter, a platelet count of less than 90,000 per cubic millimeter, pregnancy, lactation, serious illness with expected survival of less than 18 months, renal impairment (indicated by an estimated creatinine clearance of less than 30 ml per minute), clinically significant liver disease, or persistent elevation of the aminotransferase level to more than three times the upper limit of normal.

Concomitant treatment with other anticoagulants or fibrinolytic agents was not permitted. Antiplatelet drugs were also not permitted, except for aspirin in doses of up to 500 mg daily or higher doses for occasional use. Nonsteroidal antiinflammatory drugs were permitted if their half-life was less than seven hours.

STUDY DESIGN

We conducted a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The primary objective was to assess the time to a confirmed new venous thromboembolic event in order to establish the efficacy of ximelagatran as compared with placebo for the extended secondary prevention of venous thromboembolism after six months of anticoagulant therapy. A secondary objective was to estimate overall mortality and other measures of safety, with special attention to bleeding episodes.

Patients could be enrolled in the study at any time during the six months of standard anticoagulant therapy. Patients were stratified at randomization, approximately six months after the index venous thromboembolic event (range, five to seven), according to the presence or absence of active cancer during the previous five years. With the use of a computer-generated randomization list, patients were randomly assigned in equal proportions to receive either 24 mg of ximelagatran (Exanta, AstraZeneca) or placebo tablets orally twice daily. Patients discontinued standard anticoagulant therapy but were not to begin treatment with the study medication until the international normalized ratio was less than 1.5.

Study visits were scheduled 2 weeks after randomization and at 3, 6, 9, 12, 15, and 18 months. The month 18 visit included the discontinuation of treatment with the study drug and was followed by an additional visit two weeks later. The treatment period was from randomization until 18 months or, for patients who discontinued treatment with the

study medication prematurely, until a follow-up visit that occurred 2 weeks after discontinuation. The protocol was later amended to include visits at one, two, four, and five months so that samples could be collected more frequently for the measurement of aminotransferases. Visits included questions about new symptoms of venous thromboembolism, bleeding, and any other clinical events, as well as counts of tablets in order to determine the level of compliance.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the regional ethics committees in the participating countries; written informed consent was obtained from all patients. One investigator from each country participated in the steering committee. The executive committee, comprising two university-affiliated external consultants and three members from the sponsoring company, AstraZeneca, had ultimate responsibility for the performance of the study.

The sponsor held the data and performed the data analysis. All five members of the executive committee wrote this article and had full and free access to primary data. The authors had full independence in deciding whether to publish the results, and, in their opinion, no relevant data have been withheld from this article.

EFFICACY

At base line, perfusion lung scanning and standardized bilateral ultrasonography of the legs were performed to increase the accuracy of diagnosis of suspected recurrent thromboembolic events. Patients with clinically suspected deep venous thrombosis were required to undergo repeated ultrasonography and, if the results were still inconclusive, venography. The occurrence of deep venous thrombosis was verified if a common femoral or popliteal venous segment became newly noncompressible or if the diameter of a compressed residual thrombus increased by at least 3 mm from base line. Patients with suspected pulmonary embolism underwent ventilation-perfusion scanning and, if possible, bilateral compression ultrasonography. The revised classification criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis¹⁸ were used by the end-point committee, but results on spiral computed tomography (CT), pulmonary angiography, or autopsy were also acceptable for the diagnosis of pulmonary embolism. A ventilation-perfu-

sion scan assessed as class III (indicating a high probability of embolism), or class II (indicating an intermediate probability of embolism) together with the occurrence of a new deep venous thrombosis, was considered to be diagnostic. All suspected recurrent events, including those that had been deemed locally not to represent recurrent venous thromboembolism, were adjudicated by a central, independent, end-point committee that was unaware of the treatment-group assignments.

SAFETY

Major bleeding was defined as a fatal hemorrhage, a clinically overt hemorrhage associated with a decrease in the hemoglobin level of at least 20 g per liter or a need for the transfusion of at least 2 units of blood, a retroperitoneal or intracranial hemorrhage, or any bleeding event warranting permanent cessation of the study treatment. All other bleeding events were regarded as minor. The end-point committee adjudicated all the bleeding events that were reported to be major. They also classified deaths as due to venous thromboembolism, due to bleeding, or due to other causes. Autopsy was recommended in the cases of all patients who died. An independent safety committee closely surveyed the safety aspects of the study.

LABORATORY ANALYSES

Blood samples for hematologic and clinical chemical analysis and urine and fecal samples for the measurement of hemoglobin were collected throughout the study. Samples used to assess the patient's risk of thrombosis were analyzed at a central laboratory, but these results were not made available to the investigators during the study and are not reported here.

STATISTICAL ANALYSIS

It was assumed that, during the 18-month study period, a recurrence of venous thromboembolism would occur in 6 percent of the patients in the placebo group and 2 percent of those in the ximelagatran group. Under the assumption that there would be a dropout rate of 25 percent because of the duration of the treatment period, 600 patients were needed in each treatment group in order to obtain a statistical power of 90 percent, at a two-sided significance level of 0.05.

The cumulative risk of events was estimated with the use of the Kaplan-Meier procedure. The haz-

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Ximelagatran Group (N=612)	Placebo Group (N=611)
Age — yr	56±15	58±15
Range	18–87	19–90
Sex — no.		
Male	331	313
Female	281	298
Weight — kg	82±16	82±16
Range	45–145	47–150
Body-mass index†	28±5	28±5
Creatinine clearance — ml/min	114±42	110±41
Type of index event — no. (%)		
Deep venous thrombosis only	406 (66)	389 (64)
Pulmonary embolism only	106 (17)	93 (15)
Both deep venous thrombosis and pulmonary embolism	100 (16)	128 (21)
First event	534 (87)	514 (84)
Recurrent event‡	78 (13)	97 (16)
Location of deep venous thrombosis — no. (%)§		
Proximal	347 (69)	356 (69)
Distal only	158 (31)	161 (31)
Distal with pulmonary embolism	24 (15)	33 (20)
Distal and recurrent	18 (11)	27 (17)
Cancer — no. (%)	34 (6)	32 (5)

* Plus-minus values are means ±SD. Data on the type of index event were missing for one patient in the placebo group; data on the location of deep venous thrombosis were missing for one patient in the ximelagatran group.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Patients had had one to four previous events.

§ Of the patients with deep venous thrombosis, 100 in the ximelagatran group and 128 in the placebo group also had pulmonary embolism.

ard ratios for recurrent venous thromboembolism, death, and bleeding events were estimated with the use of the Cox regression model, presented with 95 percent confidence intervals and P values. The comparison of the treatment groups in terms of elevations in the aminotransferase level was based on logistic regression, and the estimated odds ratio is reported, since an assumption of proportional hazards was not justified. The influence of potential prognostic factors on the treatment effect with respect to recurrent venous thromboembolism was analyzed separately for each factor with the use of Cox regression analysis; the treatment, the prognostic factor, and the interaction between the two were included in the model for each analysis. All analyses

presented here are based on the treatment period for the intention-to-treat population, which was defined as all patients for whom any data were available after randomization and who took at least one dose of the study medication.

RESULTS

STUDY PATIENTS

Between November 1999 and October 2000, a total of 1233 patients underwent randomization at 142 centers in 18 countries, including 982 patients (80 percent) in Europe and the remainder in Argentina, Brazil, Canada, Israel, Mexico, and South Africa. Of the 1356 patients originally enrolled, 123 did not undergo randomization: 50 because they did not meet the eligibility criteria, 44 because they withdrew consent, 5 because they were lost to follow-up, 3 because of adverse events, and 21 for other reasons. Of the patients who underwent randomization, 617 were assigned to treatment with ximelagatran and 616 were assigned to placebo. Five patients in each group were excluded from the intention-to-treat population, since no data were available for them after randomization. A total of 498 patients in the ximelagatran group and 516 patients in the placebo group were included in the per-protocol analysis. The outcomes were similar in the intention-to-treat and per-protocol populations; therefore, this report describes only the intention-to-treat population. The base-line characteristics were similar in the two groups (Table 1). The weights of patients were widely distributed, with 86 of the 612 patients in the ximelagatran group (14 percent) and 85 of the 611 in the placebo group (14 percent) weighing more than 100 kg.

TREATMENT

Eighty-seven percent of the patients received their first dose of study medication within seven days after the cessation of their previous anticoagulant therapy. The median duration of treatment with the study medication was 505 days. Overall compliance with the treatment regimen was similar in the two treatment groups: 91 percent of the patients took more than 90 percent of the assigned tablets, and only 10 patients (1 percent) took less than 70 percent.

Inhibitors of platelet aggregation, predominantly aspirin, were taken by 7 percent of the patients in the ximelagatran group and 9 percent of those in the

placebo group at some time during the study-treatment period; nonsteroidal antiinflammatory drugs were taken by 17 percent and 16 percent of the patients, respectively.

EFFICACY

Recurrent venous thromboembolism was clinically suspected in 224 patients. After objective testing and central adjudication, recurrence was ruled out in 66 patients in the ximelagatran group and 75 patients in the placebo group. Centrally confirmed venous thromboembolism occurred in 12 patients in the ximelagatran group and 71 patients in the placebo group (Table 2). As compared with placebo ($P < 0.001$), ximelagatran significantly reduced the rate of recurrence of venous thromboembolic events, with a continuing reduction in the risk of recurrence over time (Fig. 1). The estimated cumulative risk of an event during the 18 months of treatment was 2.8 percent in the ximelagatran group and 12.6 percent in the placebo group ($P < 0.001$) (Table 3).

Six patients in the ximelagatran group died (two from cancer, two from sepsis, one from myocardial infarction, and one by suicide), and seven patients in the placebo group died (three from pulmonary embolism, three from cancer, and one from myocardial rupture after myocardial infarction). The deaths were distributed evenly over the study period. The hazard ratio for death from any cause is shown in Table 3.

Subgroup analyses demonstrated that among patients receiving placebo, the risk of recurrent venous thromboembolism was lower among women than among men (hazard ratio, 0.40; 95 percent confidence interval, 0.24 to 0.67) and higher among patients with more than one previous venous thromboembolic event than among those with only one previous event (hazard ratio, 1.73; 95 percent confidence interval, 1.00 to 2.99). The risk reduction was similar in all subgroups, and no interactions were observed between potential prognostic factors, such as age, sex, weight, estimated creatinine clearance, type of initial thromboembolic event, or presence or absence of cancer, and the effect of ximelagatran.

SAFETY

Major bleeding events occurred in six patients in the ximelagatran group (gastrointestinal bleeding in three, gynecological bleeding in two, and hematuria in one); such events occurred in five patients in the

Table 2. Location of the Recurrent Thromboembolic Events.

Event	Ximelagatran Group (N=12)	Placebo Group (N=71)
	no. (%)	
Pulmonary embolism only	2 (17)	15 (21)
Deep venous thrombosis only	10 (83)	48 (68)
Deep venous thrombosis and pulmonary embolism	0	8 (11)
Proximal deep venous thrombosis	6 (50)	42 (59)
Distal deep venous thrombosis only	4 (33)	13 (18)
Thrombosis in an arm vein	0	1 (1)

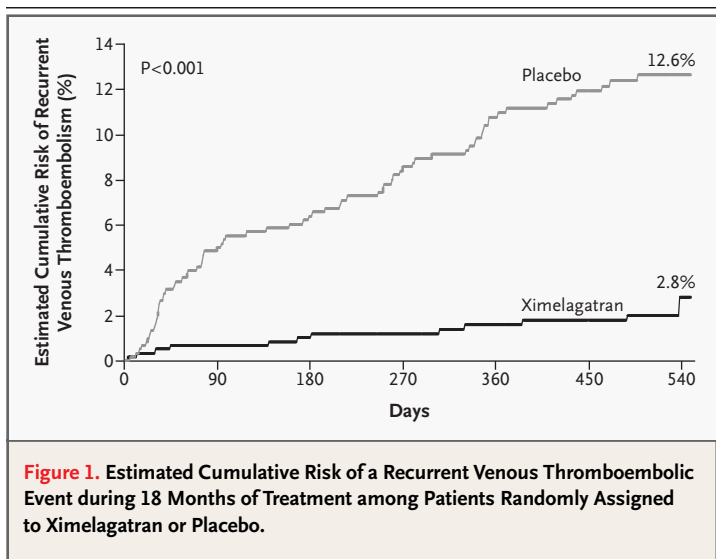


Figure 1. Estimated Cumulative Risk of a Recurrent Venous Thromboembolic Event during 18 Months of Treatment among Patients Randomly Assigned to Ximelagatran or Placebo.

placebo group (subdural bleeding in one, subarachnoid bleeding in one, vitreous-body bleeding in one, gastrointestinal bleeding in one, and gynecologic bleeding in one). None of these events were fatal. A blood transfusion was required in three of the patients with major bleeding events in the ximelagatran group and one of the patients in the placebo group. Hematuria was observed in more patients in the ximelagatran group than in the placebo group (6.2 percent vs. 3.9 percent, $P = 0.07$), but 40 percent of these events were limited to microscopic hematuria. The hazard ratios for a major bleeding event and for any bleeding event are shown in Table 3, and the estimated cumulative risk over time for any bleeding event is shown in Figure 2.

There were no significant changes in serum biochemistry except for an increased incidence of ele-

Table 3. Efficacy and Safety Outcomes.

Outcome	Ximelagatran Group (N=612)	Placebo Group (N=611)	Hazard Ratio (95% CI)*
	<i>no. (%)</i> †		
Venous thromboembolism	12 (2.8)	71 (12.6)	0.16 (0.09–0.30)
Death from any cause	6 (1.1)	7 (1.4)	0.83 (0.28–2.46)
Venous thromboembolism, death, or both	18 (3.9)	75 (13.3)	0.23 (0.14–0.39)
Major bleeding	6 (1.1)	5 (1.3)‡	1.16 (0.35–3.80)
Major bleeding, minor bleeding, or both	134 (23.9)	111 (21.0)	1.19 (0.93–1.53)

* CI denotes confidence interval.

† The percentage represents the estimated cumulative risk over an 18-month period.

‡ One event that occurred during the last month of treatment affected the estimated risk in this group.

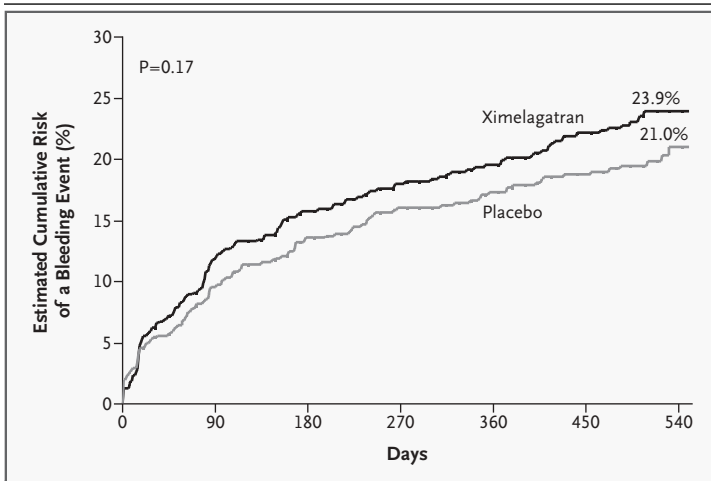


Figure 2. Estimated Cumulative Risk of a Major or Minor Bleeding Event during 18 Months of Treatment among Patients Randomly Assigned to Ximelagatran or Placebo.

ated aminotransferase levels in the ximelagatran group (Fig. 3). The incidence of an elevation in the alanine aminotransferase level to more than three times the upper limit of normal was 6.0 percent in the ximelagatran group (37 patients) and 1.0 percent in the placebo group (6 patients). The estimated cumulative risk of such an elevation at 4 months was 5.4 percent in the ximelagatran group and 0.2 percent in the placebo group; the corresponding figures at 18 months were 6.4 percent and 1.2 percent

(odds ratio, 6.5; 95 percent confidence interval, 2.7 to 15.5; $P < 0.001$).

In the ximelagatran group, the enzyme levels decreased with a similar time course whether the use of the drug was continued (in 24 patients; median time to normalization, 84 days) or discontinued (13 patients; median time to normalization, 129 days). The enzyme levels normalized in all but four patients in the ximelagatran group; two had known hepatitis with enzyme fluctuations before they were enrolled in the study, and two were asymptomatic but had levels that were 1.6 and 1.8 times the upper limit of normal at the last observation during the study period. There was no specific pattern of symptoms or signs in patients with elevated enzyme levels. We could not find any association between characteristics of the patients or concomitant medications and elevated enzyme levels.

DISCUSSION

In this randomized, double-blind study, we assessed the efficacy and safety of ximelagatran as compared with placebo for the extended secondary prevention of venous thromboembolism. After 6 months of anticoagulant therapy, treatment with a fixed oral dose of ximelagatran for an additional 18 months effectively prevented recurrences, with an incidence of bleeding similar to that in the placebo group and low overall mortality.

The initial diagnoses of venous thromboembolism were well documented. Ninety-seven percent of deep venous thromboses were diagnosed by venography, ultrasonography, or both, and 96 percent of pulmonary emboli were verified with lung scanning, pulmonary angiography, spiral CT, or some combination thereof. Since thrombi resolve with time, we performed ultrasonography of the legs and perfusion lung scanning before randomization to obtain a base-line assessment for use in the central adjudication of all suspected recurrent events. This strategy is similar to that used in a previous study of long-term anticoagulant therapy.⁵ Objective testing was required in the event of any clinically suspected recurrence. Of the suspected recurrences, 37 percent were confirmed on central evaluation, with a similar number ruled out in each of the two treatment groups. We therefore consider it unlikely that recurrences were missed.

Cancer is a major risk factor for thromboembolism.¹⁹ We included patients with cancer only when

the local investigator did not consider long-term anticoagulant therapy to be mandatory, which explains why there was a relatively low proportion of patients with cancer, as compared with other studies.²⁰ In 21 percent of the patients, the index event was isolated distal deep venous thrombosis, but 35 percent of the patients had pulmonary embolism, and 14 percent had more than one previous event, which indicates that ours was a population at moderate risk. This characterization is supported by the relatively high estimated cumulative risk of recurrence of 12.6 percent over 18 months in the placebo group, as compared with the 8.1 percent observed during a similar follow-up period in a previous trial.²

Secondary prevention with ximelagatran effectively reduced the cumulative risk of recurrence to 2.8 percent, with equal effect in subgroups that had risk factors for recurrence, including repeated previous thromboembolism, proximal deep venous thrombosis, or pulmonary embolism.² The hazard ratio for recurrence with ximelagatran as compared with placebo was 0.16, which is lower than the hazard ratio of 0.36 that was recently reported with low-intensity warfarin.⁷ In other studies, the incidence of recurrent venous thromboembolism among patients assigned to long-term treatment with standard-intensity warfarin was 2.6 percent over a 43-month period,⁴ 1.3 percent over a 10-month period,⁵ and 2.8 percent over a 9-month period.⁶ However, direct comparisons with previous studies are hampered by differences in study design or duration and intensity of follow-up^{4,6,7} or in the number of patients included.⁴⁻⁷

The mortality rate was low in both treatment groups, but three patients in the placebo group had a fatal pulmonary embolism, whereas no patients in the ximelagatran group did. In addition, the incidence of bleeding in the ximelagatran group was similar to that in the placebo group. The cumulative risk of major hemorrhage of approximately 1 percent over 18 months is low in comparison with the annual incidence of 3 to 4 percent observed with warfarin,⁴⁻⁶ but it is similar to that observed with low-dose warfarin.⁷ These results indicate that fixed-dose ximelagatran was well tolerated when used for the long-term secondary prevention of venous thromboembolism without monitoring of measures of coagulation.

An increase in the levels of liver aminotransfer-

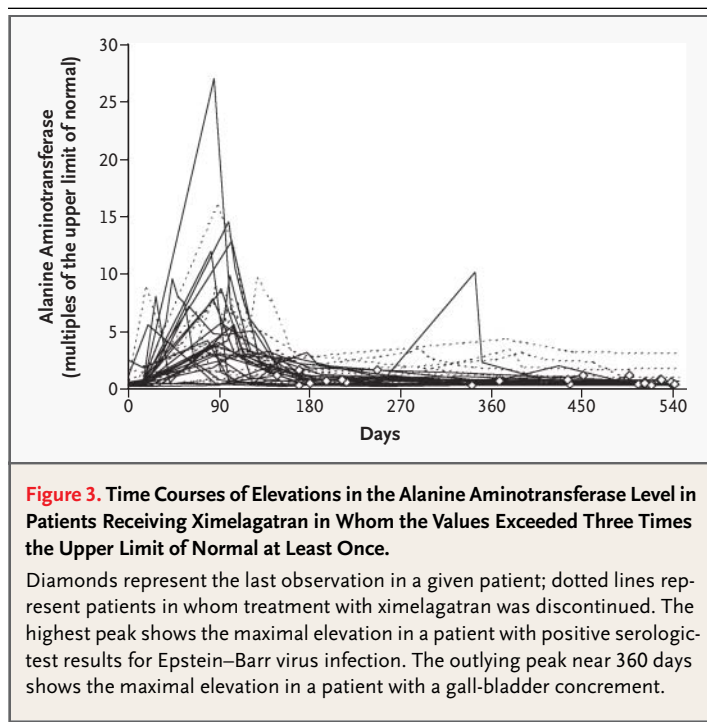


Figure 3. Time Courses of Elevations in the Alanine Aminotransferase Level in Patients Receiving Ximelagatran in Whom the Values Exceeded Three Times the Upper Limit of Normal at Least Once.

Diamonds represent the last observation in a given patient; dotted lines represent patients in whom treatment with ximelagatran was discontinued. The highest peak shows the maximal elevation in a patient with positive serologic-test results for Epstein–Barr virus infection. The outlying peak near 360 days shows the maximal elevation in a patient with a gall-bladder concrement.

ases during treatment with ximelagatran has previously been found to occur in a proportion of patients,²¹ as it did in our study. However, the increase in the incidence of elevations in the aminotransferase levels was transient and was restricted to the first four months of therapy. The aminotransferase elevations did not result in progressive hepatic dysfunction, and the levels decreased spontaneously whether treatment was continued or discontinued.

Long-term treatment with vitamin K antagonists, such as warfarin, is associated with disadvantages in terms of an increased risk of bleeding, a slow onset of action, and inconvenience. Unlike warfarin, ximelagatran has not been reported to have any clinically relevant interactions with food or with drugs metabolized by the cytochrome P-450 system.^{11,22} Our study demonstrates that long-term treatment with ximelagatran, without monitoring of coagulation or adjustments of the dose, offers a clinically meaningful reduction in the incidence of recurrent venous thromboembolism.

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APPENDIX

The THRIVE III Investigators included the following: *Executive Committee* — S. Schulman (chair), H. Eriksson (Study Coordinating Investigator), S. Billing Clason, T. Lundström, K. Wähländer; *Steering Committee* — National Coordinating Investigators: J.M. Ceresetto, R. Verhaeghe, F.H. de Abreu Maffei, J. Ginsberg, I. Muchová, S. Husted, R. Lassila, J.-N. Fiessinger, J. Harenberg, E. Bastounis, G. Sas, B. Brenner, C. Jerjes-Sánchez Díaz, P.M. Sandset, A.I. Kirienko, P. du Toit, J. Fontcuberta; *End-Point Committee* — A. Carlsson, L. Jarneborn, B. Persson, A. Thurin, J. Wallin; *Safety Committee* — F. Lindgärde, A. Odén, A. Rosengren; *Electrocardiogram Evaluator* — K. Caidahl; *Sponsor, AstraZeneca Research and Development, Mölndal, Sweden* — S. Billing Clason, T. Lundström, K. Wähländer, M. Kujacic, P. Nyström, U. Wall, L. Welin, M. Anderson, Halifax; *Argentina* (31 patients, 8 centers): S. Cerana, Rosario; J.M. Ceresetto, Buenos Aires; H. 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Harenberg, Mannheim; C. Hasslacher, Heidelberg; C.-H. Jebens, Jülich; J. Koepchen, Dortmund; H. Lawall, Dortmund; M. Offermann, Essen; J.-A. Schmidt-Lucke, Magdeburg; W. Sehnert, Herne; P. Spürk, Menden; *Greece* (17 patients, 3 centers): E. Bastounis, Athens; N. Doundoulakis, Athens; P. Panoussis, Athens; *Hungary* (147 patients, 10 centers): L. Abermann, Budapest; A. Czirágy, Budapest; C. Farsang, Budapest; A. Kovács, Szentes; J. Náfrádi, Szeged; J. Pátkay, Dunaujváros; A. Rednik, Veszprém; G. Sas, Budapest; A. Szépvölgyi, Szekesfehervár; S. Timár, Kecskemét; P. Vályi, Csorna; *Israel* (59 patients, 10 centers): A.S. Berliner, Tel Aviv; H. Bitterman, Haifa; B. Brenner, Haifa; M. Elias, Afula; D. Gavish, Holon; S. Gillis, Jerusalem; R. Hoffman, Haifa; M. Lahav, Kfar-Saba; M. Lishner, Kfar-Saba; G. Luggassy, Ashkelon; D. Varon, Tel-Hashomer; *Mexico* (62 patients, 3 centers): O. Brachet Ize, Guadalajara Jalisco; C. Jerjes-Sánchez Díaz, Monterrey; G.A. Ranero Juárez, Mexico City; *Norway* (58 patients, 6 centers): E. Brandt, Lillehammer; F. Gruber, Tromsø; H. Knutsen, Nordbyhagen; P.M. Sandset, Oslo; J.H. Solhaug, Oslo; A. Tveit, Bærum; *Russia* (39 patients, 3 centers): V.U. Bogatchev, Moscow; P.G. Brusov, Moscow; A.I. Kirienko, Moscow; *South Africa* (47 patients, 6 centers): P.J. du Toit, Johannesburg; J.M. Engelbrecht, Western Cape; G.D. le Roux, Roodepoort; F.D. Pienaar, Bloemfontein; P.A. Willcox, Cape Town; N.C. Wright, Sunninghill; *Spain* (43 patients, 13 centers): M.A. Cairóls, Barcelona; I. de Diego Salemskaya, Terrassa; J. Fontcuberta, Barcelona; J. García-Frade, Valladolid; M.J. Gutierrez-Pimentel, Granada; P. Marco-Vera, Alicante; J. Mateo, Barcelona; M. Monreal, Badalona; M.R. Quintana-Castilla, Baracaldo Bilbao; E. Rocha-Hernandez, Pamplona; F.J. Rodríguez-Martorell, Cadiz; C. Sedano, Santandreu; J. Tortosa, Valladolid; F. Velasco, Cordoba; *Sweden* (142 patients, 9 centers): J. Aagesen, Jönköping; J. Eriksson, Gothenburg; A. Hägg, Uppsala; T. Jonson, Alingsås; L. Lapidus, Gothenburg; P. Lindmarker, Stockholm; C.-G. Olsson, Lund; U. Säfvenberg, Uppsala; T. Wallén, Västerвик; J. Wallvik, Sundsvall.

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