ORIGINAL ARTICLE

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients

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ABSTRACT

BACKGROUND

Patients with acute medical illnesses are at prolonged risk for venous thrombosis. However, the appropriate duration of thromboprophylaxis remains unknown.

METHODS

Patients who were hospitalized for acute medical illnesses were randomly assigned to receive subcutaneous enoxaparin (at a dose of 40 mg once daily) for 10±4 days plus oral betrixaban placebo for 35 to 42 days or subcutaneous enoxaparin placebo for 10±4 days plus oral betrixaban (at a dose of 80 mg once daily) for 35 to 42 days. We performed sequential analyses in three prespecified, progressively inclusive cohorts: patients with an elevated D-dimer level (cohort 1), patients with an elevated D-dimer level or an age of at least 75 years (cohort 2), and all the enrolled patients (overall population cohort). The statistical analysis plan specified that if the between-group difference in any analysis in this sequence was not significant, the other analyses would be considered exploratory. The primary efficacy outcome was a composite of asymptomatic proximal deep-vein thrombosis and symptomatic venous thromboembolism. The principal safety outcome was major bleeding.

RESULTS

A total of 7513 patients underwent randomization. In cohort 1, the primary efficacy outcome occurred in 6.9% of patients receiving betrixaban and 8.5% receiving enoxaparin (relative risk in the betrixaban group, 0.81; 95% confidence interval [CI], 0.65 to 1.00; P=0.054). The rates were 5.6% and 7.1%, respectively (relative risk, 0.80; 95% CI, 0.66 to 0.98; P=0.03) in cohort 2 and 5.3% and 7.0% (relative risk, 0.76; 95% CI, 0.63 to 0.92; P=0.006) in the overall population. (The last two analyses were considered to be exploratory owing to the result in cohort 1.) In the overall population, major bleeding occurred in 0.7% of the betrixaban group and 0.6% of the enoxaparin group (relative risk, 1.19; 95% CI, 0.67 to 2.12; P=0.55).

CONCLUSIONS

Among acutely ill medical patients with an elevated D-dimer level, there was no significant difference between extended-duration betrixaban and a standard regimen of enoxaparin in the prespecified primary efficacy outcome. However, prespecified exploratory analyses provided evidence suggesting a benefit for betrixaban in the two larger cohorts. (Funded by Portola Pharmaceuticals; APEX ClinicalTrials.gov number, NCT01583218.)

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Patients who are hospitalized for acute medical illnesses such as pneumonia, stroke, and heart failure are at increased risk for venous thromboembolism.[1] Prolonged immobilization and risk factors such as an elevated D-dimer level, an age of 75 years or older, cancer, or a history of venous thromboembolism increase this risk.[2-5]

Randomized, controlled trials of parenteral anticoagulants versus placebo in such hospitalized medical patients have shown a reduction of more than 50% in the rate of venous thromboembolism, including fatal pulmonary embolism, without an increase in major bleeding.[6-10] Guidelines recommend the use of low-dose parenteral anticoagulants among patients at high risk for thromboembolism for 6 to 14 days but advise against extended-duration thromboprophylaxis after hospital discharge.[11] However, the risk of pulmonary embolism and deep-vein thrombosis remains markedly increased for at least the first month after hospital discharge.[12] In three previous trials — the Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) trial with enoxaparin, the Apixaban Dosing to Optimize Protection from Thrombosis (ADOPT) trial, and the Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin (MAGELLAN) trial — investigators did not identify an effective and safe treatment option during this vulnerable period.[5,13,14] Therefore, we undertook a randomized trial of betrixaban, an oral, direct factor Xa inhibitor, for extended thromboprophylaxis in acutely ill medical patients.

METHODS

STUDY DESIGN AND OVERSIGHT

The Acute Medically Ill VTE (Venous Thromboembolism) Prevention with Extended Duration Betrixaban (APEX) trial was a randomized, double-blind, double-dummy, active-controlled, multinational clinical trial.[15] The study was designed and supervised by an executive steering committee and sponsored by Portola Pharmaceuticals. Data were collected by Pharmaceutical Product Development, a contract research organization that was paid by the sponsor, and by the Duke Clinical Research Institute and Percutaneous–Pharmacologic Endoluminal Revascularization for Unstable Syndromes Evaluation (PERFUSE), two academic research organizations. All three organizations had access to the full database to verify and analyze the results. All the authors had full access to the data and analyses and contributed to the first and subsequent drafts of the manuscript. The authors vouch for the accuracy and completeness of the data and all analyses, as well as for the fidelity of this report to the trial protocol, available with the full text of this article at NEJM.org.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki and local regulations. The protocol was approved by the relevant local institutional review boards and ethics committees. Written informed consent was obtained from each patient before any study-specific procedures were performed.

PATIENTS, TREATMENTS, AND FOLLOW-UP

Patients were eligible if they were 40 years of age or older, had been hospitalized for less than 96 hours for a specified acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke), and had reduced mobility and specific risk factors for venous thromboembolism. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

During the course of the trial, and after consultation with and agreement by regulatory authorities, we modified the protocol to enrich the trial population for patients at high risk for venous thromboembolism. (Details are provided in the Methods section in the Supplementary Appendix.) These protocol changes, which were adopted on June 4, 2014, required the presence of an elevated D-dimer level or an age of at least 75 years as an entry criterion. We also modified the statistical analysis plan by establishing two cohorts within the overall study population. Cohort 1 included patients who had an elevated baseline D-dimer level (i.e., at least two times the upper limit of the normal range), and cohort 2 included the patients in cohort 1 plus those who were 75 years of age or older.[16] Local laboratory values of D-dimer were prespecified to define cohorts 1 and 2 for outcome analyses. The results of central laboratory testing of D-dimer performed with the use of STA-Liatest D-Di (Stago) were used to define cohorts 1 and 2 in separate prespecified exploratory analyses.

We used permuted blocks to stratify eligible patients according to geographic region (North America, Europe, Latin America, and Asia), entry criteria (enrolled in cohort 1 or not enrolled in cohort 1), and criteria for the dose of anticoagulants (renal insufficiency [creatinine clearance, ≥15 ml and <30 ml per minute], receipt of a concomitant strong P-glycoprotein inhibitor [i.e., amiodarone, verapamil, or quinidine, which can double the betrixaban exposure] without severe renal insufficiency, or neither) for a total of 24 strata.

An interactive voice-response system was used to randomly assign patients to receive one of two regimens: subcutaneous enoxaparin (at a dose of 40 mg once daily) for 10±4 days plus oral betrixaban placebo once daily for 35 to 42 days; or subcutaneous enoxaparin placebo once daily for 10±4 days plus oral betrixaban (at a loading dose of 160 mg for the first dose and then 80 mg once daily for 35 to 42 days). Patients with severe renal insufficiency received 50% of the prespecified dose of each study medication (i.e., 20 mg of enoxaparin or a loading dose of 80 mg of betrixaban and then 40 mg once daily). Patients who were receiving a concomitant P-glycoprotein inhibitor received a reduced dose of betrixaban (40 mg once daily).

During follow-up, clinicians were instructed to confirm clinically suspected cases of deep-vein thrombosis by means of ultrasonography or other vascular-imaging technique and to confirm clinically suspected pulmonary embolism on computed tomography, a ventilation–perfusion lung scan, pulmonary angiography, or autopsy. In patients without clinically confirmed venous thromboembolism, mandatory ultrasonography was performed for the detection of asymptomatic deep-vein thrombosis after the administration of the last dose of a study medication or matching placebo between day 35 and day 42.[15] All the patients were followed for 30±5 days after the assessment on day 42.

OUTCOME MEASURES

All outcomes were assessed by an independent, central end-point adjudication committee whose members were unaware of treatment assignments. There were two such committees — one for symptomatic outcomes (located at Duke Clinical Research Institute) and one for asymptomatic ultrasonographic outcomes (located at EZUS Lyon of Université Claude Bernard Lyon, France).

The primary efficacy outcome was a composite of asymptomatic proximal deep-vein thrombosis between day 32 and day 47, symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death from venous thromboembolism between day 1 and day 42. The two major secondary efficacy outcomes were a composite of symptomatic venous thromboembolism through day 42 (death from venous thromboembolism, nonfatal pulmonary embolism, or symptomatic deep-vein thrombosis) and a composite of asymptomatic proximal deep-vein thrombosis between day 32 and day 47, symptomatic deep-vein thrombosis (proximal or distal), nonfatal pulmonary embolism, or death from any cause through day 42.

The principal safety outcome was the occurrence of major bleeding at any point until 7 days after the discontinuation of all study medications. Bleeding events were classified according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) as major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding.[17,18] Definitions of all outcome events are provided in the Supplementary Appendix. All outcome events in the trial protocol are provided in Table S1 in the Supplementary Appendix and categorized according to whether the events are included in this report.

STATISTICAL ANALYSIS

Plans for the statistical analysis have been reported previously[15,16] and are available at NEJM.org. The three cohorts that were included in the efficacy analysis were prespecified in a procedure with a fixed hierarchical sequence to adjust for the type I error rate.[19] If betrixaban was superior to enoxaparin with respect to the primary efficacy outcome in cohort 1 (at an alpha level of 0.05), the trial was considered to have met its primary end point, and superiority with respect to the primary efficacy outcome was tested in cohort 2. If betrixaban was superior to enoxaparin in cohort 2, superiority with respect to the primary efficacy outcome was then evaluated in the overall study population. Subsequent analyses of the secondary end points were likewise conditioned on superiority with respect to the primary effi-

cacy outcome. If such alpha thresholds were not met, subsequent prespecified analyses were considered to be exploratory.

Patients were eligible to be included in the efficacy analyses if they had received at least one dose of a study medication and had an adequate assessment of venous thromboembolism. In addition, we used the method of Quan et al.[20] in sensitivity analyses to impute data for patients who did not have an adequate assessment of venous thromboembolism. Patients were eligible for the safety analyses if they had received at least one dose of an active study medication. For all efficacy outcomes, we used a Cochran–Mantel–Haenszel model to estimate the risk ratio of the incidence rates (betrixaban vs. enoxaparin), stratified according to two randomization factors: an elevated D-dimer level at baseline (as assessed in a local laboratory) and the criteria for the dose of anticoagulants (severe renal dysfunction, receipt of a concomitant P-glycoprotein inhibitor, or neither). Bleeding events were analyzed without stratification. All statistical tests were two-sided with a type I error rate of 5.0%; two-sided 95% confidence intervals were calculated. Subgroup analyses were presented as forest plots for subgroup risk ratios and confidence intervals; statistical tests of interaction were used. A description of the sample-size calculation is provided in the Methods section in the Supplementary Appendix.

RESULTS

STUDY POPULATIONS

From March 2012 through November 2015, we screened 8589 patients at 460 sites in 35 countries. Of these patients, 7513 were found to be eligible to participate in the study and underwent randomization (3759 in the betrixaban group and 3754 in the enoxaparin group) (Fig. 1). The characteristics of the patients at baseline, the frequency of acute medical conditions, and risk factors for venous thromboembolism were similar in the two groups (Table 1).

The definitions of the analysis populations are provided in Table S2 in the Supplementary Appendix. A total of 72 patients (1.0% of those who underwent randomization) were excluded from all analyses because they did not receive a study drug, and 1155 patients (15.4% of those who underwent randomization) were excluded from the efficacy analyses because they did not have a symptomatic event associated with venous thromboembolism and did not undergo ultrasonography between day 32 and day 47. Comparisons of the baseline characteristics of the patients who were included in each of the efficacy analysis populations are provided in Tables S3, S4, and S5 in the Supplementary Appendix. The median duration of active treatment was 36 days (interquartile range, 34 to 39) in the betrixaban group and 9 days (interquartile range, 7 to 13) in the enoxaparin group.

EFFICACY OUTCOMES

The primary outcome and its components in each of the trial cohorts are shown in Table 2. In cohort 1, the primary efficacy outcome occurred in 6.9% of the betrixaban group and 8.5% of the enoxaparin group (relative risk in the betrixaban group, 0.81; 95% confidence interval [CI], 0.65 to 1.00; P=0.054). This first test in the sequence of cohorts did not meet the prespecified threshold for statistical significance; therefore, all subsequent prespecified efficacy outcomes were considered to be exploratory and were not used to draw conclusions regarding statistical significance.

In cohort 2, the primary efficacy outcome occurred in 5.6% of the betrixaban group and 7.1% of the enoxaparin group (relative risk, 0.80; 95% CI, 0.66 to 0.98; P=0.03). In the overall population, the primary efficacy outcome occurred in 5.3% and 7.0% of the patients, respectively (relative risk, 0.76; 95% CI, 0.63 to 0.92; P=0.006). In sensitivity analyses in which we used imputation to account for missing data, similar results were obtained in cohorts 1 and 2 (Table S6 in the Supplementary Appendix). When we defined cohorts 1 and 2 using central laboratory D-dimer values, the use of betrixaban was associated with a lower rate of the primary outcome in all analyses (Table S7 in the Supplementary Appendix). There was no evidence of heterogeneity with respect to the primary outcome according to cohort or in the prespecified subgroups (Figs. S1, S2, and S3 in the Supplementary Appendix).

The key secondary end points for each cohort are provided in Table 2. In the overall population, the first secondary efficacy outcome, symptomatic venous thromboembolism, occurred in

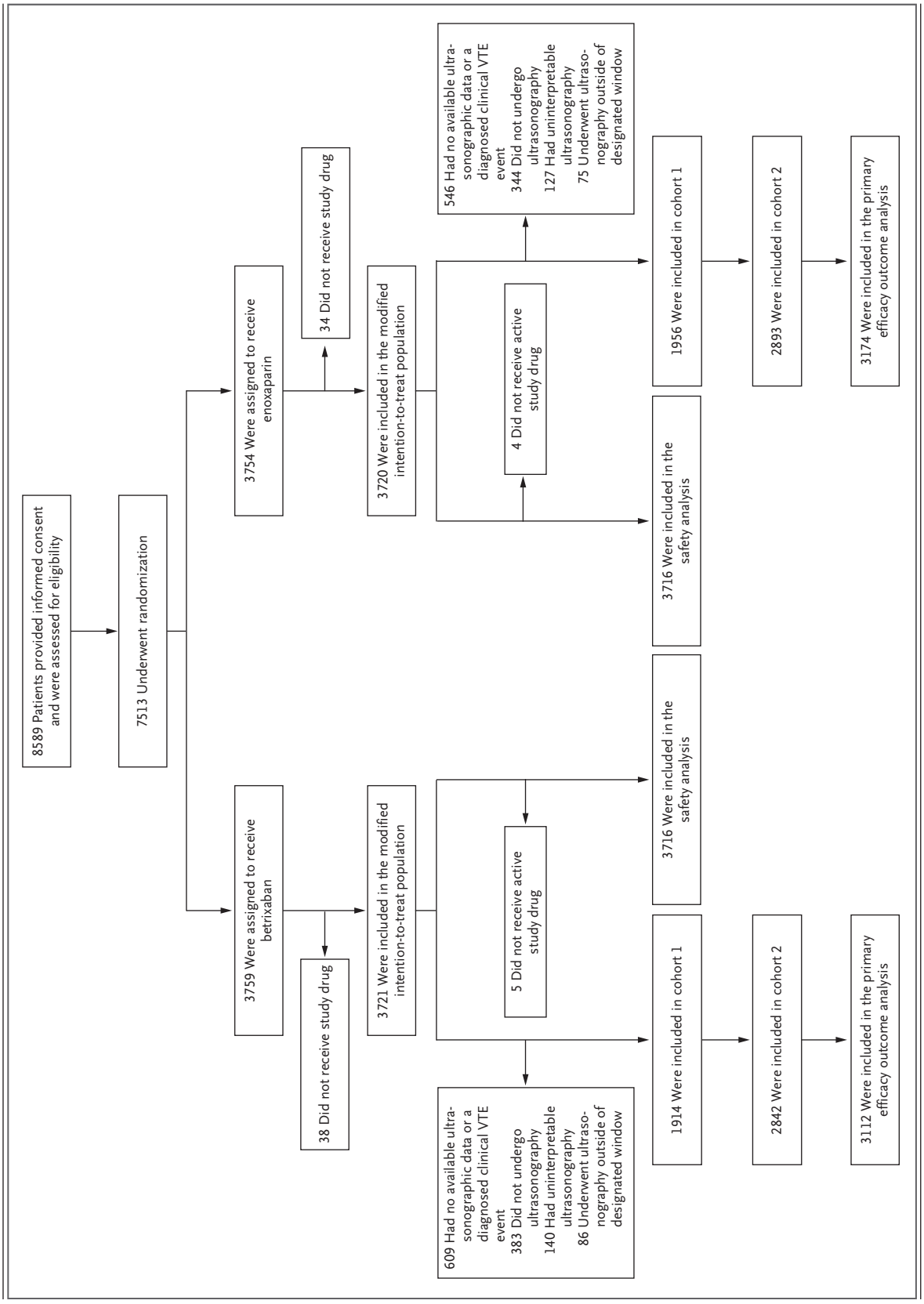

Figure 1 (facing page). Enrollment, Reasons for Exclusion, and Outcomes.

The modified intention-to-treat population included all the patients who received at least one dose of a study medication. The first secondary efficacy outcome (symptomatic venous thromboembolism) was analyzed in this population of patients (3721 in the betrixaban group and 3720 in the enoxaparin group). Among the patients in the modified intention-to-treat population, 609 in the betrixaban group and 546 in the enoxaparin group had no available ultrasonographic data and did not have a fatal or symptomatic thromboembolic event; these patients were excluded from the main efficacy analysis. Cohort 1 included patients who had an elevated baseline D-dimer level (i.e., at least two times the upper limit of the normal range), and cohort 2 included the patients in cohort 1 plus those who were 75 years of age or older. The primary efficacy outcome population included all the patients in the trial. Additional information about the analysis groups is provided in Table S2 in the Supplementary Appendix. VTE denotes venous thromboembolism.

0.9% of betrixaban group and 1.5% of the enoxaparin group (relative risk, 0.64; 95% CI, 0.42 to 0.98; P=0.04). Time-to-event curves for symptomatic venous thromboembolism are provided in Figure S4 in the Supplementary Appendix. The second secondary efficacy outcome, defined as the primary efficacy outcome with the replacement of death from venous thromboembolism by death from any cause, occurred in 9.2% of the betrixaban group and 10.8% of the enoxaparin group in the overall population (relative risk, 0.85; 95% CI, 0.73 to 0.98; P=0.02).

The net clinical benefit (a composite of any component of the primary efficacy end point or principal safety outcome) occurred in 5.8% of the betrixaban group and 7.3% of the enoxaparin group (relative risk, 0.78; 95% CI, 0.65 to 0.95; P=0.01).

SAFETY OUTCOMES

In the overall safety population, major bleeding occurred in 0.7% of the betrixaban group and 0.6% of the enoxaparin group (relative risk, 1.19; 95% CI, 0.67 to 2.12; P=0.55) (Table 3). There were two cases of intracranial bleeding in the betrixaban group and seven in the enoxaparin group. There was one case of fatal bleeding in each group. The secondary safety outcome, major or clinically relevant nonmajor bleeding, occurred in 3.1% of the betrixaban group and 1.6% of the enoxaparin group (relative risk, 1.97; 95% CI, 1.44 to 2.68; P<0.001). (The prespecified subgroups with respect to the principal safety outcome are described in Fig. S5 in the Supplementary Appendix.)

New ischemic stroke as adjudicated by the central committee occurred in 18 of 3716 patients (0.5%) in the betrixaban group and 34 of 3716 patients (0.9%) in the enoxaparin group (relative risk, 0.53; 95% CI, 0.30 to 0.94; P=0.03). The corresponding numbers for all types of strokes were 24 of 3716 patients (0.6%) and 41 of 3716 (1.1%), respectively (relative risk, 0.59; 95% CI, 0.35 to 0.97; P=0.03).

DISCUSSION

In the APEX trial, we compared the use of extended-duration betrixaban (for 35 to 42 days) with a standard enoxaparin regimen (10±4 days) for thromboprophylaxis in patients who were hospitalized with an acute medical illness. The study design specified that the primary outcome would be analyzed in a hierarchical fashion, first in patients who had an elevated D-dimer level (cohort 1), second in patients with either an elevated D-dimer level or an age of at least 75 years (cohort 2), and third in the entire trial population. Because there was no significant between-group difference in the primary outcome in cohort 1 (P=0.054), the protocol specified that all subsequent analyses were considered to be exploratory. However, taken together, these additional analyses provide support for the interpretation that the risk of venous thromboembolism was lower with betrixaban than with enoxaparin.

The decision to perform hierarchical testing of trial outcomes in subgroups of the overall trial population was based on the expectation that patients with an elevated D-dimer level or an age of at least 75 years would represent a subgroup enriched for both a greater risk of venous thromboembolism and a greater benefit of extended-duration antithrombotic therapy. These expectations were based on data for similar patients who were enrolled in the MAGELLAN trial of rivaroxaban. We found that patients with an elevated D-dimer level or who were 75 years of age or older were at modestly higher risk; however, we did not find a greater benefit of extended-duration betrixaban in this group using D-dimer levels that were assessed in a local laboratory. Thus, in the primary analysis, the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Betrixaban (N=3759)	Enoxaparin (N=3754)
Age — yr	76.6±8.46	76.2±8.31
Male sex — no. (%)	1705 (45.4)	1720 (45.8)
Mean weight — kg	79.84	80.74
Body-mass index†	29.21±6.60	29.54±6.67
Median no. of days of hospitalization (IQR)	10 (7–4)	10 (8–14)
Creatinine clearance — no. (%)‡		
<15 ml/min	1 (<0.1)	0
15 to <30 ml/min	174 (4.6)	150 (4.0)
30 to <60 ml/min	1602 (42.6)	1531 (40.8)
60 to <90 ml/min	1299 (34.6)	1346 (35.9)
≥90 ml/min	672 (17.9)	716 (19.1)
Missing data	11 (0.3)	11 (0.3)
Race or ethnic group — no. (%)§		
White	3503 (93.2)	3518 (93.7)
Asian	9 (0.2)	7 (0.2)
Black	74 (2.0)	73 (1.9)
Other	173 (4.6)	156 (4.2)
Concomitant P-glycoprotein inhibitor — no. (%)	677 (18.0)	649 (17.3)
Previous thromboprophylaxis ≤96 hr — no. (%)	1928 (51.3)	1879 (50.1)
Acute medical condition — no. (%)		
Heart failure	1677 (44.6)	1672 (44.5)
Infection	1112 (29.6)	1058 (28.2)
Respiratory failure	448 (11.9)	474 (12.6)
Ischemic stroke	411 (10.9)	432 (11.5)
Rheumatic disorder	109 (2.9)	117 (3.1)
Risk factor for venous thromboembolism — no. (%)		
Level of D-dimer ≥2× ULN	2341 (62.3)	2332 (62.1)
Age ≥75 yr	2575 (68.5)	2517 (67.0)
History of cancer	466 (12.4)	443 (11.8)
History of deep-vein thrombosis or pulmonary embolism	312 (8.3)	296 (7.9)
History of New York Heart Association class III or IV heart failure	853 (22.7)	865 (23.0)
Concurrent acute infectious disease	602 (16.0)	620 (16.5)
Severe varicosities	702 (18.7)	690 (18.4)
Hormone-replacement therapy	43 (1.1)	31 (0.8)
Hereditary or acquired thrombophilia	3 (<0.1)	5 (0.1)

* Plus–minus values are means ±SD. There were no significant differences between the two groups. IQR denotes interquartile range, and ULN upper limit of the normal range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Creatinine clearance levels were calculated with the use of the Cockcroft–Gault equation on the basis of creatinine levels on day 1. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
§ Race or ethnic group was self-reported. "Other" includes patients who were categorized as Native American, Alaska Native, Native Hawaiian or Pacific Islander, other race, or mixed race.

Table 2. Components of the Primary and Secondary Efficacy Outcomes.*

Outcome	Cohort 1				Cohort 2				Overall Population			
	Betrixaban (N=1914)	Enoxaparin (N=1956)	Relative Risk (95% CI)	P Value†	Betrixaban (N=2842)	Enoxaparin (N=2893)	Relative Risk (95% CI)	P Value†	Betrixaban (N=3112)	Enoxaparin (N=3174)	Relative Risk (95% CI)	P Value†
	no./total no. (%)				*no./total no. (%)*				*no./total no. (%)*			
Primary end point												
Primary efficacy outcome‡	132/1914 (6.9)	166/1956 (8.5)	0.81 (0.65–1.00)	0.054	160/2842 (5.6)	204/2893 (7.1)	0.80 (0.66–0.98)	0.03	165/3112 (5.3)	223/3174 (7.0)	0.76 (0.63–0.92)	0.006
Asymptomatic proximal deep-vein thrombosis	105	129	NA	NA	128	162	NA	NA	133	176	NA	NA
Symptomatic proximal or distal deep-vein thrombosis	14	19	NA	NA	14	21	NA	NA	14	22	NA	NA
Symptomatic nonfatal pulmonary embolism	5	17	NA	NA	9	18	NA	NA	9	18	NA	NA
Death from venous thromboembolism	12	11	NA	NA	13	13	NA	NA	13	17	NA	NA
Key secondary end points												
Symptomatic venous thromboembolism§	30/2314 (1.3)	44/2313 (1.9)	0.67 (0.42–1.07)	0.09	35/3407 (1.0)	49/3407 (1.4)	0.71 (0.46–1.09)	0.11	35/3721 (0.9)	54/3720 (1.5)	0.64 (0.42–0.98)	0.04
Primary efficacy outcome plus death from any cause¶	232/2014 (11.5)	264/2054 (12.9)	0.89 (0.75–1.05)	0.16	291/2973 (9.8)	329/3018 (10.9)	0.90 (0.77–1.04)	0.15	298/3245 (9.2)	359/3310 (10.8)	0.85 (0.73–0.98)	0.02
Net clinical benefit‖	141/1914 (7.4)	174/1956 (8.9)	0.82 (0.66–1.01)	0.07	174/2842 (6.1)	214/2893 (7.4)	0.82 (0.68–1.00)	0.05	179/3112 (5.8)	233/3174 (7.3)	0.78 (0.65–0.95)	0.01

* Cohort 1 included patients who had an elevated baseline D-dimer level (i.e., at least two times the upper limit of the normal range), and cohort 2 included patients in cohort 1 plus those who were 75 years of age or older. The overall population included all the patients who could be evaluated for the primary efficacy outcome. All analysis populations are further defined in Table S2 in the Supplementary Appendix. CI denotes confidence interval, and NA not applicable.

† All P values are two-sided for superiority. Since the first test in the sequence of cohorts did not meet the prespecified threshold for statistical significance, all subsequent prespecified efficacy outcomes were considered to be exploratory and were not used to determine significance.

‡ The primary efficacy outcome was a composite of asymptomatic proximal deep-vein thrombosis between day 32 and day 47 (as detected on compression ultrasonography), symptomatic proximal or distal deep-vein thrombosis, symptomatic nonfatal pulmonary embolism, or death from venous thromboembolism between day 1 and day 42. For components of the primary outcome, patients may have had multiple events, so the number of individual components may not total the number of patients who had at least one event.

§ The first major secondary efficacy outcome was a composite of death from venous thromboembolism, nonfatal pulmonary embolism, or symptomatic deep-vein thrombosis between day 1 and day 42. This outcome was analyzed in the modified intention-to-treat population, which included all the patients who had received at least one dose of a study drug.

¶ The second major secondary efficacy outcome was a composite of the primary efficacy outcome plus death from any cause (instead of death from venous thromboembolism) between day 1 and day 42.

‖ The net clinical benefit was a composite of the primary efficacy outcome and the primary safety outcome.

Table 3. Safety Outcomes.*

Outcome	Betrixaban	Enoxaparin	Relative Risk (95% CI)	P Value
	no./total no. (%)			
Principal safety outcome in cohort 1				
Major bleeding	15/2311 (0.6)	17/2310 (0.7)	0.88 (0.44–1.76)	0.72
Decrease in hemoglobin of ≥2 g/dl	9	6	NA	
Transfusion of ≥2 units of blood	10	9	NA	
Critical-site bleeding	1	7	NA	
Fatal bleeding	0	1	NA	
Major or clinically relevant nonmajor bleeding	72/2311 (3.1)	44/2310 (1.9)	1.64 (1.13–2.37)	0.009
Principal safety outcome in cohort 2				
Major bleeding	25/3402 (0.7)	21/3387 (0.6)	1.19 (0.66–2.11)	0.56
Decrease in hemoglobin of ≥2 g/dl	12	8	NA	
Transfusion of ≥2 units of blood	18	9	NA	
Critical-site bleeding	3	9	NA	
Fatal bleeding	1	1	NA	
Major or clinically relevant nonmajor bleeding	110/3402 (3.2)	58/3387 (1.7)	1.89 (1.38–2.59)	<0.001
Principal safety outcome in overall safety population				
Major bleeding	25/3716 (0.7)	21/3716 (0.6)	1.19 (0.67–2.12)	0.55
Decrease in hemoglobin of ≥2 g/dl	12	8	NA	
Transfusion of ≥2 units of blood	18	9	NA	
Critical-site bleeding	3	9	NA	
Fatal bleeding	1	1	NA	
Major or clinically relevant nonmajor bleeding	116/3716 (3.1)	59/3716 (1.6)	1.97 (1.44–2.68)	<0.001
Other safety outcomes in all patients†				
Any adverse event	2005/3716 (54.0)	1931/3716 (52.0)		
Any serious adverse event	657/3716 (17.7)	615/3716 (16.6)		
Death				
Any cause	210/3716 (5.7)	215/3716 (5.8)		
Bleeding	1/3716 (<0.1)	1/3716 (<0.1)		
Venous thromboembolism	15/3716 (0.4)	26/3716 (0.7)		
Other cardiovascular cause				
Heart failure or cardiogenic shock	40/3716 (1.1)	56/3716 (1.5)		
Arrhythmic disorder	0	1/3716 (<0.1)		
Myocardial infarction	11/3716 (0.3)	8/3716 (0.2)		
Ischemic stroke	24/3716 (0.6)	28/3716 (0.8)		
Noncardiovascular cause	95/3716 (2.6)	76/3716 (2.0)		
Undetermined or unknown cause	24/3716 (0.6)	19/3716 (0.5)		
Stroke				
Any	24/3716 (0.6)	41/3716 (1.1)		
Ischemic	18/3716 (0.5)	34/3716 (0.9)		

* Data for the principal safety outcomes include events that occurred up to 7 days after the last dose of a study drug. Other safety outcomes were evaluated during the entire duration of the trial.
† Relative risks and P values are not included for this category because the protocol did not specify a comparative analysis of adverse events.

fact that there were fewer patients in cohort 1 than in either cohort 2 or the overall population resulted in a diminished statistical power without a corresponding gain in efficacy. A benefit for betrixaban was seen when the study cohorts were evaluated in exploratory analyses according to the more specific D-dimer testing used in the central laboratory.

The widespread use of preventive strategies hinges on the safety of the intervention. Betrixaban was associated with a low frequency of major bleeding and fatal bleeding. Unlike enoxaparin in the EXCLAIM trial, apixaban in the ADOPT trial, and rivaroxaban in the MAGELLAN trial, the use of extended-duration betrixaban in our trial was not associated with significantly more major bleeding than standard-duration enoxaparin,[5,13,14] although there was significantly more clinically relevant nonmajor bleeding. Intracranial bleeding was infrequent in the two groups, but the rate was lower in the betrixaban group than in the enoxaparin group.

In the United States, approximately 7 million acutely ill medical patients at increased risk for venous thromboembolism are admitted to the hospital every year.[21] Such patients account for more than 20% of the attributable risk for venous thromboembolism.[22] In the European Union and the United States combined, more than 2 million clinical events associated with venous thromboembolism occur annually in the general population.[23,24] In our trial, betrixaban was associated with a reduction in the rates of symptomatic events and asymptomatic deep-vein thrombosis, both of which are associated with fatal and nonfatal pulmonary embolism and death in acutely ill medical patients.[25] Decreasing the rate of venous thromboembolism in this patient population would benefit public health.

In such patients, parenteral anticoagulants may be used to reduce the risk of venous thromboembolism during hospitalization, but such drugs are rarely continued after discharge. The trend toward shorter hospitalizations may have the unintended consequence that patients receive a short duration of thromboprophylaxis that is inadequate. In exploratory analyses in our trial, we found that oral betrixaban can be extended after discharge to reduce the rate of venous thromboembolism among patients who are categorized according to their admission diagnoses and predefined risk factors.

The most important limitation of our trial was the fact that approximately 15% of enrolled patients underwent either no or inadequate ultrasonography and therefore could not be included in the main analyses of the efficacy outcomes. However, this limitation was also seen in similarly designed trials, such as ADOPT and MAGELLAN, and indeed the frequency of missing data was lower in our trial.[5,13,14] The fact that the rate of symptomatic events was lower in the betrixaban group than in the enoxaparin group supports the findings of the primary outcome analyses and suggests that the missing data did not substantially influence the results.

In conclusion, in a comparison of extended-duration thromboprophylaxis with betrixaban and standard-duration enoxaparin in acutely ill medical patients, there was no significant between-group difference in the prespecified primary efficacy outcome among the patients with an elevated D-dimer level. However, prespecified exploratory analyses provided evidence suggesting a benefit for betrixaban.

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