ORIGINAL RESEARCH

Comparison of Fatal or Irreversible Events With Extended-Duration Betrixaban Versus Standard Dose Enoxaparin in Acutely Ill Medical Patients: An APEX Trial Substudy

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Background—Extended-duration betrixaban showed a significant reduction in venous thromboembolism in the APEX trial (Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study). Given the variable clinical impact of different efficacy and safety events, one approach to assess net clinical outcomes is to include only those events that are either fatal or cause irreversible harm.

Methods and Results—This was a post hoc analysis of the APEX trial—a multicenter, double-blind, randomized controlled trial comparing extended-duration betrixaban versus standard-of-care enoxaparin. A composite of all fatal or irreversible safety (fatal bleeding or intracranial hemorrhage) and efficacy events (cardiopulmonary death, myocardial infarction, pulmonary embolism, and ischemic stroke) was evaluated in a time-to-first event analysis. In patients with positive D-dimer results, betrixaban reduced fatal or irreversible events at 35 to 42 days (4.80% versus 3.54%; hazard ratio, 0.73; absolute risk reduction, 1.26%; number needed to treat, 79 [P=0.033]) and at study end at 77 days (6.27% versus 4.36%; hazard ratio, 0.70; absolute risk reduction, 1.91%; number needed to treat, 52 [P=0.005]) versus enoxaparin. In all patients, betrixaban reduced fatal or irreversible events at 35 to 42 days (4.08% versus 2.90%; hazard ratio, 0.71; absolute risk reduction, 1.18%; number needed to treat, 86 [P=0.006]) and 77 days (5.17% versus 3.64%; hazard ratio, 0.70; absolute risk reduction, 1.53%; number needed to treat, 65 [P=0.002]).

Conclusions—Among hospitalized medically ill patients, extended-duration betrixaban demonstrated an ≈30% reduction in fatal or irreversible ischemic or bleeding events compared with standard-duration enoxaparin. A total of 65 patients would require treatment with betrixaban to prevent 1 fatal or irreversible event versus enoxaparin.

Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifier: NCT01583218. **(*J Am Heart Assoc*. 2017;6: e006015. DOI: 10.1161/JAHA.117.006015.)**

Key Words: death • intracranial hemorrhage • ischemic stroke • myocardial infarction • pulmonary embolism • venous thromboembolism

Therapeutic interventions are associated with both efficacy benefits and safety hazards. The net clinical outcome of an intervention can be assessed by combining measures of efficacy and safety. Some events may be transient and reversible and result in no permanent harm, which makes them challenging to weigh against each other. One way to ensure that the clinical impact of the efficacy and safety events that are being compared is similar is to include

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Accompanying Tables S1 through S4, Figures S1 through S7, and Appendix S1 are available at http://jaha.ahajournals.org/content/6/7/e006015/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Among hospitalized medically ill patients through 77 days of follow-up, 1 fatal or irreversible event could be prevented by treating 65 patients with extended-duration betrixaban compared with standard-of-care enoxaparin.

What Are the Clinical Implications?

- Extended-duration thromboprophylaxis using an experimental oral factor Xa inhibitor may reduce the risk of fatal or irreversible events among hospitalized medically ill patients.

only those events that are either fatal or result in irreversible cell death or harm to the patient. The present study is a post hoc analysis of the APEX trial (Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study), which evaluates net clinical outcomes by comparing a composite of fatal or irreversible efficacy and safety events in patients treated with extended-duration betrixaban versus standard dosing enoxaparin for venous thromboembolism prevention among acute medically ill hospitalized patients. This article expands on the primary results of APEX, which assessed efficacy and safety end points independently. Additionally, the end point evaluated in this study includes only symptomatic events and therefore could be assessed in the modified intent-to-treat population, as opposed to the primary efficacy outcome population, which was used for the primary results.

Methods

Study Design and Population

APEX was a randomized, double-blind, double-dummy, active-controlled, multinational phase 3 clinical trial. The trial design and main results have been previously published.[1,2] In brief, acutely medically ill men and women, 40 years or older, with reduced mobility and increased risk for venous thromboembolism hospitalized for either acute heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke were eligible for enrollment. Major exclusion criteria were active bleeding or a high risk of bleeding, severe renal insufficiency with creatinine clearance <15 mL/min, or any condition requiring prolonged anticoagulation or antiplatelet therapy.

Patients were randomly assigned in a 1:1 ratio to receive either standard-duration subcutaneous enoxaparin 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 active extended-duration oral betrixaban (loading dose of 160 mg for the first dose followed by 80 mg once daily for 35–42 days). The dose of study drug was adjusted to 40 mg among patients with renal insufficiency with creatinine clearance <30 mL/min (both enoxaparin and betrixaban doses were halved) and patients receiving concomitant strong P-glycoprotein inhibitors (only betrixaban dose was halved). Clinical outcomes were assessed between day 35 and day 42 and again at an additional 30±5 days after day 42. The modified intent-to-treat cohort was used, which included all randomized patients who had at least one dose of study drug. The primary and first cohort tested (cohort 1) included patients who had positive D-dimer results (≥2 times the upper limit of normal) by local laboratory assessment. Cohort 2 included patients who had positive D-dimer results or were 75 years and older. In addition, end points were assessed in all randomized patients (Figures S1 and S2). The study was approved by the local institutional review committees, and all enrolled participants provided informed consent.

End Points

All safety and efficacy end points were adjudicated by members of a clinical events committee blinded to study group assignment. In this post hoc analysis, the primary end point was the composite of all fatal or irreversible ischemic and bleeding events. This composite end point was previously used in the clinical trial assessment of prasugrel.[3,4] An irreversible efficacy end point was defined as death from ischemic cerebral or cardiopulmonary causes, including ischemic stroke, fatal arrhythmias, heart failure, venous thromboembolism, and sudden death from unknown causes, as well as nonfatal events that resulted in necrosis of tissue including nonfatal myocardial infarction (MI), nonfatal pulmonary embolism (PE), and nonfatal ischemic stroke. An irreversible safety end point was defined as fatal bleeding or intracranial hemorrhage. Nonfatal PE was not included as an outcome in sensitivity analysis because some patients with PE do not have necrosis of lung tissue.

Statistical Analysis

In the analysis of the 80- and 40-mg dose cohorts, the actual dose the patient was treated with was used.

All statistical analyses were programmed independently by two statisticians using SAS version 9.4 (SAS Institute Inc). Characteristics of the study population were evaluated using descriptive statistics. Data were expressed as frequencies and percentages for categorical variables, with denominators including all patients with available data. A time-to-first event survival analysis with right censorship was performed using a Cox proportional hazards regression model, where event rates were expressed as Kaplan–Meier estimates, and *P* values

were reported using the log-rank test. Events were analyzed through visit 3 or day 42 to reflect the primary analysis and through end of study at day 77 as an exploratory assessment. All events (efficacy or safety) were considered to have equal statistical weight. A $P<0.05$ was considered statistically significant.

Results

The baseline characteristics of the two cohorts were well matched.[2] The median time overall on enoxaparin/enoxaparin placebo and betrixaban/betrixaban placebo was 9 (interquartile range, 7–13) and 36 (interquartile range, 34–39) days, respectively.

Table 1. Composite of Fatal and Irreversible Events

Outcome*	Through Visit 3 or Day 42		Through Day 77	
	Betrixaban	Enoxaparin†	Betrixaban	Enoxaparin†
Cohort 1				
Composite, No./total No. (%)	82/2314 (3.5)	111/2313 (4.8)	101/2314 (4.4)	145/2313 (6.3)
Ischemic events, No.				
Ischemic cardiopulmonary death‡	68	74	84	99
Nonfatal ischemic stroke	5	11	7	14
MI	11	12	12	18
Nonfatal pulmonary embolism	5	17	5	20
Bleed events, No.				
Fatal bleed	0	1	0	1
Intracranial hemorrhage	0	3	0	4
Cohort 2				
Composite, No./total No. (%)	105/3407 (3.1)	139/3391 (4.1)	133/3407 (3.9)	180/3391 (5.3)
Ischemic events, No.				
Ischemic cardiopulmonary death	81	92	103	120
Nonfatal ischemic stroke	8	15	10	20
MI	14	15	15	22
Nonfatal pulmonary embolism	9	18	9	22
Bleed events, No.				
Fatal bleed	1	1	1	1
Intracranial hemorrhage	1	5	1	6
All randomized patients				
Composite, No./total No. (%)	109/3759 (2.9)	153/3754 (4.1)	137/3759 (3.6)	194/3754 (5.2)
Ischemic events, No.				
Ischemic cardiopulmonary death	84	103	106	131
Nonfatal ischemic stroke	8	16	10	21
MI	14	17	15	24
Nonfatal pulmonary embolism	10	20	10	24
Bleed events, No.				
Fatal bleed	1	1	1	1
Intracranial hemorrhage	1	5	1	6

*Data for safety outcomes were evaluated through visit 3 or day 42. The breakdown of events adds up to more than the composite events because the composite includes only the first event the patient experienced. Modified intention-to-treat population for cohort 1 and cohort 2 analyses.

†Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days.

‡Includes fatal pulmonary embolism/venous thromboembolism—confirmed, fatal pulmonary embolism/venous thromboembolism—possible, fatal pulmonary embolism/venous thromboembolism—probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction (MI), and sudden death of unknown cause.

Composite event rates were consistently lower in the betrixaban arm across all cohorts, including and excluding nonfatal PE (Tables 1 and 2). In cohort 1 (patients with positive D-dimer results), there was a significant reduction in fatal or irreversible events at both visit 3 (35–42 days) and visit 4 (77 days) (Figure 1). Given the positive results observed in cohort 1, cohort 2 (patients with positive D-dimer results or age older than 75 years) was then evaluated, which showed a similar reduction in events at visit 3 (3.1% versus 4.1%; hazard ratio [HR], 0.75 [95% CI, 0.58–0.96]; P=0.02) and visit 4 (3.9% versus 5.3%; HR, 0.74 [95% CI, 0.59–0.92]; P=0.007) in favor of betrixaban over enoxaparin. Given the significant results in cohort 2, cohort 3 (all randomized patients) was therefore tested and also demonstrated a significant reduction in fatal or irreversible events (Figure 2) in favor of betrixaban over enoxaparin. The number needed to treat to prevent 1 efficacy event was 65 when comparing betrixaban versus enoxaparin in all randomized patients through the end of the study. Betrixaban did not show higher risk for safety events from the composite when compared with enoxaparin, thus the number needed to harm could not be calculated. In all analyses, the improvement in net clinical

Table 2. Composite of Fatal and Irreversible Events Excluding Nonfatal Pulmonary Embolism

Outcome*	Through Visit 3 or Day 42		Through Day 77	
	Betrixaban	Enoxaparin†	Betrixaban	Enoxaparin†
Cohort 1				
Composite, No./Total No. (%)	78/2314 (3.4)	96/2313 (4.2)	97/2314 (4.2)	130/2313 (5.6)
Ischemic events, No.				
Ischemic cardiopulmonary death‡	68	72	84	99
Nonfatal ischemic stroke	5	11	7	14
Nonfatal MI	11	12	12	18
Bleed events, No.				
Fatal bleed	0	1	0	1
Intracranial hemorrhage	0	3	0	4
Cohort 2				
Composite, No./Total No. (%)	98/3407 (2.9)	124/3391 (3.7)	126/3407 (3.7)	164/3391 (4.8)
Ischemic events, No.				
Ischemic cardiopulmonary death	81	90	103	120
Nonfatal ischemic stroke	8	15	10	20
Nonfatal MI	14	15	15	22
Bleed events, No.				
Fatal bleed	1	1	1	1
Intracranial hemorrhage	1	5	1	6
All randomized patients				
Composite, No./Total No. (%)	101/3759 (2.7)	136/3754 (3.6)	129/3759 (3.4)	176/3754 (4.7)
Ischemic events, No.				
Ischemic cardiopulmonary death	84	101	106	131
Nonfatal ischemic stroke	8	16	10	21
Nonfatal MI	14	17	15	24
Bleed events, No.				
Fatal bleed	1	1	1	1
Intracranial hemorrhage	1	5	1	6

*Data for safety outcomes were evaluated through visit 3 or day 42 and day 77. The breakdown of events adds up to more than the composite events because the composite includes only the first event the patient experienced. Modified intention-to-treat population for cohort 1 and cohort 2 analyses.

†Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days.

‡Includes fatal pulmonary embolism/venous thromboembolism—confirmed, fatal pulmonary embolism/venous thromboembolism—possible, fatal pulmonary embolism/venous thromboembolism—probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction (MI), and sudden death of unknown cause.

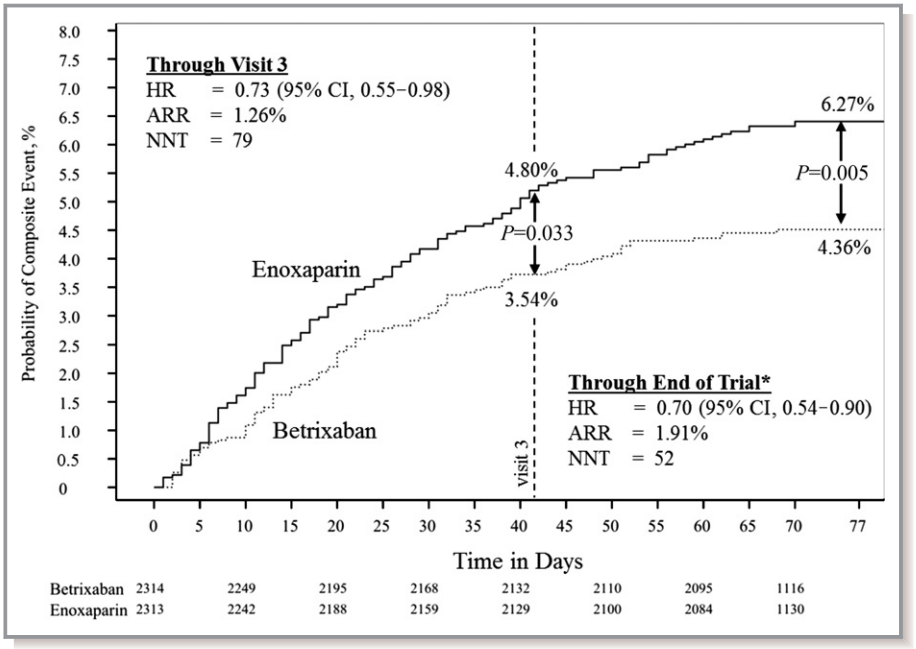

Figure 1. Time to first fatal or irreversible event in cohort 1. *End of trial defined as final follow-up visit (30+5 days after visit 3). Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days. ARR indicates absolute risk reduction; HR, hazard ratio; NNT, number needed to treat.

outcomes began to emerge during the parenteral period of therapy.

In a sensitivity analysis, which excluded nonfatal PE from the composite end point, betrixaban administration was associated with a similar reduction in the risk of the other fatal or irreversible events, which reached statistical significance at 77 days, end of study (Figures S3 and S4). In addition, in a sensitivity analysis excluding nonfatal

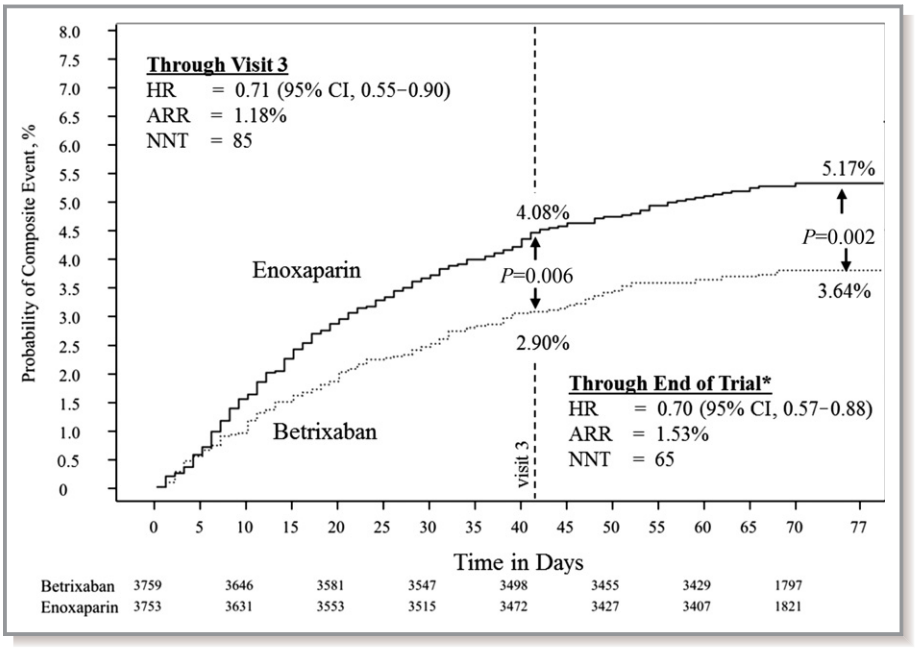

Figure 2. Time to first fatal or irreversible event in the randomized population. *End of trial defined as final follow-up visit (30+5 days after visit 3). Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days. ARR indicates absolute risk reduction; HR, hazard ratio; NNT, number needed to treat.

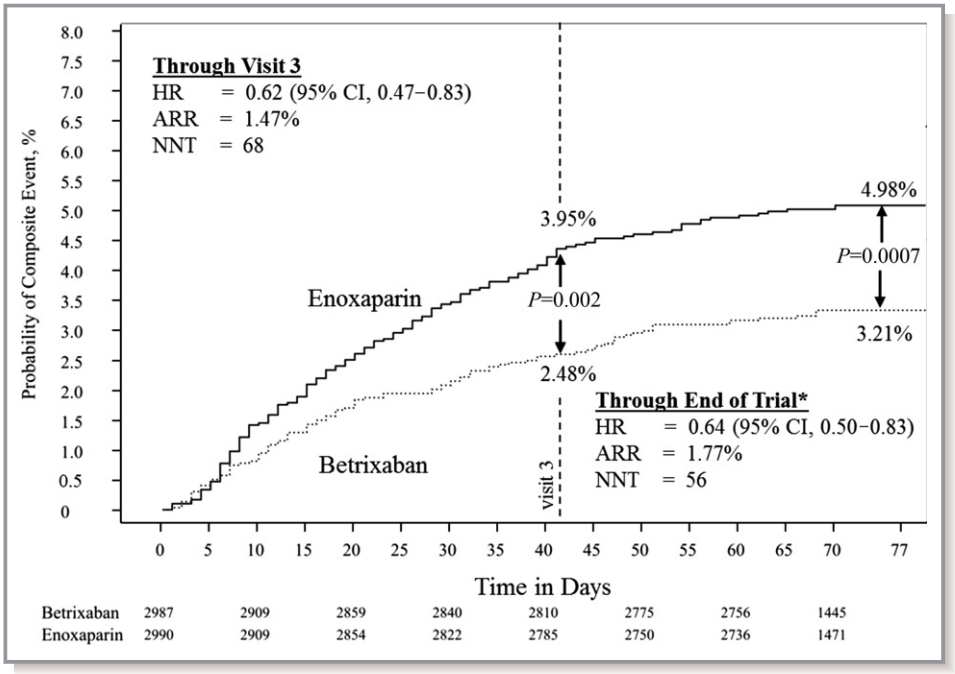

Figure 3. Time to first fatal or irreversible event in the randomized population—full dose (80 mg). *End of trial defined as final follow-up visit (30+5 days after visit 3). Enoxaparin was administered for 10±4 days, followed by oral betrixaban placebo for 35 to 42 days. ARR indicates absolute risk reduction; HR, hazard ratio; NNT, number needed to treat.

PE and MI, there was a reduction of fatal or irreversible events in all randomized patients comparing betrixaban versus enoxaparin through visit 3, or day 42 (HR, 0.71; 95% CI, 0.54–0.94 [*P*=0.016]) and through visit 4, or day 77 (HR, 0.72; 95% CI, 0.57–0.92 [*P*=0.008]). As a sensitivity analysis, the data were analyzed using the Cochran-Mantel-Haenszel test, which also yielded a significant event reduction across all cohorts of patients and time windows (Table S1). In addition, a sensitivity analysis that replaced cardiopulmonary death with all-cause mortality showed no significant benefit across all cohorts through visit 3 and the end of the study (Table S2).

In a series of similar analyses limited to patients receiving the full dose of betrixaban (80 mg), there was a consistent reduction in fatal or irreversible events as compared with enoxaparin (Table S3). Fatal or irreversible events were significantly reduced in both cohort 1 and all randomized patients (Figure 3 and Figure S5). In the smaller group of patients treated with the adjusted dose of betrixaban (40 mg), there was no significant reduction in events versus enoxaparin (Table S4 and Figure S6).

Of the 6 patients in the enoxaparin arm who experienced intracranial hemorrhages, 3 occurred while receiving enoxaparin and the remaining occurred while receiving either betrixaban placebo or no drug at all. No patients had renal insufficiency, and 5 of the 6 patients had creatinine clearances ≥60, while one had a clearance 30 to <60.

There was a significant reduction in the incidence of the traditional cardiovascular triple end point of cardiovascular death, MI, and all-cause stroke with extended-duration betrixaban versus standard duration enoxaparin in all randomized patients through visit 3 and visit 4. There was a 27% reduction in relative risk at visit 3 (2.29% versus 3.14%, *P*=0.023) and 25% at visit 4 (2.98% versus 3.97%, *P*=0.002) (Figure S7).

Discussion

Assessment of net clinical outcome, the combined impact of efficacy and safety data, is a commonly requested evaluation on the part of healthcare providers, payers, and regulators. The decision to administer an agent is a binary decision (either yes or no), and safety and efficacy in making such a decision must both be considered simultaneously. In many analyses, reversible bleeding events with no permanent sequelae are combined with intracranial hemorrhage and fatal bleeding, which cause irreversible harm. Some analyses rely on a time-to-first bleeding event methodology. In such analyses, if the first event is minor, it may obscure the clinical impact of a later event associated with fatal or irreversible harm. As a relevant precedent, the Food and Drug Administration approved prasugrel based on its reduction of fatal and irreversible events related to either ischemia end points for efficacy or bleeding for safety and

published their method to focus on fatal and irreversible events.[3] Based on this important precedent, we adopted a similar approach. The present study assessed outcomes during a relatively short period of ≈2 months. If similar risk reductions were maintained over a longer duration of follow-up, greater absolute risk reductions may have been observed.

This post hoc analysis of APEX demonstrates that extended-duration betrixaban is associated with a significant reduction in fatal or irreversible events as compared with standard-duration enoxaparin. The benefit begins to emerge during the period of parenteral therapy and increases through the period of active treatment at 35 to 42 days as well as the entire duration of follow-up at 77 days. Based on the data from all randomized patients, one would need to treat 65 patients with betrixaban to prevent 1 fatal or irreversible event as compared with enoxaparin. In general, a number needed to treat <100 is considered compelling in clinical practice.

In a traditional net clinical outcomes analysis where efficacy events (including reversible and nonfatal efficacy events such as a positive compression ultrasound for asymptomatic proximal venous thromboembolism) are combined with major bleeding events (many of which are reversible and nonfatal), there is also a benefit in favor of betrixaban.[2] Because major bleeding was not increased with betrixaban, the net benefit associated with the drug is predominantly driven by its improved efficacy. However, a numeric but not significant excess of intracranial hemorrhages in the enoxaparin strategy helped drive the net clinical outcome in favor of betrixaban.

There was a significant reduction in fatal or irreversible events in cohort 1. The full dose of betrixaban (80 mg) was associated with a reduction in fatal or irreversible events, whereas the adjusted dose (40 mg) was not. Furthermore, in patients treated with the full 80-mg dose in cohort 1, there was a robust 2.3% absolute risk reduction (P=0.002), indicating that only 43 patients with positive D-dimer results in cohort 1 would need to be treated with full-dose betrixaban to prevent 1 fatal or irreversible event.

Findings from the ADOPT (Apixaban Dosing to Optimize Protection from Thrombosis) trial[5] did not demonstrate benefit but showed an increase in major bleeding (0.47% versus 0.19%) when comparing apixaban versus enoxaparin, making it impossible to demonstrate a net clinical benefit. Although results from the MAGELLAN (Venous Thromboembolic Event [VTE] Prophylaxis in Medically Ill Patients) trial[6] demonstrated a reduction in the primary end point, this was offset by an increase in fatal bleeding (7 fatal bleeds versus 1 fatal bleed, P<0.034) and an increase in intracranial hemorrhage (2 versus 0, P<0.25), making it difficult to demonstrate a favorable reduction in fatal or irreversible events. Neither ADOPT nor MAGELLAN published analyses of fatal or irreversible end points.

It is notable that death, MI, and stroke, a combined end point often used in "arterial" cardiovascular trials, was reduced in acutely ill medical patients treated with betrixaban, a treatment, which was aimed at reducing "venous" thromboses events.

Limitations

The case report forms did not characterize whether the recurrent MIs were ST-segment elevation myocardial infarctions or non–ST-segment elevation myocardial infarctions, and infarct size of the recurrent MIs was not quantitated. In addition, adjudication was not performed to determine whether there was a segmental versus subsegmental involvement among patients with PE. Finally, this analysis did not use weighted outcomes to incorporate physician and patient preference regarding their perceived import regarding the outcomes.

Conclusions

Among hospitalized medically ill patients, extended-duration betrixaban demonstrates a favorable net clinical outcome and is associated with an ≈30% reduction in fatal or irreversible ischemic or bleeding events compared with standard-duration enoxaparin followed by placebo. A total of 65 patients would require treatment with betrixaban to prevent 1 fatal or irreversible event versus enoxaparin.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Sensitivity Analysis for Composite of Fatal or Irreversible Events Using Cochran-Mantel-Haenszel Test

	Through Visit 3 or Day 42			Through day 77		
	Betrixaban *no./total no. (%)*	**Enoxaparin** *no./total no. (%)*	**P-Value***	**Betrixaban** *no./total no. (%)*	**Enoxaparin** *no./total no. (%)*	**P-Value***
Composite						
Cohort 1	82/2314 (3.5)	111/2313 (4.8)	0.028	101/2314 (4.4)	145/2313 (6.3)	0.003
Cohort 2	105/3407 (3.1)	139/3391 (4.1)	0.017	133/3407 (3.9)	180/3391 (5.3)	0.004
All Randomized Patients	109/3759 (2.9)	153/3754 (4.1)	0.003	137/3759 (3.6)	194/3754 (5.2)	0.001
Composite - 80mg						
Cohort 1	56/1828 (3.1)	86/1826 (4.7)	0.009	70/1828 (3.8)	112/1826 (6.1)	0.001
Cohort 2	73/2720 (2.7)	109/2718 (4.0)	0.005	95/2720 (3.5)	140/2718 (5.2)	0.002
All Randomized Patients	74/118 (2.5)	118/2990 (4.0)	0.001	96/2987 (3.2)	149/2990 (5.0)	0.001
Composite - 40mg						
Cohort 1	25/484 (5.2)	24/483 (5.0)	0.940	30/484 (6.2)	32/483 (6.6)	0.679
Cohort 2	30/683 (4.4)	29/668 (4.3)	0.987	36/683 (5.3)	39/668 (5.8)	0.590
All Randomized Patients	30/730 (4.1)	31/725 (4.3)	0.893	36/730 (4.9)	41/725 (5.7)	0.512
Composite - Excluding Non-Fatal PE						
Cohort 1	78/2314 (3.4)	96/2313 (4.2)	0.151	97/2314 (4.2)	130/2313 (5.6)	0.019
Cohort 2	98/3407 (2.9)	124/3391 (3.7)	0.055	126/3407 (3.7)	164/3391 (4.8)	0.016
All Randomized Patients	101/3759 (2.7)	136/3754 (3.6)	0.014	129/3759 (3.4)	176/3754 (4.7)	0.004
Composite - Excluding Non-Fatal PE + MI						
Cohort 1	70/2314 (3.0)	89/2313 (3.9)	0.119	92/2314 (4.0)	121/2313 (5.2)	0.035

Cohort 2	89/3407 (2.6)	115/3391 (3.4)	0.048	120/3407 (3.5)	152/3391 (4.5)	0.037
All Randomized Patients	92/3759 (2.5)	127/3754 (3.4)	0.012	123/3759 (3.3)	164/3754 (4.4)	0.010

*For cohort 1, treatment and the composite endpoint were stratified by dosing criteria (creatinine clearance ≥15ml and <30 ml/min, receipt of a concomitant pgp inhibitor with severe renal insufficiency, or neither) Cohort 2 and All Randomized Patients stratification was done by dosing criteria and entry criteria (D-dimer ≥2 XULN or <2 XULN)

Table S2. Sensitivity Analysis for Composite of Fatal or Irreversible Events Using All-Cause Death

	Through Visit 3 or Day 42				Through day 77			
	Betrixaban *no./total no. (%)*	**Enoxaparin** *no./total no. (%)*	**Hazard Ratio (95% CI)**	**P-Value**	**Betrixaban** *no./total no. (%)*	**Enoxaparin** *no./total no. (%)*	**Hazard Ratio (95% CI)**	**P-Value**
Composite*								
Cohort 1	128/2314 (5.5)	149/2313 (6.4)	0.86 (0.68, 1.08)	0.196	171/2314 (7.4)	202/2313 (8.7)	0.85 (0.69, 1.04)	0.105
Cohort 2	169/3407 (5.0)	189/3391 (5.6)	0.89 (0.72, 1.09)	0.257	227/3407 (6.7)	255/3391 (7.5)	0.89 (0.74, 1.06)	0.182
All Randomized Patients	175/3759 (4.7)	208/3754 (5.5)	0.84 (0.69, 1.02)	0.084	235/3759 (6.3)	277/3754 (7.4)	0.84 (0.71, 1.01)	0.057

*In this sensitivity analysis, all-cause death has replaced cardiopulmonary death in the composite end point

Table S3. Composite of Fatal and Irreversible Events – Full Dose (80mg)

	Through Visit 3 or day 42		Through day 77	
Outcome*	**Betrixaban** *no./total no. (%)*	**Enoxaparin‡** *no./total no. (%)*	**Betrixaban** *no./total no. (%)*	**Enoxaparin‡** *no./total no. (%)*
Cohort 1				
Composite - n/N (%)	56/1828 (3.1)	86/1826 (4.7)	70/1828 (3.8)	112/1826 (6.1)
Ischemic Events – n				
Ischemic cardiopulmonary death†	47	54	59	73
Nonfatal ischemic stroke	4	10	5	12
Myocardial infarction	9	11	10	15
Nonfatal pulmonary embolism	2	13	2	16
Bleed Events – n				
Fatal Bleed	0	1	0	1
Intracranial Hemorrhage	0	3	0	4
Cohort 2				
Composite	73/2720 (2.7)	109/2718 (4.0)	95/2720 (3.5)	140/2718 (5.2)
Ischemic Events				
Ischemic cardiopulmonary death	57	69	74	90
Nonfatal ischemic stroke	7	13	8	17
Myocardial infarction	12	13	13	17
Nonfatal pulmonary embolism	4	14	4	18
Bleed Events				
Fatal Bleed	0	1	0	1
Intracranial Hemorrhage	1	5	1	6
All Randomized Patients				
Composite	74/2987 (2.5)	118/2990 (4.0)	96/2987 (3.2)	149/2990 (5.0)
Ischemic Events				
Ischemic cardiopulmonary death	58	77	75	98
Nonfatal ischemic stroke	7	14	8	18
Myocardial infarction	12	14	13	18
Nonfatal pulmonary embolism	4	14	4	18
Bleed Events				
Fatal Bleed	0	1	0	1
Intracranial Hemorrhage	1	5	1	6

* Data for safety outcomes were evaluated through visit 3 or day 42. The breakdown of events adds up to more than composite events because composite only includes first event patient experienced. Cohort 1 and Cohort 2 analyses use mITT population.
†Includes fatal PE/VTE - confirmed, fatal PE/VTE - possible, fatal PE/VTE - probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction, sudden death of unknown cause
‡Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Table S4. Composite of Fatal and Irreversible Events – Reduced Dose (40mg)

	Through Visit 3 or day 42		Through day 77	
Outcome*	**Betrixaban** *no./total no. (%)*	**Enoxaparin‡** *no./total no. (%)*	**Betrixaban** *no./total no. (%)*	**Enoxaparin‡** *no./total no. (%)*
Cohort 1				
Composite - n/N (%)	25/484 (5.2)	24/483 (5.0)	30/484 (6.2)	32/483 (6.6)
Ischemic Events – n				
Ischemic cardiopulmonary death†	20	20	24	26
Nonfatal ischemic stroke	1	1	2	2
Myocardial infarction	2	1	2	3
Nonfatal pulmonary embolism	3	3	3	3
Bleed Events – n				
Fatal Bleed	0	0	0	0
Intracranial Hemorrhage	0	0	0	0
Cohort 2				
Composite	30/683 (4.4)	29/668 (4.3)	36/683 (5.3)	39/668 (5.8)
Ischemic Events				
Ischemic cardiopulmonary death	22	23	27	30
Nonfatal ischemic stroke	1	2	2	3
Myocardial infarction	2	2	2	5
Nonfatal pulmonary embolism	4	3	4	3
Bleed Events				
Fatal Bleed	1	0	1	0
Intracranial Hemorrhage	0	0	0	0
All Randomized Patients				
Composite	30/730 (4.1)	31/725 (4.3)	36/730 (4.9)	41/725 (5.7)
Ischemic Events				
Ischemic cardiopulmonary death	22	25	27	32
Nonfatal ischemic stroke	1	2	2	3
Myocardial infarction	2	2	2	5
Nonfatal pulmonary embolism	4	3	4	3
Bleed Events				
Fatal Bleed	1	0	1	0
Intracranial Hemorrhage	0	0	0	0

* Data for safety outcomes were evaluated through visit 3 or day 42. The breakdown of events adds up to more than composite events because composite only includes first event patient experienced. Cohort 1 and Cohort 2 analyses use mITT population.
†Includes fatal PE/VTE - confirmed, fatal PE/VTE - possible, fatal PE/VTE - probable, arrhythmic event, heart failure, fatal ischemic stroke, fatal myocardial infarction, sudden death of unknown cause
‡Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Figure S1. Study Design

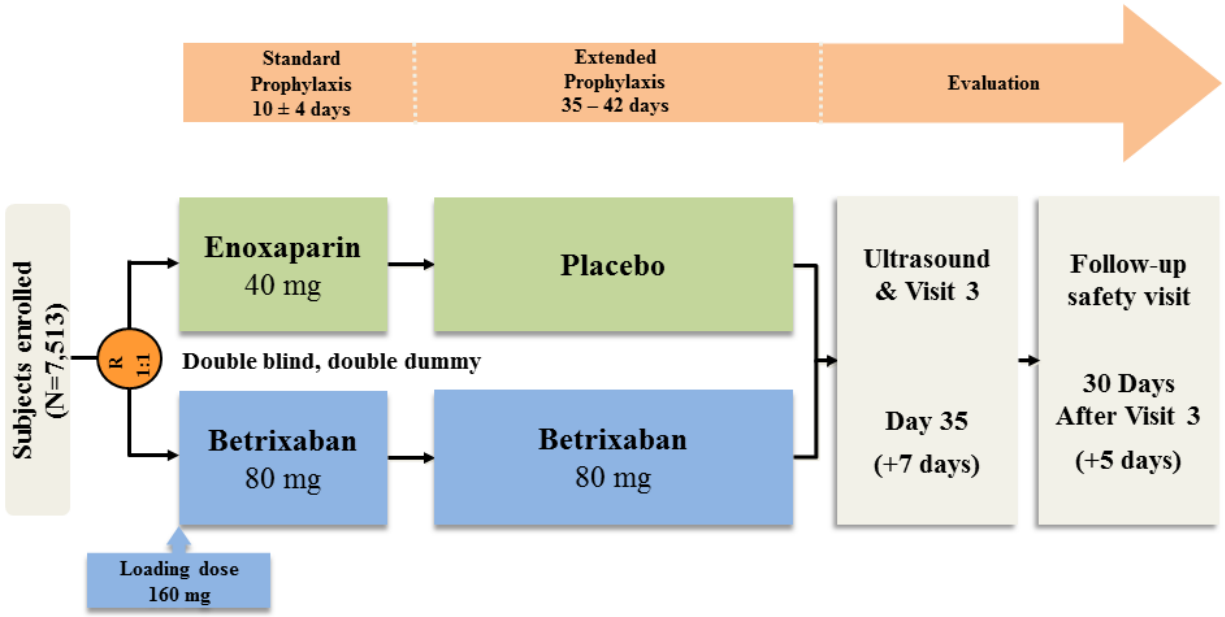


Figure S2. Study Population Flowchart

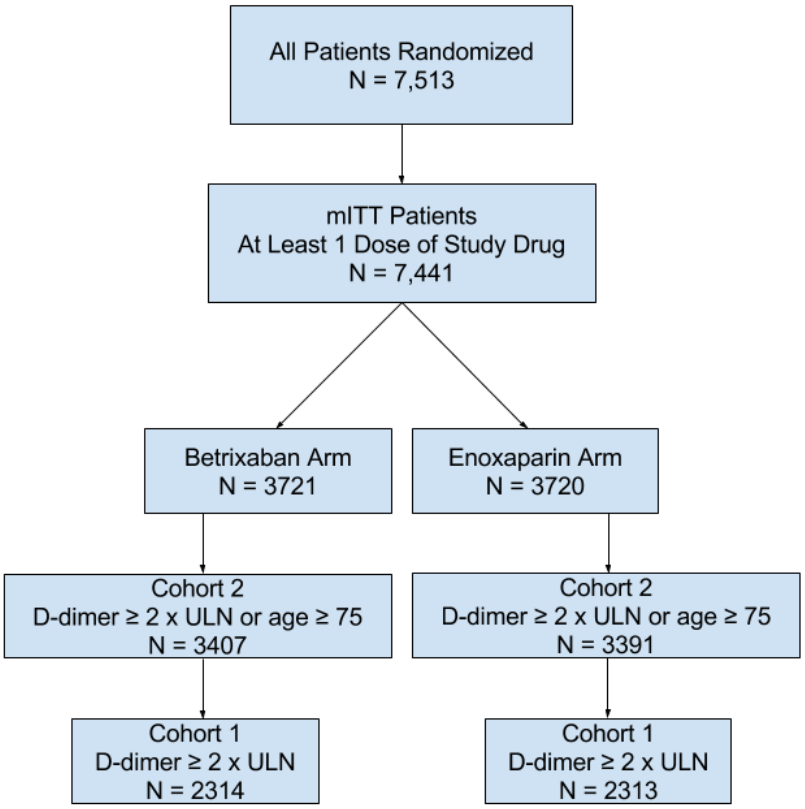
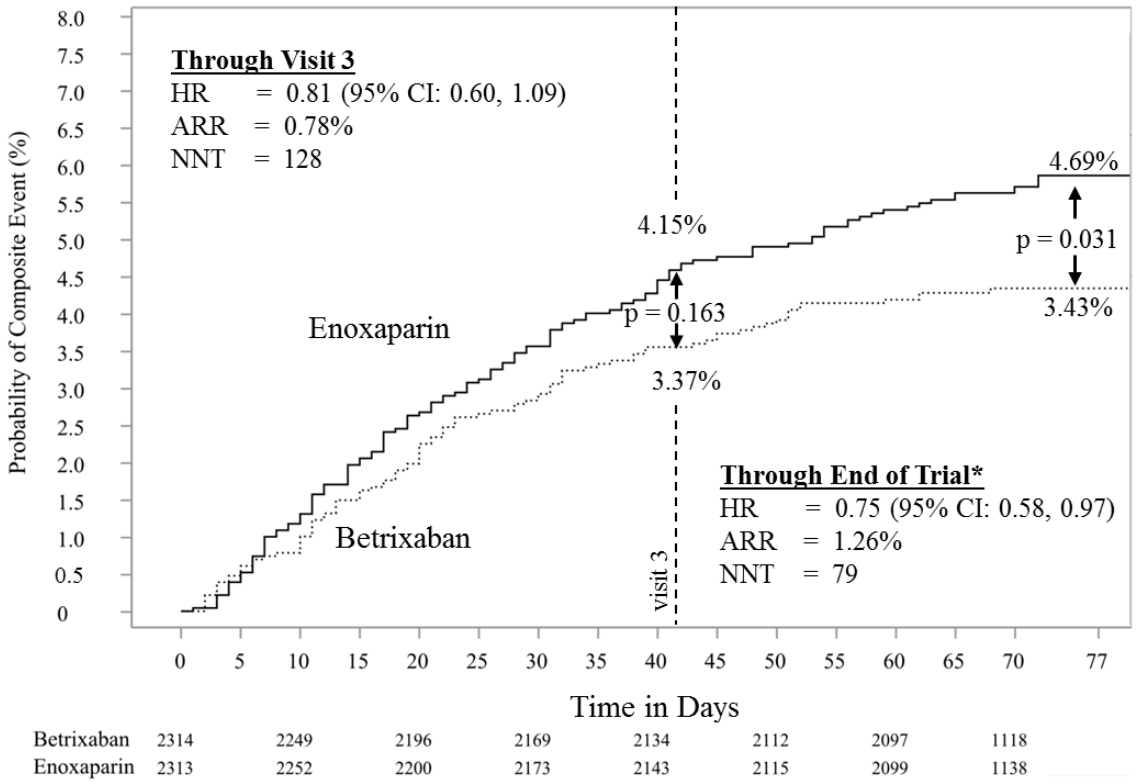
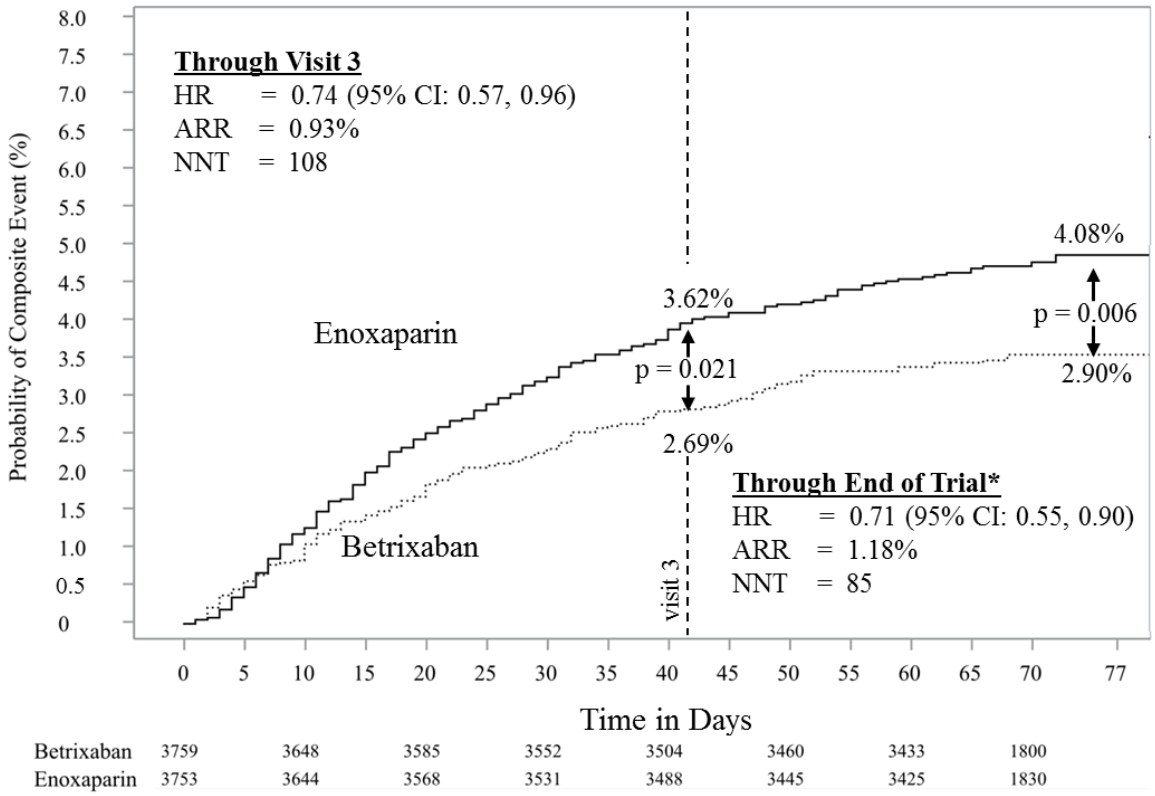


Figure S3. Time-to-First Fatal or Irreversible Event Excluding Non-Fatal PE in Cohort 1



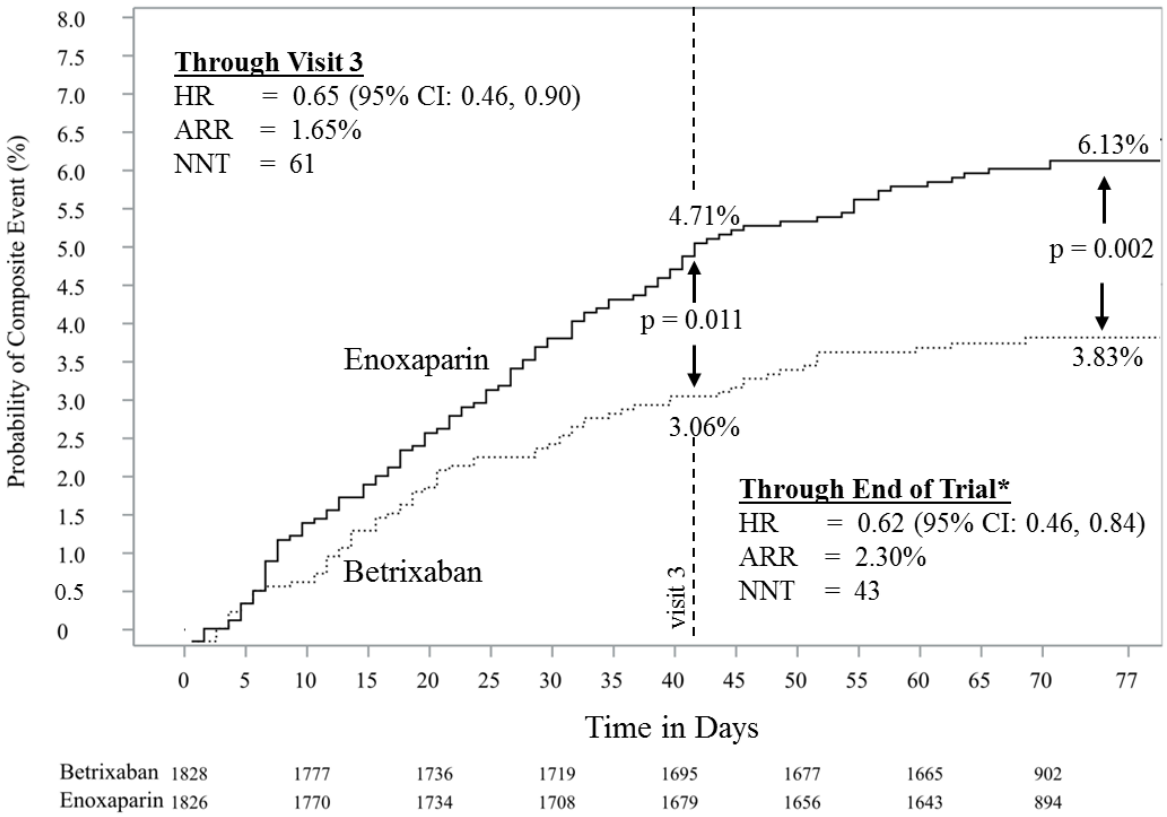
*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Figure S4. Time-to-First Fatal or Irreversible Event Excluding Non-Fatal PE in the All Randomized Population



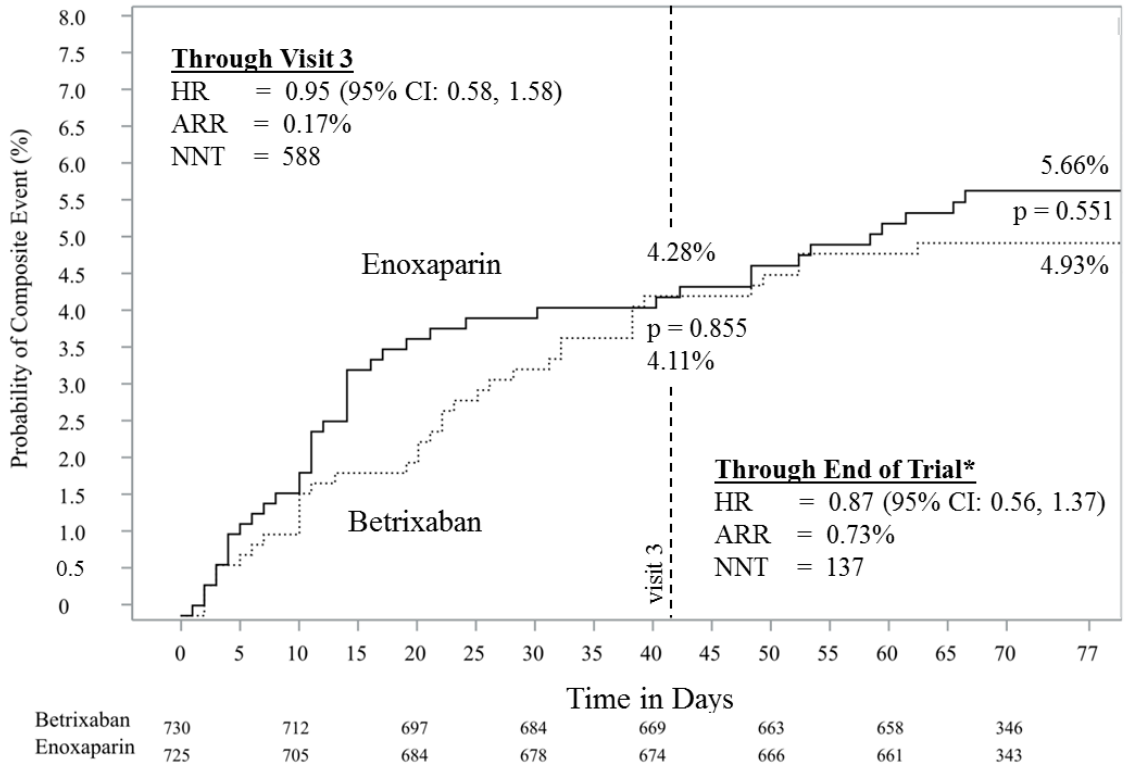
*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Figure S5. Time-to-First Fatal or Irreversible Event in Cohort 1 – Full Dose (80mg)



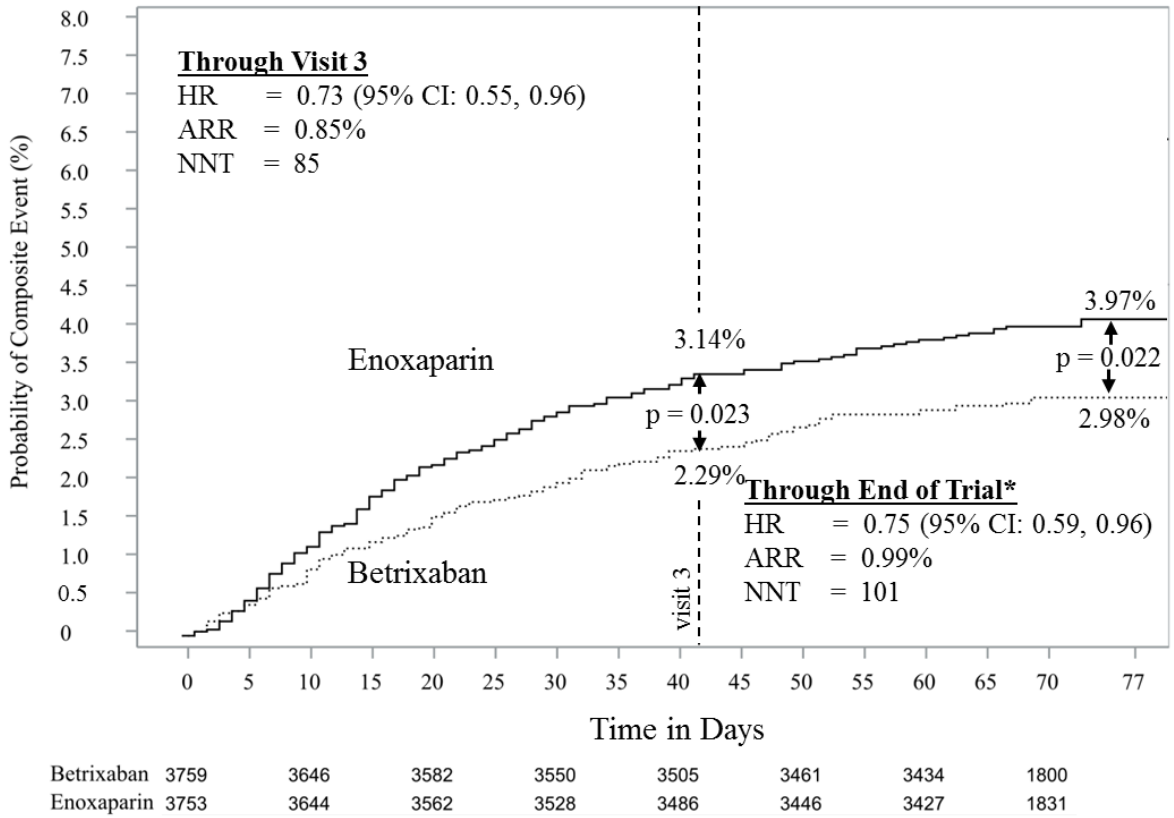
*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Figure S6. Time-to-First Fatal or Irreversible Event in the All Randomized Population – Reduced Dose (40mg)



*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Figure S7. Time-to-First CV Death, MI or Stroke in the All Randomized Population



*End of Trial defined as final follow-up visit (30 + 5 days after Visit 3)
Note: Enoxaparin was administered for 10 ± 4 days, followed by oral betrixaban placebo for 35 to 42 days

Appendix: APEX Investigators (No. of patients enrolled in each country, No. of sites):

Argentina (215 patients, 7 sites): F. Bello, A.E. Ferrari, H. Jure, S. Macin, M. Oliva, M. Parody, C. Poy; **Australia (20 patients, 5 sites):** R. Baker, D. Colquhoun, P. Coughlin, S. Finfer, G. Hammerschlag , A. Rubinfeld; **Austria (15 patients, 5 sites):** K. Huber, J. König, R. Mathies, E. Pilger, H. Schoenerr; **Belarus (69 patients, 7 sites):** I. Adzerikho, V. Koryk, E. Mikhailova, N. Mitkovskaya, S. Pimanov, L. Polonetsy, N. Soroka; **Belgium (15 patients, 5 sites):** D. Blockmans, M. Delforge, A. Dive, F. Lienart, S. Motte; **Brazil (57 patients, 8 sites):** J. Annichino Bizzacchi, E. Fiss, A. Freire, E, Manenti, E. Ramacciotti, S. Raymuno, A. Rocha, J.F. Saraiva; **Bulgaria (431 patients, 15 sites):** B. Dimov, M. Grigorov, R. Kalpachki, Z. Kamenova, M. Kostadinova, M. Milanova, V. Mincheva, G. Pencheva, D. Raev, N. Runev, N. Stoeva, M. Stoyanov, S. Syulemzova, G. Todorov, M. Tokmakova; **Canada (51 patients, 7 sites):** A. Dhar, J. Douketis, S. Kahn, G. Le Gal, M. Pearce, S. Provencher, S. Verreault; **Chile (44 patients, 4 sites):** M. Arias Alarcon, C. Olivares Cañon, M. Opazo Lazcano, S. Potthoff Cardenas; **Croatia (92 patients, 11 sites):** S. Butkovic-Soldo, S. Car, N. Ciglenecki, I. Francetic, M. Jakopovic, H. Kalinic-Grgorinic, A. Knezevic, B. Malojcic, S. Marusic, J. Sikic Vagic, V. Skerk; **Czech Republic (237 patients, 22 sites):** O. Cermak, P. Červinka, J. Chlumsky, J. Chochola, V. Cizek, M. Dunaj, J. Dusek, L. Francek, J. Havelka, M. Herold, R. Holaj, I. Horny, J. Hubac, P. Jajtner, P. Kolman, P. Lang, O. Mayer, J. Mikulova, I Podpera, P.Reiterer, R. Spacek, J. Vejvoda, M. Vyhnanek; **Denmark (12 patients, 5 sites):** H. Christensen, M. Lassen, M. Storgaard, C. Tuxen, S. Urhammer; **Estonia (205 patients, 3 sites):** M. Lember, T. Marandi, T. Uuetoa; **Finland (26 patients, 7 sites):** J. Airaksinen, J. Honkaniemi, R. Kaaja, R. Lassila, J. Saarinen, T. Tatlisumak, S. Vikman; **France (293 patients, 25 sites):** B. Agraou, S. Aquilanti, A. Belhassane, D. Brisot, G. De Geeter, P. Debourdeau, E. Decoulx, D. El Kouri, N. Falvo, C. Grange, P. Lacroix, E. Messas, P. Mismetti, K. Montaclair, D. Mottier, N. Paleiron, L. Payot, G. Pernod, P. Pottier, A. Proust, I. Quere, P-M. Roy, J. Schmidt, G. Simoneau; **Georgia (260 patients, 8 sites):** I. Datikashvili-David, G. Khabeishvili, I. Khintibidze, B. Kobulia, I. Megreladze, Z. Pagava, K. Paposhvili, T. Shaburishvili; **Germany (196 patients, 20 sites):** B. Amann, J. Berrouschot, J. Beyer-Westendorf, E. Blessing, M. Bott, T. Dengler, C. Diehm, R. Dziewas, S. Genth-Zotz, F. Hamann, T. Horacek, S. Klimpe, R. Kröning, H. Lapp, H. Lawall, M. Licka, T. Rizos, S. Schellong, J. Schmidt-Lucke, C. Singer, C. Tiefenbacher, R. Veltkamp, C. Weimar, U. Zeymer; **Hungary (252 patients, 20 sites):** B. Alkonyi, J. Faluközy, L. Futo, A. Katona, R. Kirschner, P. Kristóf, F. Lakatos, Z. Laszlo, G. Lupkovics, B. Merkely, C. Nagy András, L. Németh, A. Papp, P. Soltesz, Z. Sudár, G. Szabo, N. Szegedi, G. Tímár, J. Valcó, A. Vertes; **Israel (99 patients, 8 sites):** S. Efrati, M. Elias, A. Gafter, T. Hayek, O. Hussein, M. Lishner, G. Lugassy, D. Zeltser; **Italy (261 patients, 19 sites):** W. Ageno, I. Cerveri, A. D'Angelo, A. De Pellegrin, D. Imberti, R. Landolfi, G. Lembo, C. Lodigiani, M. Luisetti, M. Moia, M. Molteni, N. Mumoli, S. Novo, F. Orlandini, R. Parisi, A. Pizzini, F. Pomero, A. Salvi, A. Schenone, A. Visonà; **Latvia (319 patients, 5 sites):** D. Krievins, V. Martinova, N. Pontaga, V. Rozitis, I. Stukena; **Lithuania (470 patients, 12 sites):** B. Alekniene, A. Bagdonas, V. Basijokiene, Z. Butkiene, V. Griskeviciene, A. Naudziunas, R. Norvaisiene, R. Norviliene, R. Petrauskiene, R. Poskiene, D. Susinskiene, A. Valavicius; **Peru (152 patients, 7 sites):** R. Castillo Leon, R. Cotrina Pereyra, L. Farjardo Karlo, M. Horna, J. Lema Osores, M. Salas, L. Toche Yañez; **Poland (369 patients, 16 sites):** W. Fryze, Z. Gaciong, J. Gniot, D. Gorecka, P. Gruenpeter, P. Grzelakowski, D. Jastrzebski, L. Kucharski, E. Mirek-Bryniarska, G. Pulkowski, B. Sobkowicz, P. Sulik, W. Tomkowski, L. Walasek, K. Waldemar, K. Wrzesinski; **Romania (170 patients, 10 sites):** Z.E. Balogh, M. Bojinca, I. Marin, S. Mot, R. Musetescu, C. Podoleanu, M. Popescu, S. Stamate, G. Stanciulescu, L. Vida-Simiti; **Russia (971 patients, 37 sites):** A. Abashev, D. Andreev, K. Apartsin, M. Arkhipov, O. Averkov, O. Barbarash, G. Belskaya, E. Bogdanov, S. Boldueva, Z. Chefranova, Y. Dovgalevskiy, O. Ershova, B. Goloshchekin, N. Khachatryan, E. Khurs, G. Klein, Z. Kobalava, E. Kosmacheva, V. Kostenko, A. Malygin, T. Martynenko, V. Martynenko, N. Maslova, V. Mordovin, K. Nikolaev, R. Nilk, E. Panchenko, D. Popov, E. Privalova, O. Reshetko, E. Sergeeva, Y. Shapovalova, L. Shpagina, Y. Shvarts, V. Simanenkov, O.

Solovyov, E. Vishneva, A. Vishnevskiy; **Serbia (115 patients, 5 sites):** S. Apostolovic, V. Celic, S. Ilic, A. Kovacevic-Kuzmanovic, V. Miloradovic; **Singapore (1 patient, 1 site):** R.S. Tan; **Slovak Republic (105 patients, 11 sites):** S. Bodikova, A. Cervenakova, M. Dvorak, L. Gaspar, O. Herman, A. Hrubon, M. Kokles, G. Krastev, J. Payer, D. Prokop, M. Spisakova; **South Africa (91 patients, 7 sites):** D. Adler, M. Basson, J. Breedt, j. Engelbrecht, B. Jacobson, I. Mitha, C. Van Dyk; **Spain (412 patients, 18 sites)**: L.A. Alvarez Sala, C. Barbagelata López, J. Bisbe, A. Castro Guardiola, J.M. Cepeda, F. Cereto, E. Diaz Santos, R. Ferrer, J. Gomez Cerezo, J.R. Gonzales-Porras, J.Grandes, D. Jiménez, I. Martín Loeches, L. Mellibovsky, C. Richart, A. Riera, J. Trujillo, J.A. Vargas Nunez, J. Villalta; **Turkey (54 patients, 12 sites):** O. Akgul, S. Guneri, K. Kilichesmez, C. Kırma, H. Kutluk, B. Nazliel, G. Okumus, G. Ongen, K. Tigen, M. Topcuoglu, E. Tuncay; **Ukraine (886 patients, 31 sites**): O. Abrahamovych, V. Batushkin, J. Brozhyk, I. Burmak, O. Godlevska, A. Goloborodko, B. Goloborodko, Y. Goncharova, V. Gryb, O. Karpenko, M. Kopytsya, V. Koshlia, O. Krakhmalova, I. Kyrychenko, O. Legkonogov, Y. Malynovsky, V. Maslovaskyi, V. Nikonov, O. Parkhomenko, M. Perepeliuk, D. Reshotko, L. Rudenko, T. Ryabichenko, I. Svyridova, Y. Svyshchenko, V. Tseluyko, G. Ursol, I. Vakaliuk, I. Vishnivestsky, L. Voronkov, A. Yagensky; **United Kingdom (22 patients, 5 sites):** R. Body, D. Chandra, M. Davis, P. Kesteven, P. MacCallum, C. McCollum, I. Natarajan; **USA (527 patients, 68 sites):** E. Almasri, M. Amin, C. Anderson, S. Baker, J. Barney, B. Barth A. Bastani, P. Bercz, M. Bidair, T. Carman, H. Chang, C. Clark, M. Concha, J. Cornell, R. Dhingra, A. Doshi, R. Ebrahimi, B. Farley, G. Fermann, G. Foster, J. Fraiz, J. Fulmer, H. Gaggin, D. Goytia-Leos, B. Hahn, A. Haidar, A. Hamad, M. Hazelrigg, O. Ioachimescu, B. Johnson, H. Kabler, C-K. Kao, M. Kazimir, F. Kouras, M. Kung, R. Lerner, J. Lopez, A. Macchiavelli, S. Mahal, B. Margolis, G. McLaren, T. Milling Jr., M. Mittal, V. Nadar, V. Ohaju, T. Ortel, J. Overcash, K. Parthiban, R. Pearl, L. Pineda, R. Pratt, J. Pullman, O. Quintana, R. Rajan, P. Rastogi, C. Rees, W. Rodriguez, F. Saba, N. Shammas, S. Sharma. S. Sokol, S. Stoltz, D. Subich, M. Tuck, J. Updegrove, A. Warner, M. Welch, J. Welker, B. Whitman, T. Wichman, K. Yousef, R. Yusen, N. Zakai.