

# The Use of Betrixaban for Extended Prophylaxis of Venous Thromboembolism Events in Hospitalized, High-Risk Patients

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In June 2017, the FDA approved betrixaban for the prophylaxis of venous thromboembolism (VTE) events in adult patients hospitalized for an acute medical illness who are at risk for postdischarge thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.<sup>1</sup> The approval was based on data from the randomized, double-blind, double-dummy, Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Study (APEX) trial.<sup>2</sup> Investigators compared the use of betrixaban for extended-duration VTE prophylaxis with a standard enoxaparin regimen in patients hospitalized with acute medical illness who had VTE risk factors.<sup>3</sup> In this trial, investigators selected this patient cohort to test the strategy of extended prophylaxis with betrixaban.<sup>3</sup>

Paul P. Dobesh, PharmD, explained that the approval of betrixaban was important for several reasons:

- VTE events continue to occur during hospitalization and following discharge, despite the standard of care (SOC) for in-hospital prophylaxis.
- Anticoagulation initiated during hospitalization and extended for high-risk patients, post-discharge, may reduce the risk of VTE events.
- Extended-prophylaxis studies with other direct-oral anticoagulants (DOACs) did not demonstrate net clinical benefit or were associated with excess major bleeding.
- In the APEX trial, treatment with betrixaban demonstrated a significant reduction in VTE events and was not associated with excess major bleeding, producing an overall net clinical benefit.

## Pharmacological Properties of Betrixaban

Betrixaban has been specifically designed for VTE prophylaxis in acute medically ill patients. It has a distinct pharmacological properties from the other DOACs (Table 1).<sup>1,4-7</sup>

Betrixaban has an effective half-life of 19 to 27 hours.<sup>2</sup> According to Dobesh, the long half-life of betrixaban allows for true, once-daily dosing. Of the currently approved DOACs, betrixaban is the least renally excreted, with <18% cleared by the kidneys.<sup>2,4</sup> The other

## KEY TAKEAWAYS

- ▶ Betrixaban is the first FDA-approved product for extended prophylaxis of venous thromboembolism (VTE) events in acute medically ill patients.
- ▶ The betrixaban approval was based on data from the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Study (APEX) trial, which enrolled only hospitalized, acute medically ill patients who were at high risk for VTE events.
- ▶ In the APEX trial, VTE prophylaxis with betrixaban demonstrated a significant reduction in VTE events at 35 to 42 days and was not associated with excess major bleeding compared with VTE prophylaxis with enoxaparin for 14 days, producing an overall net clinical benefit.
- ▶ Various analyses have demonstrated that extended VTE prophylaxis with betrixaban could be considered a cost-effective regimen for hospitalized patients with acute medical illness at high risk of VTE, who require longer VTE prophylaxis extending to postdischarge period.
- ▶ A cost-effectiveness model among a hypothetical cohort of 10,000 acutely ill medical patients estimated that betrixaban reduced the risk of death by 0.16% and was a cost-effective regimen compared with enoxaparin, saving nearly \$1.8 million (\$178 per patient treated).
- ▶ A different cost-effectiveness analysis showed that extended VTE prophylaxis with betrixaban dominated standard VTE prophylaxis with enoxaparin, with a savings of \$780 and increased quality-adjusted life years by 0.017 per patient.
- ▶ For an average-sized hospital of 450 beds, treatment with betrixaban could result in 17 fewer VTE-related rehospitalizations compared with enoxaparin, and 36 fewer deaths or irreversible events leading to readmission with enoxaparin. In this analysis, betrixaban would save the hospital \$447,000 annually (\$182 per patient).
- ▶ Treatment with betrixaban could potentially decrease Centers for Medicare and Medicaid VTE-related readmissions penalties for hospitals.

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DOACs renal excretion range from 25% to 80%.<sup>2</sup> Because betrixaban has minimal renal excretion, it only requires dose reductions in patients with severe renal impairment. Dosage adjustments are not required in patients with mild to moderate renal impairment.<sup>1</sup>

Dobesh explained that betrixaban has a consistent anticoagulant effect over 24 hours, thereby allowing for true, once-daily dosing. Compared with some other approved DOACs, betrixaban also has a decreased propensity for drug interactions, due to a lack of any cytochrome P450 mediated metabolism DOACs. Dose reductions are only required when betrixaban is administered with P-glycoprotein (P-gp) inhibitors rather than cytochrome P450 inhibitors or inducers.<sup>3</sup>

### The APEX Trial

The APEX trial included a high-risk patient population and tested the strategy of extended VTE prophylaxis with betrixaban. Patients were eligible to participate in the APEX trial if they were aged ≥40 years, had been hospitalized for a specified acute medical illness, had decreased mobility, and had specific risk factors for VTE (Table 2).<sup>3</sup>

Table 2 includes the high-risk subsets, as defined. Major exclusion criteria are presented in Table 3.<sup>3</sup>

According to William H. Francis, MBA, RPh, “managed care providers typically need to know two things: [first], is this product for everyone, and [second], is there a well-defined group of patients who would benefit from this drug?” Francis explained, “APEX trial

investigators did a good job in defining a high-risk population that would most benefit from betrixaban.”

Stakeholders concurred that the high-risk patient population selected in the APEX trial was adequate and, in addition to existing risk factor tools, would help clinicians select appropriate treatments for patients.

A total of 7513 patients underwent randomization in the APEX trial. As shown in Figure 1, patients were randomized 1:1 to 2 possible cohorts<sup>1,3</sup>:

- Betrixaban cohort (n = 3759): oral betrixaban (160 mg loading dose on day 1, followed by 80 mg once-daily for 35-42 days) + subcutaneous enoxaparin placebo (once-daily for 10 ± 4 days)
- SOC cohort (n = 3754): subcutaneous enoxaparin (40 mg once-daily for 10 ± 4 days) + oral betrixaban placebo (once-daily for 35-42 days)

Patients with severe renal impairment (creatinine clearance, ≥15 to <30 mL/min) received dose reductions of 50% for both betrixaban and enoxaparin (ie, betrixaban 80 mg loading dose, followed by 40 mg daily or enoxaparin 20 mg daily).<sup>3</sup> Several stakeholders did question the rationale for dose reductions in patients with severe renal impairment, since betrixaban is minimally renally excreted. Patients who were receiving concomitant P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, and clarithromycin) also received betrixaban dose reductions of 50%.<sup>1,3</sup> Notably, patients with both severe renal impairment and concomitant P-gp inhibitors were excluded.

**TABLE 1.** Pharmacological Properties of Direct-Acting Oral Anticoagulants<sup>1,4-7</sup>

	Direct-Acting Oral Anticoagulant Product				
	Betrixaban	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
	Pharmacological parameter				
Half-life	19-27 hours <sup>a</sup>	9-13 hours <sup>b</sup>	12 hours <sup>c</sup>	10-14 hours <sup>b</sup>	12-17 hours <sup>b</sup>
Renal excretion (% of absorbed)	18%	36%	27%	~50%	80%
CYP3A4 metabolism	<1%	Yes	Yes	Minimal	No

CYP3A4 indicates Cytochrome P450 3A4.  
<sup>a</sup>Effective half-life  
<sup>b</sup>Terminal elimination half-life  
<sup>c</sup>Apparent half-life

**TABLE 2.** APEX Trial: Inclusion Criteria<sup>3</sup>

Criteria I	<ul style="list-style-type: none"> <li>• Male or female.</li> <li>• Hospitalized for acute medical illness for ≥96 hours.<sup>a</sup></li> </ul>	
Criteria II	<ul style="list-style-type: none"> <li>• Length of hospitalization ≥3 days</li> <li>• Expected severe immobilization for 24 hours during hospitalization and moderate and/or severe immobilization for ≥3 days after admission</li> <li>• Must be enrolled within 96 hours of presentation</li> <li>• Anticipated survival for ≥8 weeks</li> <li>• Hgb ≥10 g/dL</li> </ul>	
Criteria III	<b>AGE AND ADDITIONAL RISK FACTORS</b>	
	Aged ≥40 years and have additional risk factors <sup>b</sup> for VTE	
	<b>Age, years</b>	<b>Eligibility</b>
	≥75	All patients were eligible.
60-74	Requires 2 additional risk factors <sup>b</sup> or D-dimer ≥2x ULN	
50-59	Requires 2 additional risk factors <sup>b</sup> or D-dimer ≥2 x ULN and history of VTE and/or cancer	

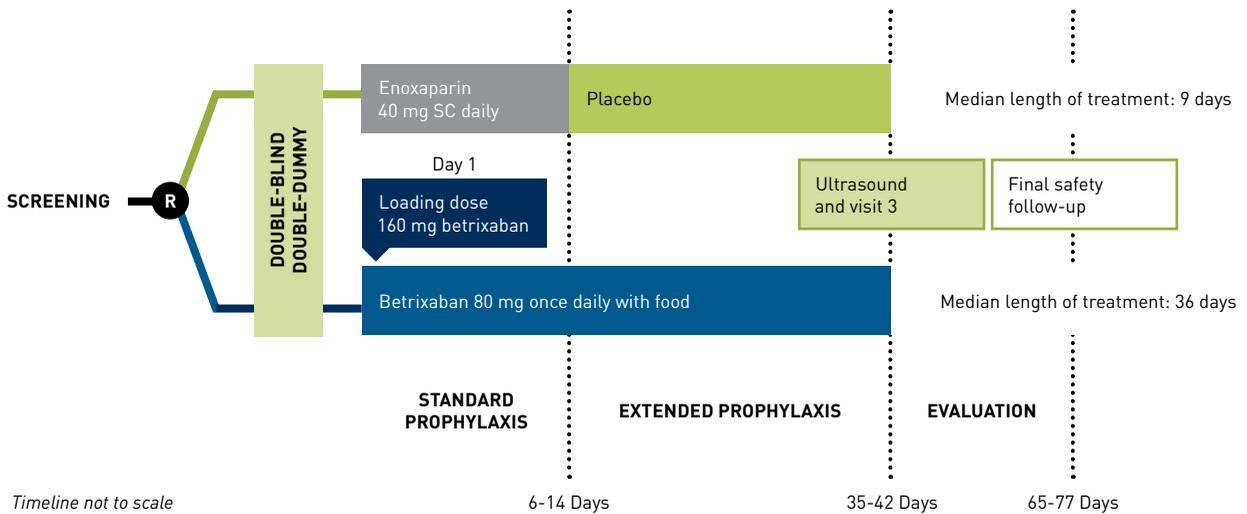
APEX indicates Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Study; BMI, body mass index; Hgb, hemoglobin; IV, intravenous; NYHA, New York Heart Association; ULN, upper limit of normal; VTE, venous thromboembolism.  
<sup>a</sup>Acute medical illnesses included heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke.  
<sup>b</sup>Additional risk factors included previous VTE or superficial vein thrombosis, history of NYHA Class III or IV heart failure, concomitant acute infections, obesity (BMI >35), history of cancer, inherited or acquired thrombophilia, current use of erythropoiesis-stimulating agents, and hormone therapy.

**TABLE 3.** APEX Trial: Exclusion Criteria<sup>3</sup>

Event	Criteria
Reduced kidney function	<ul style="list-style-type: none"> <li>End-stage renal disease (CrCl, &lt;15 mL/min) requiring dialysis, or severe renal insufficiency (CrCl, 15 to &lt;30 mL/min) and concomitant strong P-gp inhibitor</li> </ul>
Increased bleeding risk	<ul style="list-style-type: none"> <li>History of clinically significant bleeding within 6 months prior to enrollment</li> <li>History of any significant gastrointestinal, pulmonary, or urogenital bleeding; ongoing chronic peptic ulcer disease; or ongoing or acute gastritis within 2 years prior to enrollment</li> <li>Surgery, invasive procedure, or severe trauma within 3 months prior to enrollment</li> <li>Low body weight</li> </ul>
Anticoagulant use	<ul style="list-style-type: none"> <li>Contraindication to anticoagulant therapy</li> <li>Current intake of dual antiplatelet therapy</li> <li>Anticipated need for prolonged anticoagulation</li> <li>&gt;96 hours of administration of the following immediately prior to receiving study treatment: enoxaparin or another low molecular weight heparin, fondaparinux, unfractionated heparin.</li> </ul>
Reduced liver function	<ul style="list-style-type: none"> <li>Known abnormality of liver function tests (&gt;3 x ULN for serum glutamic-oxaloacetic transaminase/aspartate aminotransferase, serum glutamate pyruvate transaminase/alanine transaminase or alkaline phosphatase, or &gt;2 x ULN total bilirubin in absence of Gilbert syndrome), active liver disease, or hepatic dysfunction (eg, cirrhosis)</li> </ul>
Concomitant conditions	<ul style="list-style-type: none"> <li>Uncontrolled HIV or hypertension; taking strong P-gp inhibitor; concurrent or history of alcohol or drug abuse within 1 year prior to enrollment; pregnancy or breastfeeding; taking antiplatelet or anticoagulant medications, or anti-angiogenic therapy; contraindicated for low molecular weight heparin.</li> </ul>

APEX indicates Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study; CrCl, creatinine clearance; P-gp, P glycoprotein; ULN, upper limit of normal.

**FIGURE 1.** APEX Study Design<sup>1,3</sup>



APEX indicates Acute Medically Ill VTE Prevention With Extended Duration Betrixaban Study; SC, subcutaneous.

Clinically suspected deep vein thrombosis (DVT) events were confirmed using ultrasonography or other vascular-imaging techniques, while pulmonary embolism (PE) events were confirmed using either a computed tomography scan, a ventilation-perfusion lung scan, pulmonary angiography, or autopsy. Patients without clinically confirmed VTE events received ultrasonography after the last dose of study medication or matching placebo between days 35 and 42. All patients were followed for 30 ± 5 days after assessments (day 77).<sup>3</sup>

**End Points**

The primary efficacy end point was a composite of:<sup>3</sup>

- Asymptomatic proximal DVT, as detected by compression ultrasound between days 32 and 42
- Symptomatic proximal or distal DVT
- Symptomatic nonfatal pulmonary embolism
- Death from VTE between days 1 and 42

The composite of symptomatic VTE through day 42 was the secondary end point.<sup>3</sup> The primary safety outcome was the occurrence of major bleeding at any point until 7 days after the discontinuation of all study medications.<sup>3</sup> The occurrence of clinically relevant nonmajor bleeding was also assessed. Bleeding events in the APEX trial were classified using criteria from the International Society on Thrombosis and Haemostasis (ISTH).<sup>3,8</sup>

## Baseline Characteristics

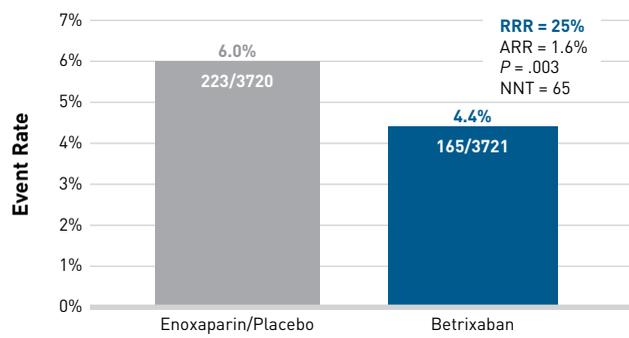
Baseline characteristics were generally well balanced between the 2 treatment groups.<sup>1</sup> Overall, 55% of patients were female. The most prevalent acute medical illnesses at hospitalization were heart failure (45%), acute infection without septic shock (29%), respiratory failure (12%), ischemic stroke (11%), and rheumatic disorders (3%). The mean age was 76.4 years. The majority of patients (68.6%) were aged  $\geq 75$  years. Ninety-seven percent of patients were severely immobilized at study entry and 62% had D-dimer  $\geq 2$  x upper limit of normal (ULN).<sup>1</sup>

Joshua D. Lenchus, DO, BSPHarm, observed that the baseline characteristics in the APEX trial were indicative of high-risk patients. "The study was very robust in patients over the age of 75 years with heart failure," he said.

## Efficacy Results

Efficacy analyses for the FDA-approved label were based on the modified intention-to-treat (mITT) population in the APEX trial.<sup>1</sup> The mITT population consisted of all patients who had received at least 1 dose of study medication and, on follow up, had reached one or more primary or secondary efficacy outcome components.<sup>1</sup> Results for the primary efficacy analysis included the mITT population who received the full (80 mg) or reduced (40 mg) dose of betrixaban. Additional analyses were performed for patients in the mITT population, stratified by betrixaban dose of 80 mg or 40 mg.<sup>1</sup>

**FIGURE 2A.** Primary Composite Endpoint (Overall mITT Population)<sup>1</sup>



mITT indicates modified Intention-to-Treat; ARR, absolute risk reduction; NNT, number needed to treat; RRR, relative risk reduction.

Following are results for the composite primary end point:

- There were significantly fewer VTE events with betrixaban (4.4%) compared with enoxaparin (6%) in the overall mITT population (**Figure 2A**).<sup>1</sup> The relative risk reduction (RR) was 25% and the absolute risk of reduction (AR) was 1.6%. The number needed to treat (NNT) to prevent one primary end point was 63.
- When including patients from the mITT population who received only full dose betrixaban (80 mg), there were also significantly fewer VTE events with betrixaban compared with enoxaparin (4.2% vs 6.2%) (**Figure 2B**).<sup>1</sup> The RR was 37.1% and the AR was 2%, with an NNT of 50.<sup>9</sup>

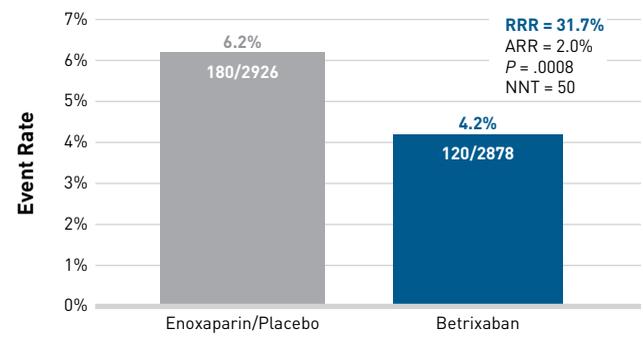
The occurrence of symptomatic VTE events at 42 days was also significantly improved with betrixaban in both groups.<sup>1</sup> In the overall mITT population, 1.5% of patients who received enoxaparin and 0.9% of patients who received betrixaban experienced a symptomatic VTE.<sup>1</sup> In the full dose betrixaban cohort, 1.4% of patients who received enoxaparin and 0.8% of patients who received betrixaban experienced a symptomatic VTE.<sup>1</sup>

Results for patients who were randomized to half dose betrixaban (patients with severe renal impairment or receiving P-gp inhibitors) were also reported. Similar VTE rates were reported with half dose betrixaban and enoxaparin (6-14 days followed by placebo).<sup>1</sup>

## Safety Results

There were no significant differences in the rates of major bleeding (with betrixaban for a median duration of 36 days) compared with enoxaparin for a median duration of 9 days (**Table 4**).<sup>1,10</sup> Overall, 0.57% of enoxaparin-treated patients and 0.67% of betrixaban-treated patients experienced major bleeding.<sup>1</sup> One patient in each group experienced fatal bleeding.<sup>1</sup> Clinically relevant nonmajor bleeding (CRNM) occurred in 2.45% of betrixaban-treated patients and 1.02% of enoxaparin-treated patients.<sup>1</sup> These cases mostly ranged from

**FIGURE 2B.** Primary Composite Endpoint (mITT Population of Patients Who Received Betrixaban 80 mg)<sup>1</sup>



mITT indicates modified Intention-to-Treat; ARR, absolute risk reduction; NNT, number needed to treat; RRR, relative risk reduction.

mild to moderate in severity (86%), and the majority (62%) did not require medical intervention or prolonged hospitalization.<sup>1</sup> The most frequent CRNM bleeding events in both treatment groups were hematuria and epistaxis, each occurring in 2% of patients. Nonbleeding adverse reactions were also reported in the APEX trial.<sup>1</sup> **Table 5** summarizes the occurrence of these nonbleeding adverse reactions.<sup>1</sup> None of these events were significantly different between the groups.

### Additional Analyses From the APEX Trial

Several post hoc analyses have further evaluated the use of extended thromboprophylaxis with betrixaban in acute medically ill patients. Key data demonstrated reductions in VTE-related rehospitalization; fatal, irreversible ischemic, or bleeding events; all-cause ischemic stroke, and VTE occurrence in patients with history of prior VTE (**Figures 3A- 3C**).<sup>2,11,12</sup>

Gibson et al evaluated 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) in a time-to-first-event analysis.<sup>11</sup> In patients with positive D-dimer results, betrixaban significantly reduced fatal or irreversible events at 35 to 42 days ( $P = .033$ ) and at study end at 77 days ( $P = .005$ ) versus enoxaparin. In all randomized patients, betrixaban reduced fatal or irreversible events at 35 to 42 days (4.08% vs 2.90%;  $P = .006$ ) and 77 days (5.17% vs 3.64%;  $P = .002$ ). Full dose betrixaban also reduced fatal or irreversible events through the end.<sup>11</sup>

Chi et al evaluated the effect of extended thromboprophylaxis with betrixaban on the risk of rehospitalization associated with VTE events.<sup>12</sup> The analysis showed that betrixaban reduced the risk of VTE-related rehospitalization when compared with enoxaparin. In the overall population, there was a 56% RR with betrixaban (35-42 days) compared with enoxaparin (6-14 days). In the population of patients who received full dose betrixaban, there was a 63% RR with betrixaban compared with enoxaparin.<sup>12</sup>

Yee et al assessed the efficacy and safety of betrixaban versus enoxaparin among subjects in the mITT population with and without prior VTE events.<sup>13</sup> The occurrence of VTE events was significantly decreased in patients with and without a history of VTE events. In patients who have had a prior VTE, 10.4% of those using betrixaban experienced VTE events compared to 18.9% of those using

**TABLE 4.** Bleeding Events in the APEX Trial Through Day 7 after Discontinuation of All Study Drugs (Safety Population)<sup>1,10</sup>

Parameter, n (%)	Betrixaban (n = 3716)	Enoxaparin (n = 3716)	Betrixaban vs Enoxaparin Relative Risk (95% CI)
Major bleeding <sup>a</sup>	25 (0.67)	21 (0.57)	1.19 (0.67-2.12); $P = .554$
Gastrointestinal	19 (0.51)	9 (0.24)	
Intracranial hemorrhage	2 (0.05)	7 (0.19)	
Intraocular	0	1 (0.03)	
Other	4 (0.11)	4 (0.11)	
Clinically relevant nonmajor bleeding <sup>b</sup>	91 (2.45)	1.02	2.39 (1.64-3.49); $P < .001$
Adverse event severity <sup>c</sup>			
Mild	38 (1.0)	17 (0.5)	
Moderate	42 (1.1)	15 (0.4)	
Severe	11 (0.3)	6 (0.2)	
Life-threatening	0	0	
Extended Hospitalization	11 (0.3)	8 (0.2)	

APEX indicates Acute Medically Ill VTE Prevention with Extended Duration Betrixaban Study.

<sup>a</sup>Major bleeding event was defined as clinically overt bleeding that met one of the following criteria: a reduction in hemoglobin of at least 2 g/dL within 48 hours of an overt bleeding event; a transfusion of at least 2 units of whole blood or packed red blood cells; a critical area [eg, intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular, pericardial, or a fatal outcome]. Retinal hemorrhages secondary to diabetic retinopathy or conjunctival bleeds did not qualify as major bleeds.

<sup>b</sup>Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention; unscheduled contact (visit or telephone call) with a physician; cessation of the study treatment (temporary or permanent); discomfort for the patient such as pain or impairment of activities of daily life.

<sup>c</sup>Mild: awareness of sign or symptom, but easily tolerated; Moderate: discomfort enough to cause interference with normal daily activities; Severe: inability to perform normal daily activities; Life-threatening: immediate risk of death from the reaction as it occurred; these bleeds would be included in the major bleed category.

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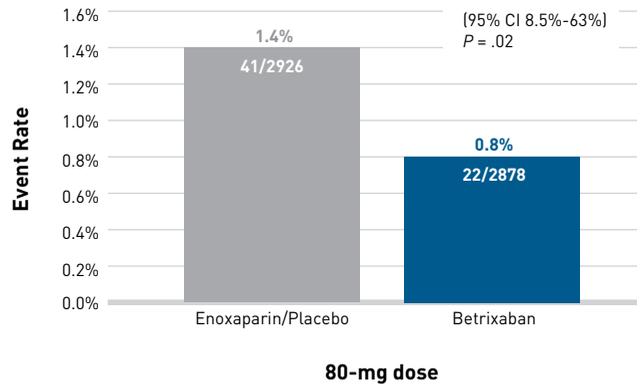
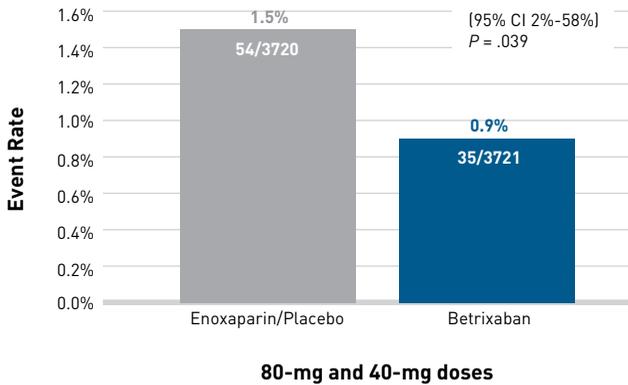
**TABLE 5.** Nonbleeding Adverse Reactions (Safety Population).<sup>1</sup>

Nonbleeding Adverse Reactions, n	Betrixaban (n = 3716)	Enoxaparin (n = 3716)
Urinary tract infection	123 (3%)	87 (2%)
Constipation	110 (3%)	102 (3%)
Hypokalemia	93 (3%)	84 (2%)
Hypertension	89 (2%)	80 (2%)
Headache	74 (2%)	59 (2%)
Nausea	67 (2%)	56 (2%)
Diarrhea	64 (2%)	61 (2%)

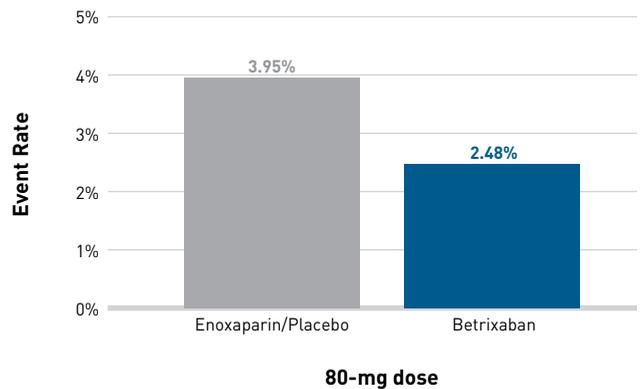
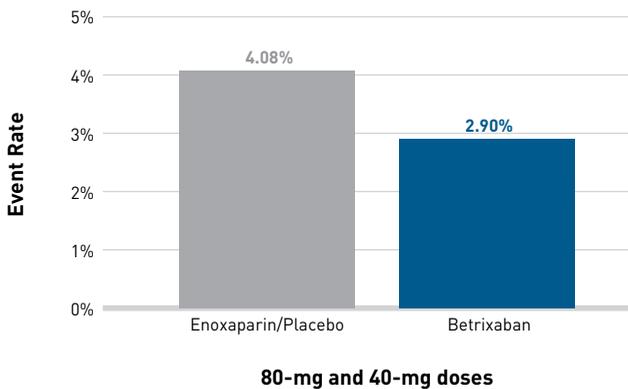
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enoxaparin. In those who did not have a prior VTE, 3.9% of patients using betrixaban experiences a VTE compared with 4.9% of those using enoxaparin. There was no significant difference in major or clinically-relevant nonmajor bleeding in patients with and without a history of VTE events.<sup>13</sup>

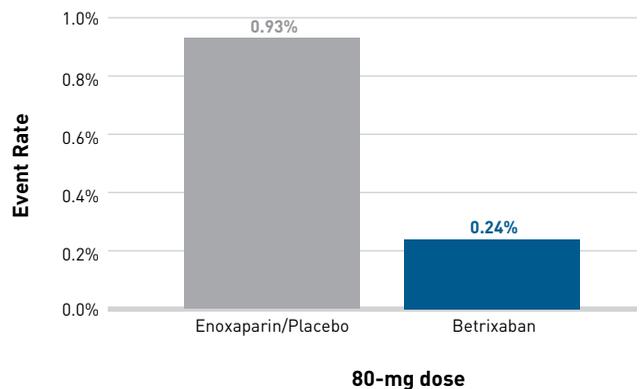
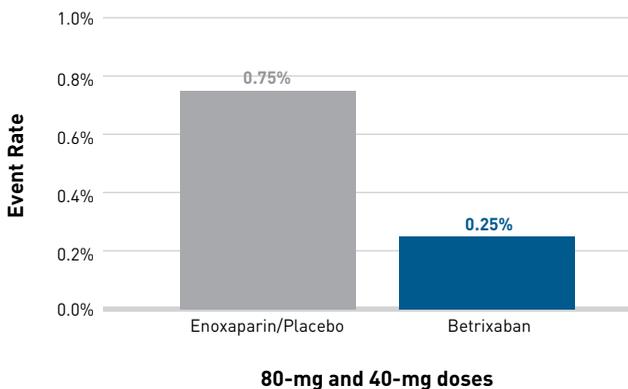
**FIGURE 3A.** Symptomatic VTE Events at 42 Days in the mITT Population<sup>2</sup>



**FIGURE 3B.** Fatal or Irreversible Outcomes in All Patients<sup>11</sup>



**FIGURE 3C.** VTE-related Rehospitalizations in the mITT Population<sup>12</sup>



mITT indicates Modified Intention-to-Treat; VTE, venous thromboembolism.

Extended-duration prophylaxis with betrixaban has been shown to reduce the risk of ischemic stroke, all strokes, and transient ischemic attack, compared with standard-duration enoxaparin.<sup>12</sup> Another study found that the occurrence of new ischemic stroke was increased with enoxaparin compared with betrixaban (0.5% vs 0.9%;  $P = .03$ ), as were all types of strokes (0.6% vs 1.1%,  $P = .03$ ).<sup>3</sup>

## Stakeholder Perspectives Regarding the APEX Trial

According to Jeffrey Nemeth, PharmD, MPA, “the biggest message conveyed in the APEX trial was that using VTE prophylaxis for an extended period post discharge was superior to doing nothing.” When evaluating the safety data of betrixaban, Frank P. Hull, MD, noted that “the safety data presented in the APEX trial really differentiated betrixaban from the other DOACs.”

Jacqueline Glee Lenoir, PharmD, explained that the “safety results from the APEX trial were responsible for the product being added to formulary at my institution.” Lenoir observed that “betrixaban was added to formulary because it was both safe and effective in medically ill patients.”

Stakeholders concurred the higher risk patient population selected in the APEX trial was adequate and would greatly help both clinicians and prescribers with the selection of patients for treatment.

## Costs and Formulary Perspectives

The economic burden associated with VTE is significant, both from a general healthcare perspective and from an individual patient perspective.<sup>14</sup> The NNT with betrixaban to prevent 1 irreversible event is 63, as compared with 102 for 1 symptomatic VTE, and 127 for 1 VTE-related hospitalization.<sup>15</sup>

Importantly, noted Dobesh, “betrixaban can prevent a \$16,000 to \$32,000 readmission for another VTE event.” He further observed that “if we have a product that is going to cost more than enoxaparin but is going to decrease hospital length of stay or reduce readmissions for subsequent VTE events, most providers and prescribers will accept that model.” The stakeholders representing managed care agreed that formulary issues with betrixaban would not be problematic if providers and prescribers used the product as it was studied and approved.

Based on clinical outcomes from the APEX study, analyses have assessed the economic value of extended versus standard VTE prophylaxis. They demonstrated that extended VTE prophylaxis with betrixaban could be considered a cost-effective treatment for hospitalized patients with acute medical illness at risk of VTE, who require longer VTE prophylaxis from hospital admission through post-discharge.<sup>16-19</sup>

A cost-effectiveness model among a hypothetical cohort of 10,000 acutely ill medical patients, identified according to the

American College of Chest Physicians (ACCP) recommendation for pharmacological VTE prophylaxis, estimated that betrixaban could reduce the risk of death by 0.16%.<sup>16</sup> Findings also suggested that betrixaban would be a cost-effective regimen compared with enoxaparin, saving nearly \$1.8 million, or \$178 per patient treated.<sup>16</sup>

Another analysis estimated the cost per quality-adjusted life-year (QALY) gained for extended-duration betrixaban (35-42 days) compared with standard-duration enoxaparin (6-14 days) from a US payer perspective over a lifetime horizon. Costs encompassed treatment and management of primary events, complications, recurrent events, and primary event complications. Results showed that extended VTE prophylaxis with betrixaban was better than standard VTE prophylaxis with enoxaparin, with a savings of \$780 and increased QALYs of 0.017 per patient.<sup>17</sup>

The budget impact model for an acute-care hospital with 20,000 admissions assumed that approximately 2,500 patients would potentially receive VTE prophylaxis with betrixaban.<sup>18,19</sup> For the average 36-day period assessed by the model, the use of betrixaban would result in the avoidance of 54 VTE events (symptomatic proximal or distal DVT; asymptomatic proximal DVT; nonfatal PE; or VTE-related death). The total cost of clinical events would be \$3.6 million for enoxaparin versus \$2.3 million for betrixaban. Including drug plus administration costs, this would result in an overall cost savings of \$447,000, or \$182 per patient treated.

Stakeholders agreed that these findings, particularly those related to readmissions, could save even more if CMS penalties to hospitals for VTE readmissions were reduced. Gary L. Johnson, MD, MS, MBA, predicted that “betrixaban will not face a lot of payer barriers.” According to Johnson, “the primary barrier will be awareness by prescribers, not barriers from payers.” Hugh Fatodu, MBA, RPh, agreed. Regarding P&T review, Fatodu asserted that betrixaban “will automatically have a leg up.”

Claudette McPherson, BSN, cautioned that “pre-authorizations could be a barrier.” Because prophylaxis begins in-hospital and continues when the patient is released from the hospital, McPherson advised that “planning is important, so that on the day of discharge, the patient can get the medication.”

## Conclusions

Based on current data, betrixaban can play an essential role in the VTE prophylaxis landscape, providing protection for the entire at-risk period that extends beyond hospitalization. The next article of this supplement presents potential solutions for implementing best practices in transitional care for patients, post discharge. ■

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