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Betrixaban: A New Oral Anticoagulant for Extended-Duration Thromboprophylaxis

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Venous thromboembolism (VTE), a designation for deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs at an 8-fold increase in patients who are acutely ill requiring hospitalization with risk factors such as immobility for 3 days or greater, various comorbid conditions, previous VTE, and age above 70 years.[1,2] These VTE events are an important cause of morbidity and mortality in the hospital but are preventable with appropriate prophylactic treatment. Clinical practice guidelines recommend a 6 to 14 day course of parenteral anticoagulant thromboprophylaxis during hospital stay, until full mobility is restored, or the patient is discharged.[3] Betrixaban, a new oral factor Xa inhibitor (FXa), was recently approved for extended-duration (35 to 42 days) thromboprophylaxis in those patients acutely ill with restricted mobility and other risk factors for VTE. Pharmacologic thromboprophylaxis with anticoagulants such as enoxaparin significantly reduce the risk of VTE in acutely medically ill patients during hospitalization as seen by the MEDENOX trial.[4] However, approximately 56% of all hospital associated VTEs occur up to 6 months following discharge, with the highest risk reported within 19 days after hospitalization.[5] Anticoagulants are effective at preventing VTE because they work by inhibiting the formation of specific clotting factors that play a role in the generation of thrombin and fibrin, thereby impairing the body's natural ability to coagulate. Common parenteral anticoagulants for thromboprophylaxis include unfractionated heparin (UFH) and low-molecular weight heparins (LMWH). Extended-duration thromboprophylaxis in acutely ill hospitalized patients, beyond hospitalization and up to 35 days, is specifically not recommended by the 2012 CHEST guidelines due to unfavorable net clinical benefit from existing trials.[3] The three previous studies that compared extended-duration enoxaparin, apixaban, and rivaroxaban to standard-of-care enoxaparin all concluded that there was no net clinical benefit and undue risk of bleeding.[6,7,8] Despite previous evidence, betrixaban gained FDA approval for its indication in extended-duration thromboprophylaxis in those patients acutely ill with restricted mobility and other risk factors due to improved outcomes compared to the standard-of-care anticoagulant, enoxaparin. This article will discuss the pharmacology, adverse event data, dosing and administration as well as the literature supporting betrixaban's approval.

IN THIS ISSUE

Pharmacology

Mechanism of Action

Betrixaban is highly specific (>86,000 fold vs. other coagulation enzymes) for both free FXa and prothrombinase complex inhibitor which does not require a cofactor, such as anti-thrombin III, for activity. At plasma concentrations ranging from 5 ng/mL to 25 ng/mL, it provides a dose-dependent and clinically effective decreases in the amount of thrombin generated without a direct effect on platelet aggregation.[9,10] Clinical effectiveness in thrombin inhibition was determined by assays that demonstrated similar thrombin inhibition with betrixaban and prophylactic doses of fondaparinux (2.5 mg SC once daily).[11]

Betrixaban's chemical structure has an affinity toward hERG channels, a type of cardiac potassium ion channel that plays a role in cardiac muscle repolarization.[9] Betrixaban has a mean predicted concentration-dependent increase in the QTc interval of 4 ms (upper 95% CI, 5 ms) at 80 mg daily.[10]

Pharmacokinetics

Betrixaban at a dose of 80 mg has an oral bioavailability of 34%, shows rapid absorption and reaches peak concentrations within 3-4 hours after administration.[9] High fatty meals may reduce the oral bioavailability and peak concentration of betrixaban with effects observed for up to 6 hours after meal intake. Betrixaban has a volume of distribution (Vd) of 32 L/kg and its terminal half-life is 37 hours while its pharmacodynamic half-life is ~20 hours.[9,10] Without a loading dose, betrixaban reaches steady state after 6 days of therapy.[10] Betrixaban is mainly found as unchanged drug in human plasma with approximately 60% being protein bound in vitro. Approximately 15-18% of the circulating drug is composed of two inactive hydrolysis-generated metabolites; PRT062802 and PRT062803.[12] Less than 1% of the minor metabolites are formed via various cytochrome P450 (CYP) enzymes (1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4).10 Approximately 85% of betrixaban is fecally eliminated while 11% is renally eliminated.[10]

Betrixaban is a major substrate for permeability glycoprotein (p-gp), and major drug-drug interactions with betrixaban are limited to potent p-gp inhibitors (e.g., ketoconazole, amiodarone, diltiazem, and verapamil) that significantly increase Cmax or

AUC.[9,10] Digoxin, a p-gp substrate, had no significant effect on AUC or Cmax when combined with betrixaban.[10] Renal impairment has been shown to greatly alter the AUC0-24 of betrixaban. A 1.89, 2.27 and 2.63-fold increase in AUC was observed when comparing healthy volunteers to mild (eGFR ≥ 60 to < 90 ml/min/1.73m2), moderate (eGFR ≥ 30 to < 60 ml/min/1.73m2), and severe (eGFR < 30 ml/min/1.73m2), respectively.[10] A dose reduction of betrixaban is currently recommended when creatinine clearance (CrCl), using actual body weight, is ≥15 to < 30 mL/min.[10] The use of betrixaban in hepatic impairment has not been studied.[10]

Clinical Trials

Betrixaban has been studied in various clinical settings, two phase II trials and in one phase III trial. Phase II clinical trials investigated betrixaban in the setting of extended VTE prophylaxis after total knee replacement (TKR) and in stroke prophylaxis in patients with atrial fibrillation.[11,13] Atrial fibrillation is not an FDA approved indication of betrixaban at this time. The phase III trial provided sufficient evidence allowing the FDA to approve betrixaban for the indication of extended VTE prophylaxis in acutely ill patients with limited mobility along with other risk factors for VTE.[14]

Phase II Trials

The EXPERT trial (A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement) was a multicenter, randomized, parallel-group clinical trial investigating the safety and efficacy of betrixaban compared to standard-of-care subcutaneous (SC) enoxaparin for the prevention of venous thromboembolism after total knee replacement (TKR).[11] The primary efficacy outcome was the occurrence of VTE up to day 10 to 14 and 4-8 weeks post -TKR.[11] VTE included proximal and/or distal DVT identified by unilateral mandatory venography of the leg, symptomatic proximal DVT, or PE. Secondary outcomes included pharmacodynamic and pharmacokinetic assessments of betrixaban. Patients and physicians were not blinded to enoxaparin allocation but they were blinded to the betrixaban dose. This study included men and women between 18 - 75 years of age undergoing elective primary unilateral TKR. Patients were excluded from this study if they met any of the following criteria; women with reproductive potential, patients with bleeding disorders, a recent episode of internal bleeding, or at high risk of bleeding and a platelet count <100,000/mm3, hemoglobin <10 g/dL or hematocrit <30%.[11] The use of aspirin up to 325 mg daily and non-steroidal-anti-inflammatory agents were allowed but discouraged.

Patients were randomly allocated to treatment groups within 6 hours of surgery completion in a 2:2:1 ratio (betrixaban 15 mg PO BID, betrixaban 40 mg PO BID, or enoxaparin 30 mg SC BID, respectively). The initial dose of betrixaban was initiated 6-8 hours after surgery and enoxaparin was administered within 12-24 hours after surgery. Treatment was continued for 10 to 14 days until mandatory venography was performed unless the patient had a VTE prior to the stop date that was confirmed with imaging. If a suspected VTE was confirmed by imaging studies, the patient underwent treatment and was withdrawn from the trial. Blood levels were obtained several times throughout the treatment period to analyze betrixaban concentrations and corresponding anticoagulation activity, measured by thrombin generated inhibition assays, anti-Xa activity, aPTT, PT and INR. The primary safety outcome was bleeding categorized as either major or clinically relevant non-major bleeding (CRNMB). Major bleeding was defined as bleeding that was fatal, involved vital organs, required additional surgery or procedure, or had a bleeding index ≥2.0 (number of units of packed red blood cells or whole blood transfused plus the hemoglobin values before the bleeding episode minus the hemoglobin levels after the bleed had stabilized). The criteria for CRNMB were not provided.[11]

A total of 214 patients received at least one dose of study drug.[11] Only 82% of patients were included in the primary analysis.[11] See **Table 1** for efficacy outcomes in the EXPERT trial. No significant difference in the primary efficacy outcome was found when comparing each of the three groups together; betrixaban 15 mg PO BID (20%; 95% CI, 11.4% to 31.3%), betrixaban 40 mg PO BID (15.4%; 95% CI, 7.6% to 26.5%), and enoxaparin 30 mg SC BID (10%; 95% CI, 2.8% to 23.7%).[11] No statistical comparison of the results was provided. Bleeding risk was similar across all groups. Only one major bleed in the enoxaparin group was reported, and two cases of CRNMB occurred in both the betrixaban 40 mg and enoxaparin group.[11]

The pharmacodynamics analyses revealed that the 40 mg dose of betrixaban achieved greater inhibition of thrombin generation than both the 15 mg betrixaban dose and enoxaparin.[11] On the other hand, the 40 mg betrixaban dose showed similar effects on anti-FXa activity compared with enoxaparin while the 15 mg showed less.

Phase III Trial

The Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients (APEX) trial was a randomized, double-blind, double-dummy, parallel-group multinational phase III clinical trial comparing extended-duration thromboprophylaxis with betrixaban to standard-duration enoxaparin in acute medically ill patients with reduced mobility.[14] The primary efficacy outcome was the composite of asymptomatic DVT between day 32 and 46, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between day 1 and 42. Patients were included in the study if they were at least 40 years of age, had been hospitalized for less than 96 hours for an acute illness (heat failure, respiratory failure, infection, rheumatic disease, or ischemic stroke), and had reduced mobility and specific risk factors.14 Patients were excluded from the trial if they had an indication for anticoagualtion, CrCl <15 mL/min, history of significant bleeding within the last 6 months or a history of hemorrhagic stroke.

After APEX enrolled 35% of the total cohort, the investigators modified the inclusion criteria to better assess the population at high risk of VTE. Data analysis was completed in 3 subgroups of the total trial population.[15] Cohort 1 included patients with a baseline D-dimer level ≥2x the upper limit of normal (ULN) and Cohort 2 included those in cohort 1 and patients age ≥75 years. Cohort 3 was the entire APEX patient population. Patients were randomly selected in a 1:1 ratio to receive either SC enoxaparin 40 mg once daily for 10±4 days plus oral placebo once daily for 35-42 days or SC enoxaparin placebo once daily for 10±4 plus oral betrixaban (loading dose [LD] of 160 mg and then 80 mg daily for 35 to 42 days). The dose of enoxaparin was reduced to 20 mg in the presence of severe renal insufficiency (CrCl <30 mL/min). Additionally, patients receiving p-gp inhibitors or with renal impairment (CrCl between 15-29 mL/min) received betrixaban 80 mg LD and then 40 mg daily for 35 to 42 days. Suspected DVT's that took place before days 35 to 42 were confirmed using ultrasonography or other vascular-imaging and suspected PEs were con-

Table 1 | Primary Outcome Data from the APEX and EXPERT trials[11,14]

APEX									
Analysis Cohort	**Cohort 1[a]**				**Cohort 2[b]**		**Overall Population**		
Treatment Group	Betrixaban (n=1914)	Enoxaparin (n=1956)	**RR (95% CI)**	Betrixaban (n=2842)	Enoxaparin (n=2893)	**RR (95% CI)**	Betrixaban (n=3112)	Enoxaparin (n=3174)	**RR (95% CI)**
Primary Efficacy Outcome[c]	6.9%	8.5%	0.81 (0.65-1.00)	5.6%	7.1%	0.80 (0.66-0.98)	5.3%	7.0%	0.76 (0.63-0.92)
EXPERT									
Treatment Group	Betrixaban 15 mg PO BID (n=70)			Betrixaban 40 mg BID (n=65)			Enoxaparin 30 mg Q12H (n=40)		
Composite Efficacy Outcome[d]	20% (11.4%-31.3%)			15.4% (7.6%-26.5%)			10.0% (2.8%-23.7%)		

a: Cohort 1 included patients with an elevated baseline D-dimer (defined as ≥2x ULN)
b: Cohort 2 included patients in cohort 1 and those aged ≥75 years
c: The primary efficacy outcome was the 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.
d The incidence (and reported 95% CI of the incidence) of centrally adjudicated VTE up to the mandatory venogram on day 10 to 14
95% CI= 95% confidence interval; **BID** = twice daily; **Q12H** = every 12 hours; **mg**= milligrams; **QD**= once daily; **RR** = relative risk; **ULN** = upper limit of normal

firmed with CT, a ventilation-perfusion lung scan, pulmonary angiography, or autopsy. Patients without suspected DVT's or PE's between day 35 and 42 underwent mandatory ultrasonography for detection of possible asymptomatic DVT. Follow-up occurred for another 30±5 days after assessment on day 42.

Two major secondary efficacy outcomes included either the composite of symptomatic VTE through day 42 or the composite of symptomatic proximal DVT between day 32 and 47, symptomatic DVT, nonfatal PE, or death from any cause through day 42. The primary safety outcome was the presence of major bleeding (defined according to the criteria of the International Society on Thrombosis and Haemostasis) at any point up to 7 days after discontinuation of all study medications. The secondary safety outcome was major bleeding or CRNMB. If superiority was not met in any Cohort 1, then the remaining cohort results were taken to be exploratory in nature. Patients were eligible for inclusion in the primary efficacy analysis if they had received one dose of study medication and had undergone acceptable VTE screening (ultrasonography) during the study. Patients were eligible for inclusion in the principal safety analysis if they had received at least one dose of study medication.

A total of 3759 patients were randomized to the betrixaban group and 3754 to the enoxaparin group.[14] The primary efficacy outcome occurred 6.9% of the betrixaban group compared to 8.5% of the enoxaparin group in Cohort 1 (relative risk [RR] = 0.81; 95% CI, 0.65-1.00). Separate analysis of the primary outcome in Cohort 1 demonstrated superiority of betrixaban (RR = 0.80; 95% CI, 0.64-0.99). In the overall population, the principal safety outcome occurred in 0.7% of the betrixaban group and 0.6% in the enoxaparin group (RR = 1.19; 95% CI, 0.67-2.12) with similar results in Cohorts 1 and 2.14 However, in the overall patient population the secondary safety outcome (major or CRNMB) occurred in 3.1% of the betrixaban group and 1.6% of the enoxaparin group (RR = 1.97; 95% CI, 1.44-2.68).14 Although extended-duration betrixaban in Cohort 1 was marginally superior for the primary efficacy outcome, Cohorts 2 and the overall population were both superior to standard-duration enoxaparin.

Post Hoc Analyses

Gibson et al. performed a post hoc substudy analysis of the APEX trial investigating the incidence of fatal and irreversible efficacy and safety outcomes within the study population.[16] The primary endpoint was the composite of all fatal or irreversible ischemic and bleeding events between the extended-duration betrixaban group and the standard-duration enoxaparin group. The primary analysis included patients with symptomatic events from day 1 to visit 3 (or day 42). Results through the end of study at visit 4 (or day 77) was an exploratory analysis. Irreversible efficacy endpoints included 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.16 Irreversible safety end points included fatal bleeding or intracranial hemorrhage, excluding nonfatal PE.[16] See **Table 2** for the composite of fatal and irreversible events.

A significant reduction in the time to first fatal or irreversible event favoring betrixaban was found when compared with enoxaparin in Cohort 1 (D-dimer ≥2x upper limit of normal) for both visit 3 (3.54% vs. 4.80%; HR, 0.73; 95% CI, 0.55-0.98) and

visit 4 (4.36% vs. 6.27; HR = 0.70; 95% CI, 0.54-0.90).[16] These findings were also present in Cohort 2 (Cohort 1 and age 75 and older) and Cohort 3 (overall patient population) for visit 3 as well as in visit 4. However, when analyzing adjusted dose betrixaban (40 mg QD) in Cohort 3, no difference was seen in composite event rates at visit 3 compared with adjusted dose enoxaparin (P=0.893). Analysis of full-dose betrixaban (80 mg QD) compared with standard-dose enoxaparin in Cohort 3 demonstrated a significant reduction in the composite outcome in all cohorts and at both visits; at visit 3 (P=0.002) and at visit 4 (P=0.0007).

Limitations of this study included the lack of an adjudicated determination on whether there was a segmental versus subsegmental involvement in patients with PE. Additionally, there was lack of quantified infarct size as well as no indication for the type of MI (non ST-segment elevated myocardial infarction (or ST -segment elevated myocardial infarction). Despite the shortcomings, this post hoc analysis provided additional data supporting its FDA approval by analyzing only the most severe cases, VTE and bleeding events, which were irreversible or fatal.

The APEX trial excluded patients from the primary analysis if they did not receive an ultrasound at follow-up. An separate analysis by Gibson et al. compared the occurrence of VTE (defined as the composite of symptomatic DVT, nonfatal PE, and VTE-related death and asymptomatic DVT) between the extended-duration betrixaban and enoxaparin groups in patients regardless if they received an ultrasound for VTE evaluation at the end of the study. The occurrence of combined symptomatic and asymptomatic VTEs occurred less with betrixaban treated patients than with enoxaparin (4.4% vs 6.0%; RR = 0.75; 95% CI, 0.61-0.91).[17] Additionally, a post-hoc analysis of the APEX study compared the rates of VTE related rehospitalization in patients treated with extended-duration betrixaban and standard-duration enoxaparin. Patients were less likely to be rehospitalized when treated with betrixaban compared to enoxaparin (HR = 0.44; 95% CI 0.25-0.80).[18]

Adverse Events

In the APEX trial, no difference in major bleeding was seen between extended-duration betrixaban and standard-duration enoxaparin (RR = 1.19; 95% CI, 0.67-2.12).[10,14] Rates of combined CRNMB and major bleeding were greater with extended-duration betrixaban (RR = 1.97; 95% CI, 1.44-2.68). However, anticoagulation exposure with betrixaban was approximately 3-4 weeks longer than enoxaparin. Further, 86% of the CRNMB events with betrixaban were mild to moderate in severity (primarily epistaxis and hematuria). Comparing betrixaban with enoxaparin, 54% and 52% experienced at least one adverse effect while 18% and 17% experienced one serious adverse event, respectively.[10] **Table 2** lists relevant bleeding information from the APEX trial.

Table 2 | Safety Outcomes from APEX[10]

Adverse Effect	Betrixaban (n=3716)	Enoxaparin (n=3716)
Major Bleeding[a] (RR; 95% CI)	25 (0.7%)	21 (0.6%) RR=1.19 (0.67-2.12)
Major or CRNMB[b] (RR; 95% CI)	116 (3.1%)	59 (1.6%) RR=1.97 (1.44-2.68)
Epistaxis	58 (2%)	24 (1%)
Hematuria	62 (2%)	28 (1%)

[a] Major bleeding event was defined as clinically overt bleeding that met one of the following criteria: a reduction in hemoglobin of a least 2 g/dL within 48 hours of an overt bleeding event; a transfusion of at least two units of whole blood or packed red blood cells; a critical area; e.g., 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 a major bleeds.
[b] CRNM 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, (temporary/permanent) cessation of the study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.
95% CI = 95% confidence interval; **RR** = relative risk

Dosing and Administration

Betrixaban (Bevyxxa®) is available as 40 mg and 80 mg capsules and is approved for the prophylaxis of VTE in adult patients hospitalized for acute medical illness with reduced mobility and risk factors for thromboembolic complications.[10] Betrixaban should be initiated with a LD of 160 mg followed by 80 mg once daily take at the same time of day for 35 to 42 days.[10] Dose adjustment for betrixaban (LD of 80 mg followed by 40 mg once daily) is recommended when the CrCl, using actual body weight, is ≥15 to <30 mL/min or if the patient is receiving or starting concomitant strong p-gp inhibitors.[10] The safety and efficacy of betrixaban has not been studied in renal failure requiring dialysis and it is unknown if hemodialysis removes betrixaban, but unlikely given that 60% of the drug is protein bound.[10] Betrixaban is not recommended to be used in patients with hepatic impairment due to lack of safety and efficacy data in addition to inherent coagulation abnormalities seen in liver impairment. If a dose is missed, the dose should be taken as soon as possible on the same day but not doubled up to make up for missed doses.[10] There is no required monitoring for laboratory markers, but patients should periodically be assessed for signs and symptoms of bleeding or thrombosis.[9] The fetal risk for betrixaban in pregnancy and lactation cannot be ruled out due to lack of data for use in these populations, therefore its use is not recommended unless the benefits outweigh the risks. The safety and efficacy of betrixaban has not been studied in the pediatric population. The geriatric population has been extensively studied in the APEX trial with 90% being over the age of 65 and no differences in safety or efficacy were observed between older and younger ages, therefore, safety and efficacy have been established in this population.[14]

Cost

The cost of a 30-day supply of betrixaban is $450-500 at a local pharmacy. The manufacturer of Bevyxxa®, Portola Pharmaceuticals©, offers a $75 off a patient's co-pay after they have paid $50 if they are privately insured or are paying cash.[19]

Summary

The transient increased risk of VTE in acutely medically ill

hospitalized patients with risk factors for VTE has been shown to extend beyond hospitalization even though current guidelines recommend a 6 to 14 day course of parenteral prophylactic anticoagulants. Betrixaban provides a safe and effective option for extended-duration thromboprophylaxis (35 to 42 days) as seen in the APEX study and in the APEX sub-study.[14,16] Clinical guidelines do not recommend extended-duration thromboprophylaxis for prevention of VTE in the acutely ill medical patient with reduced mobility; however, with new data, betrixaban provided a net clinical benefit over the standard-of-care enoxaparin.[3] Overall, betrixaban provides superior efficacy for VTE prophylaxis and statistically non-inferior bleeding (point difference favored enoxaparin) to standard therapy and standard therapy duration.[14] Betrixaban may have a benefit in preventing fatal and irreversible events extending beyond the acute phase of hospitalization in acutely medically ill patients with risk factors for VTE.

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