Betrixaban (Bevyxxa)

A Direct-Acting Oral Anticoagulant Factor Xa Inhibitor

Jessica W. Skelley, PharmD, BCACP; Angela R. Thomason, PharmD, BCPS; and Jeffery C. Nolen, PharmD Candidate

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a preventable cause of morbidity and mortality in hospitalized patients. Approximately 25% of all VTE events occur in hospitalized patients on medical inpatient service. Although VTE is more common in surgical patients, patients hospitalized for an acute medical illness have an eightfold increased risk of VTE during their course of stay.[1,2]

Several risk factors contribute to the development of VTE in acutely ill hospitalized patients, including previous VTE, active cancer, reduced mobility, recent trauma or surgery, age of 70 years or older, organ failure, infarction, obesity, acute infection, or hormonal therapy.[1,3] The Padua Prediction Score risk assessment categorizes acutely ill hospitalized patients into two categories—low risk or high risk—based on the risk factors associated with the development of VTE. In one study, 11% of patients in the high-risk category developed a VTE without prophylaxis compared with 0.3% in the low-risk group. In addition, a significant portion of these VTE events were fatal.[4]

There are two types of prevention therapies: mechanical methods and pharmacological agents. Mechanical methods for the prevention of VTE include graduated compression stockings, intermittent pneumatic compression devices, and venous foot pumps. These devices improve venous status, a risk factor associated with VTE. The advantage of medical devices over pharmacological agents is low probability of fatal or nonfatal bleeding. Currently, medical devices are reserved for high-risk patients who are either bleeding or at high risk for major bleeding.[3] Pharmacological agents are preferred for high-risk patients in the prevention of VTE during hospitalization.

The American College of Chest Physicians (ACCP) recommends anticoagulant thromboprophylaxis with low-molecular-weight heparin (once daily), low-dose subcutaneous unfractionated heparin (two or three times daily), or fondaparinux (once daily) in acutely ill hospitalized patients with increased risk of VTE (high-risk patients). Using the literature and evidence available in 2012, the guidelines recommend selection of a pharmacotherapy agent based on patient preference, compliance, cost, and ease of administration.[3,5]

The outcome of VTE prophylaxis is improved venous flow and reduction in the patient's hypercoagulable state. Short-term thromboprophylaxis (five to 14 days) in high-risk medical patients has reduced the rate of VTE, including fatal PE, with a small increase in risk of bleeding.[3] Recent trials reported that the risk of VTE in medical patients is as high as 5% to 6% at 30 days after discharge, and extended prophylaxis with pharmacotherapy for longer than 14 days up to approximately 35 days may be warranted.[6,7] Extended VTE prophylaxis is currently recommended in surgical patients; however, it remains controversial in medically ill patients due to the risk of bleeding.[3] The "Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients With Prolonged Immobilization" (EXCLAIM) study demonstrated a reduction of overall VTE with extended-duration, once-daily enoxaparin compared with placebo, but failed to show benefit in the reduction of fatal PE or overall mortality. In addition, the extended-duration enoxaparin group had a significantly higher rate of bleeding events compared with the placebo group.[6]

Since the publication of the 2012 ACCP guidelines[3] for short-term and extended thromboprophylaxis for acutely ill patients with high risk of development of VTE, two studies have been published regarding the use of direct oral anticoagulants (DOACs) in this patient population. The ADOPT trial reported that extended-duration apixaban (Eliquis, Bristol-Myers Squibb) (2.5 mg twice daily for 30 days) was not superior to short-term enoxaparin in prevention of VTE. In addition, the apixaban group had a higher rate of bleeding.[8] In the MAGELLAN trial, extended-duration rivaroxaban (Xarelto, Janssen) (10 mg once daily for 35 days) demonstrated lower rates of VTE, but had a significantly higher rate of bleeding.[7] Overall, systematic reviews show a positive decrease in the incidence of VTE with extended-duration rivaroxaban, apixaban, and enoxaparin; however, each was associated with a higher rate of fatal and nonfatal bleeding, yielding no net benefit.[9,10]

Betrixaban (Bevyxxa, Portola Pharmaceuticals) is an extremely potent factor Xa inhibitor.[11] In October 2016, Portola submitted a new drug application for betrixaban for extended-duration prophylaxis of VTE in hospitalized, acute medically ill patients with risk factors associated with VTE. It was granted priority approval by the Food and Drug Administration (FDA) in June 2017.[12,13] Betrixaban is the only FDA-approved DOAC for extended-duration prophylaxis for VTE in acute medically ill patients.

MECHANISM OF ACTION

Betrixaban inhibits free and prothrombinase bound factor Xa in a concentration-dependent manner.[11,14] Based on existing data, betrixaban at concentrations ranging from 5 ng/mL to 25 ng/mL

Dr. Skelley is an Assistant Professor of Pharmacy Practice and Dr. Thomason is a Professor of Pharmacy Practice at Samford University, McWhorter School of Pharmacy, in Birmingham, Alabama. Mr. Nolen is a Doctor of Pharmacy Candidate (2018) at that institution. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi and Associates in New York, New York.

Disclosure: The authors report no commercial or financial interests in regard to this article.

Table 1 Summary of Betrixaban Phase 2 and Phase 3 Trials[13,14,19]

Study	Indication	Evaluable Patients	Intervention Arms	Control Arms	Design	Primary Outcome
EXPERT (Phase 2)	VTE prevention in total knee replacement	175	Betrixaban 15 mg twice daily and 40 mg twice daily, both six hours postoperatively	Enoxaparin 30 mg SC twice daily 12–24 hours postoperatively	RCT, open label. Blinded to betrixaban doses	Incidence of VTE (DVT or PE through day 10–14) was 14/70 (20%; 95% CI, 11–31) for betrixaban 15 mg, 10/65 (15%; 95% CI, 8–27) for betrixaban 40 mg, and 4/40 (10%; 95% CI: 3–24) for enoxaparin
EXPLORE-Xa (Phase 2)	Stroke prevention in atrial fibrillation	508	Betrixaban 40 mg, 60 mg, or 80 mg daily	Warfarin adjusted to INR (2.0–3.0)	RCT, open label. Blinded to betrixaban doses	Time to occurrence of major or clinically relevant nonmajor bleeding was lowest with betrixaban 40 mg (HR, compared with warfarin, 0.14; 95% CI, 0.017–1.135; $P = 0.04$)
APEX (Phase 3)	Extended prophylaxis in high-VTE-risk, acute, medically ill patients	7,441	Betrixaban 160 mg loading dose followed by 80 mg once daily for 35–42 days with placebo enoxaparin for 10 ± 4 days	Enoxaparin 40 mg SC for up to 10 ± 4 days followed by placebo betrixaban	RCT, double blind, double dummy	Efficacy (measured in mITT) was assessed by composite outcome score of asymptomatic proximal DVT or symptomatic DVT, nonfatal PE or VTE-related death: betrixaban reduced the incidence of DVT and PE blood clots compared with those taking enoxaparin plus placebo (4.4% vs. 6.0%; RR, 0.75; 95% CI, 0.61–0.91) with no significant increase in major bleeding (0.67% vs. 0.57%).

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; INR = international normalized ratio; mITT = modified intent-to-treat; PE = pulmonary embolism; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneously; VTE = venous thromboembolism.

produces similar inhibition of thrombin generation as fondaparinux in humans; however, betrixaban was more potent at inhibiting thrombin–antithrombin complex and F1+2 generation compared with fondaparinux. At clinically effective antithrombotic concentrations, betrixaban did not prolong prothrombin time in *ex vivo* coagulation studies.[15–17]

PHARMACOKINETICS

Through its development and phase 1 trials, an 80-mg dose of betrixaban reached peak concentration (C_{max}) within three to four hours. The bioavailability of oral betrixaban is 34%. Studies have shown that high-fat foods reduce the area under the curve and C_{max} of betrixaban by approximately 50%, whereas low-fat foods caused an average reduction of 65%. The manufacturer recommends administration of betrixaban with food.[13]

Betrixaban is largely excreted unchanged through biliary secretion (82% to 89%) via P-glycoprotein (P-gp) efflux pumps. For this reason, agents affecting P-gp (e.g., amiodarone, verapamil) should be used with caution in patients taking betrixaban. A small amount of inactive metabolites is excreted in the urine (11%); therefore, a small portion of betrixaban is metabolized by cytochrome P450 (CYP) enzymes. No CYP interactions have been reported.[15,18] Because clearance of betrixaban is mainly via the gut through the hepatobiliary route, renal elimination of the compound is minimal (only 5% to 7% of orally administrated medication).[13,16]

After administration, the terminal half-life of betrixaban is 37 hours, and the pharmacodynamic half-life is approximately 19–27 hours. This is the longest half-life of any DOAC to date, and its long half-life gives it a low peak-to-trough concentration.[17] While these qualities are favorable for stable and predictive once-daily dosing, the long half-life and low peak-to-trough ratio minimizes the anticoagulant variability.

CLINICAL STUDIES

Phase 2 Trials

Betrixaban did not demonstrate superiority to enoxaparin in the prevention of major and nonmajor bleeding in total knee replacement patients in the phase 2 EXPERT trial; however, it demonstrated effective antithrombotic activity at 15-mg and 40-mg doses and was well tolerated, which yielded a need for further studies.[19] In the phase 2 EXPLORE-Xa trial in patients with nonvalvular atrial fibrillation, betrixaban doses of 40 mg, 60 mg, and 80 mg demonstrated the lowest occurrence of any bleeding events compared with warfarin.[14] See Table 1 for a summary of these trials.

Phase 3 APEX Trial[13,20]

The phase 3 APEX trial was a multinational, randomized, double-blind, double-dummy clinical control study (N = 7,513) designed to test the efficacy of betrixaban in treating patients with acute medical illnesses and a high

risk of VTE. The initial study inclusion criteria were: age of 40 years or older, hospitalized for less than 96 hours with an acute medical illness, and risk factors for VTE. The inclusion criteria were updated in 2014 to restrict enrollment to patients with an elevated D-dimer or an age of at least 75 years. The primary endpoint for all cohorts was a composite of asymptomatic DVT between day 32 and day 47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between day 1 and day 42. The main safety outcome was the occurrence of major bleeding at any point until one week after the discontinuation of all study medications. Patients were randomized to the betrixaban arm (betrixaban 160 mg orally on day 1, then 80 mg once daily for 35–42 days and enoxaparin subcutaneous [SC] placebo once daily for six to 14 days) or to the enoxaparin arm (enoxaparin 40 mg SC once daily for six to 14 days and betrixaban placebo orally once daily for 35–42 days) (Table 1).

The results and statistical analysis were split into three cohorts: 1) patients with elevated D-dimer levels, 2) patients with elevated D-dimer levels and age 75 years or older, and 3) all patients who received one dose of the medication. The results of the trial were examined in a tiered approach. If cohort 1 showed statistically significant data, then the results of cohort 2 would be examined; however, if one of the cohorts failed to show statistical significance, the following cohorts would only be considered exploratory. This design, guided by the FDA, was intended to identify specific benefit groups in a study population. Cohort 1 failed to show statistical significance that extended prophylaxis with betrixaban reduced the composite VTE endpoint compared with enoxaparin (6.9% versus 8.5%; $P = 0.054$). Cohort 2 showed a statistical reduction in composite VTEs with betrixaban compared with enoxaparin (5.6% versus 7.1%; $P = 0.03$) and in the overall population. No difference was noted between betrixaban and enoxaparin in major bleeding (0.7% versus 0.6%, respectively). Overall, the net clinical benefit (a composite of the efficacy VTE endpoint or principal safety outcome) occurred in 5.8% of the betrixaban group and 7.3% of the enoxaparin group ($P = 0.01$).

Overall, the APEX trial showed no superiority of betrixaban compared with enoxaparin in the reduction of the composite VTE in extended-duration VTE prophylaxis in a high-risk population with elevated D-dimers. However, betrixaban showed a reduction in VTE events compared with enoxaparin in some patients with no increase in bleeding.

SAFETY PROFILE

Boxed Warning

The prescribing information for betrixaban contains a boxed warning that epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. The manufacturer advises health care practitioners to consider these risks when scheduling patients for spinal procedures.[13]

Contraindications

Betrixaban is contraindicated in patients with active pathological bleeding or severe hypersensitivity reaction to betrixaban.[13]

Risk of Bleeding

Betrixaban increases the risk of bleeding and can cause serious and potentially fatal bleeding.[13]

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These drugs include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs.[13]

Prescribers should advise patients of the signs and symptoms of blood loss; patients should report them immediately and seek emergency care. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue betrixaban in patients with active pathological bleeding.[13]

Although agents are in development,[21,22] there is no established way to reverse the anticoagulant effect of betrixaban, which can be expected to persist for at least 72 hours after the last dose. It is unknown whether hemodialysis removes betrixaban, and protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse its anticoagulant activity.[13]

Drug Interactions

Because betrixaban is a P-gp substrate, strong P-gp inhibitors (i.e., ketoconazole, amiodarone, diltiazem) increase betrixaban concentrations[15] and may increase the risk of bleeding. The dose of betrixaban in patients receiving or starting P-gp inhibitors requires adjustment as indicated in the full prescribing information. Monitor these patients closely and promptly evaluate any signs or symptoms of blood loss.[13]

Renal and Hepatic Impairment

Patients with severe renal impairment (creatinine clearance [CrCl] equal to 15 to less than 30 mL/min, computed by Cockcroft-Gault using actual body weight) may have an increased risk of bleeding events. The dose of betrixaban for patients with severe renal impairment should be reduced. The manufacturer advises to monitor patients closely and promptly evaluate any signs or symptoms of blood loss in these patients. No dose adjustment is needed for mild or moderate renal impairment (CrCl greater than 30 mL/min, computed by Cockcroft-Gault using actual body weight).[13]

Betrixaban has not been evaluated in patients with hepatic impairment; therefore, its use is not recommended in these patients.[13]

Adverse Events

The most common adverse reactions to betrixaban occurring in more than 5% of patients in clinical trials were related to bleeding. Major bleeding occurred in less than 1% of patients. Adverse events occurring in 2% or less of patients receiving betrixaban included epistaxis, hematuria, urinary tract infection, and constipation.[13]

DOSAGE AND ADMINISTRATION

The recommended dosage of betrixaban is an initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food. Patients with severe renal impairment or patients concomitantly starting or taking P-gp inhibitors should receive a reduced initial single dose of 80 mg followed by 40 mg

Table 2 Pharmacological Characteristics of Direct Oral Anticoagulants[16–18]

Drug *Brand, Manufacturer*	Target	Bioavailability (%)	Dosing	Half-Life (hours)	Renal Clearance (%)	Fecal Excretion (%)	Drug Interactions
Dabigatran *Pradaxa, Boehringer Ingelheim*	Factor IIa	6	Twice daily	12–14	> 80	82–88	Potent inducers and inhibitors of P-gp
Rivaroxaban *Xarelto, Janssen*	Factor Xa	66	Once daily	9–13	66	26.6	Potent inducers and inhibitors of CYP3A4 and P-gp
Apixaban *Eliquis, Bristol-Myers Squibb*	Factor Xa	50	Twice daily	8–15	25	46.7–56	Potent inducers and inhibitors of CYP3A4
Edoxaban *Savaysa, Daiichi Sankyo*	Factor Xa	62	Once daily	9–11	35	62.2	Potent inducers and inhibitors of CYP3A4 and P-gp
Betrixaban *Bevyxxa, Portola Pharmaceuticals*	Factor Xa	34	Once daily	37	11	82–89	Potent inhibitors of P-gp

CYP3A4 = cytochrome P450 3A4; P-gp = P-glycoprotein.

once daily. The recommended duration of treatment for all patients is 35 to 42 days.[13]

COST

Betrixaban is available in 40-mg and 80-mg capsules. The average wholesale price for either strength is $1,800 for a package of 100 ($18.00 per capsule).[23]

P&T COMMITTEE CONSIDERATIONS

Direct comparisons of betrixaban and the other direct oral anticoagulants can be found in Table 2. Betrixaban is very similar to the other direct factor Xa inhibitors, but it has some key characteristics that could establish its clinical niche in therapy. Betrixaban's long half-life (37 hours) and lack of major CYP3A4 interactions will be very beneficial for a multitude of patients. In addition, the biliary clearance of betrixaban adds another unique feature. However, caution should be advised in patients who are also taking potent P-gp substrates. Lastly, an oral anticoagulant option for acute medically ill patients is a positive benefit of betrixaban.[20]

In comparative systematic reviews, betrixaban showed a reduction of composite VTE events with no difference in bleeding compared to enoxaparin.[24] Previous DOAC studies have shown an increase in bleeding rates in this population, further delineating betrixaban as a potentially preferred agent in this patient group.[9,10,25]

The downside of betrixaban is the lack of studied indications. Currently, betrixaban is only approved by the FDA for extended-duration VTE prevention in acute medically ill patients who are considered high risk. Even though betrixaban may be useful in patients taking medications with CYP drug interactions, betrixaban lacks indications for stroke prevention in patients with nonvalvular atrial fibrillation and VTE treatment, which effect a greater percentage of the population.

REFERENCES

1. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000;160(6):809–815.
2. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med* 2002;162(11):1245–1248.
3. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 suppl):e195S–e226S.
4. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 2010;8(11):2450–2457.
5. MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 suppl):e1S–e23S.
6. Hull RD, Schellong SM, Tapson VF, et al. Extended prophylaxis for venous thromboembolism in acutely ill medical patients with prolonged immobilization (EXCLAIM) study. *Ann Intern Med* 2010;153(1):8–18.
7. Cohen AT, Spiro TE, Büller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med* 2013;368(6):513–523.
8. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011;365(23):2167–2177.
9. Albertsen IE, Larsen TB, Rasmussen LH, et al. Prevention of venous thromboembolism with new oral anticoagulants versus standard pharmacological treatment in acute medically ill patients. A systematic review and meta-analysis. *Drugs* 2012:72(13):1755–1764.
10. Sharma A, Chatterjee S, Lichstein E, et al. Extended thromboprophylaxis for medically ill patients with decreased mobility: does it improve outcomes? *J Thromb Haemost* 2012;10(10):2053–2060.
11. Zhang P, Huang W, Wang L, et al. Discovery of betrixaban (PRT054021), N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide, a highly potent, selective, and orally efficacious factor Xa inhibitor. *Bioorg Med Chem Lett* 2009;19(8):2179–2185.
12. Portola Pharmaceuticals. Portola Pharmaceuticals announces FDA accepts new drug application for priority review and EMA validates marketing authorization application for oral factor XA inhibitor anticoagulant betrixaban. December 23, 2016. Available at: http://investors.portola.com/phoenix.zhtml?c=198136&p=irol-newsroomArticle&ID=2232798. Accessed March 21, 2017.
13. Bevyxxa (betrixaban) prescribing information. South San Francisco, California: Portola Pharmaceuticals, Inc.; 2017.
14. Connolly SJ, Eikelboom J, Dorian P, et al. Betrixaban compared with

continued on page 120

continued from page 88

warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). *Eur Heart J* 2013;34(20):1498–1505.
15. Chan NC, Hirsh J, Ginsberg JS, Eikelboom JW. Betrixaban (PRT054021): pharmacology, dose selection, and clinical studies. *Future Cardiol* 2014;10(1):43–52.
16. Chan NC, Bhagirath V, Eikelboom JW. Profile of betrixaban and its potential in the prevention and treatment of venous thromboembolism. *Vasc Health Risk Manag* 2015;11:343–351.
17. Palladino M, Merli G, Thomson L. Evaluation of the oral direct factor Xa inhibitor-betrixaban. *Expert Opin Investig Drugs* 2013;22(11):1465–1472.
18. Hutchaleelaha A, Ye C, Song Y, et al. Metabolism and disposition of betrixaban and its lack of interaction with major CYP enzymes. *Blood* 2012;120(21):2266.
19. Turpie AG, Bauer KA, Davidson BL, et al. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). *Thromb Haemost* 2009;101(1):68–76.
20. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med* 2016;375(6):534–544.
21. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016;375(12):1131–1141.
22. Greinacher A, Thiele T, Selleng K. Reversal of anticoagulants: an overview of current developments. *Thromb Haemost* 2015;113(5):931–942.
23. Red Book Online. Ann Arbor, Michigan: Truven Health Analytics. Accessed December 20, 2017.
24. Liew AY, Piran S, Eikelboom JW, et al. Extended-duration versus short-duration pharmacological thromboprophylaxis in acutely ill hospitalized medical patients: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Thrombolysis* 2017;43(3):291–301.
25. Milling TJ, Kaatz S. Preclinical and clinical data for factor Xa and universal reversal agents. *Am J Med* 2016;129(11S):S80–S88. ■