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Betrixaban: A New Oral Factor Xa Inhibitor for Extended Venous Thromboembolism Prophylaxis in High-Risk Hospitalized Patients

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Abstract

Objective: To review the pharmacology, pharmacokinetics, efficacy, and safety of the factor Xa (FXa) inhibitor betrixaban for extended-duration prophylaxis of acute medically ill patients with venous thromboembolism (VTE) risk factors. **Data Sources**: A MEDLINE/PubMed (January 1990 to October 2017) search was conducted using the following keywords: *betrixaban, PRT054021, FXa inhibitor, novel oral anticoagulant, NOAC, direct oral anticoagulant, DOAC*, and *target specific oral anticoagulant, TSOAC*. References of identified articles were searched by hand for additional relevant citations. **Study Selection and Data Extraction**: We included English-language articles evaluating betrixaban pharmacology, pharmacokinetics, efficacy, or safety in human subjects for VTE prophylaxis. **Data Synthesis**: Betrixaban is a FXa inhibitor that decreases prothrombinase activity and thrombin generation. Betrixaban efficacy and safety has been compared with that of enoxaparin for prophylaxis of VTE in acutely ill medical patients. In the APEX trial and substudies, extended-duration betrixaban was superior in efficacy to standard-duration enoxaparin in patients at high risk for VTE, including those with elevated D-dimer levels (≥2× upper limit of normal) and of older age (≥75 years). Betrixaban is noninferior to enoxaparin in rates of major bleeding, but the former is associated with more clinically relevant nonmajor bleeding events. **Conclusion**: Betrixaban is the first oral agent approved for extended-duration VTE prophylaxis in acutely ill hospitalized patients. Extended-duration thromboprophylaxis with betrixaban reduces the risk of VTE compared with standard-duration thromboprophylaxis with enoxaparin but is associated with increased risk of bleeding.

Keywords

betrixaban, PRT054021, anticoagulant, factor Xa inhibitors, pharmacology, venous thromboembolism, thromboprophylaxis

Introduction

Hospitalized patients with acute illness have an increased risk for venous thromboembolism (VTE), particularly in the presence of immobilization and one or more risk factors (Table 1).[1-4] Enoxaparin, administered at 40 mg/d for 6 to 14 days, reduces the relative risk (RR) of VTE in hospitalized patients by 37%.[5] On the basis of this risk reduction, guidelines have promulgated the short-term use of unfractionated heparin, low-molecular-weight heparins, or fondaparinux for VTE prophylaxis in this patient population.[6] However, approximately 56% of all VTEs occur up to 6 months following discharge among patients hospitalized for cancer, heart failure, severe lung disease, or infectious disease.[7] The highest risk of VTEs are reported within 19 days after hospitalization.[5,7,8] These data suggest a need for extended-duration prophylaxis beyond hospital discharge. However, prior studies demonstrated unfavorable benefit-to-risk ratios with extended-duration thromboprophylaxis, and as a consequence, this therapeutic approach has not been widely adopted. For example, extended-duration enoxaparin (in the EXCLAIM study) and rivaroxaban (in the MAGELLAN study) have been shown to reduce VTE events but are offset by increased major bleeding

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Table 1. Risk Factors for VTE.[4-6,8,10]

VTE Risk Factors	
• Age >60 years	• Expected hospitalization ≥3 days
• Active cancer	• History of stroke
• Active hormonal treatment	• ICU or CCU stay
• Acute infection requiring hospitalization	• Inherited or acquired thrombophilia
• Active pregnancy in second or third trimester	• Limited mobility
• BMI >35 kg/m^2	• Previous VTE or superficial view thrombosis
• Current lower-limb paralysis	• Prior central venous catheter or transvenous pacemaker
• Chronic respiratory failure	• Reduced mobility
• Chronic venous insufficiency	• Rheumatological disorder
• D-dimer ≥2× ULN	• Trauma or surgery (≤1 month ago)
• Decompensated heart failure (New York Heart Association class III or IV)	

Abbreviations: BMI, body mass index; CCU, coronary care unit; ICU, intensive care unit; ULN, upper limit of normal; VTE, venous thromboembolism.

compared with standard-duration enoxaparin.[9,10] Likewise, in the ADOPT study, extended-duration thromboprophylaxis with apixaban failed to show a favorable benefit-to-risk profile.[9-11]

Betrixaban (Bevyxxa, Portola Pharmaceuticals, Inc) is a new, long-acting, oral, selective factor Xa (FXa) inhibitor that has demonstrated efficacy in the APEX trial for extended-duration thromboprophylaxis starting in hospitalized medically ill patients and maintained after discharge for a total duration of 35 to 42 days.[12] This article will review betrixaban pharmacology and clinical trials assessing the efficacy and safety of betrixaban in extended-duration anticoagulation.

Data Selection

We performed a systematic review of all relevant articles indexed in the MEDLINE/PubMed database and the National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov) between January 1, 1990, and October 31, 2017. Search terms included *betrixaban, PRT054021, Factor Xa inhibitor, novel oral anticoagulant, NOAC, direct oral anticoagulant, DOAC, target specific oral anticoagulant*, and *TSOAC*. Only articles published in the English language were included in the search. References of identified articles were searched for additional relevant citations. Portola Pharmaceuticals was contacted to identify additional relevant literature.

Pharmacology

Pharmacological properties of betrixaban are summarized in Table 2. Betrixaban is an oral, selective FXa inhibitor that binds the active site of FXa and inhibits free FXa.[12-14] Direct FXa inhibition decreases prothrombinase activity and, therefore, thrombin generation. Betrixaban dosed at 40 to 80 mg daily has no clinically relevant effect on activated partial thrombin time, prothrombin time, or international normalized ratio.[15-17]

Betrixaban absorption after oral administration can be affected for up to 6 hours after a meal. Low-fat meals reduce maximum concentration (C_{max}) by 70% and area under the curve (AUC) by 61%, and high-fat meals reduce C_{max} by 50% and AUC by 48%.[13,14] Betrixaban is a permeability glycoprotein 1 (P-gp 1) efflux pump substrate, and concomitant use with strong P-gp inhibitors can more than double betrixaban AUC and C_{max}.[13] Conversely, concomitant use with P-gp inducers, theoretically, could reduce betrixaban plasma concentration, although clinical data are scarce. Concomitant use with P-gp substrates (eg, digoxin) does not appear to alter betrixaban AUC or C_{max}.

Betrixaban is metabolized primarily by cytochrome P450–independent plasma hydrolysis, forming 2 major inactive metabolites.[18] It is excreted minimally in the urine (11%-18%) and has an effective half-life of 19 to 27 hours in patients with normal renal function.[13,18] Despite limited renal excretion, the mean betrixaban AUC_{0-24} is increased 2.63-fold in patients with severe renal impairment (estimated glomerular filtration rate [$eGFR_{MDRD}$] ≥15 to <30 mL/min/1.73 m^2), 2.27-fold in moderate impairment ($eGFR_{MDRD}$ ≥30 to <60 mL/min/1.73 m^2), and 1.89-fold in mild impairment ($eGFR_{MDRD}$ ≥60 to <90 mL/min/1.73 m^2). Betrixaban has not been studied in patients on dialysis or with hepatic impairment. Whether betrixaban is removed by hemodialysis is unknown.

Clinical Trials

Betrixaban has been studied in 2 phase II trials, EXPERT and ExploreXa, and 1 phase III trial, APEX. The APEX trial assessed the safety and efficacy of extended-duration thromboprophylaxis with betrixaban compared with standard-duration thromboprophylaxis with enoxaparin. Efficacy results from APEX and its substudies are summarized in

Table 2. Select Betrixaban Pharmacology Parameters.[a]

Property	Betrixaban
Mechanism	Factor Xa inhibitor
Anti-Xa activity[b]	0.09-0.44 U/mL
Prophylactic concentration[c]	5-25 ng/mL
Bioavailability	34%
T_{max}	3-4 hours
C_{max}	44 ng/mL
AUC_{0-24}	437 ng·h/mL
V_d	32 L/kg
Protein binding[d]	60%
Metabolism	CYP450 <1%, plasma hydrolysis
Major metabolites (inactive)	PRT062802, PRT062803
Excretion	Hepatobiliary: 82%-89%; renal: 11%-18%
Terminal half-life	38 hours
Effective half-life[e]	19-27 hours
Substrate	P-gp substrate

Abbreviations: AUC_{0-24}, area under the curve from time 0 to 24 hours; C_{max}, maximum concentration; CYP450, cytochrome P450; P-gp, permeability glycoprotein; T_{max}, time to maximum concentration; V_d, volume of distribution.
[a]All values using betrixaban 80 mg daily.
[b]Anti-Xa activity at drug concentration from 5 to 25 ng/mL.
[c]Blood plasma concentration where betrixaban thrombin inhibition is roughly equivalent to 2.5 mg fondaparinux daily.
[d]In vitro protein binding.
[e]Time for drug to lose 50% efficacy.

Table 3. Safety information from phase II and III trials are discussed separately and summarized in Table 4. Of note, included in the safety data discussion are phase II trials that used betrixaban doses and patient populations different from those granted under the Food and Drug Administration (FDA)-approved indication.

Efficacy

APEX Trial. The APEX study was a phase III double-blind, double-dummy, active-controlled, multinational, randomized trial comparing the efficacy and safety of extended-duration thromboprophylaxis with betrixaban with standard-duration thromboprophylaxis with enoxaparin.[12] Initially, eligible patients were aged ≥40 years, hospitalized <96 hours for a specified illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke), and had reduced mobility and specific risk factors for VTE (age ≥75 years, D-dimer ≥2× upper limit of normal [ULN], history of VTE or cancer). Patients were randomly assigned to either (1) betrixaban 160-mg loading dose, followed by 80 mg orally once daily for 35 to 42 days, and placebo subcutaneous injection once daily for 6 to 14 days, or (2) oral placebo for 35 to 42 days and enoxaparin 40 mg subcutaneously once daily for 6 to 14 days. Patients with renal impairment (creatinine clearance [CrCl] 15-29 mL/min) in the active enoxaparin arm received a 20-mg once-daily dose. Patients in the active betrixaban arm with renal impairment or those concurrently using strong P-gp inhibitors received a 50% dose reduction in betrixaban (ie, 80-mg loading dose; 40-mg daily dose). The betrixaban doses were based off of phase I and II trial efficacy results that supported 30 to 80 mg daily.[15]

The study eligibility criteria were amended after 35% enrollment of the originally planned sample size. These amendments were prompted by 2 factors: (1) FDA encouraging trial enrichment strategies to support medication approval that encouraged enrolling patients with the greatest perceived benefit[19] and (2) recently reported results from the MAGELLAN trial demonstrating greatest VTE risk in patients with baseline D-dimer ≥2× ULN.[10] Based on these developments, APEX adjusted enrollment criteria to require a baseline D-dimer ≥2× ULN or age ≥75 years.[10] The investigators also modified the analysis plan to assess results in 3 nonmutually exclusive cohorts. Cohort 1 (betrixaban n = 1914, enoxaparin n = 1956) included all patients with a baseline D-dimer ≥2× ULN (ie, possible highest risk), whereas cohort 2 (betrixaban n = 2842, enoxaparin n = 2893) included all patients in cohort 1 and those ≥75 years old. Cohort 3 included all patients enrolled in APEX.

The primary efficacy outcome (PEO) was symptomatic proximal or distal deep venous thrombosis (DVT), symptomatic nonfatal pulmonary embolism (PE), or VTE-related death from day 1 (thromboprophylaxis start) through day 42 or asymptomatic proximal DVT (detected by ultrasound) between day 32 and 47. Statistical analysis was completed using a modified intention-to-treat (mITT) approach, including patients who received at least 1 dose of study medication and had adequate assessment of VTE. The results exclude an asymptomatic VTE event from the mITT analysis, which was reconciled after the data were unblinded.

In cohort 1 (baseline D-dimer ≥2× ULN), the PEO occurred in 6.9% of the betrixaban group and 8.5% of the enoxaparin group (RR = 0.81; 95% CI = 0.65-1.00; number needed to treat [NNT] = 63).[12] These data demonstrate, at a minimum, similar risk between treatment strategies, but more likely show significant risk reduction with extended anticoagulation using betrixaban. Separate analyses by academic research centers, unaffiliated with the sponsor, included an asymptomatic VTE event in the composite PEO and confirmed superiority of extended-duration betrixaban compared with standard-duration enoxaparin (RR = 0.80; 95% CI = 0.64-0.99) in the same cohort of patients.[20] Further in cohort 2 (baseline D-dimer ≥2× ULN or age ≥75 years), the PEO occurred in 5.6% of the betrixaban group and 7.1% of the enoxaparin group (RR = 0.80; 95% CI = 0.66 to 0.98; NNT = 67). In the overall trial population (cohort 3), the PEO occurred in 5.3% of the betrixaban group and 7.0% in the enoxaparin group (RR = 0.76; 95%

Table 3. Summary of Select Primary and Secondary Efficacy Outcomes From the APEX Trial and Post Hoc Analyses.[a]

Study	Treatment	Primary Outcome	Outcome Rate	Relative Risk (95% CI)	NNT
APEX[12,b]					
Cohort 1 (D-dimer ≥2× ULN in the APEX trail)	Betrixaban (n = 1914)	Composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE from day 1 through day 32 and 47	6.9%	0.81 (0.65 to 1.00) [0.80 (0.64 to 0.99)][19]	63
	Enoxaparin (n = 1956)		8.5%		
Cohort 2 (all patients in cohort 1 plus age ≥75 years in the APEX trial)	Betrixaban (n = 2842)		5.6%	0.80 (0.66 to 0.98)	67
	Enoxaparin (n = 2893)		7.1%		
Cohort 3 (overall study population in the APEX trial)	Betrixaban (n = 3112)		5.3%	0.76 (0.63 to 0.92)	59
	Enoxaparin (n = 3174)		7.0%		
Full- vs reduced-dose betrixaban[20,b]					
Cohort 3 (overall study population in the APEX trial)	Betrixaban 80 mg QD (n = 2506)	Composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE from day 1 through day 32 and 47	4.87%	0.70 (0.56 to 0.87)	46
	Enoxaparin (n = 2562)		7.06%		
Cohort 3 (overall study population in the APEX trial)	Betrixaban 40 mg QD (n = 603)		6.97%	1.04	—
	Enoxaparin (n = 609)		6.73%		
Betrixaban vs enoxaparin stroke risk[21,c]					
Cohort 3 (overall study population in the APEX trial)	Betrixaban (n = 3716)	Rate of all-cause stroke and ischemic stroke from day 1 through day 77 (starting from initiation of thromboprophylaxis to 30 days after drug discontinuation)	0.54%	0.56 (0.32 to 0.96)	233
	Enoxaparin (n = 3716)		0.97%		
	Betrixaban 80 mg QD (n = 2986)		0.47%	0.47 (0.25 to 0.88)	189
	Enoxaparin (n = 2991)		1.00%		
	Betrixaban 40 mg QD (n = 730)		0.82%	0.99 (0.32 to 3.07)	—
	Enoxaparin (n = 725)		0.83%		

Abbreviations: DVT, deep venous thrombosis; NNT, number needed to treat; PE, pulmonary embolism; QD, daily; RR, relative risk; ULN, upper limit of normal; VTE, venous thromboembolism.

[a]Cohort 1: patients with D-dimer ≥2× ULN in the APEX trial. Cohort 2: all patients in cohort 1 plus age ≥75 years in the APEX trial. Cohort 3: overall study population in the APEX trial.

[b]Primary outcome: composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE from day 1 through days 32 and 47.

[c]Rate of all-cause stroke and ischemic stroke from day 1 through day 77 (starting from initiation of thromboprophylaxis to 30 days after drug discontinuation).

CI = 0.63 to 0.92; NNT = 59). Unfortunately, because of the overlap in patients included in these cohort analyses, these results do not allow for determining the extent to which the apparent superiority of extended-duration anticoagulation with betrixaban extends beyond the highest-risk group (ie, D-dimer >2× ULN).

APEX Trial Substudies. A post hoc analysis of the APEX study separately compared the PEO of full-dose (80-mg) and reduced-dose (40-mg) betrixaban relative to enoxaparin.[21] In all cohorts, full-dose betrixaban was superior to enoxaparin for the PEO (Table 3). Contrarily, for the PEO, reduced-dose betrixaban was noninferior to enoxaparin in

Table 4. Select Adverse Effects of Betrixaban From Clinical Trials.[a]

Study	Treatment	Major Bleeding[b]	Major or CRNMB[c]	Any Adverse Event	Any Serious Adverse Event[d]
APEX[12,24]					
Cohort 1	Betrixaban 40-80 mg QD (n = 2311)	0.6%	3.1%	—	—
	Enoxaparin 20-40 mg QD (n = 2310)	0.7%	1.9%	—	—
Cohort 2	Betrixaban 40-80 mg QD (n = 3402)	0.7%	3.2%	—	—
	Enoxaparin 20-40 mg QD (n = 3387)	0.6%	1.7%	—	—
Cohort 3	Betrixaban 40-80 mg QD (n = 3716)	0.7%	3.1%	54.0%[e]	17.7%
	Enoxaparin 20-40 mg QD (n = 3716)	0.6%	1.6%	52.0%[e]	16.6%
EXPERT[15]					
	Betrixaban 40 mg bid (n = 65)	0	2 (2.4%)	4.7% overall	—
	Betrixaban 15 mg Bid (n = 70)	0	0	4.7% overall	—
	Enoxaparin 30 mg q12h (n = 40)	1 (2.3%)	2 (4.6%)	4.7% overall	1
Explore-Xa[22,f]					
	Warfarin (goal INR 2-3; n = 127)	5 (3.9%)	7 (5.5%)	31.5%[g]	—
	Betrixaban 80 mg QD (n = 127)	3 (2.4%)	5 (3.9%)	18.9%[g]	—
	Betrixaban 60 mg QD (n = 127)	0	5 (3.9%)	25.2%[g]	—
	Betrixaban 40 mg QD (n = 127)	0	1 (<1%)	17.3%[g]	—

Abbreviations: CRNMB, clinically relevant nonmajor bleeding; INR, international normalized ratio; QD, daily; ULN, upper limit of normal.
[a]Cohort 1: patients with D-dimer ≥2× ULN in the APEX trial. Cohort 2: all patients in cohort 1 plus age ≥75 years in the APEX trial. Cohort 3: overall study population in the APEX trial.
[b]Major bleeding associated with a reduction in hemoglobin of at least 2 g/dL or leading to a transfusion of at least 2 units of blood or packed cells, a symptomatic bleeding in a critical organ, or a fatal outcome.
[c]CRNMB: overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled patient contact with a physician, temporary cessation of study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.
[d]A serious adverse event is any adverse event that results in death, is life-threatening, requires inpatient hospitalization, results in persistent or significant disability, is a congenital anomaly/birth defect, or is an important medical event.
[e]Adverse events that occurred in ≥2% of the patient population: bleeding related, epistaxis and hematuria; Nonbleeding adverse reaction, urinary tract infection, constipation, hypokalemia, hypertension, headache, nausea, and diarrhea.
[f]Antiplatelet therapy was coadministered in 42%, 39%, 40%, and 41% of the patients receiving betrixaban 40, 60, and 80 mg and warfarin, respectively.
[g]Percentage represents any reported bleeding.

all cohorts. However, <5% (n = 175 for betrixaban, n = 150 for enoxaparin) of the study population had severe renal impairment to qualify for the reduced doses of betrixaban or enoxaparin. Notably, in the overall population, the median steady-state plasma concentration achieved in the full-dose betrixaban group was 19 ng/mL (interquartile range [IQR] = 12-32 ng/mL) compared with 11 ng/mL (IQR = 6-20 ng/mL) in the reduced-dose population ($P < 0.001$). Considering the difference in betrixaban plasma concentrations and PEO results when stratified by betrixaban dose, these data may suggest that betrixaban 40 mg is too low of a dose for patients with renal impairment.

A prespecified secondary analysis of the APEX trial analyzed the risk of all-cause stroke and ischemic stroke through 77 days of follow-up (starting from thromboprophylaxis initiation to 30 days after drug discontinuation).[22] Betrixaban was associated with significantly reduced rates of all-cause stroke compared with enoxaparin (Table 3). Only 1 hemorrhagic stroke and 1 stroke of uncertain type each occurred in the betrixaban group and enoxaparin group. No difference was observed in all-cause stroke between patients treated with reduced doses of betrixaban and enoxaparin-treated patients.

Safety

The EXPERT trial was a randomized, multicenter, parallel-group study assessing antithrombotic potential and safety of betrixaban in patients undergoing TKR.[15] The safety analysis included 175 patients randomly assigned in a 2:2:1 ratio to oral betrixaban 15 mg twice daily (n = 70), oral betrixaban 40 mg twice daily (n = 65), or subcutaneous enoxaparin 30 mg every 12 hours (n = 40) for 10 to 14 days. The primary safety outcome was clinically relevant nonmajor bleeding (CRNMB) or major bleeding (ie, fatal, involving vital organs, requiring procedures, or Bleeding Index ≥2.0). The CRNMB outcome was defined as overt bleeding associated with medical intervention, unscheduled physician contact, interruption of treatment, or patient discomfort. Overall, bleeding was infrequent, with 1 major bleed occurring in the enoxaparin group and 2 CRNMBs in both the betrixaban 40-mg and enoxaparin groups (Table 4).

Betrixaban safety was assessed in the ExploreXa trial in patients with nonvalvular atrial fibrillation.[23] Patients were randomly allocated to receive betrixaban 40, 60, or 80 mg daily or warfarin therapy (n = 127 per group, n = 508 total). The primary outcome was rate of major bleeding or CRNMB. The median follow-up for each treatment was 150 days, and the warfarin mean time in therapeutic range was 63.4%. The primary outcome occurred least frequently in the betrixaban 40-mg group and was similar between the betrixaban 60-mg, betrixaban 80-mg, and warfarin groups.

In the APEX trial, the principal safety outcome was the occurrence of major bleeding at any point until 7 days after the discontinuation of all study medications.[12] A secondary safety outcome was combined major bleeding or CRNMB (classified using the International Society on Thrombosis and Haemostasis criteria).[24] The safety mITT analysis included patients if they had received at least 1 dose of the study medication. Median exposure to thromboprophylaxis was 9 days for enoxaparin and 36 days for betrixaban. In cohort 3 (overall population), no significant difference was seen in the principal safety outcome (major bleeding). In contrast, the combined secondary outcome of major bleeding or CRNMB occurred more frequently in the betrixaban group compared with the enoxaparin group (3.1% vs 1.6%, respectively; RR = 1.97; 95% CI = 1.44-2.68; number needed to harm [NNH] = 67). Notably, 86% of the CRNMB events in the betrixaban group were assessed as mild to moderate in severity (mainly epistaxis and hematuria), with 38% of all CRNMB events requiring medical intervention.[13] Other side effects associated with betrixaban were reported to be mild.

A post hoc analysis compared the rate of irreversible adverse events in patients receiving either extended-duration betrixaban or standard-duration enoxaparin separately.[25] The PEO was a composite of death from fatal bleeding, intracranial hemorrhage, ischemic cerebral or cardiopulmonary causes, and nonfatal events, including myocardial infarction, PE, or ischemic stroke at follow-up on day 77 (thromboprophylaxis started day 1). Separate analyses were completed for combined betrixaban doses, full-dose (80 mg) only and reduced-dose (40 mg) only. In cohort 3, the PEO event rate was lower in the combined betrixaban dose group compared with the enoxaparin group (3.6% vs 5.2%, respectively; hazard ratio [HR] = 0.70; 95% CI = 0.57 to 0.88). Similarly, in cohort 3, patients taking full-dose betrixaban had a lower PEO event rate compared with enoxaparin at day 77 (3.2% vs 5.0%, respectively; HR = 0.64; 95% CI = 0.50 to 0.83). However, the same analysis with reduced-dose betrixaban (40 mg) compared with enoxaparin in cohort 3 demonstrated no difference in the PEO, which suggests that betrixaban may have been underdosed in the specified patient population (CrCl 15 to 29 mL/min or concomitant strong P-gp inhibitors).

Clinical Implications

As previously discussed, extended-duration thromboprophylaxis with other direct-acting oral anticoagulants have generally not shown favorable benefit-to-risk profiles when compared with standard-duration enoxaparin thromboprophylaxis.[9-11] In contrast, extended-duration betrixaban thromboprophylaxis demonstrated superior efficacy in reduction of VTE events to standard-duration enoxaparin in the APEX trial (NNT = 59 or 67, depending on patient population).[12] Furthermore, betrixaban was noninferior to standard-duration enoxaparin for major bleeding risk, despite longer anticoagulation duration, but was associated with more combined major bleeding and CRNMB (NNH = 67). However, making direct comparisons between these trials is challenged by heterogeneous designs and patient populations. Thus, whether betrixaban is truly a superior agent in reducing VTE risk following hospitalization remains unknown. Nevertheless, betrixaban may be an appealing option for patients who prefer oral therapy compared with subcutaneous or parenteral anticoagulation. Additionally, use of an oral agent should reduce nonadherence often seen with subcutaneous VTE thromboprophylaxis regimens.[26] However, betrixaban has additional bleed risk without a FDA-approved antidote to reverse betrixaban-related bleeding. Currently, andexanet alfa is being studied as an antidote for other FXa inhibitors in the ongoing ANNEXA-4 trial, and its protocol may be amended to incorporate betrixaban users.[27]

Dosage and Administration

Betrixaban should be administered orally at the same time each day given the effective half-life of 19 to 27 hours. As in the APEX trial, betrixaban should be taken with food, otherwise drug concentrations would be greater than studied and potentially lead to more bleeding. A loading dose of 160 mg should be administered on day 1 during hospitalization followed by 80 mg once daily thereafter for a total of 35 to 42 days.[13] Limited data are available for patients with a CrCl ≥15 to <30 mL/min (<5% of the APEX study population met this specific renal threshold), but the package insert recommends reducing the betrixaban dose to a 80-mg loading dose followed by 40 mg once daily for 35 to 42 days in patients with severe renal impairment or those using concomitant P-gp inhibitors. Betrixaban is not recommended in patients with CrCl <15 mL/min.

Clinical trial data are lacking in patients with hepatic impairment, children and adolescents, pregnant and lactating women, those on hemodialysis, and those with prosthetic heart valves, and betrixaban is not currently recommended in these populations.[28] Betrixaban use should be cautioned in patients taking concomitant drugs known to increase the risk of bleeding.

Summary

Betrixaban is a new oral agent for extended-duration VTE prophylaxis in patients with restricted mobility and either age ≥75 years or ≥2 risk factors for VTE. The APEX trial demonstrated betrixaban's efficacy in reducing VTE events among high-risk patients who begin treatment during hospitalization and continue postdischarge for a total of 42 days. Betrixaban has a risk of major bleeding similar to that of enoxaparin, but the former is associated with nearly 2-fold increased combined major bleeding or CRNMB. Limited data are available, but reduced-dose betrixaban (40 mg once daily), used in patients with renal impairment or those taking concomitant P-gp inhibitors, did not reduce VTE risk compared with enoxaparin. Given the increased risk of CRNMB with the extended duration betrixaban strategy, a prudent approach may be to minimize or avoid use in this population until more data become available.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. DeRemer has been a speaker and served on advisory boards for BMS and Pfizer and owns stock in Portola Pharmaceuticals. The other authors report no conflicts of interest.

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References

1. Alikhan R, Cohen AT, Combe S, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch Intern Med*. 2004;164:963-968. doi:10.1001/archinte.164.9.963
2. Cohen AT, Alikhan R, Arcelus JI, et al. Assessment of venous thromboembolism risk and the benefits of thromboprophylaxis in medical patients. *Thromb Haemost*. 2005;94:750-759. doi:10.1160/TH05-06-0385
3. Cohen AT, Spiro TE, Spyropoulos AC, et al. D-dimer as a predictor of venous thromboembolism in acutely ill, hospitalized patients: a subanalysis of the randomized controlled MAGELLAN trial. *J Thromb Haemost*. 2014;12:479-487. doi:10.1111/jth.12515
4. Gibson CM, Spyropoulos AC, Cohen AT, et al. The IMPROVEDD VTE risk score: incorporation of D-dimer into the IMPROVE score to improve venous thromboembolism risk stratification. *TH Open*. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0037-1603929. Accessed January 5, 2018. doi:10.1055/s-0037-1603929
5. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients: Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med*. 1999;341:793-800. doi:10.1056/NEJM199909093411103
6. 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:e195S-e226S. doi:10.1378/chest.11-2296
7. Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. *J Hosp Med*. 2012;7:231-238. doi:10.1002/jhm.1002
8. Edelsberg J, Hagiwara M, Taneja C, Oster G. Risk of venous thromboembolism among hospitalized medically ill patients. *Am J Health Syst Pharm*. 2006;63:S16-S22. doi:10.2146/ajhp060389
9. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration thromboprophylaxis in acutely ill medical patients with recent reduced mobility: methodology for the EXCLAIM study. *J Thromb Thrombolysis*. 2006;22:31-38. doi:10.7326/0003-4819-153-1-201007060-00004
10. Cohen AT, Spiro TE, Spyropoulos AC, Committee MS. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:1945-1946. doi:10.1056/NEJMoa1111096
11. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365:2167-2177. doi:10.1056/NEJMoa1110899
12. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375:534-544. doi:10.1056/NEJMoa1601747
13. Bevyxxa(R) (Betrixaban) [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals Inc; 2017.
14. Chan NC, Hirsh J, Ginsberg JS, Eikelboom JW. Betrixaban (PRT054021): pharmacology, dose selection and clinical studies. *Future Cardiol*. 2014;10:43-52. doi:10.2217/fca.13.98
15. 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;101:68-76. doi:10.1160/TH08-07-0460
16. Eriksson BI, Quinlan DJ, Weitz JI. Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. *Clin Pharmacokinet*. 2009;48:1-22. doi:10.2165/0003088-200948010-00001
17. 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. doi:10.2147/VHRM.S63060
18. Hutchaleelaha A, Ye C, Song Y, Lorenz T, Gretler D, Lambing J. Metabolism and disposition of betrixaban and its lack of interaction with major CYP enzymes. *Blood*; 2012;120:2266.
19. US Department of Health and Human Services, Food and Drug Administration. *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*. Rockville, MD: Food and Drug Administration; 2012.

20. Gibson CM, Goldhaber SZ, Cohen AT, et al. When academic research organizations and clinical research organizations disagree: processes to minimize discrepancies prior to unblinding of randomized trials. *Am Heart J*. 2017;189:1-8. doi:10.1016/j.ahj.2017.03.018
21. Gibson CM, Halaby R, Korjian S, et al. The safety and efficacy of full- versus reduced-dose betrixaban in the Acute Medically Ill VTE (Venous Thromboembolism) Prevention With Extended-Duration Betrixaban (APEX) trial. *Am Heart J*. 2017;185:93-100. doi:10.1016/j.ahj.2016.12.004
22. Gibson CM, Chi G, Halaby R, et al. Extended-duration betrixaban reduces the risk of stroke versus standard-dose enoxaparin among hospitalized medically ill patients: an APEX trial substudy (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban). *Circulation*. 2017;135:648-655. doi:10.1161/CIRCULATIONAHA.116.025427
23. Connolly SJ, Eikelboom J, Dorian P, et al. Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). *Eur Heart J*. 2013;34:1498-1505. doi:10.1093/eurheartj/eht039
24. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-694. doi:10.1111/j.1538-7836.2005.01204.x
25. Gibson CM, Korjian S, Chi G, et al. Comparison of fatal or irreversible events with extended-duration betrixaban versus standard dose enoxaparin in acutely ill medical patients: an APEX trial substudy. *J Am Heart Assoc*. 2017;6:e006015. doi:10.1161/JAHA.117.006015
26. Popoola VO, Tavakoli F, Brandyn D, et al. Exploring the impact of route of administration on medication acceptance in hospitalized patients: implications for venous thromboembolism prevention. *Thromb Res*. 2017;160:109-113. doi:10.1016/j.thromres.2017.10.012
27. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375:1131-1141. doi:10.1056/NEJMoa1607887
28. Tang AW, Greer I. A systematic review on the use of new anticoagulants in pregnancy. *Obstet Med*. 2013;6:64-71. doi:10.1177/1753495x12472642