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.2,2

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 non-fatal bleeding. Currently, medical devices are reserved for high-risk patients who are either bleeding or at high risk for major bleeding.2 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.5 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.4,5 Extended VTE prophylaxis is currently recommended in surgical patients; however, it remains controversial in medically ill patients due to the risk of bleeding.2 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 guidelines7 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 ADAPT 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.7 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.8,9,10

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...
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\text{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\text{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.15,16 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 administered 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.

Table 1 Summary of Betrixaban Phase 2 and Phase 3 Trials13,14,19

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Evaluate Patients</th>
<th>Intervention Arms</th>
<th>Control Arms</th>
<th>Design</th>
<th>Primary Outcome</th>
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<tr>
<td>EXPERT (Phase 2)</td>
<td>VTE prevention in total knee replacement</td>
<td>175</td>
<td>Betrixaban 15 mg twice daily and 40 mg twice daily, both six hours postoperatively</td>
<td>Enoxaparin 30 mg SC twice daily 12–24 hours postoperatively</td>
<td>RCT, open label. Blinded to betrixaban doses</td>
<td>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</td>
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<tr>
<td>EXPLORE-Xa (Phase 2)</td>
<td>Stroke prevention in atrial fibrillation</td>
<td>508</td>
<td>Betrixaban 40 mg, 60 mg, or 80 mg daily</td>
<td>Warfarin adjusted to INR (2.0–3.0)</td>
<td>RCT, open label. Blinded to betrixaban doses</td>
<td>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)</td>
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<tr>
<td>APEX (Phase 3)</td>
<td>Extended prophylaxis in high-VTE-risk, acute, medically ill patients</td>
<td>7,441</td>
<td>Betrixaban 160 mg loading dose followed by 80 mg once daily for 35–42 days with placebo enoxaparin for 10 ± 4 days</td>
<td>Enoxaparin 40 mg SC for up to 10 ± 4 days followed by placebo betrixaban</td>
<td>RCT, double blind, double dummy</td>
<td>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%).</td>
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\[ CL = \text{confidence interval}; \text{DVT} = \text{deep vein thrombosis}; \text{HR} = \text{hazard ratio}; \text{INR} = \text{international normalized ratio}; \text{mITT} = \text{modified intent-to-treat}; \text{PE} = \text{pulmonary embolism}; \text{RCT} = \text{randomized controlled trial}; \text{RR} = \text{relative risk}; \text{SC} = \text{subcutaneously}; \text{VTE} = \text{venous thromboembolism}. \]

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 Trial13,20

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 superiorit 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.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

DOSEAGE 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
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


