

Highlights: burden of venous thromboembolism and role of extended-duration thromboprophylaxis in acute medically ill patients

Acute medically ill patients are vulnerable to developing venous thromboembolism (VTE)—a leading but potentially preventable cause of morbidity and mortality.

- Acute medically ill patients: Patients who have been hospitalized for acute medical illnesses such as heart failure, ischaemic stroke, respiratory illnesses, infectious disease, rheumatic/inflammatory disease, or those who are receiving cancer treatment^{1,2}
- Estimated population of hospitalized medically ill patients at risk of VTE:
 - ≈5.5 million in 6 European Union (EU) countries³
 - ≈8 million in the United States (US)^{4,5}
- Mortality:
 - In the EU in 2007, the estimated number of VTE-related deaths per annum (543 454) was more than double the sum of deaths due to AIDS, breast cancer, prostate cancer, and transport-related fatalities.³
 - An estimated 70% of VTE-related deaths in the EU occurred as a consequence of hospital-related VTE.³

There is a persistent need for a treatment that can protect the acute medically ill patient population from VTE, without increasing the bleeding risk, from hospital admission through the post-discharge period.

- Because more than half of VTE events occur after hospital discharge,⁶ acute medically ill patients at high risk for VTE will benefit from thromboprophylaxis that extends beyond hospitalization.
- In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) Study, long-term thromboprophylaxis with betrixaban (35-42 days) was compared with standard-dose enoxaparin (6-14 days) in an acute medically ill population that was carefully selected due to their elevated risk of VTE.^{1,7}
- Based on clinical data from the APEX study, betrixaban has been approved by the US Food and Drug Administration for the prophylaxis of VTE in adult acute medically ill patients hospitalized for an acute medical illness who are at risk of VTE.⁸

Betrixaban is a new, oral selective factor Xa inhibitor with a distinct pharmacokinetic profile that distinguishes it from other oral factor Xa inhibitors (*Figure 1*).

- Because of the low renal clearance, betrixaban may be used in patients with renal impairment—a patient population that, until now, has had limited anticoagulant options.⁹
- Once-daily betrixaban provides consistent anticoagulant effect over 24 h due to its long half-life, low peak-to-trough ratio, and predictable duration of drug exposure.⁹
- Betrixaban is minimally metabolized by cytochrome P450 (CYP) enzymes and does not induce or inhibit CYP activity, lowering the risk of adverse drug events or interactions during concomitant administration.⁹

Betrixaban is the first oral anticoagulant to provide effective long-term prophylaxis for VTE in the acute medically ill patient population without a significant increase in major bleeding events throughout hospitalization and after discharge (*Figure 2*).

- Unlike attempts with enoxaparin, rivaroxaban, and apixaban to provide long-term thromboprophylaxis that failed to show adequate protection from VTE without also elevating the risk of bleeding,¹⁰⁻¹² extended-duration betrixaban reduced VTE events without an increase in major bleeding in hospitalized acute medically ill patients when compared to standard-duration enoxaparin in the APEX study.¹
- *Post hoc* analyses of the APEX trial provided further evidence to support the efficacy and safety of betrixaban in reducing all-cause ischaemic stroke, fatal, or irreversible ischaemic or bleeding events, as well as reducing VTE-related rehospitalization.¹³⁻¹⁵

References

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BETRIXABAN PHARMACOLOGY		
▪ Half life ≈19-27 hours	▪ Excreted primarily through bile	▪ Substrate of P-glycoprotein inhibitors
▪ T_{max} = 3-4 hours	▪ Renal excretion = 17.8% ^a	▪ Once-daily dosing
▪ Lower peak-to-trough ratio than other Factor Xa inhibitors		
POTENTIAL CLINICAL IMPLICATIONS		
Consistent anticoagulant effect over 24 hours and potential for minimal effect of a missed dose	Potential for use in renally impaired patients (CrCl <30 mL/min) who have limited anticoagulant options and were previously excluded from direct oral anticoagulant trials	Dose reduction may be required for patients taking strong P-glycoprotein inhibitors (amiodarone, verapamil, ketoconazole, clarithromycin)

Figure 1 Betrixaban pharmacology and clinical implications.^{8,9} ^aUnchanged betrixaban in urine following an intravenous betrixaban dose. T_{max} , time to maximum concentration; CrCl, creatinine clearance.

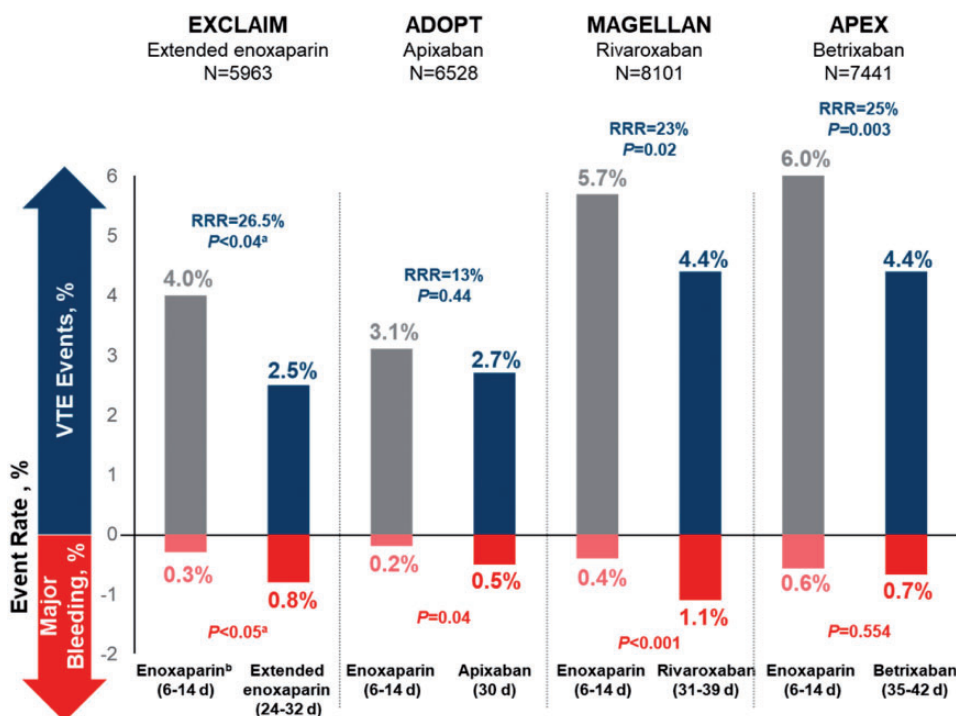


Figure 2 Extended-duration venous thromboembolism prophylaxis trials in acute medically ill patients.^{1,7-12} ^aData and Safety Monitoring Board recommended termination of study following interim analyses finding no difference in efficacy and more major haemorrhage. The trial was restarted following a protocol amendment that changed eligibility criteria to include high-risk patients. ^bPatients in both study arms received open-label enoxaparin for 6-14 days followed by placebo or extended-duration enoxaparin. RRR, relative risk reduction.

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