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EDITORIAL

Extended thromboprophylaxis with betrixaban: a new standard for acute medically ill patients

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The main advantage of understanding aetiological risks for any condition is that their recognition allows early targeted intervention in the form of preventive therapies, which ultimately reduce the burden of disease. This is particularly true for venous thromboembolism (VTE), the most significant preventable cause of morbidity and mortality in hospitalized patients.[1,2]

It has long been recognized that hospitalization for surgical and medical conditions is associated with ~50% of the total burden of VTE, and half of this burden (23% of the total burden of VTE) occurs in the 3 months following admission to hospital for an acute medical illnesses.[3] These figures are based on the presentation of symptomatic disease, and they significantly underestimate the attributable risk for VTE-related mortality. Studies have shown ~70% of hospital-associated VTE-related mortality occurs in the acutely ill medical population.[1,3]

Prior to the APEX study with betrixaban, there were no United States Food and Drug Administration (FDA)-approved therapies for extended VTE prophylaxis in acute medically ill patients at risk of VTE. Betrixaban was recognized as having unique properties that would suit the prevention of VTE in acute medically ill patients,[4] and hence, the APEX study was undertaken with this drug.[5,6] The results are clinically significant with a 36% relative risk reduction in symptomatic VTE in the overall APEX study population ($P = 0.04$), and therefore we the have the potential to reduce the overall burden of VTE by ~10%.[3] In the EU and USA, applying the APEX risk reductions to the epidemiological data means this has the potential to result in 30 000 fewer VTE-related deaths (18 000 and 12 000, respectively) and 50 000 fewer non-fatal symptomatic VTEs (30 000 and 20 000, respectively).[1,6–8] In addition, based on the APEX data, extended-duration thromboprophylaxis with betrixaban may prevent one death for every 223 acute medically ill patients treated.[9]

In this supplement, we present the background of hospital-acquired thrombosis, the unmet need related to preventing VTE with extended thromboprophylaxis, and the pharmacology of betrixaban and its properties that suit the indication for extended VTE prophylaxis from hospitalization through post-discharge, as approved by the FDA. Finally, the primary results of the APEX study as well as *post hoc* analyses are reviewed.

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References

1. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, Greer IA, Heit JA, Hutchinson JL, Kakkar AK, Mottier D, Oger E, Samama MM, Spannagl M; VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;**98**:756–764.
2. Rathbun S. Cardiology patient pages. The surgeon general's call to action to prevent deep vein thrombosis and pulmonary embolism. *Circulation* 2009;**119**:e480–e482.
3. Heit JA, Crusan DJ, Ashrani AA, Petterson TM, Bailey KR. Effect of a near-universal hospitalization-based prophylaxis regimen on annual number of venous thromboembolism events in the US. *Blood* 2017; **130**:109–114.
4. 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.
5. Cohen AT, Harrington R, Goldhaber SZ, Hull R, Gibson CM, Hernandez AF, Kitt MM, Lorenz TJ. The design and rationale for the

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Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban (APEX) study. *Am Heart J* 2014;**167**: 335–341.
6. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM; APEX Investigators. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med* 2016;**375**:534–544.
7. Heit JA, Cohen AT, Anderson FJ. Estimated annual number of incidents and recurrent, fatal and non-fatal venous thromboembolism (VTE) events in the US. *Blood* 2005;**106**:267a.
8. Gibson CM, Harrington RA, Goldhaber SZ, Hernandez AF, Hull RD, Wiens BL, Gold A, Cohen AT. VTE prevention in acutely ill medical patients with extended duration betrixaban—a multicenter, randomized, active-controlled efficacy and safety study comparing extended duration betrixaban with standard of care enoxaparin. *J Thromb Haemost* 2016;**14(Suppl 1)**:8–9.
9. Gibson CM, Nafee T, Goldhaber SZ, Hernandez AF, Hull RD, Gold A, Korjian S, Daaboul Y, Cohen AT, Harrington RA, Chi G. Full-dose betrixaban reduces venous thromboembolism-related mortality: an APEX trial substudy. *Circulation* 2017;**136**:A20393.