Extended-Duration Betrixaban Reduces the Risk of Rehospitalization Associated With Venous Thromboembolism Among Acutely Ill Hospitalized Medical Patients

Findings From the APEX Trial (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban Trial)

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Among hospitalized medically ill patients who are at risk of venous thromboembolism (VTE), pharmacological thromboprophylaxis is recommended during the period of immobilization or acute hospital stay.[1] However, the risk of VTE extends beyond the standard 10- to 14-day course of anticoagulation and persists for weeks to months after hospital discharge. About half of VTE events occur after the period of index hospitalization and may require rehospitalization.[2] Rehospitalization is an end point that adversely affects the morbidity and quality of life of patients and can be a major driver of healthcare costs. Indeed, a goal of patient-centered care is to be both alive and free of hospitalization.

The APEX trial (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban Trial; ClinicalTrials.gov: NCT01583218) was a double-blind randomized clinical trial that compared extended-duration (35–42 days) betrixaban with standard-duration (10±4 days) enoxaparin among acutely ill hospitalized medical patients at increased risk of VTE. A reduction in VTE by extended-duration betrixaban compared with standard-duration enoxaparin has been demonstrated,[3] but the impact of extended thromboprophylaxis with betrixaban on the risk of rehospitalization associated with VTE has not been studied. It was hypothesized that betrixaban would reduce VTE-related rehospitalization.

The APEX trial randomized 7513 patients to either extended-duration betrixaban or standard-duration enoxaparin for VTE prophylaxis. The full-dose regimen (betrixaban 80 mg daily) was administered to patients who had a creatinine clearance of ≥30 mL/min and were not administered a strong P-glycoprotein inhibitor. VTE-related rehospitalization was defined as any subsequent hospital admission attributed to a VTE event (including asymptomatic and symptomatic cases) occurring after discharge for the index acute medical illness. Occurrence of VTE-related rehospitalization between betrixaban versus enoxaparin was compared with the Cox proportional hazards model at 42 days (end of extended thromboprophylaxis) and at 77 days (end of study) among all subjects who received at least 1 dose of the study drug (overall population) and in the full-dose stratum. Event rate was estimated by the Kaplan-Meier method, and the risk difference between treatment arms was assessed by the log-rank test. A sensitivity analysis accounting for the competing risk of mortality was performed with the Fine-Gray method. The study was approved by the local institutional review committees, and informed consent was obtained from all study participants.

Betrixaban reduced the risk of VTE-related rehospitalization at 42 days (0.25% versus 0.75%) and at 77 days (16 of 3716 [0.45%] versus 36 of 3716 [1.04%]; hazard ratio [HR], 0.44; 95% confidence interval [CI], 0.25–0.80; *P*=0.0055; absolute risk reduction, 0.59%; number needed to treat, 170) in the overall population. Similarly, among subjects administered the full-dose regimen, betrixaban reduced

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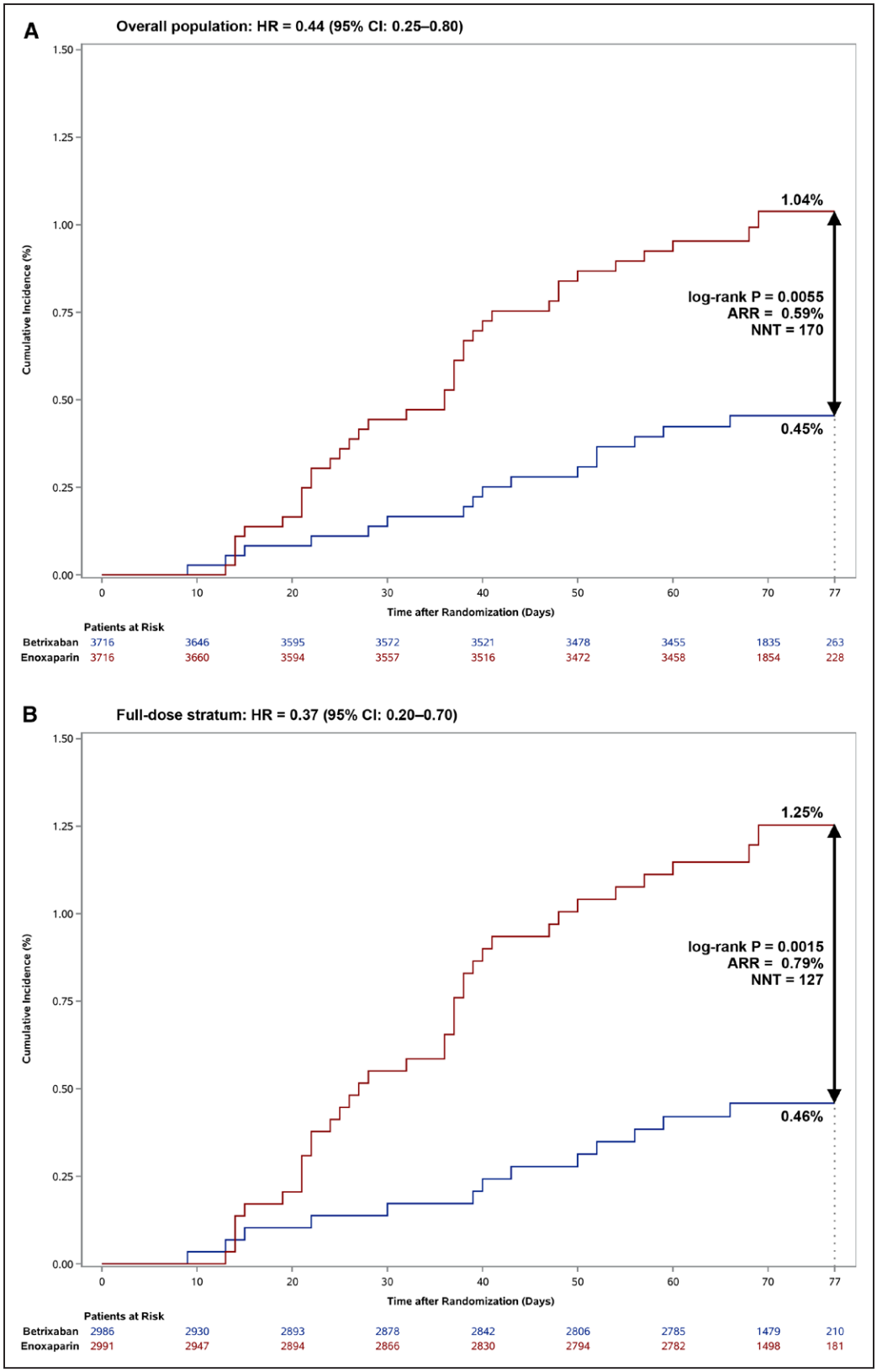

Figure. The risk of venous thromboembolism–related rehospitalization stratified by thromboprophylaxis in the overall population (A) and the full-dose stratum (B).

Compared with standard-of-care enoxaparin, extended thromboprophylaxis with betrixaban for 35 to 42 days was associated with a lower risk of recurrent hospitalization related to venous thromboembolism at 77 days. ARR indicates absolute risk reduction; CI, confidence interval; HR, hazard ratio; and NNT, number needed to treat.

VTE-related rehospitalization at 42 days (0.24% versus 0.93%) and at 77 days (13 of 2986 [0.46%] versus 35 of 2991 [1.25%]; HR, 0.37; 95% CI, 0.20–0.70; *P*=0.0015; absolute risk reduction, 0.79%; number needed to treat, 127; Figure). This relative reduction in VTE-related rehospitalization at 77 days (56% to 63%) translates into an absolute risk reduction of 0.59% to 0.79%, indicating that only 127 to 170 patients need to be treated with extended-duration betrixaban to prevent 1 rehospitalization related to VTE. Results were comparable when death was included as a competing risk through 77 days in the overall population (HR, 0.44; 95% CI, 0.24–0.79) and in the full-dose stratum (HR, 0.37; 95% CI, 0.19–0.70).

Patients are generally concerned about whether they are alive and free of rehospitalization. Thus, rehospitalization reflects not only healthcare economics but also patient-centered interests. Furthermore, rehospitalization does not require adjudication and may offer advantages and yield different insights compared with rigorously adjudicated events. Rehospitalization events are more frequent and therefore more sensitive albeit less specific compared with adjudicated events. As a result of their greater frequency, the use of rehospitalization events may provide greater statistical power in discerning treatment effects if specificity is not compromised.[4] Given their greater frequency, rehospitalization events may also more accurately ascertain the full economic burden to the healthcare system as health care moves toward capitated models and bundled payments.

The true costs of rehospitalization associated with VTE were not available because the hospital charges were not collected in the trial. However, the costs of an asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, and nonfatal pulmonary embolism could be estimated at US $6134, $11 152, and $19 730, respectively (assuming a compound annual growth rate of 2.66% based on the 2006 estimates).[5] These costs are similar to the costs for rehospitalization to treat other cardiovascular conditions such as chest pain (≈$8000), heart failure (≈$10 000), and percutaneous coronary intervention (≈$25 000). Given the reduction in VTE-related rehospitalizations, a formal cost-effectiveness analysis is warranted.

The results of this post hoc analysis were based on a randomized clinical trial with specific eligibility criteria and may not be generalizable to all hospitalized, medically ill patients. Information was not available on whether the hospitalization was for a symptomatic or asymptomatic VTE event. However, these results demonstrated that extended-duration betrixaban reduced the risk of VTE-related rehospitalization compared with standard-duration enoxaparin and have important quality of life and health economic implications.

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FOOTNOTES

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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