

Commentary

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## Commentary: Extended-Duration betrixaban reduces the risk of stroke versus standard-Dose enoxaparin among hospitalized medically ill patients

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### Article Info

#### Article Notes

Received: February 14, 2017

Accepted: May 05, 2017

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### ABSTRACT

Stroke is one of the leading causes of mortality and morbidity worldwide. It results in considerable costs to the healthcare system in the United States. Pharmacologic stroke prophylaxis has been well-studied in patients with atrial fibrillation and in patients with a history of stroke. In-hospital strokes constitute 2.2% to 17% of all strokes and often go undiagnosed in acute medically ill patients. A retrospective analysis of the APEX trial identifies an acutely ill hospitalized patient population that may benefit from extended duration prophylaxis. The hospitalized medically ill are a novel population to target for stroke prophylaxis. This article will discuss the primary results of the APEX sub-study and other trials that have demonstrated stroke reduction with extended duration anticoagulation in this population. This article additionally comments on the clinical relevance of these findings and the importance of the development of short-term risk stratification models to aid clinicians in deciding whether or not to provide pharmacologic stroke prophylaxis to their acutely ill patients at hospital admission.

In 2013, stroke was the second most common cause of death worldwide and the third most common cause of disability<sup>1</sup>. Stroke mortality is estimated at 100 per 100,000 person-years and is estimated to cost the healthcare system between \$9,000 to \$83,000 per patient per year, depending on the degree of sustained disability<sup>2</sup>.

In-hospital strokes often go undiagnosed in acutely ill patients<sup>1,2</sup>. Among hospitalized medically ill patients, stroke complicates 0.04% to 0.06% of cases. However, in-hospital strokes constitute 2.2% to 17% of all strokes<sup>3</sup>. Compared to community-onset strokes, strokes that occur during hospitalization in medically ill patients carry a poorer prognosis<sup>4,5</sup>. Although pharmacologic stroke prophylaxis has been widely studied in patients with non-valvular atrial fibrillation and in patients with a history of stroke<sup>6,7</sup>, stroke prevention in hospitalized patients with acute medical illness remains an unmet need.

The Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients (APEX) trial was a randomized, double-blind, double-dummy, active-controlled multinational clinical trial that randomized 7513 patients who were hospitalized for acute medical illnesses including heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke. Eligible patients were randomized in a 1:1 ratio to receive standard duration enoxaparin for 6 to 14 days or extended duration betrixaban for 35 to 42 days. The primary efficacy endpoint was a composite of venous thromboembolism events (VTE)

including asymptomatic deep vein thrombosis (DVT), symptomatic DVT, non-fatal pulmonary embolism (PE), and VTE-related death. The primary safety endpoint was the occurrence of International Society on Thrombosis and Hemostasis (ISTH) major bleeding within 7 days of study drug discontinuation<sup>8</sup>. Patients were followed for up to 77 days. The sample size was calculated to provide 90% power for the composite primary endpoint at a one-sided  $\alpha=0.005$ . Based on previous trials, an event rate of 7.5% was estimated in the control group and a 35% relative risk reduction was assumed with extended duration treatment<sup>9,10</sup>.

Baseline characteristics were well-balanced, with a mean age of 76.4 years and a median duration of hospitalization of 10 days. The distribution of acute medical illnesses at admission was also well balanced. Approximately 45% of patients had heart failure, 29% had an acute infection, 12% had respiratory failure, 11% had ischemic stroke, and 3% had a rheumatic disorder. The trial demonstrated that extended duration betrixaban administration was associated with a decreased risk of VTE through day 42 and no significant increase in major bleeding through 7 days after study drug discontinuation<sup>11</sup>.

Stroke was evaluated as an exploratory safety endpoint in which extended duration betrixaban administration demonstrated a significant reduction in ischemic stroke (RR: 0.53, 95% CI: 0.30-0.94,  $p=0.03$ ) and all types of stroke (RR: 0.59, 95% CI: 0.35-0.97,  $p=0.03$ ) through the time of study drug discontinuation (35-42 days), compared to standard duration enoxaparin<sup>12</sup>. Through 77 days, betrixaban administration was associated with a significant reduction in all-cause stroke (RR: 0.56; 95%CI, 0.32-0.96;  $p=0.03$ ) as well as ischemic stroke (RR: 0.53; 95%CI: 0.30-0.94;  $p=0.03$ ) when compared to enoxaparin.

The study also identified patients at high-risk of developing stroke and evaluated the efficacy endpoint in this subset of the population. Patients at high risk for stroke included those with congestive heart failure (OR: 2.45; 95% CI: 1.38-4.36;  $p=0.002$ ) or ischemic stroke (OR: 4.93; 95% CI: 2.79-8.73;  $p<0.001$ ) as their index event that required hospitalization. Among this high-risk subset, betrixaban showed larger and more significant reductions in the risk of all-cause stroke (RR=0.49; 95% CI: 0.26-0.90;  $p=0.019$ ) and ischemic stroke (RR=0.45; 95% CI: 0.24-0.87;  $p=0.014$ ) compared to enoxaparin. The results were unchanged when a history of atrial fibrillation was added to congestive heart failure or ischemic stroke as the index event. Patients with severe renal insufficiency (CrCl <30 ml/min) or those receiving concomitant strong P-glycoprotein inhibitors received a reduced dose (40 mg) of betrixaban. The reduced dosing regimen failed to demonstrate a reduction in stroke compared to enoxaparin, suggesting

that this dose may be suboptimal for stroke prophylaxis in this population. Limitations of this study include the underpowered retrospective nature of the analysis, and the short duration of follow up.

Risk stratification models for prediction of stroke in the acutely ill hospitalized patient represent a critical unmet need. Although established risk factors for long-term stroke have been identified, evidence is lacking regarding the short-term predictors of stroke. This is of particular importance in the setting of acutely ill patients in which short term complications such as hematologic abnormalities and thrombotic events may dramatically impact the course of hospitalization and, ultimately, acute morbidity and mortality<sup>1,13</sup>. Easy to use risk assessment models would provide a useful tool for clinicians to risk stratify their patients and facilitate the decision of whether or not to provide stroke prophylaxis for acutely ill patients at the time of hospital admission. Enrichment strategies may include treating patients with known risk factors for stroke such as atrial fibrillation, previous history of stroke or transient ischemic attack (TIA), hypertension, hyperlipidemia, obesity, and smoking<sup>14-16</sup>. Additionally, identifying feasible biomarkers that predict the occurrence of stroke may prove beneficial.

Hospitalized medically ill patients are a novel population to target for pharmacologic stroke prevention. Data from similar studies that assessed VTE prevention using extended duration oral anticoagulation with factor Xa inhibitors (apixaban and rivaroxaban) demonstrate numerically fewer strokes among patients on an extended duration regimen compared to standard duration enoxaparin<sup>9,17</sup>. Betrixaban is the only anticoagulant that has demonstrated a statistically significant reduction in strokes in acutely ill hospitalized medical patients using an extended duration regimen<sup>12</sup>. These studies bring to light a crucial finding that extended duration anticoagulation of acutely ill hospitalized patients not only reduces their potential for developing venous thrombosis but also reduces the risk of arterial thrombotic events. Both endpoints carry major clinical implications and have a considerable impact on patient outcomes<sup>1,13</sup>. These findings raise pertinent questions about the optimal anticoagulation strategy that would address the overall benefit of venous and arterial thrombotic event prophylaxis in this frail population.

## Acknowledgement

Funding: Portola

## Conflict of Interest Statement

We confirm that all coauthors and contributors to the manuscript have provided full disclosure regarding any relevant relationships, financial and otherwise and have no conflict of interest.

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