Extended-Duration Betrixaban Reduces the Risk of Stroke Versus Standard-Dose Enoxaparin Among Hospitalized Medically Ill Patients

An APEX Trial Substudy (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban)

Editorial, see p 656

BACKGROUND: Stroke is a morbid and potentially mortal complication among patients hospitalized with acute medical illness. The potential of extended-duration thromboprophylaxis with the factor Xa inhibitor betrixaban to reduce the risk of stroke compared with standard-dose enoxaparin in this population was assessed in this retrospective APEX trial substudy (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban).

METHODS: Hospitalized acutely medically ill subjects (n=7513) were randomized in a double-dummy double-blind fashion to either extended-duration oral betrixaban (80 mg once daily for 35–42 days) or standard-dose subcutaneous enoxaparin (40 mg once daily for 10±4 days) for venous thromboprophylaxis. Stroke events were adjudicated by an independent, blinded event adjudication committee.

RESULTS: The mean age of study participants was 76 years; 45% were male; 13% had had a stroke; and 45% had congestive heart failure. There were fewer all-cause strokes (0.54% versus 0.97%; relative risk [RR]=0.56; 95% confidence interval, 0.32–0.96; *P*=0.032; adjusted RR=0.43%; number needed to treat=233) and ischemic strokes (0.48% versus 0.91%; RR=0.53; 95% confidence interval, 0.30–0.94; *P*=0.026; adjusted RR=0.43%; number needed to treat=233) among patients treated with betrixaban versus enoxaparin through 77 days of follow-up. Among high-risk subjects, those with congestive heart failure or ischemic stroke as their index event, betrixaban reduced the risk of all-cause stroke (0.72% versus 1.48%; RR=0.49; 95% confidence interval, 0.26–0.90; *P*=0.019; adjusted RR=0.76%; number needed to treat=132) and ischemic stroke (0.63% versus 1.38%; RR=0.45; 95% confidence interval, 0.24–0.87; *P*=0.014; adjusted RR=0.75%; number needed to treat=134) compared with enoxaparin.

CONCLUSIONS: Among hospitalized medically ill patients, extended-duration betrixaban significantly reduced all-cause stroke and ischemic stroke through 77 days of follow-up

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C. Michael Gibson, MS, MD
Gerald Chi, MD
Rim Halaby, MD
Serge Korjian, MD
Yazan Daaboul, MD
Purva Jain, MPH
Douglas Arbetter, MPH
Samuel Z. Goldhaber, MD
Russel Hull, MBBS
Adrian F. Hernandez, MD
Alex Gold, MD
Olga Bandman, MD
Robert A. Harrington, MD
Alexander T. Cohen, MD
On Behalf of the APEX Investigators

Correspondence to: C. Michael Gibson, MS, MD, PERFUSE Study Group, Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 20 Overland St, Ste 540, Boston, MA 02215. E-mail mgibson@bidmc.harvard.edu

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Clinical Perspective

What Is New?

- Among hospitalized medically ill patients, extended-duration betrixaban significantly reduced all-cause stroke and ischemic stroke compared with standard-of-care enoxaparin through 77 days of follow-up.

What Are the Clinical Implications?

- Extended-duration thromboprophylaxis with an experimental oral factor Xa inhibitor may reduce the risk of stroke among hospitalized medically ill patients.

Stroke is a leading cause of morbidity and mortality worldwide.[1] In-hospital stroke complicates 0.04% to 0.06% of all hospitalizations and constitutes 2.2% to 15.2% of all strokes.[2–9] Stroke among patients hospitalized for an acute medical illness portends a less favorable outcome compared with community-onset stroke.[6] However, little is known about the effectiveness of novel oral anticoagulants for stroke prevention in this context. The APEX trial substudy (Acute Medically Ill Venous Thromboembolism Prevention With Extended Duration Betrixaban) evaluated the safety and efficacy of an extended duration of thromboprophylaxis with the oral anticoagulant betrixaban in the prevention of venous thromboembolism.[10] The aim of this retrospective substudy was to evaluate the efficacy of extended-duration betrixaban versus standard thromboprophylactic enoxaparin in the reduction of stroke among hospitalized medically ill patients.

METHODS

The APEX trial substudy design has been described in detail elsewhere.[11] This study was approved by an institutional review committee, and all subjects provided informed consent. The APEX trial substudy was a randomized, double-blind, placebo-controlled, clinical trial that randomized acutely medically ill hospitalized subjects at elevated risk for venous thromboembolism to either standard-dose subcutaneous enoxaparin (40 mg once daily for 10±4 days) or extended-duration oral betrixaban (80 mg once daily for 35–42 days). The dose of study drug was adjusted among subjects with renal insufficiency and a creatinine clearance <30 mL/min (both the enoxaparin and betrixaban doses were halved) and subjects receiving concomitant strong P-glycoprotein inhibitors (only the betrixaban dose was halved). The primary efficacy outcome for this substudy was the occurrence of all-cause stroke through 77 days of follow-up (last visit at up to 47 days of exposure plus 30 days after discontinuation to capture any rebound events following drug discontinuation).

A blinded, independent clinical events committee adjudicated all events of stroke and transient ischemic attack (TIA). Standardized definitions for stroke and related end-point events are as follows[12]: Stroke was defined as an acute neurological vascular event with focal neurological signs lasting >24 hours with or without evidence of intracranial hemorrhage. If the acute neurological event represented a worsening of a previous deficit, it must have either persisted for >1 week or persisted for >24 hours and been accompanied by an appropriate new computed tomography or magnetic resonance imaging finding.

All-cause stroke was further subclassified as ischemic, hemorrhagic, or of unknown cause on the basis of head imaging or autopsy findings. An ischemic stroke was defined as an acute neurological vascular event with focal neurological signs lasting >24 hours without evidence of primary intracranial hemorrhage. Neuroimaging may have been normal in the early hours after the event, or a brain computed tomography may have demonstrated a hypodense region that corresponds to an arterial territory. When neurological symptoms were present for <24 hours because of successful treatment with intravenous tissue-type plasminogen activator or intra-arterial therapy, the event was classified as an ischemic stroke even in the absence of neuroimaging evidence of ischemic stroke. Hemorrhagic transformation on a delayed or follow-up scan was classified as part of the index ischemic stroke episode, not as a separate event. All mechanistic subtypes of ischemic stroke were included such as those due to large-artery (extracranial and intracranial) atherosclerosis, lacunar stroke, cryptogenic stroke, and ischemic stroke of other undetermined or unusual cause.

Hemorrhagic stroke was defined as an acute neurological vascular event with focal neurological signs lasting >24 hours or sudden severe headache and meningeal signs and evidence of intracranial hemorrhage by neuroimaging or autopsy. The hemorrhagic stroke subtypes include intracerebral hemorrhage, subarachnoid hemorrhage, and intraventricular hemorrhage. Intracranial bleeding of traumatic or presumed traumatic origin such as subdural hemorrhage and epidural hemorrhage was not included in this definition. Stroke of uncertain type was defined as an acute neurological vascular event that fulfills the definition of stroke with focal neurological signs lasting >24 hours or sudden severe headache followed rapidly by coma but without neuroimaging or autopsy data to classify as either an ischemic or a hemorrhagic stroke. Sudden unexplained death without a preceding headache to suggest subarachnoid hemorrhage was not included in this definition.

TIA was defined as a transient episode of neurological dysfunction (<24 hours) caused by focal brain, spinal cord, or retinal ischemia without acute infarction. A stroke rather than a TIA was diagnosed even if the symptoms lasted <24 hours if there were neuroimaging findings consistent with infarction or intracranial bleeding.

Statistical Analysis

All efficacy outcomes were analyzed with the actual dose received (including 40 versus 80 mg betrixaban) in the modified intent-to-treat population, which as a safety population includes subjects who received at least 1 dose of study drug. The risk of stroke was compared between treatment arms with stratification by dosing strategy with the Cochran-Mantel-Haenszel statistics used to determine significance.

To identify the high-risk subset in the hospitalized medically ill population, univariate and multivariate logistic regression analyses were performed. Individuals with any of the identified risk factors were defined as high-risk subjects. The adjusted stroke risk between treatment groups was calculated by controlling for these covariates. The efficacy of betrixaban against enoxaparin was assessed in this high-risk subset and among subjects with atrial fibrillation. In addition, the time to ischemic stroke among high-risk subjects receiving betrixaban versus enoxaparin was analyzed with the use of the Cox proportional hazards model. All analyses in this substudy were exploratory and were performed with SAS version 9.4.

RESULTS

Patient Characteristics

The mean age of study participants was 76 years; 45% were male; 13% had had a stroke; and 45% had congestive heart failure.[10] The patient characteristics of the 2 groups were quite similar with the only difference between the 2 groups being a mild imbalance in the incidence of a history of stroke (12.5% [469 of 3759] for betrixaban versus 14.0% [527 of 3754] for enoxaparin; P=0.046).[10] Among the modified intent-to-treat population, 19.4% received an adjusted lower dose of study medication (19.4% [730 of 3759] versus 19.3% [725 of 3754]; P=0.91). The use of antiplatelet agent and statin was generally well balanced between the 2 groups (P=0.70 and P=0.07) and does not modify the treatment effect on stroke ($P_{interaction}$=0.28 and $P_{interaction}$=0.23; Table I in the online-only Data Supplement).

Efficacy Outcomes

All-cause stroke was reduced among subjects treated with extended-duration betrixaban versus enoxaparin (0.54% [20 of 3716] versus 0.97% [36 of 3716]; relative risk [RR]=0.56; 95% confidence interval [CI], 0.32–0.96; P=0.032; adjusted RR=0.76%; number needed to treat=132), as was ischemic stroke (0.48% [18 of 3716] versus 0.91% [34 of 3716]; RR=0.53; 95% CI, 0.30–0.94; P=0.026; adjusted RR=0.43%; number needed to treat=233; Table 1). The composite end point of all-cause stroke and TIA was also reduced among subjects treated with extended-duration betrixaban versus enoxaparin (0.65% [24 of 3716] versus 1.10% [41 of 3716]; RR=0.59; 95% CI, 0.35–0.97; P=0.034; adjusted RR=0.45%; number needed to treat=223; Table 1). There was no significant difference in the proportion of patients between treatment groups across the modified Rankin Scale score (Table II in the online-only Data Supplement).

Efficacy similar to that of the entire study population was observed among subjects who received the full 80-mg dose of extended-duration betrixaban but not the reduced 40-mg dose (Tables 2 and 3). The reduction in all-cause stroke was driven predominantly by a reduction in ischemic stroke because the risk of hemorrhagic stroke was similar.

Among hospitalized medically ill patients, 2 risk factors were associated with all-cause stroke through the end of study at 77 days: ischemic stroke as the index event (odds ratio=4.12; 95% CI, 2.36–7.19; P<0.0001) and history of congestive heart failure (odds ratio=1.93; 95% CI, 1.10–3.40; P=0.022). In the multivariate model, both ischemic stroke (odds ratio=4.93; 95% CI, 2.78–8.73; P<0.001) and congestive heart failure (odds ratio=2.45; 95% CI, 1.38–4.36; P=0.002) were independently associated with the outcome (Table 4). Accordingly, hospitalized medically ill patients with either congestive heart failure or ischemic stroke as the index event were considered high-risk subjects in the study.

Among the high-risk subjects, all-cause stroke was significantly reduced in those treated with extended-duration betrixaban versus enoxaparin (0.72% [15 of 2075] versus 1.48% [31 of 2095]; RR=0.49; 95% CI, 0.26–0.90; P=0.019), as was ischemic stroke (0.63% [13 of 2075] versus 1.38% [29 of 2095]; RR=0.45;

Table 1. Rate of Stroke or TIA (Modified Intent-to-Treat Population)

Stroke Type	Betrixaban (n=3716), n (%)	Enoxaparin/Placebo (n=3716), n (%)	RR (95% CI)	*P* Value
All-cause stroke	20 (0.54)	36 (0.97)	0.56 (0.32–0.96)	0.032*
Ischemic	18 (0.48)	34 (0.91)	0.53 (0.30–0.94)	0.026*
Hemorrhagic	1 (0.03)	1 (0.03)	1.00 (0.06–15.98)	1.00
Uncertain type	1 (0.03)	1 (0.03)	1.00 (0.06–15.98)	1.00
TIA	4 (0.11)	5 (0.13)	0.80 (0.22–2.98)	0.74
All-cause stroke or TIA	24 (0.65)	41 (1.10)	0.59 (0.35–0.97)	0.034*

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack. The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The *P* values were calculated with the Cochran-Mantel-Haenszel method.

*Significant.

Table 2. Rate of Stroke or TIA (Modified Intent-to-Treat Population; 80-mg Dose)

Stroke Type	Betrixaban (n=2986), n (%)	Enoxaparin/Placebo (n=2991), n (%)	RR (95% CI)	*P* Value
All-cause stroke	14 (0.47)	30 (1.00)	0.47 (0.25–0.88)	0.016*
Ischemic	13 (0.44)	28 (0.94)	0.47 (0.24–0.90)	0.019*
Hemorrhagic	0 (0.00)	1 (0.03)	…	0.32
Uncertain type	1 (0.03)	1 (0.03)	1.00 (0.06–16.01)	1.00
TIA	3 (0.10)	5 (0.17)	0.60 (0.14– 2.51)	0.48
All-cause stroke or TIA	17 (0.57)	35 (1.17)	0.49 (0.27–0.87)	0.012*

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack. Note: The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The *P* values were calculated with the Cochran-Mantel-Haenszel method.

*Significant.

95% CI, 0.24–0.87; *P*=0.014; Table 5). The reduction in ischemic stroke began during the period of parenteral therapy and continued to widen throughout the period of active therapy (Figure). There was no evidence of rebound after discontinuation of betrixaban at day 35 to 42 (Figure). A significant reduction in the composite of all-cause stroke and TIA was also observed among high-risk subjects treated with extended-duration betrixaban versus enoxaparin (0.87% [18 of 2075] versus 1.58% [33 of 2095]; RR=0.55; 95% CI, 0.31–0.69; *P*=0.038; Table 5). However, a similar reduction in stroke events was observed when a history of atrial fibrillation was added to ischemic stroke or congestive heart failure as the index event, although the number of additional events was quite small (Table 6).

DISCUSSION

Among acutely medically ill subjects, the administration of betrixaban was associated with a reduction in the risk of all-cause stroke or TIA. The reduction in all-cause stroke was driven predominantly by a reduction in ischemic stroke. Other factor Xa and IIa inhibitors have been used to reduce the risk of cardioembolic stroke in subjects with atrial fibrillation. However, the reduction in ischemic stroke in the present study was notable in those subjects with congestive heart failure or ischemic stroke as the index event in the absence of atrial fibrillation. There were few strokes among subjects with atrial fibrillation in the present study, so this retrospective study was not adequately powered to assess the benefit of betrixaban in this context. Despite this reduction in ischemic stroke, betrixaban was not associated with an increased risk of major bleeding (0.7% versus 0.6%; RR, 1.19; 95% CI, 0.67–2.12; *P*=0.55).[10] There was, however, like all factor Xa inhibitors, a greater rate of major or clinically relevant nonmajor bleeds in the betrixaban group versus the enoxaparin group (3.1% versus 1.6%; RR, 1.97; 95% CI, 1.44–2.68; *P*=0.03).[10]

The hospitalized medically ill population is a novel population to target for stroke reduction. The stroke prevention guidelines for patients with atrial fibrillation, after myocardial infarction, and with stroke may not be that relevant to the medically ill population. Although the rates of all-cause stroke appear to be low in the study (0.54% versus 0.95%), it must be remembered that these were 77-day crude event rates. On an annualized basis, this medically ill population had a potentially higher rate of

Table 3. Rate of Stroke or TIA (Modified Intent-to-Treat Population; 40-mg Dose)

Stroke Type	Betrixaban (n=730), n (%)	Enoxaparin/Placebo (n=725), n (%)	RR (95% CI)	*P* Value
All-cause stroke	6 (0.82)	6 (0.83)	0.99 (0.32–3.07)	0.99
Ischemic	5 (0.68)	6 (0.83)	0.83 (0.25–2.70)	0.75
Hemorrhagic	1 (0.14)	0 (0.00)	…	0.32
Uncertain type	0 (0.00)	0 (0.00)	…	…
TIA	1 (0.14)	0 (0.00)	…	0.32
All-cause stroke or TIA	7 (0.96)	6 (0.83)	1.16 (0.39–3.43)	0.79

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack. The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The *P* values were calculated with the Cochran-Mantel-Haenszel method.

Table 4. Multivariate Analysis of Treatment Effect on All-Cause Stroke Among Subjects With Either Congestive Heart Failure or Ischemic Stroke as the Index Event

Parameter	Parameter= Yes, n (%)	Parameter= No, n (%)	Odds Ratio (95% CI)	*P* Value	RR (95% CI)	*P* Value
Treatment	20/3716 (0.54)*	36/3716 (0.97)†	0.56 (0.32–0.96)	0.036‡	0.78 (0.64–0.94)	0.032‡
Ischemic stroke as index event	19/837 (2.27)	37/6595 (0.56)	4.93 (2.78–8.73)	<0.001‡	4.05 (2.34–7.00)	<0.001‡
History of CHF	38/3887 (0.98)	18/3545 (0.51)	2.45 (1.38–4.36)	0.002‡	1.93 (1.10–3.37)	0.019‡

CHF indicates congestive heart failure; CI, confidence interval; and RR, relative risk. The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The reference groups in the model are as follows: treatment=enoxaparin/placebo, ischemic stroke as index event=no, and history of CHF=no.

*Event rate is shown for subjects treated with betrixaban.

†Event rate is shown for subjects treated with enoxaparin.

‡Significant.

stroke (2.55% versus 4.59%) than that observed in the atrial fibrillation population (ROCKET AF [An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation], 2.1% versus 2.4%; ARISTOTLE [Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation], 1.3% versus 1.6%; RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy], 1.5% versus 1.1% versus 1.7%).[13–15] Consideration may be given to prophylactic strategies such as those described here to reduce the risk of stroke in this at-risk population.

Betrixaban has a 20-hour pharmacodynamic half-life, and this minimizes peak drug concentrations and increases drug concentration troughs, thereby reducing the peak-to-trough ratio.[16] This narrow range of variability between peak and trough levels may explain in part the benefit in reducing stroke observed in the study. With reduced peak drug concentrations, there may be a lower risk of hemorrhagic complications, and with increased trough concentrations, there may be a lower risk of thrombotic complications. Betrixaban also has a very low renal clearance, unlike enoxaparin, which may likewise explain, at least in part, the improved outcomes in this frail population with impaired creatinine clearance.

The dosing strategy in the APEX trial substudy was prespecified, and patients were stratified accordingly at randomization. A reduced dosage of betrixaban (loading dose of 80 mg followed by maintenance dose of 40 mg daily) was administered to subjects with severe renal insufficiency or receiving concomitant strong P-glycoprotein inhibitors. The full 80-mg dose of betrixaban (n=2986) was associated with a significant reduction in all-cause stroke or ischemic stroke compared with enoxaparin. The lack of superiority of the 40-mg dose (n=730) against enoxaparin suggests that the dosage

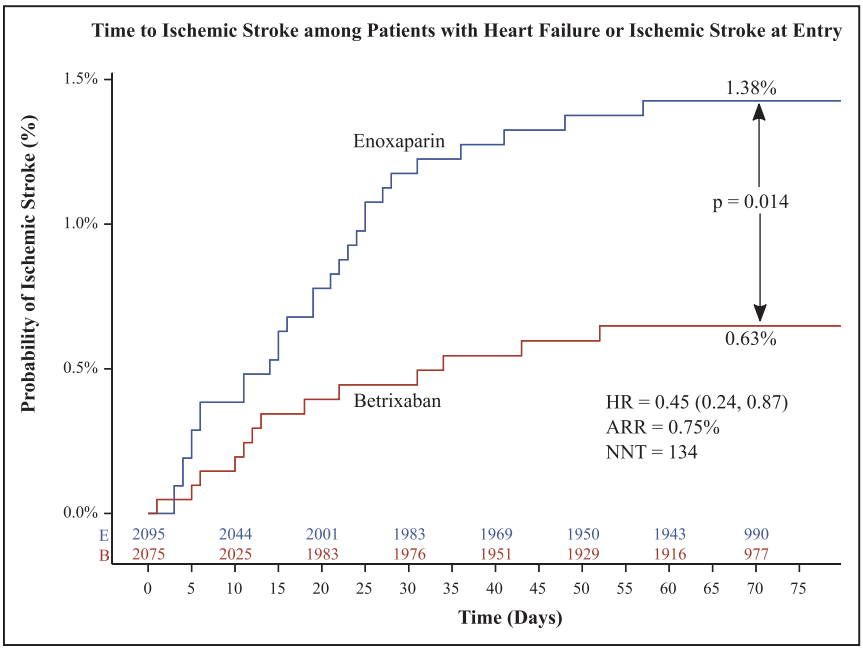

Figure. Time to ischemic stroke among subjects with congestive heart failure or ischemic stroke as index event.
The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted using actual treatment through the end of the study (day 77).

Table 5. Rate of Stroke or TIA Among Subjects With Either Congestive Heart Failure or Ischemic Stroke as the Index Event

Stroke Type	Betrixaban (n=2075), n (%)	Enoxaparin/Placebo (n=2095), n (%)	RR (95% CI)	*P* Value
All-cause stroke	15 (0.72)	31 (1.48)	0.49 (0.26–0.90)	0.019*
Ischemic	13 (0.63)	29 (1.38)	0.45 (0.24–0.87)	0.014*
Hemorrhagic	1 (0.05)	1 (0.05)	1.01 (0.06–16.13)	0.99
Uncertain type	1 (0.05)	1 (0.05)	1.01 (0.06–16.13)	0.99
TIA	3 (0.14)	2 (0.10)	1.51 (0.25–9.05)	0.65
All-cause stroke or TIA	18 (0.87)	33 (1.58)	0.55 (0.31–0.97)	0.038*

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack. The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The *P* values were calculated with the Cochran-Mantel-Haenszel method.

*Significant.

may have been excessively reduced for stroke prophylaxis in the hospitalized medically ill population.

Congestive heart failure and previous ischemic stroke were associated with an ≈2-fold and 4-fold increased risk for all-cause stroke among the study population of hospitalized patients. Unless a right-to-left shunt is present, venous thromboembolic disease should not cause an arterial stroke. In congestive heart failure, there is a potential for apical thrombus that can cause embolic stroke, whereas in prior recent stroke, there is potentially a nidus of thrombus formation in the cerebral circulation that can be a risk factor for recurrent stroke.

It is difficult to ascertain whether the strokes in the present study were cardioembolic. Ejection fraction is an independent risk factor for stroke among subjects with ventricular dysfunction.[17] Among subjects with congestive heart failure as their index event, it was not known if they had preserved ejection fractions or reduced ejection fractions because the ejection fraction was not recorded. Likewise, echocardiographic data pertaining to the presence or absence of clot were not collected during this trial. Finally, it is possible that subjects who experienced stroke had undiagnosed or nonreported atrial fibrillation, left ventricular thrombus, valvulopathy, or structural heart diseases such as patent foramen ovale that were not assessed and predisposed them to paradoxical embolism.

Ventricular dysfunction and a history of stroke are not the only conditions associated with an elevated risk of stroke[18]; infection and inflammation are also associated with a greater risk of stroke.[17,19,20] Similar to venous thromboembolism, it is possible that hospitalization and the associated stress response predispose medically ill patients with preexisting cardiovascular risk factors to stroke. Hospitalized patients are more likely to develop increases in their catecholamines, transient or sustained atrial fibrillation, dehydration, and an increased prothrombotic state, which may increase their risk for stroke. In addition, subjects with hospitalization-associated venous thromboembolism are at risk for paradoxical embolism in the presence of structural heart diseases such as patent foramen ovale.

Table 6. Rate of Stroke or TIA Among Subjects With Congestive Heart Failure or Ischemic Stroke as the Index Event or Atrial Fibrillation

Stroke Type	Betrixaban (n=2186), n (%)	Enoxaparin/Placebo (n=2219), n (%)	RR (95% CI)	*P* Value
All-cause stroke	15 (0.69)	32 (1.44)	0.48 (0.26–0.88)	0.015*
Ischemic	13 (0.59)	30 (1.35)	0.44 (0.23–0.84)	0.011*
Hemorrhagic	1 (0.05)	1 (0.05)	1.02 (0.06–16.22)	0.99
Uncertain type	1 (0.05)	1 (0.05)	1.02 (0.06–16.22)	0.99
TIA	3 (0.14)	2 (0.09)	1.52 (0.25–9.10)	0.64
All-cause stroke or TIA	18 (0.82)	34 (1.53)	0.54 (0.30–0.95)	0.029*

CI indicates confidence interval; RR, relative risk; and TIA, transient ischemic attack. The modified intent-to-treat population includes all subjects who received at least 1 dose of study drug. The analysis was conducted with actual treatment. The *P* values were calculated with the Cochran-Mantel-Haenszel method.

*Significant.

LIMITATIONS

This analysis was retrospective, and no adjustment was made for multiple comparisons. The stroke rate was modest in the study. It could be argued that the reduction in stroke was due to play of chance. However, the association of prior stroke and congestive heart failure with recurrent stroke and the fact that these subjects sustained the greatest event reduction support the biological plausibility of the observation. The fact there was a dose-dependent response with efficacy observed at the 80-mg dose and not the 40-mg dose adds to the biological plausibility of the observation and indicates that the 40-mg dose of betrixaban may have been excessively reduced in patients with severe renal insufficiency and those receiving concomitant strong P-glycoprotein inhibitors. Given the smaller sample size of the 40-mg dose group, it also may have been relatively underpowered to ascertain a difference in event rates.

Although the event rates were low during this period of follow-up, they are much higher when conveyed on an annualized basis. The ability of betrixaban to reduce the risk of stroke over a longer period of time is not known.

CONCLUSIONS

Among hospitalized medically ill patients, extended-duration betrixaban significantly reduced all-cause stroke and ischemic stroke compared with standard-of-care enoxaparin through 77 days.

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AFFILIATIONS

From Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA (C.M.G., G.C., R. Halaby, S.K., Y.D., P.J., D.A.); Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.Z.G.); Faculty of Medicine, Division of Cardiology, University of Calgary, AB, Canada (R. Hull); Duke University and Duke Clinical Research Institute Durham, NC (A.F.H.); Portola Pharmaceuticals Inc, South San Francisco, CA (A.G., O.B.); Department of Medicine, Stanford University, CA (R.A.H.); and Guy's and St Thomas' Hospitals, London, United Kingdom (A.T.C.).

FOOTNOTES

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