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Betrixaban for prevention of venous thromboembolism in acute medically ill patients

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Venous thromboembolism (VTE) is a common, potentially preventable cause of morbidity and mortality among acute medically ill patients. More than half of VTE events in this population occur after hospital discharge. Thus, providing extended-duration VTE prophylaxis from in-hospital through the post-discharge continuum may improve the quality of care in patients at risk of VTE. Betrixaban is a new oral, once-daily factor Xa inhibitor approved by the United States (US) Food and Drug Administration (FDA) for extended-duration prophylaxis of VTE in acute medically ill patients. The clinical efficacy and safety of betrixaban in acute medically ill patients perceived to be at high risk for VTE were evaluated in a large, randomized, double-blind, active-controlled, multinational clinical trial [Acute Medically Ill VTE Prevention With Extended Duration Betrixaban (APEX)]. Patients were randomized to receive subcutaneous enoxaparin (10 ± 4 days) or oral betrixaban (35–42 days) plus matching placebos. The primary efficacy outcome was a composite of asymptomatic proximal deep vein thrombosis and symptomatic VTE; the primary safety measure was major bleeding. Extended-duration betrixaban reduced VTE events without an increase in major bleeding in the modified intent-to-treat analysis. *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. In summary, analyses of the APEX study demonstrated a positive benefit–risk profile for extended prophylaxis of VTE with betrixaban in acute medically ill patients. This is likely to have important public health and health economic implications.

Introduction

Venous thromboembolism (VTE) in hospitalized, acute medically ill patients is a common, potentially preventable cause of morbidity and mortality.[1] Annually, there are

more than 5.5 million hospitalized, acute medically ill patients at risk for VTE in six countries in the European Union.[2] Standard-duration thromboprophylaxis may be given for 6–14 days in acute medically ill patients, but it is usually terminated at the time of discharge. Therefore, the length of prophylaxis in many of these patients may be inadequate, especially when they are discharged after <6 days. Indeed, more than half of the VTE events in this population occur after hospital discharge.[3,4] Other treatments, including extended enoxaparin, rivaroxaban, and

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apixaban, have been investigated for extended thrombo-prophylaxis post-discharge but did not demonstrate a net clinical benefit due to significantly increased bleeding and limited efficacy; this may have been influenced by trial design and patient inclusion and exclusion criteria.[5-8] Furthermore, due to underutilization of in-hospital thromboprophylaxis,[9] the refusal of parenteral therapies by as much as 44% of hospitalized patients who are at risk of VTE and the lack of approved post-discharge therapies, providing extended-duration VTE prophylaxis in high-risk patients remained a clinical challenge and was the rationale for performing the APEX trial.[10-12]

Betrixaban, a new oral, once-daily factor Xa (FXa) inhibitor, is the first anticoagulant approved by the US Food and Drug Administration (FDA) in June 2017 for extended-duration prophylaxis of VTE in acute medically ill patients. As discussed previously in this supplement, betrixaban is distinguished from other FXa inhibitors by a longer half-life (effective half-life = 19-27 h; see Article 2 for a discussion of the pharmacodynamic differences between FXa inhibitors) and a lower renal clearance (11% of the administered dose and 17.8% of the absorbed dose).[13] To determine whether the pharmacological characteristics of betrixaban provide a benefit in the prevention of VTE in acute medically ill patients in the in-hospital and post-discharge period, the clinical efficacy and safety of betrixaban was evaluated in a large, randomized, double-blind, double-dummy, active-controlled, multinational clinical trial [Acute Medically Ill VTE Prevention With Extended Duration Betrixaban (APEX)].[14]

APEX clinical trial

APEX randomized 7513 patients aged ≥ 40 years hospitalized for prespecified acute medical illnesses (heart failure, respiratory failure, infectious disease, rheumatic disease, or ischaemic stroke) who had reduced mobility and presented additional significant VTE risk factors at the time of hospitalization. Patients were required to have at least one of the following additional risk factors for VTE[14]:

- Aged 75 years or more
- 60 to 74 years old with D-dimer of two times the upper limit of normal (ULN) or more
- 40 through 59 years old with a D-dimer of at least two times the ULN and a history of VTE [deep vein thrombosis (DVT) or pulmonary embolism (PE)], or history of cancer (excluding non-melanoma carcinoma of the skin).

Inclusion criteria permitted the enrolment of patients with severe renal insufficiency (creatinine clearance ≥ 15 to < 30 min/min; no dialysis requirement), since betrixaban has a low fractional renal excretion.[8,14] Patients were enrolled within 96 h after hospitalization and were randomized to receive enoxaparin 40 mg once daily (qd) for 10 ± 4 days or oral betrixaban at an initial loading dose of 160 mg and then 80 mg qd for 35-42 days, and matched placebos. Study drugs were started at the day of randomization. Patients with severe renal insufficiency received 50% of the prespecified dose of each study medication (i.e. 20 mg of enoxaparin or a loading dose of 80 mg of betrixaban and then 40 mg qd). Patients who were taking a concomitant P-glycoprotein inhibitor received a reduced dose of betrixaban (40 mg qd), but received the 40 mg full dose of enoxaparin. Entry criteria were modified during the trial to enrich the prevalence of VTE risk factors leading to three prespecified, progressively inclusive cohorts to be included in the efficacy analysis[14]:

- Cohort 1: D-dimer of 2 times the ULN or more
- Cohort 2: D-dimer of 2 times the ULN or more plus all patients age ≥ 75 years
- Cohort 3: Overall study population, all eligible patients

All patients enrolled in the APEX trial were followed for an additional 30 ± 5 days after Day 42 of the trial. During the follow-up period, clinically suspected DVT was confirmed by ultrasonography or other vascular-imaging technique, while clinically suspected PE was confirmed by CT scan, ventilation–perfusion lung scan, pulmonary angiography, or, in the case of death, autopsy. Mandatory ultrasonography was performed to detect DVT in asymptomatic study participants after the last dose of betrixaban or placebo was administered between Days 35 and 42.[14]

Primary analyses

Betrixaban was compared with enoxaparin for the primary efficacy outcome (asymptomatic proximal DVT between Days 32 and 47, symptomatic proximal or distal DVT, symptomatic non-fatal PE, or death from VTE between Day 1 and Day 42) and for other composite efficacy outcomes.[13,14] The statistical analysis was designed with a fixed hierarchal sequence: if the primary endpoint was met in Cohort 1, then superiority of betrixaban with respect to the primary efficacy outcome would be tested in Cohort 2. If superiority of betrixaban was demonstrated in Cohort 2, the primary efficacy outcome would be evaluated in Cohort 3, the overall study population. Subsequent analyses of secondary endpoints were also based on superiority with respect to the primary efficacy outcome.[14]

Efficacy analyses performed in the modified intent-to-treat (mITT) population, which comprised all patients who received at least one dose of study drug and a follow-up assessment of at least one primary or secondary efficacy outcome component ($N = 7441$), were recommended by the FDA to avoid potential informative censoring and formed the basis for approval in the United States (US).[13,15] Baseline characteristics of patients were well balanced for betrixaban vs. enoxaparin treatment arms (Table 1), with only a significant but clinically modest imbalance in mean age (76.6 years vs. 76.2 years, $P = 0.028$) and mean body mass index (29.2 kg/m^2 vs. 29.5 kg/m^2, $P = 0.030$).[16] The efficacy results for the mITT population and the patients in that population who were stratified to receive 80 mg of betrixaban are listed in Table 2.[13,16] In the mITT analysis, the primary composite endpoint occurred in 4.4% of betrixaban patients and 6.0% of enoxaparin-treated patients, resulting in a relative reduction of risk (RRR) of 25% and an absolute risk reduction (ARR) of 1.6% [$P = 0.003$; number needed to treat (NNT) = 63].[13,16] Betrixaban 80 mg reduced total VTE or VTE-related death compared with enoxaparin; RRR = 32.0%; ARR of 2.0% ($P < 0.001$; NNT = 50) (Table 2).[13,16] Patients treated with 40 mg betrixaban displayed

Table 1 Patient characteristics in the modified intent-to-treat population

Characteristics	Betrixaban (N = 3721)	Enoxaparin (N = 3720)
Age, median years ± SD	76.6 ± 8.4	76.2 ± 8.3
Male, n (%)	1693 (45.5)	1699 (45.7)
Weight, mean kg ± SD	79.9 ± 19.2	80.7 ± 19.4
Body mass index, mean kg/m^2 ± SD	29.2 ± 6.6	29.5 ± 6.7
Duration of hospitalization, median days (IQR)	10 (7-14)	10 (8-14)
Creatinine clearance, n (%)		
<15 mL/min	1 (<0.1)	0
15-30 mL/min	173 (4.7)	149 (4.0)
30 to <60 mL/min	1584 (42.6)	1517 (40.8)
60 to ≤90 mL/min	1289 (34.6)	1338 (36.0)
>90 mL/min	663 (17.8)	708 (19.0)
Missing	11 (0.3)	8 (0.2)
Race, n (%)		
White	3472 (93.3)	3490 (93.8)
Asian	9 (0.2)	7 (0.2)
Black/African American	70 (1.9)	70 (1.9)
Other[a]	170 (4.6)	153 (4.1)
Concomitant strong P-gp inhibitor, n (%)	669 (18.0)	645 (17.3)
Prior thromboprophylaxis ≤96 h, n (%)	1905 (51.2)	1856 (49.9)
Acute medical conditions, n (%)		
Acute heart failure	1672 (44.9)	1666 (44.8)
Acute infection	1095 (29.4)	1041 (28.0)
Acute respiratory failure	440 (11.8)	465 (12.5)
Acute ischaemic stroke	406 (10.9)	432 (11.6)
Acute rheumatic disorder	106 (2.8)	116 (3.1)
Risk factors for VTE, n (%)		
Age ≥75 years	2555 (68.7)	2494 (67.0)
History of cancer	459 (12.3)	437 (11.7)
History of deep vein thrombosis or PE	307 (8.3)	291 (7.8)
History of heart failure (New York Heart Association Class III/IV)	849 (22.8)	859 (23.1)
Concurrent acute infectious disease	596 (16)	611 (16.4)
Severe varicosis	698 (18.8)	685 (18.4)
Hormone replacement therapy	42 (1.1)	31 (0.8)
Thrombophilia (hereditary or acquired)	3 (0.1)	5 (0.1)

IQR, interquartile range; PE, pulmonary embolism; P-gp, P-glycoprotein; SD, standard deviation; VTE, venous thromboembolism.
[a]Includes patients who were categorized as Native American, Alaska Native, Native Hawaiian or Pacific Islander, other race, or mixed race.

similar rates of the primary efficacy composite endpoint as those who received enoxaparin.[15]

The initial analysis of the primary efficacy outcome was performed in the Primary Efficacy Outcome Population, a subset of the mITT population. When first analysed by the clinical research organization (CRO), the primary efficacy outcome occurred in 6.9% of the betrixaban group and 8.5% of the enoxaparin group in Cohort 1, and this difference did not reach statistical significance [relative risk (RR) 0.81; 95% confidence interval (CI) 0.65-1.00; *P* = 0.054] (*Table 3*). In Cohort 2, the primary efficacy outcome occurred in 5.6% of the betrixaban group and 7.1% of the enoxaparin group (RR = 0.80; 95% CI 0.66-0.98; *P* = 0.029) (*Table 3*). In the overall population (Cohort 3), the primary efficacy outcome occurred in 5.3% and 7.0% of the patients, respectively (RR = 0.76; 95% CI 0.63-0.92; *P* = 0.006) (*Table 3*).

The approval of betrixaban in the US was based on the efficacy analyses in the mITT population. However, the

APEX study had analyses performed *a priori* by two independent, academic research organizations (AROs) blinded to each other. Both AROs independently interpreted the statistical analysis plan differently than the CRO. The two Academic Research Organization (ARO) analyses classified the same single VTE event with complex timing (i.e. the presentation of VTE symptoms shortly after the protocol-defined symptomatic DVT window and the demonstration of a DVT in the routine ultrasound scan) as a primary efficacy outcome; the CRO analysis did not include this event in its analysis.[17] The inclusion of this single event in the ARO analyses changed the RR in Cohort 1 from 0.806 (95% CI 0.647-1.004; *P* = 0.054) to 0.802 (95% CI 0.644-0.998; *P* = 0.048), thus reaching statistical significance in this cohort (*Table 3*).[17]

The incidence of symptomatic VTE events, a predefined secondary outcome, was lower in patients treated with extended-duration betrixaban compared with patients receiving standard-duration enoxaparin in the overall study

Table 2 Summary of efficacy outcomes in APEX trial

	Overall modified intent-to-treat population			Modified intent-to-treat population: patients stratified to 80 mg betrixaban dose		
	Betrixaban $N = 3721$ n (%)[b]	Enoxaparin $N = 3720$ n (%)[b]	Relative risk (95% CI)[c]	Betrixaban $N = 2878$ n (%)[d]	Enoxaparin $N = 2926$ n (%)[d]	Relative risk (95% CI)[c]
Composite outcome	165 (4.4)	223 (6.0)	0.75 (0.61-0.91) $P = 0.003$ NNT = 63	120 (4.2)	180 (6.2)	0.68 (0.55-0.86) $P < 0.001$ NNT = 50
Asymptomatic event	133 (3.6)	176 (4.7)		100 (3.5)	146 (5.0)	
Symptomatic DVT	14 (0.4)	22 (0.6)		11 (0.4)	17 (0.6)	
Non-fatal PE	9 (0.2)	18 (0.5)		4 (0.1)	14 (0.5)	
VTE-related death	13 (0.3)	17 (0.5)		8 (0.3)	12 (0.4)	
Symptomatic events[a]	35 (0.9)	54 (1.5)	0.64 (0.42-0.98)	22 (0.8)	41 (1.4)	0.55 (0.33-0.92)

CI, confidence interval; DVT, deep vein thrombosis; NNT, number needed to treat; PE, pulmonary embolism; VTE, venous thromboembolism.

[a]Symptomatic events include symptomatic DVT, non-fatal PE, or VTE-related death.

[b]Percentages and event rates are based on the total number of patients and events included in each treatment group.

[c]Relative risk (betrixaban arm vs. enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[d]Percentages and event rates are based on the total number of patients and events included in each treatment group and stratified to 80 mg dose.

Table 3 Primary composite endpoint (venous thromboembolism events) in clinical research organization analyses vs. academic research organization analysis

		Academic Research Organization (ARO)		Clinical Research Organization (CRO)	
Overall population (Cohort 3)	n (%) RR[a] (95% CI) P-value	Betrixaban ($n = 3112$) 165 (5.3) 0.757 (0.623-0.919) 0.005	Enoxaparin ($n = 3175$) 224 (7.1)	Betrixaban ($n = 3112$) 165 (5.3) 0.760 (0.625-0.923) 0.006	Enoxaparin ($n = 3174$) 223 (7.0)
Cohort 1	n (%) RR (95% CI) P-value	Betrixaban ($n = 1914$) 132 (6.9) 0.802 (0.644-0.998) 0.048	Enoxaparin ($n = 1957$) 167 (8.5)	Betrixaban ($n = 1914$) 132 (6.9) 0.806 (0.647-1.004) 0.054	Enoxaparin ($n = 1956$) 166 (8.5)
Cohort 2	n (%) RR (95% CI) P-value	Betrixaban ($n = 2842$) 160 (5.6) 0.796 (0.652-0.973) 0.025	Enoxaparin ($n = 2894$) 205 (7.1)	Betrixaban ($n = 2842$) 160 (5.6) 0.800 (0.655-0.977) 0.029	Enoxaparin ($n = 2893$) 204 (7.1)

A single venous thromboembolism (VTE) event with complex timing (i.e. the presentation of VTE symptoms shortly after the protocol-defined symptomatic deep vein thrombosis (DVT) window and the demonstration of a DVT in the routine ultrasound scan) as a primary efficacy outcome in the two ARO analyses; this event was not included in the CRO analysis.

[a]Relative risk (RR; betrixaban arm vs. enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing criteria.

population (0.9% vs. 1.5%, respectively)—a 36% RRR at Days 35-42 (ARR = 0.6%; NNT = 167) and a 44% reduction at the end of the trial, Day 77 (*Table 2*).[13,18]

Efficacy subanalyses for patients at risk of bioaccumulation

Among patients with severe renal impairment who were stratified to received 40 mg of betrixaban, similar rates of the composite efficacy outcome were observed in both arms [betrixaban ($n = 174$) = 6.9% vs. enoxaparin ($n = 149$) = 6.7%; RR 1.0; 95% CI 0.45-2.23].[13] Rates of the composite efficacy outcome were also similar amongst

patients receiving concomitant P-glycoprotein inhibitors in both arms [betrixaban ($n = 669$) = 4.9% vs. enoxaparin ($n = 645$) = 5.1%; RR 1.0; 95% CI 0.63-1.60].[13]

Efficacy post hoc analyses

Additional exploratory analyses of the APEX study found a lower risk of all-cause stroke, a prespecified safety outcome that was adjudicated blind to treatment allocation. This was driven by a reduction in ischaemic stroke in patients receiving extended-duration betrixaban compared with enoxaparin through 77 days of follow-up.[19] Rates of newly diagnosed ischaemic strokes (0.48%

standard-dose with betrixaban vs. 0.91% with enoxaparin; RR 0.53; 95% CI 0.30–0.94; $P = 0.026$) and all-cause strokes (0.54% with betrixaban vs. 0.97% with enoxaparin; RR 0.56; 95% CI 0.32–0.96; $P = 0.032$) were significantly lower in the betrixaban cohort (newly diagnosed ischaemic strokes: RRR = 47%, ARR = 0.43%, NNT = 233; all-cause strokes: RRR = 44%, ARR = 0.43%, NNT = 233).[19] Among the subset of high-risk patients with a history of heart failure or ischaemic stroke, the NNT to prevent 1 ischaemic or all-cause stroke, respectively, were 134 and 132.[19]

The composite of 'fatal and irreversible events', efficacy outcomes that included cardiopulmonary death, myocardial infarction, PE, and ischaemic stroke and irreversible safety events that included fatal bleeding or intracranial haemorrhage, and evaluated in a time-to-first event analysis, extended-duration betrixaban significantly reduced fatal or irreversible events at Days 35–42 [4.08% vs. 2.90%; hazard ratio (HR) 0.71; 95% CI 0.55–0.90; ARR, 1.18%; $P = 0.006$; NNT = 85] and at Day 77 (5.17% vs. 3.64%; HR 0.70; 95% CI 0.57–0.88; ARR, 1.53%; $P = 0.002$; NNT = 65).[20] These results translate to a ≈30% reduction in fatal or irreversible ischaemic or bleeding events in patients treated with extended-duration betrixaban compared with those treated with standard-duration enoxaparin.[20]

Compared with standard-duration enoxaparin, extended-duration betrixaban also reduced the risk of VTE-related rehospitalization, which, along with the reductions in fatal and irreversible events, is likely to have important health economic implications. In the overall population, betrixaban reduced the risk of VTE-related rehospitalization at Day 42 (0.25% vs. 0.76%; HR 0.33; 95% CI 0.16–0.71; $P = 0.0026$; RRR = 63%; ARR = 0.51%; NNT = 197) and at Day 77 (0.46% vs. 1.04%; HR 0.44; 95% CI 0.25–0.80; RRR = 56%; ARR = 0.58%; $P = 0.0055$; NNT = 170).[21] Similarly, among patients administered the full dose (80 mg), betrixaban reduced VTE-related rehospitalization at Day 42 (0.24%

vs. 0.93%; HR 0.26; 95% CI 0.11–0.59; RRR = 74%; ARR = 0.70%; $P = 0.0006$; NNT = 143) and at Day 77 (0.46% vs. 1.25%; HR 0.37; 95% CI 0.2–0.70; RRR = 63%; ARR = 0.79%; $P = 0.0015$; NNT = 127).[21]

Safety

For safety assessments, bleeding events were classified according to the criteria of the International Society on Thrombosis and Haemostasis. The primary safety outcome was the occurrence of major bleeding (*Table 4*).[14] Safety was evaluated in 3716 patients who received betrixaban for a median exposure of 36 days compared with 3716 patients who received enoxaparin for a median exposure of 9 days in the mITT population.[14] The overall incidence of major bleeding events was low, regardless of study drug (betrixaban = 0.67%, enoxaparin = 0.57%), and there was no significant difference between the study groups; the number needed to harm is in the thousands for a betrixaban-related major bleeding event.[13,14] The incidence of intracranial haemorrhage was 2/3716 patients in the betrixaban group and 7/3716 patients in the enoxaparin group in the mITT population.[14] Patients receiving extended-duration betrixaban had significantly higher incidence of clinically relevant non-major (CRNM) bleeding events compared with standard-duration enoxaparin (*Table 5*).[14] Differences in the incidence of CRNM bleeding were consistent with differences in the length of use of the study drugs; median exposure to betrixaban was 36 days vs. 9 days for enoxaparin.[14] Most CRNM events (86%) were mild or moderate in severity, and the majority (62%) did not require medical intervention; none were life-threatening.[13] Rehospitalizations for bleeding were more frequent in the betrixaban arm but extended hospitalization rates for CRNM bleeding events were similar in both study arms.[13]

Table 4 Bleeding events in APEX through 7 days after discontinuation

Parameter	Safety population			Patients receiving 80 mg betrixaban		
	Betrixaban (N = 3716) n (%)	Enoxaparin (N = 3716) n (%)	RR (95% CI)	Betrixaban 80 mg (N = 2986) n (%)	Enoxaparin 40 mg (N = 2991) n (%)	RR (95% CI)
Major bleeding[a]	25 (0.67)	21 (0.57)	1.19 (0.67–2.12) $P = 0.554$	15 (0.50)	16 (0.53)	0.94 (0.47–1.90)
Gastrointestinal	19 (0.51)	9 (0.24)	–	–	–	–
Intracranial Haemorrhage	2 (0.05)	7 (0.19)	–	–	–	–
Intraocular	0	1 (0.03)	–	–	–	–
Fatal bleeding	1 (0.03)	1 (0.03)	–	–	–	–
CRNM bleeding[b]	91 (2.45)	38 (1.02)	2.39 (1.64–3.49) $P < 0.001$	66 (2.21)	33 (1.10)	2.00 (1.32–3.03)

[a]Major bleeding event was defined as clinically overt bleeding that met one of the following criteria: a reduction in haemoglobin of at least 2 g/dL within 48 h of an overt bleeding event; a transfusion of at least two units of whole blood or packed red blood cells; a critical area; e.g. intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular, pericardial, or a fatal outcome. Retinal haemorrhages secondary to diabetic retinopathy or conjunctival bleeds did not qualify as major bleeds.

[b]Clinically relevant non-major (CRNM) bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary/permanent) cessation of the study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

Table 5 Clinically relevant non-major (CRNM) bleeding in safety population

	Betrixaban (N = 3716)	Enoxaparin (N = 3716)
Median duration of prophylaxis (IQR)	36 days (34-39)	9 days (7-13)
Number of patients with CRNM bleeds; n (%)	91 (2.45)	38 (1.02)
Adverse event severity; n (%)		
Mild	38 (1.0)	17 (0.5)
Moderate	42 (1.1)	15 (0.4)
Severe	11 (0.3)	6 (0.2)
Life-threatening	0	0
Extended hospitalization; n (%)	11 (0.3)	8 (0.2)

Safety population included 3716 patients treated with betrixaban for a median of 36 days, and 3716 patients treated with enoxaparin for a median of 9 days. Patients in both groups were followed for safety for up to 77 days.

CRNM, clinically relevant non-major; IQR, interquartile range.

Safety subanalyses for patients at risk of bioaccumulation

In patients with severe renal impairment treated with reduced doses of betrixaban (40 mg) and enoxaparin (20 mg), rates of major bleeding and CRNM bleeding were similar across treatment arms through 7 days after treatment discontinuation.[13] There were also no significant differences in major bleeding and CRNM bleeding rates in patients who were receiving a reduced dose of betrixaban (40 mg) and a concomitant P-glycoprotein inhibitor and those who were treated with 40 mg enoxaparin and a concomitant P-glycoprotein inhibitor.[13,16]

Discussion

The clinical profile of the patient population observed in the APEX trial has most likely benefited from the learnings of prior trials of extended-duration thromboprophylaxis. The APEX trial was designed to enrich for a patient population at higher risk for VTE and lower risk of bleeding compared with the previous studies.[8] The mobility criteria in APEX were more stringent than those in ADOPT and EXCLAIM; patients had to be severely immobilized for 24 h and either moderately or severely immobilized for ≥3 days during hospitalization, thus elevating the risk of VTE.[8] Based on findings from a MAGELLAN subgroup analysis,[22] the APEX trial underwent a protocol modification during the course of the trial. Patients in APEX were required to have an additional factor associated with even higher risk for VTE: age > 75 years or elevated D-dimer levels. These factors resulted in moderately higher risk for VTE in APEX and informed the hierarchal statistical testing plan.[8] Finally, an interim 10-day ultrasound was not included in the APEX study design, despite its use in other extended-duration prophylaxis studies.[8] Interim ultrasounds are not typically included in standard-of-care management, thus omission of this test may better reflect real-world practice, while avoiding potential identification of asymptomatic events during the treatment period and allowing more focus on symptomatic events and the end-of-treatment period ultrasound.[8]

In summary, the APEX trial demonstrated that extended-duration betrixaban reduced VTE without a significant increase in major bleeding compared with standard-duration enoxaparin. Findings from the trial supported a positive benefit-risk profile for extended prophylaxis of VTE with betrixaban in acute medically ill patients at risk for developing VTE and led to the first US FDA approval for extended prophylaxis in this patient population.[14,19] Despite this broad label indication, the introduction of betrixaban into a wider patient population should follow the APEX inclusion and exclusion criteria. Patient risk-benefit assessment should be undertaken prior to initiation of therapy and re-evaluated throughout the duration of treatment.

Funding

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