Intensive Care Med (2019) 45:477–487
https://doi.org/10.1007/s00134-019-05565-6

ORIGINAL

Extended-duration betrixaban versus shorter-duration enoxaparin for venous thromboembolism prophylaxis in critically ill medical patients: an APEX trial substudy

Gerald Chi[1*], C. Michael Gibson[2], Arzu Kalayci[1], Alexander T. Cohen[3], Adrian F. Hernandez[4], Russell D. Hull[5], Farima Kahe[1], Mehrian Jafarizade[1], Sadaf Sharfaei[1], Yuyin Liu[6], Robert A. Harrington[7] and Samuel Z. Goldhaber[8]

Abstract

Purpose: To assess the efficacy and safety of betrixaban for venous thromboembolism (VTE) prophylaxis among critically ill patients.

Methods: The APEX trial randomized 7513 acutely ill hospitalized patients to betrixaban for 35–42 days or enoxaparin for 10 ± 4 days. Among those, 703 critically ill patients admitted to the intensive care unit were included in the analysis, and 547 patients who had no severe renal insufficiency or P-glycoprotein inhibitor use were included in the full-dose stratum. The risk of VTE, bleeding, net clinical benefit (composite of VTE and major bleeding), and mortality was compared at 35–42 days and at 77 days.

Results: At 35–42 days, extended betrixaban reduced the risk of VTE (4.27% vs 7.95%, $P = 0.042$) without causing excess major bleeding (1.14% vs 3.13%, $P = 0.07$). Both VTE (3.32% vs 8.33%, $P = 0.013$) and major bleeding (0.00% vs 3.26%, $P = 0.003$) were decreased in the full-dose stratum. Patients who received betrixaban had more non-major bleeding than enoxaparin (overall population: 2.56% vs 0.28%, $P = 0.011$; full-dose stratum: 3.32% vs 0.36%, $P = 0.010$). Mortality was similar at the end of study (overall population: 13.39% vs 16.19%, $P = 0.30$; full-dose stratum: 13.65% vs 16.30%, $P = 0.39$).

Conclusions: Compared with shorter-duration enoxaparin, critically ill medical patients who received extended-duration betrixaban had fewer VTE without more major bleeding events. The benefit of betrixaban was driven by preventing asymptomatic thrombosis and offset by an elevated risk of non-major bleeding. The APEX trial did not stratify by intensive care unit admission and the present study included a highly selected population of critically ill patients. These hypothesis-generating findings need to be validated in future studies.

Clinical trial registration: http://www.clinicaltrials.gov. Unique identifier: NCT01583218.

Keywords: Venous thrombosis, Anticoagulants, Betrixaban, Enoxaparin, Critical care

*Correspondence: geraldcchi@gmail.com
[1] Division of Cardiovascular Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
Full author information is available at the end of the article

Springer

Introduction

Venous thromboembolism (VTE) is a preventable yet common complication among critically ill patients. The increased risk of VTE in the intensive care unit (ICU) setting may be attributed to multiple factors that collectively constitute Virchow's triad [1]. First, critically ill patients with prolonged immobilization, cardiopulmonary failure, intra-abdominal hypertension, or the use of neuromuscular blocking agents are prone to blood stasis. Second, factors such as sepsis, inflammation, chronic kidney disease, transfusion, and erythropoietin-stimulating agents could promote a hypercoagulable state. Lastly, sepsis, inflammation, chronic kidney disease, vasoactive agents, central venous catheter, and surgical injury have been associated with endothelial dysfunction. Without prophylactic measures, the incidence of deep vein thrombosis (DVT) in ICU patients ranges from 13% to 31% [2]. Previous randomized controlled trials demonstrate that DVT risk may be minimized to a risk of 11–15.5% with low molecular weight heparin or low-dose unfractionated heparin [3–5].

Critically ill patients are also at an increased risk of bleeding due to underlying comorbidities, admitting illness, and the use of medications or interventions that may cause hemorrhage. In a prospective multicenter registry (IMPROVE; International Medical Prevention Registry on Venous Thromboembolism) that enrolled acutely ill hospitalized medical patients, ICU stay was shown to be an independent predictor for both VTE and bleeding [6, 7]. The concurrent risk of VTE and bleeding in this vulnerable population poses a conundrum in the decision of thromboprophylaxis, as anticoagulation may come at the expense of bleeding. Few head-to-head trials have compared the efficacy and safety of pharmacological thromboprophylaxis agents, particularly in the medical ICU setting [8, 9]. Furthermore, little is known about the effect of direct oral anticoagulants for VTE prophylaxis among these high-risk patients.

In certain hospitalized patients, the risk of VTE may persist for weeks to months after hospital discharge [10]. It has been estimated that 75% of VTE events occur after hospital discharge, with a median time-to-event of 19.5 days [11]. The APEX trial (Acute Medically Ill Venous Thromboembolism Prevention with Extended Duration Betrixaban Trial; ClinicalTrials.gov identifier: NCT01583218) was conducted to examine the hypothesis that extended prophylaxis with betrixaban will have a positive risk/benefit profile over shorter prophylaxis with enoxaparin for medical inpatients at increased risk of VTE [12]. In this non-prespecified post hoc analysis, we investigated the rates of VTE and bleeding events in critically ill medical patients admitted to the ICU during the index hospitalization who were randomized to receive betrixaban or enoxaparin. The study was presented at the European Society of Cardiology Congress 2018 and published as an abstract in the *European Heart Journal* [13].

Take-home message

Concurrent risk of VTE and bleeding among critically ill patients poses a conundrum in thromboprophylaxis decision, as anticoagulation comes at the expense of bleeding. Compared with shorter-duration enoxaparin, critically ill medical patients who received extended-duration betrixaban had fewer VTE but more clinically relevant non-major bleeding events.

Methods

APEX study design and endpoints

APEX was a multicenter, double-blind randomized controlled trial that enrolled 7513 patients with the following eligibility criteria: (1) hospitalized for an acute medical illness, including acute decompensated heart failure, acute respiratory failure, acute infection, acute rheumatic disorder, acute disabling ischemic stroke; (2) age 75 years or more, age 60–74 years with D-dimer at least two times the upper limit of normal range (ULN), or age 40–59 years with D-dimer at least two times the ULN and a history of VTE or cancer; (3) anticipated severe immobilization for at least 24 h followed by moderate or severe immobilization for 3 days or more; and (4) anticipated hospitalization for 3 days or more. Key exclusion criteria included (1) a recent history of clinically significant bleeding or severe trauma; (2) requiring major surgery or invasive procedure within 3 months; (3) end-stage renal disease with creatinine clearance (CrCl) of less than 15 mL/min or requiring dialysis; (4) contraindication to anticoagulant therapy; and (5) concomitant dual antiplatelet therapy with any two of the following: aspirin, dipyridamole, or any thienopyridine. Patients were randomly assigned in a 1:1 ratio to oral betrixaban for 35–42 days or subcutaneous enoxaparin for 10 ± 4 days [12]. Individuals who had a nasogastric or feeding tube in place received betrixaban or matching placebo that was dissolved in water and followed by a nutritional supplement. Randomization of the APEX trial was generated using random permuted blocks within geographic region, stratified by both dosing criteria and entry criteria but not ICU admission. Randomization methods, blinding methods, and sample size calculation are provided in the electronic supplementary material.

The study population in the present analysis included patients with an acute medical illness who were either (1) initially admitted to the ICU during the index hospitalization or (2) initially admitted to the ward and subsequently transferred to the ICU because of clinical

deterioration during the index hospitalization. The full-dose stratum (betrixaban 80 mg daily vs enoxaparin 40 mg daily) comprised subjects who had a CrCl of at least 30 mL/min and without concomitant use of strong P-glycoprotein inhibitors.

The primary efficacy endpoint was the occurrence of VTE, defined as a composite of asymptomatic proximal DVT detected by compression ultrasound, symptomatic DVT, non-fatal pulmonary embolism (PE), or VTE-related mortality. The first secondary efficacy endpoint was symptomatic VTE (a composite of symptomatic DVT, non-fatal PE, or VTE-related mortality). The second secondary efficacy endpoint was the composite of asymptomatic proximal DVT, symptomatic DVT, non-fatal PE, or death. The primary and secondary safety endpoints were major bleeding and clinically relevant non-major bleeding [14, 15]. Net clinical benefit was defined as the composite of primary efficacy endpoint (VTE) and primary safety endpoint (major bleeding). Other prespecified endpoints such as the individual components of VTE and cause-specific mortality were also analyzed.

Efficacy analysis and net clinical benefit analysis were performed at 35–42 days (end of extended thromboprophylaxis; third follow-up visit) and at 77 days (end of study). Safety analysis was performed through 7 days after study drug or matching placebo discontinuation and at 77 days (end of study). All events were adjudicated by an independent clinical events committee blinded to thromboprophylaxis allocation.

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Baseline characteristics of study participants were compared using the Chi-squared test for categorical variables and one-way analysis of variance for continuous variables. Efficacy was analyzed in subjects who received at least one dose of study medication (planned treatment) and had data for at least one component of the composite endpoint. Safety was analyzed in all randomized patients who received at least one dose of study medication (actual treatment). Absolute risk difference and relative risk between treatment was compared using the Chi-squared test or Fisher's exact test. As a sensitivity analysis for examining the robustness of results, net clinical benefit of betrixaban versus enoxaparin was compared using the Cox proportional hazards model. Event rates were estimated by the Kaplan–Meier method, and the risk difference between treatment arms was assessed by the log-rank test. Additionally, subdistribution proportional hazards models were fitted to examine the effect of death as competing events using the Fine–Gray method. All analyses were performed using two-sided tests at a significance level of 0.05. In view of the exploratory nature of this substudy, no adjustment was made to account for multiplicity.

Results

Baseline characteristics

A total of 703 critically ill medical patients were included (Fig. 1 in electronic supplementary material). The full-dose stratum included 547 (77.8%) patients. Baseline characteristics were generally balanced (Table 1), except that patients in the betrixaban group were slightly older than those in the enoxaparin group (75.9 vs 74.6 years; $P=0.04$).

Efficacy at 35–42 days

With respect to VTE composite, betrixaban reduced the risk of VTE by 3.68% as compared with enoxaparin (4.27% vs 7.95%, $P=0.042$) (Table 2). Full-dose betrixaban reduced the risk of VTE by 5.01% (3.32% vs 8.33%, $P=0.013$). Patients who received betrixaban had a numerically lower risk of symptomatic VTE than those who received enoxaparin. With respect to VTE and all-cause mortality, betrixaban was associated with a 6.59% lower risk than enoxaparin (15.26% vs 21.85%, $P=0.033$). Given the inflated alpha risk, this may have occurred as a result of chance.

Efficacy at 77 days

At 77 days, compared with shorter-duration enoxaparin, patients who received extended-duration betrixaban had a lower risk of VTE (overall population: 5.24% vs 10.88%; full-dose stratum: 4.21% vs 11.40%). The remaining efficacy outcomes are summarized in Table 3.

Safety at 35–42 days

With respect to major bleeding, the betrixaban group had a numerically lower risk than the enoxaparin group (1.14% vs 3.13%, $P=0.07$) (Table 2). Patients who received full-dose betrixaban had a significantly lower rate of major bleeding compared with those who received enoxaparin (0.00% vs 3.26%, $P=0.003$). With respect to non-major bleeding, betrixaban was associated with a higher risk than enoxaparin (overall population: 2.56% vs 0.28%, $P=0.011$; full-dose stratum: 3.32% vs 0.36%, $P=0.010$).

Table 1 Baseline characteristics stratified by thromboprophylaxis

Characteristic	Betrixaban (*N* = 351)	Enoxaparin (*N* = 352)	*P* value
Age, mean (SD), years	75.9 (8.4)	74.6 (8.7)	0.041
Male sex, *n* (%)	153 (43.6)	159 (45.2)	0.67
Race, *n* (%)			0.72
White	344 (98.0)	341 (96.9)	
Black/African American	3 (0.9)	3 (0.9)	
Asian	1 (0.3)	2 (0.6)	
Others	3 (0.9)	6 (1.7)	
Body mass index, mean (SD), kg/m^2	29.5 (6.5)	29.4 (6.2)	0.88
Creatinine clearance, *n* (%)			0.85
< 30 mL/min	15 (4.3)	13 (3.7)	
≥ 30 to < 60 mL/min	153 (43.6)	147 (41.8)	
≥ 60 to < 90 mL/min	112 (31.9)	112 (31.8)	
≥ 90 mL/min	71 (20.2)	80 (22.7)	
Duration of ICU stay, mean (SD), days	6.2 (4.7)	6.6 (5.7)	0.31
Duration of hospital stay, mean (SD), days	13.3 (8.5)	14.4 (10.2)	0.13
Previous anticoagulation ≤ 96 h, *n* (%)	202 (57.5)	214 (60.8)	0.38
Severity of immobilization[a]			0.65
Severely immobilized	348 (99.4)	347 (99.1)	
Moderately immobilized	2 (0.6)	3 (0.9)	
Concomitant antiplatelet therapy[b]	209 (59.5)	208 (59.1)	0.90
Platelet count, mean (SD), × 10^9/L	224.2 (81.6)	222.1 (71.3)	0.74
Bilirubin, mean (SD), mg/dL	0.6 (0.4)	0.6 (0.4)	0.95
Creatinine, mean (SD), mg/dL	1.1 (0.4)	1.0 (0.5)	0.91
Mechanical device for VTE prophylaxis, *n* (%)			0.15
Graduated compression stock	56 (16.0)	41 (11.6)	
Sequential compression device	5 (1.4)	4 (1.1)	
Both	0 (0.0)	4 (1.1)	
Others[c]	9 (2.6)	10 (2.8)	
None	281 (80.1)	293 (83.2)	
Acute medical condition, *n* (%)			0.52
Acute heart failure	173 (49.3)	151 (42.9)	
Respiratory failure	30 (8.5)	37 (10.5)	
Infection	61 (17.4)	64 (18.2)	
Rheumatic disorder	13 (3.7)	14 (4.0)	
Ischemic stroke	74 (21.1)	86 (24.4)	
VTE risk factor, *n* (%)			
History of VTE	18 (5.1)	26 (7.4)	0.22
Known thrombophilia[d]	1 (0.3)	1 (0.3)	1.00
Current lower-limb paralysis	34 (9.7)	29 (8.2)	0.50
Active cancer	15 (4.3)	9 (2.6)	0.21
Age > 60 years	331 (94.3)	330 (93.8)	0.76
IMPROVE VTE risk score, mean (SD)	2.4 (0.9)	2.4 (0.9)	0.99
D-dimer ≥ 2 × ULN, *n* (%)	233 (66.4)	235 (67.1)	0.83
Modified IMPROVE VTE risk score, mean (SD)	3.6 (1.1)	3.6 (1.1)	0.87
Modified IMPROVE score ≥ 4 or 2–3 plus D-dimer ≥ 2 × ULN, *n* (%)	263 (74.9)	274 (77.8)	0.36

ICU intensive care unit, *SD* standard deviation, *ULN* upper limit of the normal range, *VTE* venous thromboembolism

[a] Three patients had missing information for severity of immobilization. Severely immobilized was defined as confined to a bed or chair for the majority of the day and can only be independently mobile to the in-room toilet. Moderately immobilized was defined as independently mobile to the in-room or ward toilet; can be mobilized by physical therapy or nursing staff; and can be off-ward with assistance

[b] Includes acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, ticlopidine, cilostazol, eptifibatide, or dipyridamole

Table 1 (continued)

[c] Includes elastic bandages, leg pressure sleeves, and motor physiotherapy

[d] Includes inherited or acquired disorder of hemostasis including antithrombin III deficiency, protein C deficiency, and protein S deficiency

Table 2 Efficacy and safety of betrixaban vs enoxaparin at 35–42 days

Population	Betrixaban	Enoxaparin	ARD (95% CI)	RR (95% CI)	*P* value
Primary efficacy endpoint: composite of asymptomatic proximal DVT, symptomatic DVT, nonfatal PE, or VTE-related mortality					
Overall population	15/351 (4.27%)	28/352 (7.95%)	− 3.68% (− 7.21 to − 0.15%)	0.54 (0.29–0.99)	0.042
Full-dose stratum	9/271 (3.32%)	23/276 (8.33%)	− 5.01% (− 8.91 to − 1.12%)	0.40 (0.19–0.85)	0.013
First secondary efficacy endpoint: composite of symptomatic DVT, nonfatal PE, or VTE-related mortality					
Overall population	7/351 (1.99%)	11/352 (3.13%)	− 1.13% (− 3.46 to 1.20%)	0.64 (0.25–1.63)	0.34
Full-dose stratum	4/271 (1.48%)	11/276 (3.99%)	− 2.51% (− 5.23 to 0.21%)	0.37 (0.12–1.15)	0.07
Second secondary efficacy endpoint: composite of asymptomatic proximal DVT, symptomatic DVT, nonfatal PE, or all-cause mortality					
Overall population	47/308 (15.26%)	71/325 (21.85%)	− 6.59% (− 12.61 to − 0.56%)	0.70 (0.50–0.98)	0.033
Full-dose stratum	34/231 (14.72%)	55/257 (21.40%)	− 6.68% (− 13.47 to 0.10%)	0.69 (0.47–1.01)	0.06
Primary safety endpoint: major bleeding					
Overall population	4/351 (1.14%)	11/352 (3.13%)	− 1.99% (− 4.12 to 0.14%)	0.36 (0.12–1.13)	0.07
Full-dose stratum	0/271 (0.00%)	9/276 (3.26%)	− 3.26% (− 5.36 to − 1.17%)	–	0.003
Secondary safety endpoint: clinically relevant non-major bleeding					
Overall population	9/351 (2.56%)	1/352 (0.28%)	2.28% (0.54–4.02%)	9.03 (1.15–70.86)	0.011
Full-dose stratum	9/271 (3.32%)	1/276 (0.36%)	2.96% (0.71–5.21%)	9.17 (1.17–71.86)	0.010
Net clinical benefit: composite of primary efficacy endpoint and primary safety endpoint[a]					
Overall population	20/351 (5.70%)	38/352 (10.80%)	− 5.10% (− 9.15 to − 1.05%)	0.53 (0.31–0.89)	0.014
Full-dose stratum	10/271 (3.69%)	31/276 (11.23%)	− 7.54% (− 11.89 to − 3.19%)	0.33 (0.16–0.66)	< 0.001

ARD absolute risk difference, *CI* confidence interval, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *RR* relative risk, *VTE* venous thromboembolism

[a] Net clinical benefit included VTE or major bleeding events that occurred through the third follow-up visit (35–42 days)

Table 3 Efficacy and safety of betrixaban vs enoxaparin at 77 days

Population	Betrixaban	Enoxaparin	ARD (95% CI)	RR (95% CI)	*P* value
Primary efficacy endpoint: composite of asymptomatic proximal DVT, symptomatic DVT, nonfatal PE, or VTE-related mortality					
Overall population	15/286 (5.24%)	31/285 (10.88%)	− 5.63% (− 10.08 to − 1.19%)	0.48 (0.27–0.87)	0.013
Full-dose stratum	9/214 (4.21%)	26/228 (11.40%)	− 7.20% (− 12.12 to − 2.27%)	0.37 (0.18–0.77)	0.005
First secondary efficacy endpoint: composite of symptomatic DVT, nonfatal PE, or VTE-related mortality					
Overall population	7/351 (1.99%)	14/352 (3.98%)	− 1.98% (− 4.49 to 0.53%)	0.50 (0.20–1.23)	0.12
Full-dose stratum	4/271 (1.48%)	14/276 (5.07%)	− 3.60% (− 6.56 to − 0.64%)	0.29 (0.10–0.87)	0.018
Second secondary efficacy endpoint: composite of asymptomatic proximal DVT, symptomatic DVT, nonfatal PE, or all-cause mortality					
Overall population	54/308 (17.53%)	75/325 (23.08%)	− 5.54% (− 11.79 to 0.70%)	0.76 (0.56–1.04)	0.08
Full-dose stratum	40/231 (17.32%)	59/257 (22.96%)	− 5.64% (− 12.73 to 1.45%)	0.75 (0.53–1.08)	0.12
Primary safety endpoint: major bleeding					
Overall population	5/351 (1.42%)	12/352 (3.41%)	− 1.98% (− 4.25 to 0.28%)	0.42 (0.15–1.17)	0.09
Full-dose stratum	1/271 (0.37%)	10/276 (3.62%)	− 3.25% (− 5.57 to − 0.93%)	0.10 (0.01–0.79)	0.007
Secondary safety endpoint: clinically relevant non-major bleeding					
Overall population	11/351 (3.13%)	1/352 (0.28%)	2.85% (0.94–4.76%)	11.03 (1.43–84.99)	0.004
Full-dose stratum	10/271 (3.69%)	1/276 (0.36%)	3.33% (0.97–5.68%)	10.18 (1.31–79.02)	0.006
Net clinical benefit: composite of primary efficacy endpoint and primary safety endpoint[a]					
Overall population	20/351 (5.70%)	41/352 (11.65%)	− 5.95% (− 10.09 to − 1.81%)	0.49 (0.29–0.82)	0.005
Full-dose stratum	10/271 (3.69%)	34/276 (12.32%)	− 8.63% (− 13.11 to − 4.15%)	0.30 (0.15–0.59)	< 0.001

ARD absolute risk difference, *CI* confidence interval, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *RR* relative risk, *VTE* venous thromboembolism

[a] Net clinical benefit included VTE or major bleeding events that occurred through the end-of-study visit (up to 77 days)

Safety at 77 days

At 77 days, the difference in the rate of major bleeding was significant in the full-dose stratum (0.37% vs 3.62%) but not in the overall population (1.42% vs 3.41%). The remaining safety outcomes are summarized in Table 3.

Net clinical benefit

At 35–42 days, betrixaban was favorable over enoxaparin in preventing VTE or causing major bleeding in the overall population (5.70% vs 10.80%, $P=0.014$) as well as in the full-dose stratum (3.69% vs 11.23%, $P<0.001$) (Fig. 1, Table 2). The net clinical benefit was maintained up to 77 days (Table 3). Results derived from the time-to-event analysis were consistent with the Chi-squared frequency test (Fig. 2).

VTE components and cause-specific mortality

Compared with enoxaparin, risk reduction by betrixaban did not attain statistical difference in the individual VTE components at 35–42 days (Table 1 in electronic supplementary material) or at 77 days (Table 2 in electronic supplementary material).

There was no significant difference in all-cause mortality between betrixaban and enoxaparin at 35–42 days or at 77 days (Table 3 in electronic supplementary material). The rate of cardiovascular death was insignificantly lower in patients who received betrixaban than those who received enoxaparin at 35–42 days. A signal for cardiovascular death reduction was observed in full-dose betrixaban at 77 days (6.27% vs 11.23%, $P=0.040$). One fatal bleeding occurred in the enoxaparin group but not in the betrixaban group throughout the study.

Competing risk analysis

Results were comparable when death was included as competing events against the events of interest such as VTE (overall population: SHR = 0.467 [0.253–0.864]; full-dose stratum: SHR = 0.342 [0.161–0.728]), major bleeding (overall population: SHR = 0.413 [0.146–1.172]; full-dose stratum: SHR = 0.100 [0.013–0.773]), and net clinical benefit (overall population: SHR = 0.471 [0.276–0.802]; full-dose stratum: SHR = 0.287 [0.142–0.579]) (Table 4 and Fig. 2 in electronic supplementary material).

Discussion

This APEX substudy demonstrated that among critically ill medical patients, extended-duration betrixaban reduced the risk of VTE without causing excess major bleeding. Both VTE and major bleeding were decreased in the full-dose stratum. Compared with enoxaparin, betrixaban increased the risk of clinically relevant non-major bleeding by approximately 2–3% within 7 days after discontinuation. Mortality rate was similar between treatment groups.

Current guidelines recommend the use of low molecular weight heparin or low-dose unfractionated heparin thromboprophylaxis over no prophylaxis for critically ill patients [16, 17]. Betrixaban is a direct oral factor Xa

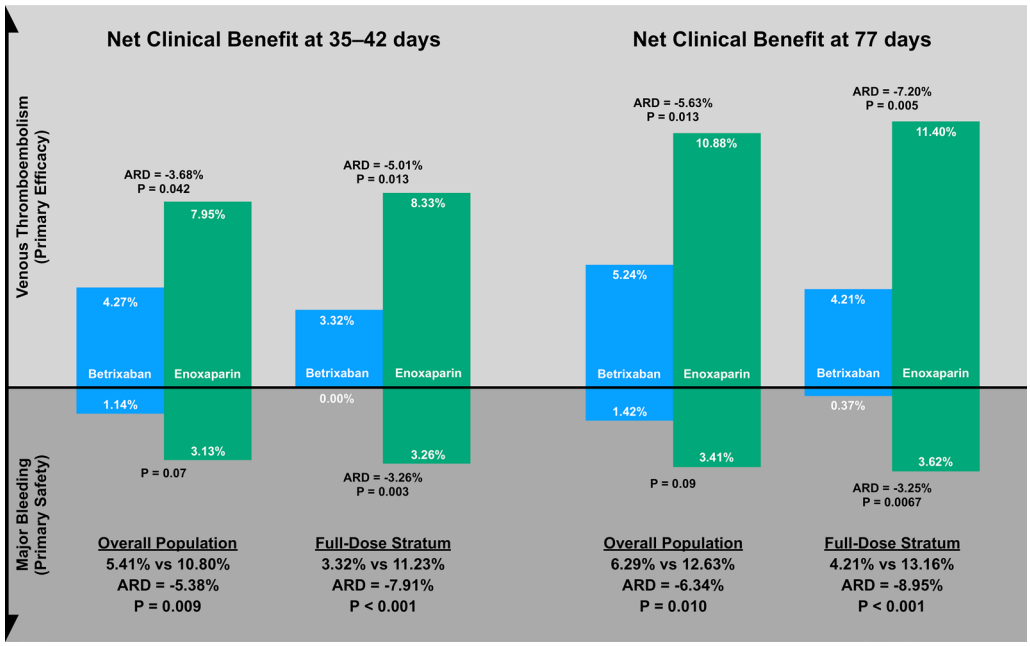

Fig. 1 Net clinical benefit of betrixaban vs enoxaparin in critically ill medical patients

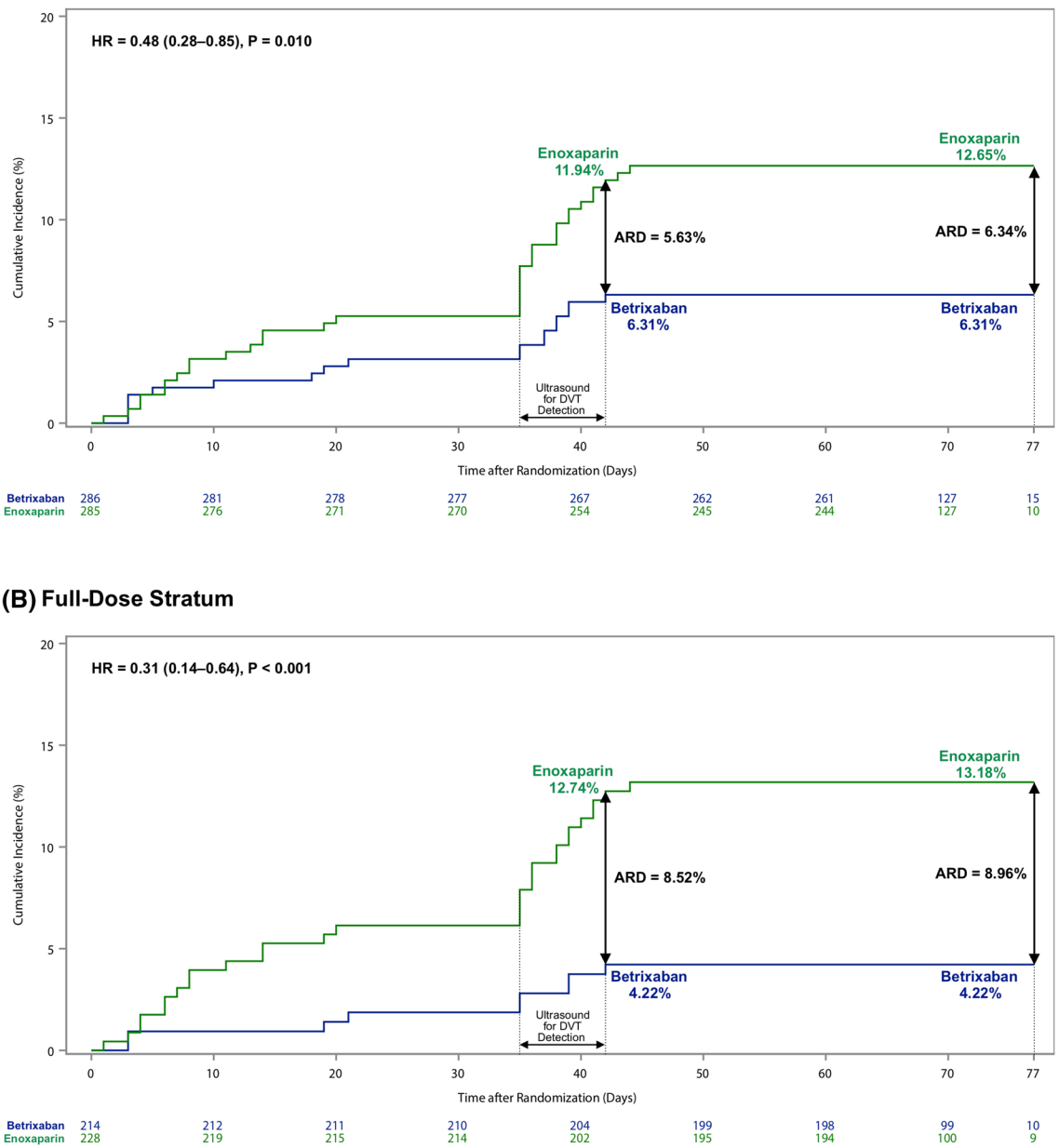

Fig. 2 Kaplan–Meier curves for net clinical benefit of betrixaban vs enoxaparin in critically ill medical patients

inhibitor approved for the prophylaxis of VTE in adult medical inpatients at risk of thromboembolic complications based on the APEX trial results. To control the study-wise type I error rate in the APEX trial, a gatekeeping procedure with a fixed hierarchical sequence was implemented [18]. As the superiority of extended-duration betrixaban over shorter-duration enoxaparin in VTE reduction was not achieved in cohort 1 (patients with D-dimer at least two times the ULN), findings from the present study should be considered exploratory and interpreted in the context of an inflated alpha error [12]. In the APEX trial, stratified randomization by dosing and entry criteria was implemented to control the potential influence of severe renal insufficiency, concomitant strong P-gp inhibitor, or D-dimer on treatment assignment. Although ICU admission—a factor with prognostic impact on VTE and bleeding—was not included in the stratification method, baseline covariates were balanced

between treatment groups except that the mean age was slightly higher in the betrixaban arm than the enoxaparin arm (Table 1). In addition, the findings were consistent after accounting for the competing risk of death. It is therefore unlikely that the lack of stratification by ICU admission would have substantially altered these results. However, benefit signals associated with extended betrixaban in this critically ill subgroup should be considered descriptive and hypothesis-generating.

In the IMPROVE study, ICU stay was independently associated with a 1.8 times greater risk of VTE at 3 months after hospitalization and included in the IMPROVE risk score [6]. To select high-risk patients who had been hospitalized with an acute medical condition, the MARINER trial enrolled subjects with a modified IMPROVE risk score of at least 4 or 2–3 plus D-dimer more than two times the ULN [19, 20]. The observed rate of symptomatic VTE in the placebo group at 45 days after hospital discharge was 1.1%, which was lower than the expected incidence of 2.5% [21]. In the present study, the mean modified IMPROVE score was 3.6, and 76% of the patients met the MARINER enrollment criteria. Notably, symptomatic VTE occurred in 3.13% of the individuals who received enoxaparin (corresponding to the placebo arm in MARINER), supporting the conjunctive use of modified IMPROVE score and D-dimer in identifying high-risk subsets. It should be cautioned that D-dimer measurement could vary with analytical methods and reporting standards from different laboratories [22]. D-dimer level may also be influenced by age and conditions such as cancer, heart failure, infection, and inflammation [23]. Further research is warranted to validate this risk stratification strategy.

Randomized trials of thromboprophylaxis commonly include asymptomatic proximal DVT detected by study-mandated screening as a component of the primary endpoint [24]. Inclusion of asymptomatic events in the comparison of antithrombotic efficacy is in accordance with the European Medicines Agency (EMA) guidance and based upon several premises [25]. First, it has been argued that most thrombi are initially asymptomatic and may undergo recanalization or, conversely, extension and dislodgement with subsequent embolization [26, 27]. Second, a paralleled decrease in symptomatic or fatal PE has been observed with the reduction of asymptomatic events, supporting the validity of screening-detected DVT as a surrogate endpoint for clinical VTE events [28–30]. Last, development of asymptomatic DVT may reflect the burden of underlying comorbidities and possess prognostic importance in view of its association with mortality [31, 32]. On the other hand, symptomatic VTE is a patient-important outcome and a naturalistic measure for clinicians. In the MARINER trial, the primary efficacy endpoint was a composite of fatal or symptomatic VTE and the primary safety endpoint was major bleeding [21]. As these two endpoints may have comparable clinical significance, a net benefit can be derived without speculating the sequelae of asymptomatic thrombotic events. Weighing symptomatic VTE against major bleeding has also been adopted in the bivariate analysis associated with antithrombotic regimens [33]. On the basis of the APEX study protocol [12], asymptomatic DVT was included in the VTE composite, whereas non-major bleeding was not included in the net clinical benefit. The favorable net clinical benefit associated with extended-duration betrixaban was primarily driven by reducing asymptomatic events without accounting for the elevated risk of non-major bleeding. While the clinical relevance of asymptomatic DVT in the ICU setting remains unsettled, a definitive benefit of extended thromboprophylaxis in reducing symptomatic events should also be explored in future studies targeting critically ill patients.

A noteworthy finding is the potential "legacy effect" of extended thromboprophylaxis, defined as the difference in the cumulative incidence that accrues after treatment discontinuation. As suggested by the EMA guideline [21], assessing the occurrence of VTE within a 30-day follow-up after trial drug discontinuation is appropriate for ruling out an early rebound hypercoagulability. In the present analysis, there was no additional VTE event within 35 days after discontinuation of betrixaban, while three more VTE events occurred in the enoxaparin arm during the follow-up. Prolonging the anticoagulation course has been demonstrated to lower the prevalence of asymptomatic DVT in surgical patients [34, 35], possibly by promoting spontaneous thrombolysis and preventing thrombus formation [26]. Additionally, extended therapy could have sustained its protective effect via reducing the thrombus burden of DVT [36], which eventually resulted in a lower rate of VTE after treatment cessation. A formal landmark analysis from an adequately powered study will be required to confirm this hypothesis.

Alternatively, the superior effect of betrixaban in thromboembolic prevention may be attributed to its unique pharmacokinetic and pharmacodynamic properties. First, betrixaban has an elimination half-life of 19–27 h that allows for daily dosing without routine laboratory monitoring [37]. The durable half-life, on the contrary, may complicate the management of patients who develop serious bleeding or require urgent surgery [38]. Patients who receive betrixaban may necessitate a prolonged course of supportive therapy for bleeding or prolonged delay of surgery if a reversal agent is not administered. Second, the low peak-to-trough plasma concentration ratio of betrixaban provides a consistent anticoagulation activity. Third, betrixaban has a low renal

clearance of 11%, rendering it more suitable for critically ill patients that often suffer from varying degrees of renal insufficiency. Finally, betrixaban demonstrates minimal hepatic cytochrome P450 metabolism (less than 1%) and fewer drug–drug interactions [39]. This is particularly relevant in critically ill patients who are more likely to receive multiple medications for their comorbidities. However, in view of the study design, the observed benefit in VTE reduction cannot be exclusively attributed to the legacy effect of extended prophylaxis or the distinctive pharmacologic properties of betrixaban.

Through 7 days after treatment discontinuation, the betrixaban group had 13 clinically important bleeding events (4 major and 9 non-major), whereas the enoxaparin group had 12 bleeding events (11 major and 1 non-major). Although the rate of major bleeding was similar, extended-duration betrixaban was associated with a greater risk of non-major bleeding, which could adversely impact the prognosis and economic burden [40]. Indeed, direct oral anticoagulants may reduce intracranial hemorrhage but increase gastrointestinal hemorrhage [41].

Limitations

First, this is a post hoc analysis from a population that agreed to participate in a clinical trial with specific enrollment criteria. For instance, the study excluded patients who had life expectancy of less than 8 weeks, septic shock, required prolonged or curative anticoagulation or dual antiplatelet therapy, were unable to receive enteral nutrition, or at substantial risk of bleeding (e.g., body weight less than 45 kg, recent clinically significant bleeding, major trauma, history of bronchiectasis or active lung cancer, end-stage renal disease, requiring dialysis, or known abnormality of liver function tests). The results are only applicable to medical patients with ICU admission indicated for thromboprophylaxis who match the eligibility criteria of the APEX trial. Second, although a consistent signal of risk reduction favoring betrixaban was observed across all VTE components, APEX was not powered on the basis of individual components of the VTE composite. Third, information regarding the use of mechanical ventilation, sedative agents, vasopressors, or central venous catheterization was unavailable and not controlled for in the analysis. In addition, the mean duration of ICU and hospital stay was 6 and 14 days and the majority of patients had CrCl of at least 30 mL/min, suggesting that the study participants were not representative of the more severely ill ICU patients. Unlike the typical composition of the ICU population [42], the APEX study participants had a low rate of infection (18%) and respiratory failure (10%) but a high rate of heart failure (46%) and stroke (23%), thus limiting the external validity of these data. Finally, according to the study protocol and statistical analysis plan, the APEX trial did not stratify by ICU admission and this post hoc analysis did not adjust for multiplicity. These findings should be interpreted as exploratory and hypothesis-generating.

Conclusions

Compared with shorter-duration enoxaparin, critically ill medical patients who received extended-duration betrixaban had fewer VTE without more major bleeding events. The benefit of betrixaban was driven by preventing asymptomatic thrombosis and offset by an elevated risk of non-major bleeding. The APEX trial did not stratify by intensive care unit admission and the present study included a highly selected population of critically ill patients. These hypothesis-generating findings need to be validated in future studies.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05565-6) contains supplementary material, which is available to authorized users.

Abbreviations

CrCl: Creatinine clearance; DVT: Deep vein thrombosis; ICU: Intensive care unit; PE: Pulmonary embolism; ULN: Upper limit of normal; VTE: Venous thromboembolism.

Author details

[1] Division of Cardiovascular Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. [2] Boston Clinical Research Institute, Newton, MA, USA. [3] Department of Haematological Medicine, Guy's and St Thomas' Hospitals, King's College London, London, UK. [4] Duke University and Duke Clinical Research Institute, Durham, NC, USA. [5] Division of Cardiology, Faculty of Medicine, University of Calgary, Calgary, AB, Canada. [6] Baim Institute for Clinical Research, Boston, MA, USA. [7] Division of Cardiovascular Medicine, Department of Medicine, Stanford University, Stanford, CA, USA. [8] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

Compliance with ethical standards

Conflicts of interest

The study was sponsored by Portola Pharmaceuticals, Inc. The funding source had no role in (1) design and conduct of the study; (2) collection, management, analysis, and interpretation of the data; (3) preparation, review, or approval of the manuscript; and (4) decision to submit and disseminate the results for publication. Dr. Chi receives modest research grant support paid to the Beth Israel Deaconess Medical Center, Harvard Medical School from Portola Pharmaceuticals, Bayer, and Janssen Scientific Affairs. Dr. Gibson receives consultant fees from Portola Pharmaceuticals and reports grants from Angel Medical Corporation and CSL Behring; grants and other support from Bayer Corporation; grants and personal fees from Janssen, Johnson & Johnson, and Portola Pharmaceuticals; and personal fees from The Medicines Company, Boston Clinical Research Institute, Cardiovascular Research Foundation, Eli Lilly, Gilead Sciences Inc, Novo Nordisk, Pfizer, Web MD, UpToDate in Cardiovascular Medicine, Amarin Pharma, Amgen, Arena Pharmaceuticals, Bayer Corporation, Boehringer Ingelheim, Chiesi, Merck & Co, PharmaMar, Sanofi, Somahlution, St Francis Hospital, and Verreseon Corporation. Dr. Cohen reports grant support, personal fees, and non-financial support from Portola Pharmaceuticals during the conduct of the study; grant support, personal fees, and non-financial support from Daiichi–Sankyo, Bristol–Myers Squibb, Pfizer, Janssen, and Bayer Pharmaceuticals, personal fees from Boehringer Ingelheim and Sanofi, and personal fees and non-financial support from Johnson & Johnson and Aspen Pharmaceuticals outside the submitted work. Dr. Hernandez reports receipt

of grant support from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Luitpold, Merck, and Novartis; and personal fees from Amgen, AstraZeneca, Bayer, Bristol–Myers Squibb, Boston Scientific, Luitpold, and Novartis outside the submitted work. Dr. Hull reports grant support from Portola Pharmaceuticals during the conduct of the study, and grant support and personal fees from Leo Pharma outside the submitted work. Dr. Harrington reports grant support from Portola Pharma during the conduct of the study; grant support from CSL Behring, AstraZeneca, GlaxoSmithKline, Regado, and Sanofi Aventis, grant support and personal fees from Merck and The Medicines Company, personal fees from Amgen, Gilead Sciences, MyoKardia, and WebMD, and other support from Scanadu, SignalPath, Element Science, Vida Health, and Adverse Events outside the submitted work. Dr. Goldhaber has provided consulting for Boehringer Ingelheim, Bayer, Portola, Daiichi–Sankyo, Janssen, BiO2 Medical, EKOS/BTG, BMS, and Zafgen. All remaining authors declare no conflicts of interest.

Ethical approval
All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent
Informed consent was obtained from all individual participants included in the study.

Publisher's Note

Received: 3 September 2018 Accepted: 5 February 2019
Published online: 18 February 2019

References

1. Minet C, Potton L, Bonadona A, Hamidfar-Roy R, Somohano CA, Lugosi M, Cartier JC, Ferretti G, Schwebel C, Timsit JF (2015) Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Crit Care 19:287
2. Geerts W, Cook D, Selby R, Etchells E (2002) Venous thromboembolism and its prevention in critical care. J Crit Care 17:95–104
3. Cade JF (1982) High risk of the critically ill for venous thromboembolism. Crit Care Med 10:448–450
4. Kapoor M, Kupfer YY, Tessler S (1999) Subcutaneous heparin prophylaxis significantly reduces the incidence of venous thromboembolic events in the critically ill. Crit Care Med 27:A69
5. Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M, Herbecq P, Pordes R, Poussel JF, Roux L, The Association of Non-University Affiliated Intensive Care Specialist Physicians of France (2000) Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. Am J Respir Crit Care Med 161:1109–1114
6. Spyropoulos AC, Anderson FA Jr, Fitzgerald G, Decousus H, Pini M, Chong BH, Zotz RB, Bergmann J-F, Tapson V, Froehlich JB (2011) Predictive and associative models to identify hospitalized medical patients at risk for VTE. Chest 140:706–714
7. Decousus H, Tapson VF, Bergmann J-F, Chong BH, Froehlich JB, Kakkar AK, Merli GJ, Monreal M, Nakamura M, Pavanello R (2011) Factors at admission associated with bleeding risk in medical patients: findings from the improve investigators. Chest 139:69–79
8. Goldhaber S, Kett D, Cusumano C, Kuroki C (2000) Low molecular weight heparin versus minidose unfractionated heparin for prophylaxis against venous thromboembolism in medical intensive care unit patients: a randomized controlled trial. J Am Coll Cardiol 35(2 suppl A):325A2000
9. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, Vallance S, Qushmaq I, Rocha M, Berwanger O, Vlahakis NE (2011) Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 364:1305–1314
10. Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S (2012) Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. J Hosp Med 7:231–238
11. Heit JA, Crusan DJ, Ashrani AA, Petterson TM, Bailey KR (2017) Effect of a near-universal hospitalization-based prophylaxis regimen on annual number of venous thromboembolism events in the US. Blood 130:109–114
12. Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM, APEX Investigators (2016) Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med 375:534–544
13. Chi G, Gibson CM, Hernandez AF, Hull RD, Cohen AT, Harrington RA, Alkhalfan F, Kalayci A, Kerneis M, Nafee T, Goldhaber SZ, APEX Investigators (2018) Betrixaban versus enoxaparin for venous thromboembolism prophylaxis in critically ill patients: findings from the APEX trial. Eur Heart J 39:Ehy563.4321–Ehy4563.4321
14. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 3:692–694
15. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 13:2119–2126
16. Sr Kahn, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, Cook DJ, Balekian AA, Klein RC, LE H, Schulman S, Murad MH (2012) Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:E195s–E226s
17. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, de Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, Mcintyre LA, Mclean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van Der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377
18. Cohen AT, Harrington R, Goldhaber SZ, Hull R, Gibson CM, Hernandez AF, Kitt MM, Lorenz TJ (2014) The design and rationale for the acute medically ill venous thromboembolism prevention with extended duration betrixaban (APEX) study. Am Heart J 167:335–341
19. Raskob GE, Spyropoulos AC, Zrubek J, Ageno W, Albers G, Elliott CG, Halperin J, Haskell L, Hiatt WR, Maynard GA, Peters G, Spiro T, Steg PG, Suh EY, Weitz JI (2016) The mariner trial of rivaroxaban after hospital discharge for medical patients at high risk of VTE. Design, rationale, and clinical implications. Thromb Haemost 115:1240–1248
20. Gibson CM, Spyropoulos AC, Cohen AT, Hull RD, Goldhaber SZ, Yusen Rd, Hernandez AF, Korjian S, Daaboul Y, Gold A, Harrington RA, Chi G (2017) The IMPROVEDD VTE risk score: incorporation of D-dimer into the IMPROVE score to improve venous thromboembolism risk stratification. Th Open 1:E56–E65
21. Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JI, Hiatt WR, Maynard GA, Steg PG, Weitz JI, Suh E, Spiro TE, Barnathan ES, Raskob GE, MARINER Investigators (2018) Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. N Engl J Med 379:1118–1127
22. Lippi G, Tripodi A, Simundic AM, Favaloro EJ (2015) International survey on D-dimer test reporting: a call for standardization. Semin Thromb Hemost 41:287–293
23. Weitz JI, Fredenburgh JC, Eikelboom JW (2017) A test in context: D-dimer. J Am Coll Cardiol 70:2411–2420
24. Guyatt GH, Eikelboom JW, Gould MK, Garcia DA, Crowther M, Murad MH, Kahn SR, Falck-Ytter Y, Francis CW, Lansberg MG, Akl EA, Hirsh J (2012) Approach to outcome measurement in the prevention of thrombosis in

surgical and medical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:E185s–E194s
25. European Medicines Agency (2016) Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in non-surgical patients (Formerly CPMP/EWP/6235/04). EMA, London
26. Kearon C (2003) Natural history of venous thromboembolism. Circulation 107:I22–I30
27. Markel A (2005) Origin and natural history of deep vein thrombosis of the legs. Semin Vasc Med 5(1):65–74.
28. Eikelboom JW, Quinlan DJ, Douketis JD (2001) Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. Lancet 358:9–15
29. Hull RD, Pineo GF, Stein PD, Mah AF, Macisaac SM, Dahl OE, Butcher M, Brant RF, Ghali WA, Bergqvist D, Raskob GE (2001) Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med 135:858–869
30. Cohen AT, Bailey CS, Alikhan R, Cooper DJ (2001) Extended thrombo-prophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty–a meta-analysis. Thromb Haemost 85:940–941
31. Vaitkus PT, Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Goldhaber SZ, PREVENT Medical Thromboprophylaxis Study Group (2005) Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. Thromb Haemost 93:76–79
32. Kalayci A, Gibson CM, Chi G, Mk Yee, Korjian S, Datta S, Nafee T, Gurin M, Haroian N, Qamar I, Hull RD, Hernandez AF, Cohen AT, Harrington RA, Goldhaber SZ (2018) Asymptomatic deep vein thrombosis is associated with an increased risk of death: insights from the APEX trial. Thromb Haemost 118:2046–2052
33. Chi G, Goldhaber SZ, Kittelson JM, Turpie AGG, Hernandez AF, Hull RD, Gold A, Curnutte JT, Cohen AT, Harrington RA, Gibson CM (2017) Effect of extended-duration thromboprophylaxis on venous thromboembolism and major bleeding among acutely ill hospitalized medical patients: a bivariate analysis. J Thromb Haemost 15:1913–1922
34. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, Dietrich-Neto F, ENOXACAN II Investigators (2002) Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 346:975–980
35. Eriksson BI, Lassen MR, PENTasaccharide in HIp-FRActure Surgery Plus Investigators (2003) Duration of prophylaxis against venous thrombo-embolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 163:1337–1342
36. Chi G, Goldhaber SZ, Hull RD, Hernandez AF, Kerneis M, Al Khalfan F, Cohen AT, Harrington RA, Gibson CM (2017) Thrombus burden of deep vein thrombosis and its association with thromboprophylaxis and d-dimer measurement: insights from the APEX trial. Thromb Haemost 117:2389–2395
37. Chan NC, Bhagirath V, Eikelboom JW (2015) Profile of betrixaban and its potential in the prevention and treatment of venous thromboembolism. Vasc Health Risk Manag 11:343–351
38. Levy JH, Douketis J, Weitz JI (2018) Reversal agents for non-vitamin K antagonist oral anticoagulants. Nat Rev Cardiol 15:273–281
39. Hutchaleelaha A, Ye C, Song Y, Lorenz T, Gretler D, Lambing JL (2012) Metabolism and disposition of betrixaban and its lack of interaction with major CYP enzymes. Blood 120:2266
40. Cook DJ, Griffith LE, Walter SD, Guyatt GH, Meade MO, Heyland DK, Kirby A, Tryba M, Canadian Critical Care Trials Group (2001) The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. Crit Care 5:368–375
41. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 383:955–962
42. Bagshaw SM, Stelfox HT, Iwashyna TJ, Bellomo R, Zuege D, Wang X (2018) Timing of onset of persistent critical illness: a multi-centre retrospective cohort study. Intensive Care Med 44:2134–2144