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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Betrixaban Compared with Enoxaparin for Venous Thromboembolism Prophylaxis in Nonsurgical Patients with Acute Medical Illness in the United States

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Abstract

Background Studies show that the risk of venous thromboembolism (VTE) continues post-discharge in nonsurgical patients with acute medical illness. Betrixaban is the first anticoagulant approved in the United States (US) for VTE prophylaxis extending beyond hospitalization.

Objective The aim was to establish whether betrixaban for VTE prophylaxis in nonsurgical patients with acute medical illness at risk of VTE in the US is cost-effective compared with enoxaparin.

Methods A cost-effectiveness analysis was conducted, estimating the cost per quality-adjusted life-year (QALY) gained with betrixaban (35–42 days) compared with enoxaparin (6–14 days) from a US payer perspective over a lifetime horizon. A decision tree (DT) estimated primary VTE events, thrombotic events, and treatment complications in the first 3 months based on data from the phase III Acute Medically Ill VTE Prevention with Extended Duration Betrixaban study. A Markov model estimated recurrent events and long-term complication risks from published literature. EuroQoL-5 Dimensions utility data and costs inflated to 2017 US dollars (US$) were from published literature. Results were discounted at 3.0% per annum. Deterministic and probabilistic sensitivity analyses explored uncertainty.

Results Betrixaban dominated enoxaparin, with savings of US$784 and increased QALYs of 0.017 per patient. In addition, betrixaban dominated enoxaparin across all sensitivity analyses, but was most sensitive to utilities and DT probabilities. Furthermore, probabilistic sensitivity analysis found that betrixaban was more cost-effective than enoxaparin at all willingness-to-pay thresholds.

Conclusion Betrixaban can be considered cost-effective for nonsurgical patients with acute medical illness at risk of VTE, requiring longer VTE prophylaxis from hospitalization through post-discharge.

Key Points for Decision Makers

Prophylaxis of venous thromboembolism (VTE) from hospitalization through post-discharge is a new option for acute medically ill patients at high risk of thromboembolic events.

In the US, a 35–42-day regimen with betrixaban, from hospitalization through post–hospital-discharge, was found to accrue more quality-adjusted life-years (QALYs) and less costs compared with a 6–14-day prophylaxis with enoxaparin, due to a reduced incidence of thromboembolic events and lower associated costs, for nonsurgical patients with acute medical illness at risk of VTE.

Betrixaban dominated enoxaparin, with 0.017 additional QALYs accrued and cost savings of US$784 per patient.

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1 Introduction

Venous thromboembolism (VTE) is a life-threatening condition and a leading but preventable cause of morbidity and mortality [1–3]. VTE typically originates as a deep-vein thrombosis (DVT), which can travel to the lungs causing a pulmonary embolism (PE), potentially causing sudden death. Surviving patients may require intensive care, and recovery can take several weeks or months. Patients with VTE are also at risk for recurrent VTE and other debilitating complications, including post-thrombotic syndrome (PTS) or chronic thromboembolic pulmonary hypertension (CTEPH) [4, 5].

Short-term, in-hospital subcutaneous VTE prophylaxis for nonsurgical patients includes unfractionated heparin (UFH), fondaparinux sodium, and low molecular weight heparins (LMWHs), e.g., enoxaparin [6, 7]. However, despite extensive use of in-hospital prophylaxis, VTE incidence remains high in at-risk patients [8]. With up to 800,000 VTE events and 30,000 VTE-related deaths occurring annually in the US [9] and less than 50% of patients estimated to have received VTE prophylaxis [10], greater uptake of VTE prophylaxis both in-hospital and post-discharge could reduce VTE morbidity and mortality. Studies have shown that the risk of VTE and VTE-related death associated with hospitalization persists for 1–3 months post-hospital discharge in high-risk acute medically ill patients [3, 10–15]. Approximately half of VTE events occur following discontinuation of in-hospital prophylaxis and after hospital discharge in at-risk patients. Therefore, previous studies investigated VTE prophylaxis through post-discharge compared with in-hospital prophylaxis, but investigated anticoagulants were associated with significantly increased major bleeding (MB), outweighing the net benefit of longer VTE prophylaxis [16–18]. Therefore, VTE prophylaxis extending through post-discharge is not currently recommended in this population, limiting the guidance on improving VTE prevention in acute medically ill patients at high risk of VTE [10, 14, 15, 19, 20].

Betrixaban is a direct oral anticoagulant for VTE prophylaxis that is a potent and specific inhibitor of human factor Xa, a key component in the formation of blood clots. Studies have highlighted several pharmacological properties that make betrixaban appropriate to treat the acute medically ill population: effective half-life (19–27 h) permitting once-daily dosing, low peak-to-trough concentration ratio, low renal clearance, and lack of cytochrome P450 (CYP450) enzyme interactions [21, 22]. These properties provide consistent anticoagulation over 24 h, without needing dose adjustment for patients with mild or moderate renal impairment (patients with severe renal impairment or receiving P-glycoprotein inhibitors require dose adjustment) and a low propensity for drug–drug interactions on the CYP450 reaction pathway.

The average length of hospital stay for medical patients fell from 9.0 to 5.1 days between 1990 and 2015, augmenting the need for VTE prophylaxis through post-hospital discharge [23–26]. Approved in June 2017 in the US, by the Food and Drug Administration (FDA), betrixaban is indicated for VTE prophylaxis in adult patients hospitalized for an acute medical illness at risk of thromboembolic complications due to moderate or severe restricted mobility and other VTE risk factors [27, 28]. The pivotal phase III Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) study (NCT01583218) (Table 1) demonstrated that 35–42-day prophylaxis with betrixaban reduced VTE occurrence in acute medically ill nonsurgical patients compared with 6– 14-day prophylaxis with enoxaparin, without significant increase in MB [29, 30]. Online Resource 1 (see the electronic supplementary material) presents the baseline characteristics of the APEX population.

Net clinical benefit was defined as the composite of the primary efficacy and principal safety endpoints in APEX [30]. In the overall efficacy population, net clinical benefit occurred in 5.8% and 7.3% of the betrixaban and enoxaparin cohorts, respectively; favorable for betrixaban compared with enoxaparin ($p = 0.01$) [30–32]. However, cost-effectiveness was not investigated.

Therefore, this study aimed to establish the cost-effectiveness of betrixaban compared with enoxaparin for VTE prophylaxis in nonsurgical patients with acute medical illness at risk of VTE in the US.

2 Methods

A cost-effectiveness model was developed in Microsoft® Excel 2010 (Redmond, WA, US) to estimate the expected costs and outcomes for VTE prophylaxis with betrixaban (35–42 days) compared with enoxaparin (6–14 days) in nonsurgical patients with acute medical illness at risk of VTE. The primary outcome was the incremental cost-effectiveness ratio, expressed as cost per quality-adjusted life-year (QALY) gained.

Occurrence rates of VTE events and acute complications were clinical outcomes assessed in the APEX trial and were used in this cost-effectiveness analysis. A systematic literature review (SLR) (Online Resource 2, see the electronic supplementary material) was conducted to inform the model structure, costs, quality-of-life (QoL), and clinical inputs, where APEX trial data were not available. The SLR revealed a paucity of evidence for VTE prophylaxis through post-discharge, with previous studies reporting increased risk of MB with prophylaxis through post-discharge compared with in-hospital and US guidelines currently recommending in-hospital VTE prophylaxis [16–20].

Table 1 APEX trial characteristics

Study design	Phase III, large ($n = 7513$), international, multicenter, double-blind, RCT
Population	Patients 40 years of age or older, who had been hospitalized for less than 96 h for a specified acute medical illness (heart failure, respiratory failure, infectious disease, rheumatic disease, or IS), and had reduced mobility and specific risk factors for VTE Efficacy analyses were performed based on the mITT population (patients who received at least one dose of study drug and completed a follow-up assessment for at least one efficacy outcome)
Intervention	Betrixaban, oral, at a loading dose of 160 mg for the first dose and then 80 mg once daily for 35–42 days (plus SC enoxaparin placebo for 6–14 days) Patients with severe renal impairment or who were receiving a concomitant P-glycoprotein inhibitor received a half dose of the study medication: a loading dose of 80 mg for the first dose and then 40 mg once daily for 35–42 days (plus SC enoxaparin placebo for 6–14 days)
Comparator	Enoxaparin SC at a dosage of 40 mg once daily for 6–14 days (plus oral betrixaban placebo for 35–42 days) Patients with severe renal impairment received a half dose of this study medication: 20 mg once daily for 6–14 days (plus oral betrixaban placebo for 35–42 days)
Method of randomization	Patients were randomized 1:1 to receive betrixaban or enoxaparin once daily using random permutated blocks within geographic region, stratified by dosing and entry criteria, and an interactive voice-response system
Efficacy outcomes	The primary outcome was a composite of ADVT between day 32 and day 47, or SDVT, PE, or VTE-related death through day 42 The two major secondary outcomes were a composite of symptomatic VTE through day 42, and a composite of ADVT between day 32 and day 47, SDVT, non-fatal PE, or death from any cause through day 42
Safety outcomes	The principal safety endpoint was occurrence of MB at any point until 7 days after study drug discontinuation

APEX Acute Medically Ill VTE Prevention with Extended Duration Betrixaban, *ADVT* asymptomatic deep-vein thrombosis, *IS* ischemic stroke, *MB* major bleeding, *mITT* modified intent-to-treat, *PE* pulmonary embolism, *RCT* randomized controlled trial, *SC* subcutaneous, *SDVT* symptomatic deep-vein thrombosis, *VTE* venous thromboembolism

2.1 Target Population

Betrixaban's approved FDA label was informed by the eligible population for the APEX study, also used by the model: adults hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and are aged ≥ 75 years, aged 60–74 years with D-dimer ≥ 2 × upper limit of normal (ULN), or aged 40–59 years with D-dimer ≥ 2 × ULN and a history of either VTE or cancer [27, 28, 30].

A subgroup analysis was conducted using betrixaban 80 mg and enoxaparin 40 mg data only: data from patients with severe renal impairment in both study arms or patients who received P-glycoprotein inhibitors in the betrixaban arm who received a reduced study intervention dose were excluded, to investigate the impact of dose size on results.

2.2 Interventions

The interventions entering the model were betrixaban and enoxaparin. In the APEX study, patients were randomized 1:1 to receive oral betrixaban 80 mg once daily (with an initial loading dose of 160 mg then 80 mg once daily for 35–42 days) or enoxaparin 40 mg subcutaneously once daily for 10 ± 4 days [30]. Actual treatment duration in the model (36 days betrixaban, 9 days enoxaparin) was based on the median treatment duration in APEX [30]. Patients with severe renal impairment in both study arms or patients who received P-glycoprotein inhibitors in the betrixaban arm received 50% of the study dose [28, 30].

2.3 Model Structure

A decision analytic model was constructed with a decision-tree component (evaluating short-term costs and outcomes of prophylaxis) followed by a Markov model component (evaluating long-term costs and outcomes post-prophylaxis). This structure aligns with several published US-perspective VTE prophylaxis cost-effectiveness studies, whose model structures consist of a decision tree, Markov model, or combination of both [33–38]. Model health states were selected to capture events that impact VTE at-risk patients requiring prophylaxis, based on events captured in previous studies and outcomes observed in the APEX study [30].

Two 1000-patient cohorts entered the model, receiving either betrixaban or enoxaparin. A decision-tree structure was used to capture VTE events, myocardial infarction (MI), ischemic stroke (IS), pharmacological prophylaxis complications (intracranial hemorrhage [ICH], MB, clinically relevant non-MB, heparin-induced thrombocytopenia [HIT], and HIT with thrombosis [HITT]), and death in the 3 months following initiation of prophylaxis (Fig. 1). HIT and HITT are potentially life-threatening complications in VTE at-risk patients [33–35, 39]. Treatment involves discontinuation of heparin-anticoagulants and initiation of non-heparin anticoagulation [39].

Two sub-trees captured pharmacological prophylaxis complications and death following a VTE (Online Resource

3, see the supplementary electronic material) or MI event (Online Resource 4). A third sub-tree captured severity of IS and death following IS (Online Resource 5, see the supplementary electronic material). The first two sub-trees carried the additional risk of complications that arise with increased anticoagulation therapy for VTE and MI events. Following an IS event (sub-tree 3), US guidelines recommend aspirin therapy over anticoagulation, so patients are modelled to either survive or enter the non-VTE-related death health state and are not considered to be at risk of additional anticoagulation complications [40].

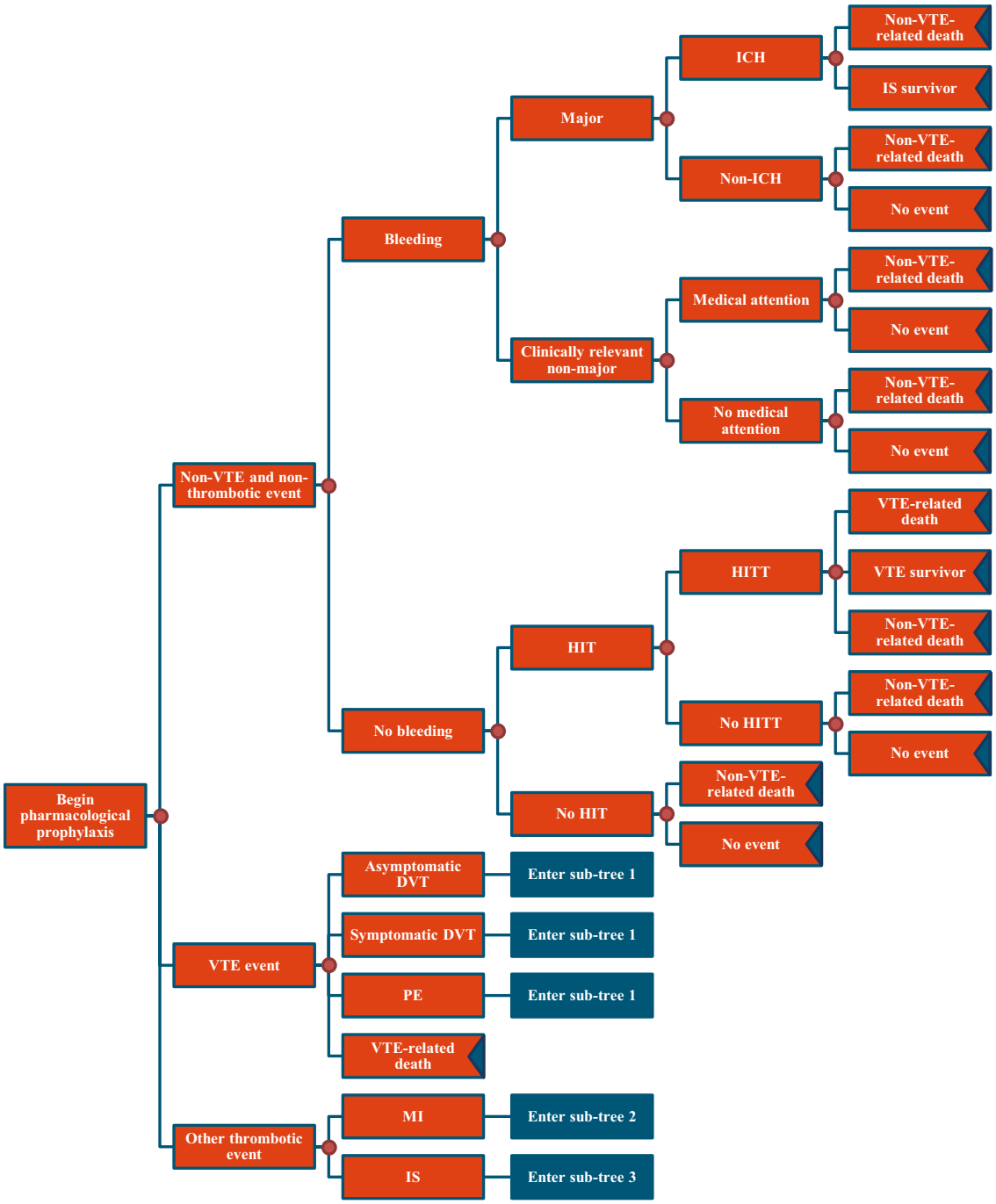

Fig. 1 Initial decision tree. *DVT* deep-vein thrombosis, *HIT* heparin-induced thrombocytopenia, *HITT* heparin-induced thrombocytopenia with thrombosis, *ICH* intracranial hemorrhage, *IS* ischemic stroke, *MI* myocardial infarction, *PE* pulmonary embolism, *VTE* venous thromboembolism

The severity of IS was defined according to the modified Rankin scale; scores of 0–2, 3–4, and 5–6 were classified as mild, moderate, and severe, respectively. Within the subtrees, a "VTE-related death" was only possible following a VTE event or HITT event and a "non-VTE-related death" included death by other causes. If a patient survived an ICH, they transitioned into the "IS survivor" health state in the model to maintain model simplicity; it was assumed that the QoL and further costs would be similar for ICH survivors and IS survivors. Note that if a patient enters "IS survivor" state after an ICH event, they are not an "IS survivor", but are modelled to experience similar impact on QoL and costs. This is a conservative assumption since ICH survivors incur more costs and have reduced survival compared with IS survivors. It was reported that over 4 years, costs of US$38,023 and US$48,327 were accrued for survivors of ICH and subarachnoid hemorrhage, a subtype of ICH, whereas IS survivors accrue US$39,396 [41]. Likewise, 1-year fatality was 58% for ICH, compared with consistently below 53% for IS [42, 43].

After 3 months, patients entered a Markov model with 3-monthly cycles based on their end state in the decision tree (Fig. 2). Patients could reside in one of the following health states: no event, VTE survivor, MI survivor, IS survivor, VTE-related death, and non-VTE-related death. Following a primary event, VTE, MI, and IS survivors were at risk of recurrent or fatal events, with VTE survivors also at risk of PTS and CTEPH. These event probabilities were sourced from published literature.

Costs and QALYs were calculated based on the occurrence of events in the decision tree, and then for each Markov cycle, based on the patient distribution across all health states and probabilities of events relevant to health states. These accumulate over the time horizon, giving the total costs and QALYs.

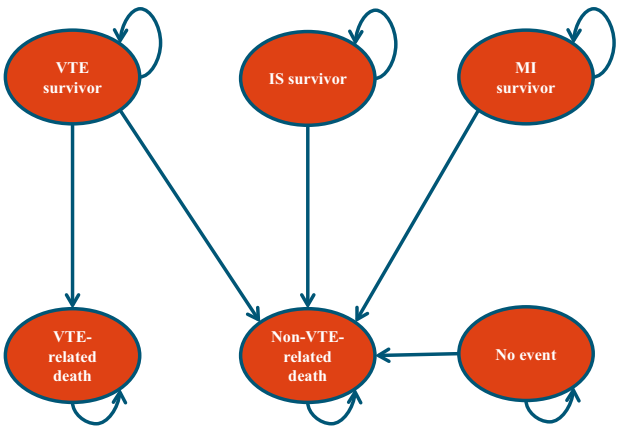

Fig. 2 Markov model structure. *IS* ischemic stroke, *MI* myocardial infarction, *VTE* venous thromboembolism

2.4 Time Horizon, Discounting, and Perspective

To capture the ongoing risk of recurrent or fatal events and VTE-related complications, a lifetime horizon was used in the model (25 years). This was based on the mean age of patients in the APEX study (76 years), and assumed that no patients survive beyond 100 years [30]. Costs and outcomes were discounted at 3% per annum in line with World Health Organization guidelines [44]. The analysis was conducted from the US payer perspective.

2.5 Model Inputs

2.5.1 Clinical Parameters

The APEX study directly informed decision-tree event occurrence and patient demographics at baseline (age 76 years, sex 46% male) as it is the only randomized controlled trial (RCT) directly comparing betrixaban with enoxaparin [30]. Table 2 shows the number of patients in each Markov model health state post-decision tree. Online Resource 6 (see the supplementary electronic material) displays the percentages of patients who experienced an asymptomatic DVT, symptomatic DVT, or PE in the decision tree, from APEX patient-level data, and Markov model event probabilities, from published literature.

For the decision tree, patient flow was sourced from APEX patient-level data through to study end at day 77. Since there were no HIT or HITT cases during APEX, the associated probabilities were zero. The percentage of patients reaching each health state at the Markov model entry was determined by summing the percentages of a patient traversing each appropriate tree path. Since the incidence rate of symptomatic events plateaued between day 42 and 77 for betrixaban, it was conservatively assumed that patients experienced no more primary events after day 77 [31, 45]. Therefore, patients remained in the resultant health state until entry into the Markov model.

Table 2 Number and percentage of patients in each health state[a] following the decision tree

Health state	Betrixaban, *n* (%)	Enoxaparin, *n* (%)
No event	901 (90.14)	879 (87.93)
VTE survivor	40 (3.95)	54 (5.40)
Myocardial infarction survivor	2 (0.16)	3 (0.32)
Ischemic stroke survivor	2 (0.19)	6 (0.65)
VTE-related death	4 (0.40)	7 (0.70)
Non-VTE-related death	52 (5.16)	50 (5.00)

VTE venous thromboembolism

[a]Number of patients in each health state is scaled to the 1000-person cohort per treatment arm

Recurrent event probabilities (Online Resource 7, see the supplementary electronic material) in the Markov model were assumed to be the same regardless of pharmacological prophylaxis received. Once patients experienced either PTS or CTEPH, they were assumed to experience the complication for life, except in cases of successful CTEPH surgery. Probabilities of death were based on all-cause mortality probabilities adjusted for decreased life expectancy following hospitalization for acute medical illnesses, using a hazard ratio of 1.367, derived from a study reporting decreased life expectancy following heart failure, one of the possible eligibility criteria for APEX [30, 46, 47].

2.5.2 Resource Utilization and Cost Inputs

Direct healthcare costs were informed by published literature. Where required, costs were inflated to 2017 US dollars using the Consumer Price Index medical inflation rates for the US [48]. Model costs and resource use are summarized in Online Resource 8 (see the supplementary electronic material).

Prophylaxis costs were aligned with the duration and dosing as per the APEX study, with patients hospitalized for the first 5 days of treatment and remaining doses being self-administered at home [30]. Dosing regimens included 37 doses of betrixaban (two loading and 35 maintenance; 80 mg as standard, 40 mg for those with severe renal impairment or for those receiving P-glycoprotein inhibitors) and nine doses of enoxaparin (40 mg as standard, 20 mg for those with severe renal impairment).

Since enoxaparin is administered subcutaneously, it was assumed that a nurse would administer treatment in hospital. Though in APEX all doses were received during hospitalization, the model conservatively assumes a mean stay of 5 days so that patients self-administer the final doses, despite a nurse typically administering all doses. Costs and resource use for in-hospital blood-count monitoring of enoxaparin patients were also included. Mean treatment costs per patient for 36-day betrixaban and 9-day enoxaparin were US$525.00 and US$232.58, respectively.

Costs associated with the management of pharmacological prophylaxis complications captured in the decision tree included bleeding (ICH, non-ICH major, and clinically relevant non-major requiring medical attention), HIT, and HITT. Management costs for VTE events and other thrombotic events in the decision tree were incurred for DVT, PE, and VTE-related death, and IS and MI. Corresponding management costs in the Markov model included costs for recurrent VTE, VTE-related death, and VTE complications (PTS and CTEPH), and recurrent IS and MI. For each event, costs were applied instantaneously to appropriate patients in the decision tree and were applied as they occur in the Markov model.

Finally, VTE survivors received follow-up costs for complications (CTEPH and PTS), applied on a by-cycle basis for patients who developed either condition and remained alive. Additionally, IS and MI survivors incurred lifelong follow-up costs applied from day 77 until decision-tree exit and every cycle in the Markov model until death.

2.5.3 Utilities

Since QoL data were not collected in APEX, utility and disutility data were sourced from published literature, using EuroQol-5 Dimensions utility data where possible. Online Resource 9 and Online Resource 10 (see the supplementary electronic material) display the utilities and disutilities applied within the model. A "hospitalized medically ill" utility was applied for the first 5 days in the decision tree, as required for betrixaban eligibility [38]. Following hospitalization, a "no event" utility was applied to patients who experienced no event [38]. The utility of a VTE survivor was approximated by subtracting the weighted average of PE and DVT survivors (symptomatic and asymptomatic) disutilities from the "no event" utility [49, 50]. Similarly, the utilities of MI and IS survivors were estimated by subtracting the MI and IS disutility from the "no event" utility, respectively [51, 52]. Since IS was stratified by severity, the disutility was weighted according to the number of events in the decision tree.

Direct disutility event data were used where reported, and were otherwise obtained by subtracting event utility from baseline utility in the reported study [51–54].

2.5.4 Sensitivity Analyses

Deterministic sensitivity analyses consisted of scenario analyses and one-way sensitivity analysis (OWSA) to test structural and parameter uncertainty in the model. Table 3 details the scenario analyses conducted.

The OWSA considered 95% confidence intervals sourced from the original data or pre-specified probabilistic distributions. Standard error was assumed to be 20% of the mean value, where unreported. A tornado diagram was used to illustrate the uncertainty level of parameters by considering the incremental net monetary benefit (INMB) upper and lower bounds.

Probabilistic sensitivity analysis assigned distributions to model parameters and ran 10,000 simulations to further explore parameter uncertainty. The cohort size, time horizon, cycle length, discount rates, all-cause mortality rates, PTS, lifelong disutility duration, mean drug costs per day, and treatment duration were kept fixed. Dirichlet distributions were assigned to baseline decision-tree data for betrixaban and enoxaparin. Beta distributions were used for the proportion of male patients, event probabilities, utilities,

Table 3 Scenario analyses

Parameter	Scenario
Discount rate	Discounting costs and outcomes at 0, 1.5, and 6% per annum
Time horizon	Applying shorter time horizons of 3 months, 1 year, 5 years, 10 years, and 15 years
Hazard ratio of death following hospitalization for an acute medical illness	Hazard ratios for death of 1, 1.2, 1.5, and 2
Betrixaban efficacy[a]	Varying the total number of VTE events, other thrombotic events, and VTE-related deaths by 20%
Exclusion of asymptomatic DVT events	Patients experiencing an asymptomatic DVT event reallocated in the decision tree to experience a non-VTE/non-thrombotic event or a VTE-related death
Betrixaban and enoxaparin dosing subgroup analysis	Using only data from patients who received betrixaban 80 mg daily compared with enoxaparin 40 mg daily in the decision tree and for the baseline characteristics
Inclusion of D-dimer testing for betrixaban patients	While on treatment in APEX, betrixaban patients aged ≤ 75 years received a single D-dimer test to establish their VTE-risk factor. From APEX, it was concluded that 19% of all patients would be identified as high risk of VTE by this method and therefore this proportion of betrixaban patients were assumed to have a D-dimer test
Treatment duration	Using the mean, lower and upper bound (of the interquartile range) for the treatment duration of betrixaban and enoxaparin from APEX rather than the median

APEX Acute Medically Ill VTE Prevention with Extended Duration Betrixaban, *DVT* deep-vein thrombosis, *VTE* venous thromboembolism

[a]Varying the efficacy of betrixaban was performed in the decision tree by raising the incidence of events in relevant arms by 20%, which affected how many patients were filtered through each node of the decision tree

disutilities, percentage of patients with CTEPH receiving surgery, and success rate of CTEPH surgery. Gamma distributions were used for age, number of IS events by severity, hazard ratios, duration of disutilities, costs, and platelet monitoring test frequency per patient.

A cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) were plotted using the probabilistic results.

2.5.5 Validation

The model structure was based on approaches used in previous US cost-effectiveness studies investigating VTE prophylaxis identified by the SLR [33–38]. Clinical data within the model were informed by APEX trial data and SLR-identified published literature. Expert clinical opinion (ATC and SD) informed the model where published literature for resource utilization, costs, and utility inputs were not available, as stated in Online Resource 8 and Online Resource 10 (see the supplementary electronic material). The model was developed internally by two independent health economists, and quality-assessed by a third independent external health economist. Model structure, clinical data inputs, and long-term projections predicted by the model were conceptually validated by two leading clinical experts in VTE prophylaxis (ATC and SD). All feedback obtained by internal and external ratification constructed the final model.

3 Results

3.1 Base Case

Over a lifetime horizon, the cohort receiving betrixaban accrued 3.240 QALYs at a cost of $2236 per patient. Patients receiving enoxaparin accrued 3.223 QALYs at a cost of $3020. The corresponding incremental cost per QALY gained was dominating in favor of betrixaban, such

Table 4 Base-case results per patient

Treatment	Total			Incremental			ICER (2017 US$)
	Costs (2017 US$)	LYG	QALYs	Costs (2017 US$)	LYG	QALYs	
Enoxaparin	3020	4.765	3.223	–	–	–	
Betrixaban	2236	4.780	3.240	− 784	0.015	0.017	Dominating

ICER incremental cost-effectiveness ratio, *LYG* life-year gained, *QALY* quality-adjusted life-year, *US$* United States dollar

Table 5 Disaggregated base-case results per patient

	Betrixaban	Enoxaparin
Decision tree		
Prophylaxis cost (2017 US$)	525	233
Primary event and prophylaxis complications cost (2017 US$)	672	986
LYG	0.236	0.236
QALYs	0.157	0.156
Markov model		
Costs of complications and follow-up for primary events (2017 US$)	890	1555
Recurrent event cost (2017 US$)	149	246
LYG	4.544	4.529
QALYs	3.083	3.067
Total		
Total costs (2017 US$)	2236	3020
LYG	4.780	4.765
QALYs	3.240	3.223

LYG life-year gained, *QALY* quality-adjusted life-year, *US$* United States dollar

that betrixaban was associated with greater QALYs and fewer costs (Table 4). Table 5 presents the disaggregated results per patient.

3.2 Sensitivity Analyses

3.2.1 Scenario Analyses

Scenario analyses results, displayed in Table 6, indicate that the model was most sensitive to the time horizon, hazard ratio of death following hospitalization for an acute medical illness, and exclusion of asymptomatic DVT events. Betrixaban dominated enoxaparin in all analyses, with adjustment of betrixaban efficacy having minimal impact on results. The subgroup analysis for betrixaban 80 mg and enoxaparin 40 mg data only showed an increased cost saving of US$136 and increased gain of 0.004 QALYs for betrixaban 80 mg relative to the base case.

3.2.2 One-Way Sensitivity Analyses

Figure 3 illustrates that the two parameters with greatest impact on the INMB were the "no event" utility and the baseline decision-tree distribution. However, betrixaban remained dominant over enoxaparin, and the INMB remained positive, for all analyses at a US$50,000/QALY willingness-to-pay threshold.

3.2.3 Probabilistic Sensitivity Analyses

The mean results of the probabilistic sensitivity analysis (Table 7) were similar to the base case. The cost-effectiveness plane (Fig. 4) and CEAC (Fig. 5) show that betrixaban dominated enoxaparin in the majority (75.30%) of simulations and is more likely to be cost-effective than enoxaparin at all willingness-to-pay thresholds considered between US$0 and US$100,000. The CEAC shows that the probability of betrixaban being cost-effective at a willingness-to-pay threshold of US$50,000 was 91.44%.

4 Discussion

This analysis compared the costs and QALYs of 36-day betrixaban with 9-day enoxaparin VTE prophylaxis in non-surgical patients with acute medical illness at high risk of VTE using APEX trial data. Base-case results found that betrixaban dominated enoxaparin, accruing cost savings of US$784 and increased QALYs of 0.017 per patient over a lifetime horizon. Cost savings were driven by prevention of primary events, recurrent events, and VTE-related complications, which far outweighed the higher treatment cost of betrixaban relative to enoxaparin. QALY gains were driven by reduced risk of VTE-related death and enhanced QoL due to prevention of primary events, recurrent events, and VTE-related complications.

Across sensitivity analyses, betrixaban remained dominating despite significant variations to the time horizon and underlying efficacy of betrixaban, resulting in cost savings and increased QALYs. The OWSA showed greatest variation in the INMB for the "no event" utility and baseline decision-tree distribution parameters, but the INMB remained positive for all analyses at a willingness-to-pay threshold of US$50,000, indicating the model results are robust to variation in model parameters. Finally, the corresponding probabilistic results indicated a lifetime cost saving of US$793 with an increase of 0.018 QALYs compared with enoxaparin, similar to deterministic results confirming model robustness.

The subgroup analysis of betrixaban 80 mg and enoxaparin 40 mg data provides strong evidence suggesting the clinical and cost benefits of a 36-day betrixaban regimen compared with 9-day enoxaparin are greater for patients who receive betrixaban 80 mg relative to the base case (whereby patients with severe renal impairment in both study arms or patients who received P-glycoprotein inhibitors in the betrixaban arm received betrixaban 40 mg or enoxaparin 20 mg).

Statistics show the average length of hospital stay is decreasing in the US [23–26]. As in-hospital VTE prophylaxis duration decreases and becomes increasingly inadequate, the risk of post-discharge VTE rises, increasing the need for VTE prophylaxis extending beyond hospitalization. Additionally, an oral regimen could improve adherence to

Table 6 Scenario analyses results

Parameter varied	Betrixaban total costs (US$)	Betrixaban total QALYs	Incremental costs (US$)	Incremental QALYs	ICER
Base case	2236	3.240	− 784	0.017	Dominating
Discount rate: 0%	2372	3.615	− 877	0.020	Dominating
Discount rate: 1.5%	2300	3.417	− 828	0.018	Dominating
Discount rate: 6%	2128	2.941	− 710	0.015	Dominating
Time horizon: 3 months	1197	0.157	− 22	0.001	Dominating
Time horizon: 1 year	1310	0.608	− 128	0.003	Dominating
Time horizon: 5 years	1859	2.229	− 531	0.011	Dominating
Time horizon: 10 years	2163	3.027	− 737	0.016	Dominating
Hazard ratio of death following hospitalization for an acute medical illness: 1	3175	5.946	− 1419	0.032	Dominating
Hazard ratio of death following hospitalization for an acute medical illness: 1.2	2577	4.231	− 1016	0.023	Dominating
Hazard ratio of death following hospitalization for an acute medical illness: 1.5	2042	2.666	− 650	0.014	Dominating
Hazard ratio of death following hospitalization for an acute medical illness: 2	1656	1.482	− 379	0.008	Dominating
Betrixaban efficacy: 20% more VTE events	2446	3.235	− 574	0.012	Dominating
Betrixaban efficacy: 20% more other thrombotic events	2327	3.236	− 692	0.013	Dominating
Betrixaban efficacy: 20% more fatal VTE events	2235	3.238	− 785	0.015	Dominating
Exclusion of asymptomatic DVT events	1467	3.252	− 578	0.015	Dominating
Betrixaban and enoxaparin dosing subgroup analysis (patients receiving betrixaban 80 mg or enoxaparin 40 mg)	2101	3.304	− 920	0.021	Dominating
Treatment duration (mean): 33 days for betrixaban and 10 days for enoxaparin	2,191	3.240	− 843	0.017	Dominating
Treatment duration (lower bound of the interquartile range): 34 days for betrixaban and 7 days for enoxaparin	2206	3.240	− 786	0.017	Dominating
Treatment duration (upper bound of the interquartile range): 39 days for betrixaban and 13 days for enoxaparin	2281	3.240	− 796	0.017	Dominating
Inclusion of D-dimer tests for 19% of betrixaban patients[a]	2241	3.240	− 780	0.017	Dominating

APEX Acute Medically Ill VTE Prevention with Extended Duration Betrixaban, *DVT* deep-vein thrombosis, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *US$* United States dollar, *VTE* venous thromboembolism

[a]D-dimer testing was carried out in the APEX study, but is not usual in clinical practice. It has been assumed that 50% of patients aged ≤ 75 years would be identified as at-risk of VTE by a single D-dimer test whilst receiving betrixaban treatment. In APEX, the proportion of patients aged ≤ 75 years was 38%; hence 19% of all betrixaban patients were assumed to have a D-dimer test

therapy as studies show that administration routes have an impact on patient preferences and adherence, with patients more likely to comply with oral regimens compared with injections [55–57]; such regimens avoid the issues associated with injection regimens, including patient discomfort with self-injections, problems with adherence to therapy, and costs incurred due to nurse administration of the medication.

Several relevant US-perspective cost-effectiveness studies were identified, although these were based on short-term, in-hospital VTE prophylaxis. Two studies investigated the cost-effectiveness of VTE prophylaxis with enoxaparin, UFH, and no prophylaxis in hospitalized medical patients [33, 34]. One study compared the cost-effectiveness of LMWH against no prophylaxis [37], one compared enoxaparin with no prophylaxis [36], one compared enoxaparin with UFH [35], and one compared dalteparin with UFH [58]. Another study compared ultrasound screening with a DVT prevention program in patients receiving LMWH [38]. Four of the studies [33–35, 58] used a payer perspective, and six studies used a decision tree, a Markov model, or a combination of both to evaluate cost-effectiveness [33–38]. Of the studies incorporating a Markov model, two studies used a lifetime horizon and a discount rate of 3% per annum [37, 38] and the other used a 2-year time horizon (discount rate not reported) [34]. As none of the previous cost-effectiveness studies involved betrixaban, no direct comparison between results can be made. However, one study identified that dalteparin

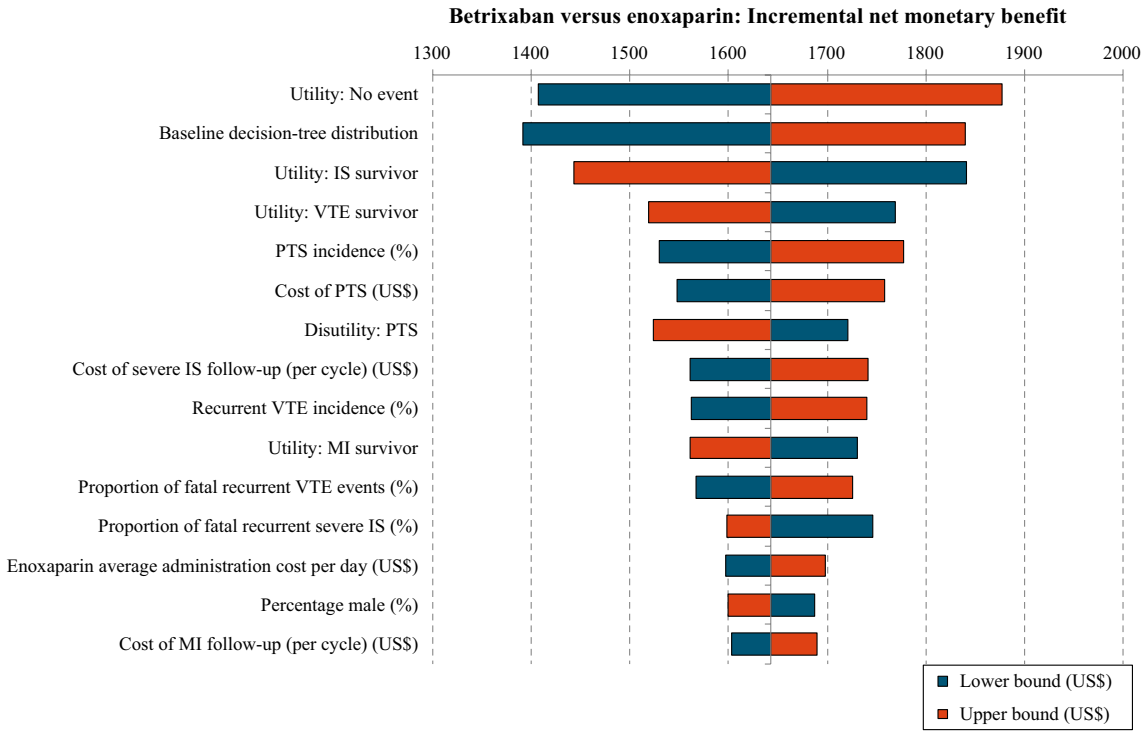

Fig. 3 Tornado diagram of the 15 most sensitive parameters. NMB assigns a cost value to health benefits and compares this against the cost of treatment using the formula NMB = (QALYs) × (WTP) − *C*, where *C* is the cost of treatment. A higher NMB corresponds to a more cost-effective strategy; hence the positive INMB found by comparing prophylaxis with betrixaban to enoxaparin indicated that betrixaban was a more cost-effective strategy. *INMB* incremental net monetary benefit, *IS* ischemic stroke, *MI* myocardial infarction, *NMB* net monetary benefit, *PTS* post-thrombotic syndrome, *QALY* quality-adjusted life-year, *US$* United States dollar, *VTE* venous thromboembolism, *WTP* willingness-to-pay

dominated UFH and three studies found that enoxaparin dominated UFH [33–35, 58].

Six studies did not report or determine total QALYs gained for patients receiving enoxaparin or other LMWH [33–37, 58]. One study estimated critically ill patients receiving an unspecified LMWH accrued 5.93 QALYs, compared with 3.22 reported herein [38]. However, the analyses consider significantly different scenarios, making direct comparison infeasible: different populations and eligibility criteria, different baseline ages (65 vs 76), different settings (intensive care vs ward), different baseline utility sources (mechanical ventilation vs acute medically ill patients), and different treatment durations (22 vs 9 days). Additionally, the intervention received was unspecified in the study, preventing comparability with the QALY estimate for enoxaparin patients.

This analysis has a number of strengths. The model structure captured short- and long-term events, and was aligned to that adopted by other cost-effectiveness analyses considering VTE prophylaxis [33–38]. Clinical effectiveness data are based on a large well-conducted RCT comparing betrixaban with enoxaparin. Published literature provided sufficient data to parameterize costs and utilities. Results were validated with two leading experts in VTE prophylaxis (ATC and SD).

The main limitation of the analysis was the necessity of using published literature to inform rates of recurrence and VTE-related complications, since APEX only reported data through to day 77. It is unclear how generalizable these reported data are to the nonsurgical medically ill population;

Table 7 Disaggregated probabilistic sensitivity analysis results

Treatment	Total		Incremental		ICER (2017 US$)
	Costs (2017 US$)	QALYs	Costs (2017 US$)	QALYs	
Enoxaparin	3042	3.228	–	–	–
Betrixaban	2249	3.245	− 793	0.018	Dominating

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *US$* United States dollar

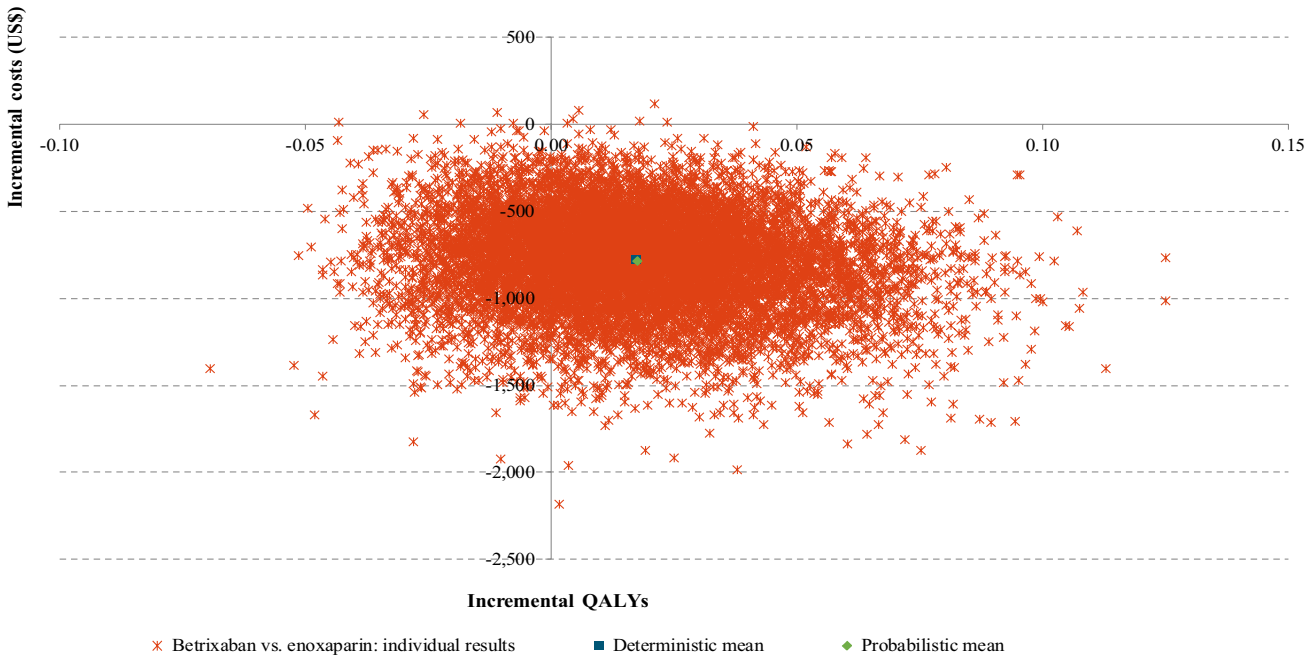

Fig. 4 Incremental cost-effectiveness plane. *QALY* quality-adjusted life-year, *US$* United States dollar

indeed, rates may be under- or over-estimated for this analysis. Nevertheless, extensive sensitivity analyses were performed, all of which found that betrixaban dominated enoxaparin.

Additionally, paucity of clinical trial data comparing VTE prophylaxis through post-hospital discharge with betrixaban versus enoxaparin in the target population limited this analysis. The EXCLAIM, MAGELLAN, and ADOPT

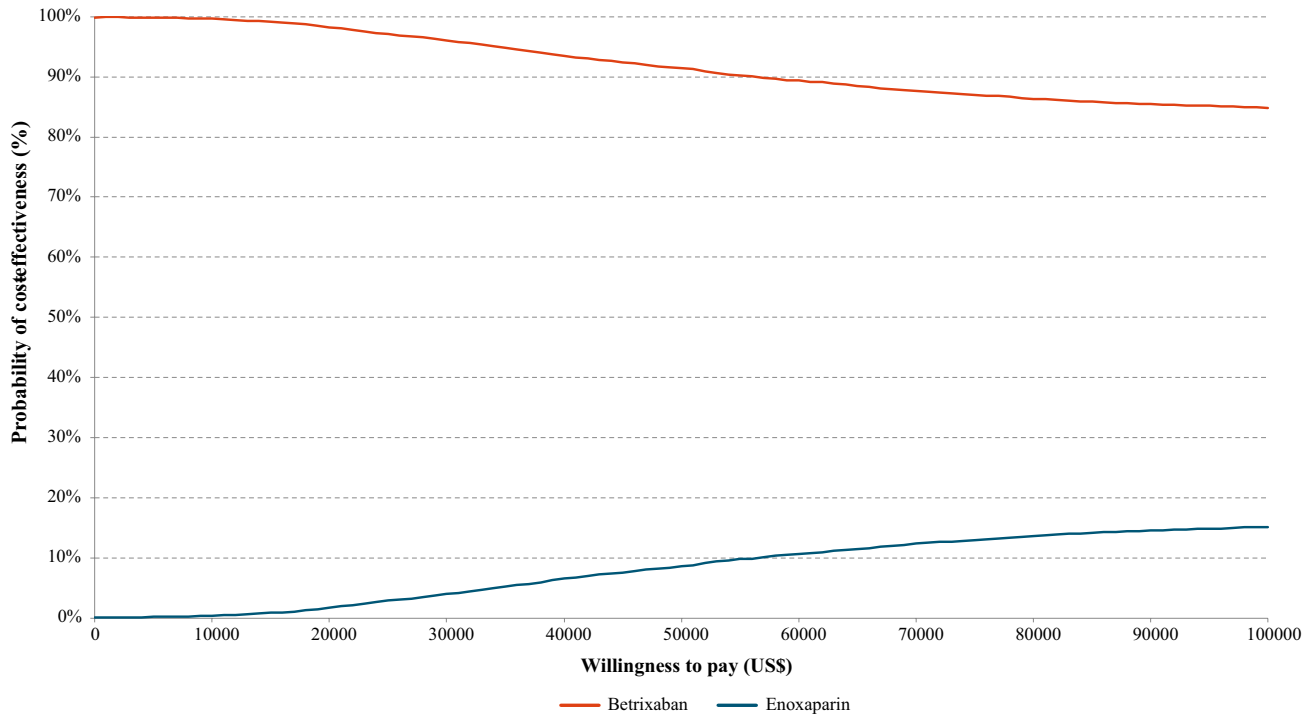

Fig. 5 Cost-effectiveness acceptability curve. *US$* United States dollar

trials, which respectively compared through post-discharge regimens of enoxaparin, rivaroxaban, and apixaban, with in-hospital enoxaparin, all found that longer prophylaxis reduced VTE risk, but increased MB, making these regimens unsuitable comparators [16–18]. APEX analyzed prophylaxis with betrixaban through post-discharge compared with enoxaparin in-hospital and reported promising results [30]. As the pivotal study investigating betrixaban through post-discharge, it was the only source of patient-level data for betrixaban available for this analysis.

Future research could expand the scope of this analysis to estimate the cost-effectiveness of betrixaban with other current prophylactic treatments; this might generalize this analysis to other populations at risk of VTE and broaden the understanding of clinical and economic benefits of VTE prophylaxis from hospitalization through post-discharge.

5 Conclusion

Driven by improved clinical outcomes in APEX, betrixaban was associated with improvements in survival and QALYs, and was less costly than enoxaparin. This analysis suggests that betrixaban is a cost-effective alternative to enoxaparin for nonsurgical patients with acute medical illness at risk of VTE and could lead to significant savings for payers in the US, with a mean saving of US$784 per patient and an improvement in a patient's QoL of 0.017 QALYs.

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Compliance with Ethical Standards

Conflict of interest HG, VL, and MF are employees of FIECON Ltd, a health-economics outcomes research agency, which performed the analyses presented in the manuscript, funded by Portola Pharmaceuticals, Inc. WRN and IB are employees of Portola Pharmaceuticals, Inc. SD has received consulting fees or honoraria, fees for provision of medicines, equipment, or administrative support, and payment for lectures from Portola Pharmaceuticals, Inc, Pfizer, Janssen and BMS. SD has received support for travel to meetings from Portola Pharmaceuticals, Inc and fees for expert testimony from Janssen. ATC has received consulting fees, research support, and honoraria from AbbVie, ACI Clinical, Aspen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, CSL Behring, Daiichi-Sankyo, GlaxoSmithKline, GLG, Guidepoint Global, Johnson and Johnson, Leo Pharma, Medscape, McKinsey, Navigant, ONO, Pfizer, Portola Pharmaceuticals, Inc, Sanofi, Takeda, Temasek Capital, and TRN.

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Research involving human participants and/or animals For this type of study, formal consent is not required.

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