Common Drug Review
Clinical Review Report

August 2015

Drug	rivaroxaban (Xarelto)
Indication	Treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE
Listing request	Use of Xarelto (15 mg and 20 mg tablets) for the treatment of pulmonary embolism for up to six (6) months.
Manufacturer	Bayer Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in respirology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
CIAC	central independent adjudication committee
CUS	compression ultrasonography
DVT	deep vein thrombosis
INR	international normalized ratio
ITT	intention-to-treat
LMWH	low-molecular-weight heparin
NIM	non-inferiority margin
PE	pulmonary embolism
PP	per protocol
RCT	randomized controlled trial
SAE	serious adverse event
sCT	spiral computed tomography
VKA	vitamin K antagonist
VTE	venous thromboembolism
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two manifestations of venous thromboembolism (VTE), and they share the same predisposing factors.[1] Rivaroxaban is a highly selective, direct factor Xa inhibitor with high oral bioavailability.[2] The recommended dosage is 15 mg administered orally twice daily for three weeks, followed by 20 mg once daily, for the continued treatment of VTE.[2] The duration of therapy should be a minimum of three months; however, it could be extended over a longer period of time if the benefits exceed the risk of bleeding.[2,3]

Indication under review
Treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE
Listing criteria requested by sponsor
Use of XARELTO (15 mg and 20 mg tablets) for the treatment of PE for up to six (6) months

The objective of this report is to perform a systematic review of the beneficial and harmful effects of rivaroxaban 15 mg and 20 mg for the treatment of DVT and/or PE.

Results and Interpretation

Included Studies

Two published, manufacturer-sponsored, open-label, randomized controlled trials (RCTs) were included in this systematic review: EINSTEIN DVT (N = 3,449),[4,5] and EINSTEIN PE (N = 4,832).[6,7] The two trials evaluated the non-inferiority of rivaroxaban versus an established standard treatment with enoxaparin and a vitamin K antagonist (VKA) for symptomatic recurrent VTE, defined as the composite outcome of recurrent DVT or non-fatal or fatal PE. The non-inferiority margin was based on a meta-analysis of 14 studies that provided four different values of the non-inferiority margin (NIM); these values were hazard ratios ranging from 1.54 to 2.00, depending on the calculation method. The manufacturer used the most liberal value estimated from the meta-analysis and did not specify any clear justification for the choice of this NIM.[8] A review of the basis of this estimate revealed some discrepancies in data and methods used for the NIM estimation; the revision of these issues led to an estimated NIM that ranged from 1.49 to 2.28, depending on the calculation method. Other outcomes included health care resources utilization and clinically relevant bleeding.

Efficacy

The overall incidence of death was similar for rivaroxaban and enoxaparin/VKA; the differences between the two groups did not reach statistical significance in the individual trials.

Results from EINSTEIN DVT met the pre-specified and the revised NIMs with an observed hazard ratio of [redacted] ([redacted] in the PP population; results were similar for the intention-to-treat [ITT] analysis). On the other hand, results from EINSTEIN PE trial met the pre-specified and the revised NIMs based on the arithmetic scale; the trial failed to meet the revised margins when they were estimated on the geometric scale. The observed hazard ratio was [redacted] ([redacted] in the PP population; results were similar for ITT).

Hospitalization and length of hospitalization were reported in the EINSTEIN trials as part of the health care utilization assessment. [redacted] These differences were not tested statistically.

Harms

The overall incidence of adverse events, serious adverse events, and withdrawals due to adverse events during the EINSTEIN trials did not differ significantly between rivaroxaban and enoxaparin/VKA, and were not higher than would be expected in this patient population in clinical practice.

Clinically relevant bleeding was the primary safety outcome and was defined as a composite of major and clinically relevant non-major bleeding. In both trials, results were similar between treatment groups for this composite outcome. Results for major bleeding events varied for the two trials; in the EINSTEIN DVT trial (rivaroxaban: 14 [0.8%] versus enoxaparin/VKA: 20 [1.2%]); however, in the EINSTEIN PE trial, major bleeding events were significantly lower with rivaroxaban than with comparator treatment (26 [1.1%] versus 52 [2.2%]).

Pharmacoeconomic Summary

Rivaroxaban (Xarelto) is available as 15 mg and 20 mg tablets. The manufacturer has priced rivaroxaban at $2.84 per tablet regardless of strength (flat pricing), or at $5.68 daily (days 1 to 21) and $2.84 daily (day 22 onward). The manufacturer assumed equal efficacy and harms compared with low-molecular-weight heparins plus VKA (based on the EINSTEIN PE trial) and submitted a cost-minimization analysis. It considered treatment regimens used in the EINSTEIN PE trial and treatment durations of three, six, and 12 months. The manufacturer concluded that rivaroxaban is cost saving at three and six months, with results driven by the lower monitoring costs for rivaroxaban. However, given that the cost of rivaroxaban is significantly greater than that of VKA, for longer treatment duration of ≥ 12 months (indicated for a considerable proportion of patients), rivaroxaban is more costly.

Conclusions

The review included two open-label RCTs, EINSTEIN DVT and EINSTEIN PE. The two trials compared the anticoagulation effects of rivaroxaban and enoxaparin/VKA for the treatment and prevention of recurrence of DVT and/or PE. Overall survival in the two trials showed similar incidence of all-cause mortality between the two study treatments. The EINSTEIN DVT trial showed that rivaroxaban was non-inferior to enoxaparin and a VKA for the treatment of DVT in patients without symptomatic PE. However, although rivaroxaban was found to be non-inferior to enoxaparin/VKA in the treatment and prevention of recurrent VTE based on the pre-specified NIM for EINSTEIN PE, there is uncertainty around the NIM used. CADTH Common Drug Review re-evaluation of the margin suggests a tighter and more conservative one than that used in EINSTEIN PE. Rivaroxaban appeared similar to enoxaparin/VKA with respect to clinically relevant harms outcomes such as bleeding and serious adverse events. The incidence of adverse events did not differ significantly between treatment groups in either trial.

TABLE 1: SUMMARY OF RESULTS

Outcome	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
All-cause death, ITT				
n/N (%)	38/1,731 (2.2)	49/1,718 (2.9)	58/2,419 (2.7)	50/2,413 (2.1)
Hazard ratio (95% CI)	0.67 (0.44 to 1.02)		1.13 (0.77 to 1.65)	
Symptomatic recurrent VTE (composite of recurrent DVT or non-fatal or fatal PE – primary efficacy outcome), PP				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]	
Symptomatic recurrent VTE (composite of recurrent DVT or non-fatal or fatal PE – primary efficacy outcome), ITT				
n/N (%)	36/1,731 (2.1)	51/1,718 (3.0)	50/2,419 (2.1)	44/2,413 (1.8)
Hazard ratio (95% CI)	0.68 (0.44 to 1.04)		1.12 (0.75 to 1.68)	
Symptomatic recurrent VTE: 3-month treatment durations, ITT				
n/N (%)	5/208 (2.4)	3/203 (1.5)	6/127 (4.7)	2/122 (1.6)
Hazard ratio (95% CI)	[redacted]		[redacted]	
Symptomatic recurrent VTE: 6-month treatment durations, ITT				
n/N (%)	25/1,083 (2.3)	29/1,083 (2.7)	27/1,387 (1.9)	24/1,387 (1.7)
Hazard ratio (95% CI)	[redacted]		[redacted]	
Symptomatic recurrent VTE: 12-month treatment durations, ITT				
n/N (%)	6/440 (1.4)	19/432 (4.4)	17/905 (1.9)	18/904 (2.0)
Hazard ratio (95% CI)	[redacted]		[redacted]	
Safety results				
Withdrawals; Total/N (%)	298/1,731 (17.2)	338/1,718 (19.7)	258/2,419 (10.7)	297/2,413 (12.3)
WDAEs; n/N (%)	85/1,718 (4.9)	81/1,711 (4.7)	123/2,412 (5.1)	99/2,405 (4.1)
SAEs; n/N (%)	207/1,718 (12.0)	233/1,711 (13.6)	504/2,412 (20.9)	497/2,405 (20.7)
AEs; n/N (%)	1,078/1,718 (62.7)	1,080/1,711 (63.1)	1,937/2,412 (80.3)	1,901/2,405 (79.0)
First major/clinically relevant non-major bleeding				
n/N (%)	139/1,718 (8.1)	138/1,711 (8.1)	249/2,412 (10.3%)	274/2,405 (11.4%)
Major bleeding only				
n/N (%)	14/1,718 (0.8)	20/1,711 (1.2)	26/2,412 (1.1%)	52/2,405 (2.2%)

AEs = adverse events; CI = confidence interval; DVT = deep vein thrombosis; ITT = intention-to-treat; PE = pulmonary embolism; PP = per protocol; SAEs = serious adverse events; VKA = vitamin K antagonist; VTE = venous thromboembolic event; WDAEs = withdrawal due to adverse events.

1. INTRODUCTION

1.1 Disease Prevalence/Incidence

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two manifestations of venous thromboembolism (VTE), and they share the same predisposing factors.[1] It is believed that PE can be a consequence of DVT.[1] Among patients with proximal DVT, about 50% have an associated asymptomatic PE found on lung scans.[1,9] Reciprocally, in about 70% of patients with PE, DVT is found in the lower limbs if sensitive diagnostic methods are used.[1,10,11]

Venous thromboembolism is the third most common cardiovascular disease worldwide.[12] The manufacturer provided estimates of the incidence of PE in Canada; based on information from the Régie de l'assurance maladie du Québec (RAMQ), the incidence of first definite or probable PE event is 4.5/10,000 person-years.[13] Based on this, it was estimated that there are 15,700 annual incident cases of PE across Canada. This compares with approximately 27,000 annual incident cases of DVT in Canada.[13]

The etiopathology of VTE can be interpreted as an interaction between patient-related and setting-related risk factors.[1,14,15] High to moderate risk factors related to immobilization or setting include lower limb fractures, hip or knee replacement, major general surgery or trauma, spinal cord injury, central venous lines, and chemotherapy.[1,16] Patient-related risk factors include obesity, chronic heart or respiratory failure, hormone replacement therapy, malignancy, oral contraceptive therapy, paralytic stroke, pregnancy, previous VTE, and thrombophilia.[1,16,17] Of note, the risk of VTE increases exponentially with age; for example, the annual incidence at ages below 40 years is 1/10,000, and it rises to 1/1,000 and 1/100 for the age ranges 60 to 69 years and above 80 years, respectively.[17] PE can be classified as primary or secondary according to the absence or presence of predisposing factors that are common with VTE.[1]

Signs and symptoms of DVT include unilateral leg pain, swelling, tenderness, increased temperature, pitting edema, and prominent superficial veins.[17] The clinical presentation of PE is composed of non-specific signs and symptoms. These signs may include dyspnea, chest pain, cough, hemoptysis, and syncope. Also, the clinical signs may include tachypnea, tachycardia, hypotension, raised jugular venous pressure signs of DVT, focal signs in chest, fever, and cyanosis.[1,17]

When VTE is suspected, the clinical probability of PE and/or DVT can be evaluated by using clinical decision rules.[17] These rules rely mainly on the clinical presentation and the predisposing factors of VTE. The revised Geneva score and the revised Wells score are examples of validated decision tools to assess the probability of PE and DVT, respectively.[1,17-20] The results of this initial assessment dictate the diagnostic strategy.[17] Confirmation of the diagnosis can be obtained by computed tomography pulmonary angiogram, in the case of PE, and contrast venography and ultrasound examination, for DVT.[1,17]

Mortality and morbidity following PE are primarily due to hemodynamic interruption in the pulmonary arterial bed.[1] Pulmonary embolism might increase pulmonary vascular resistance to a level of afterload that cannot be matched by the right ventricle. Therefore, death may occur as a result of electromechanical dissociation.[1,21] In patients presenting with syncope and/or systemic hypotension, death might also occur as a result of right ventricular failure.[1,22] Among patients with suspected PE, mortality risk can be stratified into high or low based on the occurrence of syncope and/or systemic hypotension, right ventricular dysfunction, and myocardial injury.[1]

1.2 Standards of Therapy

Resuscitation is the mainstream therapy in the acute phase of suspected PE; this includes respiratory and hemodynamic support.[23] Empiric anticoagulation should be started as soon as possible when PE is highly suspected from the clinical presentation and patient's medical history.[23] If PE diagnosis is confirmed, anticoagulants should be continued. The objective of the anticoagulation therapy is to prevent mortality by preventing recurrent PE.[20] In the case of DVT, anticoagulant treatment aims to prevent further extension of the thrombus, which could eventually travel to the lung and progress to acute PE.[24] Other objectives are to avoid the recurrence of DVT and to preclude the development of complications.[24]

Initial anticoagulation for DVT and PE, is achieved with parenteral treatment options, including low-molecular-weight heparins (LMWHs) or fondaparinux, both of which are recommended over unfractionated heparin.[3] However, oral treatment options are usually preferred for the extended treatment of VTE.[3,24] The American College of Chest Physicians 2012 clinical practice guideline[3] recommends the use of an oral vitamin K antagonist (VKA), such as warfarin, initiated at the same time as parenteral therapy because of VKAs' delayed onset of action. The two treatments should overlap for a minimum of five days or until the international normalized ratio (INR) results reach the target value of 2.0 to 3.0.[3] Afterward, warfarin alone should be maintained for a minimum of three months; however, extending anticoagulant therapy beyond that may prove beneficial for patients with persistent risk factors or experiencing recurrent or unprovoked idiopathic VTE.[3] Although it is widely used, warfarin is the source of various concerns, especially considering its narrow therapeutic window of adequate coagulation without bleeding, as well as its highly variable dose-response relation among individuals and numerous interactions with food and other drugs.[25-27] As a result, frequent monitoring is required. In patients unable or unwilling to use warfarin, extended anticoagulation with LMWH is expected to provide similar effectiveness without increasing the risk of bleeding.[24]

1.3 Drug

Rivaroxaban is a highly selective, direct factor Xa inhibitor with high oral bioavailability.[2] Activation of factor Xa has a key role in the cascade of blood coagulation by converting prothrombin to thrombin.[2] Therefore, inhibition of this pathway prevents thrombin generation and thrombus development.

In Canada, rivaroxaban is indicated for:

- prevention of VTE in patients who have undergone elective total hip replacement or total knee replacement surgery
- treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE
- prevention of stroke and systemic embolism in patients with atrial fibrillation in whom anticoagulation is appropriate.[2]

The recommended dosage is 15 mg administered orally twice daily for three weeks, followed by 20 mg once daily for the continued treatment of VTE.[2] The duration of therapy should be a minimum of three months; however, it could be extended over a longer period if the benefits exceed the risk of bleeding.[2,3] For example, treatment for three months is recommended in patients experiencing a first episode of DVT and or PE secondary to transient risk factors, while treatment for six months is recommended in patients with a first episode of idiopathic VTE.[2] Longer duration of therapy should be based on permanent risk factors and risk/benefit of longer-term treatment. Rivaroxaban 15 mg and 20 mg tablets should be taken with food because of reduced absorption under fasting conditions.[2]

Indication under review
Treatment of VTE (deep vein thrombosis [DVT] and pulmonary embolism [PE]) and prevention of recurrent DVT and PE
Listing criteria requested by sponsor
Use of Xarelto (15 mg and 20 mg tablets) for the treatment of PE for up to six months

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of rivaroxaban 15 mg and 20 mg for the treatment of pulmonary embolism and/or DVT.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with confirmed PE and/or DVT Subgroups: • intended treatment duration • cancer versus non-cancer status • age • renal function
Intervention	Rivaroxaban 15 mg b.i.d. for the first three weeks and 20 mg q.d. thereafter for at least 3 months
Comparators	Heparins[a] plus VKA Fondaparinux plus VKA LMWH alone
Outcomes	**Key efficacy outcomes:** Survival rate Recurrent PE and or DVT Quality of life Length of hospitalization Post-thrombotic syndrome Degree of pulmonary reperfusion Pulmonary hypertension **Harms outcomes:** SAEs, WDAEs, and AEs **Adverse events of interest:** Bleeding (major and minor), and hospitalization due to bleeding Heparin-induced thrombocytopenia Liver function
Study Design	Published and unpublished RCTs

AE = adverse event; b.i.d. = twice daily; q.d. = once daily; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Unfractionated heparin (intravenously or subcutaneously administered) or low-molecular-weight heparin.

Supplemental Issues

- Evaluation of the non-inferiority margin (NIM) used in the EINSTEIN PE trial
- Summary of EINSTEIN DVT extension trial

The literature search was performed by an information specialist using a peer-reviewed literature search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings (MeSH), and keywords. The main search concepts were Xarelto, rivaroxaban, venous thromboembolism, DVT, and PE.

No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on June 12, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on October 16, 2013. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical trial registries, and professional associations. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in Appendix 3.

3. RESULTS

3.1 Findings From the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

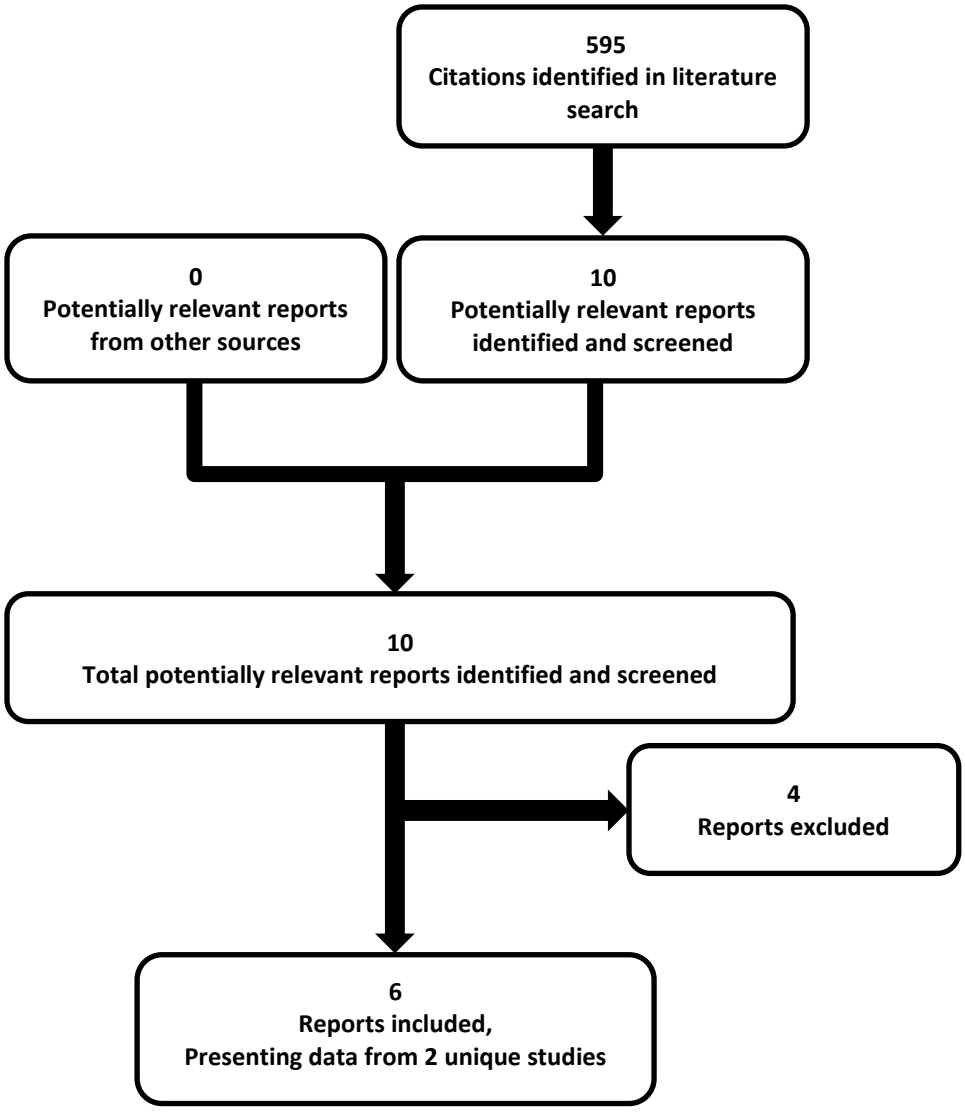


TABLE 3: DETAILS OF INCLUDED STUDIES

		EINSTEIN DVT	EINSTEIN PE
DESIGNS & POPULATIONS	**Study design**	Multi-centre, randomized, open-label, parallel-group, active controlled, event-driven non-inferiority study; central independent adjudication committee for suspected clinical outcomes was blinded to treatment allocation	
	Locations	Approximately 300 centres worldwide in more than 30 countries including US, Canada, Australia, and countries from western and eastern Europe, Asia, and Africa	
	Randomized (N)	3,449 patients	4,832 patients
	Inclusion criteria	Confirmed proximal DVT without symptomatic PE	Confirmed acute symptomatic PE with or without symptomatic DVT
	Exclusion criteria	• Thrombectomy, insertion of a caval filter, or use of a fibrinolytic drug to treat the current thrombotic episode • Treatment with therapeutic dosages of heparin, LMWH, or fondaparinux for more than 48 hours pre-randomization, or more than a single dose of VKA pre-randomization • Creatinine clearance < 30 mL/min • Active bleeding or high risk of bleeding, contraindicating treatment with enoxaparin or VKA, as well as any other contraindication listed in the local labelling of warfarin, acenocoumarol, or enoxaparin	
DRUGS	**Intervention**	Rivaroxaban 15 mg b.i.d. for 3 weeks, followed by 20 mg q.d. P.O.	
	Comparator(s)	Enoxaparin 1 mg/kg b.i.d. SC VKA (acenocoumarol or warfarin) INR 2.0-3.0 P.O.	
DURATION	**Phase:**		
	Active treatment	3, 6, or 12 months	
	Follow-up	30 days	
OUTCOMES	**Primary end point**	Recurrent VTE, i.e., the composite of recurrent DVT or non-fatal or fatal PE	
	Other end points	• Composite of the primary efficacy outcome and all deaths • Health care resources utilization • Net clinical benefit as composite of the primary efficacy outcome and major bleeding events • Individual components of the primary and secondary efficacy outcome	
NOTES	**Publications**	The EINSTEIN Investigators 2010,[5] Buller et al. 2008,[28] and the Clinical Study Report[4]	Buller et al. 2012,[6] Van Es et al. 2013[29] and the Clinical Study Report[7]

b.i.d. = twice daily; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; P.O. = oral administration; q.d. = once daily; SC = subcutaneously; VKA = vitamin K antagonist; VTE = venous thromboembolic event.

3.2 Included Studies

3.2.1 Description of studies

EINSTEIN DVT and EINSTEIN PE trials were two multi-centre, randomized, open-label, parallel-group, active controlled, event-driven non-inferiority studies with a treatment duration of three, six, or 12 months.

The primary objective of the two EINSTEIN trials was to evaluate whether rivaroxaban is at least as effective as enoxaparin/VKA in the treatment of patients with acute symptomatic VTE and in the prevention of its recurrence.

The main difference between the two trials was that the EINSTEIN DVT trial evaluated rivaroxaban in patients who had symptomatic DVT without symptomatic PE, while the EINSTEIN PE trial was concerned with patients who had PE with or without symptomatic DVT.

In both trials, allocation was stratified by country and by the intended treatment duration.

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients were eligible for inclusion in the EINSTEIN PE trial if they presented with symptomatic PE and/or DVT. The PE diagnosis criteria included the following:

- an intraluminal filling defect in segmental or more proximal branches on spiral computed tomography (sCT) scan
- an intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on pulmonary angiogram
- a perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy
- inconclusive sCT, pulmonary angiography, or lung scintigraphy results, with demonstration of DVT in the lower extremities by compression ultrasound (CUS) or venography.

On the other hand, the EINSTEIN DVT trial included patients with symptomatic proximal DVT only, and no symptomatic PE. In both trials, the diagnosis of DVT was based on the following criteria:

- a non-compressible proximal vein on CUS
- an intraluminal filling defect in the proximal veins on venography.

In addition to the exclusion criteria in Table 3, patients were excluded if they used VKA for indications other than PE or DVT, had significant liver disease (e.g,. acute hepatitis, chronic active hepatitis, cirrhosis) or an alanine transaminase level more than three times the upper limit of normal, suffered from bacterial endocarditis, or used strong CYP3A4 inhibitors (e.g., HIV protease inhibitors, systemic ketoconazole) or strong CYP3A4 inducers such as rifampicin. Patients were also excluded if they had a life expectancy of less than three months or severe hypertension; women of child-bearing age without proper contraceptive measures, and women who were pregnant or breast feeding were also excluded.

b) Baseline characteristics

A summary of the baseline characteristics for both trials is presented in Table 4 and Table 5. Baseline characteristics were balanced between treatment groups in the included trials. The mean age was 57 years; the EINSTEIN PE trial included more patients older than 75 years (17%) than the EINSTEIN DVT trial (13%). The mean weight was around 82 kg, while approximately 30% of patients had a body mass index ≥ 30 kg/m^2. Caucasian was the major ethnic group.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	EINSTEIN-DVT[4,5]		EINSTEIN PE[6,7]	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413
Sex, n (%)				
Male	993 (57.4)	967 (56.3)	1,309 (54.1)	1,247 (51.7)
Age (years)				
Mean (SD)	55.8 (16.4)	56.4 (16.3)	57.9 (17.3)	57.5(17.2)
< 65 years, n (%)	1,145 (66.1)	1,111 (64.7)	1,461 (60.4)	1,479 (61.3)
65 to < 75 years, n (%)	371 (21.4)	382 (22.2)	517 (21.4)	532 (22.0)
≥ 75 years, n (%)	215 (12.4)	225 (13.1)	441 (18.2)	402 (16.7)
Weight (kg)				
Weight (kg), Mean (SD)	82.1 (18.4)	81.6 (18.9)	82.9(19.2)	83 (18.8)
BMI < 25, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
BMI 25 to < 30, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
BMI ≥ 30, n (%)	511 (29.5)	484 (28.2)	741 (30.6)	755 (31.3)
Race, n (%)				
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]

BMI = body mass index; DVT = deep vein thrombosis; PE = pulmonary embolism; SD = standard deviation; VKA = vitamin K antagonist.

The majority of the included patients had normal renal function (i.e., creatinine clearance ≥ 80 mL/min) in both trials; about 7% of patients had creatinine clearance < 50 mL/min. Spontaneous VTE was reported in > 60% of the DVT trial population and in > 64% of the PE trial. The main reasons reported for provoked VTE were recent surgery/trauma, immobilization, and use of estrogen. Previous VTE events were reported in almost 19% of included patients in both trials.

The perfusion score was recorded in the PE trial as an indicator for severity; a score of 0 indicates perfusion defect in all lung lobes, and 1 means no perfusion defect. Almost 71% of the trial patients had a perfusion score above 0.75.

TABLE 5: BASELINE MEDICAL HISTORY AND DIAGNOSIS

Clinical Characteristic or History	EINSTEIN DVT[4,5]		EINSTEIN PE[6,7]	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N =2,413
Creatinine clearance, n (%)				
Missing data	24 (1.4)	20 (1.2)	16 (0.7)	10 (0.4)
< 30 mL/min	6 (0.3)	9 (0.5)	4 (0.2)	2 (< 0.1)
30 to < 50 mL/min	115 (6.6)	120 (7.0)	207 (8.6)	191 (7.9)
50 to < 80 mL/min	393 (22.7)	399 (23.2)	637 (26.3)	593 (24.6)
≥ 80 mL/min	1,193 (68.9)	1,170 (68.1)	1,555 (64.3)	1,617 (67.0)
Perfusion score [a], %				
Missing data	NA		[redacted]	[redacted]
Mean %, (SD)			[redacted]	[redacted]
< 0.75%, n (%)			[redacted]	[redacted]
≥ 0.75%, n (%)			[redacted]	[redacted]
Cause of initial VTE, n (%)				
Spontaneous	1,055 (60.9)	1,083 (63.0)	1,566 (64.7)	1,551 (64.3)
Secondary DVT/PE	676 (39.1)	635 (37.0)	853 (35.3)	862 (35.7)
Recent surgery/ trauma	338 (19.5)	335 (19.5)	415 (17.2)	398 (16.5)
Immobilization	265 (15.3)	260 (15.1)	384 (15.9)	380 (15.7)
Estrogen therapy	140 (8.1)	115 (6.7)	207 (8.6)	223 (9.2)
Puerperium	6 (0.3)	11 (0.6)	6 (0.2)	5 (0.2)
Active cancer	118 (6.8)	89 (5.2)	114 (4.7)	109 (4.5)
Risk factors, n (%)				
Previous DVT/PE	336 (19.4)	330 (19.2)	455 (18.8)	489 (20.3)
Known thrombophilic condition	107 (6.2)	116 (6.8)	138 (5.7)	121 (5.0)

DVT = deep vein thrombosis; NA = not applicable; PE = pulmonary embolism; SD = standard deviation; VKA = vitamin K antagonist; VTE = venous thromboembolism.

[a] Perfusion score = 0 means perfusion defect in all lung lobes, perfusion score = 1 means no perfusion defect at all.

3.2.3 Interventions

In both trials, patients were treated for a duration of three, six, or 12 months. The decision concerning the duration of anticoagulation was based on the risk profile of the patient and on local treatment guidelines, and was made by the investigator at the time of randomization. Risk factors that were taken into consideration included active cancer, previous episodes of DVT/PE, and known thrombophilic conditions.[5] Patients' assignment to one of the three treatment periods varied between the two trials. In the DVT trial, 12% of patients were assigned to the three-month, 60% to the six-month, and 25% to the 12-month group. In the PE trials, the distribution was 5%, 57%, and 37%, respectively (Table 6).

Pre-randomization treatment with any anticoagulant was allowed for a maximum duration of 48 hours. However, only a single pre-randomization dose of VKA was allowed. Table 6 summarizes the pre-randomization treatments. As a result, 72% of patients in the DVT trial and 92% in the PE trial received pre-randomization treatment with LMWH, unfractionated heparin, or fondaparinux. The length of pre-randomization treatment varied between the two trials. In the DVT trial, about 67% of patients received the pre-medication for one day and 4% received it for two days, whereas in the PE trial, 72% of the

patients received it for one day and 19% received for two days. There were no differences between treatment groups within each study.

The time elapsed from the VTE event to randomization was higher in the DVT trial (10.5 days) compared with the PE trial (8.7 days) (Table 6). After randomization, patients allocated to the rivaroxaban group received rivaroxaban 15 mg twice daily for three weeks, followed by rivaroxaban 20 mg once daily. Patients allocated to the comparator group received enoxaparin twice daily for at least five days in combination with VKA (overlap four to five days) and continued with VKA only after the INR had been ≥ 2.0 for two consecutive measurements at least 24 hours apart. Warfarin and acenocoumarol were allowed as VKAs. The actual treatment durations are presented in Table 11 in Appendix 4 and are summarized in the Patient Disposition section.

TABLE 6: PRE-RANDOMIZATION TREATMENT

	EINSTEIN DVT[4,5]		EINSTEIN PE[6,7]	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N =2,413
Pre-randomization treatment (LMWH or heparin or fondaparinux), n (%)				
No treatment	467 (27.0)	505 (29.0)	182 (7.5)	190 (7.9)
Treatment given	1,264 (73.0)	1,213 (71.0)	2,237 (92.5)	2,223 (92.1)
Duration of pre-randomization treatment (LMWH or heparin or fondaparinux), n (%)				
1 day	1,192 (68.9)	1,139 (66.3)	1,754 (72.5)	1,760 (72.9)
2 days	68 (3.9)	67 (3.9)	460 (19.0)	443 (18.4)
> 2 days	4 (0.2)	7 (0.4)	23 (1.0)	20 (0.8)
Days; mean (SD)	0.8 (1.0)	0.8 (0.6)	1.1 (0.6)	1.1 (0.5)
Duration of pre-randomization treatment with VKA, Days				
No initial treatment; n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Days; mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Duration from index event (DVT or PE) to randomization, Days				
Missing data, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Intended treatment duration, n (%)				
3 months	208 (12.0)	203 (11.8)	127 (5.3)	122 .1)
6 months	1,083 (62.6)	1,083 (63.0)	1,387 (57.3)	1,387 (57.5)
12 months	440 (25.4)	432 (25.1)	905 (37.4)	904 (37.5)

DVT = deep vein thrombosis; PE = pulmonary embolism; SD = standard deviation; VKA = vitamin K antagonist; VTE = venous thromboembolism.

3.2.4 Outcomes

a) Efficacy

The primary efficacy outcome in both trials was symptomatic recurrent VTE, defined as the composite of recurrent DVT or non-fatal or fatal PE. In addition to the fixed-interval contacts with the two trial sites, patients were informed about the sign and symptoms of efficacy and safety events, and they were instructed to immediately contact the study site if these occurred. The events for primary efficacy and safety outcomes were evaluated by a central, blinded, independent adjudication committee (CIAC). Definitions used by the CIAC for the primary outcome events are reported in Appendix 6. All confirmed

events were considered up to one month after the intended duration of treatment, irrespective of the actual treatment duration. Secondary outcomes in both trials included the composite of recurrent DVT, non-fatal PE, and all-cause mortality. Net clinical benefit was another secondary outcome that was defined as the composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome) and major bleeding events. A post hoc analysis evaluated a modified net clinical benefit, defined as the composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome), major bleeding events, cardiovascular deaths, myocardial infarctions, strokes, and non-central nervous system systemic embolisms.

b) Safety

Clinically relevant bleeding was the primary safety outcome and was defined as the composite of major or clinically relevant non-major bleeding. If a patient had more than one event within the time window for a composite outcome, only the first event was counted and displayed among the components.

A bleeding event was considered major if it was clinically overt and accompanied by at least one of the following:

- a fall in hemoglobin level of 20 g/L (2 g/dL) or more
- transfusion of two or more units of packed red blood cells or whole blood
- bleeding that was retroperitoneal, intracranial, occurred in a critical site or contributed to death.

Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with at least one of the following:

- medical intervention or unscheduled contact with a physician
- interruption or discontinuation of study treatment
- bleeding associated with any other discomfort (e.g., pain or impairment of activities of daily life).

An adverse event (AE) was defined as any untoward medical occurrence in a patient who had been administered a pharmaceutical product.

3.2.5 Statistical analysis

a) Efficacy criteria

The primary efficacy analysis was based on the time to the first event of the composite primary efficacy outcome during the intended treatment period or the one-month observation period. A Cox proportional hazards model was used for the analysis, with intended treatment duration as stratum, adjusted for the baseline presence of cancer. To demonstrate non-inferiority, the manufacturer intended to maintain at least 66% of the difference between the proven efficacy of standard therapy versus placebo, no treatment, or "less effective" treatments.[8] Prins and Lensing conducted a meta-analysis in order to support the estimation of the NIM,[8] and they identified 14 studies. Based on this meta-analysis, four different values of the NIM were reported; these values were provided in terms of hazard ratios that ranged from 1.54 to 2.00, depending on the calculation method. The manufacturer used the most liberal value estimated from the meta-analysis and did not specify any clear justification why this NIM was used.[8]

The trial size was based on the assumption of equal efficacy and on the requirement for a total of 88 events to give a power of 90% to demonstrate the non-inferiority of rivaroxaban over a standard therapy consisting of enoxaparin and a VKA at a two-sided alpha level of 0.05.[5,6] With an estimated 3% incidence for the primary outcome, the trial needed to enrol a total of approximately 3,000 patients.[5,6] If the planned number of events were reached before all patients had completed the intended treatment duration, the study would be stopped and the remaining patients would be treated to reach the intended treatment duration, but only up to a maximum of six months.

b) Analysis populations

Analyses were performed using the intention-to-treat (ITT) population, with an additional supportive analysis using the per protocol (PP) population. In non-inferiority trials, ITT analysis tends to bias the results toward non-inferiority and, therefore, is not considered a conservative approach. The PP analysis, however, is composed of a selected group of patients, which may provide a partial perspective and result in bias in either direction.[30] Both PP and ITT analyses should be reported and should have equal importance in drawing a conclusion.[31] In the EINSTEIN trials, patients who discontinued study drug prematurely were to be followed until the end of the intended treatment period and included in the ITT analysis.

The ITT population consisted of all randomized patients; patients were analyzed according to the assigned treatment group. On the other hand, the PP population consisted of all randomized patients without any major deviation from the protocol. Reasons for exclusion from the PP population included baseline VTE not confirmed by the CIAC, not receiving the allocated treatment, and inadequate compliance with the study treatment.

The safety population consisted of all randomized patients who received at least one dose of study drug and were analyzed according to the treatment actually received.

3.3 Patient Disposition

Patient disposition is summarized in Table 7. A total of 3,449 patients in the EINSTEIN DVT and 4,832 patients in the EINSTEIN PE trial were randomized. Premature discontinuation was higher in the DVT trial than in the PE trial; discontinuation on rivaroxaban was 17.2% and 10.7% and on enoxaparin/VKA was 19.7% and 12.3% in DVT and PE trials, respectively. These were similar between treatment groups, and also similar in terms of reason for discontinuation. However, twice as many patients withdrew consent in the enoxaparin/VKA treatment groups than in the rivaroxaban groups (4.5% versus 2.1% and 4.9% versus 2.7% in the DVT and PE trials, respectively).

TABLE 7: SUMMARY OF PATIENT DISPOSITION

	EINSTEIN DVT[4,5]		EINSTEIN PE[6,7]	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
Screened, N	3,459		3,459	
Randomized, N (%)	1,731 (100)	1,731 (100)	2,419 (100)	2,413 (100)
Received study medication, n (%)	1,724 (99.6)	1,724 (99.6)	2,412 (99.7)	2,405 (99.7)
Discontinued, n (%)	298 (17.2)	298 (17.2)	258 (10.7)	297 (12.3)
AEs	74 (4.3)	74 (4.3)	111 (4.6)	92 (3.8)
Consent withdrawal	36 (2.1)	36 (2.1)	66 (2.7)	118 (4.9)
Clinical end point reached[a]	[redacted]	[redacted]	[redacted]	[redacted]
Death	19 (1.1)	19 (1.1)	Data not available	
Lost to follow-up	12 (0.7)	12 (0.7)		
Non-compliance with treatment	[redacted]	[redacted]	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]	[redacted]	[redacted]
Terminated by sponsor[b]	[redacted]	[redacted]	Data not available	
ITT, N (%)	1,731 (100)	1,731 (100)	2,419 (100)	2,413 (100)
PP, N (%)	1,525 (88.1)	1,525 (88.1)	2,224 (91.4)	2,238 (92.7)
Safety, N (%)	1,718 (99.2)	1,718 (99.2)	2,412 (99.7)	2,405 (99.7)

AE = adverse event; DVT = deep vein thrombosis; ITT = intention-to-treat; PE = pulmonary embolism; PP = per protocol; VKA = vitamin K antagonist.

[a] Patients who have end points are normally censored in survival analysis; however, EINSTEIN trials did not specifically mention that.

[b] After the planned number of events had been reached (pre-specified in the study protocol).

3.4 Exposure to Study Treatments

Table 11, Appendix 4 summarizes the actual study treatments. The majority of patients in both EINSTEIN trials were allocated to the six-month anticoagulation regimen (approximately 63% in the DVT trial and 57% in the PE trial). However, the two trials differed in the percentages of patients assigned to the three-month and 12-month durations (12% and 25% in the DVT trial, respectively, compared with 5% and 37% in the PE trial, respectively). In general, the percentage of patients who had ≥ 80% compliance with the study treatment [redacted]

Table 12, Appendix 4 summarizes the INR compliance in the EINSTEIN trials. Overall, the majority of patients treated with enoxaparin/VKA in both trials had mean INR within the therapeutic range (62.4% in the DVT trial and 63.4% in the PE trial). The percentage of time spent within the therapeutic range was 57.7% in the DVT trial and 62.7% in the PE trial.[4,7]

Table 13, Appendix 4 provides a summary of the concomitant antithrombotic medications in the EINSTEIN trials. [redacted]

[redacted] The reason and impact of this additional anticoagulation was not reported.

3.5 Critical Appraisal

3.5.1 Internal validity

a) Validity of the non-inferiority margin

CDR reviewers retrieved the full published texts of studies included in the Prins and Lensing study[8] and verified the quality of the extracted data and the validity of the meta-analysis calculation methods; Appendix 5 provides a summary of the non-inferiority validation. This review revealed three main issues with the estimated NIM. First, the meta-analysis included five trials in which patients with distal DVT comprised all or a proportion of the trial patients.[32-36] Another trial included patients with unstable angina or arterial ischemia along with VTE patients.[37] The management and outcomes of these patients might not reflect the proximal DVT patients included in the EINSTEIN trials. Second, some discrepancies between the reported recurrence rates and the original articles were found. Finally, the assessment of the meta-analysis calculation method showed that the use of the fixed treatment effects model was not justified, and the random effects model would have been more appropriate given the clinical heterogeneity in the included studies. The use of the corrected data set that excluded patients with non-proximal DVTs and of the random effects model produced NIM estimates that ranged from 1.49 to 1.60 on the geometric scale (on the arithmetic scale, the random effect model produced margins that ranged from 1.75 to 2.28). These margins are considerably lower than the NIM of 2.0 used in the EINSTEIN trials, highlighting uncertainty concerning the margin chosen for the trials. However, in considering such evaluation, one should keep in mind that the EINSTEIN trials were powered based on a NIM of 2.0, and using a lower margin a posteriori may raise further uncertainties concerning the conclusions.

b) Selection, allocation, and disposition of patients

The EINSTEIN trials were open-label non-inferiority trials. No justification was provided as to why a double-blind design was not selected and a double-dummy technique not used to maintain blinding. However, events were evaluated by a CIAC.[4,7] Therefore, the open-label design is unlikely to have influenced outcome measurement.[38]

c) Intervention and comparator

Patients treated with enoxaparin/VKA in the trials spent 58% to 63% of the time within the target INR values of 2.0 to 3.0. Non-optimal INR results obviously affect treatment efficacy and safety in the comparator group, which may bias the results in favour of rivaroxaban. However, this also improves generalizability, since INR values are expected to vary naturally. In discussion with the clinical expert involved in the review, the time spent within the target INR range was consistent with clinical practice.

[redacted] The clinical relevance of this finding and impact on the trials' results are uncertain.

3.5.2 External validity

a) Patient characteristics

Although inclusion and exclusion criteria were generally relevant and reasonable, important sub-populations were excluded from the trial, including patients with a high risk of bleeding or significant renal or hepatic disease. In addition, the two trials included only a small proportion of patients with active cancer, which is a common cause of DVT and an important risk factor for recurrent VTE. For these patients, the treatment of choice is long-term LMWH.[39] Therefore, the findings from EINSTEIN trials are unlikely to be generalizable to these categories of patients.

In EINSTEIN DVT, 25% of patients had a planned treatment duration of 12 months; however, premature discontinuation of study drug lowered the average to 10 months. More than 60% of these patients were treated between nine and 12 months, while only 10% actually reached 12 months of treatment with the study drug. This is an issue, considering that more than 60% of patients in the trial had an unprovoked DVT, for which treatment duration in clinical practice may often be indefinite. The most frequent reason for premature discontinuation was "study terminated by sponsor," which limited treatment duration to six months rather than 12 months for the last included patients. No data are available to compare the benefits and risks of rivaroxaban with those of a standard treatment for more than 12 months, although several patients with irreversible risk factors may require chronic treatment.

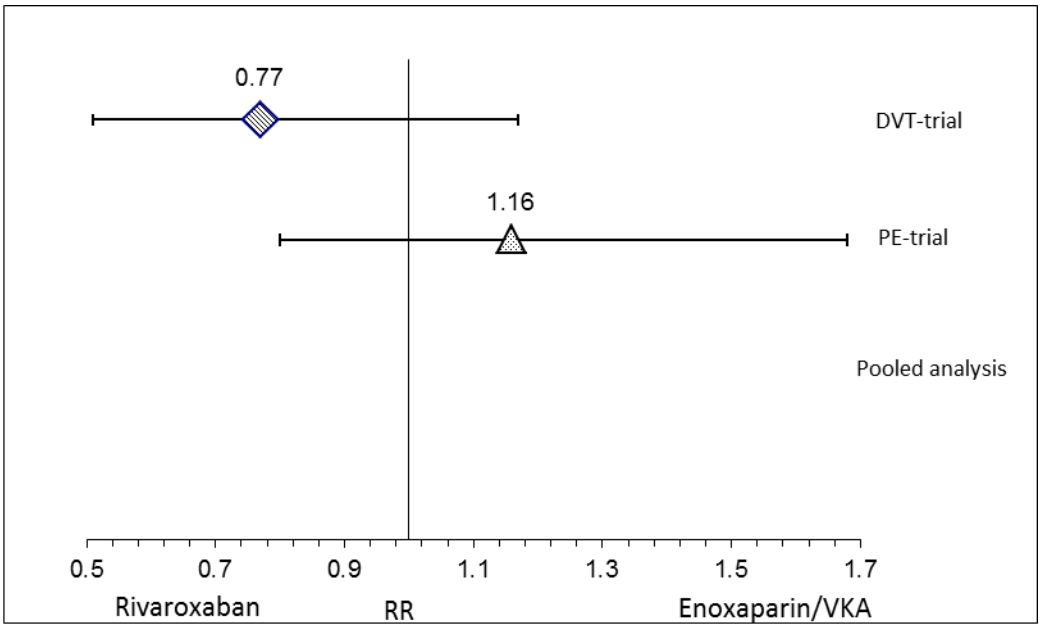
3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (see Section 2.2, Table 2). See Appendix 4: Detailed Outcome Data.

3.6.1 Survival

Mortality rates are summarized in Table 14, Appendix 4 for the ITT population and in Table 15, Appendix 4 for the safety population; Figure 2 presents the relative risks of mortality in each EINSTEIN trial and the trials' pooled results. All-cause mortality and death by cause were reported as part of the composite outcomes in the trials, and individually as secondary outcomes. The EINSTEIN DVT trial recorded numerically fewer all-cause death events in the rivaroxaban group (2.2%) than in the enoxaparin/VKA group (2.9%). In contrast, the EINSTEIN PE trial showed numerically higher incidence of all-cause death in the rivaroxaban group (2.4%) compared with the comparator group (2.1%).

FIGURE 2: PLOT PRESENTATION OF THE RELATIVE RISK OF MORTALITY IN THE EINSTEIN TRIALS



CONFIDENTIAL DATA REGARDING MORTALITY WERE REMOVED FROM FIGURE 2 AT THE MANUFACTURER'S REQUEST.

Subgroup analysis by the intended treatment duration is summarized in Table 16, Appendix 4. vvvvvvv vvv vvvvvvvvvv vvvvvv vvv vvv vvvvvv vvvvvvvv vvvvvv vvvvvvvvvvvv vvvvvvvvvv vvvvvvvv vv vvvvvvvv vvv vvvvvvvvv vv vvv vvvvvvvv vvvv vvvvvvv vvvvvvvvvvv vv vvv vvvvvvv vvvvvvvvv vvvvvvvvv vvv vv vvv vv vvvvv vv vvv vvvvvvvvvv vvvvv vvv vvvvv vvvvvvv vv vvv vvvvvv vvvvvvvv vvvvvv vvvvvv vvv vvv vvvvvvv vvvvvvvvv vvvvvv vvvvv vvvvv vvvvvvvv vvvv vvv vvv vvv vvvvvv vvvvv v vvvvv the change in mortality vvvvvvvv vvvvv vv vvv vvvvvvvv vvvvvvvvv Figure 3 shows the change in mortality incidence based on the treatment durations.

FIGURE 3: TREND OF THE RELATIVE RISK OF MORTALITY BY THE INTENDED TREATMENT DURATION CONTAINED *CONFIDENTIAL DATA AND WAS REMOVED AT THE MANUFACTURER'S REQUEST.*

Morality in the subgroup of patients with active cancer at baseline was reported in the clinical study reports for the trials in terms of hazard ratios only. [redacted] (Table 17, Appendix 4). These results should be interpreted with caution because of the small number of cancer patients included in both studies (Table 5).

Survival rates based on age subgroups or renal function were not reported in either EINSTEIN trial.

3.6.2 Recurrent pulmonary embolism and/or deep vein thrombosis

Recurrence of VTEs was recoded as primary and secondary outcomes. The primary outcome, in both EINSTEIN trials, was the composite of symptomatic recurrent VTE, defined as the composite of recurrent DVT or non-fatal or fatal PE. The secondary recurrent VTE outcome included the individual end points included in the primary outcome, plus all-cause mortality. All confirmed events were considered up to one month after the end of the intended treatment period, irrespective of the actual treatment duration. Results for the primary and secondary recurrence outcomes are summarized in Table 18, Appendix 4 and Table 19, Appendix 4 for the ITT and PP datasets.

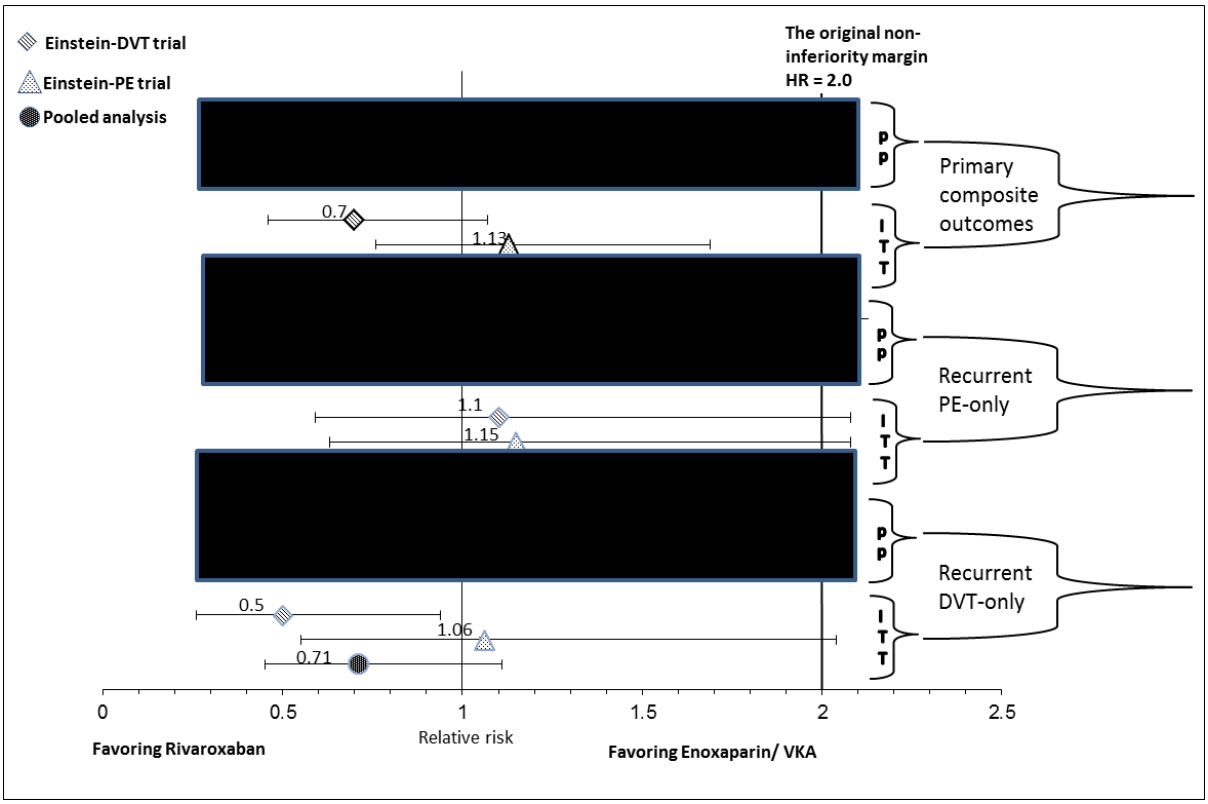
a) Recurrent venous thromboembolism: composite of recurrent deep vein thrombosis or non-fatal or fatal pulmonary embolism

Figure 4 provides a plot summary of the VTE recurrence in the EINSTEIN trials.

Results for the EINSTEIN DVT trial showed that rivaroxaban met the pre-specified NIM of 2.0 for the upper limit of the two-sided 95% CI associated with the observed hazard ratio. This result was consistent in the PP and ITT data; the hazard ratio in the PP data was [redacted] and in the ITT data 0.68 (95% CI, 0.44 to 1.04). In the DVT trial, rivaroxaban was associated with numerically fewer events than enoxaparin/VKA (PP data: 32 [2.1%] versus 46 [2.9%], respectively). In EINSTEIN PE, however, rivaroxaban was associated with numerically more events (38 [1.7%]) than the comparator group (36 [1.6%]); the associated hazard ratio was [redacted] in the PP data and 1.12 (95% CI, 0.75 to 1.68) in the ITT data. The upper limit of the confidence interval was below the pre-specified NIM for the trial.

[redacted]

FIGURE 4: PLOT PRESENTATION OF THE RISK OF VTE RECURRENCE IN THE EINSTEIN TRIALS



CONFIDENTIAL DATA REGARDING VTE RECURRENCE WERE REMOVED FROM FIGURE 4 AT THE MANUFACTURER'S REQUEST.

b) Individual outcomes included in the composite

Death events in both trials are summarized in the Survival section. Events of symptomatic PE only (without symptomatic DVT) occurred at similar rates in the treatment groups in both trials. [redacted] On the other hand, the incidence of symptomatic DVT alone varied in the two trials. The EINSTEIN DVT trial had numerically lower events in the rivaroxaban group (PP dataset: [redacted]) than in the enoxaparin/VKA group [redacted]. In the EINSTEIN PE trial, the two treatment groups showed similar event rates: 0.7% in the rivaroxaban group and 0.6% in the comparator group. [redacted]

c) Subgroup analysis

Table 20, Appendix 4 summarizes the subgroup analyses for the primary composite outcome, recurrent VTE. Only results in the ITT population were reported and presented in the table. Of note, none of the reported subgroups had a statistically significant interaction with the recurrence of VTE.

By intended treatment duration

In both trials, the sample size for patients with a three-month intended treatment duration was small, and a low number of events was observed for the primary efficacy outcome, which limits the conclusion that can be drawn. The majority of patients in the trial had an intended treatment duration of six months. The recurrence incidence among patients in the six-month duration subgroup of EINSTEIN DVT was numerically lower in the rivaroxaban group (2.3%) than in the comparator group (2.7%); the hazard ratio did not reach statistical significance. In the EINSTEIN PE trial, the rivaroxaban group had a slightly higher incidence rate (1.9%) than the comparator (1.7%); the difference did not reach statistical significance. Results for the 12-month treatment duration showed that rivaroxaban was associated with a statistically significantly lower incidence of recurrence (1.4%) than enoxaparin/VKA (4.4%); the hazard ratio was 0.3 (95% CI, 0.12 to 0.75). The EINSTEIN PE trial provided similar incidence rates for the two treatment groups; the difference did not reach statistical significance. [redacted]

Malignancy at baseline

A small number of patients with cancer were included in the two studies, and the recurrence rate in this population was very low. [redacted] Results for non-cancer patients were similar to the overall results of both trials.

Patients' age

[redacted]

Renal function

Both EINSTEIN trials excluded patients with severe renal dysfunction; nevertheless, subgroups based on baseline renal function could be helpful in observing rivaroxaban performance in patients with borderline renal function (i.e., creatinine clearance < 50 mL/min). Both EINSTEIN studies conducted subgroup analyses by baseline renal function (subgroups: < 50 mL/min, 50 to 80 mL/min, and ≥ 80 mL/min). For this subgroup, the differences in recurrence rates between rivaroxaban and the control group did not reach statistical significance.

d) Recurrent venous thromboembolism/all-cause mortality: composite of recurrent deep vein thrombosis or non-fatal or fatal pulmonary embolism

For both trials, results for this composite variable were consistent with those for the primary outcome. [redacted]

3.6.3 Quality of life

Quality of life was not evaluated in the EINSTEIN trials.

3.6.4 Length of hospitalization

Length of hospitalization was reported in the EINSTEIN trials as part of the health care utilization assessment. Results for health care utilization were reported for the ITT population only and are presented in Table 21, Appendix 4.

[redacted]

[redacted]

3.6.5 Post-thrombotic syndrome

Post-thrombotic syndrome was not evaluated in the EINSTEIN PE trial.

3.6.6 Degree of pulmonary reperfusion

Pulmonary reperfusion was not evaluated in the EINSTEIN PE trial.

3.6.7 Pulmonary hypertension

[redacted] Table 8 [redacted]

TABLE 8: INCIDENCE OF PULMONARY HYPERTENSION EVENTS (SAFETY POPULATION)

	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban N = 1,718	Enoxaparin/VKA N = 1,711	Rivaroxaban N = 2,412	Enoxaparin/VKA N = 2,405
Pulmonary hypertension, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

DVT = deep vein thrombosis; PE = pulmonary embolism.

TABLE 9: KEY EFFICACY OUTCOMES

Outcome	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
All-cause death, ITT				
n/N (%)	38/1,731 (2.2)	49/1,718 (2.9)	58/2,419 (2.4)	50/2,413 (2.1)
Hazard ratio (CI)	0.67 (0.44 to 1.02)		1.13 (0.77 to 1.65)	
Symptomatic recurrent VTE (composite of recurrent DVT or non-fatal or fatal PE – Primary efficacy outcome), PP				
n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]	
Symptomatic recurrent VTE: 3-month treatment durations, ITT				
n/N (%)	5/208 (2.4)	3/203 (1.5)	6/127 (4.7)	2/122 (1.6)
Hazard ratio (CI)	[redacted]		[redacted]	
Symptomatic recurrent VTE: 6-month treatment durations, ITT				
n/N (%)	25/1,083 (2.3)	29/1,083 (2.7)	27/1,387 (1.9)	24/1,387 (1.7)
Hazard ratio (CI)	[redacted]		[redacted]	
Symptomatic recurrent VTE: 12-month treatment durations, ITT				
n/N (%)	6/440 (1.4)	19/432 (4.4)	17/905 (1.9)	18/904 (2.0)
Hazard ratio (CI)	[redacted]		[redacted]	
Hospitalization; n/N (%), ITT				
Initial episode	[redacted]	[redacted]	[redacted]	[redacted]
Suspected VTE	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed DVT	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed PE	[redacted]	[redacted]	[redacted]	[redacted]
Duration of hospitalization; mean duration in days, ITT				
Initial episode	[redacted]	[redacted]	[redacted]	[redacted]
Suspected VTE	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed DVT	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed PE	[redacted]	[redacted]	[redacted]	[redacted]

DVT = deep vein thrombosis; ITT = intention-to-treat; PE = pulmonary embolism; PP = per protocol; VKA = vitamin K antagonist; VTE = venous thromboembolic event.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2. Methods).
See Appendix 4: Detailed Outcome Data.

3.7.1 Adverse events

The overall incidence of AEs was similar between treatment groups in the two trials. A total of 62.7% and 80.3% of patients in the rivaroxaban groups experienced at least one treatment-emergent AE compared with 63.1% and 79.0% of patients in the enoxaparin/VKA group in EINSTEIN DVT and EINSTEIN PE, respectively. The most common AEs, in both treatment groups, included nasopharyngitis, headache, epistaxis, pain in extremity, and cough; chest pain was common in both groups in the EINSTEIN PE trial (Table 22, Appendix 4).

3.7.2 Serious adverse events

The incidence of serious adverse events (SAEs) was similar between rivaroxaban and enoxaparin/VKA in EINSTEIN DVT (12.0% versus 13.6%, respectively) and in EINSTEIN PE (20.9% versus 20.7%, respectively). In general, the incidence of individual SAEs was small (< 0.1% of patients). For both treatment groups, the most common SAEs (Medical Dictionary for Regulatory Activities [MedDRA] terms) were cardiac disorders, gastrointestinal disorders, infections and infestations, respiratory disorders, and neoplasms (Table 23, Appendix 4). Of note, these SAEs occurred more frequently in the EINSTEIN PE trial than in the EINSTEIN DVT trial.

3.7.3 Withdrawals due to adverse events

Table 24, Appendix 4 summarizes withdrawals due to adverse events (WDAEs).

Overall, the rate of WDAEs was low and similar between rivaroxaban and enoxaparin/VKA groups (4.9% versus 4.7% in EINSTEIN DVT and 5.1% versus 4.1% in EINSTEIN PE, respectively).

3.7.4 Bleeding and hospitalization due to bleeding

Table 25, Appendix 4 presents the rates of confirmed bleeding events.

Treatment-emergent clinically relevant bleeding was the primary safety outcome in both trials, and it was defined as the composite of major or clinically relevant non-major bleeding. Only the first event for each patient was counted. For this outcome, results were similar between treatment groups in EINSTEIN DVT (8.1% in both groups). For EINSTEIN PE, rivaroxaban had a numerically lower incidence rate (10.3%) than enoxaparin/VKA (11.4%).

A total of five fatal bleeding events were reported for rivaroxaban in both trials combined, as compared with eight events in the enoxaparin/VKA group.

TABLE 10: HARMS

	EINSTEIN DVT		EINSTEIN PE	
AEs	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
Patients with > 0 AEs, N (%)	1,078 (62.7)	1,080 (63.1)	1,937 (80.3)	1,901 (79.0)
Most common AEs (> 5%), N (%)				
Nasopharyngitis	93 (5.4)	84 (4.9)	181 (7.5)	189 (7.9)
Headache	91 (5.3)	68 (4.0)	193 (8.0)	174 (7.2)
Epistaxis	89 (5.2)	74 (4.3)	218 (9.0)	197 (8.2)
Pain in extremity	76 (4.4)	66 (3.9)	154 (6.4)	154 (6.4)
Cough	72 (4.2)	51 (3.0)	155 (6.4)	169 (7.0)
Diarrhea	54 (3.1)	40 (2.3)	125 (5.2)	124 (5.2)
Chest pain	36 (2.1)	31 (1.8)	183 (7.6)	185 (7.7)
SAEs				
Patients with > 0 SAEs, N (%)	207 (12.0)	233 (13.6)	504 (20.9)	497 (20.7)
Most common SAEs (> 2.5 MedDRA terms), N (%)				
Infections and infestations	28 (1.6)	48 (2.8)	87 (3.6)	77 (3.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	47 (2.7)	42 (2.5)	71 (2.9)	72 (3.0)
WDAEs				
WDAEs, N (%)	**85 (4.9)**	**81 (4.7)**	**123 (5.1)**	**99 (4.1)**
Most common reasons (by MedDRA SOC with > 5 patients)				
Neoplasm	18 (1.0)	19 (1.1)	19 (0.8)	24 (1.0)
Gastrointestinal disorders	11 (0.6)	11 (0.6)	18 (0.7)	12 (0.5)
Nervous system disorders	10 (0.6)	5 (0.3)	12 (0.5)	8 (0.3)
Bleeding				
First major/clinically relevant non-major bleeding	139 (8.1)	138 (8.1)	249 (10.3)	274 (11.4)
Major bleeding only	14 (0.8)	20 (1.2)	26 (1.1)	52 (2.2)

AE = adverse event; DVT = deep vein thrombosis; MedDRA = Medical Dictionary for Regulatory Activities; PE = pulmonary embolism; SAE = serious adverse event; SOC = system organ class; VKA = vitamin K antagonist; WDAE = withdrawal due to adverse event.

4. DISCUSSION

4.1 Summary of Available Evidence

Two published, manufacturer-sponsored, open-label, randomized controlled trials (RCTs) were included in this systematic review: EINSTEIN DVT[4,5] and EINSTEIN PE.[6,7] The two trials evaluated the non-inferiority of rivaroxaban versus an established standard treatment with enoxaparin and a VKA. A meta-analysis was conducted to estimate the NIM; the analysis provided four estimates for the NIM that ranged from 1.54 to 2.0, depending on the effect estimator and scale. The manufacturer selected the most liberal of these estimates: a NIM of 2.0 for the upper limit of the 95% CI associated with the hazard ratio; however, no clear rationale for this choice was provided. A review of the basis of this estimate revealed some discrepancies in data and methods used for the NIM estimation; re-evaluation of the NIM estimate by the CDR reviewers suggested a NIM that ranges from 1.58 and 1.69.

Enoxaparin was administered concomitantly with oral warfarin or acenocoumarol at a dose adjusted to maintain an INR between 2.0 to 3.0, and the enoxaparin was to be discontinued after at least five days of treatment, when the target INR was attained for two consecutive days. Warfarin was the drug selected in most patients in the enoxaparin/VKA treatment groups. Based on the patient's risk profile and local treatment guidelines, patients were assigned to an intended treatment duration of three, six, or 12 months at the time of randomization. All confirmed events were considered up to one month after the end of the planned treatment period, irrespective of the actual treatment duration.

Both EINSTEIN trials likely had appropriate randomization and allocation concealment strategies, similar treatment groups at baseline, as well as balanced withdrawal rates that were ≤ 20% across treatment groups. Inclusion and exclusion criteria appeared relevant and reasonable, and baseline characteristics suggested that the trial population was likely representative of most real-life patients. Although not ideal, the open-label design is unlikely to have influenced outcome measurement, considering the adjudication of events by a blinded central independent committee.

Patients treated with VKA were within the therapeutic range (INR of 2.0 to 3.0) 58% and 63% of the time in the EINSTIEN DVT and PE trials, respectively. This less than optimal time in the therapeutic range may have biased the results in favour of rivaroxaban; however, this suboptimal TTR is generally reflective of clinical practice, which improves the generalizability of the results.

No data are available to compare the benefits and risks of rivaroxaban with a standard treatment option for more than 12 months, although several patients with irreversible risk factors, such as anticardiolipin antibody, may require chronic therapy. Moreover, patients with idiopathic VTE have moderate to high risk of recurrent events if anticoagulation is stopped (about 10% yearly).[40] Between 25% to 46% of first-time VTE patients may have idiopathic VTE and, thus, be eligible for prolonged treatment.[41]

Another limitation to generalizability is that only a small proportion of patients with active cancer were included in the two trials. Therefore, the findings from the two included trials are not generalizable to cancer patient populations.

4.2 Interpretation of Results

4.2.1 Efficacy

All-cause mortality was a secondary outcome in the EINSTEIN trials. The overall incidence of death was similar for rivaroxaban and enoxaparin/VKA. However, individual trials showed slight differences in death rates between the study treatments, which did not reach statistical significance in either trial.

The primary efficacy outcome in EINSTEIN DVT was symptomatic recurrent VTE, defined as the composite of recurrent DVT or non-fatal or fatal PE. All confirmed events centrally adjudicated by a blinded committee were considered up to one month after the end of the intended treatment period, irrespective of the actual treatment duration.

Results from EINSTEIN DVT met the pre-specified and CDR-estimated NIMs for the upper limit of the two-sided 95% CI associated with the observed hazard ratio for symptomatic recurrent VTE. Results were consistent in both the PP and the ITT populations. As a result, the two treatment options may be considered effective to prevent recurrent VTE in patients with DVT. However, the EINSTEIN PE trial achieved non-inferiority with the pre-specified margin (hazard ratio of 2.0), which was the highest value in the manufacturer's range of estimated NIMs.[8] However, it would fail the non-inferiority criterion if the choice of NIM were conservative (i.e., the lower values of the estimated NIMs from both the manufacturer's [1.54][8] and CDR's [1.58] calculations). This difference in rivaroxaban performance between DVT and PE patients was even more obvious when recurrence of DVT and PE was assessed individually in the two trials. Although the EINSTEIN trials were not powered to assess the individual components of the composite outcome, rivaroxaban had better performance in preventing DVT than in preventing PE. Results for the secondary efficacy outcome of recurrent VTE/all-cause mortality were consistent with those for the primary outcome.

While an acute episode of provoked (secondary) VTE is usually treated with anticoagulant therapy for an initial period of three months,[3] there is uncertainty around the optimal duration after completing three months of initial therapy in the case of unprovoked or recurrent VTE.[42,43] For example, Shulman et al. treated patients who had a second VTE event with either six months or indefinite anticoagulant duration.[36] The follow-up of these patients for four years showed a statistically significant recurrence prevention with the prolonged anticoagulant treatment. In the EINSTEIN trials, the majority of patients had a planned duration of treatment of six months, and most of these patients completed the treatment period while receiving the study drug. In this subgroup, results for the primary outcome of recurrent VTE were similar between rivaroxaban and enoxaparin/VKA. The EINSTEIN PE trial provided similar recurrence rates for the two treatments when they were used for 12 months.

Hospitalization was reported in the two trials as part of composite health care resource utilization. In general, resource utilization data did not suggest any major differences between rivaroxaban and enoxaparin/VKA in terms of visits to health care providers, hospitalizations and duration of stay, intensive care unit admissions, rehabilitations, or diagnostic tests. Some small differences were noted between treatment groups; for example, the duration of the hospital stay was often numerically shorter with rivaroxaban than with enoxaparin/VKA. On the other hand, slightly higher proportions of rivaroxaban patients required hospitalization due to recurrent VTE, as well as a numerically higher number of diagnostic tests in the context of suspected VTE and bleeding episodes. However, no statistical analysis was reported, and small sample sizes often limited the interpretation of the results. In addition, there appear to be discrepancies between health care resource utilization data reported in EINSTEIN DVT and Canadian clinical practice: in Canada, few patients with DVT are hospitalized, and LMWH and warfarin are generally administered and monitored in an outpatient setting.

4.2.2 Harms

The overall incidence of AEs, SAEs, and WDAEs during EINSTEIN DVT did not differ significantly between rivaroxaban and enoxaparin/VKA and were not higher than would be expected in this patient population in clinical practice. Although data on hepatotoxicity have led to concern about some oral anticoagulant drugs, the analysis of liver-related events reported by the investigators did not indicate any particular signal related to liver safety for patients treated with rivaroxaban.[44] Similarly, cardiovascular events were infrequent (< 1%), and their analysis did not provide signals of rebound events after cessation of rivaroxaban.[44]

Clinically relevant bleeding was the primary safety outcome and was defined as the composite of major or clinically relevant non-major bleeding. Results for this outcome were similar between treatment groups. Slightly lower event rates were observed with the use of rivaroxaban than with the comparator for major bleeding in the EINSTEIN DVT trial (14 [0.8%] versus 20 [1.2%], respectively); however, in the EINSTEIN PE trial, major bleeding events were significantly lower with rivaroxaban than with comparator treatment (26 [1.1%] versus 52 [2.2%], respectively). However, this particular outcome occurred infrequently, and the EINSTEIN trials were not powered to detect a difference in this individual outcome. Therefore, findings from the included trials suggest that rivaroxaban was likely similar to enoxaparin/VKA with regard to bleeding events.

The management of hemorrhagic occurrences is complicated by the lack of an antidote to reverse the effects of rivaroxaban. Because the drug has a half-life of approximately 5 to 13 hours,[2] major bleeding may persist for some time even after the drug is stopped. Hemorrhagic complications would have to be managed through appropriate symptomatic treatment, such as mechanical compression, surgical hemostasis, fluid replacement and hemodynamic support, as well as blood products or platelets, until the bleeding can be controlled.[2] This is a general concern with the new anticoagulant drugs, considering also the particularities and issues with blood-product supplies.

In a double-blind, randomized, placebo-controlled extension trial with a maximum follow-up of one year, the incidence of death and major bleeding was low and did not differ significantly between rivaroxaban 20 mg daily and placebo.[5] There were no reports of fatal bleeding.[5]

5. CONCLUSIONS

The review included two open-label RCTs, EINSTEIN DVT and EINSTEIN PE. The two trials compared the anticoagulation effects of rivaroxaban and enoxaparin/VKA for the treatment and recurrence prevention of DVT and or PE. Overall survival in the two trials showed similar incidence of all-cause mortality between the two study treatments. The EINSTEIN DVT trial showed that rivaroxaban was non-inferior to enoxaparin and a VKA for the treatment of DVT in patients without symptomatic PE. However, although rivaroxaban was found to be non-inferior to enoxaparin/VKA in the treatment and prevention of recurrent VTE based on the pre-specified NIM for EINSTEIN PE, there is uncertainty around the NIM used. CDR re-evaluation of the margin suggests a tighter and more conservative one than that used in EINSTEIN PE. Rivaroxaban appeared similar to enoxaparin/VKA with respect to clinically relevant harms such as bleeding and SAEs. The incidence of AEs did not differ significantly between treatment groups in either trial.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by Canadian Agency for Drugs and Technologies in Health (CADTH) staff based on the input provided by patient groups. It has not been systematically reviewed.

No input was received from patient groups regarding rivaroxaban for DVT and PE.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 12, 2013
Alerts:	Weekly search updates until October 16, 2013
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line #	Search Strategy
1	(rivaroxaban* or Xarelto* or BAY 59-7939 or BAY59-7939 or BAY597939 or BAY 597939).ti,ot,ab,sh,rn,hw,nm. or (366789-02-8 or 9NDF7JZ4M3).rn,nm.
2	exp Pulmonary embolism/ or ((lung* or pulmonary) adj4 (emobol* or microembol* or thromboembol*)).ti,ab.
3	exp Venous Thrombosis/ or Venous Thromboembolism/ or (Thrombosis/ and Veins/)
4	((thrombotic or thromboembolic* or thrombo-embo* or thrombos* or thromboembolis* or thrombus* or DVT or phlebothrombos* or thrombophlebitis) adj3 (vein* or venous)).ti,ab.
5	(blood adj clot* adj3 (vein* or venous)).ti,ab.
6	1 and (2 or 3 or 4 or 5)
7	6 use pmez
8	*rivaroxaban/ or (rivaroxaban* or Xarelto* or BAY 59-7939 or BAY59-7939 or BAY597939 or BAY 597939).ti,ab.
9	*Lung embolism/ or ((lung* or pulmonary) adj4 (emobol* or microembol* or thromboembol*)).ti,ab.
10	*Deep vein thrombosis/ or *Vein thrombosis/ or *Venous thromboembolism/ or (*Thrombosis/ and *Vein/)
11	((thrombotic or thromboembolic* or thrombo-embo* or thrombos* or thromboembolis* or thrombus* or DVT or phlebothrombos* or thrombophlebitis) adj3 (vein* or venous)).ti,ab.
12	(blood adj clot* adj3 (vein* or venous)).ti,ab.
13	8 and (9 or 10 or 11 or 12)
14	13 use oemezd
15	14 not conference abstract.pt.
16	7 or 15
17	remove duplicates from 16

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used
Trial registries (Clinicaltrials.gov and other)	Same keywords and limits used as per MEDLINE search

Grey Literature

Dates for Search:	June 3 to 7, 2013
Keywords:	Xarelto, rivaroxaban, venous thromboembolism, deep vein thrombosis, pulmonary embolism
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- databases (free)
- Internet search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Agnelli G, et al. Circulation. 2007 Jul 10;116(2):180-7. Buller HR. Ann Intern Med. 2012;157(4):JC4-6.	***Not the intervention of interest***
Douketis J. Ann Intern Med. 2011 May 17;154(10):JC5-6.	***Not a study design of interest***
Cohen AT and Dobromirski M. Thromb Haemost. 2012 Feb 28;107(6):1035-43.	***Inappropriate control group***

APPENDIX 4: DETAILED OUTCOME DATA

Exposure to Study Treatments

TABLE 11: DURATION OF ACTUAL STUDY TREATMENT AFTER RANDOMIZATION

Treatment Characteristics	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413
Intended treatment: Planned duration of treatment, n (%)				
3 months	208 (12.0)	203 (11.8)	127 (5.3)	122 (5.1)
6 months	1,083 (62.6)	1,083 (63.0)	1,387 (57.3)	1,387 (57.5)
12 months	440 (25.4)	432 (25.1)	905 (37.4)	904 (37.5)
Actual treatment with study drug (PP population):				
Duration, days (overall population)				
Mean ± SD	194.4 ± 89.7	188.7 ± 92.5	219.4 ± 97.0	216.9 ± 99.2
Median (IQR)	182 (178 to 190)	181 (176 to 189)	183.0 (179 to 352)	183 (179 to 351)
For 3-month intended treatment group				
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	93 (91 to 96)	93 (91 to 96)	93 (92 to 97)	92 (90 to 96)
≥ 1 to < 3 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months	[redacted]	[redacted]	[redacted]	[redacted]
For 6-month intended treatment group				
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	182 (179 to 184)	181 (178 to 183)	182 (179 to 184)	181 (178 to 183)
≥ 1 to < 3 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months	[redacted]	[redacted]	[redacted]	[redacted]
For 12-month intended treatment group				
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	354 (269 to 358)	353 (266 to 357)	355 (278 to 358)	354 (274 to 357)
≥ 1 to < 3 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Categorized, n (%)				
< 3 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 to < 6 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6 to < 9 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 9 to < 12 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]	[redacted]	[redacted]
≥ 80% Compliance with study drug, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

IQR = interquartile range; PP = per protocol; SD = standard deviation; VKA = vitamin K antagonist.
Source: EINSTEIN DVT Publication; EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 12: INTERNATIONAL NORMALIZED RATIO COMPLIANCE FOR THE ENOXAPARIN/VITAMIN K ANTAGONIST TREATMENT GROUP

INR value	EINSTEIN DVT N = 1,704			EINSTEIN PE N = 2,419		
	< 2.0	2.0 to 3.0	> 3.0	< 2.0	2.0 to 3.0	> 3.0
INR at the time of discontinuation of LMWH, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time spent in each INR category, %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PE = pulmonary embolism.
Note: According to the study procedures, INR measurements had to be performed initially at least every two to three days, then at least monthly.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 13: INCIDENCE OF ANTITHROMBOTICS WITHIN THE INTENDED TREATMENT DURATION EXCLUDING STUDY MEDICATION

Antithrombotic	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413
Any antithrombotics	[redacted]	[redacted]	[redacted]	[redacted]
VKA	[redacted]	[redacted]	[redacted]	[redacted]
Heparin group	[redacted]	[redacted]	[redacted]	[redacted]
Platelet aggregation inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Enzymes	[redacted]	[redacted]	[redacted]	[redacted]
Direct thrombin inhibitors	[redacted]		[redacted]	[redacted]
Fondaparinux	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]		[redacted]	[redacted]

DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

Efficacy Results

Survival

TABLE 14: MORTALITY (BY CAUSE OF DEATH) UNTIL THE INTENDED END OF STUDY TREATMENT— INTENTION-TO-TREAT POPULATION

	EINSTEIN DVT		EINSTEIN PE		Pooled Analysis	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413	Rivaroxaban N = 4,150	Enoxaparin/VKA N = 4,131
All-cause death, n (%)	38 (2.2)	49 (2.9)	58 (2.4)	50 (2.1)	[redacted]	[redacted]
Hazard ratio/Relative risk (95% CI)	HR 0.67 (0.44 to 1.02); P^a = 0.06 RR[b] 0.77 (0.51 to 1.17)		HR 1.13 (0.77, 1.65); P^a = 0.526 RR[b] 1.16 (0.80, 1.68)		[redacted]	
By cause of death, n (%)						
Death due to PE	1 (< 0.1)	0	3 (0.1)	1 (< 0.1)	[redacted]	[redacted]
PE cannot be excluded	3 (0.2)	6 (0.3)	8 (0.3)	6 (0.2)	[redacted]	[redacted]
Bleeding	1 (< 0.1)	5 (0.3)	5 (0.2)	4 (0.2)	[redacted]	[redacted]
Cardiovascular	2 (0.1)	4 (0.2)	10 (0.4)	3 (0.1)	[redacted]	[redacted]
Other causes	6 (0.3)	14 (0.8)	32 (1.3)	36 (1.5)	[redacted]	[redacted]
Cancer	25 (1.4)	20 (1.2)	20 (0.8)	23 (1.0)	[redacted]	[redacted]

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; PE = pulmonary embolism; RR = relative risk; VKA = vitamin K antagonist.

[a] Test of superiority.

[b] CADTH Common Drug Review calculation.

Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 15: INCIDENCE RATES OF ALL POST-RANDOMIZATION MORTALITY (BY ADJUDICATED CAUSE OF DEATH) — SAFETY POPULATION

	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban N = 1,718	Enoxaparin/VKA N = 1,711	Rivaroxaban N = 2,412	Enoxaparin/VKA N = 2,405
All-cause death, n (%)	41 (2.4)	52 (3.0)	63 (2.6)	51 (2.1)
Relative Risk (95% CI)	0.79 (0.52 to 1.18)[a]		1.23 (0.86 to 1.77)[a]	
By cause of death				
Death due to PE	1 (< 0.1)	0	3 (0.1)	1 (< 0.1)
PE cannot be excluded	3 (0.2)	6 (0.4)	8 (0.3)	6 (0.2)
Bleeding	2 (0.1)	5 (0.3)	5 (0.2)	4 (0.2)
Cancer	27 (1.6)	20 (1.2)	22 (0.9)	23 (1.0)
Septicemia	0	2 (0.1)	2 (< 0.1)	0
Multi-organ failure	0	0	1 (< 0.1)	0
Myocardial infarction	0	0	2 (< 0.1)	1 (< 0.1)
Ischemic stroke	1 (< 0.1)	4 (0.2)	2 (< 0.1)	1 (< 0.1)
Other vascular events	1 (< 0.1)	1 (< 0.1)	3 (0.1)	0
Infectious disease	3 (0.2)	9 (0.5)	9 (0.4)	6 (0.2)
Heart failure	0	0	5 (0.5)	0
Other cardiac death	0	0	0	1 (< 0.1)
Other respiratory failure	0	0	0	3 (0.1)
Cachexia	1 (< 0.1)	0	0	1 (< 0.1)
Pneumonia	0	1 (< 0.1)	0	0
Inflammatory disease	0	0	1 (< 0.1)	0
Amyotrophic lateral sclerosis	0	0	0	1 (< 0.1)
Renal failure	1 (< 0.1)	0	0	0
Diabetic coma	1 (< 0.1)	0	0	0
Polytrauma	0	0	0	1 (< 0.1)
Advanced age	0	0	0	1 (< 0.1)
Suicide	0	1 (< 0.1)	0	0
Liver disease	0	1 (< 0.1)	0	0

CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist.
[a] CADTH Common Drug Review calculation.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 16: INCIDENCE RATES OF MORTALITY BY INTENDED TREATMENT DURATION — INTENTION-TO-TREAT POPULATION

	EINSTEIN DVT		EINSTEIN PE		Pooled analysis	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413	Rivaroxaban N = 4,150	Enoxaparin/VKA N = 4,131
3-month treatment, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
Death due to PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE cannot be excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other causes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-month treatment, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
Death due to PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE cannot be excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other causes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-month treatment, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
Death due to PE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PE cannot be excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other causes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 17: INCIDENCE RATES OF MORTALITY AMONG PATIENTS WITH CANCER AT BASELINE — INTENTION-TO-TREAT POPULATION

	EINSTEIN DVT		EINSTEIN PE		Pooled Analysis	
	Rivaroxaban N = 118	Enoxaparin/VKA N = 89	Rivaroxaban N = 114	Enoxaparin/VKA N= 109	Rivaroxaban N = 232	Enoxaparin/VKA N= 198
All-cause Death[a], n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio[b]/Relative risk[c] (95% CI)	[redacted]		[redacted]		[redacted]	
By Cause of Death						
- PE cannot be excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- Other causes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; PE = pulmonary embolism; RR = relative risk; VKA = vitamin K antagonist.
[a] Reported as part of the primary composite outcome.
[b] As reported by the manufacturer.
[c] Relative risk calculated by CADTH Common Drug Review based on the event numbers reported in the table.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE-CSR.

Symptomatic Recurrence of Venous Thromboembolism

TABLE 18: INCIDENCE RATES OF RECURRENT VENOUS THROMBOEMBOLISM UNTIL THE INTENDED TREATMENT DURATION (INTENTION-TO-TREAT)

	EINSTEIN DVT		EINSTEIN PE		Pooled Analysis	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413	Rivaroxaban N = 4,150	Enoxaparin/VKA N = 4,131
Recurrent VTE (primary composite outcome),[a] n (%)	36 (2.1)	51 (3.0)	50 (2.1)	44 (1.8)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.68 (0.44 to 1.04)		1.12 (0.75 to 1.68)		[redacted]	
Relative risk[b] (95% CI)	0.70 (0.46 to 1.07)		1.13 (0.76 to 1.69)		[redacted]	
Individual outcomes included in the composite outcome – assessed separately[c]						
Death (PE)	1 (< 0.1)	0	3 (0.1)	1 (< 0.1)	[redacted]	[redacted]
Death (PE cannot be excluded)	3 (0.2)	6 (0.3)	8 (0.3)	6 (0.2)	[redacted]	[redacted]
Symptomatic PE and DVT	1 (< 0.1)	0	0	2 (< 0.1)	[redacted]	[redacted]
Symptomatic PE only	20 (1.2)	18 (1.0)	23 (1.0)	20 (0.8)	[redacted]	[redacted]
Relative risk[b] (95% CI)	1.10 (0.59 to 2.08)		1.15 (0.63 to 2.08)		[redacted]	
Symptomatic DVT only	14 (0.8)	28 (1.6)	18 (0.7)	17 (0.7)	[redacted]	[redacted]
Relative risk[b] (95% CI)	0.50 (0.26 to 0.94)		1.06 (0.55 to 2.04)		[redacted]	
Recurrent VTE (secondary composite outcome),[d] n (%)	69 (4.0)	87 (5.1)	97 (4.0)	82 (3.4)	[redacted]	[redacted]
Hazard ratio (95% CI)	0.72 (0.53 to 0.99)		1.16 (0.86 to 1.55)		[redacted]	
Relative risk[b] (95% CI)	0.79 (0.58 to 1.07)		1.18 (0.88 to 1.57)		[redacted]	

CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

[a] Composite of recurrent DVT or non-fatal or fatal PE; events were measured up to one month after the intended treatment duration, irrespective to the actual treatment duration.

[b] CADTH Common Drug Review calculation.

[c] The sum of the individual outcomes is higher than the reported current VTE; there was no explanation reported for this discrepancy.

[d] Included the same individual outcomes as the primary efficacy outcome, plus all-cause mortality.

Data source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 19: INCIDENCE RATES OF RECURRENT VENOUS THROMBOEMBOLISM UNTIL THE INTENDED TREATMENT DURATION (PER PROTOCOL)

	EINSTEIN DVT		EINSTEIN PE		Pooled Analysis	
	Rivaroxaban N = 1,525	Enoxaparin/VKA N = 1,571	Rivaroxaban N = 2,224	Enoxaparin/VKA N = 2,238	Rivaroxaban N = 3,749	Enoxaparin/VKA N = 3,809
Recurrent VTE (primary composite outcome),[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
Relative risk[b] (95% CI)	[redacted]		[redacted]		[redacted]	
Individual outcomes included in the composite outcome – assessed separately[c]						
Death (PE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death (PE cannot be excluded)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic PE and DVT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic PE only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk[b] (95% CI)	[redacted]		[redacted]		[redacted]	
Symptomatic DVT only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk[b] (95% CI)	[redacted]		[redacted]		[redacted]	
Recurrent VTE (secondary composite outcome),[d] n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]		[redacted]		[redacted]	
Relative risk[b] (95% CI)	[redacted]		[redacted]		[redacted]	

CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.
[a] Composite of recurrent DVT or non-fatal or fatal PE; events were measured up to one month after the intended treatment duration, irrespective of the actual treatment duration.
[b] CADTH Common Drug Review calculation.
[c] The sum of the individual outcomes is higher than the reported current VTE; there was no explanation reported for this discrepancy.
[d] Included the same individual outcomes as the primary efficacy outcome, plus all-cause mortality.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 20: SUMMARY OF THE SUBGROUP ANALYSIS FOR RECURRENT VENOUS THROMBOEMBOLISM (PRIMARY OUTCOME) (INTENTION-TO-TREAT)

Subgroups	EINSTEIN DVT		EINSTEIN PE		Pooled analysis	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413	Rivaroxaban N = 4,150	Enoxaparin/VKA N = 4,131
Intended treatment duration; n/N (%) – hazard ratio and relative risk (95% CI)[a, b]						
P value for interaction						
3 months	5/208 (2.4)	3/203 (1.5)	6/127 (4.7)	2/122 (1.6)		
6 months	25/1,083 (2.3)	29/1,083 (2.7)	27/1,387 (1.9)	24/1,387 (1.7)		
12 months	6/440 (1.4)	19/432 (4.4)	17/905 (1.9)	18/904 (2.0)		
Malignancy at baseline; n/N (%) – hazard ratio and relative risk (95% CI)[a, b]						
P value for interaction						
No active cancer	32/1,613 (2.0)	46/1,629 (2.8)	48/2,305 (2.1)	41/2,304 (1.8)		
Active cancer	4/118 (3.4)	5/89 (5.6)	2/114 (1.8)	3/109 (2.8)		
Age at baseline; n/N (%) – hazard ratio and relative risk (95% CI)[a, b]						
P value for interaction						
< 60 years						
≥ 60 years						
< 65 years	26/1,145 (2.3)	30/1,111 (2.7)	29/1,461 (2.0)	23/1,479 (1.6)		
65 to 75 years	6/371 (1.6)	11/382 (2.9)	10/517 (1.9)	8/532 (1.5)		

Subgroups	EINSTEIN DVT		EINSTEIN PE		Pooled analysis	
	Rivaroxaban N = 1,731	Enoxaparin/VKA N = 1,718	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413	Rivaroxaban N = 4,150	Enoxaparin/VKA N = 4,131
	[redacted]		[redacted]		[redacted]	
≥ 75 years	4/215 (1.9)	10/225 (4.4)	11/441 (2.5)	13/402 (3.2)	15/656 (2.3)	23/627 (3.7)
	[redacted]		[redacted]		[redacted]	
Renal function at baseline, creatinine clearance; n/N (%) – hazard ratio and relative risk (95% CI)[a, b]						
P value for interaction	[redacted]		[redacted]		Not applicable	
Missing	1/24 (4.2)	1/20 (5.0)	1/16 (6.3)	1/10 (10.0)	2/40 (5.0)	2/30 (6.7)
	-		HR: -		-	
≥ 80 mL/min	19/1,193 (1.6)	30/1,170 (2.6)	30/1,555 (1.9)	22/1,617 (1.4)	49/2,748 (1.8)	52/2,787 (1.9)
	[redacted]		[redacted]		[redacted]	
50 to < 80 mL/min	12/393 (3.1)	14/399 (3.5)	12/637 (1.9)	16/593 (2.7)	24/1030 (2.3)	30/992 (3.0)
	[redacted]		[redacted]		[redacted]	
< 50 mL/min	4/121 (3.3)	6/129 (4.7)	7/211 (3.3)	5/193 (2.6)	11/332 (3.3)	11/322 (3.4)
	[redacted]		[redacted]		[redacted]	

CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; PE = pulmonary embolism; VKA = vitamin K antagonist.

[a] Symptomatic recurrent DVT and fatal and non-fatal PE.

[b] CADTH Common Drug Review calculation.

Data source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 21: HEALTH CARE RESOURCE UTILIZATION — INTENTION-TO-TREAT POPULATION

Health Care Resource Utilization[a, b]	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
Initial Episode				
N	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration, days	[redacted]	[redacted]	[redacted]	[redacted]
ICU admissions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rehabilitation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most utilized diagnostic tests	[redacted]	[redacted]	[redacted]	[redacted]
Clinically Suspected Recurrent DVT and/or PE				
N	[redacted]	[redacted]	[redacted]	[redacted]
Visits to other health care providers, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration, days	[redacted]	[redacted]	[redacted]	[redacted]
ICU admissions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rehabilitation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most utilized diagnostic tests	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed DVT				
N	[redacted]	[redacted]	[redacted]	[redacted]
Visits to other health care providers, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration, days	[redacted]	[redacted]	[redacted]	[redacted]
ICU admissions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rehabilitation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most utilized diagnostic tests	[redacted]	[redacted]	[redacted]	
Confirmed PE				
N	[redacted]	[redacted]	[redacted]	[redacted]

Health Care Resource Utilization[a, b]	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
Visits to other health care providers, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration, days	[redacted]	[redacted]	[redacted]	[redacted]
ICU admissions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rehabilitation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most utilized diagnostic tests	[redacted]	[redacted]	[redacted]	[redacted]
Suspected Bleeding				
N	[redacted]	[redacted]	[redacted]	[redacted]
Visits to other health care providers, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration, days	[redacted]	[redacted]	[redacted]	[redacted]
ICU admissions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rehabilitation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most utilized diagnostic tests	[redacted]	[redacted]	[redacted]	[redacted]
Confirmed Bleeding				
N	[redacted]	[redacted]	[redacted]	[redacted]
Visits to other health care providers, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalizations, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean duration, days	[redacted]	[redacted]	[redacted]	[redacted]
ICU admissions, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Rehabilitation, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most utilized diagnostic tests	[redacted]	[redacted]	[redacted]	[redacted]

DVT = deep vein thrombosis; ICU = intensive care unit; PE = pulmonary embolism; VKA = vitamin K antagonist.

[a] Assessed by hospitalizations, admissions to ICU and rehabilitation in hospitalized patients and use of diagnostic tests.

[b] Results for the per protocol population were not reported.

Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

Safety Results

TABLE 22: ADVERSE EVENTS — SAFETY POPULATION

AE	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban (n = 1,718)	Enoxaparin/VKA (n = 1,711)	Rivaroxaban (n = 2,412)	Enoxaparin/VKA (n = 2,405)
Any AEs[a], n (%)	**1,103 (64.2)**	**1,107 (64.7)**	**1,959 (81.2)**	**1,928 (80.2)**
Treatment-emergent[b] AEs, n (%)	**1,078 (62.7)**	**1,080 (63.1)**	**1,937 (80.3)**	**1,901 (79.0)**
Most common treatment-emergent[b] AEs (≥ 2.5% of patients), n (%)				
Nasopharyngitis	93 (5.4)	84 (4.9)	181 (7.5)	189 (7.9)
Headache	91 (5.3)	68 (4.0)	193 (8.0)	174 (7.2)
Epistaxis	89 (5.2)	74 (4.3)	218 (9.0)	197 (8.2)
Pain in extremity	76 (4.4)	66 (3.9)	154 (6.4)	154 (6.4)
Cough	72 (4.2)	51 (3.0)	155 (6.4)	169 (7.0)
Diarrhea	54 (3.1)	40 (2.3)	125 (5.2)	124 (5.2)
Contusion	53 (3.1)	68 (4.0)	92 (3.8)	129 (5.4)
Back pain	50 (2.9)	31 (1.8)	88 (3.6)	131 (5.4)
Menorrhagia	49 (2.9)	19 (1.1)	73 (3.0)	45 (1.9)
Constipation	48 (2.8)	43 (2.5)	139 (5.8)	131 (5.4)
Nausea	47 (2.7)	38 (2.2)	106 (4.4)	122 (5.1)
Pyrexia	43 (2.5)	38 (2.2)	67 (2.8)	70 (2.9)
Arthralgia	43 (2.5)	38 (2.2)	85 (3.5)	77 (3.2)
Edema peripheral	41 (2.4)	41 (2.4)	87 (3.6)	94 (3.9)
Hematuria	39 (2.3)	41 (2.4)	72 (3.0)	72 (1.9)
Hematoma	37 (2.2)	59 (3.4)	57 (2.4)	92 (3.8)
Urinary tract infection	37 (2.2)	32 (1.9)	93 (3.9)	95 (4.0)
Dizziness	38 (2.2)	22 (1.3)	64 (2.7)	86 (3.6)
Chest pain	36 (2.1)	31 (1.8)	183 (7.6)	185 (7.7)
Gingival bleeding	36 (2.1)	28 (1.6)	57 (2.4)	76 (3.2)
Insomnia	28 (1.6)	18 (1.1)	67 (2.8)	76 (3.2)
Bronchitis	24 (1.4)	34 (2.0)	108 (4.5)	89 (3.7)
Anxiety	24 (1.4)	11 (0.6)	80 (3.3)	76 (3.2)
Alanine aminotransferase increased	20 (1.2)	52 (3.0)	52 (2.2)	77 (3.2)
AEs of special interest				
All vascular events[c]	**12 (0.7)**	**14 (0.8)**	**35 (1.5)**	**37 (1.5)**
Death (cardiovascular)	1 (< 0.1)	0	7 (0.3)	3 (0.1)
Death (other vascular event)	1 (< 0.1)	0	1 (< 0.1)	0
STEMI	1 (< 0.1)	0	4 (0.2)	2 (< 0.1)
NSTEMI	4 (0.2)	1 (< 0.1)	2 (< 0.1)	10 (0.4)
UA	1 (< 0.1)	1 (< 0.1)	9 (0.4)	9 (0.4)
TIA	1 (< 0.1)	5 (0.3)	2 (< 0.1)	6 (0.2)
Ischemic stroke	3 (0.2)	5 (0.3)	10 (0.4)	6 (0.2)
Non-CNS systemic embolism	2 (0.1)	2 (0.1)	5 (0.2)	3 (0.1)
Hepatic AEs (any events)	**83 (4.8)**	**161 (9.4)**	**199 (8.3)**	**299 (12.4)**
Hepatobiliary disorders	21 (1.2)	21 (1.2)	71 (2.9)	82 (3.4)
Investigations	54 (3.1)	141 (8.2)	128 (5.3)	222 (9.2)

AE	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/VKA	Rivaroxaban	Enoxaparin/VKA
	(n = 1,718)	(n = 1,711)	(n = 2,412)	(n = 2,405)
Thrombocytopenia	**3 (0.2)**	**3 (0.2)**	**3 (0.1)**	**7 (0.3)**
Renal failure	**6 (0.3)**	**9 (0.5)**	**6 (0.4)**	**9 (0.4)**

AE = adverse event; CNS = central nervous system; DVT = deep vein thrombosis; NSTEMI = non–ST-elevation myocardial infarction; PE = pulmonary embolism; STEMI = ST-elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina; VKA = vitamin K antagonist.

[a] Including events occurring during the 30-day observational period.

[b] Events occurring or worsening after randomization but no more than seven days after stop of study medication.

[c] Not including PE-related death. Event rates are for the safety population and may differ compared with per protocol or intention-to-treat population.

Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 23: INCIDENCE OF SERIOUS ADVERSE EVENTS OCCURRING IN ≥ 1% OF ANY TREATMENT GROUP — SAFETY DATA SET (MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES [MEDDRA])

SAE	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban N = 1,718	Enoxaparin/VKA N = 1,711	Rivaroxaban N = 2,412	Enoxaparin/VKA N = 2,405
Any SAEs, n (%)	**207 (12.0)**	**233 (13.6)**	**471 (19.5)**	**463 (19.3)**
Blood and lymphatic system disorders	15 (0.9)	9 (0.5)	20 (0.8)	13 (0.5)
Cardiac disorders	15 (0.9)	17 (1.0)	56 (2.3)	58 (2.4)
Gastrointestinal disorders	27 (1.6)	31 (1.8)	55 (2.3)	56 (2.3)
General disorders and administration site conditions	15 (0.9)	10 (0.6)	45 (1.9)	43 (1.8)
Infections and infestations	28 (1.6)	48 (2.8)	72 (3.0)	69 (2.9)
Injury, poisoning, and procedural complications	13 (0.8)	17 (1.0)	29 (1.2)	35 (1.5)
Investigations	8 (0.5)	20 (1.2)	22 (0.9)	31 (1.3)
Musculoskeletal and connective tissue disorders	11 (0.6)	15 (0.9)	34 (1.4)	37 (1.5)
Neoplasms: benign, malignant and unspecified (including cysts and polyps)	47 (2.7)	42 (2.5)	63 (2.6)	62 (2.6)
Nervous system disorders	18 (1.0)	17 (1.0)	44 (1.8)	35 (1.5)
Renal and urinary disorders	9 (0.5)	10 (0.6)	19 (0.8)	25 (1.0)
Respiratory, thoracic, and mediastinal disorders	16 (0.9)	17 (1.0)	74 (3.1)	74 (3.1)

DVT = deep vein thrombosis; PE = pulmonary embolism; SAE = serious adverse event; VKA = vitamin K antagonist.
Source: EINSTEIN DVT clinical study report (CSR); EINSTEIN PE CSR.

TABLE 24: ADVERSE EVENTS LEADING TO WITHDRAWAL — SAFETY POPULATION

WDAE	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/ VKA	Rivaroxaban	Enoxaparin/ VKA
	(n = 1,718)	(n = 1,711)	(n = 2,412)	(n = 2,405)
WDAEs (by MedDRA system organ class with > 5 patients), n (%)	**85 (4.9)**	**81 (4.7)**	**123 (5.1)**	**99 (4.1)**
Neoplasm	18 (1.0)	19 (1.1)	19 (0.8)	24 (1.0)
Gastrointestinal disorders	11 (0.6)	11 (0.6)	18 (0.7)	12 (0.5)
Nervous system disorders	10 (0.6)	5 (0.3)	12 (0.5)	8 (0.3)
Respiratory / thoracic / mediastinal disorders	8 (0.5)	7 (0.4)	11 (0.5)	9 (0.4)
Blood and lymphatic system disorders	7 (0.4)	4 (0.2)	8 (0.3)	6 (0.2)
Vascular disorders	6 (0.3)	5 (0.3)	4 (0.2)	2 (<0.1)
Investigations	6 (0.3)	4 (0.2)	10 (0.4)	5 (0.2)
Infections and infestations	5 (0.3)	8 (0.5)	4 (0.2)	3 (0.1)
Injury, poisoning, and procedural complications	4 (0.2)	3 (0.2)	5 (0.2)	12 (0.5)

WDAE	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban	Enoxaparin/ VKA	Rivaroxaban	Enoxaparin/ VKA
	(n = 1,718)	(n = 1,711)	(n = 2,412)	(n = 2,405)
Skin and subcutaneous tissue disorders	4 (0.2)	5 (0.3)	12 (0.5)	5 (0.2)

DVT = deep vein thrombosis; PE = pulmonary embolism; VKA = vitamin K antagonist; WDAE = withdrawal due to adverse events.
Source: EINSTEIN DVT Clinical Study Report (CSR); EINSTEIN PE CSR.

TABLE 25: ALL CONFIRMED TREATMENT-EMERGENT MAJOR BLEEDING EVENTS — SAFETY POPULATION

	EINSTEIN DVT		EINSTEIN PE	
	Rivaroxaban N = 1,718	Enoxaparin/VKA N = 1,711	Rivaroxaban N = 2,412	Enoxaparin/VKA N = 2,405
Any confirmed bleeding, n (%)				
Total number of events	139 (8.1)[a]	138 (8.1)[a]	757 (31.4)	774 (32.2)
Major bleeding, n (%)				
Total number of events	14 (0.8)	20 (1.2)	26 (1.1)	52 (2.2)
Fatal bleeding	1 (< 0.1)	5 (0.3)	2 (< 0.1)	3 (0.1)
Intracranial	0	2 (0.3)	2 (< 0.1)	2 (< 0.1)
Retroperitoneal	0	0	0	1 (< 0.1)
Gastrointestinal	1 (< 0.1)	2 (0.1)	NR	NR
Thorax	0	1 (< 0.1)	NR	NR
Non-fatal critical organ bleeding	3 (0.2)	3 (0.2)	7 (0.3)	26 (1.1)
Intracranial	2 (0.1)	0	1 (< 0.1)	10 (0.4)
Retroperitoneal	0	1 (< 0.1)	1 (< 0.1)	7 (0.3)
Intra-articular	0	1 (< 0.1)	0	3 (0.1)
Ocular	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	2 (< 0.1)
Non-fatal non-critical organ bleeding[b]	10 (0.6)	12 (0.7)	17 (0.7)	25 (1.0)
Gastrointestinal	3 (0.2)	4 (0.2)	9 (0.4)	16 (0.7)
Uterus	5 (0.3)	0	3 (0.1)	0
Clinically relevant non-major bleeding, n (%)				
Total number of events	129 (7.5)	122 (7.1)	228 (9.5)	235 (9.8)

DVT = deep vein thrombosis; NR = not reported; PE = pulmonary embolism; VKA = vitamin K antagonist.
[a] First major or clinically relevant non-major bleeding occurring during treatment.
[b] Fall in Hb ≥ 2 g/dL and/or transfusions ≥ 2 units.
Source: European Medicines Agency review for Xarelto;[45] EINSTEIN PE Clinical Study Report.

APPENDIX 5: VALIDITY OF THE NON-INFERIORITY MARGIN

Introduction

The purpose of this section is to appraise the non-inferiority margin (NIM) used in the EINSTEIN trials. Both EINSTEIN trials were designed to test whether rivaroxaban was non-inferior to the standard of care in reducing the recurrence of VTE events.[8] The standard of care was considered to be heparin for the initial period post-VTE event, administered concomitantly with VKA, and the VKA was continued alone once its therapeutic range was attained. The NIM for the hazard ratio, in the EINSTEIN trials, was derived from historical trials controlled by placebo, no treatment, or standard of care.[5,8] The indirect confidence interval comparison method was used. This method estimated the NIM from the upper limit of the 95% confidence interval of the odds ratio for the standard of care versus placebo or no treatment, and the upper limit of the 95% confidence interval of the hazard ratio for rivaroxaban versus the standard of care for the statistical test.

Summary of the Historical Trials and Constancy Assumption

A meta-analysis published by Prins and Lensing summarized the historical trials used for the NIM estimation.[8] The characteristics of the included studies are presented in Table 27. The trials included patients with PE only (two trials),[46,47] DVT only (seven trials)[32,34,48-52], and both PE and DVT (five trials).[35-37,53,54] The EINSTEIN trials included proximal DVT patients only; however, the meta-analysis included five trials in which patients with distal DVT were also included.[32-36] Another trial included patients with unstable angina or arterial ischemia along with VTE patients.[37] The management and outcomes of these patients might not reflect the proximal DVT patients included in the EINSTEIN trials. Although arguments can be made to include or exclude non-proximal DVT events in calculating the NIM, it was not a major determinant of the NIM in the ENSTIEN trials.

Additionally, the intervention and comparator groups used in this meta-analysis were not those typically used to estimate the NIM; estimation of the NIM is usually based on the comparison between the comparator used in the new trial and placebo.[55,56] For the EINSTEIN trials, a meta-analysis of randomized controlled trials (RCTs) comparing anticoagulation with unfractionated heparin plus VKA with placebo would be the most appropriate to estimate the NIM. The meta-analysis by Prins and Lensing identified two placebo-controlled trials;[46,57] however, these studies were > 25 years old and used anticoagulant therapy for short duration (14 days or three months only). For these reasons, the authors judged that the NIM could not be estimated from these trials alone. Instead, the meta-analysis also included RCTs that compared different anticoagulation interventions. These interventions were grouped as “more effective” and “less effective” treatments. The meta-analysis did not provide a specific definition for the “more/less effective” groups; these included different durations of anticoagulants, different heparin formulations, and placebo or no treatment.

Finally, the outcome in the included studies was recurrence of VTE events; however, mortality was not specified as part of this outcome. The odds ratios consistently favoured the “more effective” treatment, except in one trial that compared the use of VKA for one week with 12 weeks. This trial showed that the rate of recurrence, within six months, was higher in the longer-duration treatment group, but the difference was not statistically significant.[8,54]

Calculation Method

The meta-analysis by Prins and Lensing estimated the odds ratio and the relative risk, using both arithmetic and geometric scales.[8] The odds ratio was calculated using the Mantel–Haenszel procedure,

which assumed a fixed treatment effect. Our observation is that there are two schools of thought related to using fixed or random effects models. Some would advocate evaluating heterogeneity and then determining whether a fixed or random effects model is more appropriate. Others would advocate using only the more conservative approach using a random effects model. The modelling approach in determining the NIM appears to suggest the random effects model.[58,59] Schumi and Wittes note in their article:[60] "The FDA Guidance suggests a preference for so-called 'random-effects models' in meta-analysis that will be used to establish the margin in non-inferiority trials. These models in contrast to MH [Mantel–Haenszel] and Peto approaches, make very specific assumptions about the distribution of the effect sizes across all potential studies." In fact, the Prins and Lensing meta-analysis grouped different regimens and durations of anticoagulation interventions into the "more-effective" and "less-effective" groups; these interventions produced upper limits of the 95% confidence interval for the odds ratios that ranged from 0.0 to 17.9.[8]

Based on methods used in the meta-analysis, the odds ratio was 0.18 (95% CI, 0.14 to 0.25) and the relative risk was 0.19 (95% CI, 0.12 to 0.28). The NIM was estimated from these effect sizes using the following formula:

$$\text{NIM (arithmetic scale)} = 1 + (1 - efficacy\ preservation\ \%) * \left(\frac{1}{ULCI\ of\ the\ pooled\ \widehat{OR}} - 1\right)^{55}$$

where ULCI = upper limit of the confidence interval

AND

$$\text{Non inferiority margin (geometric scale)} = \exp[(1 - efficacy\ preservation\ \%) * \log(LLCI\ of\ the\ reversed\ \widehat{OR})]$$

where LLCI = lower limit of the reversed confidence interval and reversed confidence interval = 1/confidence interval

The associated NIMs were reported as follows:[8]

TABLE 26: NON-INFERIORITY MARGIN ESTIMATES BY MEASURE OF EFFECT, SCALE, AND PERCENTAGE OF POOLED EFFECT PRESERVED

Pooled Effect Preserved	Non-inferiority Margin			
	Odds Ratio[a] Based on		Risk Ratio Based on	
	Arithmetic Scale	Geometric Scale	Arithmetic Scale	Geometric Scale
Preservation of 50% of effect	2.50	2.00	2.29	1.89
Preservation of 66% of effect	2.00	1.60	1.86	1.54
Preservation of 75% of effect	1.75	1.41	1.64	1.37

[a] Based on the fixed treatment effect model.

The EINSTEIN trials used the highest NIM estimated (2.00), but the trial protocol did not provide justifications for the choice of odds ratio over risk ratio or the arithmetic scale over the geometric scale for the NIM estimation. Prins and Lensing reported that the geometric scale would be the logical choice when evaluating event rates in a "no-treatment" group, but the arithmetic or linear scale was used instead because the event rates were compared with the standard of care.[8]

CADTH Common Drug Review Re-assessment of the Non-inferiority Margin

Based on the aforementioned observations on the calculation method and the data discrepancies, CDR reviewers recalculated the NIM using the recurrence rates reported by Prins and Lensing, based on fixed and random treatment effects model for the odds ratio and relative risk. Random effects models were chosen for the CDR calculations, given the clinical heterogeneity between the studies included in the Prins and Lensing meta-analysis; hence, a common effect size could not be assumed.[58,59,61] Another methodological uncertainty is that the NIM estimation was based on the arithmetic scale rather than the geometric scale estimations, despite both being calculated by Prins and Lensing. The use of arithmetic scale induces some bias when the sample size is small and the prevalence of the outcome is low.[62] The rationale behind using the geometric scale when conducting a meta-analysis is to overcome the issue of skewed data. This was illustrated in sections 7.7.3.4 and 9.4.5.3 of the Cochrane handbook; however, the handbook used the example of continuous data without specifying the case for dichotomous variables.[63] The paper by Ukoumunne et al. confirms that the geometric scale is may be used on binary outcomes.[62] Although the paper was about cluster RCTs rather than meta-analyses, it provided additional evidence that the geometric scale should be used whenever skewness of the data is suspected. Furthermore, two key papers on the statistical derivation of NIMs demonstrated that margins can be estimated using the logarithmic form of the effect size (i.e., on the geometric scale).[64,65] In his paper, Wang reported that the evaluation of non-inferiority is made while the effect size and the NIM are on the logarithmic scale (i.e., the geometric form); he reported "if the upper 100(1-γ)% confidence limit for the risk difference log(Treatment) - log(Control) is less than the margin log(NIM) in the active controlled trial, then it can be concluded that the new treatment is not inferior to the active control in the sense of preserving the specified fraction of the control effect."[65] It was not clear from the Prins and Lensing article why the arithmetic scale was used instead of the geometric scale in estimating the NIM. For the CDR re-assessment, NIMs were estimated using the arithmetic and geometric scales. The resulting odds ratio, relative risk, and the associated NIMs are summarized in Table 27.

TABLE 27: SUMMARY OF THE CADTH COMMON DRUG REVIEW RECALCULATED NON-INFERIORITY MARGINS

Source of data	Non-Inferiority Margin[a]	Odds Ratio[b]		Risk Ratio[b]	
		Fixed Effect	Random Effect	Fixed Effect	Random Effect
Event rates as reported by Prins and Lensing 2013[8] (all trials included)	**Effect size (95% CI)**	0.15 (0.10 to 0.22)	0.16 (0.11 to 0.25)	0.17 (0.11 to 0.25)	0.19 (0.12 to 0.28)
	NIM (arithmetic scale)	2.21	2.00	2.00	1.87
	NIM (geometric scale)	1.67	1.60	1.60	1.54

CI = confidence interval; NIM = non-inferiority margin.
[a] NIM was estimated by preserving 66% of the comparator effect.
[b] Calculated using Review Manager 5.2 and the Mantel–Haenszel procedure.

The recalculated NIMs ranged from 1.87 to 2.21 on the arithmetic scale. The hazard ratios for VTE recurrence in the EINSTEIN trials were 0.68 (95% CI, 0.44 to 1.04) in the DVT trial and 1.12 (95% CI, 0.75 to 1.68) in the PE trial; therefore, the use of arithmetic scale estimation did not affect the non-inferiority conclusion. However, the geometric scale estimation produced NIMs of 1.54 to 1.67 (both fixed and

random effect models are considered); these estimates for the NIM raise uncertainty for the non-inferiority conclusion in the PE trial.

Conclusion

The EINSTEIN trials used a NIM that was based on a meta-analysis of historical trials; the NIM used was the higher value estimated from the meta-analysis (when preserving 66% of the pooled treatment effect).[8] Furthermore, the assessment of the meta-analysis calculation method suggested that the use of the random effects model would have been more appropriate. Estimating the NIMs based on the geometric scale raises some uncertainty about the non-inferiority conclusion of the EINSTEIN PE trial; the EINSTEIN DVT trial was not affected by the new NIMs.

TABLE 28: STUDY CHARACTERISTICS

Study	Patient population	Comparators/Duration			Total Treatment Duration	Outcome	Comments
		Initial Phase	Acute Phase	Prevention Phase			
PE only							
Barritt et al. 1960[46]	PE only	UFH + VKA **versus no treatment**/ 14 days	NA	NA	14 days	PE death and non-fatal recurrence at 12 months	Trial was stopped earlier than planned. OL, RCT
Agnelli et al. 2003[47]	PE only	Not provided	VKA (3 months)	VKA (additional 3 or 9 months, depending on risk factors) **versus no treatment**	12 months	VTE (including death)	The trial was excluded from the CDR recalculation of NIM because the results were not reported for the period during which the two groups received different coagulation therapy. OL, RCT
DVT only							
Hull 1979[32]	DVT only (calf vein 47.1%)	UFH (14 days)	VKA versus UFH (low dose, 12 weeks)	NA	12 weeks	VTE (death was not specified)	OL, RCT
Holmgren 1985[48]	DVT only (proximal 83%; calf vein 17%)	UFH + VKA (5 days)	VKA (1 month versus 6 months)	NA	6 months	VTE (death included)	OL, RCT
Lagerstedt 1985[34]	DVT (calf vein 100%)	UFH + VKA (5 days)	VKA versus **no treatment** (3 months)	NA	12 weeks	VTE (death was not specified)	OL, RCT
Hull et al. 1986[49]	DVT-proximal	UFH versus SC UFH (10 days)	VKA (3 months)	NA	6 months	VTE + PE death	DB, RCT
Brandjes et al. 1992[50]	DVT-proximal	UFH + VKA versus VKA alone (7 days)	VKA (3 months)	NA	6 months	Symptomatic extension of DVT, symptomatic PE, or	DB, RCT

Study	Patient population	Comparators/Duration			Total Treatment Duration	Outcome	Comments
		Initial Phase	Acute Phase	Prevention Phase			
						symptomatic recurrence of VTE	
Levine et al. 1995[51]	DVT-proximal	UFH alone (> 5 days)	VKA alone (4 weeks)	VKA 12 weeks (8 additional weeks) **versus** placebo	3 months	VTE (at 2 and 11 months)	DB, RCT
Agnelli et al. 2001[52]	DVT-proximal	UFH or LMWH	VKA (3 months)	VKA/ 12 months (9 additional) **versus** No treatment	12 months	VTE	OL, RCT
DVT or PE							
Raschke et al. 1993[37]	VTE (73.9%); unstable angina (22.6%); arterial ischemia (3.5%)	"Weight-based" UFH versus "standard care" UFH	VKA (started after 48 hours)/ Not reported	NR	NR	VTE at three months (secondary outcome)	OL, RCT
Schulman et al. 1995[35]	VTE (38.7% distal DVT)	UFH or LMWH + VKA (≥ 5 days)	VKA (6 weeks)	VKA (6 months) **versus** no treatment	6 months	VTE at 24 months	OL, RCT
Kearon et al. 1999[53]	VTE (proximal DVT and/or PE)	UFH or LMWH / not reported	VKA (3 months)	VKA (24 months) **versus** placebo	24 months	VTE during the 24 months after randomization	DB, RCT – trial terminated at 10 months
Pinede et al. 2001[54]	VTE (proximal DVT and/or PE)	UFH or LMWH	VKA (started during the first 5 days, 6 weeks) (C-DVT – below popliteal vein) or 12 weeks (P-DVT or PE)	VKA (12 weeks) **versus** no treatment (C-DVT) OR (24 weeks) versus no treatment (P-DVT or PE)	24 weeks	VTE at 12 months	OL, RCT

Study	Patient population	Comparators/Duration			Total Treatment Duration	Outcome	Comments
		Initial Phase	Acute Phase	Prevention Phase			
Schulman et al. 1997[36]	Second episode VTE (26.4% distal DVT)	UFH or LMWH + VKA	VKA (6 months)	VKA (indefinite duration) **versus** no treatment	Indefinite	VTE at 4 years	OL, RCT

DB = double-blind; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; NA = not applicable; NR = not recorded; OL = open-label; PE = pulmonary embolism; RCT = randomized controlled trial; SC = subcutaneous; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism.

APPENDIX 6: DEFINITIONS OF PRIMARY OUTCOMES USED IN THE EINSTEIN TRIALS

The following definitions were applied by the central independent adjudication committee to confirm a suspected episode of symptomatic recurrent DVT or PE:

1. Suspected (recurrent) DVT with one of the following findings:
   a. abnormal compression ultrasound (CUS) where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression
   b. an extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography.

   or

2. Suspected PE with one of the following findings:
   a. a (new) intraluminal filling defect in segmental or more proximal branches on spiral computed tomography scan
   b. a (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram
   c. a (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on ventilation/perfusion lung scintigraphy
   d. inconclusive spiral computed tomography, pulmonary angiography, or lung scintigraphy with demonstration of DVT in the lower extremities by CUS or venography.

3. Fatal PE was:
   a. PE based on objective diagnostic testing, autopsy
   b. death which cannot be attributed to a documented cause and for which DVT/PE cannot be ruled out (unexplained death).

Without objective testing (see Section 3), a suspected episode of DVT or PE was to be considered as confirmed if it led to a change in anticoagulant treatment at therapeutic dosages for more than 48 hours.

APPENDIX 7: SUMMARY OF OTHER STUDIES

Aim

The objective of this appendix is to provide a summary of the extension phase of study EINSTEIN DVT, named EINSTEIN Extension.[5]

Findings

EINSTEIN DVT was an open-label RCT enrolling patients with acute symptomatic deep vein thrombosis (DVT). Patients were randomized to oral rivaroxaban alone (15 mg twice daily for three weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (VKA) for three, six, or 12 months. The purpose of EINSTEIN Extension was to explore the benefit-to-risk ratio when treatment with rivaroxaban is administered after six to 12 months of anticoagulation. This was a double-blind, event-driven superiority study. Eligible patients were randomized using a computerized voice-response system with stratification by country. The intended treatment duration was determined by the treating physician. The primary outcome in this extension study was recurrent venous thromboembolism (VTE). Major bleeding was the key safety outcome, which was defined consistently with that in EINSTEIN DVT. Analyses of the treatment effects and bleeding were performed in pre-specified subgroups.

The trial characteristics are summarized in Table 29.

TABLE 29: EINSTEIN EXTENSION STUDY CHARACTERISTICS

Objective	To evaluate the efficacy and safety of continued treatment with rivaroxaban alone, once daily, in patients who have received treatment for acute DVT or PE, compared with placebo
Population	**The included** patients had confirmed symptomatic DVT or PE, had been treated for 6 to 12 months with VKA (acenocoumarol or warfarin) or rivaroxaban, and if there was equipoise with respect to the need for continued anticoagulation. **Patients were excluded from the trial for the following:** • another indication for a VKA • impaired renal/hepatic functions • bacterial endocarditis • active bleeding or a high risk of bleeding • contraindicating anticoagulant treatment • systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg • concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers.
Interventions	**Rivaroxaban:** 20 mg q.d., orally, for 6 to 12 months
Comparator	**Matching placebo:** for 6–12 months
Outcomes	**Primary efficacy outcome:** recurrent VTE (composite of DVT or non-fatal/fatal PE) **Secondary efficacy outcomes:** • all-cause mortality • vascular events (acute coronary syndrome, ischemic stroke, transient ischemic attack, or systemic embolism) • net clinical benefit (defined as the composite of the primary efficacy outcome or major bleeding)
Design	Double-blind, randomized, placebo-controlled, superiority study

DVT = deep vein thrombosis; PE =pulmonary embolism; q.d. = once daily; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Table 30 summarizes the trial findings. EINSTEIN Extension included 1,197 patients: 34.1% of the patients had completed EINSTEIN DVT, 19.1% had completed EINSTEIN PE, and the remaining 47.5% were referred from outside both EINSTEIN DVT and PE. Six hundred and two patients were randomized to continuous rivaroxaban therapy, and 595 patients were randomized to placebo (one was excluded from intention-to-treat (ITT) analysis due to invalid informed consent).

Patient characteristics between EINSTEIN DVT and EINSTEIN Extension were similar with respect to gender, weight, and creatinine clearance. In EINSTEIN Extension, the demographic and clinical characteristics of patients in the two groups were comparable; the mean age was 58 years, and the median time from onset of symptoms to randomization was 204 days in the rivaroxaban group and 206 days in the placebo group. The duration of treatment was shorter than intended for 156 patients (25.9%) in the rivaroxaban group and for 148 patients (24.9%) in the placebo group. Follow-up for the primary efficacy outcome was completed for 99.8% of the patients in both groups. More patients in the rivaroxaban group discontinued study because of adverse events (AEs) than those in the placebo group.

Continuous rivaroxaban therapy was associated with an 82% reduction in recurrent VTE compared with placebo (eight events in the rivaroxaban group and 42 events in the placebo group; hazard ratio 0.18; 95% CI, 0.09 to 0.39). The difference between the two groups was statistically significant. The majority of the VTE events were non-fatal pulmonary embolism (PE) and recurrent DVT.

Rivaroxaban-treated patients experienced more major bleeding (four in the rivaroxaban group and none in the placebo group), although the difference between the two groups was not statistically significant. More clinically relevant non-major bleeding events were reported in the rivaroxaban group as well. There were three deaths in EINSTEIN Extension, one (PE-related) in the rivaroxaban group, and two (one PE-related, one cancer-related) in the placebo group. No patient in either group had an elevated alanine aminotransferase level exceeding three times the upper limit of the normal range, or a bilirubin level exceeding twice the upper limit of the normal range.

TABLE 30: EINSTEIN EXTENSION STUDY MAIN FINDINGS

	Rivaroxaban	Placebo
N	602	594
Age, mean ± SD	58.2 ± 15.6	58.4 ± 16
Male, n (%)	354 (58.8)	339 (57.1)
Initial diagnosis, n	DVT: 386 PE: 216	DVT: 356 PE: 238
Median time from onset of symptoms to randomization, days	204	206
Intended duration of treatment, n (%) 6 months 12 months	 360 (59.8) 242 (40.2)	 357 (60.1) 237 (39.9)
Median duration of treatment, days 6-month period 12-month period	 181 264	 NR 265
Premature study discontinuation, n (%) AEs Consent withdrawn Lost to follow-up	 39 (6.5) 22 (3.7) 1 (0.2)	 18 (3.0) 19 (3.2) 1 (0.2)
Efficacy results (ITT population: 602 with rivaroxaban, 594 with placebo)		
Recurrent VTE	8 (1.3)	42 (7.1)
	HR*: 0.18 (95% CI: 0.09 to 0.39), $P < 0.001$	
Type of recurrent VTE Fatal PE PE cannot be ruled out Non-fatal PE Recurrent DVT	 0 1 2 5	 1 0 13 31
Safety results (safety population: 598 with rivaroxaban, 590 with placebo)		
Major bleeding, n (%)	4 (0.7)	0
	HR[a]: NA, $P = 0.11$	
Clinically relevant non-major bleeding, n (%)	32 (5.4)	7 (1.2)
Total death	1 (0.2)	2 (0.3)
PE, or PE not ruled out	1	1
Bleeding	0	0
Cancer	0	1
Cardiovascular disease	0	0
Other	0	0

AE = adverse event; CI = confidence interval; DVT = deep vein thrombosis; HR = hazard ratio; ITT = intention-to-treat; NA = not applicable; NR = not rated; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolism.
[a] HRs were for rivaroxaban as compared with placebo.

EINSTEIN Extension was sponsored by the manufacturer, which collected and maintained the data, whereas all suspected outcome events were classified by a central independent adjudication committee, members of which were unaware of the treatment assignments. Power calculation for this superiority trial was provided and deemed appropriate. Data were analyzed in the ITT population. Loss to follow-up was low in both groups in this study.

Summary

In EINSTEIN Extension, patients' baseline characteristics were comparable between rivaroxaban and placebo, and were also similar to the initial EINSTEIN DVT trial. The incidence of death was similar for rivaroxaban and placebo (one patient [0.2%] versus two [0.3%], respectively). Patients treated with continuous rivaroxaban reported significantly lower rates of recurrent VTE (1.3% with rivaroxaban versus 7.1% with placebo, hazard ratio = 0.18 [95% CI, 0.09 to 0.39], $P < 0.001$). Major bleeding was reported in four patients treated with rivaroxaban, but not in placebo-treated patients (0.7% versus 0, $P = 0.11$). Higher rates of clinically relevant non-major bleeding were observed in the rivaroxaban group compared with placebo (32 patients [5.4%] versus 7 [1.2%], respectively).

Compared with the results from EINSTEIN DVT, patients who received continuous rivaroxaban after six to 12 months of acute anticoagulation therapy had lower death rates, lower recurrent VTE, and fewer major bleeding events. For patients treated with rivaroxaban, the rate of withdrawal due to AEs was slightly higher in EINSTEIN Extension than in EINSTEIN DVT (6.5% versus 4.9%, respectively).

This placebo-controlled trial concluded that monotherapy with rivaroxaban provided an effective and safe approach to the continued treatment of venous thrombosis, without the need for laboratory monitoring. However, compared with another anticoagulant, there is a lack of evidence of long-term clinical efficacy and safety of rivaroxaban, particularly for patients with active cancer, for the treatment and prevention of recurrence of VTE.

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