Common Drug Review
Clinical Review Report

June 2016

Drug	apixaban (Eliquis)
Indication	Treatment of venous thromboembolic events (deep vein thrombosis, pulmonary embolism) and prevention of recurrent deep vein thrombosis and pulmonary embolism.
Listing request	Treatment of venous thromboembolic events (deep vein thrombosis and pulmonary embolism) and prevention of recurrent deep vein thrombosis and pulmonary embolism.
Manufacturer	Bristol-Myers Squibb Canada and Pfizer Canada

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 hematology who provided input on the conduct of the review and the interpretation of findings.

Through the 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.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

AE	adverse event
CDEC	CADTH Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CrI	credible interval
CRNM	clinically relevant, non-major
DB	double-blind
DIC	deviance information criterion
DVT	deep vein thrombosis
IDC	indirect comparison
INR	international normalized ratio
ITT	intention-to-treat (population)
LMWH	low-molecular-weight heparin
NI	non-inferiority
NMA	network meta-analysis
NOAC	new oral anticoagulant drug
PE	pulmonary embolism
PP	per-protocol (population)
RCT	randomized controlled trial
RD	risk difference
RR	relative risk
SAE	serious adverse event
SD	standard deviation
UFH	unfractionated heparin
VKA	vitamin K antagonist
VTE	venous thromboembolic event
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Venous thromboembolic events (VTE), which include deep vein thrombosis (DVT) and pulmonary embolism (PE), are a significant health care concern leading to increased morbidity and mortality.[1,2] Signs and symptoms of DVT include unilateral leg pain, swelling, tenderness, increased temperature, and prominent superficial veins. The clinical presentation of PE is composed of non-specific signs and symptoms, which may include dyspnea, chest pain, cough, hemoptysis, and syncope.[3] Anticoagulant therapy aims to treat the current episode and prevent VTE recurrence.[1] Initial anticoagulation is achieved with parenteral treatment options such as low-molecular-weight heparins (LMWHs).[4] However, the use of an oral vitamin K antagonist (VKA) such as warfarin, initiated at the time parenteral therapy is started, is usually preferred for the extended treatment of VTE.[1,4] Despite being widely used, warfarin is the source of various concerns[4-6] and requires frequent monitoring. Anticoagulation should be maintained for a minimum of three months; however, extending treatment beyond that may prove beneficial for patients with persistent risk factors or who are experiencing recurrent or unprovoked idiopathic VTE.[4]

Apixaban is an orally active, direct factor Xa inhibitor.[6-8] Apixaban has a Health Canada indication for the treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE.[7] The manufacturer has requested that apixaban be reimbursed according to the Health Canada indication. The objective of this report was to perform a systematic review of the beneficial and harmful effects of apixaban for the treatment of VTE, i.e., DVT and PE, and for the prevention of recurrent DVT and PE.

Results and Interpretation

Included Studies

Two manufacturer-sponsored, double-blind (DB), randomized controlled trials (RCTs) were included in the systematic review. AMPLIFY (N = 5,400)[9,10] evaluated whether apixaban is non-inferior (NI) to the combination of enoxaparin and warfarin in the acute treatment of VTE in adult patients with symptomatic proximal DVT or PE with a risk of recurrence. Patients randomized to apixaban received 10 mg twice daily for seven days, followed by 5 mg twice daily for six months. The primary efficacy outcome was the incidence of symptomatic, recurrent VTE or VTE-related death at six months. Non-inferiority would be demonstrated if the upper bound of the corresponding 95% confidence interval (CI) was below the NI margins of 1.8 for the relative risk (RR) and 0.035 for the risk difference (RD). If NI were demonstrated, then superiority for major bleeding, the primary safety outcome, would be tested, followed by superiority for the primary efficacy outcome.

AMPLIFY-EXT (N = 2,486)[11,12] was a pivotal study evaluating the superiority of apixaban compared with placebo for continued VTE prevention in patients who had previously completed six to 12 months of anticoagulation therapy following the diagnosis of symptomatic DVT or PE without experiencing a VTE recurrence. In accordance with the Health Canada–recommended dose, patients receiving apixaban 2.5 mg twice daily in the AMPLIFY-EXT study were considered in this review. The primary efficacy outcome was the incidence of symptomatic recurrent VTE or all-cause mortality after 12 months.

Both AMPLIFY and AMPLIFY-EXT were conducted with methodological rigour, and AMPLIFY provides evidence regarding the efficacy and safety of apixaban for acute VTE treatment. However, the use of placebo as a comparator in AMPLIFY-EXT was identified as a major limitation. While uncertainty remains regarding the optimal treatment duration, major guidelines[4] and the experience of a specialist in clinical

practice suggest that the patient population in AMPLIFY-EXT should have been treated with an anticoagulant rather than a placebo. Therefore, there is a lack of evidence with which to directly compare apixaban to other anticoagulants for treating patients beyond six months who are at risk of a recurrent VTE. There is a similar lack of direct evidence with which to compare apixaban to other new oral anticoagulants (NOACs) (dabigatran and rivaroxaban), as these drugs were not included as comparators in the AMPLIFY or the AMPLIFY-EXT trial.

Efficacy

Results from AMPLIFY for the acute treatment of VTE met the pre-specified NI margins (RR = 1.8 and RD = 0.035) for the primary efficacy outcome of recurrent VTE/VTE-related death after six months of treatment. The use of apixaban was associated with an RR = 0.84 in the intention-to-treat (ITT) population (95% CI, 0.60 to 1.18; $P < 0.0001$ for NI) and an RR = [redacted] in the per-protocol (PP) population (95% CI [redacted], *P* [redacted]). The relative efficacy of apixaban was not statistically significantly better than the combination of enoxaparin and warfarin. Results for the secondary efficacy outcome of recurrent VTE or all-cause mortality were consistent with those of the primary outcome in demonstrating that apixaban is NI to the combination of enoxaparin and warfarin. Overall, the results of AMPLIFY suggest that apixaban may be considered as effective as combination therapy with enoxaparin and warfarin for acute VTE treatment (up to six months).

The AMPLIFY-EXT study provided evidence to assess continued VTE prevention (up to 12 months, following six to 12 months of initial therapy). Results for the primary outcome of recurrent VTE or all-cause mortality demonstrated that apixaban was superior to placebo after 12 months of study treatment (18 to 24 months of anticoagulant treatment in total). The use of apixaban was associated with an RR = 0.33 (95% CI, 0.22 to 0.48; $P < 0.0001$ for superiority). A substantially greater proportion of patients in the placebo treatment group experienced a VTE recurrence (11.6%) compared with the apixaban group (3.8%), which suggests that the use of placebo was not appropriate for this patient population.

To address the issue of a lack of direct comparative evidence for apixaban versus other NOACs, the CADTH Common Drug Review (CDR) reviewed two indirect comparisons (IDCs) submitted by the manufacturer, as well as five published IDCs, which assessed the efficacy and safety of apixaban compared with other anticoagulants, including NOACs, for the acute treatment and continued prevention of VTE. The results of these IDCs are consistent with the conclusion that there are no major differences among the efficacy of the NOACs in treating and preventing recurrent VTE both in the short term (up to six months) and the long term (up to 12 months), as there were no statistically significant differences among treatments for the outcomes of VTE and VTE-related death, non-fatal PE, DVT, myocardial infarction, overall treatment discontinuation, and all-cause mortality among treatments. However, the small number of studies available for IDC and the rarity of the events that were analyzed mean that the heterogeneity among studies renders the conclusions related to comparative efficacy highly uncertain.

Harms

Results from AMPLIFY demonstrated the superiority of apixaban over the combination of enoxaparin and warfarin for the primary safety outcome of major bleeding (RR = 0.31; 95% CI, 0.17 to 0.54; $P < 0.0001$ for superiority). Notable harms included fatal bleeding (one patient with apixaban versus two patients with enoxaparin plus warfarin), intracranial bleeding (three patients versus six patients, respectively), and gastrointestinal bleeding ([redacted] versus [redacted], respectively). Apixaban was

also superior to enoxaparin plus warfarin for clinically relevant, non-major (CRNM) bleeding (RR = 0.48; 95% CI, 0.38 to 0.60; *P* < 0.0001 for superiority).

Mortality, as well as the overall incidence of serious adverse events (SAEs) during AMPLIFY, did not differ significantly between apixaban and the combination of enoxaparin and warfarin, and was not higher than would be expected in this patient population in clinical practice. The frequency for most commonly reported SAEs was similar and low (less than 1.5%) for both treatments and included PE, DVT, pneumonia, overdose, gastrointestinal hemorrhage, and hematuria. The proportion of patients experiencing AEs was slightly lower with apixaban compared with the combination of enoxaparin and warfarin (67% versus 72%, respectively). Few patients discontinued treatment due to adverse events (AEs) in both treatment groups.

The comparison between apixaban and placebo for the continued prevention of VTE in the AMPLIFY-EXT study yielded inconclusive results for the primary safety outcome of major bleeding. The small number of events reported in both the apixaban (n = 2) and the placebo (n = 4) treatment groups leads to substantial uncertainty surrounding the results. The use of apixaban compared with placebo was associated with a fewer deaths ([redacted] for apixaban versus [redacted] for placebo), SAEs (13.3% versus 19.1%, respectively) and withdrawals due to adverse events (WDAEs) (8.0% versus 16.2%, respectively), but these results reflect the higher proportion of patients reporting a DVT or PE episode due to the absence of a therapeutic effect in the placebo treatment group. Similar proportions of patients experienced AEs in both treatment groups (71.0% and 73.4%, respectively). The most common AEs reported were similar to those for the AMPLIFY study.

The results of two IDCs submitted by the manufacturer and five published IDCs of the safety of apixaban compared with other anticoagulants including other NOACs yielded inconsistent results for bleeding-related outcomes, as apixaban was not consistently superior to other NOACs for all bleeding outcomes. Specifically, in the acute-treatment IDC, apixaban was significantly less likely to cause major bleeding compared with dabigatran, but not compared with rivaroxaban. By contrast, for the extended-treatment IDC, rivaroxaban was associated with a significantly higher risk of major bleeding or CRNM bleeding compared with apixaban, but there were no differences between apixaban and dabigatran for these outcomes. The results of the published IDCs for acute treatment were similar to the manufacturer's analysis in that there were differences between apixaban and the other NOACs with respect to major bleeding; however, all but one of the IDCs that examined extended treatment differed from the manufacturer's results in failing to detect differences among NOACs for major bleeding or CRNM bleeding. Given the aforementioned limitations of the IDCs (most notably, the small number of studies and the rarity of bleeding events), there is a high degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban compared with other NOACs.

Conclusions

The results of the AMPLIFY study demonstrated that apixaban is NI, but not superior, to the combination of enoxaparin and warfarin for the acute treatment of VTE (up to six months) in patients with a risk of recurrent VTE, based on the frequency of recurrent symptomatic VTE or VTE-related mortality. In the same study, apixaban was associated with significantly fewer bleeding events than enoxaparin plus warfarin. The results of the AMPLIFY-EXT study demonstrated that apixaban is superior to placebo for extended (up to 12 months) VTE prevention, based on the frequency of recurrent symptomatic VTE or all-cause mortality. However, low event rates in this study precluded any conclusion regarding the relative effect of apixaban versus placebo on bleeding. The results of two IDCs submitted by the manufacturer and five published IDCs of the efficacy and safety of apixaban compared with other NOACs

were consistent with the conclusion that apixaban is as efficacious as other NOACs in treating and preventing VTE, for both acute and extended treatment, and that apixaban is as least as safe as the other NOACs with respect to the risk of bleeding.

TABLE 1: SUMMARY OF RESULTS

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban	Enoxaparin plus Warfarin	Apixaban 2.5 mg	Placebo
Key Efficacy Outcomes	**N = 2,691**	**N = 2,704**	**N = 840**	**N = 829**
Symptomatic VTE (non-fatal DVT or PE)/VTE-Related Death				
ITT analysis, n (%)	59 (2.3), N = 2,609	71 (2.7), N = 2,635	[redacted]	[redacted]
RR (95% CI)	**0.84 (0.60 to 1.18)**		[redacted]	
P value	***P* < 0.0001 for NI[a]**		[redacted]	
RD (95% CI)	[redacted]		[redacted]	
P value	[redacted]		NR	
PP analysis, n (%)	[redacted]	[redacted]	NR	NR
RR (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
RD (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
Symptomatic VTE (non-fatal DVT or PE) or All-Cause Mortality				
ITT analysis, n (%)	84 (3.2), N = 2,609	104 (3.9), N = 2,635	32 (3.8)	96 (11.6)
RR (95% CI)	**0.82 (0.61 to 1.08)**		**0.33 (0.22 to 0.48)**	
P value	***P* = 0.155 for superiority**		***P* < 0.0001 for superiority**	
Non-fatal DVT				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
Non-fatal PE				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
VTE-related death				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
All-cause mortality				
n (%)	41 (1.6), N = 2,608	52 (2.0), N = 2,630	[redacted]	[redacted]
RR (95% CI)	0.79 (0.53 to 1.19)		[redacted]	
Key Harms Outcomes	**N = 2,676**	**N = 2,689**	**N = 840**	**N = 826**
Major bleeding				
n (%)	15 (0.6)	49 (1.8)	2 (0.2)	4 (0.5)
RR (95% CI)	**0.31 (0.17 to 0.54)**		**0.49 (0.09 to 2.64)**	
P value for superiority	***P* < 0.0001**		[redacted]	

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban	Enoxaparin plus Warfarin	Apixaban 2.5 mg	Placebo
Key Harms Outcomes	**N = 2,676**	**N = 2,689**	**N = 840**	**N = 826**
CRNM bleeding				
n (%)	103 (3.8)	215 (8.0)	25 (3.0)	19 (2.3)
RR (95% CI)	0.48 (0.38 to 0.60)		1.29 (0.72 to 2.33)	
P value	[redacted]		[redacted]	
SAEs, n (%)	417 (15.6)	410 (15.2)	112 (13.3)	158 (19.1)
AEs, n (%)	1,795 (67.1)	1,923 (71.5)	596 (71.0)	606 (73.4)
WDAEs, n (%)	162 (6.1)	199 (7.4)	67 (8.0)	134 (16.2)

AE = adverse event; CI = confidence interval; CRNM = clinically relevant, non-major; DVT = deep vein thrombosis; ITT = intention-to-treat; NI = non-inferiority; NR = not reported; PE = pulmonary embolism; PP = per-protocol; RD = risk difference; RR = relative risk; SAE = serious adverse event; VTE = venous thromboembolic event; WDAE = withdrawal due to adverse event.

[a] AMPLIFY: *P* value for superiority non-significant; otherwise, superiority not tested.

Note: Patients with missing outcome were excluded from the efficacy analyses.

Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report; Agnelli et al. (2013); AMPLIFY-EXT Clinical Study Report.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Venous thromboembolic events (VTE) are a significant health care concern leading to increased morbidity and mortality, especially in hospitalized patients or in the presence of various inherited or acquired disorders.[1,2] The clinical manifestations include deep vein thrombosis (DVT) and pulmonary embolism (PE).[1,2] DVT is often seen in the lower extremity and may occur in a distal or proximal location, the latter of which is considered to be of greater clinical importance, considering its association with higher PE and mortality rates.[1] VTE is often a result of an interaction between patient-related and setting-related risk factors.[13-15] Patient-related risk factors include age, obesity, chronic heart or respiratory failure, oral contraceptive therapy or hormone replacement therapy, previous VTE, and thrombophilia.[3,13,16] Other significant factors related to immobilization or setting include lower limb fractures, joint replacement surgery, and major general surgery or trauma.[13,16]

Signs and symptoms of DVT include unilateral leg pain, swelling, tenderness, increased temperature, and prominent superficial veins.[3] The clinical presentation of PE is composed of non-specific signs and symptoms, which may include dyspnea, chest pain, cough, hemoptysis, and syncope.[3] The manufacturer provided estimations of the incidence of VTE in Canada reaching 43,000 cases per year.[8] The long-term burden of VTE includes a high risk of recurrence persisting for several years,[2] as well as complications such as chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome, which are characterized by symptoms of venous insufficiency.[1,2]

1.2 Standards of Therapy

Anticoagulant DVT treatment aims to prevent further extension of the thrombus, which could eventually travel to the lung and progress to PE.[1] Resuscitation is the mainstream therapy in the acute phase of PE; however, anticoagulation should be started as soon as possible.[17] The objectives of anticoagulant therapy are to avoid the recurrence of VTE and to preclude the development of complications.[1] Initial anticoagulation is achieved with parenteral treatment options, including low-molecular-weight heparins (LMWHs) and fondaparinux, both recommended over unfractionated heparin (UFH).[4] However, oral treatment options are usually preferred for the extended treatment of VTE.[1,4] The American College of Chest Physicians 2012 Clinical Practice Guidelines[4] recommend the use of an oral vitamin K antagonist (VKA) such as warfarin, initiated at the time parenteral therapy is started due to a 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 2.5 (range of 2.0 to 3.0).[4] 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 who are experiencing recurrent or unprovoked idiopathic VTE.[4] Despite being widely used, warfarin is the source of various concerns, especially considering a narrow therapeutic window of adequate coagulation without bleeding as well as a highly variable dose-response relation among individuals and numerous interactions with food and other drugs.[4-6] 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.[1]

Other treatment options include the new oral anticoagulants (NOACs) apixaban, dabigatran, and rivaroxaban. All NOACs have a Health Canada indication for the treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE. The efficacy and safety of apixaban are reviewed in this report. To date, the CADTH Common Drug Review (CDR) has not received a drug submission for dabigatran.

A previous review of rivaroxaban resulted in the Canadian Drug Expert Committee (CDEC) recommending that the drug be listed for the treatment of VTE and prevention of recurrent DVT and PE, for a duration of up to six months.

1.3 Drug

Apixaban is a potent, direct, and highly selective factor Xa inhibitor, which holds a key position in the cascade of blood coagulation while showing a limited role outside coagulation.[6-8] This orally active drug prevents thrombin generation and hence thrombus development.[7,8] Apixaban has a Health Canada indication for the treatment of VTE (DVT and PE) and the prevention of recurrent DVT and PE.[7] Apixaban is also indicated for VTE prevention in adult patients who have undergone elective knee or hip replacement surgery, as well as for the prevention of stroke and systemic embolism in patients with atrial fibrillation.[7] The recommended dose of apixaban for the treatment of acute DVT or PE is 10 mg by mouth twice daily for seven days, followed by 5 mg by mouth twice daily; the recommended dose for the continued prevention of recurrent VTE is 2.5 mg by mouth twice daily after at least six months of treatment for DVT or PE.[7] Duration of therapy should be individualized after careful assessment of the balance between anticoagulant treatment benefit and the individual's risk of bleeding; patients with transient risk factors should receive treatment for at least three months, while extended duration therapy is recommended for patients with permanent risk factors or idiopathic VTE.[7]

Indication under review
Treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE.
Listing criteria requested by sponsor
Treatment of VTE (DVT and PE) and prevention of recurrent DVT and PE.

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolic event.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of apixaban at the recommended dose for the treatment of VTE — i.e., DVT and PE — and for the prevention of recurrent DVT and PE.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other phase 3 studies were selected for inclusion based on the selection criteria presented in Table 2.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with confirmed DVT and/or PE
Intervention	*Treatment of acute DVT and/or PE*: Apixaban 10 mg PO b.i.d. × 7 days, followed by 5 mg PO b.i.d. *Continued prevention of recurrent DVT and/or PE*: Apixaban 2.5 mg PO b.i.d. after at least 6 months of treatment for DVT or PE
Comparators	• VKA in combination with LMWH as initial treatment • LMWH alone • Rivaroxaban alone • Dabigatran in combination with LMWH as initial treatment • VKA in combination with fondaparinux as initial treatment

Outcomes	**Key efficacy outcomes:**
	• Survival
	• Recurrent DVT and/or PE
	• HRQoL
	• Hospitalizations
	• Chronic thromboembolic pulmonary hypertension
	• Post-thrombotic syndrome
	
	Harms outcomes:
	• Mortality
	• SAEs
	• WDAEs
	• AEs including but not limited to:
	  ○ major bleeding events
	  ○ CRNM bleeding events

Study Design	Published and unpublished RCTs

AE = adverse event; b.i.d. = twice daily; CRNM = clinically relevant, non-major; DVT = deep vein thrombosis; HRQoL = health-related quality of life; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PO = orally; RCT = randomized controlled trial; SAE = serious adverse event; VKA = vitamin K antagonist; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed 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), and keywords. The main search concepts were Eliquis (apixaban) and venous thromboembolism.

A methodological filter was applied to limit retrieval to randomized controlled trials (RCTs) and controlled clinical trials. 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 November 27, 2014. Regular alerts were established to update the search until the meeting of CDEC on April 8, 2015. 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 websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials and databases (free). 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 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: EXCLUDED STUDIES.

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 3 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

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

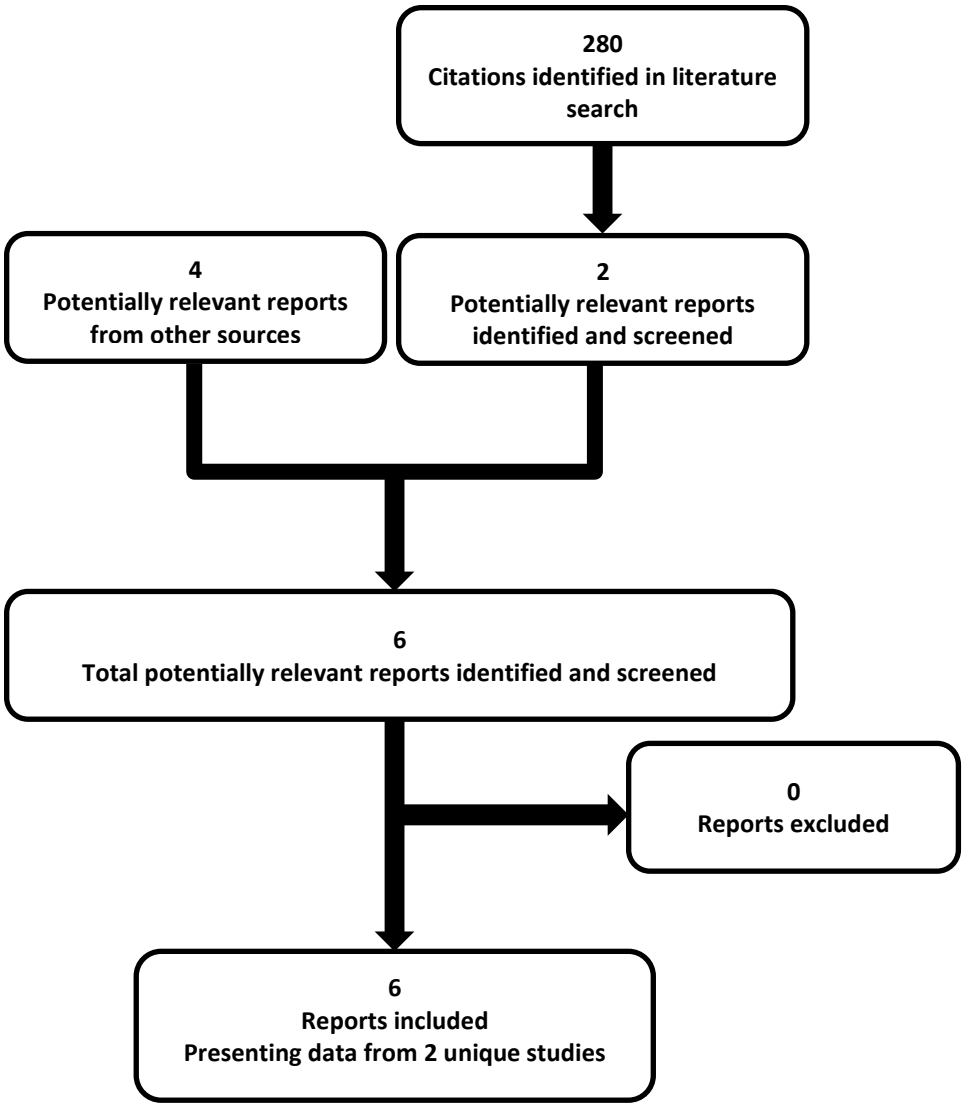


TABLE 3: DETAILS OF INCLUDED STUDIES

		AMPLIFY *Acute VTE Treatment*	AMPLIFY-EXT *Continued VTE Prevention*
DESIGNS & POPULATIONS	**Study Design**	DB NI RCT	DB PL-controlled RCT
	Locations	Multi-centre (28 countries): Europe, USA, Canada (n = 299), South America, Asia	Multi-centre (28 countries): Europe, USA, Canada (n = 54), Asia, South America
	Randomized (N)	5,400	2,486
	Inclusion Criteria	Patients ≥ 18 years of age with adjudicated acute symptomatic DVT or PE who are at risk of recurrence.	Patients ≥ 18 years of age with adjudicated acute symptomatic DVT or PE who are at risk of recurrence, who completed 6 to 12 months of anticoagulant treatment, and experienced no symptomatic VTE recurrence.
	Exclusion Criteria	Unprovoked VTE without risk of recurrence; planned treatment duration < 6 months; active bleeding or high risk for bleeding; use of LMWH for at least 6 months in patients with cancer; presence of another indication for long-term VKA treatment; recent serious bleeding; clinically significant liver disease; uncontrolled hypertension; concomitant ASA or dual antiplatelet therapy.	Unprovoked VTE without risk of recurrence; planned treatment duration < 12 months; presence of indications for long-term VKA treatment; cancer patients requiring indefinite anticoagulation therapy; recent serious bleeding; clinically significant liver disease; uncontrolled hypertension; prior use of oral direct factor Xa inhibitors or oral direct thrombin inhibitors (except for patients who participated in AMPLIFY); concomitant ASA or dual antiplatelet therapy.
DRUGS	**Intervention**	Apixaban 10 mg PO b.i.d. × 7 days, followed by 5 mg PO b.i.d. × 6 months.	Apixaban 2.5 mg PO b.i.d. × 12 months, or apixaban 5 mg PO b.i.d. × 12 months.
	Comparator	Warfarin PO q.d., dosing to target INR range between 2.0 to 3.0 × 6 months; and enoxaparin 1 mg/kg SC b.i.d. as initial treatment until INR ≥ 2.	Placebo
DURATION	**Phase**		
	DB phase	6 months	12 months
OUTCOMES	**Primary End Point**	**Efficacy** Adjudicated composite of: • symptomatic, recurrent VTE (non-fatal DVT or PE); or • VTE-related death. **Safety** Adjudicated major bleeding.	**Efficacy** Adjudicated composite of: • symptomatic, recurrent VTE (non-fatal DVT or PE); or • all-cause mortality. **Safety** Adjudicated major bleeding.

		AMPLIFY *Acute VTE Treatment*	AMPLIFY-EXT *Continued VTE Prevention*
	Other End Points	**Efficacy** Non-fatal DVT; non-fatal PE; VTE-related death; all-cause mortality; hospitalizations. **Safety** Adjudicated CRNM bleeding; minor bleeding; SAEs; AEs.	
NOTES	**Publications**	Agnelli et al. (2013)[9], Agnelli et al. (2013)[18]	Agnelli et al. (2013)[11], Agnelli et al. (2013)[19]

AE = adverse event; ASA = acetylsalicylic acid; b.i.d. = twice daily; DB = double-blind; CRNM = clinically relevant, non-major; DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NI = non-inferiority; PE = pulmonary embolism; PL = placebo; PO = orally; q.d. = once daily; RCT = randomized controlled trial; SC = subcutaneous; SAE = serious adverse event; VKA = vitamin K antagonist; VTE = venous thromboembolic event.
Note: Three additional reports were included.[8,10,12]
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR); Agnelli et al. (2013); AMPLIFY-EXT CSR.[9-12]

3.2 Included Studies

3.2.1 Description of Studies

Two published, manufacturer-sponsored, double-blind (DB) RCTs were included in the systematic review.

AMPLIFY (N = 5,400)[9,10] evaluated the non-inferiority (NI) of apixaban compared with a regimen of warfarin in combination with enoxaparin as initial anticoagulant treatment in patients with confirmed symptomatic DVT or PE. Patients randomized to apixaban received a dose of 10 mg twice daily for seven days, followed by 5 mg twice daily for six months; patients randomized to the enoxaparin plus warfarin regimen received warfarin for six months, at a dose adjusted to maintain a target INR range between 2.0 and 3.0, in combination with enoxaparin 1 mg/kg subcutaneously twice daily for at least five days as initial treatment until INR ≥ 2.

AMPLIFY-EXT (N = 2,486)[11,12] evaluated the superiority of two different doses of apixaban compared with placebo for extended VTE treatment in patients who had been previously diagnosed with symptomatic DVT or PE, who had completed approximately six to 12 months of anticoagulation therapy, and who did not experience a VTE recurrence during that treatment period. Patients were randomized to receive apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, or placebo for 12 months. However, only the apixaban dose of 2.5 mg twice daily falls within the Health Canada–recommended dosage and was considered in this systematic review. The AMPLIFY-EXT study met the inclusion criteria based on the fact that it is considered a pivotal trial.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients were eligible for the AMPLIFY and AMPLIFY-EXT trials if they were at least 18 years of age with adjudicated, acute, symptomatic proximal DVT with evidence of proximal thrombosis that involved at least the popliteal vein, or acute symptomatic PE. The target population was patients who had had an unprovoked index event with a risk of recurrence.[10] AMPLIFY-EXT was conducted during the extended treatment of VTE; therefore, patients were required to have completed approximately six to 12 months of anticoagulant treatment, including but not limited to patients who participated in the AMPLIFY trial,

and in order to be admissible for inclusion, needed to have experienced no symptomatic VTE recurrence.

The key exclusion criteria for both trials included unprovoked events without the existence of a persistent risk factor for recurrence, as well as a planned duration of anticoagulation that was less than six months for AMPLIFY and less than 12 months for AMPLIFY-EXT. Patients were also excluded if they had another indication for long-term VKA treatment; recent serious bleeding that was considered clinically relevant; active and clinically significant liver disease; uncontrolled hypertension; and abnormal targeted laboratory findings. The use of acetylsalicylic acid at a dose exceeding 165 mg per day or dual antiplatelet therapy also figured as exclusion criteria.

Patients were excluded from AMPLIFY in the presence of active bleeding or a high risk for bleeding preventing treatment with LMWH and a VKA, or if treatment of the current VTE episode required either thrombectomy, insertion of a cava filter, or medication with a fibrinolytic drug. Prior use of apixaban, as well as repeated doses of a VKA, fondaparinux, LMWH, or continuous infusion of UFH before the administration of study drug was prohibited. Patients with cancer who had been treated for at least six months with LMWH therapy could not enter the trial.

Patients were excluded from AMPLIFY-EXT if they had used any oral direct factor Xa inhibitor, any oral direct thrombin inhibitor, or any investigational antithrombotic drug during the acute treatment of the initial event, with the exception of patients who had participated in the AMPLIFY study. Patients with cancer who had been treated indefinitely with anticoagulation therapy could not enter the trial.

b) Baseline Characteristics

Details regarding baseline characteristics are provided in Table 4 and Table 5. Overall, baseline characteristics were balanced between treatment groups in both the AMPLIFY and AMPLIFY-EXT studies.

AMPLIFY

Patients enrolled in the AMPLIFY trial had a mean age of 57 years, with the trial population ranging from [redacted] to [redacted] years. A total of [redacted] of patients were between 65 and 75 years old and [redacted] of patients were at least 75 years old. Close to 60% of patients were male and [redacted] were Caucasian. Mean weight was 85 kg ± 19.8 kg; however, 19% of patients weighed 100 kg or more. Less than 7% of patients had experienced moderate or severe renal impairment. Several patients reported relevant comorbidities that could have an impact on the risk of VTE, including [redacted] ([redacted] of patients) and [redacted] ([redacted]).

The majority of patients (65%) had experienced a DVT as the qualifying diagnosis; other initial events included PE alone (25%), and PE with DVT (less than 10%). Unprovoked events were the most frequent clinical presentation of VTE and encompassed 90% of patients. Consequently, 66% of patients presented no risk factor for recurrent VTE; of those who did, 16% had experienced a previous VTE, while only a few patients had a known thrombophilia or active cancer. The median time elapsed from the VTE event up to randomization was five days. As treatment of the initial VTE with an injectable anticoagulant at therapeutic doses prior to randomization was allowed under certain conditions, a majority of patients received pre-treatment with either LMWH, heparin, or fondaparinux.

AMPLIFY-EXT

The population included in AMPLIFY-EXT was similar to that of the AMPLIFY study in terms of baseline demographics. Patients enrolled had a mean age of 57 years, with the trial population ranging from [redacted]

to [redacted] years. A total of [redacted] of patients were between 65 and 75 years old and [redacted] of patients were at least 75 years old. Close to 60% of patients were male and [redacted] were Caucasian. Mean weight was 86 kg ± 20 kg in the apixaban group and 85 kg ± 19 kg in the placebo group. Less than 10% of patients experienced moderate or severe renal impairment. Several patients reported relevant comorbidities that could have an impact on the risk of VTE, including cigarette smoking (19% of patients) and obesity (27%). A total of 34% of patients had participated in the AMPLIFY study before being enrolled in AMPLIFY-EXT.

The majority of patients (65%) had experienced a DVT as the qualifying diagnosis; other initial events included PE (34%). Unprovoked events were the most frequent clinical presentation of VTE and encompassed 92% of patients. Consequently, 68% of patients presented no risk factor for recurrent VTE; of those who did, 12% had experienced a previous VTE, while few patients had a known thrombophilia or active cancer. A total of [redacted] of patients had received prior anticoagulant treatment with [redacted], while [redacted] had received another one of the drugs allowed; almost all patients were treated for six to 12 months. The nature of the anticoagulant treatment received was not reported for [redacted] of patients, including patients who had participated in the AMPLIFY study. The mean treatment duration was [redacted], with a range of [redacted] for the apixaban group and of [redacted] for the placebo group.

TABLE 4: SUMMARY OF BASELINE DEMOGRAPHICS

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Age				
Mean ± SD, years	57.2 ± 16.0	56.7 ± 16.0	56.6 ± 15.3	57.1 ± 15.2
Range, years	[redacted]	[redacted]	[redacted]	[redacted]
65 years to < 75 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Sex, n (%)				
Male	1,569 (58.3)	1,598 (59.1)	487 (58.0)	468 (56.5)
Female	1,122 (41.7)	1,106 (40.9)	353 (42.0)	361 (43.5)
Weight				
Mean ± SD, kg	84.6 ± 19.8	84.6 ± 19.8	85.7 ± 19.8	84.7 ± 18.6
≤ 60 kg, n (%)	231 (8.6)	245 (9.1)	58 (6.9)	48 (5.8)
> 60 kg to < 100 kg, n (%)	1,932 (71.8)	1,936 (71.6)	> 60 kg: 780 (92.9)	> 60 kg: 778 (93.8)
≥ 100 kg, n (%)	522 (19.4)	518 (19.2)		
Missing data	6 (0.2)	5 (0.2)	2 (0.2)	3 (0.4)
Race, n (%)				
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
African-American	[redacted]	[redacted]	[redacted]	[redacted]
Native American	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Missing data	[redacted]	[redacted]	[redacted]	[redacted]
Renal status (creatinine clearance), n (%)				
Normal (> 80 mL/min)	1,721 (64.0)	1,757 (65.0)	595 (70.8)	564 (68.0)
Mild impairment (> 50 to ≤ 80 mL/min)	549 (20.4)	544 (20.1)	174 (20.7)	194 (23.4)
Moderate impairment (> 30 to ≤ 50 mL/min)	161 (6.0)	148 (5.5)	47 (5.6)	44 (5.3)
Severe impairment (≤ 30 mL/min)	14 (0.5)	15 (0.6)	1 (0.1)	2 (0.2)
Missing data	246 (9.1)	240 (8.9)	23 (2.7)	25 (3.0)
Comorbidities, n (%)				
Cigarette smoking	[redacted]	[redacted]	156 (18.6)	158 (19.1)
Diabetes mellitus	[redacted]	[redacted]	100 (11.9)	93 (11.2)
Hypercholesterolemia	[redacted]	[redacted]	243 (28.9)	241 (29.1)
Hypertension	[redacted]	[redacted]	336 (40.0)	356 (42.9)
Obesity	[redacted]	[redacted]	228 (27.1)	219 (26.4)
Participation in the AMPLIFY study				
n (%)	2,691 (100)	2,704 (100)	282 (33.6)	282 (34.0)

NR = not reported; SD = standard deviation; VTE = venous thromboembolic event.
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR); Agnelli et al. (2013); AMPLIFY-EXT CSR.[9-12]

TABLE 5: SUMMARY OF RELEVANT BASELINE CHARACTERISTICS

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Qualifying diagnosis, n (%)				
DVT	1,749 (65.0)	1,783 (65.9)	544 (64.8)	551 (66.5)
PE alone	678 (25.2)	681 (25.2)	All PE events: 296 (35.2)	All PE events: 278 (33.5)
PE with DVT	252 (9.4)	225 (8.3)		
Missing data	12 (0.4)	15 (0.6)		
Extent of PE, n/N (%)				
Limited	79/930 (8.5)	89/906 (9.8)	NR	NR
Intermediate	392/930 (42.2)	395/906 (43.6)	NR	NR
Extensive	357/930 (38.4)	326/906 (36.0)	NR	NR
Missing data	102/930 (11.0)	96/906 (10.6)	NR	NR
Time from onset of symptoms to randomization				
Median, days	5.0	5.0	NR	NR
Interquartile range	3.0 to 9.0	3.0 to 9.0	NR	NR
Clinical presentation of VTE, n (%)				
Unprovoked	2,416 (89.8)	2,429 (89.8)	783 (93.2)	755 (91.1)
Provoked	272 (10.1)	272 (10.1)	56 (6.7)	72 (8.7)
Missing data	3 (0.1)	3 (0.1)	[redacted]	[redacted]
Risk factors for recurrent VTE at the time of the qualifying diagnosis, n (%)				
No risk factor	[redacted]	[redacted]	[redacted]	[redacted]
Previous VTE	463 (17.2)	409 (15.1)	99 (11.8)	99 (11.9)
Persistent or permanent immobilization	[redacted]	[redacted]	19 (2.3)	22 (2.7)
Known thrombophilia or prothrombotic genotype	74 (2.8)	59 (2.2)	32 (3.8)	36 (4.3)
Active cancer	66 (2.5)	77 (2.9)	15 (1.8)	18 (2.2)

DVT = deep vein thrombosis; NR = not reported; PE = pulmonary embolism; VTE = venous thromboembolic event.
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR); Agnelli et al. (2013); AMPLIFY-EXT CSR.[9-12]

TABLE 6: ANTICOAGULANT THERAPIES RECEIVED PRIOR TO RANDOMIZATION

AMPLIFY — *Acute VTE Treatment*			AMPLIFY-EXT — *Continued VTE Prevention*		
	Apixaban	Enoxaparin plus Warfarin		Apixaban 2.5 mg	Placebo
LMWH, heparin, or fondaparinux, n (%)			**Vitamin K antagonist, n (%)**	[redacted]	[redacted]
None	358 (13.3)	381 (14.1)	6 to 12 months	[redacted]	[redacted]
≤ 12 hours	371 (13.8)	341 (12.6)	**Other anticoagulant, n (%)**	[redacted]	[redacted]
> 12 to 24 hours	1,116 (41.5)	1,126 (41.6)	6 to 12 months	[redacted]	[redacted]
> 24 to 36 hours	587 (21.8)	613 (22.7)	**NR, n (%)**	[redacted]	[redacted]
> 36 to 48 hours	231 (8.6)	211 (7.8)	**Duration, months**		
> 48 hours	22 (0.8)	26 (1.0)	Mean	[redacted]	[redacted]
Missing data	6 (0.2)	6 (0.2)	Range	[redacted]	[redacted]

LMWH = low-molecular-weight heparin; NR = not reported; VTE = venous thromboembolic event.
[a] [redacted]
Sources: Agnelli et al. (2013);[9] AMPLIFY Clinical Study Report (CSR);[10] Agnelli et al. (2013);[11] AMPLIFY-EXT CSR.[12]

3.2.3 Interventions

AMPLIFY evaluated the efficacy and safety of apixaban for the treatment of VTE and the prevention of recurrence at the recommended dose of 10 mg twice daily for seven days, followed by 5 mg twice daily for six months. The comparator was a standard regimen consisting of enoxaparin 1 mg/kg subcutaneously twice daily for at least five days as initial treatment; warfarin was administered concomitantly and maintained for a total of six months at a dose adjusted to maintain a target INR range between 2.0 and 3.0. As the study was blinded, patients also received matching placebos.

AMPLIFY-EXT evaluated the efficacy and safety of apixaban compared with placebo for the continued prevention of VTE recurrence at the recommended dose of 2.5 mg twice daily for 12 months, after at least six months of acute VTE treatment. The trial also included an apixaban 5 mg twice-daily treatment group that will not be discussed in this systematic review, as the dose exceeds the Health Canada recommendations.

The concomitant use of various medications or therapies was prohibited throughout the AMPLIFY and AMPLIFY-EXT trials. These included potent inhibitors of cytochrome P450 3A4, acetylsalicylic acid > 165 mg/day, dual antiplatelet therapy, other antithrombotic drugs, and glycoprotein IIb/IIIa inhibitors. If their use became necessary, the study drug was temporarily interrupted. Although not proscribed, chronic nonsteroidal anti-inflammatory drugs were to be administered with caution due to the increased risk of bleeding.

3.2.4 Outcomes

a) Efficacy

The primary efficacy outcome for AMPLIFY was the incidence of an adjudicated composite of symptomatic recurrent VTE (non-fatal DVT or PE) or VTE-related death throughout the planned trial duration of six months, regardless of whether patients were receiving the study medication.

The primary efficacy outcome for AMPLIFY-EXT was the incidence of an adjudicated composite of symptomatic recurrent VTE (non-fatal DVT or PE) or all-cause mortality throughout the planned trial duration of 12 months, regardless of whether patients were receiving the study medication.

Secondary efficacy outcomes in both trials included non-fatal DVT, non-fatal PE, VTE-related death, all-cause mortality, and hospitalizations.

b) Safety

The primary safety outcome for both AMPLIFY and AMPLY-EXT was the incidence of adjudicated major bleeding, which was defined according to an adaptation of the widely known and accepted International Society on Thrombosis and Haemostasis definition.[20]

Major bleeding was defined as acute, clinically overt bleeding associated with:

- a fall in the hemoglobin level of 2 g/dL or more; or
- transfusion of two or more units of packed red blood cells or 1,000 mL or more of whole blood; or
- bleeding in a critical site, including intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal; or
- bleeding that was fatal.

Clinically relevant non-major (CRNM) bleeding was among the secondary safety outcomes, and was defined as acute, clinically overt bleeding consisting of:

- any bleeding compromising hemodynamics or leading to hospitalization; or
- large subcutaneous hematoma or intramuscular hematoma; significant epistaxis, hematuria, or gastrointestinal hemorrhage; spontaneous gingival bleeding; rectal blood loss; hemoptysis; or
- bleeding with clinical consequences, including medical intervention or unscheduled contact with a physician, temporary cessation of a study drug, or pain or impairment of activities of daily life.

Other safety outcomes included adverse events (AEs), serious adverse events (SAEs), minor bleeding, clinical laboratory results, and vital signs.

An independent central adjudication committee review and adjudication occurred without awareness of treatment allocation for all suspected occurrences of venous or arterial thromboembolic events, episodes of bleeding, and deaths that occurred during the study period and the post-treatment observation period.

3.2.5 Statistical Analysis

a) AMPLIFY

In order to demonstrate the NI of apixaban compared with the enoxaparin plus warfarin regimen in the AMPLIFY trial, two hypotheses were tested: one based on relative risk (RR) and the second based on risk difference (RD). NI would be demonstrated if the upper bound of the corresponding 95% confidence interval (CI) was below the NI margin for each hypothesis. The manufacturer selected an NI margin of RR = 1.8. A total of 26 studies were identified by the manufacturer through a literature search to support the estimation of this NI margin, intending to maintain at least 50% of the proven efficacy of enoxaparin plus warfarin versus placebo response. The NI margin of RD = 0.035 would protect against higher than expected event rates in the control group.[10]

AMPLIFY utilized a hierarchical hypothesis-testing plan that was agreed upon by the US FDA. Statistical testing of the primary efficacy and safety outcomes was achieved in the following hierarchical order:

1. NI for VTE or VTE-related death (one-sided alpha = 0.025); if NI was demonstrated, then
2. superiority for major bleeding (two-sided alpha = 0.05); if superiority was demonstrated, then
3. superiority for VTE or VTE-related death (two-sided alpha = 0.05); if superiority was demonstrated, then
4. superiority for major bleeding or CRNM bleeding (two-sided alpha = 0.05).

The sample size was computed for an NI margin of 1.8. With the assumption that 3% of patients in the enoxaparin plus warfarin group would experience VTE or VTE-related death throughout the trial duration, enrolment of 4,094 patients would have 90% power to demonstrate NI (one-sided alpha = 0.025) assuming a true RR of 1. The sample size was, however, adjusted to 4,816 patients (2,408 per group), in order to provide adequate power for a second analysis based on a per-protocol (PP) data set, based on the assumption that approximately 15% of patients would discontinue treatment early but complete the trial follow-up. However, a review of the blinded aggregate rate for the primary efficacy outcome by the committee once 80% of patients had been randomized led to a sample size increase up to the maximum of 5,400 patients planned in the study protocol.

No imputation for missing data was planned for the primary efficacy analysis, as the primary efficacy data set included only those randomized patients with non-missing primary outcome information. Patients were considered to have a missing primary outcome if that outcome could not be determined on or after 22 weeks of the intended treatment period, whether the primary outcome had occurred.

b) AMPLIFY-EXT

The primary objective of AMPLIFY-EXT was to test for the superiority of apixaban compared with placebo for the composite outcome of symptomatic recurrent VTE or all-cause mortality after 12 months of extended treatment, based on the RR. The sample size was computed with the assumption that 2% of patients taking apixaban and 6% of patients taking placebo would experience VTE or VTE-related death throughout the trial duration; other deaths included in the outcome of all-cause mortality were assumed to be distributed equally between placebo and active therapy. For this three-group study, inclusion of 2,430 patients would provide 90% power to reject the null hypothesis and demonstrate superiority (two-sided alpha = 0.05).

In the primary and secondary efficacy analyses, patients with missing outcome information were classified as having had the efficacy event.

c) Analysis Populations

AMPLIFY

The efficacy outcome analyses included events that occurred at any time from randomization until the end of the originally intended treatment period, regardless of whether patients were receiving study medication (using the intention-to-treat [ITT] principle). Efficacy analyses included only patients with a non-missing primary outcome; patients whose outcome information for the composite of VTE or VTE-related death could not be documented on or after study day 154 were considered to have a missing outcome and were excluded for the primary efficacy analysis. The primary efficacy outcome was also analyzed using the PP population, which consisted of a subset of patients with no major protocol deviation.

The safety data set (as-treated) consisted of all randomized patients who had received at least one dose of the study drug. For the purpose of safety analyses, patients were categorized to the group to which they were assigned unless incorrect study treatment was received throughout the study, in which case the patient was categorized according to the treatment received.

AMPLIFY-EXT

The primary efficacy analysis included all randomized patients. Patients were categorized according to the group to which they had been assigned at randomization, regardless of the treatment actually received (ITT principle). No PP analysis was reported.

The safety data set (as-treated) consisted of all randomized patients who had received at least one dose of the study drug. For the purpose of safety analyses, patients were categorized to the group to which they had been assigned unless incorrect study treatment was received throughout the study, in which case the patient was categorized according to the treatment received.

3.3 Patient Disposition

A total of [redacted] patients were enrolled in AMPLIFY; of these, 5,395 patients were randomized. Discontinuation rates throughout the study duration, as well as the reasons for discontinuation, were balanced between treatment groups. A total of 14% of patients randomized to apixaban and 15% of patients receiving the combination of enoxaparin and warfarin discontinued from the trial; the most frequent reasons for discontinuation were adverse events (WDAEs) (5.6% and 6.7%, respectively) and withdrawal of consent (1.8% in each treatment group).

A total of [redacted] patients were enrolled in AMPLIFY-EXT; of these, 2,486 patients were randomized. Discontinuation rates throughout the study duration were higher in the placebo treatment group, and reasons for discontinuation were unbalanced between treatment groups. A total of 14% of patients randomized to apixaban and 23% of patients receiving placebo discontinued from the trial; the most frequent reasons for discontinuation were adverse events (8% versus 15%, respectively), death (0.1% versus 1.1%), and lost to follow-up (0.2% versus 1.0%). Further details are provided in Table 7.

TABLE 7: PATIENT DISPOSITION

Patient Disposition	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban	Enoxaparin Plus Warfarin	Apixaban 2.5 mg	Placebo
Enrolled, N	[redacted]		[redacted]	
Randomized — overall	5,395		2,486	
Randomized — per group	2,691	2,704	840	829
Randomized and treated, n (%)	2,676 (99.4)	2,689 (99.4)	840 (100)	826 (99.6)
Discontinued, n (%)	377 (14.0)	413 (15.3)	114 (13.6)	188 (22.7)
Most frequent reasons for discontinuation, n (%)				
AE	150 (5.6)	182 (6.7)	65 (7.7)	126 (15.2)
Death	20 (0.7)	26 (1.0)	1 (0.1)	9 (1.1)
Withdrawal of consent	49 (1.8)	49 (1.8)	7 (0.8)	6 (0.7)
Lost to follow-up	14 (0.5)	14 (0.5)	2 (0.2)	8 (1.0)
Other reasons	144 (5.4)	142 (5.3)	39 (4.6)	39 (4.7)
Analysis sets				
ITT,[a] N	2,609	2,635	840	829
PP, N	2,257	2,235	–	–
Safety, N	2,676	2,689	840	826

AE = adverse event; ITT = intention-to-treat; PP = per-protocol; VTE = venous thromboembolic event.
[a] Patients for whom the outcome status at month 6 was documented.
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR); Agnelli et al. (2013); AMPLIFY-EXT CSR.[9-12]

3.4 Exposure to Study Treatments

Exposure to study treatments was balanced between treatment groups. Further details are presented in Table 8.

In the AMPLIFY study, [redacted] of patients had a treatment duration ranging between approximately [redacted] and [redacted]. The mean length of exposure was approximately five months in both treatment groups. In the AMPLIFY-EXT study, 82% of patients receiving apixaban and 75% of patients receiving placebo had a treatment duration ranging between approximately nine and 12 months. The mean length of exposure was approximately 11.1 months in the apixaban treatment group and 10.4 months in the placebo treatment group.

TABLE 8: EXTENT OF EXPOSURE

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
Length of exposure				
Category, n (%)				
≤ 7 days	[redacted]	[redacted]	[redacted]	[redacted]
8 to 15 days	[redacted]	[redacted]	[redacted]	[redacted]
16 to 30 days	[redacted]	[redacted]	[redacted]	[redacted]
31 to 90 days	[redacted]	[redacted]	[redacted]	[redacted]
91 to 172 days[a]	[redacted]	[redacted]	[redacted]	[redacted]
> 172 days	[redacted]	[redacted]	[redacted]	[redacted]
91 to 180 days	[redacted]	[redacted]	[redacted]	[redacted]
181 to 270 days	[redacted]	[redacted]	[redacted]	[redacted]
271 to 367 days	[redacted]	[redacted]	[redacted]	[redacted]
> 367 days	[redacted]	[redacted]	[redacted]	[redacted]
Mean ± SD, days	[redacted]	[redacted]	[redacted]	[redacted]
Median, days	[redacted]	[redacted]	[redacted]	[redacted]
Range, days	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation; VTE = venous thromboembolic event.
[a] Approximately 3 to 5.7 months.
Note: Six-month trial duration = approximately 180 days.
Source: AMPLIFY Clinical Study Report (CSR); AMPLIFY-EXT CSR.[10,12]

The time spent in therapeutic range in the enoxaparin and warfarin treatment group of the AMPLIFY trial was 61%, which means that patients spent 39% of the time outside the targeted INR range of 2.0 to 3.0. The time spent in suboptimal INR was 23%, while 16% of the time was spent above the INR target (Table 9).

TABLE 9: TIME SPENT IN THERAPEUTIC RANGE

	AMPLIFY Enoxaparin Plus Warfarin N = 2,704
TTR spent in each INR category, % (target INR between 2.0 and 3.0)	
INR < 2.0	22.9
2.0 ≤ INR ≤ 3.0	60.9
INR > 3.0	16.1

INR = international normalized ratio; TTR = time spent in therapeutic range.
Note: Included INRs from first INR measurement after day 15 through last INR measurement on or before last dose of medication and excluded the time period (if applicable) when warfarin dosing was temporarily interrupted.
Source: AMPLIFY Clinical Study Report.[10]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Study Design, Intervention, and Comparator

AMPLIFY was a DB, NI trial that was likely conducted with methodological rigour, which is further illustrated by the fact that results for the PP and the ITT analyses were consistent with one another. The comparator was an adequate treatment regimen consisting of enoxaparin as initial treatment and warfarin, for a total duration of six months. The quality of INR control was adequately reported through time spent in the therapeutic range. Patients treated with warfarin spent 61% of the time within the target INR values of 2.0 to 3.0. Non-optimal INR results affect the treatment efficacy and safety in the comparator group, which may bias the results in favour of apixaban. However, this also improves generalizability, as INR values are expected to vary naturally; in the AMPLIFY study, results appear to be generally reflective of clinical practice.

AMPLIFY-EXT was a DB, placebo-controlled trial evaluating the use of apixaban for continued VTE prevention during extended anticoagulant treatment in patients who completed six to 12 months of therapy and who did not experience a VTE recurrence. The trial was likely conducted with methodological rigour. While uncertainty remains regarding the optimal treatment duration, recommendations from major guidelines[4] and experience of specialists in clinical practice suggest that the decision to extend anticoagulation be based upon an individual's risk-versus-benefit profile. (This issue is further discussed in Appendix 7.) As such, if the ratio favours pursuing anticoagulation, comparing an active treatment to placebo potentially affects the interpretation of the findings in favour of the active treatment.

b) Selection, Allocation, and Disposition of Patients

Both trials used appropriate allocation strategies. Randomization was performed centrally through an interactive voice response system. The trials used a triple-dummy design with matching placebos and, in the AMPLIFY study, sham INR results for patients receiving apixaban.

Baseline characteristics were balanced between treatment groups in both the AMPLIFY and AMPLIFY-EXT studies. Discontinuation rates throughout the AMPLIFY study duration, as well as the reasons for discontinuation, were also balanced between treatment groups. However, discontinuation rates throughout the AMPLIFY-EXT study duration were higher in the placebo treatment group. This is mainly due to a higher proportion of patients discontinuing due to the AEs of DVT and PE, which is consistent with an unsatisfactory treatment effect in the placebo group.

c) Outcome Measures

The choice of outcome measures and definitions for efficacy and safety outcomes in both trials is appropriate. VTE recurrence and major bleeding events are widely accepted outcomes used to assess response to anticoagulant treatment. Events were evaluated by a central, blinded, independent adjudication committee.

d) Statistical Analysis

For the AMPLIFY trial, 26 studies were identified by the manufacturer through a literature search to support the estimation of the pre-specified NI margin of RR = 1.8. The manufacturer intended to maintain at least 50% of the proven efficacy of enoxaparin plus warfarin versus placebo response. Although there is uncertainty regarding the optimal NI margin to be selected for VTE trials, an NI margin of RR = 1.8 does not appear to be unreasonable.

Both trials had sufficient power to demonstrate statistical significance for testing of the primary hypothesis. No imputation for missing data was planned in the AMPLIFY study; in AMPLIFY-EXT, patients with missing outcome information were classified as having had the efficacy event, which is appropriate.

3.5.2 External Validity

a) Patient Selection

Inclusion and exclusion criteria appeared relevant and reasonable in both trials. However, patients who had experienced an initial event without the existence of a persistent risk factor for recurrence were excluded; therefore, the included patients were likely at higher risk of VTE recurrence than the overall real-life population. In addition, various groups of patients with comorbid conditions were excluded, including recent clinically relevant bleeding or liver disease, and uncontrolled hypertension. Furthermore, only 2% to 3% of patients had active cancer. Therefore, the findings from AMPLIFY and AMPLIFY-EXT are not generalizable to these categories of patients. Other baseline characteristics seem representative of real-life patients according to the clinical expert consulted by CDR reviewers.

b) Treatment Regimen and Length of Follow-up

The AMPLIFY study used an appropriate and realistic treatment regimen for acute VTE treatment. However, there is a gap in the evidence for continued VTE prevention due to the use of placebo as a comparator in AMPLIFY-EXT. Recommendations from major guidelines[4] and experience of specialists in clinical practice suggest that a number of real-life patients will likely require a treatment duration exceeding the six-month follow-up period in the AMPLIFY trial. However, AMPLIFY-EXT does not provide information on how apixaban compares to other anticoagulants in patients requiring extended anticoagulant treatment once a decision to maintain anticoagulation has been made, which is the objective of our systematic review. Placebo was not targeted as a comparator in the CDR systematic review protocol (Table 2), but the AMPLIFY-EXT study was included on the basis that it was a pivotal study.

A generalizability issue of AMPLIFY-EXT is that the majority of patients included in the trial were previously treated with an anticoagulant drug other than apixaban for the initial VTE, with few details reported regarding their acute-treatment regimens. As it is not standard practice to switch anticoagulant drugs in the middle of treatment without a valid reason, the trial design is not representative of real-life treatment characteristics. The impact on the findings is, however, uncertain.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported (Section 2.2, Table 2). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data. No data were reported for the outcomes of health-related quality of life, chronic thromboembolic pulmonary hypertension, and post-thrombotic syndrome.

3.6.1 Symptomatic VTE or VTE-Related Death

a) Acute VTE Treatment

In the AMPLIFY study, results for the primary outcome of symptomatic VTE or VTE-related death met the pre-specified NI margins of 1.8 for the RR and 0.035 for the RD (using the upper bound of the 95% CI). The use of apixaban was associated with a relative risk reduction (RRR) of 16% compared with the combination of enoxaparin and warfarin in the ITT population (RR = 0.84; 95% CI, 0.60 to 1.18; $P < 0.0001$ for NI), and reached an RRR of [redacted] in the PP population (RR = [redacted]; 95% CI, [redacted]; *P* [redacted]). However, the superiority of apixaban over enoxaparin plus warfarin could not be demonstrated, as results for such testing did not achieve statistical significance. The proportions of patients

experiencing an event in each individual treatment group remained low (less than 3%) according to the clinical expert consulted by the CDR review team. Detailed results are presented in Table 10: Key Efficacy Outcomes.

b) Continued VTE Prevention

In the AMPLIFY-EXT study, results for the secondary outcome of VTE or VTE-related death show that apixaban is associated with a RRR of [redacted] versus placebo (RR = [redacted]; 95% CI, [redacted], *P* [redacted]). The proportion of patients experiencing an event was [redacted] in the apixaban treatment group compared with [redacted] in the placebo treatment group.

3.6.2 Symptomatic VTE or All-Cause Mortality

a) Acute VTE Treatment

The use of apixaban in the AMPLIFY study for the secondary outcome of symptomatic VTE or all-cause mortality was associated with a RRR of 18% compared with the combination of enoxaparin and warfarin (RR = 0.82; 95% CI, 0.61 to 1.08). The only statistical testing reported for this outcome pertained to the superiority of apixaban over enoxaparin plus warfarin, and did not reach statistical significance.

b) Continued VTE Prevention

In the AMPLIFY-EXT study, results for the primary outcome of symptomatic VTE or all-cause mortality show the superiority of apixaban over placebo, with a RRR of 67% (RR = 0.33; 95% CI, 0.22 to 0.48; $P < 0.0001$ for superiority). The proportion of patients experiencing an event was 3.8% in the apixaban treatment group compared with 11.6% in the placebo treatment group.

3.6.3 Individual Event Types

Individual event types in both trials included DVT, PE, VTE-related death, and all-cause mortality.

a) Acute VTE Treatment

In the AMPLIFY study, results for the individual event types were reported for the ITT population and show that apixaban was associated with an RRR of [redacted] for non-fatal DVT (RR = [redacted]; 95% CI, [redacted]), and with an RRR of [redacted] for VTE-related death (RR = [redacted]; 95% CI, [redacted]). There were numerically a few more non-fatal PE events with apixaban compared with enoxaparin plus warfarin ([redacted] versus [redacted]; RR = [redacted]; 95% CI, [redacted]); however, the overall incidence of PE remained low and similar in both treatment groups (1.0% and 0.9%, respectively). Of note, there were more PEs than DVTs in the apixaban treatment group. Apixaban was also associated with an RRR of 21% compared with the combination of enoxaparin and warfarin for the secondary outcome of all-cause mortality (1.6% versus 2.0%, respectively [RR = 0.79; 95% CI, 0.53 to 1.19]). The outcome of death and the most frequent causes of death are further discussed in Section 1.12.1 — Mortality.

b) Continued VTE Prevention

In the AMPLIFY-EXT study, the use of apixaban yielded an RRR of [redacted] compared with placebo for the outcome of non-fatal DVT (RR = [redacted]; 95% CI, [redacted]; *P* [redacted]); this was the only individual event type in which apixaban demonstrated superiority over placebo. The proportion of patients experiencing an event was [redacted] in the apixaban treatment group compared with [redacted] in the placebo treatment group. Apixaban was associated with an RRR of [redacted] compared with placebo for the outcome of non-fatal PE (RR = [redacted]; 95% CI, [redacted]), an RRR of [redacted] for the outcome of VTE-related death (RR = [redacted]; 95% CI, [redacted]), and an RRR of [redacted] for the outcome of all-cause mortality (RR = [redacted]; 95% CI, [redacted]); none of the results for these outcomes reached statistical significance.

3.6.4 Hospitalizations

a) Acute VTE Treatment

The proportion of patients requiring hospitalization while receiving study treatment was slightly lower in the apixaban treatment group compared with the combination of enoxaparin and warfarin ([redacted] versus [redacted], respectively). The duration of the hospital stay was [redacted] on average for patients receiving apixaban compared with enoxaparin plus warfarin ([redacted] versus [redacted], respectively). However, no statistical analysis to compare the two treatment groups was reported. The most common reasons for all admissions or visits to a health care professional, including hospitalizations, rehabilitations, nursing home admissions, emergency room visits, and doctor's office visits, were bleeding ([redacted] for apixaban versus [redacted] for enoxaparin plus warfarin) and VTE ([redacted] versus [redacted], respectively). Detailed results are presented in Table 14: Hospitalizations.

b) Continued VTE Prevention

The proportion of patients requiring hospitalization was also slightly lower in the apixaban treatment group compared with placebo (5.0% versus 7.5%, respectively). The duration of the hospital stay was [redacted] on average for patients receiving apixaban versus placebo ([redacted] versus [redacted], respectively). However, no statistical analysis to compare the two treatment groups was reported. The most common reasons for all admissions or visits to a health care professional were [redacted] ([redacted] for apixaban versus [redacted] for placebo) and [redacted] ([redacted] versus [redacted], respectively).

TABLE 10: KEY EFFICACY OUTCOMES

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin Plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Composite of Symptomatic VTE (Non-fatal DVT or PE) or VTE-Related Death				
ITT analysis				
n (%)	59 (2.3), N = 2,609	71 (2.7), N = 2,635	[redacted]	[redacted]
RR (95% CI)	**0.84 (0.60 to 1.18)**		[redacted]	
P value	***P* < 0.0001 for NI[a]**		[redacted]	
RD (95% CI)	[redacted]		[redacted]	
P value	[redacted]		NR	
PP analysis				
n (%)	[redacted]	[redacted]	NR	NR
RR (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
RD (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
Composite of Symptomatic VTE (Non-fatal DVT or PE) or All-Cause Mortality				
ITT analysis				
n (%)	84 (3.2), N = 2,609	104 (3.9), N = 2,635	32 (3.8)	96 (11.6)
RR (95% CI)	**0.82 (0.61 to 1.08)**		**0.33 (0.22 to 0.48)**	
P value	***P* = 0.155 for superiority**		***P* < 0.0001 for superiority**	
RD (95% CI)	[redacted]		[redacted]	
P value	NR		[redacted]	

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin Plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Individual Event Types				
Non-fatal DVT				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Non-fatal PE				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
VTE-related death				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
All-cause mortality				
n (%)	41 (1.6), N = 2,608	52 (2.0), N = 2,630	[redacted]	[redacted]
RR (95% CI)	**0.79 (0.53 to 1.19)**		[redacted]	
P value	NR		[redacted]	
Hospitalizations				
n patients (%)	153 (5.7)	190 (7.1)	42 (5.0)	62 (7.5)
Mean length of stay ± SD, days	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DVT = deep vein thrombosis; ITT = intention-to-treat; NI = non-inferiority; NR = not reported; PE = pulmonary embolism; PP = per-protocol; RD = risk difference; RR = relative risk; VTE = venous thromboembolic event.
[a] *P* value for superiority non-significant; otherwise superiority not tested in the AMPLIFY study.
Note: Patients with missing outcome were excluded from the analyses in the AMPLIFY study.
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR); Agnelli et al. (2013); AMPLIFY-EXT CSR.[9-12]

3.7 Harms

Only those harms identified in the review protocol are reported (see Section 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Mortality

a) Acute VTE Treatment

A similar proportion of patients in both treatment groups died during the AMPLIFY trial ([redacted] for apixaban and [redacted] for enoxaparin plus warfarin). The most frequent causes of death (≤ [redacted] in each treatment group) included [redacted] One patient receiving apixaban versus two patients receiving the combination of enoxaparin and warfarin died due to bleeding.

b) Continued VTE Prevention

The proportion of patients who died during the AMPLIFY-EXT trial was numerically lower in the apixaban treatment group compared with placebo ([redacted] for apixaban versus [redacted] for placebo). The

most frequent cause of death in the placebo group was [redacted]. There were no deaths due to bleeding in either of the two treatment groups.

3.7.2 Serious Adverse Events

a) Acute VTE Treatment

Similar proportions of patients experienced SAEs in both treatment groups in AMPLIFY, with a total of 15.6% and 15.2% of patients in the apixaban and enoxaparin plus warfarin treatment group, respectively. The most common SAEs reported (less than 1.5% in each treatment group) included PE, DVT, pneumonia, overdose, gastrointestinal hemorrhage, and hematuria.

b) Continued VTE Prevention

The proportion of patients who experienced SAEs during the AMPLIFY-EXT trial was numerically lower in the apixaban treatment group compared with placebo (13.3% versus 19.1%, respectively). The most common SAEs reported (less than 5% in each treatment group) included PE, DVT, pneumonia, and hematuria.

3.7.3 Adverse Events

a) Acute VTE Treatment

The proportion of patients experiencing AEs in the AMPLIFY trial was numerically lower with apixaban compared with the combination of enoxaparin and warfarin (67% versus 72%, respectively). The most common AEs reported (less than 6.5% in each treatment group) included headache, epistaxis, pain in an extremity, peripheral edema, and nausea.

b) Continued VTE Prevention

Similar proportions of patients experienced AEs in both treatment groups in AMPLIFY-EXT, with a total of 71.0% and 73.4% of patients in the apixaban and placebo treatment group, respectively. The most common AEs reported (less than or equal to 6.5% in each treatment group) included headache, pain in an extremity, peripheral edema, and nausea.

3.7.4 Withdrawals Due to Adverse Events

a) Acute VTE Treatment

The proportion of patients discontinuing AMPLIFY due to AEs was 6.1% in the apixaban group and 7.4% in the enoxaparin plus warfarin group. The most frequent reasons for discontinuation due to AEs (less than 1% in each treatment group) included DVT, PE, gastrointestinal hemorrhage, hematuria, hematoma, and increased INR (in the enoxaparin plus warfarin treatment group only).

b) Continued VTE Prevention

The proportion of patients discontinuing AMPLIFY-EXT due to AEs was lower in the apixaban treatment group than in the placebo group (8.0% versus 16.2%, respectively). The most frequent reasons for discontinuation due to AEs included DVT (0.5% with apixaban versus 6.7% with placebo) and PE (0.5% versus 2.3%, respectively).

3.7.4 Notable Harms — Bleeding

a) Acute VTE Treatment

In the AMPLIFY study, results for the primary safety outcome of major bleeding show that apixaban was associated with an RRR of 69% compared with the combination of enoxaparin and warfarin in the safety population (0.6% versus 1.8%, respectively [RR = 0.31; 95% CI, 0.17 to 0.54]); therefore, the superiority of apixaban over enoxaparin plus warfarin was demonstrated ($P < 0.0001$). Among the relevant

individual event types were fatal bleeding (one patient with apixaban versus two patients with enoxaparin plus warfarin), intracranial bleeding (three patients versus six patients, respectively), and gastrointestinal bleeding (versus , respectively).

Results from AMPLIFY also demonstrated the superiority of apixaban compared with enoxaparin plus warfarin for the secondary safety outcome of CRNM bleeding, with an RRR of 52% (3.8% versus 8.0%, respectively [RR = 0.48; 95% CI, 0.38 to 0.60; *P* < 0.0001]).

b) Continued VTE Prevention

In the AMPLIFY-EXT study, results for the primary safety outcome of major bleeding are characterized by a low number of events reported in both treatment groups: two patients experienced an event with apixaban, compared with four patients with placebo. Therefore, results for the RR are surrounded by uncertainty, with a 95% CI ranging from 0.09 to 2.64 and a non-statistically significant *P* value for superiority.

However, apixaban was associated with numerically more CRNM bleeding events than placebo (3.0% versus 2.3%, respectively [RR = 1.29; 95% CI, 0.72 to 2.33]).

TABLE 11: KEY HARMS OUTCOMES

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
Mortality, n (%)				
Most common SAEs with outcome of death:				
SAEs, n (%)	**417 (15.6)**	**410 (15.2)**	**112 (13.3)**	**158 (19.1)**
Most common SAEs:				
AEs, n (%)	**1,795 (67.1)**	**1,923 (71.5)**	**596 (71.0)**	**606 (73.4)**
Most common AEs:				

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	**162 (6.1)**	**199 (7.4)**	**67 (8.0)**	**134 (16.2)**
Most common reasons:				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms				
Major bleeding				
n (%)	15 (0.6)	49 (1.8)	2 (0.2)	4 (0.5)
RR (95% CI)	**0.31 (0.17 to 0.54)**		**0.49 (0.09 to 2.64)**	
P value for superiority	***P* < 0.0001**		[redacted]	
Relevant individual event type, n:				
Fatal bleeding	1	2	0	0
Intracranial bleeding	3	6	[redacted]	[redacted]
Gastrointestinal bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Clinically relevant, non-major bleeding				
n (%)	103 (3.8)	215 (8.0)	25 (3.0)	19 (2.3)
RR (95% CI)	**0.48 (0.38 to 0.60)**		**1.29 (0.72 to 2.33)**	
P value	***P* < 0.0001**		[redacted]	

AE = adverse event; CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism; RR = relative risk; SAE = serious adverse event; VTE = venous thromboembolic event; WDAE = withdrawal due to adverse event.
Source: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR); Agnelli et al. (2013); AMPLIFY-EXT CSR.[9-12]

4. DISCUSSION

4.1 Summary of Available Evidence

Two published, manufacturer-sponsored, DB RCTs were included in the systematic review. AMPLIFY (N = 5,400)[9,10] evaluated the NI of apixaban compared with the combination of enoxaparin and warfarin in the acute treatment of symptomatic DVT or PE. AMPLIFY-EXT (N = 2,486)[11,12] evaluated the superiority of apixaban compared with placebo for continued VTE prevention in patients who had previously completed six to 12 months of anticoagulation therapy following the diagnosis of symptomatic DVT or PE, without experiencing a VTE recurrence. Patients randomized to apixaban in the AMPLIFY study received 10 mg twice daily for seven days, followed by 5 mg twice daily for six months. In accordance with the Health Canada–recommended dose, only patients receiving apixaban 2.5 mg twice daily for 12 months in the AMPLIFY-EXT study were considered in this systematic review.

Both AMPLIFY and AMPLIFY-EXT were conducted with methodological rigour. AMPLIFY provided adequate evidence regarding the efficacy and safety of apixaban for acute VTE treatment. However, there is a gap in the evidence for continued VTE prevention due to the use of placebo as a comparator in AMPLIFY-EXT. While uncertainty remains regarding the optimal treatment duration, recommendations from major guidelines[4] and experience of specialists in clinical practice suggest that the decision to extend anticoagulation be based upon an individual's risk-versus-benefit profile; as such, if the ratio favours pursuing anticoagulation, comparing an active treatment to placebo potentially affects the interpretation of the findings in favour of the active treatment. This systematic review aimed to compare apixaban to other NOACs; therefore, additional evidence was gathered in the form of indirect comparisons (IDCs). The trial populations mostly consisted of patients who had experienced an unprovoked VTE and who were at risk of recurrence. Despite this high risk of recurrence, patients included in the AMPLIFY-EXT study needed to have had no VTE recurrence during the six-to-12-month acute-treatment period that preceded the trial. Therefore, the findings of AMPLIFY and AMPLIFY-EXT are generalizable to these categories of patients.

4.2 Interpretation of Results

4.2.1 Efficacy

Results from AMPLIFY met the pre-specified NI margins (RR = 1.8; RD = 0.035) for the primary efficacy outcome of recurrent VTE or VTE-related death after six months of acute VTE treatment in adult patients with symptomatic DVT or PE and a risk of recurrence. A literature search, as well as input from clinical experts, investigators, and health authorities, was used by the manufacturer to support the estimate of the NI margin of RR = 1.8, which does not appear to be unreasonable. Consistent results reaching statistical significance for NI were obtained in both the PP and ITT populations. More precisely, the use of apixaban was associated with numerically fewer events compared with enoxaparin and warfarin; however, the magnitude of the difference was small and likely not of any clinical relevance. Indeed, the superiority of apixaban could not be demonstrated, as the results did not achieve statistical significance for such testing. Therefore, apixaban may be considered as effective as combination therapy with enoxaparin and warfarin for acute VTE treatment.

Results for the secondary efficacy outcome of recurrent VTE or all-cause mortality were consistent with the aforementioned findings. Although AMPLIFY was not powered to assess the individual components of the composite outcomes, apixaban performed better in preventing DVT than either PE or VTE-related death. However, the proportions of patients experiencing each individual event in each treatment group remained low and acceptable (≤ 2%) according to the clinical expert consulted by CDR, especially

considering that patients experienced an unprovoked initial event, placing them at higher risk of VTE recurrence compared with the overall real-life population.

In the AMPLIFY-EXT study, results for the primary outcome of symptomatic VTE or all-cause mortality show the superiority of apixaban over placebo after 12 months of study treatment for continued VTE prevention in patients who had previously completed six to 12 months of anticoagulation therapy without experiencing a VTE recurrence. Although AMPLIFY-EXT was not powered to assess the individual components of the composite outcomes, apixaban performed better in preventing DVT than either PE or VTE-related death. The incidence of recurrent VTE or VTE-related death with apixaban in AMPLIFY-EXT was [redacted], which was consistent with the findings from both treatment groups in AMPLIFY. However, [redacted] of patients in the placebo treatment group experienced this outcome, which is higher than what would normally be expected based on experience of specialists in clinical practice. The decision to extend anticoagulation is largely influenced by a patient's risk factors for VTE recurrence,[21] and AMPLIFY-EXT included patients with an initial unprovoked VTE who had a high risk of recurrence; as such, if the risk-versus-benefit profile favours pursuing anticoagulation, comparing an active treatment to placebo potentially affects the interpretation of the findings in favour of the active treatment.

There is a gap in the evidence for extended VTE treatment due to the use of placebo as a comparator in AMPLIFY-EXT. While uncertainty remains regarding the optimal treatment duration, recommendations from major guidelines[4] and experience from specialists in clinical practice suggest that a number of real-life patients will likely require a treatment duration exceeding the six-month follow-up period in the AMPLIFY trial. However, AMPLIFY-EXT does not provide information on how apixaban compares to other anticoagulants drugs in patients requiring extended anticoagulant treatment. Most notably, no direct comparison of apixaban versus another NOAC was identified. Therefore, additional evidence was gathered in the form of IDCs.

The CDR review team conducted a critical appraisal of two IDCs submitted by the manufacturer that assessed the efficacy and safety of apixaban compared with other NOACs for the acute treatment and continued prevention of VTE (further details in Appendix 6). In both indications, there were no significant differences for the outcomes of VTE and VTE-related death, non-fatal PE, DVT, VTE-related death, myocardial infarction, overall treatment discontinuation, and all-cause mortality between treatments. A literature review was conducted by CDR to compare the results of the IDC performed by the manufacturer with other IDCs found in the literature. Five additional IDCs were retrieved; the results of these IDCs are consistent with the conclusion that there is no substantial difference among the efficacy of the NOACs in treating and preventing recurrent VTE in both the short and long term. However, the small number of studies available and the relative rarity of the events being analyzed mean that the effects of heterogeneity among studies on the comparative efficacy of treatment are highly uncertain. The one IDC[22] comparing rivaroxaban with apixaban that demonstrated similar results for major bleeding noted that results should be interpreted with caution, as only one study investigated rivaroxaban for major bleeding and no major bleeding was reported in the placebo group (zero event), resulting in uncertain estimates of effect.

4.2.2 Harms

In the AMPLIFY study, results for the primary safety outcome of major bleeding, as well as for the secondary outcome of CRNM bleeding, show the superiority of apixaban over the combination of enoxaparin and warfarin. Superiority for major bleeding was tested in accordance with the hierarchical hypothesis-testing plan, as NI was demonstrated for the primary efficacy outcome.

Mortality, as well as the overall incidence of SAEs, during AMPLIFY did not differ significantly between apixaban and the combination of enoxaparin and warfarin, and were not higher than would be expected in this patient population in clinical practice. The most commonly reported SAEs with both drugs were infrequent (less than 1.5%). The proportion of patients experiencing AEs was slightly lower with apixaban compared with the combination of enoxaparin and warfarin. The most common AEs included headache, pain in an extremity, peripheral edema, and nausea. Small proportions of patients discontinued due to AEs in both treatment groups, suggesting adequate tolerability.

Results for major bleeding in the AMPLIFY-EXT study are inconclusive. The small number of events reported in both the apixaban and the placebo treatment groups led to substantial uncertainty surrounding the results. Although apixaban was associated with slightly more CRNM bleeding events than placebo, results once again did not reach statistical significance and are inconclusive.

Mortality, as well as the overall incidence of SAEs and WDAEs, during AMPLIFY-EXT was slightly lower in the apixaban treatment group compared with placebo. These results are mostly influenced by the higher proportion of patients reporting a DVT or PE episode, and reflect the absence of a therapeutic effect in the placebo group. Similar proportions of patients experienced AEs in both treatment groups. The most common AEs reported were similar to those from the AMPLIFY study in the acute treatment of VTE.

Therefore, the overall harms results did not raise any obvious unknown safety signal. A small proportion of patients with active cancer were included in the AMPLIFY and AMPLIFY-EXT trials; therefore, there is substantial uncertainty regarding the safety of apixaban in these patients.

No data are available to compare the risks of apixaban versus an active treatment option for more than six months, although some patients with unprovoked events or non-reversible risk factors may require prolonged therapy, and no direct comparison of apixaban versus another NOAC was identified. However, two IDCs submitted by the manufacturer and five published IDCs of the safety of apixaban compared with other NOACs yielded inconsistent results for bleeding-related outcomes, as apixaban was not consistently superior to both NOACs for all bleeding outcomes, illustrating the uncertainty regarding the statistically significant differences between apixaban and dabigatran or rivaroxaban for outcomes such as major bleeding. For acute VTE treatment, the IDC submitted by the manufacturer suggests that apixaban is significantly less likely to cause major bleeding compared with dabigatran, but not compared with rivaroxaban. By contrast, for the extended VTE treatment, rivaroxaban was associated with a significantly higher risk of major bleeding or CRNM bleeding compared with apixaban, but there were no differences between apixaban and dabigatran for these outcomes. The results of the published IDCs for acute treatment were similar to the manufacturer's analysis in that there were differences between apixaban and the other NOACs with respect to major bleeding, but the publications that examined extended treatment differed from the manufacturer's results in failing to detect differences among NOACs for major bleeding or CRNM bleeding. Given the aforementioned limitations of the IDCs (most notably the small number of studies and the rarity of events), there is a high degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban compared with other NOACs.

Of note, the management of hemorrhagic occurrences is complicated by the lack of an antidote to reverse the effects of apixaban. Hemorrhagic complications would have to be managed through appropriate enoxaparin plus warfarin, such as surgical hemostasis, blood volume replacement, or administration of blood products, until the bleeding can be controlled.[7] This is a generic concern with the NOACs, considering the particularities and issues with blood product supplies.

5. CONCLUSIONS

The results of the AMPLIFY study demonstrated that apixaban is NI, but not superior, to the combination of enoxaparin and warfarin for the acute treatment of VTEs (up to six months) in patients with a risk of recurrent VTE, based on the frequency of recurrent symptomatic VTE or VTE-related mortality. In the same study, apixaban was associated with significantly fewer bleeding events than enoxaparin plus warfarin. The results of the AMPLIFY-EXT study demonstrated that apixaban is superior to placebo for extended (up to 12 months) VTE prevention, based on the frequency of recurrent symptomatic VTE or all-cause mortality. However, low event rates in this study precluded any conclusion regarding the relative effect of apixaban versus enoxaparin plus warfarin on bleeding. The results of two IDCs submitted by the manufacturer and five published IDCs of the efficacy and safety of apixaban compared with other new oral anticoagulants (NOACs) were consistent with the conclusion that apixaban is as efficacious as other NOACs in treating and preventing VTE, both for acute and extended treatment, and that apixaban is as least as safe as the other NOACs with respect to the risk of bleeding.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups.

1. Brief description of patient group supplying input

The Heart and Stroke Foundation of Canada (HSFC) is a national, volunteer-based organization. Through health promotion and countrywide advocacy programs, the organization sets out to prevent cardiovascular and cerebrovascular disease, save lives, and promote recovery.

HSFC has received unrestricted financial support from Bristol-Myers Squibb Canada and/or Pfizer Canada Inc. in the last five years to develop educational and awareness activities, educational materials, and to provide research award funding across Canada. No conflicts of interest were declared in the preparation of this submission.

2. Condition and Current Therapy-Related Information

To obtain information from patients and caregivers, HSFC used a two-week online survey. Additional information was obtained through literature searches of publications, HSFC health information, and from guidelines and policies from organizations such as the Canadian Cardiovascular Society. Of the 152 online-survey participants, 45 patients indicated they had blood clots and 11 indicated they were caregivers; responses from these participants only were used to inform this submission.

Approximately 200,000 Canadians a year are affected with deep vein thrombosis (DVT), with up to 60,000 of these patients require hospitalization. Responses from the 45 survey participants with blood clots indicate that their day-to-day lives have been affected, mostly due to the requirement of having to take medications at specific times or multiple times during the day. Some patients also mentioned having to manage their disease with other forms of therapy, changing their diets, and having to take time off work. More than half of the patients indicated that their ability to do activities has not changed, but some reported they are unable to do the activities they have done in the past, such as exercise or lifting items. Symptoms experienced by patients included fatigue, general swelling of the legs and ankles, leg pain or leg cramping, shortness of breath, depression, and bruising. A small number of patients were unsatisfied with their health care providers' communication surrounding the condition.

Of the 11 caregivers who responded to the survey, some indicated that they faced no additional challenges, while others reported newly associated challenges. Some caregivers reported feeling more overwhelmed and busier, anxious or stressed, and that they do not have as much freedom as they did previously. Some even reported that their own health suffered. Several caregivers reported that their daily routines were affected, as they are responsible for providing medications multiple times per day and at specific times, or they are required to provide transportation to various health care appointments. This resulted in some caregivers needing to take time off work.

Most of the patients reported having been prescribed medication to either prevent or control blood clots. These included warfarin, nonsteroidal anti-inflammatories, Plavix, Xarelto, and Pradaxa. Many patients believed that these medications have helped to control their conditions, while others were unsure of their effects. Almost half of the respondents indicated that they have to take more than one medication to control their condition. Reported adverse events included bruising, swelling, bleeding, dizziness, drowsiness, tingling in the hands and feet, and joint pain.

3. Related Information About Apixaban

Eight of the respondents with blood clots had been prescribed apixaban; six patients were identified as having atrial fibrillation, four as having heart disease, and three as having experienced a stroke. Patients actively taking apixaban reported that their condition was under control, while one patient was uncertain of its effectiveness. Half of the respondents indicated they had to take medication in addition to apixaban in order to control their condition. More than half of apixaban users reported adverse events, including allergic reactions, bruising and swelling, bleeding, and nausea. One person noted that they would feel better if there was some reversal drug for apixaban.

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:	November 27, 2014
Alerts:	Bi-weekly search updates until April 8, 2015(date of CDEC meeting)
Study Types:	randomized controlled trials; controlled clinical trials
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
MeSH	Medical 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)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.rn	CAS registry number
.nm	Name of substance word
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		
#	**Searches**	**Results**
1	(apixaban* or Eliquis or Eliques or BMS 562247 or BMS562247).ti,ot,ab,sh,rn,hw,nm.	4294
2	503612-47-3.rn,nm.	2683
3	1 or 2	4294
4	Venous Thromboembolism/ or exp Venous Thrombosis/	157117
5	(deep adj4 (thromb* or clot* or thromboembol* or thrombo-embol* or thrombophleb*)).ti,ab.	48912
6	(DVT or phlebothromb* or vena thromb*).ti,ab.	19426
7	(VTE or (venous adj2 (thromboemboli* or thrombo-emboliL*)) or venous thrombos*).ti,ab.	78871
8	exp Pulmonary Embolism/ or (pulmonary embol* or pulmonary thromboembol* or pulmonary microembol* or lung embol* or lung microembol* or lung thromboemb* or pulmonary infarction*).ti,ab.	115238
9	or/4-8	261001
10	3 and 9	1748
11	10 use pmez	369
12	*apixaban/ or (BMS 562247 or BMS562247 or apixaban* or Eliquis or Eliques).ti,ab.	2490
13	Deep vein thrombosis/ or lower extremity deep vein thrombosis/ or upper extremity deep vein thrombosis/	58795
14	(deep adj4 (thromb* or clot* or thromboembol* or thrombo-embol* or thrombophleb*)).ti,ab.	48912
15	(DVT or phlebothromb* or vena thromb*).ti,ab.	19426
16	(VTE or (venous adj2 (thromboemboli* or thrombo-emboli*)) or venous thrombos*).ti,ab.	79203
17	Lung Embolism/ or (pulmonary embol* or pulmonary thromboembol* or pulmonary microembol* or lung embol* or lung microembol* or lung thromboemb* or pulmonary infarction*).ti,ab.	102238
18	or/13-17	194562
19	12 and 18	882
20	19 use oemezd	575
21	20 not conference abstract.pt.	438
22	11 or 21	807
23	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	486895
24	Randomized Controlled Trial/	756684
25	Randomized Controlled Trials as Topic/	160646
26	"Randomized Controlled Trial (topic)"/	60811
27	Controlled Clinical Trial/	479000
28	Controlled Clinical Trials as Topic/	8539
29	"Controlled Clinical Trial (topic)"/	3393
30	Randomization/	148085
31	Random Allocation/	148085
32	Double-Blind Method/	251177
33	Double-Blind Procedure/	118502
34	Double-Blind Studies/	212397
35	Single-Blind Method/	39712
36	Single Blind Procedure/	19032
37	Single-Blind Studies/	39712
38	Placebos/	293947
39	Placebo/	259915

MULTI-DATABASE STRATEGY		
#	**Searches**	**Results**
40	Control Groups/	69847
41	Control Group/	69847
42	(random* or sham or placebo*).ti,ab,hw.	2361431
43	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	402851
44	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	942
45	(control* adj3 (study or studies or trial*)).ti,ab.	752673
46	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	64569
47	allocated.ti,ab,hw.	91440
48	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	53606
49	or/23-48	2970203
50	22 and 49	343
51	remove duplicates from 50	261

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

Grey Literature

Dates for Search:	November 14–24, 2014
Keywords:	Eliquis, Venous thromboembolism
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
- Drug Class Reviews
- Databases (Free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

All publications marked as potentially relevant met the criteria for inclusion in the systematic review; therefore, there were no excluded studies.

APPENDIX 4: DETAILED OUTCOME DATA

Efficacy Outcomes

TABLE 12: SYMPTOMATIC VENOUS THROMBOEMBOLIC EVENT (VTE) OR VTE-RELATED DEATH

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin Plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Symptomatic VTE (Non-fatal DVT or PE) or VTE-Related Death Primary Outcome in the AMPLIFY Trial				
Primary Efficacy Analyses — ITT	**Patients with missing outcome excluded**		**With imputation for missing data[b]**	
n (%)	59 (2.3), N = 2,609	71 (2.7), N = 2,635	[redacted]	[redacted]
RR (95% CI)	0.84 (0.60 to 1.18)		[redacted]	
P value	*P* < 0.0001 for NI[a]		[redacted]	
RD (95% CI)	[redacted]		[redacted]	
P value	[redacted]		NR	
Primary Efficacy Analyses — PP	**Patients with missing outcome excluded**		**PP population not reported**	
n (%)	[redacted]	[redacted]	NR	
RR (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
RD (95% CI)	[redacted]		NR	
P value	[redacted]		NR	
Sensitivity Analyses	**All randomized patients**		**Without imputation for missing data[c]**	
n (%)	59 (2.2), N = 2,691	71 (2.6), N = 2,704	14 (1.7)	73 (8.8)
RR (95% CI)	0.83 (0.59 to 1.17)		0.19 (0.11 to 0.33)	
P value	*P* < 0.0001 for NI[redacted]		*P* < 0.0001 for superiority	
RD (95% CI)	[redacted]		[redacted]	
P value	[redacted]		NR	
Subgroup Analysis by Event Type				
Non-fatal DVT				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	
Non-fatal PE				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin Plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
VTE-related death				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
RR (95% CI)	[redacted]		[redacted]	
P value	[redacted]		[redacted]	

CI = confidence interval; DVT = deep vein thrombosis; ITT = intention-to-treat; NI = non-inferiority; NR = not reported; PE = pulmonary embolism; PP = per-protocol; RD = risk difference; RR = relative risk; VTE = venous thromboembolic event.
[a] AMPLIFY: *P* value for superiority non-significant; otherwise superiority not tested.
[b] Patients with missing outcome information were classified as having had an event during the intended treatment period.
[c] Sensitivity analysis was based on the assumption that no patient with missing data regarding VTE or all-cause mortality during the intended treatment period in both treatment groups would achieve the outcome.
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR) body, p. 88–89, 98; Agnelli et al. (2013); AMPLIFY-EXT CSR body, p. 94, 96.[9-12]

TABLE 13: SYMPTOMATIC VENOUS THROMBOEMBOLIC EVENT OR ALL-CAUSE MORTALITY

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,691	Enoxaparin Plus Warfarin N = 2,704	Apixaban 2.5 mg N = 840	Placebo N = 829
Symptomatic VTE (Non-fatal DVT or PE) or All-Cause Mortality Primary Outcome in the AMPLIFY-EXT Trial				
Primary Efficacy Analyses	**Patients with missing outcome excluded**		**With imputation for missing data**	
n (%)	84 (3.2), N = 2,609	104 (3.9), N = 2,635	32 (3.8)	96 (11.6)
RR (95% CI)	0.82 (0.61 to 1.08)		0.33 (0.22 to 0.48)	
P value	*P* = 0.155 for superiority		*P* < 0.0001 for superiority	
RD (95% CI)	[redacted]		[redacted]	
P value	NR		[redacted]	
Sensitivity Analyses	**No sensitivity analysis reported**		**Without imputation for missing data**	
n (%)	NR		[redacted]	
RR (95% CI)	NR		[redacted]	
P value	NR		[redacted]	
RD (95% CI)	NR		[redacted]	
P value	NR		NR	
Individual Event Type — All-Cause Mortality				
n (%)	41 (1.6) N = 2608	52 (2.0) N = 2630	[redacted]	
RR (95% CI)	0.79 (0.53 to 1.19)		[redacted]	
P value	NR		[redacted]	

CI = confidence interval; NR = not reported; RD = risk difference; RR = relative risk; VTE = venous thromboembolic event.
Sources: AMPLIFY Clinical Study Report (CSR) body, p. 97–8; AMPLIFY-EXT CSR body, p. 86, 97.[10,12]

TABLE 14: HOSPITALIZATIONS

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
Hospitalizations Only				
n patients (%)	153 (5.7)	190 (7.1)	42 (5.0)	62 (7.5)
Length of Stay				
Mean ± SD, days	[redacted]	[redacted]	[redacted]	[redacted]
Most Frequently Reported Reason for All Visits or Admissions,[a] n:				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SD = standard deviation; VTE = venous thromboembolic event.

[a] Including hospitalizations, rehabilitations, nursing home admissions, emergency room visits, and doctor's office visits.

[b] [redacted]

Sources: AMPLIFY Clinical Study Report (CSR) body, p. 3589–90; AMPLIFY-EXT CSR body, p. 2092–93.[10,12]

Safety Outcomes

TABLE 15: MORTALITY AND OTHER SERIOUS ADVERSE EVENTS

Number of Patients With Harms Outcome	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
Mortality				
n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most frequently reported SAEs with outcome of death, ≥ [redacted] in at least one treatment group, n (%):				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs				
n (%)	417 (15.6)	410 (15.2)	112 (13.3)	158 (19.1)
Most frequently reported SAEs, ≥ 8 patients in at least one treatment group, n (%):				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

DVT = deep vein thrombosis; GI = gastrointestinal; MI = myocardial infarction; PE = pulmonary embolism; SAE = serious adverse events; VTE = venous thromboembolic event.

Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR) body, p. 117, 132–3, 134–7; Agnelli et al. (2013); AMPLIFY-EXT CSR p. 128, 129–30.[9-12]

TABLE 16: BLEEDING EVENTS

	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
Major Bleeding[a]				
n (%)	15 (0.6)	49 (1.8)	2 (0.2)	4 (0.5)
RR (95% CI)	0.31 (0.17 to 0.54)		0.49 (0.09 to 2.64)	
P value for superiority	*P* < 0.0001		[redacted]	
Major Bleeding Characteristics, n				
Fatal bleeding	1	2	0	0
Bleeding at a critical site:				
Intracranial	3	6	[redacted]	[redacted]
Retroperitoneal	1	3	[redacted]	[redacted]
Intraocular	0	2	[redacted]	[redacted]
Intraarticular	0	2	[redacted]	[redacted]
Other critical organ	[redacted]	[redacted]	[redacted]	[redacted]
Bleeding at other site:				
Gastrointestinal	[redacted]	[redacted]	[redacted]	[redacted]
Intramuscular	0	5	[redacted]	[redacted]
Nasal	1	1	[redacted]	[redacted]
Rectal	[redacted]	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]	[redacted]
Urogenital	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Fall in hemoglobin ≥ 2 g/dL or transfusions ≥ 2 units	[redacted]	[redacted]	NR	NR
Clinically Relevant, Non-Major Bleeding				
n (%)	103 (3.8)	215 (8.0)	25 (3.0)	19 (2.3)
RR (95% CI)	0.48 (0.38 to 0.60)		1.29 (0.72 to 2.33)	
P value	*P* < 0.0001		[redacted]	

CI = confidence interval; NR = not reported; RR = relative risk; VTE = venous thromboembolic event.

[a] Primary safety outcome in the trials.

Source: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR) body, p. 109–110, 114; Agnelli et al. (2013); AMPLIFY-EXT CSR p. 107, 109.[9-12]

TABLE 17: ADVERSE EVENTS

Number of Patients With Harms Outcome	AMPLIFY *Acute VTE Treatment*		AMPLIFY-EXT *Continued VTE Prevention*	
	Apixaban N = 2,676	Enoxaparin Plus Warfarin N = 2,689	Apixaban 2.5 mg N = 840	Placebo N = 826
AEs				
n (%)	**1,795 (67.1)**	**1,923 (71.5)**	**596 (71.0)**	**606 (73.4)**
Most frequently reported AEs, > 3% in at least one treatment group, n (%):				
WDAEs				
n (%)	**162 (6.1)**	**199 (7.4)**	**67 (8.0)**	**134 (16.2)**
Most frequently reported reasons, ≥ 4 patients in at least one treatment group, n (%):				

AE = adverse event; DVT = deep vein thrombosis; GI = gastrointestinal; INR = international normalized ratio; PE = pulmonary embolism; VTE = venous thromboembolic event; WDAE = withdrawal due to adverse event.
Sources: Agnelli et al. (2013); AMPLIFY Clinical Study Report (CSR) body, p. 117, 120, 127–8; Agnelli et al. (2013); AMPLIFY-EXT CSR p. 118, 124.[9-12]

APPENDIX 5: SUMMARY OF COMPARATOR CHARACTERISTICS

1. Objective

To compare and contrast the pharmacological characteristics of each of the drugs and drug classes approved for the treatment of deep vein thrombosis (DVT) in Canada.

2. Findings[23,24]

	Dabigatran	Rivaroxaban	Apixaban	LMWH	Fondaparinux	VKA
Therapeutic Class	Direct thrombin inhibitor	Direct factor Xa inhibitor		Indirect factor Xa inhibitor		Vitamin K antagonist
DVT Indication	VTE (DVT and PE) and prevention of DVT and PE	VTE (DVT and PE) and prevention of DVT and PE	VTE (DVT and PE) and prevention of DVT and PE	DVT	Acute DVT Acute PE	Venous thrombosis and PE
Mechanism of Action	Competitive, reversible direct thrombin inhibitor	Direct factor Xa inhibitor	Factor Xa inhibitor	Indirect inhibitors of thrombin and factor Xa	Indirect inhibitor of factor Xa	Indirect inhibition of coagulation factors II, VII, IX, and X through vitamin K antagonism.
Route of Administration	Oral	Oral	Oral	SC	SC	Oral

	Dabigatran	Rivaroxaban	Apixaban	LMWH	Fondaparinux	VKA
Dosing	Recommended daily dose of Pradaxa is 300 mg taken orally as one 150 mg capsule b.i.d. following treatment with a parenteral anticoagulant for 5 to 10 days. The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g., surgery, trauma, immobilization) and extended duration should be based on permanent risk factors or idiopathic DVT or PE.	Recommended dose for initiating treatment of DVT: 15 mg b.i.d. for 3 weeks (with food), followed by 20 mg q.d. for the continued treatment of DVT.	Recommended dose for treatment of acute DVT or PE is 10 mg taken orally b.i.d. for 7 days, followed by 5 mg taken orally b.i.d. The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilization) and extended duration should be based on permanent risk factors or idiopathic DVT or PE.[a]	*Enoxaparin:* 1.5 mg/kg SC q.d. **OR** 1 mg/kg SC every 12 hours. Single daily dose should not exceed 180 mg.[b] *Dalteparin:* 200 anti-Xa IU/kg SC q.d. Single daily dose should not exceed 18,000 IU[a] For patients at increased risk of bleeding: 100 anti-Xa IU/kg SC b.i.d. **OR** 100 anti-Xa IU/kg over 12 hours IV as a continuous infusion.[b] *Nadroparin:* 171 anti-Xa IU/kg SC once daily. Single daily dose should not exceed 17,100 IU. For patients at higher risk of bleeding: 86 anti-Xa IU/kg SC b.i.d. [b] *Tinzaparin:* 175 anti-Xa IU/kg SC q.d. [b]	Recommended dose: 5 mg (body weight < 50 kg), 7.5 mg (body weight 50 kg to 100 kg), or 10 mg (body weight > 100 kg) SC q.d. Concomitant oral anticoagulation treatment should be initiated as soon as possible, usually within 72 hours. Fondaparinux should be continued for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0).	Administered q.d.; individualized dosing Include warfarin and nicoumalone (also known as acenocoumarol)

	Dabigatran	Rivaroxaban	Apixaban	LMWH	Fondaparinux	VKA
Pharmacokinetics	Characterized by a rapid increase in plasma concentrations with C_{max} attained 0.5 to 2.0 hours post-administration. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of approximately 11 hours in healthy elderly patients. Following administration of multiple doses, a terminal half-life of about 12 to 14 hours was observed, with the half-life independent of dose. C_{max} and AUC were dose-proportional.	Extremes in body weight (< 50 kg or > 120 kg) of patients taking a 10 mg tablet caused less than a 25% change in the plasma concentration of rivaroxaban; no information is provided for the 20 mg dose. Extent of absorption is reduced for 20 mg dose under fasting conditions resulting in an oral bioavailability of 66%; concurrent food intake increases the mean AUC by 39%.	Rapidly absorbed with C_{max} appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or C_{max} at the 10 mg dose. Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability.	LMWHs have more predictable PK than UFH. LMWHs have longer t1/2 than UFH.	Mostly excreted unchanged in urine.	Racemic mixture of the R- and S-enantiomers; in the case of warfarin, the S-enantiomer possesses the majority of anticoagulant activity. Warfarin is completely absorbed after oral administration versus ≥ 60% for nicoumalone. Nicoumalone is approximately twice as potent as warfarin. Elimination occurs primarily by metabolism through CYP450 system.

	Dabigatran	Rivaroxaban	Apixaban	LMWH	Fondaparinux	VKA
Drug–Drug Interactions	Potent P-glycoprotein inducers or inhibitors. Not metabolized by the human CYP450 system.	P-glycoprotein inhibitors, CYP3A4 inhibitors.	Inhibitors of both CYP3A4 and P-glycoprotein. Inducers of both CYP3A4 and P-glycoprotein. Drug products affecting hemostasis.		Not metabolized by liver, so CYP450 interactions not considered an issue.	Numerous drug–drug and drug–food interactions, both pharmacodynamic (e.g., vitamin K–containing foods) and pharmacokinetic [enzyme induction or inhibition]).
Monitoring	In certain infrequent situations — such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances — assessment of the anticoagulant effect of dabigatran may be appropriate.	No requirement for monitoring.	Although there is no need to monitor during routine clinical practice, in certain infrequent situations —such as overdosage, acute bleeding, urgent surgery, in cases of suspected non-compliance, or in other unusual circumstances — assessment of the anticoagulant effect of apixaban may be appropriate.	Factor Xa is sometimes measured; otherwise, no monitoring.		Frequent monitoring required due to narrow therapeutic index and numerous drug interactions.

AUC = area under the curve; b.i.d. = twice daily; C_{max} = maximum concentration; CYP3A4 = cytochrome P3A4; CYP450 = cytochrome P450; DVT = deep vein thrombosis; INR = international normalized ratio; IU = international units; IV = intravenous; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PK = pharmacokinetics; PO = orally; q.d. = once daily; SC = subcutaneous; UFH = unfractionated heparin; VKA = vitamin K agonist; VTE = venous thromboembolic event.

[a] Further to the course of a minimum of six months of treatment for DVT or PE, the recommended dose for the continued prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily.

3. Summary

Apixaban, dabigatran, and rivaroxaban are all new oral anticoagulants indicated for treatment of venous thromboembolism events in Canada; older approved drugs include vitamin K antagonists, low-molecular-weight heparin (LMWH), and fondaparinux. These anticoagulant drug classes are distinguished by the elements they inhibit in the coagulation cascade, the nature of the inhibition (direct or indirect), and by the pharmacokinetic characteristics such as route of administration (oral or parenteral), propensity for drug interactions, and monitoring requirements. For the treatment of DVT, apixaban, dabigatran, and rivaroxaban may represent a more convenient therapeutic modality than the standard of care (i.e., enoxaparin plus warfarin therapy); specifically, their lack of monitoring requirements, easy dosing strategies, rapid onset of effect (obviating the need for initial bridging with an LMWH, except for dabigatran), and oral formulation (enoxaparin is administered intravenously) may appeal to both patients and prescribers.

APPENDIX 6: SUMMARY OF INDIRECT COMPARISONS

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Objective

Due to the absence of any studies that compare apixaban directly to other new oral anticoagulants (NOACs) used in the treatment and prevention of venous thromboembolic events (VTEs), the objective of this Appendix is to summarize the evidence available, including two manufacturer-sponsored indirect comparisons (IDCs), regarding the comparative efficacy of apixaban versus relevant comparators for the treatment and prevention of VTE in adults who had received prior treatment for a VTE.

Manufacturer's indirect comparisons

Methods

The manufacturer conducted a systematic review followed by two network meta-analyses (NMAs) to compare the clinical efficacy and safety of apixaban and relevant comparators for the treatment and secondary prevention of VTE in adult patients (at least 18 years old) with a previous deep vein thrombosis (DVT) and/or pulmonary embolism (PE).[8] The systematic review was carried out to identify all randomized controlled trials (RCTs) comparing NOACs with the current standard of care for VTE; namely anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs). The manufacturer also included placebo and Aspirin as comparators. Specific exclusion criteria were not provided.

The first NMA focused on the acute (initial, short-term) treatment following a VTE event, while the second NMA focused on extended treatment following the short-term treatment of an initial VTE event. Both NMAs were conducted using Bayesian meta-analysis. Model fit was assessed using the deviance information criterion (DIC) and by comparing the residual deviance with the number of data points in the model. In both NMAs, analyses were conducted using the intention-to-treat (ITT) population for the outcomes listed in Table 18, except for bleeding outcomes for which the safety population was used.

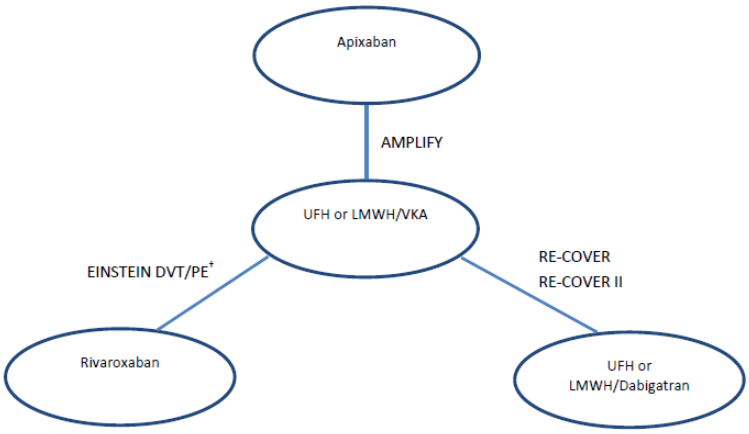
TABLE 18: OUTCOMES INCLUDED IN THE MANUFACTURER'S NETWORK META-ANALYSIS

VTE and VTE-related death
Non-fatal PE
DVT
VTE-related death
Myocardial infarction
All-cause mortality
Treatment discontinuations
Major bleeding
CRNM bleeding

CRNM = clinically relevant, non-major; DVT = deep vein thrombosis; NMA = network meta-analysis; PE = pulmonary embolism; VTE = venous thromboembolic event.

Network diagrams can be found in Figure 2 and Figure 3 for the acute-treatment and extended-treatment NMAs, respectively.

FIGURE 2: NETWORK OF ELIGIBLE COMPARISONS FOR ACUTE-TREATMENT NETWORK META-ANALYSIS



DVT = deep vein thrombosis; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist.
Source: Manufacturer's submission.[8]

FIGURE 3: NETWORK OF ELIGIBLE COMPARISONS FOR EXTENDED-TREATMENT NETWORK META-ANALYSIS

b.i.d = twice daily; DVT = deep vein thrombosis; INR = international normalized ratio; NMA = network meta-analysis; q.d. = once daily; VKA = vitamin K antagonist.
Source: Manufacturer's submission.[8]

For the acute-treatment NMA, five RCTs were included in the meta-analysis (Table 19). Three of the five included RCTs were double-blind (DB), while the remaining two were open-label. There were two separate EINSTEIN study publications according to the primary VTE event of the patient (PE or DVT), but the subsequent pooled analysis was used in the NMA. All included studies had a treatment duration of six months, except for the EINSTEIN DVT and EINSTEIN PE studies, which had treatment periods of three, six, and 12 months. The baseline characteristics of the included studies were similar, except for the proportion of patients with unprovoked VTE, which varied among studies and was not reported (Table 19).

TABLE 19: BASELINE CHARACTERISTICS OF INCLUDED STUDIES IN ACUTE-TREATMENT NETWORK META-ANALYSIS

Trial	Treatment, Number Randomized	Mean Age in Years (SD)	Unprovoked VTE, %	Time on Treatment
AMPLIFY DB RCT	Apixaban 10 mg b.i.d./ 5 mg b.i.d. (n = 2,691)	57.2 (16.0)	89.8	6 months
	Enoxaparin/warfarin INR 2.0 to 3.0 (n = 2,704)	56.7 (16.0)		
RE-COVER DB RCT	UFH or LMWH/dabigatran 150 mg b.i.d. (n = 1,274)	55.0 (15.8)	NR	
	UFH or LMWH /warfarin INR 2.0 to 3.0 (n = 1,265)	54.4 (16.2)		
RE-COVER II DB RCT	UFH or LMWH/dabigatran 150 mg b.i.d. (n = 1,279)	54.7 (16.2)		
	UFH or LMWH /warfarin INR 2.0 to 3.0 (n = 1,289)	55.1 (16.3)		
EINSTEIN DVT/ EINSTEIN PE OL RCTs (pooled data)	Rivaroxaban 15 mg b.i.d./20 mg q.d. (n = 4,151)	57.0 (17.0)	63.5	3, 6, or 12 months
	Enoxaparin/VKA INR 2.0 to 3.0 (n = 4,131)	57.0 (16.8)		

b.i.d. = twice daily; DB = double-blind; DVT: deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NR = not reported; OL = open-label; PE = pulmonary embolism; q.d. = once daily; RCT = randomized controlled trial; SD = standard deviation; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolic event.

For the extended-treatment NMA, 11 unique RCTs were included in the meta-analysis (Table 20). Nine of the included 11 RCTs were DB, while the remaining two RCTs were open-label. Baseline characteristics for the included RCTs for the acute-treatment NMA are presented in Table 19. The study durations of the included RCTs varied widely, ranging from three months to 37.2 months. Similarly, there was a wide range in the proportion of patients in each study who had idiopathic VTE.

TABLE 20: BASELINE CHARACTERISTICS OF INCLUDED STUDIES IN EXTENDED-TREATMENT NMA

Trial	Treatment, number randomized	Mean age (SD)	Idiopathic/ Unprovoked VTE, %	Time on Treatment
AMPLIFY-EXT DB, superiority RCT	Apixaban 2.5 mg b.i.d. (n = 840)	56.6 (15.3)	91.7	12 months
	Apixaban 5 mg b.i.d. (n = 813)	56.4 (15.6)		
	Placebo (n = 829)	57.1 (15.2)		
EINSTEIN-EXT DB, inferiority RCT	Rivaroxaban 20 mg q.d. (n = 602)	58.2 (15.6)	73.7	8.7 months
	Placebo (n = 595)	58.4 (16.0)		
RE-SONATE DB RCT	Dabigatran 150 mg b.i.d. (n = 681)	56.1 (15.5)	NR	6 months
	Placebo (n = 662)	55.5 (15.1)		
RE-MEDY DB RCT	Dabigatran 150 mg b.i.d. (n = 1,430)	55.4 (15.0)	NR	3 to 12 months
	Warfarin INR 2.0 to 3.0 (n = 1,426)	53.9 (15.3)		
LAFIT DB RCT	Warfarin INR 2.0 to 3.0 (n = 79)	59 (16)	100	10 months
	Placebo (n = 83)	58 (16)		
ELATE DB RCT	Warfarin INR 1.5 to 1.9 (n = 369)	57 (16)	100	2.2 years
	Warfarin INR 2.0 to 3.0 (n = 369)	57 (16)		
WODIT DVT OL RCT	VKA/acenocoumarol continuation (n = 134)	66.8 (6.7)	100	37 months
	VKA/acenocoumarol discontinuation /observation (n = 133)	67.7 (7.3)		
WODIT PE OL RCT	VKA/acenocoumarol continuation (n = 165)	62.9 (16.3)	55.9	33.8 months
	VKA/acenocoumarol discontinuation /observation (n = 161)	61.0 (15.5)	56.5	
PREVENT DB RCT	Warfarin INR 1.5 to 1.9 (n = 255)	53 (NR)	100	2.1 years
	Placebo (n = 253)	53 (NR)		

b.i.d. = twice daily; DB = double-blind; DVT = deep vein thrombosis; INR = international normalized ratio; NMA = network meta-analysis; NR = not reported; OL = open-label; PE = pulmonary embolism; q.d. = once daily; RCT = randomized controlled trial; SD = standard deviation; VKA = vitamin K antagonist; VTE = venous thromboembolic event.

Results

As noted above, the manufacturer included all relevant comparators in its NMAs. Because the focus of this Appendix is the comparative efficacy of apixaban versus the other NOACs, we have limited this report to the comparisons among the NOACs. The comparisons among all comparators that comprised the NMAs can be seen in the manufacturer's submission.

Acute-Treatment Network Meta-analysis

A summary of the results of the manufacturer's acute-treatment NMA for the comparisons of key outcomes among the NOACs, specifically apixaban (5 mg twice daily), dabigatran (150 mg twice daily), and rivaroxaban (15 mg twice daily or 20 mg once daily) is presented in Table 21. There were no statistically significant differences between apixaban and the other NOACs with respect to VTE and VTE-related death, overall treatment discontinuation, and all-cause mortality. Dabigatran was associated with a statistically significant greater risk of major bleeding compared with apixaban ([redacted]), while rivaroxaban was associated with a statistically significant greater risk of clinically relevant, non-major (CRNM) bleeding ([redacted]) compared with apixaban 5 mg.

TABLE 21: SELECTED RESULTS FOR ACUTE-TREATMENT NETWORK META-ANALYSIS

	Treatment vs. Apixaban 5 mg b.i.d.		
Outcome	**Dabigatran 150 mg b.i.d.**	**Rivaroxaban 15 mg b.i.d./ 20 mg q.d.**	**UFH or LMWH/VKA**
RR (95% CrI)			
VTE and VTE-related death	[redacted]	[redacted]	[redacted]
Overall treatment discontinuation	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
Major bleeding	[redacted]	[redacted]	[redacted]
CRNM bleeding	[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; CrI = credible interval; CRNM = clinically relevant, non-major; LMWH = low-molecular-weight heparin; NMA = network meta-analysis; q.d. = once daily; RR = relative risk; UFH = unfractionated heparin; VKA = vitamin k antagonist; VTE = venous thromboembolic event.

Extended-Treatment Network Meta-Analysis

A summary of the results of the manufacturer's extended-treatment NMA for the comparisons of key outcomes among the NOACs, specifically apixaban (2.5 mg twice daily and 5 mg twice daily), dabigatran (150 mg twice daily), and rivaroxaban (20 mg once daily) is presented in Table 22. There were no statistically significant differences between any of the NOACs with respect to VTE and VTE-related death, overall treatment discontinuation, and all-cause mortality. Rivaroxaban was associated with a statistically significantly higher risk of major bleeding compared with apixaban 2.5 mg twice daily and apixaban 5 mg twice daily ([redacted]). Rivaroxaban was also associated with a statistically significantly higher risk of CRNM bleeding ([redacted]) compared with apixaban 2.5 mg twice daily.

TABLE 22: SELECTED RESULTS FOR EXTENDED-TREATMENT NETWORK META-ANALYSIS

	Treatment vs. Apixaban 2.5 mg b.i.d.				Treatment vs. Apixaban 5 mg b.i.d.		
	Apixaban 5 mg b.i.d.	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg q.d.	Warfarin INR 2.0 to 3.0	Dabigatran 150 mg b.i.d.	Rivaroxaban 20 mg q.d.	Warfarin INR 2.0 to 3.0
Outcome	**RR (95% CrI)**						
VTE and VTE-related death[a]	[redacted]						
Overall treatment discontinuation	[redacted]						
All-cause mortality	[redacted]						
Major bleeding	[redacted]						
CRNM bleeding	[redacted]						

b.i.d. = twice daily; CrI = credible interval; CRNM = clinically relevant, non-major; NMA = network meta-analysis; q.d. = once daily; RR = relative risk; VTE = venous thromboembolic event.

[a] Includes patients from the WODIT DVT trial (n = 134 VKA continuation, n = 133 VKA discontinuation/observation).

Critical Appraisal of Manufacturer-Performed Indirect Comparison

The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details and commentary for each of the relevant items identified by ISPOR are provided in Table 23.

Strengths

Both NMAs for acute treatment and extended treatment appear to satisfy the ISPOR criteria. The rationale and objectives for the both IDCs were clearly stated. The inclusion criteria for individual RCTs were clearly stated. The study selection and data extraction process were provided. A comprehensive search strategy was employed to identify and select relevant RCTs. The quality of the included RCTs was assessed based on the National Institute for Health and Care Excellence (NICE) quality assessment tool. The outcome measures assessed in the indirect and mixed-treatment comparisons were appropriate and clearly stated. Model fit was assessed using the DIC and by comparing the residual deviance with the number of data points in the model. Sensitivity analyses were performed incorporating pooled data from RE-COVER I and RE-COVER II studies. Individual study results were provided.

Limitations

The main limitation in both NMAs was the small number of included studies. In the acute-treatment NMA, apixaban was represented by one study, dabigatran and rivaroxaban by two studies each, and UFH or LMWH plus VKA by four studies. In the extended-treatment NMA, apixaban (both 2.5 mg twice daily and 5 mg twice daily doses) and rivaroxaban were represented by one study each, dabigatran by

two studies, and warfarin (INR 1.5 to 1.9, or 2.0 to 3.0) by either one or two studies, depending on the study outcome.

In the acute-treatment NMA, it was unclear whether heterogeneity among studies had been assessed. There was heterogeneity in the baseline characteristics in the included studies. Specifically, there was variation in the baseline risk of VTE among studies, as AMPLIFY reported 89.8% of patients as having unprovoked VTE, whereas 61.9% and 64.5% of patients were reported for EINSTEIN DVT and EINSTEIN PE, respectively; this information was not reported for other studies. According to the investigators, a clinical advisory board was assembled to discuss differences in baseline characteristics to determine whether imbalances may have potentially biased findings of the NMA. The advisory board concluded that although the AMPLIFY study contained a higher proportion of patients with unprovoked (idiopathic) VTE (and therefore a higher baseline risk of recurrent VTE compared with the other studies for which this information was available), there was insufficient evidence to determine whether this had affected the findings. Nevertheless, AMPLIFY was the only study in which apixaban had been used. Therefore, despite the conclusion reached by the aforementioned clinical advisory board, it is impossible to determine the effects of heterogeneity in the proportion of patients with unprovoked VTE on the results of the IDC for acute treatment.

In the extended-treatment NMA, the investigators stated that heterogeneity among studies was examined for each random effects model, but all analyses proved to be underpowered to estimate the between-study heterogeneity. There was heterogeneity in baseline characteristics in the included studies, as there was variation between studies in prior treatment duration ranging from three to 18 months; there were also differences in the extended treatment period between studies as the treatment ranged from six months to 37.2 months. This likely reflects substantial differences in the baseline risk of VTE (as noted above for the acute-treatment NMA). Indeed, patients in the ASPIRE, ELATE, and AMPLIFY-EXT studies may have had a higher risk of recurrence at baseline, as these studies VTE (> 90%) compared with the EINSTEIN-EXT study (26%). As for the acute-treatment NMA, baseline characteristics for the extended-treatment NMA were discussed with a clinician to determine whether imbalances may have potentially biased findings of the NMA. It was concluded that there was insufficient evidence to suggest that the greater proportion of patients with unprovoked VTE may have affected the findings. However, as was noted for the acute-treatment NMA, the absence of sufficient evidence means that there is a corresponding lack of certainty regarding the effects of heterogeneity in the proportion of patients with unprovoked VTE on the results of the IDC for extended treatment.

Summary of Other Indirect Comparisons Identified by the CADTH Common Drug Review

A systematic literature review was conducted by CDR to compare the results of the IDCs performed by the manufacturer against other IDCs. The search yielded three publications presenting IDCs for the acute treatment of VTE and three publications presenting IDCs for extended treatment of VTE. A summary of the IDCs found in the literature is described in Table 24.

TABLE 23: CDR APPRAISAL OF MANUFACTURER-SUBMITTED NMAS USING ISPOR CRITERIA

ISPOR Checklist Item		Acute-treatment NMA	Extended-treatment NMA
1.	Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an NMA and the study objectives were clearly stated.	
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• Eligibility criteria for individual RCTs clearly stated • Search strategy, study selection process, and data extraction clearly stated for all comparators. • Search strategy was provided. • Study selection and data extraction process were identified. Assessment of the risk of bias and study quality was conducted using the NICE quality assessment tool, though results were not provided	
		• Unclear whether statistical heterogeneity between studies was assessed.	• The heterogeneity between studies was examined for each random effects model, but all analyses proved to be underpowered to estimate the between-study heterogeneity.
3.	Are the outcome measures described?	• Specific outcomes were clearly stated.	
4.	Is there a description of methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description of the statistical model was provided. • A Bayesian approach with a fixed effects model was used. • Relative effect measures were used. In the instances where there were zero events in treatment groups, models were run without a continuity correction. If the model failed or did not converge, then a continuity correction (0.5 was added to each cell of the study outcome) was applied.	
5.	Are sensitivity analyses presented?	• Sensitivity analyses were performed incorporating pooled data from RE-COVER I/ RE-COVER II studies	• Sensitivity analyses were performed excluding studies with zero events in both treatment groups.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A table with study characteristics was provided. • A figure showing the network of studies was provided. Individual study results were provided.	
7.	Does the study describe an assessment of model fit?	• Model fit was assessed using the DIC and by comparing the residual deviance with the number of data points in the model.	
8.	Are the results of the evidence synthesis presented clearly?	• Tables were provided with relative results for each outcome.	

CDR = CADTH Common Drug Review; DIC = deviance information criterion; ISPOR = International Society of Pharmacoeconomics and Outcomes Research; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; RCT = randomized controlled trial.

TABLE 24: SUMMARY OF OTHER INDIRECT COMPARISONS FOR VTE FOUND IN THE LITERATURE

Study	Population	Interventions[a]	Outcomes	Conclusions	Major Strengths	Major Limitations
Acute-Treatment NMAs						
Hirschl et al. (2014)[25]	Patients with acute VTE	• Apixaban 10 mg/5 mg b.i.d. dabigatran 150 mg b.i.d. • Rivaroxaban 15 mg b.i.d. / 20 mg q.d. • VKA control	• Recurrent VTE • Major bleeding • Major and CRNM bleeding.	• No difference in recurrent VTE between NOACs • Major bleeding significantly lower with apixaban vs. dabigatran • Major and CRNM bleeding was statistically significantly reduced with apixaban compared with dabigatran and rivaroxaban	• Low risk of bias in most studies (except performance bias in open-label studies)	• Few included studies • Heterogeneity in patient baseline characteristics (# patients with DVT, PE, both) and treatment durations between studies
Kang et al. (2014)[26]			• Recurrent VTE • PE • DVT • All-cause mortality • Major bleeding	• No differences for mortality, recurrent VTE, PE, or DVT between NOACs • Major bleeding significantly greater with dabigatran compared with apixaban		• Few included studies • Heterogeneity in patient baseline characteristics (# patients with DVT, PE, both) and treatment durations between studies • Model fit and between-study heterogeneity was not assessed
Castellucci et al. (2014)[22]			• Recurrent VTE • PE • DVT • Major bleeding	• No difference in recurrent VTE, PE or DVT between NOACs • Major bleeding was statistically significantly reduced with	• Low risk of bias in most studies (except performance bias in open-label studies) • Model fit and between-study heterogeneity was assessed	• Few included studies

Study	Population	Interventions[a]	Outcomes	Conclusions	Major Strengths	Major Limitations
				apixaban compared with dabigatran	• Sensitivity analyses performed to address heterogeneity treatment durations between studies	
Extended-Treatment NMAs						
Alotaibi et al. (2014)[27]	Adult patients with confirmed symptomatic proximal DVT or PE with approved anticoagulant for 6 to 12 months	• Apixaban 2.5 mg b.i.d. • Apixaban 5 mg b.i.d. • Dabigatran 150 mg b.i.d. • Rivaroxaban 20 mg daily	• Recurrent VTE • Major bleeding • All-cause mortality	• No difference in risk for recurrent VTE, major bleeding, or all-cause mortality between NOACs	• Low risk of bias in most studies	• IDC included only one study per treatment • Heterogeneity in several baseline characteristics (e.g., females, proportion of thrombophilia)
Rollins et al. (2014)[28]	Patients aged ≥ 15 years with a history of ≥ 1 VTE episode and who received anticoagulation therapy for a minimum duration of 6 months	• Apixaban 2.5 mg b.i.d. • Apixaban 5 mg b.i.d. • Dabigatran 150 mg • Rivaroxaban 20 mg daily • Warfarin 1.5 to 2 INR • Warfarin 2 to 3 INR	• Recurrent VTE • All-cause mortality • DVT • Non-fatal PE • CRNM bleeding	• No difference in recurrent VTE, all-cause mortality, non-fatal PE, DVT, or non-major or CRNM bleeding between NOACs	• Low risk of bias in all studies • Evaluated closed loops within the network for heterogeneity and inconsistency	• A study measuring acute VTE (AMPLIFY) was included • Few included studies • Heterogeneity in several baseline characteristics (e.g., # patients with previous VTE, females)
Castellucci et al. (2013)[29]	Patients with confirmed, symptomatic DVT or PE treated for a minimum of 3 months with anticoagulant treatment		• Recurrent VTE • Major bleeding	• No difference in recurrent VTE between NOACs • Major bleeding was statistically significantly reduced with apixaban compared with rivaroxaban	• Low risk of bias in most studies (except performance bias in OL studies) • Model fit and between-study heterogeneity was assessed	• Few included studies

Study	Population	Interventions[a]	Outcomes	Conclusions	Major Strengths	Major Limitations
					• Sensitivity analyses performed to address heterogeneity treatment durations between studies	

b.i.d = twice daily; CRNM = clinically relevant, non-major; DVT = deep vein thrombosis; IDC = indirect comparison; INR = international normalized ratio; NMA = network meta-analysis; NOAC = new oral anticoagulant; OL = open-label; PE = pulmonary embolism; q.d. = once daily; VKA = vitamin K antagonist; VTE = venous thromboembolic event.
[a] Only interventions of interest that meet the a priori systematic review protocol for this review are listed in this table.

Acute-Treatment Network Meta-Analyses

Hirschl et al. (2014)[25]

A systematic review was carried out by the investigators to compare the efficacy of apixaban 10 mg/5 mg twice daily, apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 15 mg twice daily/20 mg once daily compared with heparin and VKA control. The investigators performed an IDC using parameter estimates and covariance matrices (general linear model with binomial proportions) using a fixed-effect approach with the SPSS 22.0 statistical software. The risk for major bleeding was statistically significantly reduced with apixaban compared with dabigatran with RR = 0.42 (95% CI, 0.21 to 0.86). The risk for major and CRNM bleeding was statistically significantly reduced with apixaban compared with dabigatran (RR = 0.71 [95% CI, 0.52 to 0.95]), and compared with rivaroxaban (RR = 0.47 [95% CI, 0.37 to 0.61]). There were no statistically significant differences between NOACs for recurrent VTE. There was heterogeneity in several baseline characteristics (e.g., number patients with DVT, PE, or both) and treatment durations between studies. The IDC with rivaroxaban was based on two open-label studies and may have been subject to performance bias due to the lack of blinding. It remains uncertain whether between-study heterogeneity or the potential bias seen in the rivaroxaban studies affected the IDC results.

The analyses by Hirschl et al. (2014)[25] consisted of the same five included studies from the manufacturer's indirect analyses. Results were nearly identical and support the findings of the manufacturer's IDC.

Kang et al. (2014)[26]

A systematic review was carried out by the investigators to compare the efficacy of apixaban 10 mg/5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 15 mg twice daily/20 mg once daily. Two independent reviewers assessed the data to establish whether relevant outcomes had been sufficiently and appropriately reported. Studies were included if they were RCTs that had evaluated patients with acute VTE treated with an NOAC and reported at least one outcome of interest: mortality, recurrent VTE, recurrent DVT, recurrent PE, or major bleeding. Only studies evaluating the FDA-approved dosing regimen for rivaroxaban were included, and only studies using the same dosing regimen evaluated in phase 3 studies were included for the remaining NOACs. No specific exclusion criteria were provided. Study quality assessment was performed using the Cochrane Collaboration's risk-of-bias tool. The investigators performed an IDC using the Bucher method with a random effects model using a publicly available tool for adjusted indirect meta-analysis developed by CADTH. The risk of major bleeding increased with dabigatran compared with apixaban (RR = 2.69 [95% CI, 1.19 to 6.07]). The risk for major bleeding was statistically significantly reduced with apixaban compared with VKA (RR = 0.31 [95% CI, 0.17 to 0.54]). There were no statistically significant differences for mortality, recurrent VTE, PE, or DVT among NOACs. Results should be interpreted with caution as the analyses included open-label and non-randomized studies. There was heterogeneity in several baseline characteristics (e.g., the number patients with DVT, PE, or both) and treatment durations between studies. Model fit and between-study heterogeneity were not assessed.

The analyses by Kang et al. (2014)[26] consisted of the same five included studies from the manufacturer's indirect analyses and the analyses by Hirschl et al. (2014).[25] Results were consistent with, and support the findings of, the manufacturer's IDC.

Castellucci et al. (2014)[22]

A systematic review was carried out by the investigators to compare the efficacy of apixaban 10 mg/5 mg twice daily, LMWH/dabigatran 150 mg twice daily, rivaroxaban 15 mg twice daily/20 mg

once daily, and the combination of parenteral anticoagulants with VKA. Two independent reviewers assessed the data to establish whether relevant outcomes had been sufficiently and appropriately reported. Studies were included if: 1) they were RCTs that evaluated patients with acute VTE and who had qualifying recurrent VTE events that were symptomatic and objectively confirmed; 2) patients had received treatment with an NOAC, a LMWH alone, or the combination of a parenteral anticoagulant with VKA; and 3) they reported at least one outcome of interest: recurrent VTE, recurrent DVT, recurrent PE, and major bleeding. Studies were excluded if: 1) patients had been randomized to placebo or observation; 2) patients had been randomized to idraparinux or ximelagatran; 3) only patients with cancer-associated thrombosis had been included; 4) study design was phase 1 or 2; and 5) they evaluated extended VTE treatment for secondary prevention. Study quality assessment was performed using the Cochrane Collaboration's risk-of-bias tool. The investigators performed an NMA using both random and fixed effects models with the WinBUGS software. Model fit was assessed based on the comparison of residual deviance to the number of unconstrained data points, assessment of the deviance information criterion (DIC), and between-study standard deviation. Additionally, NMA results were qualitatively compared with direct frequentist pairwise estimates. The risk for major bleeding was statistically significantly reduced with apixaban compared with the combinations of UHF/VKA (hazard ratio [HR] = 0.26 [95% CI, 0.12 to 0.54]), fondaparinux/VKA (HR = 0.30 [95% CI, 0.12 to 0.68]), and with dabigatran (HR = 0.42 [95% CI, 0.17 to 0.99]). There were no statistically significant differences for recurrent VTE, PE, or DVT compared with rivaroxaban or LMWH alone. To adjust for variation in study treatment duration between studies, a sensitivity analysis for restricting studies to those that had had a minimum of six months of treatment was performed. Results aligned with those of the primary analysis. Similar to other IDCs found in the literature, it remains uncertain whether the inclusion of open-label and non-randomized studies affected the IDC results.

The analyses by Castellucci et al. (2014)[22] comparing NOACs with LMWH/VKA consisted of the same five included studies from the manufacturer's indirect analyses. Results were consistent with, and support the findings of, the manufacturer's IDC.

Extended-Treatment Network Meta-Analyses

Alotaibi et al. (2014)[27]

A systematic review was carried out by the investigators to compare the efficacy of apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, dabigatran 150 mg twice daily, and rivaroxaban 20 mg daily. Two independent reviewers assessed the data to establish whether relevant outcomes had been sufficiently and appropriately reported. The following inclusion criteria were used: 1) random allocation to treatment group; 2) placebo-control; 3) follow-up of at least six months; 4) diagnosis of PE and DVT done objectively by a clinician using any accepted threshold of any valid diagnostic tools; 5) reported one or more of the following outcomes: recurrent VTE, major bleeding, major bleeding or clinically relevant, non-major bleeding, acute coronary syndrome, and all-cause mortality. Studies were excluded if they included pregnant patients, healthy patients, if they compared new oral anticoagulants to an active comparator, or used the NOACs for indications other than VTE. Study quality assessment was performed using the Cochrane Collaboration's risk-of-bias tool. The investigators performed an IDC using the Bucher method with the indirect meta-analysis tool, METCARDIO. There were no statistically significant differences between NOACs for risk of recurrent VTE, major bleeding, or mortality. As results are based on a single study for each treatment with heterogeneity in baseline patient characteristics (e.g., females, proportion of thrombophilia) between studies, the robustness of the results remain uncertain. There were also insufficient details regarding the methodology of the IDCs (e.g., whether fixed or random effects models were used, or whether a covariate analysis had been performed).

The analyses by Alotaibi et al. (2014)[27] included three (EINSTEIN-EXT, AMPLIFY-EXT, RE-SONATE) of the nine studies from the manufacturer's IDCs for extended VTE treatment. The difference in included studies is based on the criterion of including only placebo-controlled studies; thus the REMEDY study (dabigatran versus warfarin) was not included in the analysis by Alotaibi et al. (2014).[27] Most results were similar and support the findings from the manufacturer's IDC. One notable finding that differed from the manufacturer's analysis was major bleeding with apixaban (2.5 mg or 5 mg) and with rivaroxaban. The analysis by Alotaibi et al. (2014)[27] concluded that there was no statistical difference between the two NOACs for major bleeding, while the analysis by the manufacturer concluded that there was a marginally significant difference favouring apixaban. This difference in findings may be a result of the different analyses that were performed. With only placebo-controlled studies, a Bucher pairwise IDC was performed by Alotaibi et al. (2014)[27] compared with the manufacturer's Bayesian NMA.

Rollins et al. (2014)[28]

A systematic review was carried out by the investigators to compare the efficacy of apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg daily, and warfarin (INR 1.5 to 2, or 2 to 3). Two independent reviewers assessed the data to establish whether relevant outcomes had been sufficiently and appropriately reported. The following inclusion criteria were used: patients aged 15 years or older with a history of one or more VTE episodes who had received anticoagulation therapy for a minimum duration of six months. Studies were excluded if they did not assess oral treatments that were not considered the standard of care, such as Aspirin; did not evaluate prophylactic doses; and/or did not evaluate a parenteral anticoagulant. Study quality assessment was assessed using the Jadad scale. The investigators performed an IDC using a Bayesian NMA, using the Aggregate Data Drug Information to build a Markov chain Monte Carlo analysis of oral anticoagulants for the extended treatment of VTE. Continuity correction was applied in the analyses of major bleeding by assigning a value of 1 if zero events had been reported. There was a statistically significant greater risk of major bleeding with warfarin compared with apixaban (RR = 4.24 [95% credible interval (CrI), 1.28 to 25.0]).There were no statistically significant differences between NOACs for recurrent VTE, all-cause mortality, non-fatal PE, DVT, or CRNM bleeding. Results should be interpreted with caution as the analyses included open-label and non-randomized studies. Additionally, for unknown reasons, the analyses included an additional apixaban study (AMPLIFY)[11] that measured acute treatment for VTE. There was heterogeneity in several baseline characteristics (e.g., the number of patients with previous VTE, females). There was also insufficient detail concerning the methodology of the IDCs (e.g., whether fixed or random effects models had been used, or whether a covariate analysis had been performed).

The analyses by Rollins et al. (2014)[28] included all nine relevant studies from the manufacturer's NMA. For the included AMPLIFY-EXT study, only the 5 mg apixaban treatment (not the 2 mg treatment) and placebo groups were included in the analyses. Another notable difference compared with the manufacturer's analyses was the continuity correction. While the manufacturer applied a value of 0.5 for zero events, Rollins et al. (2014)[28] chose a value of 1. Although there were differences in methodology, the results from Rollins et al. (2014)[28] similarly concluded no statistically significant differences for the risk for recurrent VTE and all-cause mortality when apixaban was compared with other NOACs, and they support the findings from the manufacturer's IDC.

Castellucci et al. (2014)[22]

A systematic review was carried out by the investigators to compare the efficacy of apixaban 2.5 mg twice daily, apixaban 5 mg twice daily, dabigatran 150 mg twice daily, rivaroxaban 20 mg daily, and a

standard adjusted dose VKA (warfarin INR 2 to 3) and low-dose VKA (warfarin INR 1.5 to 2). Two independent reviewers assessed the data to establish whether relevant outcomes had been sufficiently and appropriately reported. Studies were included if: 1) there was prospective enrolment of consecutive patients with objectively confirmed, symptomatic DVT or PE treated for a minimum of three months with anticoagulant treatment; 2) patients were randomized to receive an antiplatelet drug (acetylsalicylic acid), an oral anticoagulant drug (VKA, rivaroxaban, apixaban, dabigatran, or ximelagatran), or a placebo or observation for secondary prevention of VTE; and 3) one or more of the primary outcomes (recurrent VTE and major bleeding) or secondary outcomes (fatal recurrent VTE and fatal bleeding episodes) had been reported. Studies were excluded if patients had been risk stratified at the end of the initial anticoagulation period or if studies had included asymptomatic VTE. Study quality assessment was performed using the Cochrane Collaboration's risk-of-bias tool. The investigators performed an NMA using both random and fixed effects models with the WinBUGS software. Model fit was assessed using the DIC and by comparing the residual deviance with the number of data points in the model. The NMA results were qualitatively compared with direct frequentist pairwise estimates.

Rivaroxaban was associated with a statistically significantly higher risk of major bleeding compared with apixaban 2.5 mg twice daily and apixaban 5 mg twice daily (OR = 50.9 [95% CrI, 1.44 to 45,740]) and OR = 136.5 (95% CrI, 2.51 to 195,000), respectively. There was no statistically significant difference between apixaban 2.5 mg twice daily and apixaban 5 mg twice daily compared with dabigatran for major bleeding. There were no statistically significant differences for recurrent VTE between apixaban 2.5 mg twice daily and apixaban 5 mg twice daily with other NOACs. To adjust for variation in study treatment duration between studies, a sensitivity analyses for restricting studies to those that had had a minimum of six months of treatment was performed. The results aligned with those of the primary analysis. It remains uncertain whether the inclusion of open-label and non-randomized studies affected the IDC results. As noted by the investigators, results for rivaroxaban should be interpreted with caution, as only one study investigated rivaroxaban for major bleeding and contained a zero cell (0 of 590 patients receiving placebo and four of 598 patients receiving rivaroxaban), which resulted in uncertain estimates of effect.

The analyses by Castellucci et al. (2013)[29] included all nine relevant studies from the manufacturer's NMA. One notable difference compared with the manufacturer's analyses was the inclusion of an additional open-label randomized study that compared standard dose VKA for a fixed duration versus an extended duration. Results were consistent with, and support the findings of, the manufacturer's IDC.

Discussion

The methodology of the manufacturer's two NMAs was appropriate and provided an up-to-date comparison of treatment efficacy and safety of apixaban versus dabigatran, rivaroxaban, and VKAs. Overall, the results from the acute-treatment NMA suggested no significant difference in the efficacy of apixaban compared with rivaroxaban and dabigatran, as there were no significant differences between treatments for the outcomes of VTE and VTE-related death, non-fatal PE, DVT, VTE-related death, myocardial infarction, overall treatment discontinuation, and all-cause mortality. Similar results were obtained for the comparative efficacy of these drugs in the extended-treatment NMA. The results of two additional IDCs identified in the literature are consistent with the manufacturer's findings, although this is not surprising given that the evidence base was largely the same in all of the available IDCs. Therefore, it would appear that there are no substantial differences among the efficacy of the NOACs in treating and preventing recurrent VTE both in the short term and long term. However, a major limitation associated with this conclusion is the fact that there are a very small number of studies available to represent the treatment effects of each NOAC. This fact, in addition to the relative rarity of the events

being analyzed, means that the effects of heterogeneity among studies on the comparative efficacy of treatment are highly uncertain.

The results of the comparisons of the NOACs with respect to bleeding-related outcomes are more variable and are somewhat more difficult to interpret. For the acute-treatment IDC, apixaban was significantly less likely to cause major bleeding compared with dabigatran, but not compared with rivaroxaban. By contrast, for the extended-treatment IDC, rivaroxaban was associated with a significantly higher risk of major bleeding or CRNM bleeding compared with apixaban, but there were no differences between apixaban and dabigatran for these outcomes. The results of the three other published IDCs for acute treatment were similar to the manufacturer's analysis in that there were differences between apixaban and dabigatran with respect to major bleeding, but two of three IDCs that examined extended treatment differed from the manufacturer's results in failing to detect differences among NOACs for major bleeding or CRNM bleeding. The one IDC[22] that demonstrated similar results comparing rivaroxaban with apixaban for major bleeding noted that the results should be interpreted with caution, as only one study investigated rivaroxaban for major bleeding and no major bleeding was reported in the placebo group (zero event), resulting in uncertain estimates of effect. The inconsistency between the manufacturer's results for bleeding-related outcomes and the independently conducted published IDCs further illustrates the uncertainty regarding the statistically significant differences between apixaban and dabigatran or rivaroxaban for outcomes such as major bleeding. Although statistically significant results for major bleeding were seen favouring apixaban compared with dabigatran for major bleeding in acute treatment and rivaroxaban for extended treatment, apixaban was not consistently superior to both NOACs for all bleeding outcomes. Therefore, given the limitations noted for the NMAs (most notably the small number of studies and the rarity of events), there is a high degree of uncertainty related to interpreting the comparative bleeding risks associated with apixaban compared with other NOACs.

Conclusions

The evidence available from IDCs of apixaban compared with other NOACs is consistent with the conclusion that apixaban is equally efficacious as dabigatran and rivaroxaban in treating and preventing VTE, for both acute and extended treatment. Apixaban was associated with significantly less major bleeding than dabigatran for acute treatment and rivaroxaban for extended treatment, but apixaban was not consistently better than other NOACs across all bleeding-related outcomes for both acute and extended treatment. Any conclusions regarding the relative effects of the apixaban and other NOACs on outcomes such as major bleeding are uncertain due to limitations with the available data.

APPENDIX 7: DURATION OF ANTICOAGULATION THERAPY

1. Objective

To review the available evidence on the duration of anticoagulant therapy in the secondary prevention of venous thromboembolic events (VTEs) following initial treatment of acute deep vein thrombosis (DVT).

2. Findings

Introduction

Anticoagulant therapy following VTE is divided into three distinct phases:[4]

- Parenteral anticoagulation for up to seven days
- Long-term anticoagulation treatment with oral drug for up to three months; the use of parenteral treatment options may be preferable in special populations of patients
- Extended anticoagulation treatment for a duration ranging between longer than three months to indefinite.

The aim of anticoagulant therapy in VTE is twofold: to resolve the acute episode (i.e., first three months of therapy), and to prevent subsequent VTE episodes (i.e., longer than three months). While an acute episode of provoked (or secondary) DVT, whether proximal or distal, is usually treated with anticoagulant therapy for three months (Table 25),[4] there is uncertainty regarding the optimal duration after completing three months of initial therapy in the case of unprovoked (or idiopathic) DVT.[30,31]

TABLE 25: AMERICAN COLLEGE OF CHEST PHYSICIANS RECOMMENDATIONS FOR LONG-TERM ANTICOAGULATION OF ACUTE DVT OF THE LEG[4]

Nature of Acute DVT	Recommended Anticoagulant Treatment Duration
Provoked	3 months
• Surgical risk factor	
• Non-surgical transient risk factor	
Unprovoked	≥ 3 months[a]
• First event, proximal DVT	
○ low or moderate bleeding risk	Extended
○ high bleeding risk	3 months
• First event, distal DVT	3 months
○ low or moderate bleeding risk	
○ high bleeding risk	
• Second event	
○ low or moderate bleeding risk	Extended
○ high bleeding risk	3 months

DVT = deep vein thrombosis.
[a] After three months of treatment, risk-benefit ratio for extended therapy should be evaluated.
Note: In the case of incidental, asymptomatic DVT, the same approach used for initial and long-term anticoagulation in symptomatic DVT is suggested.

Once this initial treatment period has been completed, the risk of VTE recurrence is largely influenced by the effectiveness of these first three months of anticoagulation therapy in resolving the acute event and the individual patient's risk factors for VTE[21] (Table 26).

TABLE 26: TRANSIENT RISK FACTORS FOR VENOUS THROMBOEMBOLIC EVENTS[21]

Transient Risk Factors for VTE
Major (within past month):
• Surgery (with general anesthesia)
• Plaster cast immobilization of a leg
• Hospitalization
Minor:
• Estrogen therapy
• Pregnancy
• Prolonged travel (> 8 hours)
• Less-marked leg injury
• Major risk factor occurring 1 to 3 months before VTE diagnosis

VTE = venous thromboembolic event.

The decision to prolong treatment is critically informed by the identification of precipitants of the initial event, if possible, which determine the risk for recurrent VTE (Table 27). Other decisions to extend anticoagulation therapy (i.e., treatment > three months that may be continued indefinitely) may be based on DVT location and extension and whether the acute DVT is a first event.[4] An assessment of the benefit of treatment compared with the risk of bleeding (Table 28, **Error! Reference source not found.Error! Reference source not found.**) in consideration with patient preferences is typically undertaken and reviewed annually for changes, in the event that extended therapy is chosen.[4,21]

TABLE 27: RISK OF RECURRENT VTE AFTER INITIALLY COMPLETING MORE THAN THREE MONTHS OF ANTICOAGULATION THERAPY FOR PROXIMAL DVT OR PE[4]

VTE Event Type	Risk of Recurrence	
	After 1 year	After 5 years
Provoked		
Surgical risk factor	1%	3%
Non-surgical risk factor[a]	5%	15%
Unprovoked (i.e., idiopathic)	10%	30%

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolic event.
[a] E.g., estrogen therapy, pregnancy, leg trauma, and prolonged air travel (> 8 hours).

TABLE 28: RISK FACTORS FOR BLEEDING WITH ANTICOAGULANT THERAPY[4]

Age > 65 years
Age > 75 years
Previous bleeding
Cancer
Metastatic cancer
Renal failure
Liver failure
Thrombocytopenia
Previous stroke
Diabetes
Anemia
Antiplatelet therapy
Poor anticoagulant control
Comorbidity and reduced functional capacity
Recent surgery
Frequent falls
Alcohol abuse

TABLE 29: ESTIMATED ABSOLUTE RISK OF MAJOR BLEEDING IN LOW-, MODERATE-, AND HIGH-RISK CATEGORIES[4]

Categorization of Risk of Bleeding	Risk of Bleeding		
	Low	Moderate	High
Anticoagulation 0 to 3 months			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6	3.2	12.8
Anticoagulation after first 3 months			
Baseline risk (%/year)	0.3	0.6	≥ 2.5
Increased risk (%/year)	0.5	1.0	≥ 4.0
Total risk (%/year)	0.8	1.6	≥ 6.5

Low = zero risk factors; moderate = one risk factor; high = two or more risk factors.

TABLE 30: ESTIMATED ABSOLUTE DIFFERENCE IN RECURRENT VTE AND MAJOR BLEEDING EVENTS (INCLUDING FATAL EVENTS) WITH 5 YEARS OF VERSUS NO EXTENDED ANTICOAGULATION[4]

	Outcomes After 5 Years of Treatment	Risk of Bleeding		
		Low	Intermediate	High
First VTE provoked by surgery	Recurrent VTE reduction/1,000	↓ 26 (19 to 27) (1 fatal)		
	Major bleeding increase/1,000	↑ 24 (2 to 73) (3 fatal)	↑ 49 (1 to 173) (5 fatal)	↑ 98 (1 to 346) (11 fatal)
First VTE provoked by a non-surgical factor/first unprovoked distal DVT	Recurrent VTE reduction/1,000	↓ 132 (93 to 137) (5 fatal)		
	Major bleeding increase/1,000	↑ 24 (2 to 73) (3 fatal)	↑ 49 (1 to 173) (5 fatal)	↑ 98 (1 to 346) (11 fatal)
First unprovoked proximal DVT or PE	Recurrent VTE reduction/1,000	↓ 264 (186 to 273) (10 fatal)		
	Major bleeding increase/1,000	↑ 24 (2 to 73) (3 fatal)	↑ 49 (1 to 173) (5 fatal)	↑ 98 (1 to 346) (11 fatal)
Second unprovoked VTE	Recurrent VTE reduction/1,000	↓ 396 (279 to 409) (14 fatal)		
	Major bleeding increase/1,000	↑ 24 (2 to 73) (3 fatal)	↑ 49 (1 to 173) (5 fatal)	↑ 98 (1 to 346) (11 fatal)

↑ = increased; ↓ = decreased; DVT = deep vein thrombosis; VTE = venous thromboembolic event.

Studies Investigating Duration

In a meta-analysis by Holley et al. (2010),[30] several finite durations of anticoagulation therapy were compared in patients with an initial, acute unprovoked VTE to determine whether simply providing longer initial treatment courses resulted in greater protection against recurrent VTE once acute therapy had been stopped. Ten studies (n = 3,225), including six randomized controlled trials (RCTs), met the inclusion criteria. A mean duration of initial anticoagulant therapy for each study was used for comparison. Outcomes were analyzed both as continuous variables (i.e., by increasing the length of therapy) and categorical variables (three to six months, six to 12 months, > 12 months of treatment). Summary point estimates for VTE recurrence rates were 5.31 (95% CI, 4.26 to 6.36) for three to six months of treatment, 6.08 (95% CI, 3.71 to 8.45) for six to 12 months of treatment, and 5.42 (95% CI, 4.27 to 6.58) for > 12 months of treatment. No statistically significant differences in the rate of VTE recurrence were found in response to varying the duration of initial therapy (*P* = 0.82). Although major bleeding was reported, direct comparisons could only be performed in three of the included studies; these studies suggested an increase in bleeding risk with extended durations of treatment. The authors conclude that extending therapy beyond three to six months in patients with unprovoked VTE will not decrease the risk of VTE recurrence once therapy is stopped.

Hutten at al. (2006)[32] published a Cochrane meta-analysis of patients with symptomatic VTE, which examined the efficacy and safety of various durations of treatment with vitamin K antagonists (VKAs). Eight randomized trials were identified for a total of 2,994 patients. Long-term anticoagulant treatment durations (following initial therapy for the acute event) ranged from an additional two months to "indefinitely" (i.e., four years of follow-up), compared with up to six months of additional treatment or discontinuation. Statistically significant reductions in recurrent VTE were observed for the three-month versus six-month therapy comparisons (OR = 0.13; 95% CI, 0.05 to 0.33) and three-month versus 12-month long-term therapy comparisons (OR = 0.22; 95% CI, 0.11 to 0.44). The authors noted, however, that there are diminishing returns with treatment longevity, in that the risk for recurrent VTE lessens as the interval from the index

event increases but the risk for major bleeding remains. Although the data prevent making a recommendation for optimal treatment duration, the authors postulate that the substantial inter-individual variability in the risk for recurrent VTE might make a decision-analytic method useful for weighing the risks and benefits of long-term anticoagulation in individual patients.

In a 2003 meta-analysis by van Dongen et al.,[33] the risk of recurrent VTE was examined in relation to the interval from the index event following initial treatment with a VKA. Eighteen studies were identified, 16 of which were RCTs. Five categories of time intervals since the index event were created (one to three months, three to six months, six to nine months, nine to 12 months, and 12 to 18 months) for each treatment group, along with three categories of initial VKA therapy duration (short: four to six weeks, medium: three months, and long: four to six months) to enable comparisons among the included studies. A monthly VTE recurrence rate following VKA cessation was calculated according to the time interval category for each treatment group. Results showed that after initial treatment with a VKA, the monthly incidence of recurrent VTE declined over time, with a plateau in the rate after nine months, regardless the duration of initial VKA treatment. However, several limitations to this meta-analysis were noted from the included studies — likely a reflection of the state of clinical practice at the time of publication — notably, discrepancies in the therapeutic INR range employed, use of prothrombin time in some cases instead of INR, use of venography instead of compression ultrasound to objectively confirm DVT in some studies, and an overall lack of distinction between provoked versus unprovoked DVT, all of which could have affected the summary findings.

Prandoni et al. (2009)[31] conducted a randomized, multi-centre, open-label trial of 538 patients who had initially completed three months of anticoagulation therapy for a first symptomatic proximal DVT event. The study took place in Italy across nine hospital centres specializing in VTE management. The objective was to compare two anticoagulation strategies for secondary prevention — flexible-duration versus fixed-duration anticoagulation — on the rate of recurrent VTE. Patients were stratified according to study centre and whether the initial DVT was provoked or unprovoked. Patients randomized to the fixed-duration anticoagulation strategy received no months or three additional months of anticoagulation in the case of provoked or unprovoked DVT, respectively, while those randomized to the flexible-duration anticoagulation strategy received anticoagulation therapy for nine to 21 months in the case of unprovoked DVT as long as there was ultrasonographic evidence of persistent residual thrombi (i.e., non-recanalized veins). Patients were followed for a total of 33 months for the major clinical outcome of recurrent VTE, while major bleeding events were evaluated during anticoagulation treatment plus one additional month. Recurrent VTE events (n = 78) were statistically significantly more frequent in the fixed-duration group (n = 46 [17.2%]) compared with the flexible-duration group (n = 32 [11.9%]) (adjusted HR = 0.64; [95% CI, 0.39 to 0.99]). Major bleeding events occurred in a total of six patients, two (0.7%) of whom were in the fixed-duration group and four (1.5%) of whom were in the flexible-duration group. An important limitation that should be noted is that investigators, in the absence of widely established criteria for defining vein recanalization, held a consensus meeting prior to the start of the study to set operational criteria for assessing this surrogate outcome.

3. Summary

While there seems to be consensus that three months of anticoagulation therapy is sufficient in the case of an initial episode of acute, provoked DVT, uncertainty remains regarding the optimal duration of anticoagulation therapy following three months of initial treatment for acute, unprovoked DVT. Complicating this issue is the fact that some studies suggest a reduction in VTE risk over time while bleeding risk remains, potentially setting up a condition of diminishing returns. In the absence of compelling evidence, it would seem that the determination of which patients may benefit most from prolonged therapy remains a largely clinical decision based upon an individual patient's risk-versus-benefit profile.

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